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Insulin Pump Therapy: Patient Practices and Glycemic Outcomes

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Keywords
insulin pump therapy, diabetes, hypoglycemia, hyperglycemia

Insulin pump therapy (IPT) is an effective method for achieving glycemic control that provides flexibility both in basal infusion rates and the timing and frequency of prandial and correctional bolus dosing.[1] This flexibility allows significant variability among patients in the number of bolus insulin doses administered on a daily basis, which if excessive can increase risk for hyperglycemia or hypoglycemia.[2-4] The European Association for the Study of Diabetes and the American Diabetes Association Diabetes Technology Working Group have recently called for an evaluation of human performance with IPT in the clinic setting as a way of identifying and avoiding potential adverse outcomes associated with these devices.[2]

The purpose of this investigation was to examine associations between patient practices and glycemic measures in patients using Medtronic® IPT (Fridley, MN, USA) for ≥6 months. This initiative was reviewed by the University Institutional Review Board and approved as a quality improvement project. Two weeks of deidentified IPT data (all insulin doses and blood glucose [BG] measures) from 100 consecutive patients was downloaded at time of scheduled office visits (May 2016-June 2017). IPT data were grouped according to mean bolus frequency of <5 and ≥5 times/day. Statistical analyses for group comparisons were performed using SPSS® (Version 24).

When compared to patients bolusing <5 times/day, those bolusing ≥5 times/day administered more meal and correction doses using the pump calculator (wizard), and performed more overrides of the wizard function (Table 1). This group had better glycemic control by HbA1c and mean BG with less frequent hyperglycemia, and more frequent mild but not moderate or severe hypoglycemia. Among all patients, inverse correlations were observed for bolus frequency with HbA1c ($r = –.383$, $P < .01$) and frequency of hyperglycemia ($r = –.358$, $P < .01$). No correlations were observed for bolus frequency with glycemic variability or hypoglycemia ($P = .17$).

These observations are consistent with prior reports demonstrating that frequent bolus administration is associated with better glycemic control.[5,6] The T1D Exchange reported that patients with HbA1c <6.5% were more likely to report administering ≥5 boluses/day when compared to those with HbA1c ≥8.5%.[6] To our knowledge, this is the first report of an increase in mild hypoglycemia events with higher bolus frequency with IPT.

A limitation to the findings in this report is that only two weeks of data were obtained from each patient which may not reflect their practice over longer time periods. Data were obtained only from Medtronic pump devices without continuous glucose monitoring devices (CGM) (except for one patient), which limits the ability to extend these results to other devices with or without CGM.

In summary, these findings reveal that patients administering ≥5 insulin boluses/day have better glycemic control compared to those bolusing less frequently. This improvement in glycemic control occurs with an increased risk for mild but not moderate or severe hypoglycemia. The introduction of sensor-augmented IPT may more reliably guide adjustments of insulin boluses to achieve desired levels of glycemic control with lower risk for hypoglycemia.

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Table 1. Patient Demographics, Glycemic Measures and Pump Practice Patterns.

	<5 bolus/day (n = 45)	≥5 bolus/day (n = 55)	P[a]
Age (mean)	44.6 ± 16.5	44.3 ± 15	.93
Gender (% female)	64%	62%	.79
Race (% Caucasians)	98%	96%	.68
Type of diabetes (T1DM)	96%	95%	.83
HbA1c (%)	8.3 ± 1.3	7.4 ± 1.0	<.001
Duration of diabetes (years)	27.3 ± 14.6	25.5 ± 11.6	.49
Weight (Kg)	80.4 ± 14.7	78.6 ± 20.3	.62
BMI (kg/m^2)	28.2 ± 4.9	27.3 ± 5.2	.36
Creatinine (mg/dl)	0.93 ± 0.28	0.87 ± 0.2	.31
# BG checks/day	4.5 ± 4.4	5.8 ± 3.0	.091
# of total boluses/day	3.7 ± 0.8	7.3 ± 2.1	<.001
# of manual boluses/day	0.3 ± 0.5	1.2 ± 2.4	.012
# of wizard boluses/day	3.4 ± 1	6.1 ± 2.5	<.001
# of boluses with food/day	2.5 ± 1.0	4.0 ± 1.8	<.001
# of boluses with correction/day	2.3 ± 0.8	3.4 ± 1.6	<.001
# bolus overrides/day	0.6 ± 0.8	1.1 ± 1.4	.018
Average suspend duration/day (minutes)	14.5 ± 26.7	19.6 ± 44.9	.503
Total daily dose (TDD) insulin (units)	47.5 ± 17.7	47.8 ± 26.5	.94
TDD insulin (units/kg/day)	0.6 ± 0.2	0.6 ± 0.2	.980
% of TDD as bolus insulin	44 ± 13.9	50.9 ± 10	.005
# site changes/14 days	4.1 ± 1.1	4.5 ± 1.5	.091
Mean BG/14 days (mg/dl)	200.6 ± 49.5	175.8 ± 44.3	.01
BG CV	39.3 ± 11.9	40.1 ± 9.4	.669
%BG >180 mg/dl	50.0 ± 23.2	38.3 ± 22.1	.013
%BG >300 mg/dl	14.3 ± 16.0	7.9 ± 10.6	.019
%BG 50-69 mg/dl	3.2 ± 4.0	5.2 ± 5.3	.044
%BG 40-49 mg/dl	0.5 ± 1.3	0.7 ± 1.5	.434
%BG <40 mg/dl	0.1 ± 0.4	0.9 ± 0.5	.242

Results shown as mean ± standard deviation.
[a]*t* test for between group comparisons.

Abbreviations

BG, blood glucose; BMI, body mass index; CV, coefficient of variability; IPT, insulin pump therapy; TDD, total daily dose; T1DM, type 1 diabetes.

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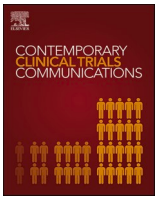

Study protocol for family model diabetes self-management education with Marshallese participants in faith-based organizations

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ABSTRACT

Background: Culturally-appropriate family models of diabetes self-management education and support (DSMES) using community health workers (CHWs) have been shown to help address barriers to improving type 2 diabetes mellitus (T2DM) self-management for racial/ethnic minority communities; however, there is limited DSMES research among Marshallese and other Pacific Islanders. Using a community-based participatory research approach, we engaged community stakeholders to co-design a study to implement a culturally adapted family model DSMES (F-DSMES) intervention in faith-based organizations (FBOs) (i.e., churches).

Methods: Using a cluster-randomized controlled trial design, we will assess the effectiveness of the F-DSMES intervention for Marshallese patients with T2DM in Arkansas and Oklahoma. Twenty-four FBOs (with 12 primary participants per FBO) will be randomized to one of two study arms: the intervention arm or the wait-list control arm. Primary participants must have at least one family member willing to attend education sessions and data collection events. The F-DSMES intervention consists of ten h of diabetes education delivered by CHWs over eight to ten weeks. Data will be collected from the intervention arm at pre-intervention (baseline), immediate post-intervention (12 weeks), and three months post-intervention. The wait-list control arm will complete a second pre-intervention data collection before receiving the intervention. The primary study outcome will be glycemic control, as measured by HbA1c. Secondary measures include glucose, weight, body mass index, blood pressure, diabetes self-management behaviors, and diabetes management self-efficacy.

Conclusion: The knowledge gained from this research will inform future DSMES and other health promotion interventions conducted with Marshallese and other Pacific Islander communities.

1. Introduction

The Pacific Islander population is rapidly increasing in the United States (US), with significant growth in rural southern and midwestern states [1]. Arkansas is home to the largest Marshallese community in the continental US with approximately 18,000 migrants residing in Arkansas [1,2]. Oklahoma also has a large Marshallese community with approximately 15,000 Marshallese residents [2].

While Pacific Islanders are underrepresented in health research and prior research has often grouped Pacific Islanders and Asians into a single racial category [3–6], the limited data available document significant health disparities between Pacific Islanders and other racial/ethnic populations in the US [7–13]. According to a Centers for Disease Control and Prevention report, 15.2% of Native Hawaiian and Pacific Islander adults reported a diagnosis of type 2 diabetes mellitus (T2DM), which was higher than the percentages among all U.S. (8.5%), white (7.9%), and Asian (7.9%) adults [14]. For the Marshallese community, estimates of T2DM range from 20% to 40% [15], and T2DM is the

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leading cause of premature death and years of life lost in Marshallese patients in the Republic of the Marshall Islands (RMI) [16]. A local needs assessment with Marshallese participants in northwest Arkansas found an extremely high incidence of T2DM (38.4%) and prediabetes (32.6%) [15].

These health disparities are exacerbated by the historical trauma of extensive nuclear testing conducted in the RMI by the US military between 1946 and 1957 [17]. The nuclear testing exposed Marshallese residents on multiple atolls to significant levels of nuclear fallout [17,18]. US scientists studied the effects of the nuclear fallout on the exposed Marshallese individuals in a project called "Project 4.1"; however, study materials were not translated into Marshallese, and participants did not provide informed consent [17]. The nuclear tests also contaminated local fresh water and food sources, which significantly altered the traditional diet of Marshallese [17–19]. Commodity foods such as rice and canned meats provided as aid by the US gradually replaced fresh fish, fruits, and vegetables [20,21], and this became the diet of choice among Marshallese migrants to the US, contributing significantly to their high rates of T2DM [19,20].

Diabetes self-management education and support (DSMES) is an evidence-based intervention that has been shown to improve modifiable risk factors and help patients effectively manage their condition [22–26]. However, positive results are not shared equally across all racial/ethnic groups [27–29]. Marshallese migrants face many social ecological barriers to self-management of their T2DM. Culturally-appropriate family models of DSMES using community health workers (CHWs) have been shown to help address barriers to improving diabetes self-management for African-American, Hispanic, and Native American communities [26–32]; however, there is limited DSMES research among Marshallese and other Pacific Islanders [33,34]. The authors previously developed and tested a family model of DSMES (F-DSMES) with Marshallese participants in Arkansas [35,36]. While the previous study of F-DSMES demonstrated effectiveness with Marshallese in Arkansas when delivered in participants' homes with a Certified Diabetes Educator present, the intervention was very costly. The Marshallese community is highly collectivist, and more than 90% state they attend church regularly. Therefore, the researchers worked with community stakeholders to co-design a study to implement the culturally adapted F-DSMES in faith-based organizations (FBOs).

This paper presents the study protocol for a cluster-randomized controlled trial (cRCT) to evaluate the effectiveness of F-DSMES when delivered in a group setting by CHWs in FBOs with Marshallese T2DM patients in Arkansas and Oklahoma. The study was reviewed and approved by the University of Arkansas for Medical Sciences (UAMS) Institutional Review Board (IRB #229034).

2. Materials and methods

2.1. Study aim and design

This study will use a cRCT design to evaluate the effectiveness of F-DSMES among Marshallese and their family members when delivered in a group setting by CHWs in FBOs in Arkansas and Oklahoma. The primary aim of the study is to improve diabetes-related outcomes for Marshallese patients with T2DM.

2.2. Community-based participatory research partnership

The study uses a community-based participatory research (CBPR) approach. CBPR engages community stakeholders and incorporates their collaboration during every stage of the research [37–42]. CBPR makes the research more culturally acceptable and increases the likelihood of sustainability by ensuring that community knowledge informs the research process [43–45]. CBPR encourages research that is equitable and ethical. The CBPR approach will allow the team to utilize contextually- and culturally-situated knowledge, practices, and resources of the Marshallese community. The research team developed strong relationships with 41 Marshallese FBOs through our CBPR approach, which will allow us to facilitate the engagement of social support from the FBOs. Over half of the staff and investigators on the study are Marshallese. Our previous CBPR collaborations with the Marshallese community are published in several articles [35,46–52].

2.3. Sample size, population, and study setting

The cRCT will be conducted at 24 FBOs in Arkansas and Oklahoma. FBOs (i.e., churches) are central to Marshallese culture, and prior needs assessments show that 97% of Marshallese report regular attendance at a church [53]. FBOs in the Marshallese community represent the primary social and hierarchical institution of clan and atoll affiliation with pastors and madam pastors serving respected leadership roles more akin to a chief than strictly a religious leader [53]. Approximately 12 primary participants with T2DM and 12 family members will be recruited from each of the 24 FBOs, for a final sample of 288 primary participants with T2DM and 288 family member participants.

2.4. Recruitment

Recruitment and enrollment of FBOs will be conducted in cycles of six to ten FBOs. FBOs will be recruited and enrolled in four cycles or until we reach our recruitment goal (N = 288 primary participants). Recruitment of FBOs will be conducted by bilingual study staff (Marshallese and English). Staff will contact FBO leadership to determine interest and work with leadership to coordinate informational sessions with FBO attendees. After a FBO agrees to partner, an informational session will be held at the FBO to discuss the study and begin recruiting participants. Eligibility screeners will be completed at informational sessions or any time prior to consent for individuals interested in joining the research study. Research staff will conduct the eligibility screening, which will include a finger stick to determine hemoglobin A1C (HbA1c). If the patient is determined to be eligible per eligibility criteria, the patient will be invited to consent and enroll. All recruitment information will be provided in both English and Marshallese and will use plain language. Both male and female adults are eligible to participate.

2.5. Randomization

Randomization will occur at the FBO-level (i.e., cluster-level) with 1:1 assignment of FBOs to each arm (intervention or waitlist control). FBOs will be enrolled and randomized in cycles as they are recruited and enrolled. Within each cycle, randomization of FBOs will be conducted utilizing a random number generation function. Except for the biostatistician co-investigator who will conduct the randomization, the allocation for each cycle will be concealed from study staff until after the cycle has been recruited and randomized. The biostatistician co-investigator will have no interactions with potential participants and will have no supervisory role over study staff responsible for recruitment or intervention delivery.

2.6. Participant inclusion and exclusion criteria

Marshallese adults (aged 18 or older) with T2DM (defined as having an HbA1c $\geq$ 6.5%) and at least one adult family member willing to participate in all educational sessions and data collection events will be considered eligible for the study as primary participants.

Exclusion criteria include persons who are not Marshallese, have received DSMES in the past five years, plan to move out of the geographic region, or have a condition that makes it unlikely that the participant will be able to follow the protocol. For the purposes of this study, a condition that makes it unlikely to participate in the protocol may also include an illness that would be contraindicative for participation in DSME (e.g., terminal illness, severe mental illness, severely

impaired vision or hearing) and conditions that present health risks for research staff or other participants in the group (e.g., tuberculosis, COVID-19).

For the purposes of this study, a "family member" is defined as someone that lives with or near the primary participant. Family members must be 18 years of age or older to consent and participate.

2.7. Consent

Consent materials will be available in English or Marshallese and presented in the participants' preferred language. Consent materials will use plain language to accommodate differences in literacy levels. The study will be explained using a video consent to ensure a standardized delivery of study information to each participant. If the consent video is unable to be viewed for any reason, bilingual staff will read the consent document with each participant. The consent will allow participants to choose if they consent to: linking their data to other UAMS studies they have participated in, using their de-identified data in future diabetes-related research, and agreeing to be contacted for future research opportunities. Participants will also be asked to consent to a HIPAA release for medical record data abstraction. After potential participants have watched the video of the consent material or read the consent, they will be able to ask bilingual staff members any questions about the study. Finally, they will be given the opportunity to provide consent. Written consent with the participant's signature will serve as documentation. Participants will be asked to invite family members to join the study. Family members who are willing to participate will complete the same consent process.

2.8. Theoretical framework

Integrated Acculturation Theory (IAT) and Social Cognitive Theory (SCT) inform the study's overall conceptual framework [54,55]. IAT conceptualizes the Marshallese migration experience as shaped by an array of barriers and facilitators. Both IAT and SCT emphasize the dynamic and reciprocal interaction between individuals, their environment, and their behavior [54,56]. F-DSMES is designed to increase social support as a mechanism for mitigating migrant-specific challenges and barriers that allow Marshallese migrants with T2DM to improve self-management behavior and ultimately improve health outcomes [54,56]. F-DSMES works to increase the support people receive from their family and increase self-efficacy for both people with T2DM and their family members. The F-DSMES teaches primary participants to recognize how supportive and non-supportive health behaviors affect their self-management, as well as factors in the families' physical environments that serve as facilitators and barriers to behavior change. In the F-DSMES, patients and family members learn, increase motivation, develop strategies, and set goals together. This collaborative learning experience is expected to improve family support and self-efficacy, which will improve self-management behavior and ultimately improve outcomes for the person with T2DM.

2.9. Intervention

Primary participants and family members will participate in ten h of education delivered in eight sessions over a period of ten weeks, with extra time allowed to accommodate for church cancellations, holidays, and make-up sessions. Each session will provide between one and two h of education and will include time after each session dedicated to goalsetting. Group educational classes led by trained Marshallese CHWs will be held at the participating FBOs. The CHWs will utilize an adapted version of the standard DSMES curriculum, which covers all of the Association of Diabetes Care and Education Specialists' seven self-care behaviors: being active, healthy eating, understanding blood glucose and following doctor prescribed medications, reducing risks and healthy coping, problem solving, mitigating complications of diabetes, and goal setting [57].

The cultural adaptation of the standard DSMES curriculum was guided by Bernal's eight dimensions of culturally sensitive interventions to put specific focus on leveraging cultural strengths to overcome migrant-specific barriers to effective self-management [58,59]. Many in the Marshallese community face significant social, economic, and environmental barriers to self-management, including low income, unstable housing, food insecurity, access to healthcare, language, and transportation [53,60–64]. The curriculum is based on a collectivist approach, is conducted exclusively in Marshallese, and uses familiar contexts and analogies such as the role of spirituality, nature analogies, the value of traditional Pacific medicine, and "talk story." [47] The F-DSMES includes family members as secondary participants and focuses on family motivational interviewing, setting goals as a family, and family behavioral change [35,47]. Family members can hinder or aid in a person's diabetes self-management through their attitudes, behaviors, communication, and habits [65–67]. The curriculum is specifically designed to provide participants with education on supportive and non-supportive family behaviors [35,47]. The curriculum aims to increase supportive family member behaviors such as developing a healthy family meal plan, exercising together, and assisting in management activities such as blood sugar checks and taking medications. The curriculum aims to reduce non-supportive family member behaviors such as criticizing and arguing about the person's behaviors, buying and cooking unhealthy foods, and making the person feel that they must manage their diabetes alone. The curriculum is asset-based and works to overcome barriers facing Marshallese participants by leveraging culturally specific facilitators of healthy behavioral change.

2.10. Data collection

Data will be collected from both the primary participants with T2DM and the family member participants. For the intervention arm, data will be collected at pre-intervention (baseline), immediate post-intervention (12 weeks), and three months post-intervention. For the wait-list control arm, data will be collected during the same pre-intervention data collection window as the intervention arm. Instead of receiving the intervention immediately, the control arm will wait 12 weeks and will then participate in an additional pre-intervention data collection event before receiving the intervention. This second pre-intervention data collection will correspond with the post-intervention data collection event for the intervention arm and serve as the post-intervention control data. The control arm will then receive the intervention, and data will be collected at post-intervention and three months post-intervention (Fig. 1).

Data collection events will take place in the FBOs, and all data will be collected by trained bilingual staff. All data collection staff will have prior experience collecting both biometric and survey data. A HIPAA release will be obtained during consent to allow medical record abstraction for UAMS patients at 12, 18, and 24-months post-intervention. Research Electronic Data Capture (REDCap) will be utilized to capture, store, and manage study data [68]. To prevent/minimize missing data, REDCap includes a missing data report in the Quality Assurance tool [68]. This allows convenient quality assurance validation and monitoring as well as prompt collection of missing data.

2.11. Biometric data

The primary study outcome will be glycemic control, as measured by HbA1c. Secondary biometric measures include glucose, weight, height, body mass index (BMI), and blood pressure. Point of Care tests will be used to test HbA1c. Staff will use a Siemens DCA Vantage Analyzer to collect HbA1c via finger prick blood collection [69]. Participants' weight (without shoes) will be measured to the nearest 0.5 lb (0.2 kg) using a calibrated scale. Height (without shoes) will be measured to the

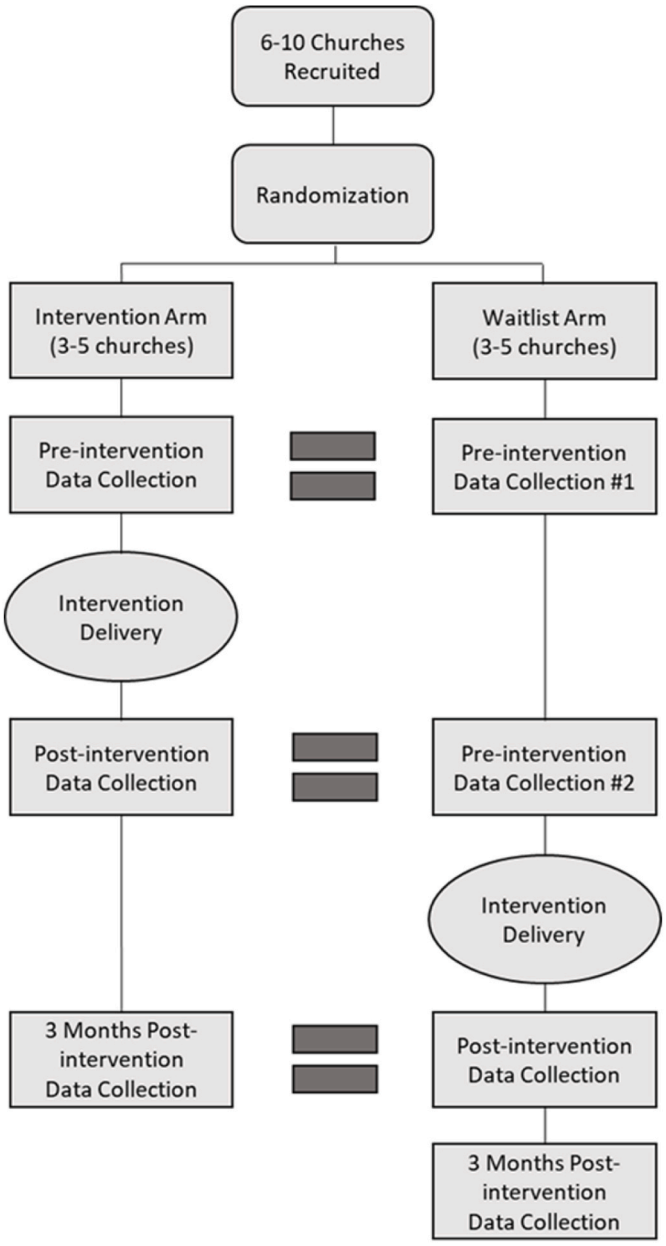

Fig. 1. Illustration of study cycle recruitment, randomization, and alignment of data collection intervals.

nearest 0.25 inch using a stadiometer. Weight and height will be used to compute a continuous measure of BMI (kg/m^2). Blood pressure will be measured using a digital blood pressure device, with the participant seated and arm supported and elevated to place the cuff at approximately heart height. Blood pressure readings will be taken after allowing participants to rest (i.e., seated for at least five min or standing still for one to three min). At least two measurements will be taken, waiting at least 60 s between readings. The average of those two measurements will be recorded as the participant's blood pressure reading. If there is > 5 mmHg difference between the first and second readings, an additional two readings will be obtained, and the average of these four readings will be used [70,71]. Trained study staff will collect biometric data from both primary participants and family members. By collecting biometric data from family members, it will allow us to explore the effects of the intervention on their biometric outcomes as well. If a participants' biometric reading is out of normal/healthy range, study staff will provide referrals to local clinics.

2.12. Survey data

A survey instrument has been developed with input from Marshallese stakeholders that includes internally developed items and scales, as well as items and scales adapted from the Diabetes Care Profile [72] and the Behavioral Risk Factor Surveillance System [73]. Participants will answer different questions in the survey instrument depending on their qualification as 1) a primary participant with T2DM, 2) family member participant with T2DM, or 3) family member participant without T2DM (Table 1). All survey instruments will be translated into Marshallese and presented in both Marshallese and English. The surveys will be administered at the pre-intervention and post-intervention data collection events but not at three months post-intervention. Surveys will either be self-administered or interviewer-administered, depending on the preference and/or literacy of the participant. Bilingual research staff will be present at all data collection events.

Table 1
Study measures for surveys designed for Primary Participants (PP), Family Members without Diabetes (FM), and Family Members with Diabetes (FMD).

Constructs	Participant	Measure/Item Descriptions
Demographic, Socioeconomic, & Household Characteristics	PP, FM, FMD	Age, sex, primary language spoken at home, English speaking ability, marital status, education level, employment status, household size, household income, length of residence in the US, household food security status [74]
Health Status	PP, FM, FMD	Self-reported general health status and prior diagnosed chronic health conditions including hypertension and diabetes
Access to Care	PP, FM, FMD	Health insurance status, having a primary care physician, barriers to primary care, barriers to medication adherence
	PP, FMD	Barriers to diabetic testing supplies
Diabetes-Related Treatments	PP, FMD	Currently taking insulin, currently using a continuous glucose monitor
Diabetes Self-Efficacy	PP, FMD	Diabetes Management Self-Efficacy Scale [75] will capture participants' confidence in performing important self-care behaviors including following a diet plan, engaging in regular exercise, and knowing what to do when blood sugar levels get out of range
Diabetes Self-Care Behaviors/Health Behaviors	PP, FMD	Summary of Diabetes Self-Care Activities (SDSCA) scale [76] and items from the Behavioral Risk Factor Surveillance System's (BRFSS) self-management module and sugar-sweetened beverage module will assess participants' level of engagement in self-care behaviors
Health Behaviors	FM	Subscales of the SDSCA focused on diet and exercise, BRFSS sugar-sweetened beverage module
Diabetes Understanding	PP, FMD	Diabetes Care Profile's Understanding module [72] will capture how well participants understand important concepts including how to cope with stress and the role of exercise in diabetes care
Support for Diabetes Self-Management	PP, FMD	Family and Friend Involvement in Adults' Diabetes (FIAD) scale [77] will capture perceived helpful and harmful friend/family involvement in diabetes self-management
	FM	Family member version of the FIAD will capture family member's assessment of their own helpful and harmful involvement in the PP's diabetes self-management [77]

2.13. Medication data

A list of current medications will be collected at each data collection event to provide consideration of variations in medications during the analytical phase, and changes in glycemic control will be appropriately attributed to the DSME rather than confounding factors.

2.14. Fidelity data

Fidelity will be determined by evaluating 1) fidelity of intervention delivery by the CHW educator, 2) recruitment and retention rates for data collections, and 3) attendance at F-DSMES sessions. Trained study staff will observe intervention sessions using a fidelity checklist to ensure fidelity and adherence to the curriculum. Primary participant and family member enrollment will be tracked and reported weekly as FBOs are being recruited and enrolled. Primary participant and family member retention will be tracked and reported at each data collection event. Attendance of primary participants and family members for each F-DSMES session will be recorded and reported weekly.

2.15. Remuneration

Remuneration will be provided to both primary participants and family member participants. Participants will receive $30 gift cards for data collection events that include collection of both survey and biometric data. For data collection events that do not include the survey (i.e., biometric-only), participants will receive $20 gift cards. Participants will only receive gift cards for the data collection events they attend. Participants included in the intervention arm of the study will be eligible to collect two $30 gift cards and one $20 gift card for a total of $80 for those who participate in all three data collection events. Participants in the wait-list control arm will have one additional data collection event (second pre-intervention) and will, therefore, be eligible to collect two $20 cards and three $30 gift cards for a total of $110 for those who participate in all four data collection events. An additional $20 gift card will be provided to those who attend all of the educational sessions. Participants in the intervention arm attending all data collection events and educational sessions will receive a total of $100 in gift cards. Participants in the control arm attending all data collection events and educational sessions will receive a total of $130 in gift cards.

3. Statistical analysis

3.1. Sample size calculations

All power calculations were conducted with PASS12. Sample size estimates are based on our previous RCT data obtained on the main outcome measure, HbA1c, in the Marshallese population from this region [36]. The previously tested F-DSMES intervention resulted in an HbA1c reduction of 1.09% (NGSP units) (effect size = 0.87) relative to baseline. Assuming a cluster-randomized design, intracluster correlation of 0.01, and significance level $\alpha = 0.05$, sample sizes of 144 primary participants in each treatment arm (12 FBOs x 12 primary participants, accounting for an estimated 20% attrition rate) will achieve greater than 90% power to reject the null hypothesis of equal mean change in HbA1c between groups. We will analytically maximize the use of all collected data by implementing multiple imputation methods that produce valid statistical inferences [78]. For both primary participant and family member outcomes, we have sufficient sample size and power to detect small to medium effects within the proposed design.

3.2. Outcome analyses

Outcomes will be analyzed using all available data from all randomized participants, using either multiple imputed data sets or full-information maximum likelihood (FIML) estimation. We will use Markov Chain Monte Carlo monotone regression-based multiple random imputation of the outcomes by treatment arm using SAS PROC MI, and we will assume that data are missing at random. The analysis will be carried out in multiple data sets, and results will be combined using standard methods (SAS PROC MIANALYZE) to produce summary effect and standard error estimates that incorporate the imputation error. As a sensitivity check, we will also carry out a secondary analysis without imputation or FIML estimation, to compare results from a complete cases analysis.

3.3. Analysis of primary outcome

The primary outcome is change in HbA1c between pre-intervention and post-intervention. We will also evaluate change in HbA1c at three months, 12 months, 18 months, and 24 months post-intervention. Our primary analytic approach will use general linear models (GLM) such as mixed linear regression analysis for continuous repeated measures to model the mean outcome differences and covariance structures between the treatment arms while accounting for cluster-randomized design with repeated measures. Using these models, treatment, time, and interaction effects will be estimated and tested by comparing group-specific means at post-intervention, three months, 12 months, 18 months, and 24 months post-intervention, while conservatively adjusting for additional covariates. The criterion for statistical significance will be $\alpha = 0.05$.

3.4. Analysis of secondary outcomes

Analytic strategies similar to those used to evaluate our primary outcome will be employed to examine the proposed secondary measures. We will examine treatment effects, time effects, and the interaction between them on other measures (blood pressure, fasting glucose, BMI, and survey instrument data) using mixed and general/generalized linear mixed models, depending on the measurement scale of the outcome. Additional analyses will expand the existing multivariate models to include several covariates (e.g., demographics and socioeconomic factors) for adjustments and to examine their associations with the outcomes. Finally, we will examine the association between treatment adherence, such as program participation, and the outcome measures in order to determine the magnitude of impact each additional intervention session has on the change in the outcome (e.g., how much of the reduction in HbA1c is attributed to each additional unit of program participation).

3.5. Mediation analysis

An innovative aspect of the study is the examination of changes in perceived social (family) support as a potential mediator of the effect of F-DSMES on participants' outcomes. Meditation will be assessed by examining the appropriate 95% confidence interval for the indirect effect of F-DSMES on participant outcomes as mediated by perceived social support. Mediation analyses will be conducted using Mplus software [79], and inferences will be made based on a bootstrapped 95% confidence interval.

3.6. Dissemination plan

The data gained from the research will help healthcare providers offer effective DSMES for Marshallese, as well as other Pacific Islander communities. The first priority will be to disseminate results back to participants and their family members. Through an existing CBPR collaborative, the research team will also provide a summary of the results back to the broader Marshallese community, ensuring that primary participant and family member confidentiality is maintained. Study reports will be disseminated to health care providers serving the Marshallese and other Pacific Islander communities. The study reports disseminated to health care providers will also be distributed to national

Pacific Islander advocacy groups and health organizations. Additionally, study results will be used for academic presentations, posters, and publications. These materials will not contain any identifiable information that could be linked to a primary participant or family member.

4. Summary

This study is grounded in a CBPR approach, which engages Marshallese community members in the research process and builds on the relationship that the study team has cultivated with the Marshallese communities in Arkansas and Oklahoma. This study will add to a growing body of literature on family models of DSMES [65,66,80]. This study will provide new and innovative information on the effectiveness of F-DSMES delivered by CHWs in an FBO setting with Marshallese patients with T2DM. The knowledge gained from this research will inform development and implementation of DSMES interventions conducted with Marshallese and other Pacific Islander communities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Meta-Analysis

Adverse Events Related to Tirzepatide

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Abstract

Context: Tirzepatide is a dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved by the US Food and Drug Administration in May 2022 for patients with type 2 diabetes mellitus (T2DM).

Objective: We aimed to determine the rates of individual adverse events (AEs) related to 3 studied doses of tirzepatide.

Methods: We performed a systematic review with meta-analysis including 5 databases (PubMed, Embase, CINAHL, Scopus, and Web of Science) for all clinical trials reporting AEs related to tirzepatide. The safety data from individual studies were extracted and analyzed through meta-regression to assess rates of individual AEs. Study quality assessment was performed using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Results: Ten trials (6836 participants) were included. Gastrointestinal (GI) AEs were the most commonly reported AEs and were dose dependent 39% (95% CI, 35%-43%), 46% (95% CI, 42%-49%), and 49% (95% CI, 38%-60%) for the 5, 10, and 15 mg dose, respectively. Among all GI AEs, nausea and diarrhea were most frequent at any dose of tirzepatide. Drug discontinuation due to AEs was highest with the 15 mg dose of tirzepatide (10%). Incidence of mild hypoglycemia (blood glucose < 70 mg/dL) was highest with tirzepatide 10 mg dose 22.6% (9.2%-39.8%). Rates of fatal AEs, severe hypoglycemia, acute pancreatitis, cholelithiasis, and cholecystitis were extremely low (≤ 1%) across all doses of tirzepatide.

Conclusion: Tirzepatide is associated with a dose-dependent increase in incidence of GI AEs and AEs leading to drug discontinuation. Severe hypoglycemia, fatal AEs, acute pancreatitis, cholelithiasis, and cholecystitis are rare with this medication.

Key Words: LY3298176, dual GIP/GLP-1 receptor agonist, tirzepatide, safety, adverse events, diabetes, glucose, systematic review, meta-analysis

Abbreviations: AE, adverse event; ANOVA, analysis of variance; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HbA_{1c}, glycated hemoglobin A_{1c}; MACE, major adverse cardiovascular events; T2DM, type 2 diabetes mellitus.

The term "*incretin*" was first described in 1932, referring to the hormones released from the gut that regulate the insulin response to a meal [1]. It is also known as a glucose-dependent insulinotropic polypeptide (GIP), which lowers the glucagon level by increasing the release of insulin in response to glucose ingestion. Elrick et al [2] first demonstrated a significant and sustained rise in plasma insulin response following an oral glucose load compared to a parental glucose load. This phenomenon was later known as "the incretin effect" and accounts for up to 65% of postprandial insulin secretion [3]. The 2 principal incretin hormones responsible for the incretin effect are glucagon-like peptide 1 (GLP-1) and GIP.

GLP-1 acts by stimulating insulin release and inhibiting glucagon secretion in the hyperglycemic and normoglycemic states. Extra pancreatic effects of GLP-1 include delayed gastric emptying, increased satiety, and reduced food intake leading to reduction in body weight and glycated hemoglobin A_{1c} (HbA_{1c}) in patients with type 2 diabetes mellitus (T2DM) [4-6]. GLP-1 receptor agonists (GLP-1 RAs) have been approved for the treatment of T2DM since 2005 and are recommended, as per the latest guidelines, early in the treatment algorithm given the associated weight reduction, glycemic efficacy, and favorable cardio-nephrovascular outcomes [7, 8].

GIP also stimulates glucose-dependent insulin secretion and is responsible for a greater proportion of the incretin effect than GLP-1. It differs from GLP-1 in its effect on glucagon secretion: It has a glucagonotropic property in the normoglycemic and hypoglycemic state, and glucagonostatic in the hyperglycemic state [9-11]. It also enhances the sensitivity of adipose tissue to insulin and the postprandial lipid-buffering

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capacity of white adipose tissue [12, 13]. Although it was thought to have no potential as a glucose-lowering therapy because of observations showing no insulinotropic effect from supraphysiological infusion in people with T2DM, recent evidence showed that there is a synergistic effect of GLP-1 and GIP, resulting in significantly increased insulin response and glucagonostatic response [10]. This led to the development of the dual GIP/GLP-1 RA.

Tirzepatide was recently approved by the US Food and Drug Administration in May 2022 for the treatment of T2DM. In addition to the 39 amino acids, it has a 20-carbon fatty diacid moiety that has the capacity to bind to albumin, prolonging its half-life to 5 days, allowing once-weekly dosing. It has a comparable GIP receptor binding affinity to native GIP. However, it has a 5 times lower GLP-1 receptor affinity than that of native GLP-1 [14, 15]. The SURPASS clinical trial programs assessed the efficacy and safety of tirzepatide at 3 different doses (5, 10, and 15 mg) in patients with T2DM. The recommended dose-escalation algorithm is to start at a dose of 2.5 mg weekly for the first 4 weeks followed by increments of 2.5 mg every 4 weeks until the maintenance dose based on the maximum tolerated side effects [15]. The SURPASS-5 trials showed that diarrhea, nausea, and vomiting were the most common treatment-emergent adverse events (AEs) in the groups receiving tirzepatide; however, the incidence of new AEs decreased over time in the groups and there were no deaths were recorded during the study [16]. Since this drug was recently approved for use, it is of considerable importance to assess the rate of AEs reported in different clinical trials. This meta-analysis is aimed to assess pooled rates of AEs associated with the use of tirzepatide at 5, 10 or 15 mg doses.

Materials and Methods

Study Design and Selection Criteria

This systematic review and meta-analysis was performed using the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements (PRISMA) [17]. We included all the clinical trials reporting any AE related to tirzepatide published before March 12, 2022. We excluded the following studies: (a) preclinical studies, and (b) nonclinical trial publications such as comments, reviews, editorials, opinions, etc. The outcomes of interest in this study consisted of 3 overall safety outcomes and other specific outcomes. The overall safety outcomes were any serious AEs, any AEs leading to drug discontinuation, and any AEs leading to death. The specified safety outcomes were gastrointestinal (GI) AEs, gall bladder and pancreatic AEs, appetite and weight changes, hypoglycemia, severe hypoglycemia, allergic reactions, and multisystem AEs. Given that this drug was recently approved and has a limited number of randomized controlled trials available, we also included data from a phase 1 clinical trial in our meta-analysis [18].

Search Strategy

We conducted a comprehensive search of the following 5 databases: (a) PubMed/Medline, (b) Embase, (c) CINAHL, (d) Scopus, and (e) Web of science. We restricted our search to articles published in the English language. The search strategy was designed by following the Population, Intervention, Comparison, and Outcome (PICO) Principle. Using our methodology, the following key words were identified: "Tirzepatide" OR "LY3298176" OR "LY-3298176." Next, the bibliographies of the selected articles were manually searched for any additional studies. After screening for duplicate studies, 2 reviewers (R.R. and R.M.) independently reviewed the title and abstract of the identified publications. We then excluded studies that did not address our research question based on our prespecified inclusion/exclusion criteria. Finally, the full texts of the remaining articles were examined to determine the final exclusion for our systematic review. Any conflicts during the study selection process were resolved by the 2 reviewers by thorough discussion. Fig. 1 shows the schematic diagram of the study selection process.

Data Extraction

Data were extracted from each eligible study included in the meta-analysis: study title, primary author, year of publication, sample size, patient demographics study details (single vs multicenter), study duration, average HbA1c, duration of diabetes, and tirzepatide dose assessed. Table 1 summarizes the details of the studies included in the meta-analysis.

Data Synthesis

Compiled data were summarized for completion and evaluated through meta-regression by analysis of variance (ANOVA). To perform this, we performed first a meta-analysis on event proportions done per parameter evaluated (32 parameters) across all tirzepatide doses (3 doses and the placebo). Owing to low availability of replication studies, the 12, 1, and 0.5 mg doses were dropped from the analysis; therefore, we considered only the more popular 15, 10 and 5 mg doses of tirzepatide and the placebo when reported. All initial meta-analysis were performed using MedCalc v.20.106 (MedCalc Software Ltd) using the Meta-analysis: proportion function. Because of variations in heterogeneity across all parameters and doses evaluated, only random-effect models were further used in the analysis.

Second, we performed meta-regression and ANOVA using SAS/STAT v9.4 (SAS Institute Inc) with the use of generalized linear models (GLMs) through PROC GLM, where the weights estimated for each study in the initial meta-analysis were used as the weights for the meta-regression. Differences between doses groups (15, 10, and 5 mg tirzepatide) were evaluated along with the placebo group. Associations were declared statistically significant when the probability of the ANOVA test was significant after a multiple testing adjustment (0.05/32 tests, using the Bonferroni approach).

Quality Assessment

Two independent reviewers (R.R. and R.M.) assessed the study quality and risk of bias in the included studies using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Study Quality Assessment Tools; https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Any disagreements were resolved by discussing with other reviewers (G.E. and L.K.). Based on 14 questions, an overall rating was assigned as good, fair, and poor for study quality, corresponding to low, moderate, or high risk of bias.

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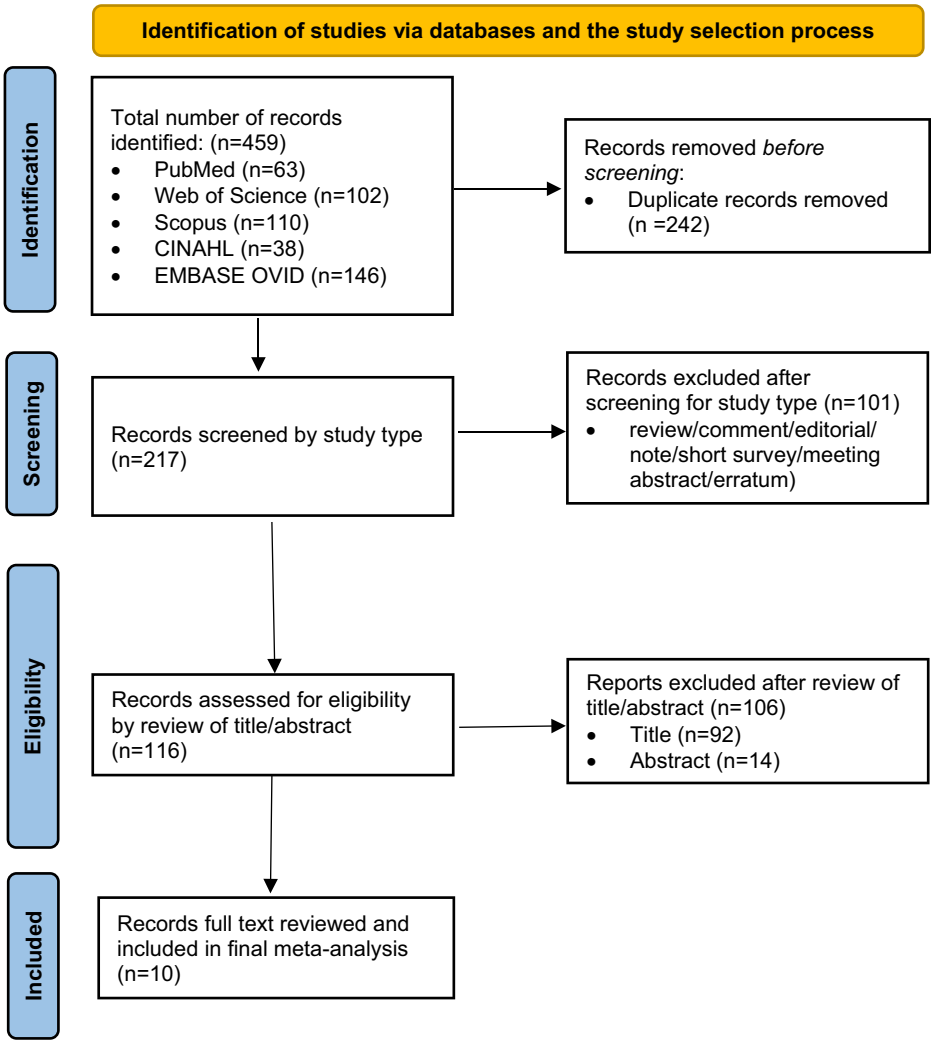

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the study selection process.

Results

Eligible Studies and Characteristics

A total of 459 studies were retrieved through the search of databases (PubMed 63; Web of Science 102; Scopus 110; CINAHL 38; Embase 146). After removing duplicates, we obtained 217 records. Of these, 101 studies were excluded based on the study types and the remaining 116 studies were selected for screening by title and abstract. Ten studies were included for full-text assessment, all of which met the inclusion criteria for the study. The study flowchart is shown in Fig. 1. The 10 studies involving a total of 6836 adult participants were published between 2018 to 2022, and the baseline characteristics of the included studies are shown in Table 1. Mean age, diabetes duration, HbA_{1c}, and number of females were 58.9 years, 9.6 years, 8.3 gm%, and 44.7% (n = 3056). Control and tirzepatide groups had 2215 and 4621 participants, respectively. Data from one study by Frias et al [19], in which participants received incremental doses of tirzepatide with a peak dose of 15 mg (2.5, 7.5, and 15 mg during 0-3, 4-7, and 8-11 weeks), was combined with a 15-mg group for analysis of AEs. In another study by Coskun et al [14], there was titration of tirzepatide doses until peak of 10 and 15 mg for respective group participants. Table 2 summarizes AEs seen with tirzepatide use. Using the study quality assessment tool, 9 studies were rated "good," and 1 study was rated "fair"; none was rated "poor," eliminating increased risk of bias in the studies included in our meta-analysis (Supplementary File 1) [20].

Severity Graded Adverse Events

Specific AEs were reported by a variable number of studies. The proportion of serious AEs was 7.52% with 5 mg and about 7.32% with 10 mg and 5.57% with 15-mg doses of tirzepatide. The 15-mg dose had the highest proportion of patients with AEs leading to treatment discontinuation. The proportion of fatal AEs was 1.07% with 5 mg, below 0.72% with 10, and 0.90% with 15-mg doses. ANOVA *P* values were not statistically significant for any of these AEs among different doses. Severity grade AEs are also represented in Fig. 2.

Incidence of Gastrointestinal Adverse Events

GI AEs were reported by most of the studies included in the meta-analysis. "All GI AEs" were reported in 2 studies [14, 21] for placebo and 3 studies [21-23] for the tirzepatide

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Table 1. Baseline characteristics of included studies

Author	Tirzepatide doses, mg	Control arm	Control arm (N)	Tirzepatide arm (N)	Mean age, y	Female N (%)	Mean diabetes, duration y	Mean baseline A_{1c}, gm%
Frías, 2018	1, 5, 10, 15	Placebo, dulaglutide	105	211	57	148 (47)	9	8.1
Coskun, 2018	Incremental doses	Placebo	11	42	56.8	25 (47)	NA	8.4
Frías, 2020	Incremental doses	Placebo	26	85	57.4	45 (40)	9.1	8.4
Rosenstock, 2021	5, 10, 15	Placebo	115	363	54.1	231 (48)	4.7	7.9
Urva, 2021	5	NA	NA	45	60.3	15 (33)	NA	NA
Ludvik, 2021	5, 10, 15	Insulin (degludec)	360	1077	57.4	635 (44)	8.4	8.17
Del Prato, 2021	5, 10, 15	Insulin (glargine)	1000	995	63.6	749 (38)	11.8	8.52
Frías, 2021	5, 10, 15	Placebo	469	1409	56.6	996 (53)	8.6	8.28
Furihata, 2022	Incremental doses	Placebo	9	39	57.4	1 (2)	8.5	8
Dahl, 2022	5, 10, 15	Placebo	120	355	60.6	211 (44)	13.3	8.3

Abbreviation: NA, not available.

arm. Three studies reported all GI AEs with tirzepatide. A significantly higher proportion of patients experienced GI AEs with tirzepatide, and the pooled proportion for all GI AEs were 39.05% (95% CI, 35.33%-42.83%), 45.57% (95% CI, 41.74%-49.43%), and 49.25% (95% CI, 38.44%-60.08%) for the 5, 10, and 15 mg dose, respectively. Among all GI AEs, nausea and diarrhea were the most frequently reported AEs with any doses of tirzepatide. Individual GI AEs such as nausea, vomiting, diarrhea, and dyspepsia were reported by a variable number of studies. Nine studies [14, 16, 18, 21-26] reported rates of nausea, vomiting, diarrhea, and dyspepsia. One study [18] did not report rates of nausea, vomiting, and diarrhea with the 10-mg dose of tirzepatide. Data for dyspepsia from Frias 2020 [19] were analyzed with the 15-mg dose, as mentioned earlier. The pooled proportion of nausea was 13.27% (95% CI, 10.79%-15.97%), 17.89% (95% CI, 14.91%-21.08%), and 24.08% (95% CI, 20.21%-28.13%) for the 5-, 10-, and 15-mg dose, respectively. Similar rates of diarrhea were seen with tirzepatide and were 13.19%, 17.22%, and 20.79% for the 5-, 10-, and 15-mg dose, respectively. Vomiting was less frequent with pooled proportions of 5.67%, 8.32%, and 13.98% with the 5-, 10-, and 15-mg dose, respectively. The proportion of any GI AEs increased with increasing doses of tirzepatide. Surprisingly, dyspepsia and constipation were most frequently seen with the 10-mg dose of tirzepatide, and the rates were 8.52% (95% CI, 6.62%-10.65%) and 8.86% (95% CI, 4.67%-14.22%), respectively. The pooled proportion of abdominal distension, abdominal discomfort, eructation, and abdominal pain was highest with the 15-mg dose of tirzepatide (16.29%, 14.86%, 16.42% and 7.57%, respectively).

Incidence of Gallbladder and Pancreatic Adverse Events

Cholelithiasis was reported in 5 studies [16, 21, 23-25]. The pooled proportion was nonsignificant at 0.95% (95% CI, 0.51%-1.52%) with the 5-mg dose and decreased further with the 10- and 15-mg doses. The pooled proportion of cholecystitis was 0.01% (95% CI, 0.00%-0.43%), 0.55% (95% CI, 0.01%-1.89%), and 0.24% (95% CI, 0.02%-0.71%) for the 5-, 10-, and 15-mg dose, respectively. Seven studies [14, 16, 21-25] reported acute pancreatitis with the 5- and 10-mg dose while 8 studies reported acute pancreatitis with the 15 mg dose. The pooled proportion for acute pancreatitis was 0.39% (95% CI, 0.05%-1.07%), 0.36% (95% CI, 0.12%-0.74%), and 0.32% (95% CI, 0.10%-0.67%) for the 5-, 10-, and 15-mg dose, respectively. Five studies [14, 16, 19, 21, 22] with a placebo arm had a similar pooled proportion for acute pancreatitis of 0.33% (95% CI, 0.01%-1.24%). Four studies reported increased lipase levels with a pooled proportion of 3.58% (95% CI, 2.15%-5.36%), 3.88% (95% CI, 1.75%-6.82%), and 6.86% (95% CI, 4.87%-9.17%) for the 5-, 10-, and 15-mg dose, respectively. The pooled proportion of lipase was highest with the 15 mg dose. Additionally, the pooled proportion of elevated lipase was higher with any dose of tirzepatide compared to placebo (pooled proportion of 2.28% [95% CI, 0.62%-4.93%], reported in 3 studies [16, 22, 26] with a placebo arm).

Incidence of Hypoglycemia

The incidence of plasma glucose less than or equal to 70 mg/dL and less than or equal to 54 mg/dL were reported by 6 [14, 16, 21, 22, 24, 25] and 5 studies [16, 21, 23-25] respectively for different doses of tirzepatide. Data from one study [19] were considered only for the 15-mg dose for all hypoglycemic AEs. The proportion of hypoglycemic events did not differ significantly with different dose of tirzepatide. The pooled proportion (95% CI) of glucose levels less than or equal to 70 mg/dL was at maximum with 10 mg (22.6% [9.18%-39.83%]), followed by the 15-mg (20.99% [8.85%-36.68%]) and 5-mg dose (17.39% [4.73%-35.77%]), respectively. The pooled proportion (95% CI) of glucose levels less than 54 mg/dL was nearly the same at all 3 doses (3.64% [0.56%-9.27%] for 5 mg, 3.29% [0.34%-9.12%] for 10 mg, and 3.49% [0.95%-7.56%] for the 15-mg dose of tirzepatide). Three studies reported an incidence of 3.91% (0.01%-14.53%) for blood glucose less than or equal to 54 mg/dL in the placebo group. The pooled incidence of severe hypoglycemia (defined by an event during which the patient requires the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) was reported among 5 studies [14, 16, 19, 21, 22] for placebo, and 7 studies [14, 16, 21-25]

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Table 2. Adverse events summary

	Placebo		Tirzepatide, mg						
			5		10		15		
AEs	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	ANOVA *P*
Severity graded AEs									
Serious AEs	NA	NA	6 (1458)	7.52 (4.85-10.72)	7 (1460)	7.32 (3.90-11.72)	8 (1501)	5.57 (3.15-8.62)	.773
Fatal AEs	NA	NA	5 (1333)	1.07 (0.14-2.88)	5 (1329)	0.72 (0.34-1.25)	6 (1369)	0.90 (0.33-1.75)	.688
AEs leading to treatment discontinuation	NA	NA	6 (1449)	7.23 (5.20-9.56)	6 (1448)	8.68 (7.29-10.18)	7 (1489)	10.39 (7.978-13.09)	.248
GI AEs									
All GI AEs[a]	2 (166)	15.46 (7.81-25.11)	3 (646)	39.05 (35.33-42.83)	3 (641)	45.57 (41.74-49.43)	3 (644)	49.25 (38.44-60.08)	**.004**
Nausea[a]	6 (332)	4.94 (2.89-7.50)	9 (1514)	13.27 (10.79-15.97)	8 (1472)	17.89 (14.91-21.08)	9 (1517)	24.08 (20.21-28.13)	**< .001**
Diarrhea[a]	6 (332)	8.32 (5.62-11.49)	9 (1514)	13.19 (10.89-15.69)	8 (1472)	17.22 (15.28-19.25)	9 (1517)	20.79 (16.20-25.80)	**< .001**
Vomiting[a]	6 (332)	2.73 (1.26-4.73)	9 (1514)	5.67 (4.57-6.89)	8 (1472)	8.32 (6.38-10.50)	9 (1517)	13.98 (9.62-19.01)	**< .001**
Dyspepsia[a]	6 (332)	2.16 (0.90-3.99)	8 (1469)	5.97 (4.65-7.46)	8 (1472)	8.52 (6.62-10.65)	9 (1517)	6.79 (5.31-8.44)	**< .001**
Abdominal distension	3 (71)	3.76 (0.66-9.25)	4 (120)	8.28 (2.01-18.25)	3 (75)	11.95 (5.74-20.02)	3 (81)	16.29 (0.27-49.36)	.471
Constipation	5 (321)	1.54 (0.49-3.16)	6 (1102)	6.07 (4.75-7.56)	6 (1100)	8.86 (4.67-14.22)	7 (1146)	7.57 (4.30-11.67)	.476
Abdominal discomfort	2 (60)	4.36 (0.74-10.80)	2 (66)	2.52 (0.16-7.54)	2 (63)	7.89 (0.01-28.07)	2 (69)	14.86 (2.43-35.18)	.139
Abdominal pain	2 (37)	4.24 (0.26-12.70)	3 (837)	2.62 (1.65-3.81)	3 (841)	4.64 (3.33-6.16)	4 (869)	7.61 (4.34-11.72)	.251
Eructation	NA	NA	2 (125)	5.27 (2.08-9.82)	2 (131)	4.35 (1.46-8.68)	2 (132)	16.42 (0.25-49.86)	.756
Gall bladder and pancreatic AEs									
Cholelithiasis[a]	2 (235)	0.21 (0.03-1.198)	5 (1394)	0.95 (0.51-1.52)	5 (1397)	0.53 (0.22-0.97)	5 (1408)	0.52 (0.21-0.97)	**.008**
Cholecystitis	2 (77)	0.62 (0.10-3.54)	3 (742)	0.09 (0.00-0.43)	3 (739)	0.55 (0.01-1.89)	4 (778)	0.24 (0.02-0.71)	.359
Acute pancreatitis	5 (323)	0.33 (0.01-1.24)	7 (1458)	0.39 (0.05-1.07)	7 (1460)	0.36 (0.12-0.74)	8 (1501)	0.32 (0.10-0.67)	.527
Increased lipase[b]	3 (180)	2.28 (0.62-4.93)	4 (511)	3.58 (2.15-5.36)	4 (510)	3.88 (1.75-6.82)	4 (527)	6.86 (4.87-9.17)	**.019**
Appetite and weight									
Decreased appetite	6 (332)	1.97 (0.77-3.73)	8 (1469)	11.06 (7.01-15.90)	8 (1472)	13.64 (9.37-18.57)	9 (1517)	19.38 (13.01-26.67)	.106
Decreased weight	NA	NA	2 (64)	4.11 (0.67-10.18)	2 (63)	12.09 (5.36-21.06)	2 (65)	8.91 (0.63-25.25)	.195
Hypoglycemic AEs									
Hypoglycemia (plasma glucose ≤ 70 mg/dL	NA	NA	6 (988)	17.39 (4.73-35.77)	6 (991)	22.6 (9.18-39.83)	7 (1031)	20.99 (8.85-36.68)	.937
Hypoglycemia (plasma glucose ≤ 54 mg/dL)	3 (261)	3.91 (0.01-14.53)	5 (1394)	3.64 (0.56-9.27)	5 (1397)	3.29 (0.34-9.12)	6 (1436)	3.49 (0.95-7.56)	.998
Severe hypoglycemia	5 (323)	0.33 (0.01-1.24)	7 (1458)	0.25 (0.06-0.58)	7 (1460)	0.17 (0.02-0.50)	8 (1501)	0.54 (0.23-1.05)	.197
Respiratory AEs									

(*continued*)

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Table 2. Continued

AEs	Placebo		Tirzepatide, mg						
			5		10		15		
	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	Studies (sample size)	Proportion (95% CI)	ANOVA *P*
Upper respiratory tract infection	NA	NA	2 (66)	7.14 (2.28-14.41)	2 (63)	5.85 (1.50-12.80)	2 (69)	3.82 (0.65-9.49)	.496
Nasopharyngitis	NA	NA	5 (979)	6.05 (2.85-10.34)	5 (979)	5.07 (3.79-6.53)	5 (991)	6.42 (4.07-9.27)	.762
Influenza	NA	NA	2 (176)	5.57 (2.69-9.41)	2 (172)	4.9 (0.98-11.58)	2 (174)	0.89 (0.04-4.34)	.287
Allergic reaction									
Injection site reaction	5 (323)	1.15 (0.24-2.73)	7 (1458)	1.89 (0.75-3.54)	7 (1460)	2.44 (1.34-3.85)	8 (1501)	3.11 (1.47-5.34)	.229
Hypersensitivity	4 (312)	3.88 (1.14-8.17)	5 (1120)	3.23 (1.92-4.86)	5 (1120)	3.03 (2.11-4.12)	6 (1151)	2.42 (1.48-3.58)	.751
Multisystem AEs									
Headache	NA	NA	5 (241)	4.00 (1.92-6.80)	4 (196)	5.16 (1.10-11.96)	5 (230)	10.71 (4.84-18.54)	.429
Hypertension	NA	NA	3 (529)	2.61 (1.22-4.51)	3 (530)	2.04 (1.01-3.41)	3 (532)	2.61 (1.43-4.14)	.755
Diabetic retinopathy	NA	NA	3 (1157)	0.59 (0.02-1.91)	3 (1157)	0.57 (0.04-1.71)	3 (1167)	0.43 (0.02-1.40)	.935
MACE	NA	NA	2 (474)	0.73 (0.17-1.70)	2 (479)	1.02 (0.32-2.12)	2 (479)	0.56 (0.09-1.43)	.935
Malignant neoplasms	NA	NA	2 (474)	1.21 (0.43-2.39)	2 (479)	1.44 (0.57-2.70)	2 (479)	0.72 (0.16-1.69)	.485

Abbreviations: AE, adverse event; ANOVA, analysis of variance; GI, gastrointestinal; MACE, major adverse cardiovascular events; NA, not available.
[a]On comparing with placebo, the proportion of AEs for all 3 doses (5, 10, and 15 mg) of tirzepatide had a *P* value less than or equal to .05 (Depicted in bold in Table 2).
[b]On comparing with placebo, the proportion of AEs had a *P* value less than or equal to .05 only for the 15 mg dose of tirzepatide.

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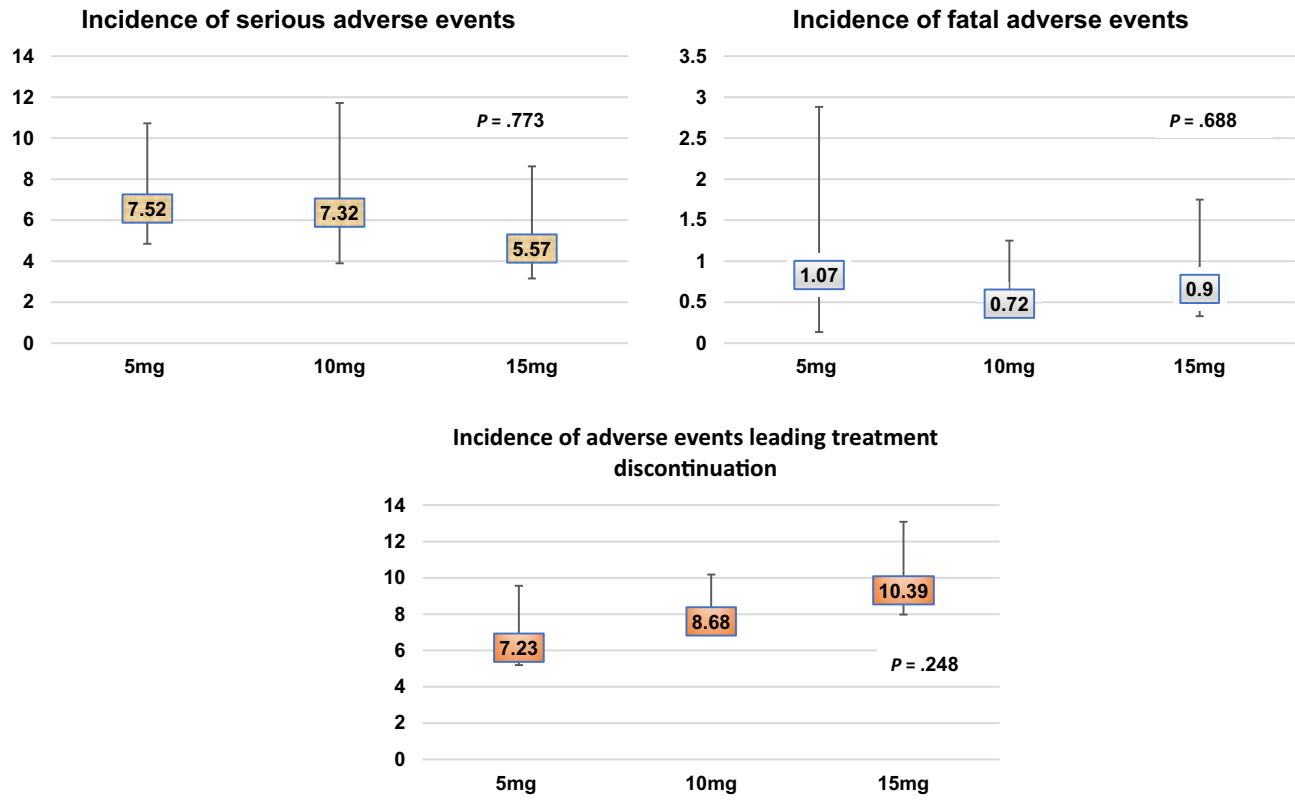

Figure 2. Incidence (%) of serious adverse events, fatal adverse events, and adverse events leading to treatment discontinuation with tirzepatide 5, 10, and 15 mg, respectively.

for different doses of tirzepatide. The incidence rate (95% CI) of severe hypoglycemia was 0.33% (0.01-1.24) for placebo 0.25% (0.06-0.58) for 5 mg, 0.17% (0.02-0.50) for 10 mg, and 0.54% (0.23-1.05) for the 15-mg dose of tirzepatide.

Incidence of Other Adverse Events

Injection site reaction was reported by 5 studies for placebo [14, 16, 19, 21, 22], 7 studies [14, 16, 21-25] at 5 and 10 mg, and 8 studies (including [19]) for the 15-mg dose of tirzepatide. Pooled proportion (95% CI) of injection site reaction was 1.15% (0.24%-2.73%) with placebo, 1.89% (0.75%-3.54%) with 5 mg, 2.44% (1.34%-3.85%) with 10 mg, and 3.11% (1.47%-5.34%) with the 15-mg dose of tirzepatide. Hypersensitivity reaction was assessed by 4 studies [16, 19, 21, 22] for a placebo group (3.88% [1.14%-8.17%]), 5 studies [16, 21-23, 25] for 5 mg (3.23% [1.92%-4.86%]), and 10 mg (3.03% [2.11%-4.12%]) doses, and 6 studies [16, 19, 21-23, 25] for 15 mg (2.42% (1.48%-3.58%]). Among respiratory AEs, nasopharyngitis was assessed in 5 studies [16, 21, 22, 24, 25], while upper respiratory tract infection [23, 26] and influenza [21, 23] were assessed in 2 studies each. Incidence (95% CI) of nasopharyngitis was similar with different doses (6.05% [2.85%-10.34%] with 5 mg, 6.42% [4.07%-9.27%] with 15 mg, and 5.07% [3.79%-6.53%] with 10 mg) of tirzepatide. Incidence (95% CI) of headache was observed to increase with increasing dose of tirzepatide (4% [1.92%-6.80%], 5.16% [1.10%-11.96%], and 10.71% [4.84%-18.54%]) for the 5-, 10-, and 15-mg dose. Rarely, hypertension, diabetic retinopathy, major adverse cardiovascular events (MACE), and malignant neoplasms were observed in 3 or fewer studies, without any significant association with different doses of tirzepatide (see Table 2).

Discussion

In our meta-analysis, we have summarized the most precise and up-to-date data on the AEs of tirzepatide using previously published articles. The mean age of the studied population was 59 years with an average duration of diabetes of 10 years and a mean HbA_{1c} of 8.3%. Our systematic review provides details on the incidence rate of each specific AEs at 3 doses of tirzepatide (5, 10, and 15 mg). Besides commonly encountered AEs associated with tirzepatide, our study also evaluated rare AEs associated with tirzepatide including gall bladder and pancreatic AEs. In our study, we found GI AEs to be the most commonly encountered AEs with incidence rates of up to 50% with the 15-mg dose of tirzepatide. For the majority of GI AEs, we found a significant dose-dependent relationship with higher dose being associated with higher incidence rates of AEs. A recent study by Yu et al [27] reported increased total AEs and GI AEs (relative risk [RR] 1.17; $P = .02$) with 10 mg, and increased total AEs (RR 1.10; $P = .0001$) with 15-mg compared to the 5-mg dose of tirzepatide. No statistically significant differences were observed in total AEs and GI AEs for 15-mg compared to 10-mg tirzepatide. In addition, we observed that higher doses of tirzepatide were more likely to be associated with drug discontinuation due to AEs. In particular, the rate of drug discontinuation due to AEs was up to 10% (8%-13%) with the 15-mg dose of tirzepatide. The study by Yu and our colleagues [27] and our study have similar findings for no significant difference in AEs including

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MACE, hypertension, cancer, and hypoglycemic events with 3 different doses of tirzapatide. In a study by Karagiannis et al [28], the authors found 2-fold higher odds of study drug discontinuation at the highest dose of tirzepatide. Interestingly, our study found that the proportion of serious AEs declined with increasing doses of tirzepatide (7.52%, 7.32%, and 5.37% for the 5-, 10-, and 15-mg doses, respectively) while the incidence rates of cholelithiasis, cholecystitis, and acute pancreatitis were near similar across all 3 doses of tirzepatide (5, 10, and 15 mg). Dutta et al [29], however, reported no significant difference in treatment-emergent AEs and severe AEs in their study comparing tirzepatide with an active control group. Our study also found a higher incidence of hypoglycemia (glucose < 70 mg/dL) with tirzepatide 10 mg, which highlights the need for more careful monitoring during dose titration to avoid hypoglycemia.

Compared to prior meta-analyses assessing the safety and efficacy of tirzepatide [28-31], our study has major differences in the objective and the methodology, making our study unique and noncomparable to previous works. Our meta-regression focused solely on the safety of tirzepatide, with a special focus on establishing the rates of each individual AE at 3 doses of tirzepatide (5, 10, and 15 mg). In the previous meta-analyses, the primary outcome was efficacy (eg, HbA_{1c} reduction, weight reduction), and the safety outcomes were secondary end points of the study. In comparison, our study solely focused on a detailed analysis of safety outcomes. In addition, our study has compiled all the major AEs associated with this agent compared to the previously published meta-analyses. For example, besides commonly encountered AEs associated with tirzepatide, our study also evaluated rare AEs associated with tirzepatide, including gall bladder and pancreatic AEs. The methodology used in our study also differed significantly compared to previously published meta-analyses. For example, compared to the prior work by Karagiannis et al [28], in our study, instead of calculating the odds ratio, we calculated the incidence rates of each individual AE associated with tirzepatide. With the increasing use of tirzepatide beyond the scope of diabetes, knowing the incidence rate of individual AEs would be especially important from a practical standpoint for a broader group of health care providers (such as endocrinologists, primary care physicians, bariatricians, and clinicians treating obesity), who may find this meta-analysis extremely relevant to identify and be vigilant about rare AEs along with commonly reported AEs.

In our meta-analysis, we found the mean age to be 58.9 years, suggesting fewer younger patients in the previous trials. Hence, future studies involving younger patients with diabetes may be necessary to more precisely assess the AEs related to tirzepatide in different age groups. Considering the significant glycemic improvement and weight reduction associated with tirzepatide in previous randomized clinical trials, the use of tirzepatide among patients with or without diabetes is expected to increase in the coming future. Hence, the findings from our study will help clinicians recognize tirzepatide-related AEs at different doses and determine the best treatment strategies for their patients.

Despite its comprehensive methodology, there are several limitations in our study that merit attention. First, in our meta-analysis, individual patient-level variables were unavailable, and analyses were conducted at the study level, which can lead to bias in assessment. Second, the use of meta-analysis to pool published data can be associated with a lack of standardization among the included studies in terms of patient population and outcomes measured, including the severity and definition of each reported AE. Third, most of the included studies reported tirzepatide-related AEs as secondary end points in the original studies. Nonetheless, with careful interpretation of data, the pooled analysis provides valuable information regarding the risk of AEs. Fourth, our meta-analysis included studies published since inception through March 2022 (2018-2022), which is still a short duration to predict long-term AEs, specifically cardiovascular events.

Conclusion

Our meta-regression provides more precise data on the incidence rate of individual AEs related with tirzepatide use at 3 different doses (5, 10, and 15 mg). We found GI AEs to be the most common AEs associated with tirzepatide use and included nausea, vomiting, dyspepsia, decreased appetite, diarrhea, and constipation. We found tirzepatide to have similar AEs profile as GLP-1 RA. Tirzepatide has been considered a great addition to the arsenal of next-generation medications for T2DM, as evidenced by dose-dependent reduction in HbA_{1c} in prior studies. Our study showed that tirzepatide is safe and has a tolerable AE profile and is expected to play a huge role in the management of T2DM, insulin resistance, and weight loss soon.

Disclosures

The authors declare no conflicts of interest.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in "References."

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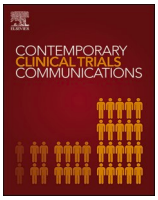

Lessons learned from the pilot family model of diabetes self-management intervention in the Republic of the Marshall Islands

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ABSTRACT

Background: The Republic of the Marshall Islands (RMI) has a high rate of type 2 diabetes mellitus (T2DM). To address the high rate of T2DM, we tested a culturally adapted family model of diabetes self-management education and support (F-DSMES). We report the results of the 12-month post-intervention data collection and describe the lessons learned from the delivery of the F-DSMES intervention.

Methods: Recruitment took place in four churches in Majuro and included 10 h of content delivered over 8–10 weeks. Forty-one participants with T2DM were included. The primary study outcome was glycemic control measured by a change in HbA1c. We also conducted participant interviews to document the participant-reported barriers encountered during the F-DSMES intervention.

Results: Participants did not show improvements in their biometric markers; however, participants did show improvement on multiple measures of diabetes knowledge and family support. We identified five areas to improve future interventions: 1) issues with recruitment, retention, and attendance; 2) needing help accessing information and additional healthcare provider counseling; 3) struggles with adhering to diet recommendations; 4) difficulty getting exercise, and 5) improving lessons within the intervention.

Conclusion: Although the biomarker data did not show improvement, valuable information was gained to improve the development of larger-scale trials. The results provide evidence of the need for these trials and the desire of participants to continue pursuing this effort. Others doing similar work in other low-to-middle income countries will need to take into consideration the potential barriers and facilitators within participants' social and physical environments.

1. Introduction

The Republic of the Marshall Islands (RMI) is an independent United States (US) Affiliated Pacific Islands nation [1]. Marshallese living in the Marshall Islands face numerous health disparities, including high prevalence rates of type 2 diabetes mellitus (T2DM) [2–7]. Nearly a third of Marshallese living in the RMI have been diagnosed with T2DM [8], compared with lower rates in the US (11.3%) and globally (9.3%). These health disparities were likely perpetuated by historical trauma, including the nuclear weapons testing in the RMI by the US military throughout the 1940s and 1950s, which drastically altered the Marshallese lifestyle [9].

Socioecological barriers present in the RMI pose unique issues for the management of diabetes and other comorbidities. High rates of unemployment and a low minimum wage make it difficult to access fresh and nutritious foods [1]. Marshallese living in the RMI rely heavily on foods

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imported from the US, including rice and processed foods [12]. Gym memberships are cost-prohibitive for many in the RMI, and sidewalks are not widely available. Additionally, the infrastructure in the RMI limits the availability of health care and other resources, leaving many without a regular source of health care and posing difficulties obtaining diabetes testing supplies and medication [13].

Diabetes self-management education and support (DSMES) is critical for persons to effectively manage diabetes and reduce the risk of complications [14–18]. Yet, research regarding the use of DSMES in Marshallese and other Pacific Islander populations, especially among those living in the RMI, is limited [12,19,20]. Given the high rates of T2DM in the RMI, creating an effective DSMES intervention that can be widely implemented and disseminated is crucial.

In partnership with the local Marshallese community, the authors developed and tested a culturally tailored family model of DSMES (F-DSMES) in Arkansas [21–23]. Engagement in diabetes self-care is determined in large part by one's social environment; given the collectivist nature common in Marshallese culture, interventions with a focus on family support are part of culturally appropriate care. The F-DSMES intervention addressed diabetes management behaviors by focusing on behavioral changes in the context of family using motivational family interviewing, family goal-setting, and family education on supportive and non-supportive behaviors [14–19].

In Arkansas, a trained bilingual community health worker (CHW) provided F-DSMES in the homes of people with diabetes [24,25]. A certified diabetes educator (CDE) attended all sessions. Compared to standard DSMES delivered by CDEs in a group setting, the F-DSMES demonstrated effectiveness when delivered in the home by CHWs [24,25]. However, the F-DSMES implementation methods are not easily transferred to the RMI [24,25]. The RMI has limited resources to deliver standard DSMES, and most homes in the RMI are too small to utilize for administering family education. Therefore, several important adaptations from the prior F-DSMES trial conducted in Arkansas needed to be introduced as part of the implementation of F-DSMES in the RMI. The F-DSMES intervention was delivered solely by trained CHWs, and the curriculum was delivered in faith-based organizations (FBOs) rather than in the home.

Our aim is to report the results of our pilot's 12 months post-intervention data, as well as to evaluate and document the participant-reported barriers encountered during the F-DSMES intervention. This pilot evaluation will be used to further improve future DSMES interventions in the RMI and to help to inform others who are doing similar work in other low-to-middle income countries.

2. Methods

2.1. Study aims and approach

The study's goal was to determine the acceptability, feasibility, and preliminary effectiveness of a culturally adapted and linguistically appropriate F-DSMES intervention.

2.2. Participant recruitment, enrollment, and consent

All materials and the study protocol were adapted from the materials developed as part of the Arkansas F-DSMES randomized controlled trial (RCT) (University of Arkansas for Medical Sciences [UAMS] Institutional Review Board [IRB] #203482) (Clinical Trial #NCT02407132) [24]. The pilot study was reviewed and approved by the UAMS IRB (#239272) and by the RMI Ministry of Health & Human Services [27].

Four churches on Majuro in the RMI agreed to participate in recruitment of study participants. Participants were required to meet inclusion criteria, including: (1) Marshallese, (2) ≥18 years, (3) a diagnosis of T2DM by a physician or a HbA1c indicative of diabetes (≥6.5%), (4) a family member in the same household willing to participate with the participant, and (5) willing to participate in all of the F-DSME sessions and in data collection. Participants were ineligible to participate in the study if they had participated in a DSMES program in the previous 5 years, if they planned to leave the area while the study was ongoing, or if they had any medical condition that the Data Safety and Monitoring team deemed would prevent successful completion of the program.

As recommended by the American Association of Diabetes Educators and the American Diabetes Association, the intervention included 10 h of education delivered over 8–10 weeks. Eight core elements are covered in the content: healthy diet, healthy levels of physical activity, monitoring blood glucose, understanding treatment of blood glucose and medications needs, problem-solving, risk management and coping skills, diabetes complications, and goal-setting [24]. One-hundred and twenty-five individuals were enrolled in the intervention. Of a total sample of 97, 41 participants had T2DM, and 56 family members agreed to participate. Further details on the study, including study design, recruitment, consent, inclusion and exclusion criteria, and intervention dosage, are available in prior publications [13,27,28].

2.3. Data collection

Research staff collected biometric data, including HbA1c, blood pressure, weight, and height measurements. HbA1c was collected via finger stick blood collection and point-of-care analyzer (Siemens DCA Vantage Analyzer) [27]. While the participant was seated, a research assistant used an OMRON digital blood pressure monitor to measure systolic and diastolic blood pressure. Pulse pressure was determined by subtracting the diastolic blood pressure reading from the systolic blood pressure reading. Participant height and weight were collected without shoes using a portable stadiometer and a digital scale. Body mass index (BMI) was calculated using weight in pounds and height in inches. Participants also completed a survey utilizing questions adapted from the Behavioral Risk Factor Surveillance System (BRFSS) survey's Diabetes and Healthcare Access Core Modules, as well as from the Diabetes Care Profile [24,29]. Participants could refuse to participate in any part of the data collection and still participate in the F-DSMES educational intervention. Participants were given their results from the health screening, as well as private health counseling and a referral to a healthcare provider if warranted.

To capture lessons learned to inform a larger RCT of the F-DSMES intervention in the RMI, the research staff conducted interviews with eight participants. Bilingual (Marshallese and English) study staff trained in qualitative methods facilitated the focus groups, and participants were encouraged to speak in their preferred language. The interviews allowed participants to describe their experiences; topics explored included facilitators and barriers to participation, parts of the intervention the participants found useful, and where they saw need for improvement.

2.4. Analytical methods

Quantitative analysis. The mean and standard deviation for continuous variables and proportions for categorical variables are provided for participant sociodemographic data, biometric data, and self-reported health status compared to 12 months ago. In addition, we provide descriptive statistics of participants' diabetes management and diabetes knowledge, barriers to obtaining care, and family support. Wilcoxon Ranked Sign tests were used for mean comparisons, and McNemar's tests and Bowkers [30] tests of symmetry were used for the comparisons of counts or proportions. Although the small sample size of the study limits the strength of the conclusions from the hypothesis tests, it allows for assessment of trends that could be anticipated to result in a meaningful change in clinically relevant outcomes. In addition, we include an assessment of individual participant changes in the outcomes of interest. This assessment allows us to examine whether aggregate changes were consistent across participants or whether they were magnified by one or

more outliers. All analyses were conducted using SAS 9.4 [31].

Qualitative analysis. All interviews were audio recorded, transcribed, and translated verbatim into English by bilingual study staff. The content analysis, conducted by the lead and second author, was completed by reviewing and manually coding the interview transcripts to interpret meaning and assign labels to data segments with initial codes [32–34]. Initial coding was conducted by the first author, labeling data segments with concise summary codes in order to organize the data for more focused coding and to develop a preliminary codebook of emergent themes. Confirmation coding on the transcripts was completed by the second author, and the research team reviewed the coded interview transcripts together to categorize the data and develop themes [34,35]. The research team discussed any discrepancies; all discrepancies were resolved by consensus. The most illustrative quotes for each theme were identified and are presented.

3. Results

3.1. Quantitative results

Table 1 reports the sociodemographic characteristics of the participants at baseline and at 12-month follow-up. Twenty-eight of the original 41 baseline participants returned for the 12-month follow-up visit. The mean age of the participants at the 12-month follow-up was 52.6 years (SD = 13.1). Among the participants in the 12-month follow-up sample, 82.1% were females, and 71.4% were married or a member of an unmarried couple. The majority of participants (60.7%) had less than a high school education, and approximately half (53.6%) reported speaking English well or very well. The participants completed a mean of 5.4 (±3.6) h of education classes; 17% (7) completed 8–10 h, 34% (14) completed 5–7 h, and 49% (20) completed four or less hours of the intervention, as reported in a previous publication [13].

Table 2 presents the health profiles of the participants with both baseline and 12-month post-intervention data. Changes in health measures were not statistically significant. Participants had a mean increase in HbA1c of 0.6% (p = .089) and a mean decrease in BMI of 0.7 kg/m2 (p = .431). Random blood glucose showed a mean increase of 23.4 mg/dL (p = .107). There was a mean increase in total cholesterol of 6.5 mg/dL (p = .617), a mean increase in triglycerides of 14.4 mg/dL (p = .558), a mean decrease in low-density lipoprotein (LDL) of 0.9 mg/dL (p = .528), and a mean increase in high-density lipoprotein (HDL) of 1.2 mg/dL (p = .192). Participants had a mean decrease in diastolic and systolic blood pressure of 4.1 mmHg (p = .142) and 4.2 mmHg (p = .676), respectively. There was no mean change in pulse pressure, self-reported health status, or health status compare to 12 months prior.

Disaggregated results for participant changes in HbA1c, random glucose testing, blood pressure, HDL cholesterol, and LDL cholesterol from baseline to 12-month post-intervention are provided in the supplemental tables. For HbA1c, 11 of the participants showed improvements from baseline to 12-month post-intervention, while one showed no change and 15 had higher HbA1c results. Improvements ranged from 0.1% to 2.0%, and seven of the 11 participants had improvements of 0.5% or higher. Increases in HbA1c ranged from 0.3% to 5.3%, with 13 of the 15 participants experiencing increases in HbA1c of 0.5% or higher. Eight of the participants showed improved random glucose numbers, ranging from a decrease of 1 mg/dL to 219 mg/dL. Twenty participants had an increase in random glucose numbers, ranging from 4 mg/dL to 170 mg/dL. Fourteen of the participants had an improved systolic blood pressure, with a decrease ranging between 2 mmHg and 47 mmHg. Fifteen participants had an improved diastolic blood pressure, with a decrease between 2 mmHg and 33 mmHg. Fifteen participants had an improvement in HDL, ranging between 1 mg/dL and 18 mg/dL. Three participants had no change in HDL. Fourteen participants had an improvement in LDL, with a decrease between 3 mg/dL and 52 mg/dL.

Participants showed statistically significant improvement in their diabetes knowledge at 12-month follow-up (Table 3). Participants reported gained knowledge on how to manage their diabetes (p = .005) and cope with stress (p = .017), as well as a better understanding of the

Table 1
Sociodemographic characteristics of primary participants – Baseline and 12-month follow-up.

	Baseline (N = 41)	12 Months (N = 28)
	Mean ± SD or n (%)	*Mean ± SD or n(%)*
Age (in years)	51.3± 12.4	52.6 ± 13.1
Sex (Female)	31(73.8)	23(82.1)
Marital Status		
Married/Member of unmarried couple	32(76.2)	20(71.4)
Single/Divorced/Widowed	10(23.8)	8(28.6)
Education		
Less than HS diploma	30(66.7)	17(60.7)
HS diploma/Some college	13(31.0)	10(35.7)
College degree or more	1(2.4)	1(3.6)
Speak English		
Very well/Well	19(45.2)	15(53.6)
Not well/Not at all	23(54.8)	13(46.4)

Table 2
Health profiles of study participants – Baseline and 12-month follow-up comparison.

	Baseline (n = 28)		12 Months (n = 28)		p^a
	Mean ± SD or n (%)	*Median*	*Mean ± SD or n (%)*	*Median*	
Blood Glucose					
HbA1c	10.2 ± 2.3	10.7	10.8 ± 2.5	11.2	0.089
Random glucose	203.6 ± 85.6	198.5	227.0 ± 78.2	218.0	0.107
Weight					
Weight (in lbs.)	162.9 ± 35.4	162.6	158.8 ± 33.9	155.2	0.212
BMI	31.3 ± 6.0	6.0	30.6 ± 5.9	30.5	0.431
BMI < 30	12(42.9)	–	12(42.9)	–	1.000
BMI ≥ 30	16(57.1)	–	16(57.1)	–	
Blood Pressure					
Diastolic	77.1 ± 11.4	77.0	73.0 ± 10.6	75.0	0.142
Systolic	124.3 ± 18.2	121.0	120.1 ± 14.8	121.0	0.676
Pulse pressure	47.1 ± 15.6	45.0	47.1 ± 12.2)	46.0	0.934
Cholesterol Levels					
HDL	32.8 ± 9.5	9.5	34.0 ± 6.6	35.0	0.192
LDL	111.7 ± 22.9	113.5	110.8 ± 28.3	111.5	0.528
Triglycerides	135.0 ± 52.0	131.0	149.4 ± 88.7	128.0	0.558
Total cholesterol	166.4 ± 27.8	164.0	172.9 ± 28.8	171.0	0.617
Self-Rated Health					
Current Health Status		1.000			
Excellent/Good	10(35.7)	–	10(35.7)	–	
Fair/Poor	18(64.3)	–	18(64.3)	–	
Current Health Status Compared to 12 Months Ago		0.481			
Better	8(28.6)	–	12(42.9)	–	
About the same	14(50.0)	–	12(42.9)	–	
Worse	6(21.4)	–	4(14.3)	–	

Note: Sample sizes vary due to missing data; BMI and weight missing values are due to participant limitations.

[a] Wilcoxon Ranked Sign test for mean comparisons, McNemar's & Bowkers [30] test of symmetry for counts/proportions.

Table 3
Diabetes knowledge – Baseline and 12-month follow-up comparison among participants with prior diabetes diagnosis ($n = 22$).

	Baseline	12 Months	p[a]
	n(%)	*n(%)*	
How well do you understand … ?			
How to manage your diabetes?			**0.005**[b]
Not at all	1(4.6)	1(4.6)	
A little	21 (95.5)	9(40.9)	
A lot	0(0.0)	12(54.6)	
How to cope with stress?			**0.017**
Not at all	5(22.7)	2(9.1)	
A little	15 (68.2)	8(36.4)	
A lot	2(9.1)	12(54.6)	
How to eat for blood sugar control?			0.059
Not at all	4(18.2)	2(9.1)	
A little	17 (77.3)	10(45.5)	
A lot	1(4.6)	10(45.5)	
The role of exercise in diabetes care?			**0.007**
Not at all	2(9.1)	1(4.6)	
A little	18 (81.8)	7(31.8)	
A lot	2(9.1)	14(63.6)	
How to take your medications correctly?			**0.038**
Not at all	4(18.2)	1(4.6)	
A little	11 (50.0)	5(22.7)	
A lot	7(31.8)	16(72.7)	
How to use the results of blood sugar monitoring?			0.372
Not at all	5(22.7)	2(9.1)	
A little	8(36.4)	7(31.8)	
A lot	9(40.9)	13(59.1)	
How diet, exercise, and medications affect blood sugar levels?			**0.006**
Not at all	3(13.6)	2(9.1)	
A little	18 (81.8)	7(31.8)	
A lot	1(4.6)	13(59.1)	
How to prevent and treat high blood sugar?			**0.010**[b]
Not at all	5(22.7)	2(9.1)	
A little	17 (77.3)	9(40.9)	
A lot	0(0.0)	11(50.0)	
How to prevent and treat low blood sugar?			**0.019**
Not at all	6(27.3)	2(9.1)	
A little	14 (63.6)	8(36.4)	
A lot	2(9.1)	12(54.2)	
How to prevent long-term complications of diabetes?			**0.006**
Not at all	5(22.7)	2(9.1)	
A little	16 (72.7)	7(31.8)	
A lot	1(4.6)	13(59.1)	
How to take care of your feet?			**0.016**
Not at all	4(18.2)	1(4.6)	
A little	14 (63.6)	5(22.7)	
A lot	4(18.2)	16(72.7)	
The benefits of improving blood sugar control?			**0.007**
Not at all	3(13.6)	1(4.6)	
A little	17 (77.3)	8(36.4)	
A lot	2(9.1)	13(59.1)	

[a] Bowker's test of symmetry [30].
[b] Weighted count, accounting for zero(s).

role of exercise in diabetes care (p = .007), how diet, exercise, and medications affect blood sugar levels (p = .006), and how to take their medications correctly (p = .038). Participants also reported increased knowledge of how to treat high (p = .010) and low (p = .019) blood sugar, how to prevent long-term complications of diabetes (p = .006), how to take care of their feet (p = .016), and the benefits of improving blood sugar control (p = .007). Reported changes in knowledge related to how to eat for blood sugar control (p = .059) or how to use the results of blood sugar monitoring (p = .372) were not significant. Participants reported statistically significant improved family support for taking their diabetes medicine (p = .029), for taking care of their feet (p = .015), and in handling their feelings about their diabetes (p = .038); however, no statistically different change in reported family support was found for following a meal plan (p = .518), getting enough physical activity (p = .308), or testing blood sugar (p = .287; see Table 4).

3.2. Qualitative results

Participants discussed their experiences with the intervention in qualitative interviews. The research team identified five themes from participants' experiences related to the acceptability and feasibility study: 1) issues with recruitment, retention, and attendance; 2) needing help accessing information and additional healthcare provider counseling; 3) struggles with adhering to diet recommendations; 4) difficulty getting exercise, and 5) improving lessons within the intervention.

Issues with recruitment, retention, and attendance. Participants noted there were many people who were interested in classes but did not attend church services, or attended services at churches who were not part of the recruitment and were unsure if they could participate. Participants said recruitment should be more widespread, additional churches should be included in the recruitment process, and placing flyers at other local establishments (e.g., stores) would increase the number of people who would participate. Participants stated class schedules were difficult to remember, making it difficult to attend. Participants did stop attending classes and data collection events over time. A participant explained: "I did ask other people who stopped attending the classes, and they said they stopped because their family

Table 4
Family support for diabetes management – Baseline and 12-month follow-up comparison among participants with prior diabetes diagnosis ($n = 22$).

	Baseline	12 Months	p[a]
	n(%)	*n(%)*	
My family helps me to … ?			
Follow my meal plan			0.518
Not at all	1(4.6)	1(4.6)	
A little	10(45.5)	5(22.7)	
A lot	11(50.0)	16(72.7)	
Take my medicine			**0.029**
Not at all	2(9.1)	2(9.1)	
A little	11(50.0	2(9.1)	
A lot	9(40.9)	18(81.8)	
Take care of my feet			**0.015**
Not at all	6(27.3)	1(4.6)	
A little	10(45.5)	4(18.2)	
A lot	6(27.3)	17(77.3)	
Get enough physical activity			0.308
Not at all	1(4.8)	1(4.8)	
A little	10(47.6)	4(19.1)	
A lot	10(47.6)	16(76.2)	
Test my blood sugar			0.287
Not at all	2(9.1)	1(4.6)	
A little	10(45.5)	5(22.7)	
A lot	10(45.5)	16(72.7)	
Handle my feelings about diabetes			**0.038**
Not at all	1(4.6)	1(4.6)	
A little	13(59.1)	4(18.2)	
A lot	8(36.6)	17(77.3)	

[a] Bowker's test of symmetry [30].

members stopped attending. I told them even if other family members stopped attending, they should keep attending."

Needing help accessing information and additional healthcare provider counseling. Participants requested that additional information on their health conditions be in the lessons. Participants also requested additional help with accessing physicians to discuss medications such as insulin, as well as diabetes comorbidities such as hypercholesterolemia: "We wanted to have diabetes doctors at screenings to provide more direct care at the churches. Many of us didn't know we had high cholesterol, or high blood pressure, or blood sugar, until you had the screenings. So provide more personal direct counseling to screenings."

Struggles with adhering to diet recommendations. Participants reported struggling with diet changes and adhering to dietary recommendations. Vegetables are costly and hard to access in the RMI, and rice is a staple in the Marshallese diet. Participants felt rice helped with satiation, making it difficult to limit portion sizes and feel as though they had enough to eat. For example, one participant noted, "We just couldn't eat vegetables." She went on to say, "We couldn't seem to get full or satisfied on a small amount of rice! There needs to be plenty of rice." Additionally, the use of a portion plate was difficult because of both the lack of food options and traditional meals being different from what the program taught. One participant stated, "The portion plate was sort of difficult because we were so used to having like 3 scoops of rice, but now we have to reduce that!"

Difficulty getting exercise. Participants noted getting exercise was difficult for various reasons, including a lack of good walking shoes, limited access to walking areas, and the cost of gym memberships. One participant described their experiences with attempting to get more exercise:

Sometimes I walk over to the Mormon Church and walk around the area and exercise. I tried to exercise often but I don't have good walking shoes. I had walking shoes that my son send from the Hawaii. The shoes were really nice and light. My neighbor's sister borrowed my shoes, but when she moved, she never brought them back. I also exercise outside my house, but now there's construction as you can see.

Improving lessons within the intervention. Participants stated they enjoyed the lessons and found them informative and not too long; however, participants also mentioned needing more explanations or demonstrations incorporated into lesson plans. For example, participants said, "Only more demonstrations because we really enjoyed the classes that had the demonstrations like the foot model and such," and "Topic or lessons were good, just provide more details or spend more time explaining lessons."

4. Discussion

Participants did not show statistically significant improvements in their biometric markers. Research has shown that improvements in diabetes knowledge and family support have the ability to improve health outcomes, including HbA1c [36,37]. However, despite the improvement in most knowledge domains and some family support domains, we did not see an improvement in HbA1c. The socioecological barriers in the RMI may make it more difficult to apply the knowledge and support gained through the F-DSMES intervention. The socioecological barriers in the RMI are numerous. Unemployment hovers around 40%, and the national minimum wage is low, making fresh, healthy foods difficult to obtain due to cost [1]. As participants noted in their interviews, Marshallese living in the RMI rely heavily on cheaper, and what they perceive as more filling, options such as rice and processed foods. Many Marshallese living in the RMI find fresh, unprocessed foods cost-prohibitive [12]. Further, participants stated they have a lack of access to good footwear and that roads lack sidewalks, making exercise difficult. Further, prior work has shown many Marshallese living in the RMI do not have a regular source of care to go to for information on their health and often report difficulties affording diabetes testing supplies and medication [13]. The immense number of socioecological barriers makes managing diabetes and other comorbidities difficult and may have contributed to the lack of improvement seen in the results both for the biometric measures and in the few areas where knowledge and family support did not increase (meal planning, exercise, and using blood sugar results).

There are a few limitations to keep in mind when interpreting these results. Participants have very limited access to healthcare services; therefore, we are unable to obtain a complete list of pre-existing medical conditions which may affect biometric readings (e.g., anemia and HbA1c). The F-DSMES intervention struggled with retention and attendance. Nearly a third of the participants were lost to follow-up. The high attrition may limit the generalizability to the RMI as a whole, as well as to other locations. Further, as only eight participants were interviewed, we may not have a full picture of the barriers to participation experienced. Despite these limitations, the participants did provide us with valuable insight to adapt the F-DSMES intervention used in the RMI, which will likely improve the results.

4.1. Future directions

In future trials of the F-DSMES intervention in the RMI, we plan to work to address the barriers to recruitment, attendance, and retention as well as the socioecological barriers, which make controlling diabetes more difficult. These efforts will be directed by the suggestions made by the participants during their interviews and our community advisory board. We plan to expand recruitment efforts to additional locations. We will design a reminder card to remind participants of the upcoming classes, with a place to make notes if a schedule does change.

Although bringing physicians and other care providers to in-person screenings and lessons may be difficult, we will work with the RMI Ministry of Health & Human Services to have additional healthcare providers on site whenever possible, and we are exploring the potential for Marshallese care providers to host 'ask me anything' sessions using Zoom/telemedicine. Marshallese providers could be based in the RMI and/or in US to answer more general questions related to diabetes and other comorbidities. Additionally, we will work with RMI-based CHWs to provide care navigation to providers in the RMI.

Further, we will work to assist participants in meeting their diet and exercise recommendations. This will include additional work on creating healthy meals that meet nutrition goals using only available and traditional foods, providing healthy food boxes, and/or providing opportunities for participants and communities to create raised gardens to supplement the available fruit and vegetable supply. We will work toward supplying appropriate walking shoes and will collaborate with the appropriate community-based organizations to create resources for both group-based and individual exercise.

Finally, in order to adapt the F-DSMES to meet the needs of Marshallese living in the RMI, we will make the F-DSMES program more interactive and spend more time incorporating anatomical models and demonstrations into the curriculum.

5. Conclusion

This study is one of the first to provide culturally appropriate care for people with diabetes living in the RMI by implementing a family-based diabetes self-management and education program within faith-based organizations (churches). In addition, it is the first to outline participant feedback on the intervention. Although the biomarker data did not show improvement, we have gained valuable information to incorporate in the development of larger scale trials and have provided evidence of both the need for these trials and the desire of participants to continue pursuing this effort. We urge others who are doing similar work in other low-to-middle income countries to take into consideration the potential barriers and facilitators within participants' social and physical environments and to work towards ensuring that participants have access to the resources and information they need to successfully navigate

barriers present in the RMI.

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Data availability

The deidentified data underlying the results presented in this study may be made available upon reasonable request from the corresponding author, Dr. Pearl A. McElfish, at pamcelfish@uams.edu.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101086.

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Pharmacological approaches to the prevention of type 2 diabetes mellitus

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About 1 in 10 adults worldwide are estimated to have diabetes mellitus. They are at risk of developing life-threatening complications resulting in reduced quality of life, increased mortality and higher healthcare costs. The ability to prevent or delay type 2 diabetes mellitus (T2DM) by modifying some of its risk factors has been hypothesized for decades. The long and often gradual time-course of increasing dysglycemia prior to diabetes diagnosis suggests that interventions during that period could be effective in preventing T2DM. In addition to lifestyle modifications, certain drugs prevent or slow development of hyperglycemia. Recently, drugs used for obesity management were shown to prevent T2DM. In this review, we discuss various pharmacotherapeutic options for preventing T2DM.

KEYWORDS

type 2 diabetes mellitus, prevention, metformin, prediabetes, remission, pharmacotherapy

Introduction

The epidemic of diabetes mellitus and its complications pose major global health threat. The global prevalence of diabetes and impaired glucose tolerance (IGT) quadrupled in the past three decades. This pace of change in diabetes prevalence in many countries has been heightened by rapid urbanization (1, 2). The global prevalence of diabetes was estimated to be 463 million (9.3% of adults 20–79 years of age) and this estimate is projected to rise to 700 million by 2045 (3). Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM) (4). T2DM is also associated with increased health care cost; estimated to be $850 billion globally (5). The enormous human and financial costs that accompany T2DM, and the challenge of treating it effectively once it is diagnosed, make it an ideal target for prevention.

The ability to prevent or delay T2DM by modifying some of its risk factors has been hypothesized for decades. The long and gradual time-course of increasing dysglycemia prior to T2DM diagnosis suggests that interventions during that period could be effective in prevention of the disease. Substantial progress has been made in recent years in evaluating

effective preventive strategies. In addition to lifestyle modifications, certain drugs were shown to prevent or delay development of hyperglycemia. Recently, drugs targeting obesity, have also been studied for T2DM prevention.

In this review, we discuss various pharmacotherapeutic options for preventing T2DM and discuss the evidence behind them as summarized in Tables 1, 2.

Glucose-lowering medications

Metformin

Metformin, a biguanide, primarily decreases hepatic glucose production by inhibiting gluconeogenesis. It enhances peripheral insulin sensitivity in the skeletal muscle by increasing insulin receptor tyrosine kinase activity and glucose transporter (GLUT)-4 translocation to the cell membrane (36). Metformin also improves beta-cell responsiveness to a glucose load through correction of glucotoxicity (37).

The Diabetes Prevention Program (DPP) study was a multi-center trial which enrolled 3,234 subjects with prediabetes and randomized them to either intensive lifestyle intervention (intended to achieve 7% body weight loss), metformin (850mg twice daily) or standard lifestyle recommendations (38). Participants in the study were overweight or obese (mean BMI 34 kg/m^2), mostly middle-aged adults with IGT or impaired fasting glucose (IFG) with values between 95-126 mg/dL. In the ensuing 2.8 years, T2DM incidence was reduced by 58% with lifestyle intervention and by 31% with metformin compared to placebo (6). It is interesting to note that genome-wide association studies in the DPP cohort revealed novel ethnic-specific associations with metformin response and may have implications for individualized therapy (39).

A secondary analysis of the DPP study was performed in subjects with history of gestational diabetes (GDM). Women with history of GDM were compared with women with previous live birth but without GDM history. It was found that progression to T2DM is more common among women with history of GDM compared with those without it, despite equivalent degrees of IGT at baseline. Both lifestyle modifications (LSM) (53% reduction in T2DM incidence) and metformin (50% reduction in T2DM incidence) were highly effective in delaying T2DM in women with IGT and history of GDM (40).

Eighty-eight percent of the surviving DPP cohort enrolled in a long-term follow up study, the Diabetes Prevention Program Outcomes Study (DPPOS). During the DPPOS, unmasked metformin was continued as a study intervention in the original metformin group. T2DM incidence was reduced by 34% in the lifestyle group and 18% in the metformin group compared to placebo in the following 10 years (7). Significant reduction in T2DM incidence persists in the metformin group at 15-year (relative risk reduction/RRR 18%; p=0. 001) (8) and 22-year follow up (RRR 18%) (9).

Similarly, The Indian Diabetes Prevention Program (IDPP) randomized 531 Asian Indian subjects with IGT (mean BMI 25.8 kg/m2) to 4 groups: LSM or metformin (250-500mg twice daily) or LSM plus metformin or control group (standard healthcare advice). The median follow-up period was 30 months. The 3-year cumulative incidences of diabetes were 39.3%, 40.5%, 39.5% and 55.0%, respectively. The RRR was 26.4% with metformin (95% CI 19.1–35.1, p=0.029) and 28.2% with LSM plus metformin (95% CI 20.3–37.0, p=0.022), as compared to the control group (10).

The Chinese Diabetes Prevention Program (CDPP) evaluated the preventive effect of lifestyle intervention with diet and exercise, acarbose, and metformin on T2DM progression in 321 subjects with IGT. Annual T2DM incidence was 11.6, 8.2, 2.0, and 4.1% in the control, lifestyle intervention, acarbose, and metformin groups, respectively (11).

The Early Diabetes Intervention Trial (EDIT) analyzed the effects of metformin and acarbose in T2DM prevention in 631 subjects with IFG. At three years, there was an 8% risk reduction with acarbose and 37% with metformin, compared to placebo (12) but there was no difference in the relative risk for T2DM at six-year of follow-up. For patients with IGT at baseline, the RRR was significant with acarbose (0.66) but not with metformin (1.09), suggesting different effects of different therapies in subjects with IGT and IFG (13).

A study by Begum et al. (2009) showed that occurrence of GDM among women with polycystic ovarian syndrome (PCOS) was significantly lower in the metformin treatment group with only one subject (3.44%) vs nine of the 30 pregnancies (30%) without metformin (14). Similarly, Glueck et al. (2002) reported the odds ratio for GDM in women with metformin vs those without metformin was 0.093 (95% CI: 0.011 to 0.795) (15).

Recent studies showed promising effects of metformin in combination with glucagon-like peptide-1 (GLP-1) receptor agonists (16) and dipeptidyl peptidase 4 (DPP-4) inhibitors (17, 18) for T2DM prevention.

According to the American Diabetes Association (41), metformin should be considered for T2DM prevention in adults with BMI ≥35 kg/m2, age ≤ 60 years, higher fasting plasma glucose (≥ 110 mg/dL), and higher A1C (≥ 6.0%), and in women with prior GDM.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizers. They activate gamma isoform of peroxisome proliferator-activated receptor (PPAR γ), enhance glucose uptake by skeletal muscles and adipocytes, improve insulin sensitivity and consequently improve pancreatic beta-cell function (42, 43).

The Troglitazone in Prevention of Diabetes (TRIPOD) study (19) compared Troglitazone with placebo in 266 nondiabetic Hispanic women (mean age 34.6 years; mean BMI 30.5 kg/m^2) with previous GDM, about 70% of whom had IGT at entry into the trial. Troglitazone treated group had a 55% reduction in the incidence of T2DM over 2.5 years. The drug was recalled before the planned study-end because of reports of hepatic failure.

The Pioglitazone in Prevention of Diabetes (PIPOD) study (20) was an open-label follow-up of 89 women from TRIPOD who had not developed diabetes (A1C <7%). These participants showed an

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TABLE 1 Summary of clinical trials on T2DM prevention with glucose lowering drugs and weight-loss medications.

Study (year)	Eligibility	Number of Subjects	Interventions	Results	Mean or Median Follow up in years	Comments
A) Metformin						
DPP (1996–2001) (6)	IFG and IGT	3234 study participants 531 subjects with IGT	LSM vs. Metformin 850mg BD vs. placebo	LSM group reduced their risk of developing T2DM by 58% and metformin by 31%	2.8	**10-year follow-up** (7): T2DM incidence was reduced by 34% (24–42) in the lifestyle group and 18% (7–28) in the metformin group compared with placebo. **15 years follow-up** (8): T2DM incidence was reduced by 27% in the lifestyle intervention group (HR 0.73, 95% CI 0.65-0.83; p<0.0001) and by 18% in the metformin group (0.82, 0.72-0.93; p=0. 001), compared with placebo **22-year follow-up** (9): Relative risk reduction in T2DM by 25% in the lifestyle intervention and by 18% in the metformin group.
IDPP (2006) (10)	IGT	531	LSM vs. Metformin vs. LSM + metformin vs. placebo	Risk reduction for T2DM with LSM was 28.5%, metformin 26.4%, and combination 28.2% compared to placebo	30 months	
CDPP (2001) (11)	IGT	321	LSM vs. Acarbose 50 mg TID vs. metformin 250 mg TID vs. placebo	Annual incidence of T2DM was 11.6% for the control, 8.2% for LSM, 2% for acarbose, and 4.1% for metformin.	3.0	
EDIT (2003) (12)	IGT and IFG	631	Acarbose 50 mg TID vs. metformin 500 mg TID vs. placebo	8% risk reduction with acarbose and 37% with metformin, compared to placebo	6.0	6-year follow-up (13): No differences in relative risk for diabetes with acarbose (1.04, P = 0.81), Metformin (0.99, P = 0.94) or combination therapy (1.02, P = 0.91). In those with IGT at baseline, relative risk was reduced significantly with acarbose (0.66, P = 0.046) but not Metformin (1.09, P = 0.70) or combination therapy (0.72, P = 0.27).
Begum MR et al. (2009) (14)	Nondiabetic – PCOS. Pregnant	29 patients on metformin during pregnancy compared with 30 controls.	Metformin 2 – 2.5 g per day vs. controls	GDM developed in 3.44% of patients on metformin compared to 30% in controls	Gestation period	PCOS use of metformin throughout pregnancy is associated with and might be responsible for a ninefold reduction (30-3.44%) of GDM
Glueck et al. (2002) (15)	Nondiabetic – PCOS. Pregnant	33 patients on metformin compared with 39 controls	Metformin 850 mg TID vs. controls	In PCOS use of metformin is associated with a 10-fold reduction in GDM (31 to 3%)	Gestation period	
Tao Tao et al. (2021) (16)	PCOS + prediabetes (IFG and/or IGT)	150 women with PCOS	Exenatide (10-20µg daily), Metformin (1500-2000 mg daily), or Combination (Exenatide plus Metformin)	Remission rate of prediabetes: Combination group (64%, 32/50) and exenatide group (56%, 28/50) was significantly higher than that of the metformin group (32%, 16/50) (P = .003 and.027, respectively)	12 weeks	
Guardado-Mendoza	IGT	144	Linagliptin 5 mg + metformin	T2DM incidence was higher in M group in comparison to LM	2.0	

(Continued)

TABLE 1 Continued

Study (year)	Eligibility	Number of Subjects	Interventions	Results	Mean or Median Follow up in years	Comments
et al. (2019) (17)			1700 mg daily + lifestyle (LM group) or metformin 1700 mg daily + lifestyle (M group)	group (HR 4.0, 95% CI: 1.24-13.04, p = .020). The probability of achieving normoglycemia was higher in LM group (OR 3.26 CI 95% 1.55-6.84).		
Daniele G et al. (2020) (18)	History of GDM + IGT or IFG	40	Sitagliptin (100 mg qd), Metformin (850 mg bid) or both (50 + 850 mg bid) for 16 weeks	Among Metformin + sitagliptin women, 33% reverted to normal glucose tolerance (NGT) compared with 14% with Metformin alone and 7% with Sitagliptin (P < 0.05)	16 weeks	
B) Thiazolidinediones						
TRIPOD (2002) (19)	Hispanic women with previous GDM	266	Troglitazone 400 mg/day vs. placebo	55% reduction in the incidence of T2DM in troglitazone arm	2.5	
PIPOD (2006) (20)	Hispanic women with previous GDM	Open label study on 89 women without T2DM in TRIPOD A	Pioglitazone 45 mg/day	Annual T2DM incidence was 4.6%		
ACT NOW (2011) (21)	IGT Mean BMI 33.4 kg/m2	602	Pioglitazone 45 mg/day vs. placebo	Annual incidence rates for T2DM mellitus were 2.1% in the pioglitazone group and 7.6% in the placebo group, and the hazard ratio for conversion to T2DM in the pioglitazone group was 0.28	2.4	Weight gain was greater with pioglitazone than with placebo (3.9 kg vs. 0.77 kg, P<0.001), and edema was more frequent (12.9% vs. 6.4%, P=0.007)
DREAM (2006) (22, 23)	IGT and/or IFG Mean BMI 30.8 kg/m2	5269	Rosiglitazone 8 mg/day vs. placebo and Ramipril 15 mg/day vs. placebo	3-year T2DM incidence: Ramipril: HR 0.91 (0.80–1.03) Rosiglitazone: HR 0.38 (0.33–0.44) HF results: 14 (0·5%) participants in the rosiglitazone group and two (0·1%) in the placebo group developed heart failure (p=0·01).	3.0	Balancing both the benefits and risks suggests that for every 1000 people treated with rosiglitazone for 3 years, about 144 cases of T2DM will be prevented, with an excess of four to five cases of congestive heart failure.
C) Alpha-glucosidase inhibitors						
CDPP	**See above**					
STOP NIDDM (2002) (24)	IGT Mean BMI 31.0 kg/m2	1418	Acarbose 100 mg TID vs. placebo	25% relative risk reduction on acarbose compared to placebo. Absolute risk reduction after 3.3 years was 9.1%.	3.3	Additional studies showed that acarbose was associated with 49% reduction in cardiovascular events (15 vs. 32 subjects; HR 0.51, 95% CI 0.01–0.95, p=0.03). Interpret with caution due to small number of events. NNT 11 for 3.3 years
Ryuzo Kawamori et al. (2010) (25)	IGT	1780	Voglibose 0.2 mg TID vs. placebo	Subjects treated with voglibose had a significantly lower risk for the progression to T2DM than placebo (50/897 vs 106/881: hazard ratio 0.595).	4.0	810 (90%) of 897 patients in the voglibose group had adverse events. Serious adverse events (all one each) in the voglibose group were cholecystitis, colonic polyp, rectal neoplasm, inguinal hernia, liver dysfunction, and subarachnoid hemorrhage.
EDIT	**See above**					

(Continued)

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TABLE 1 Continued

Study (year)	Eligibility	Number of Subjects	Interventions	Results	Mean or Median Follow up in years	Comments
D) Sodium-glucose co-transporter 2 (SGLT2) inhibitors						
Rossing, et al. (2022) (26)	No h/o diabetes and HbA1C less than 6.5%. Mean GFR: 58.7 Mean BMI: 27.4 kg/m2	4003 (1398 [34·9%] from the DAPA-CKD trial and 2605 [65·1%] from the DAPA-HF trial)	Dapagliflozin vs placebo	126 (6·3%) of 2008 patients in the placebo group (event rate 3·9 per 100 patient-years) and 85 (4·3%) of 1995 patients in the dapagliflozin group (event rate 2·6 per 100 patient-years) developed T2DM (hazard ratio 0·67 [95% CI 0·51 to 0·88]; p=0·0040).	1.8	
Weight-loss medications:						
A) Orlistat						
XENDOS (2004) (27)	Obese and normal (79%) or IGT (21%) Mean BMI 37.3 kg/m2	3,305	LSM plus either orlistat 120 mg or placebo, three times daily.	Diabetes risk reduction of 45% compared to placebo	4.0	Overall, 4% of placebo patients and 8% of orlistat patients withdrew from the study because of adverse events, primarily GI due to gastrointestinal events.
B) Phentermine-Topiramate						
CONQUER (2011) (28)	Overweight or obese adults and two or more comorbidities (hypertension, dyslipidemia, T2DM or prediabetes, or abdominal obesity) Mean BMI 36.2 kg/m2 (low dose) 36.6 kg/m2 (high dose)	2487 (1684 (68%) had IGT or IFG)	Placebo vs once-daily phentermine 7·5 mg plus topiramate 46·0 mg vs once-daily phentermine 15·0 mg plus topiramate 92·0 mg.	the relative risk (vs placebo) was 0·78 (0·40–1·50) with phentermine 7·5 mg plus topiramate 46·0 mg, and 0·47 (0·25–0·88) with phentermine 15·0 mg plus topiramate 92·0 mg	1.0	
C) Lorcaserin						
CAMELLIA-TIMI 61 (29)	BMI ≥27 kg/m^2 with or at high risk for atherosclerotic vascular disease; Age ≥ 40 years	Total N: 12,000 At baseline, 6816 patients (56.8%) had T2DM, 3991 (33.3%) prediabetes, and 1193 (9.9%) normoglycemia.	Lorcaserin 10mg BID or placebo	Lorcaserin reduced T2DM incidence by 19% (HR, 0.81; 95% CI: 0.66– 0.99) in patients with prediabetes and by 23% in patients without diabetes (HR 0·77, 95% CI: 0·63–0·94).	3.3	

DPP, Diabetes Prevention Program; IDPP, Indian Diabetes Prevention Program; CDPP, Chinese Diabetes Prevention Program; EDIT, Early Diabetes Intervention Trial; STOP NIDDM, Study to prevent non-insulin dependent diabetes; TRIPOD, Troglitazone in Prevention of Diabetes; PIPOD, Pioglitazone in Prevention of Diabetes; ACT NOW, Actos Now for the prevention of diabetes; DREAM, Diabetes Reduction Approaches with Ramipril and Rosiglitazone Medications; LSM, Lifestyle modifications; IGT, Impaired glucose tolerance; IFG, Impaired fasting glucose; GDM, Gestational diabetes mellitus; BD, Twice daily; TID, Thrice daily; CKD, chronic kidney disease; GFR, Glomerular Filtration Rate; XENDOS: XENical in the prevention of diabetes in obese subjects study, CONQUER: Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults, CAMELLIA-TIMI: Effect of lorcaserin on treatment and prevention of type 2 diabetes in overweight and obese patients.

average rate of diabetes of 4.6% per year during treatment with pioglitazone for three years, which was much lower compared with the rate of 12.1% per year that was observed during placebo treatment in the TRIPOD study.

Actos Now for the Prevention of Diabetes (ACT NOW) study (21) was an RCT conducted to examine the effectiveness of pioglitazone in preventing T2DM among 602 subjects (mean age 52 years; mean BMI 34 kg/$m^{2)}$ with IGT. The annual rate of T2DM

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TABLE 2 Summary of evidence on T2DM prevention with medications promoting both glucose-lowering and weight-loss.

Study (year)	Eligibility	Number of Subjects	Interventions	Results	Mean or Median Follow up in years	Comments
A) Glucagon-like peptide-1 agonists						
Rosenstock, et al. (2014) (30)	Obese, subjects, Mean BMI: 39.6 kg/m2 and IGT or IFG	152	Placebo vs Exenatide plus LSM	IGT or IFG normalized at end point in 77% of exenatide vs 56% of placebo subjects.	24 weeks	
Le Roux et al. (2017) (31)	Prediabetes plus BMI of at least 30 kg/m2 or 27 kg/m2 with comorbidities.	2254	Once-daily subcutaneous liraglutide 3·0 mg or matched placebo plus LSM	In the liraglutide group 26 individuals (2%) of 1472 were diagnosed with T2DM vs 46 (6%) of 738 in the placebo group. The time to onset of T2DM over 160 weeks among all randomized individuals was 2·7 times longer with liraglutide than with placebo (95% CI 1·9 to 3·9, p<0·0001)	160 weeks	
Garvey, et al. (2022) (32) Wilding, et al. (2021) (33) - STEP 1	BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 with at least one weight-related complication, excluding T2DM	1961	Once a week 2.4mg semaglutide vs placebo	Risk scores decreased from 18% to 7% with semaglutide, and 18% to 16% with placebo (61% vs. 13% reduction [p<0.01]	68 weeks	10-yr T2D risk was calculated *post hoc*, from STEP 1 (68 weeks) and STEP 4 (20-wk run-in on semaglutide, 48-wk randomized withdrawal)
Garvey, et al. (2022) (32) Rubino, et al. (2021) (34)- STEP 4	BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 with at least one weight-related complication, excluding T2DM	902	Once a week 2.4mg semaglutide vs placebo	Risk score reduction with semaglutide occurred during wks 0-20, from 21% to 8% but increased to 15% with switch to placebo (32% reduction vs. 41% increase [p<0.01]	20-wk run-in on sema, 48-wk randomized withdrawal	As above
B) Tirzepatide						
SURMOUNT-1 (35)	BMI ≥ 30 kg/m2 or ≥ 27 kg/m2 with at least one weight-related complication, excluding T2DM	At baseline, 40.6% (n=1032 out of 2539) of subjects had prediabetes	Tirzepatide (5 mg, 10 mg, or 15 mg) or placebo	95.3% of the participants with prediabetes at baseline in the treatment groups had reverted to normoglycemia, as compared with 61.9% of participants in the placebo group.	1.4	

BMI, body-mass index; LSM, lifestyle modifications; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus; STEP, Semaglutide Treatment Effect in People with Obesity; SURMOUNT: Efficacy and safety of Tirzepatide once weekly in participants without type 2 diabetes who have obesity or are overweight with weight- related comorbidities.

was 7.6% in placebo-treated vs. 2.1% in pioglitazone treated subjects (HR 0.28, p<0.0001) over 2.4 years.

Concerns over adverse effects of TZDs has dampened the enthusiasm to use pioglitazone for T2DM prevention. Undesirable effects of TZDs include fluid retention, increased risk of heart failure, weight gain and loss of bone density increasing fracture risk.

Alpha-glucosidase inhibitors

These drugs act by competitively inhibiting alpha- glucosidase enzyme and decreasing carbohydrate absorption from the small intestine, thus reducing postprandial glucose levels (44).

The Study TO Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) (24) evaluated the effects of acarbose in delaying progression of IGT to T2DM in 1429 subjects. Over the 3.3-year follow-up period, there was a 25% reduction in the incidence of T2DM in the acarbose group compared to placebo. Furthermore, acarbose significantly increased the regression of IGT to normal glucose tolerance (HR 1.42, 95% CI 1.24–1.62; p<0·0001). About one-quarter of the cohort did not complete the study, and this was attributed to the gastrointestinal side effects of acarbose.

Kwawamori et al., randomized 1780 Japanese subjects with IGT to either receiving voglibose 0.6 mg/day or placebo. At the end of the study (11 months; ended early due to efficacy) the T2DM hazard ratio (voglibose vs. placebo) was 0.60 (95% CI 0.43–0.82) (25).

Sodium-glucose co-transporter-2 inhibitors

The SGLT2 is expressed in the proximal tubule and mediates reabsorption of approximately 90 percent of the filtered glucose

load to the kidneys. SGLT2 inhibitors promote renal excretion of glucose and thereby modestly lower elevated blood glucose levels (45).

Pre-specified pooled analysis (26) of the DAPA-CKD and DAPA-HF trials suggests that dapagliflozin (10 mg daily) may reduce new-onset T2DM compared with placebo (HR 0·67 [95% CI 0·51–0·88]). In pooled analysis of selected 4,003 participants who had no previous diagnosis of T2DM (mean age 63 years, mean A1C 5.7%), dapagliflozin reduced new-onset T2DM incidence (defined as having A1C ≥6.5% on two consecutive follow-up visits, or a clinical diagnosis of T2DM that led to initiation of a glucose-lowering agent) by approximately one-third. The overall incidence of new-onset T2DM was 2.6 events per 100 patient-years in the dapagliflozin group vs 3.9 events per 100 patient-years in the placebo group (HR 0.67; 95% CI 0.51–0.88; p=0.0040). Treatment was predominantly beneficial in participants with prediabetes. Possible mechanisms include protection of pancreatic beta-cells from glucotoxicity, weight loss, and improvement in hepatic insulin sensitivity. Improvement in CKD and heart failure may have contributed to insulin sensitivity (26). A prospective RCTs is needed to confirm whether dapagliflozin truly prevents T2DM.

Although empagliflozin did not demonstrate significant benefit for T2DM prevention among patients with heart failure and prediabetes in EMPEROR-Preserved study (46) (HR: 0.84; 95% CI 0.65–1.07) and EMPEROR-Reduced study (47) (HR: 0.86; 95% CI 0.62–1.19), the hazard ratios were consistent with potential benefit. A recent meta-analysis of four RCTs showed that SGLT2 inhibitors (empagliflozin and dapagliflozin) were significantly associated with a lower risk of new-onset diabetes (relative risk, 0.79; 95% CI, 0.68-0.93) (48). This meta-analysis included 5655 participants with pre-diabetes. The relative risks of new-onset diabetes in dapagliflozin and empagliflozin were 0.68 (95% CI, 0.52-0.89) and 0.87 (95% CI, 0.72-1.04), respectively.

Weight-loss medications

Orlistat

Orlistat acts by reversibly inhibiting gastric and pancreatic lipases (49). It also increases postprandial glucagon-like peptide 1 (GLP-1) levels. In a pooled analysis by Heymsfield et al. (50) orlistat compared to placebo, reduced 2-year cumulative diabetes incidence by 61% (7.6% in the placebo group vs. 3.0% in the orlistat group) among those with IGT. However, due to the side effects of orlistat, only 69% of the participated subjects completed the study.

Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study (27) was a 4-year, double-blind, prospective study where 3,305 obese subjects with prediabetes were randomized to either lifestyle intervention plus orlistat 120 mg or plus placebo. It showed that the cumulative incidence of T2DM was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (p=0.0032). Independent of orlistat or placebo treatment, the relative risk of developing T2DM was greater in patients with IGT, men, older subjects, and subjects with a higher BMI.

Phentermine/topiramate

Phentermine is a sympathomimetic drug, which stimulates norepinephrine release in the hypothalamus, suppresses appetite and increases satiety. Topiramate's action is not well understood but hypothesized to work on alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and kainite receptors to reduce food cravings, and on Gamma-aminobutyric acid (GABA) receptors to increase energy expenditure (51).

The CONQUER study evaluated the efficacy of phentermine/topiramate combination as an adjunct to LSM for weight loss and metabolic risk reduction in individuals who are overweight and obese, with two or more risk factors (28). They enrolled 84% of subjects without T2DM at baseline. In this population, development of T2DM was less in phentermine 15 mg/topiramate ER 92 mg group compared to placebo after 56 weeks of intervention (1.7% versus 3.6%; HR, 0.47; 95% CI, 0.25–0.88).

In the long-term follow up study, SEQUEL, a total of 78.1% of subjects in the original CONQUER study continued to take blinded medication over 108 weeks. The annual incidence rates for progression to T2DM were 0.9% in high dose phentermine/topiramate group and 3.7% in the placebo group (P=0.008) (52). These studies were not performed to assess prevention of T2DM as a primary outcome.

A subgroup analysis of the CONQUER study including subjects with prediabetes and/or metabolic syndrome at baseline showed that the annual incidence of T2DM was 1.3% for high dose phentermine/topiramate and 6.1% in placebo (53).

Naltrexone/bupropion

Bupropion is a norepinephrine and dopamine reuptake inhibitor which stimulates proopiomelanocortin (POMC) neurons in the hypothalamus, with a downstream effect of increased satiety. Naltrexone prevents rebound inhibition of POMC neurons by β-endorphin, and synergistically works with bupropion to increase satiety (51).

There were four Contrave Obesity Research (COR) studies looked at the weight loss effects of Naltrexone/Bupropion (NB): the COR-I, COR-II, COR-BMOD (behavior modification), COR-Diabetes (54–57). None of these studies were designed to analyze progression of IGT to T2DM, but COR-I study (54) showed significant decrease in fasting plasma glucose in response to naltrexone SR 32 mg/bupropion SR 16 mg combination treatment. COR-Diabetes study (57) including subjects with T2DM reported improvements in glucose homeostasis, resulting in A1C reduction of 0.6% in the NB group, and the A1C goal of ¾7% was achieved in 44% in NB group vs 26% in placebo group.

Further longer-term studies are needed to establish the effect of this medication in T2DM prevention.

Drugs promoting glucose-lowering and weight-loss

Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) mimic the action of endogenous GLP-1 in enhancing glucose-dependent insulin secretion and suppress glucagon production from pancreatic alpha cells and thus used to treat T2DM. Apart from glycemic control, they are also thought to reduce neuroinflammation, promote nerve growth, improve cardiac function, suppress appetite, delay gastric emptying, regulate lipid metabolism and reduce fat deposition (58).

In a study (30) of 152 obese patients (mean age 46 years; mean BMI 39.6 kg/m2) with and without prediabetes (IGT or IFG), blood glucose was normalized in 77% and 56% after exenatide and placebo, respectively. There was a significantly higher weight loss with exenatide of 5.1 kg vs 1.6 kg with placebo.

In the SCALE study Obesity and Prediabetes trial (31), 2,254 adults with prediabetes and BMI ≥30 kg/m^2 or ≥27 kg/m^2 with comorbidities (mean age 47 years, mean BMI 39 kg/m^2) were randomized to receive liraglutide 3mg/day vs a matched placebo, as an adjunct to LSM. Time to onset of diabetes in the treatment group was 2.7 times longer with liraglutide compared to placebo (95% CI 1·9 to 3·9, p<0·0001; HR 0.21, 95% CI 0.13–0.34). However, about half the participants withdrew from the study. Based on an analysis imputing the missing data, T2DM incidence was reduced by 66% (HR 0.34, 95% CI 0.22–0.53) with liraglutide vs 36% with placebo.

Recently, the effect of semaglutide in T2DM prevention was assessed in comparison to placebo in overweight or obese individuals in the Semaglutide Treatment Effect in People with Obesity (STEP) studies. In a *post-hoc* analysis (32) of the STEP 1 (33) (68 weeks) and STEP 4 (34) (20-week run-in on semaglutide, 48-week randomized withdrawal) trials, it was shown that semaglutide 2.4 mg could reduce the 10-year risk of progression to T2DM by 61%, regardless of the initial glycemic status (vs 13% reduction in the placebo group (p<0.01). In this analysis, the 10-year risk of T2DM was calculated using Cardiometabolic Disease Staging (CMDS). Most of the risk reduction occurred during the initial weeks (0-20 weeks), from 21% to 11%. Risk scores further decreased with continued semaglutide (weeks 20-68) but increased with switch to placebo (32% reduction vs. 41% increase, p<0.01).

Dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist

Tirzepatide, the dual GIP/GLP-1 receptor agonist was recently approved by the FDA in May 2022 for treatment of T2DM. In the 72-week SURMOUNT-1 trial (35), 40.6% of the patients had prediabetes at baseline. At the end of the trial, 95.3% of those participants reverted back to normoglycemia, as compared with 61.9% of participants in the placebo group. There was also a notable decrease in the fasting insulin levels in the treatment groups. This is probably attributed to the significant weight loss that was seen in association with tirzepatide (15-20.9% weight loss), however future dedicated studies are still needed to confirm the role of tirzepatide for T2DM prevention.

Other medications

Renin angiotensin aldosterone system blockade

Various trials (23, 59–65) suggested that RAAS inhibition may reduce the incidence of new onset T2DM in patients with or without hypertension or at high risk of T2DM. The risk reduction was explained by hemodynamic effects such as improved delivery of insulin and glucose to the peripheral skeletal muscle, non-hemodynamic effects, including direct effects on glucose transport and insulin signaling pathways, which collectively decrease insulin resistance.

A meta-analysis (66) of new-onset T2DM in select comparative outcome trials involving the use of RAAS blockade vs non-RAS blockade showed a lower risk ratio (RR 0.78; 95% CI 0.74-0.88). However, most of these trials did not include T2DM incidence as the pre-specified end point.

Vitamin D

The Vitamin D and Type 2 Diabetes (D2d) Study (67), randomly assigned 2,423 adults with prediabetes to receive 4,000 units of vitamin D3 per day or placebo, regardless of their baseline vitamin D status. After a median follow-up of 2.5 years, T2DM occurred in 293 participants in the vitamin D group, and 323 in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). The hazard ratio for vitamin D compared with placebo was 0.88 (95% CI, 0.75 to 1.04; p=0.12), failing to show a significant decrease in T2DM incidence among the study population.

However, subsequent meta-analyses of studies in patients with pre-diabetes demonstrated that vitamin D supplementation at moderate to high doses significantly reduced the incidence risk of T2DM (68, 69). A secondary analysis of the D2d study showed that participants who maintained higher intratrial serum vitamin D levels during follow-up had a reduced risk of diabetes (70).

Testosterone

Men who are overweight frequently have low serum testosterone (T) concentrations, which is in turn associated with increased risk of T2DM (71).

T4DM (72) was a randomized, placebo-controlled trial, which included 1,007 men who were enrolled in lifestyle intervention program and randomly assigned to receive T or placebo. At 2 years, 21% of the subjects in the placebo group failed OGTT vs 12% in the T group (RR 0.59, CI 0.43-0.80, p=0.007). Treatment effect was

independent of baseline serum testosterone level. So far, testosterone use is not approved for T2DM prevention or treatment.

Conclusion

The rates of T2DM have been rising, parallel to the rates of obesity, largely due to sedentary lifestyle and increased access to highly obesogenic foods. T2DM is one of the leading risk factors for cardiovascular mortality.

Trials involving lifestyle therapies (38, 73, 74) have shown that 5-10% weight loss in obese and overweight individuals with prediabetes is effective in preventing or delaying development of T2DM. Bariatric surgery (75) is particularly effective in preventing T2DM. However, majority of patients are unable to sustain lifestyle changes (76) or accept bariatric surgery as a preventive tool. Appropriate pharmacotherapy is an attractive option to prevent or delay development of T2DM. Metformin should be considered for T2DM prevention in adults with BMI ≥35 kg/m2, age ≤ 60 years, higher fasting plasma glucose (≥ 110 mg/dL), and higher A1C (≥ 6.0%), and in women with prior GDM (41).

Newer therapies like GLP-1 receptor agonists or dual GIP/GLP-1 receptor agonists have unique ability to suppress appetite, and improve pancreatic insulin production, resulting in profound weight loss, improved insulin sensitivity. Although there are several emerging data to show benefits of these therapies in preventing T2DM, further randomized prospective studies are required.

Author contributions

PM and FO contributed to the conception and design of the manuscript. PM and FO wrote the first draft of the manuscript. DE and OH wrote sections of the manuscript. OH edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer GW declared a past collaboration with the author PM to the handling editor.

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MINIREVIEWS

Gut microbiome supplementation as therapy for metabolic syndrome

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Abstract

The gut microbiome is defined as an ecological community of commensal symbiotic and pathogenic microorganisms that exist in our body. Gut microbiome dysbiosis is a condition of dysregulated and disrupted intestinal bacterial homeostasis, and recent evidence has shown that dysbiosis is related to chronic inflammation, insulin resistance, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), and obesity. It is well known that obesity, T2DM and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diets, and sedentary lifestyle. However, recent evidence from human and mouse models suggest that the gut microbiome is also an active player in the modulation of metabolic syndrome, a set of risk factors including obesity, hyperglycemia, and dyslipidemia that increase the risk for CVD, T2DM, and other diseases. Current research aims to identify treatments to increase the number of beneficial microbiota in the gut microbiome in order to modulate metabolic syndrome by reducing chronic inflammation and insulin resistance. There is increasing interest in supplements, classified as prebiotics, probiotics, synbiotics, or postbiotics, and their effect on the gut microbiome and metabolic syndrome. In this review article, we have summarized current research on these supplements that are available to improve the abundance of beneficial gut microbiota and to reduce the harmful ones in patients with metabolic

syndrome.

Key Words: Gut dysbiosis; Metabolic syndrome; Diabetes mellitus; Prebiotics; Probiotics; Postbiotics

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Core Tip: Gut microbiome dysbiosis is related to chronic inflammation, insulin resistance, metabolic syndrome, cardiovascular diseases (CVD), and obesity. It is well known that obesity, type 2 diabetes mellitus and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diets, and sedentary lifestyle. However, recent evidence from human and mouse models suggest that the gut microbiome is also an active player in modulation of these metabolic diseases. Hence it is important to review the role of microbiome supplementation that has been shown to improve the gut microbiome in patients with metabolic syndrome.

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INTRODUCTION

The gut microbiome is defined as an ecological community of commensal symbiotic and pathogenic microorganisms that exist in the body[1,2]. Gut microbiome dysbiosis is defined as dysregulated and disrupted intestinal bacterial homeostasis [2,3]. Recent evidence has shown that dysbiosis is related to chronic inflammation, insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), and obesity[2]. It is known that obesity, T2DM and CVD are caused or worsened by multiple factors like genetic predisposition, environmental factors, unhealthy high calorie diet, and sedentary lifestyle[4-6]. However, recent evidence from human and mouse models suggests that the gut microbiome is also an active player in the modulation of these diseases[7]. Host and gut microbiome dysbiosis can influence local or systemic immunity and inflammation by regulating intestinal barrier permeability or by triggering the innate immune system as seen in obesity and T2DM[7]. *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* are among the protective bacteria that play a significant role in maintaining this intestinal barrier[7]. Hyperglycemia in T2DM can disrupt this intestinal barrier, which causes gram negative bacterial products like lipopolysaccharides (LPS) to enter the systemic circulation, leading to endotoxemia, and further local and systemic inflammation[3,7].

Metabolism is the process used by the body to create energy from the food we eat, and metabolic diseases, such as type 2 diabetes and obesity, occur due to metabolic dysregulation. Metabolic syndrome refers to a set of risk factors including hyperglycemia, dyslipidemia, and obesity that increases the risk for CVD, T2DM, non-alcoholic fatty liver, and other diseases[8]. Animal studies have shown a causal link between the gut microbiome profile and metabolic syndrome[8]. A study in mice fed a 30-d high fat diet showed significant increase of bacteria of the phylum *Firmicutes* and *Proteobacteria* with reduction of *Bacteroidetes* and *Verrucomicrobia*[9]. Another study with high-glucose or high-fructose fed mice showed the gut microbiome of these mice to be significantly altered with an increase in *Proteobacteria* and decrease in *Bacteroidetes* [10].

The gut microbiota consume the host's diet and produces certain metabolites which act on the host receptors and exert their endocrine effects, leading to hormone secretion, inflammation, and insulin resistance[11]. Studies have shown that these microbiota are sensitive to the host's diet composition and the microbiome diversity changes with animal vs. plant-based diets[1]. The gut microbiome produces certain beneficial metabolites like short chain fatty acids (SCFA)[2], such as butyrate which promotes colonic health and is protective against T2DM and CVD[1,3,7,11]; propionate which promotes the release of glucagon like peptide-1 and peptide YY, which improves insulin sensitivity and weight[2]. Secondary bile acids are converted from primary bile acids by the gut microbes, which activate takeda G protein coupled receptor 5, increasing cyclic adenosine monophosphate production, improving insulin sensitivity, interacting with the farnesoid X receptor, pregnane X receptor and vitamin D receptor to regulate lipid metabolism and glucose metabolism, subsequently slowing the progression of CVD and T2DM[7,11]. Other favorable metabolites are esculin, anthocyanin, urolithin A, and enterolactone[3].

Research has also revealed some unfavorable metabolites produced by the gut microbiome, of which trimethylamine is the most prominent. Trimethylamine is oxidized to trimethylamine N-oxide which works by increasing low-density lipoprotein uptake in cells, reducing cholesterol excretion, and promoting recruitment of activated leukocytes and platelet aggregation, and thus, trimethylamine promotes atherosclerosis, thrombosis, CVD and diabetes[3,12]. In patients with chronic kidney disease (CKD), studies have shown that high indoxyl sulfate levels predict major adverse cardiac events, high P-cresyl sulfate levels correlate with CVD and all-cause mortality, and phenylacetylglutamine is associated with overall mortality and CVD[13,14]. Since all of the above mentioned metabolites are uremic toxins, CKD can increase the buildup and worsen the effects of these metabolites resulting in CVD progression[3].

Current research is directed towards finding treatment options for improving the number of beneficial gut microbes and to reduce the harmful ones with the use of probiotics and prebiotics[7]. Efforts are also underway to identify novel gut microbiome-host interactions, their associations and mechanisms leading to T2DM, CVD and to design new therapies to modulate these disease processes[11]. The purpose of this article is to summarize the use of microbiome supplementation to improve the abundance of the beneficial gut microbes and to reduce the harmful ones in patients with diabetes mellitus and metabolic syndrome.

PREBIOTIC, PROBIOTIC, SYNBIOTIC AND POSTBIOTIC SUPPLEMENTATION

Microbiome supplementation has been found to alter the composition of the gut microbiome and possibly have effects on human health and diseases[15]. There are four types of supplements that are studied. In 2016, the International Scientific Association for Probiotics and Prebiotics (ISAPP) defined prebiotics as a substrate utilized selectively by microorganisms in the host and conferring a benefit to the host's health[16]. The widely accepted scientific definition of probiotics as defined by an expert panel convened by the ISAPP in 2013 is "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[17]. In 2019, the ISAPP convened and defined synbiotics as, "a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host"; thus, synbiotics are a combination of prebiotics and probiotics[18]. Lastly, in 2019, ISAPP defined postbiotics to be inanimate microorganisms with or without their components that confer a health benefit to the host[19]. This section will review the current data for each of these supplements and directions for future research. Table 1 summarizes the definitions and examples of the each of these supplements and we have summarized the similarities and differences between each supplements' influence on metabolic syndrome in Table 2 and presented the same in a figure format in Figure 1.

Prebiotic

Prebiotics are consumable substances selectively utilized by microorganisms in the host and confer a benefit to the host [16]. Prebiotic effects have been studied in several metabolic diseases with animal studies, but few studies have been done on humans. Inulin, lactulose, fructooligosaccharides (FOS), and galactooligosaccharides (GOS) are the most widely known prebiotics[20]. Other prebiotics include human milk oligosaccharides, polydextrose, pectic oligosaccharides, arabinoxylans, and xylooligosaccharides[21]. Prebiotics confer a wide range of health benefits, including immune modulation through increased production of interleukins and immunoglobulins with reduction of pro-inflammatory interleukins and production of SCFAs, such as butyrate and acetate[21]. SCFAs indicate bacterial fermentation in the gastrointestinal tract and improve the health of the gut through mucus production, protecting against inflammation, and promoting the intestinal barrier integrity[21]. Production of SCFAs also results in a reduction on intestinal pH, inhibiting the growth of pathogenic bacteria[21].

Bacteria that promote gut health, such as *Bifidobacterium* and *Lactobacillus*, proliferate upon consumption of prebiotics [11]. Inulin oligofructose supplementation in mice fed a high fat diet showed a reduction in the *Firmicutes* to *Bacteroidetes* ratio[22], and reduction in the *Firmicutes* to *Bacteroidetes* ratio has been the hallmark of obesity[23,24]. A study done with a group of 10 elderly women over 19 days of inulin supplementation showed an increase in *Bifidobacteria* and decrease in *Enterococci* and *Enterobacteriaceae*[21], which is associated with a decreased risk of inflammatory bowel disease[25]. FOS supplementation in a rat model improved the gut microbiome by increasing *Bifidobacterium*[26]. Additional, fermentation of FOS generates SCFAs, decreasing the luminal pH and increasing the bioavailability of minerals in the gut[21]. GOS supplementation for prolonged periods in mice fed with a western diet led to increased abundance in *Akkermansia mucinophila* and *Prevotella*[27]. In another study, the activity of GOS was analyzed in sequencing fecal samples from humans after GOS administration, and the data showed an increased in *Facecalibacterium prausnitzii* and *Bifidobacteria* with a decrease in *Bacteroides*[21]. *Facecalibacterium prausnitzii* produces the SCFA butyrate and is associated with reduced inflammation[28]. *Bifidobacteria* promotes gut health, decreases expression of inflammatory cytokines, and improves insulin sensitivity[29]. Decrease in *Bacteroides* is beneficial to humans, as it is a pathogen common in anaerobic infections with significant antibiotic resistance[30].

Additional studies found that treatment with prebiotics improved glucose homeostasis and increased leptin sensitivity [31]. It also decreased inflammation by improving gut barrier integrity, thus decreasing the number of endotoxins able to leak from the gut lumen into the bloodstream[32]. They have also been shown to have a regulatory effect on metabolic disorders, especially those associated with obesity such as dyslipidemia, hypertension, diabetes, and liver steatosis[33]. Thus, several *in vivo* and *in vitro* studies have shown that prebiotics have beneficial impact on diabetes and obesity. Many prebiotics cause an increase in the growth of *Lactobacillus* and *Bifidobacterium*, but it is not fully understood how prebiotics cause these changes in the gut microbiome[21]. It is well-known that prebiotics are fermented by gut microbiota, leading the production of SCFAs, lowering the pH of the colon[21]. Figure 2 summarizes the beneficial effects of prebiotics leading to improved glucose homeostasis and reduced inflammation. Further research is necessary to elucidate the impact of prebiotics on the gut microbiome and the molecular signaling mechanisms of SCFAs.

Synbiotic

Synbiotics are combinations of prebiotics and probiotics, consisting of a combination of live microorganisms and substances that are selectively utilized by the host microbiota to confer a benefit to the host[18]. The benefits of synbiotics are thought to come from the initial selection of beneficial commensal microbiome species and aiding these species in subsequent food processing and fermentation[34]. These include reduced oxidative stress on intestinal cells and overall

Table 1 Definition and examples of prebiotics, probiotics, synbiotics, and postbiotics

Category	Definition	Examples
Prebiotic	Non-digestible substances utilized by microbiota and confer a benefit to the host	Inulin
		Lactulose
		Fructooligosaccharides
		Galactooligosaccharides
Probiotic	Live microorganisms that provide a benefit to the host	*Bifidobacterium*
		Lactobacillus
Synbiotic	Prebiotics and probiotics taken together	
Postbiotic	Inanimate strains with or without their byproducts that provide a benefit to the host	Heat killed *Akkermansia Mucinophila*
		Heat inactivated *Lactobacillus paracasei*
		Heat-inactivated *Bifidobacterium bifidum*
		Byproduct of the above inanimate strains: Butyrate and Proprionate

Table 2 The influence of prebiotics, probiotics, and postbiotics on metabolic syndrome

Category		Influence	
Prebiotic	Inulin	Decrease *Firmicutes* to *Bacteroidetes* ratio[22]	Improvement in Obesity
	Fructooligosaccharides	Increase *Bifidobacterium*[26]	Promotes gut health
			Decrease expression of inflammatory cytokines
			Improved Insulin sensitivity
	Galactooligosaccharides	Increase *Akkermansia mucinophila*. Increase in *Prevotella*[27]	Intestinal barrier protection
			Improved Insulin sensitivity
			Decrease inflammation
Probiotic	Bifidobacterium	Increasing *Akkermansia mucinophila*[56]	Intestinal barrier protection
			Improved Insulin sensitivity
			Decrease inflammation
	Lactobacillus	Decreasing *Firmicutes* to *Bacteroidetes* ratio[57]	Improvement in Obesity
Postbiotic	Heat-killed *Akkermansia mucinophila*		Improves metabolic state in Obesity
	Heat-inactivated *Lactobacillus paracasei*		Reduces the risk of pharyngitis, laryngitis, and diarrhea
	Heat-inactivated *Bifidobacterium bifidum*		Reduces symptoms of irritable bowel syndrome
	Butyrate (SCFA produced by the inactive microbe)	Increasing *Lachnospiraceae*[46]	Protection against diabetes and cardio-vascular diseases
		Increasing *Proteobacteria*[46]	Increased gut mucus production
		Decreasing *Clostridiaceae*[46]	Increased gut barrier integrity

SCFAs: Short Chain Fatty Acids.

decreased inflammation, thus maintaining the gut barrier[35]. Studies show that supplementation with synbiotics or probiotics may lead to beneficial reduction in fasting blood glucose (FBG), although the impact on FBG was more pronounced when multispecies probiotics were used instead of single species probiotics[36]. Current synbiotics include the most well-studied probiotics, including *Bifidobacterium* and *Lactobacillus*, which ferment indigestible sugars, such as FOS[34]. Thus, synbiotic administration of probiotics with FOS aims to increase the abundance of FOS fermentation products in the gut, such as lactic acid[34].

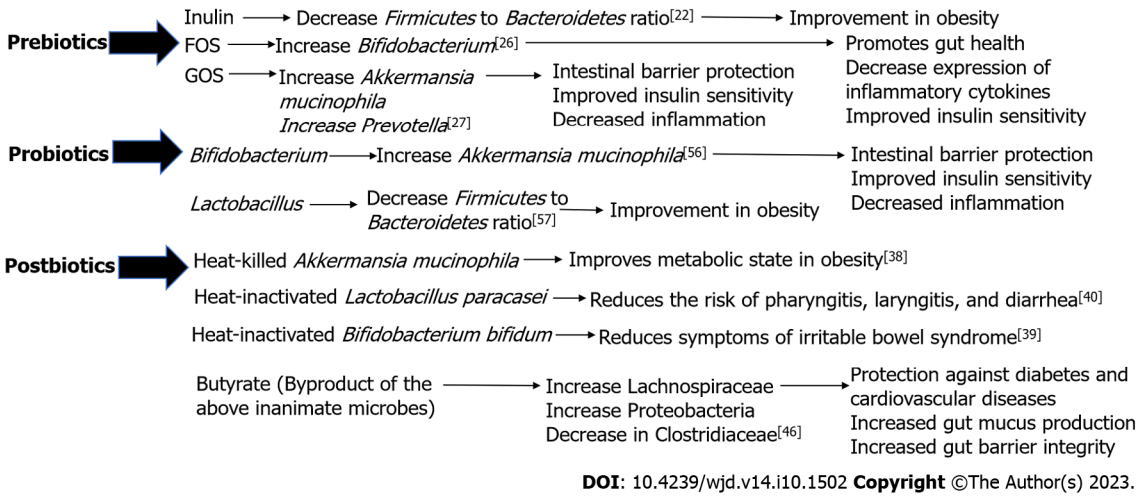

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Figure 1 The overall beneficial effects of gut microbiome supplementation on metabolic syndrome. FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; SCFAs: Short Chain Fatty Acids.

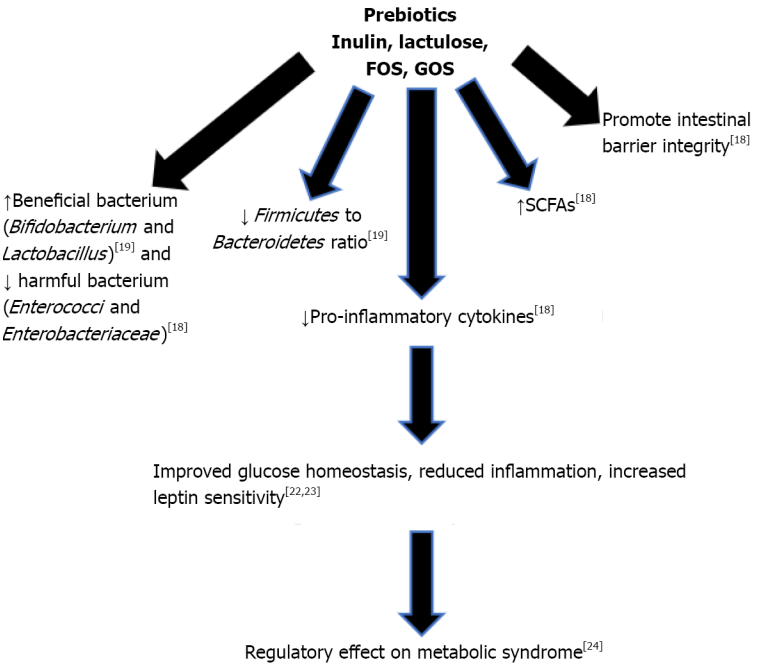

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Figure 2 The beneficial effects of prebiotics on metabolic syndrome. FOS: Fructooligosaccharides; GOS: Galactooligosaccharides; SCFAs: Short Chain Fatty Acids.

Many species rely on products from other species for survival, for example some species require lactic acid for substrate production and thus rely on lactic acid-producing species. This suggests that synbiotics will need to become more complex and involve multiple strains rather than just one, in addition to the prebiotics required for survival[34]. The effects of these supplements may also be altered by the individual's characteristics[37]. Person-to-person variation in gene expression was shown in one study to be the main determinant for differences in transcriptomes created post-supplementation[37]. This may be a species-specific phenomenon or even location specific, i.e., in the duodenum but not in the jejunum; thus, further trials are required.

Postbiotic

Postbiotics consist of inanimate microorganisms with or without their components and metabolites that confer a health benefit to the host[38]. Contrasting with probiotics, which consist of live microorganisms, postbiotics consist of microorganisms that are no longer alive, such as heat-killed *Akkermansia mucinophila*[38]. There are several challenges to the survival of probiotics during production and storage of food, such as reactions with chemical compounds, acidity, and storage temperature[38]. It has long been known that non-viable microbes in addition to their components and

metabolites can have significant impact on health[38]. In one clinical trial, heat-inactivated *Bifidobacterium bifidum* was found significantly alleviate the symptoms of irritable bowel syndrome[39]. In a similar study, *Akkermansia muciniphila* was found to improve the metabolic state of obese and overweight participants in both its living and inactive forms[38]. In another systematic review, postbiotics were studied for the prevention and treatment of infectious diseases in children under five years of age, revealing treatment with heat-killed *Lactobacillus acidophilus* reduced the duration of diarrhea and heat-inactivated *Lactobacillus paracasei* reduced the risk of pharyngitis, laryngitis, and diarrhea[40].

Postbiotics are promising for the development of food supplements with longer stability in comparison to prebiotic supplements[38]. Additionally, postbiotics have the potential to broaden the spectrum of microbes used for supplementation, as microbes that could not be administered live due to safety concerns can be administered in the inanimate form. The mechanism of action of postbiotics is due to both the components of the inactivated microbes and the metabolites produced by the microbes, such as SCFAs[38].

An inverse relationship between decline in anti-inflammatory microbiome species and abnormal SCFA production has been demonstrated[41]. SCFAs, such as butyrate and propionate, are among the metabolites produced from inactive microbes. Gut microbiome produced SCFA have been shown to have strong effects on metabolic and cardiovascular health through a variety of tissue-specific mechanisms including appetite regulation, glucose homeostasis and metabolism, proper gut barrier and colonocyte maintenance and function, and immunomodulation[41]. For example, butyrate is integral in colonocytes for energy production and expanding the regulatory T cell population in the immune system, while propionate is suggested to have a role in gluconeogenesis[42]. However, increase in acetate production has been shown to activate glucose-stimulated insulin secretion, increase ghrelin secretion and hyperphagia, leading to obesity and related diseases[43]. This suggests that to develop a treatment protocol, the specific proportion of postbiotics in a patient will need to be examined to allow for appropriate adjustment. Increased production of acetate has been found in obesity and decreased production of butyrate and propionate is seen in T2DM[44,45]. In mice studies, butyrate was shown to be associated with increased production of *Lachnospiraceae* and *Proteobacteria* and decreased production of *Clostridiaceae*[46].

However, the mechanism directly responsible remains elusive, and some results from animal models conflict with results from human trials. Many metabolic diseases are associated with a chronic state of low-grade inflammation. The maintenance of the gut barrier is also critical for reducing the amount of pro-inflammatory bacterial byproducts that can cross into the bloodstream, thus potentially decreasing the level of inflammation in the body. Specifically, a high fat diet reduces expression of tight junction genes, thus leading to a leaky barrier[47]. This allows inflammatory bacterial byproducts, such as LPS, to circulate in the body leading to an inflammatory response[48]. Hyperglycemia can also increase this leakiness and cause hyperpermeability, leading to a similar inflammatory phenomenon[49]. However, these findings are mainly in animal studies and further studies in humans are required. Additionally, there is a need for studies on the impact of inanimate microbes on the host without associated metabolites to determine the extent that health benefits are conferred. There is also need for additional research on the mechanisms that are driving the benefits of postbiotics. Figure 3 summarizes the beneficial effects of postbiotics, leading to improved glucose homeostasis and reduced inflammation.

Probiotic

Probiotics are live microorganisms that confer a benefit to the host when administered[17]. *Bifidobacterium* and *Lactobacillus* are the two most widely known probiotics. Various studies in animals have shown their benefits in improving gut microbiome composition[50,51]. Probiotic administration has been shown to be potential therapeutic target for metabolic syndrome prevention and treatment[52]. There is a fine balance between the host's immune system and gut microbiome, and imbalance can lead to systemic inflammation through passage of bacteria and bacterial fragments, such as LPS, through the gut barrier and into systemic circulation[52]. Chronic systemic inflammation can lead to the development of insulin resistance and obesity[52].

Additionally, many diseases have been found to have microbial dysbiosis either from an overgrowth of pathogenic species or a loss of microbiome diversity[53]. However, it should be noted that there is not a clear definition of a healthy gut microbiome composition, so the term "dysbiosis" is inherently vague[45]. This change in microbial composition is found to be associated with increased inflammation, specifically in obese patients since low-grade inflammation is a common finding in many metabolic disorders[45]. This suggests that microbiome composition affects the inflammatory state of people. An increase of pro-inflammatory bacterial species has also been found in patients with T2DM, especially with a decrease of anti-inflammatory species[41].

The microbiome present in obese individuals has been found to be different from that of lean individuals though specific differences are difficult to qualify[54]. In a study with obese and lean adolescents, it was found that a lower amount of *Bacteroidetes* and higher proportion of *Firmicutes* was associated with obesity[55]. The microbiome of obese individuals has been shown in animal models to extract more energy from the diet, and this phenomenon still occurs when the microbiome from obese mice is transplanted into lean mice[54]. *Bifidobacterium* supplementation in diet-induced obese and insulin resistant mice showed an increase in *Akkermansia mucinophila*[56]. In another study, *Lactobacillus* supplementation in high-fat diet induced hypertensive mice showed a reduction in the ratio of *Firmicutes* to *Bacteroidetes*[57].

Probiotics have been found to have an influence on the expression of inflammation-related genes and proteins[58]. Many animal studies have shown interactions between the gut microbiome and the immune system[45]. These studies reduced the gene expression of immune system components with known or theorized links to metabolic dysfunction. Researchers then studied the effects or interactions of these mutation with the gut microbiome. Knock out of toll-like receptor 5 (TLR5) in mice was found to cause the hallmark features of metabolic syndrome in correlation with changes to the gut microbiome and findings of colitis[59]. Upon transfer of the microbiome from the knock-out mice to wild-type germ-free mice, metabolic dysfunction was also transferred, leading to hyperlipidemia, hypertension, and insulin

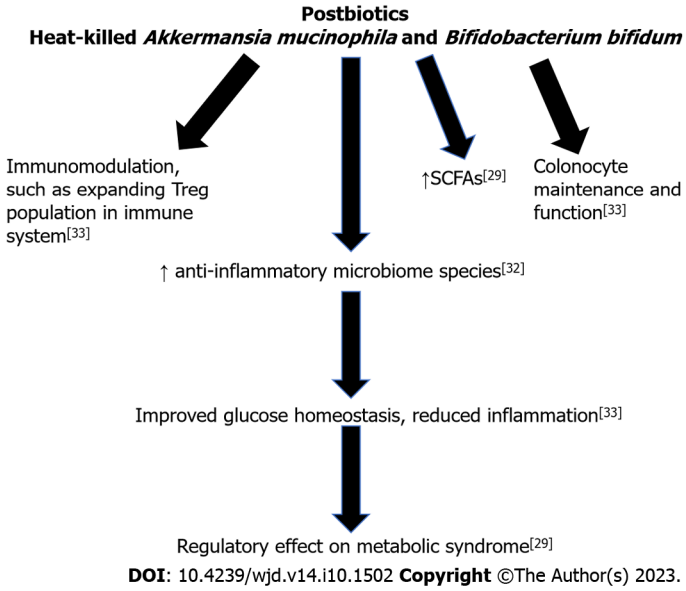

Figure 3 The beneficial effects of postbiotics on metabolic syndrome. Treg: Regulatory T cell; SCFAs: Short Chain Fatty Acids.

resistance. Food restriction was able to prevent obesity but had no effect on insulin resistance, suggesting that the TLR5 and subsequent microbiome changes have a metabolic effect. Additionally, deletion of myeloid differentiation factor 88 and a high fat diet induced hyperglycemia, leading to metabolic syndrome in knock-out mice along with an increase in bacterial translocation across the intestinal barrier[29]. The mice were then given *Bifidobacterium animalis* subsp. lactis 420 (B420) as a probiotic. The result was a general normalization of gut microbiome composition, a decrease in the expression of major inflammatory cytokines, and a complete normalization of insulin sensitivity and levels, although glucose metabolism was only moderately affected[29]. However, data on specific benefits conflict from study to study. Improvements in glucose metabolism is more significant in patients with T2DM, and some studies report little effect on cholesterol and lipid levels[45]. Supplementation of *Akkermansia muciniphila* has been found in rodents and humans to improve insulin sensitivity and decrease inflammation[60]. The findings are less prominent in humans but indicate the supplement's clinical potential. Another study with 40 participants with insulin resistance were placed in a double-blind trial and given either *Akkermansia muciniphila* or a placebo, and the study showed reduction in inflammatory markers and improved insulin sensitivity in the *Akkermansia muciniphila* group[61].

Only a small number of studies have been conducted to analyze the effect of probiotic administration on weight and glycemic control in humans. In one study, 87 subjects with higher body mass index (BMI) (24.2-30.7 kg/m^2) were randomly assigned to a group received fermented milk containing *Lactobacillus* (LG2055) or fermented milk without *Lactobacillus* for 12 wk. It was found that the group receiving the milk containing LG2055 experienced a significant reduction in abdominal visceral and subcutaneous fat and BMI[62]. Another study showed probiotic yogurt consumption reduced FBG and HgbA1c in patients with type 2 diabetes[63]. A double-blind trial with 21 participants showed administration of *Lactobacillus reuteri* improved insulin and incretin secretion[64]. Thus, the results from clinical experiments are encouraging, but larger trials are needed to confirm the effect of probiotics on improving insulin sensitivity and weight loss[65]. Figure 4 summarizes the beneficial effects of probiotics, leading to improved glucose homeostasis and reduced inflammation.

Future directions

Future research is needed to confirm the clinical efficacy of microbiome supplementation. Several times, studies have reached opposing or ambiguous conclusions, even though the research was of high methodological quality[58]. This may be due to several factors including data collection methods, different analysis parameters and metrics, and varied methods of interpretation[58]. Some studies used self-reporting surveys to measure patient quality of life and psychosocial effects. Others looked at lab values that may not necessarily have significance clinically, such as inflammatory markers or glucose metabolism protein levels in generally healthy individuals. Some studies had animal models while others involved human subjects and may have been observational or randomized with placebo controls. There is also the question of funding and conflicts of interest, as some studies are funded or linked to probiotic companies. While that does not necessarily bias the project, independent research should be a focus in the future.

Additionally, research on the effects of specific strains is lacking and may even vary from stain to strain, thus weakening the argument for the use of specific strains in a project[58]. One study found that both mice and humans had colonization resistance to probiotics based on the current composition of their gut microbiome, and that in humans this resistance varies from person to person because microbiome composition is individualized based on person-specific needs, geographic region, and diet among other factors[66]. In fact, many of the live probiotic strains were found to still be viable in stool samples after passage through the GI tract[66], and it remains unclear if the colonization that does occur persists after supplementation ceases. This contradicts *in vitro* studies in which probiotics were able to adhere to human

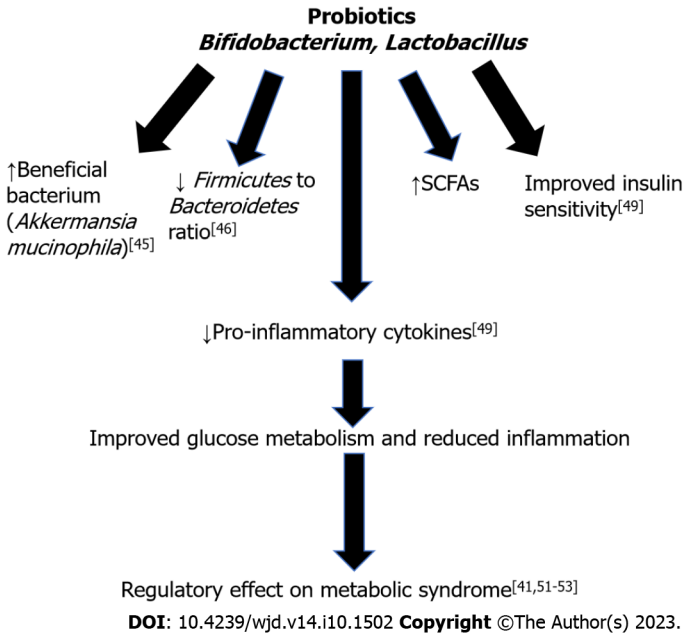

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Figure 4 The beneficial effects of probiotics on metabolic syndrome. SCFAs: Short Chain Fatty Acids.

GI mucosal cells[67], indicating that lab-based work may be a poor predictor of efficacy in human subjects[58]. *In vitro* studies in general may be poor models for this topic of research since it does not include *in vivo* signaling and factors that may play an important role in colonization and efficacy[58]. This could also contribute to conflicting results and would require further *in vivo* studies.

Additional studies have also looked at whether the effects of probiotics change depending on a person's specific microbiome composition and have found that it does make a difference. Song *et al*[68] classified fifty obese but otherwise healthy subjects based on the ratio of two bacterial species, *Prevotella* and *Bacteroidetes*, two of the major enterotypes[68]. The administration of probiotics improved obesity-related markers, but the efficacy was greater in the *Prevotella*-dominant enterotype. This, along with colonization resistance, could explain why previous studies have found such varied results and accounting for these differences could help reconcile conflicting data[66]. This highlights the need for a patient-centered protocol rather than general supplementation.

Postbiotics is the newest area of research and thus will require the most work in future studies. There is the potential to alter bacteria to produce new biological compounds. In one study using a mouse model of alcoholic liver disease, *Lactobacillus reuteri* was engineered to produce interleukin-22 (IL-22), an anti-inflammatory cytokine, after it was determined that chronic alcohol use reduces intestinal production of IL-22[69]. IL-22 has been found in previous studies to protect against atherosclerosis and CVD[70] as well as protect against beta cell stress and normalize hyperglycemia and insulin levels [71]. The increased levels of IL-22 allowed for increased expression of the regenerating islet-derived genes (REG3-gamma gene), which creates a protein that prevents bacterial translocation across the gut barrier. This reduced ethanol-induced steatohepatitis, a direct hepato-protective effect made possible by genetically altered probiotic supplementation. Through this, we have found that it is possible to manipulate commensal bacteria to fit the roles needed in the patient and can treat an enormous variety of metabolic diseases.

Meta analyses may help resolve some of the ambiguity but are not impervious to biases[58]. They may include studies that involve different strains of bacteria and thus are difficult to compare. They may also include outlier studies that skew the data and conclusions or be diluted by papers without significant findings. Therefore, efforts should be placed in developing randomized, large-scale, and high-quality experiments and clinical trials to assess the use of prebiotics, probiotics, and postbiotics to modify the gut microbiome and affect various metabolic syndromes.

CONCLUSION

The relationship between human health and the microbiome has piqued researchers' curiosity in the last decade. Our knowledge of the gut microbiome's composition and functions has considerably improved over the past several years due to rapid advancements in metagenomic sequencing techniques. As a result, it is evident that almost no area of host physiology is fully immune to the effects of gut microbes and their products. Indeed, the gut microbiota's influence extends beyond the gastrointestinal tract's traditional digestion function to include altering the physiology of other organ systems such as the liver, adipose tissue, lung, and brain. With better insight into the interactions between the host and microbiota, human gut microbiome supplementation has emerged as a promising novel therapeutic target. Current research is directed towards finding treatment options for improving the number of beneficial gut microbiota and to reduce the harmful ones with the use of prebiotics, probiotics, synbiotics, and postbiotics**.** Efforts are also underway to

identify novel gut microbiota-host interactions, their mechanisms, and associations with T2DM, CVD and to design new therapies to modulate these disease processes.

FOOTNOTES

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Case Report

SAGE Open Medical Case Reports

A case of giant prolactinoma and pituitary hemorrhage with the late recovery of pituitary function: A case report

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Lakshmi P Menon and Dinesh Edem

Abstract

Hypogonadotropic hypogonadism is a common finding in patients who are diagnosed with a prolactinoma. It can be accompanied by the presence of other pituitary hormone deficits, including secondary adrenal insufficiency and central hypothyroidism. While the proportion of improvement in endocrine deficits over the short term is well characterized, there is not enough literature about the recovery of pituitary function over the longer term. We present the case of a 23-year-old man with a giant prolactinoma who initially presented with pituitary hemorrhage and panhypopituitarism. He underwent decompression of the pituitary tumor followed by treatment with cabergoline. Over a 9-year follow-up period, we noted that the hypogonadotropic hypogonadism resolved after 4 years and the secondary adrenal insufficiency resolved after 8 years. This case suggests that partial or complete recovery of the pituitary function is possible over the long-term even in patients with a giant prolactinoma.

Keywords

Prolactinoma, pituitary hemorrhage, cabergoline, hypogonadotropic hypogonadism, adrenal insufficiency

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Introduction

Pituitary apoplexy (PA) is a rare complication of pituitary adenomas which results from hemorrhage or infarction of the tumor.[1] The presenting feature of PA is sudden onset of headache which can be accompanied by the presence of visual field impairment and oculomotor palsies. Incidental radiological appearance of pituitary hemorrhage without the associated clinical features of PA can occur, which has a prevalence of 20.3% in macroprolactinomas.[2] Cabergoline therapy has been noted to be a precipitating factor for PA in patients with prolactinoma but PA can also occur in the absence of any precipitating factors.[3] It can lead to the development of multiple pituitary hormone deficits, which are typically permanent. We report the case of a 23-year-old man with a giant prolactinoma and pituitary hemorrhage who had panhypopituitarism at diagnosis. He underwent surgical resection of the macroprolactinoma and treatment with cabergoline, hydrocortisone, and levothyroxine. Recovery of pituitary function was noted over a 9-year follow-up period.

Case presentation

A 23-year-old man with no chronic medical problems was admitted to the hospital for further investigation of a newly diagnosed sellar mass. The sellar mass was discovered when he had a CT scan of his head done at a local emergency room after he reported a 2–3-month history of progressively worsening headaches and vision loss. On examination following admission to the hospital, blood pressure was 96/69 mm Hg, pulse was 48, and body mass index was 35.44 kg/m^2. Bitemporal hemianopsia was noted. He had gynecomastia with a breast bud of approximately 9 cm bilaterally. His testicular volume was 10 mL bilaterally and his pubic hair was consistent with Tanner stage IV. Thus, puberty had been halted before completion. X-ray to assess bone was considered but was unfortunately not obtained. Laboratory evaluation revealed an elevated prolactin level of 4130.43 ng/dL (reference range: 2.64–13.13 ng/dL) (Table 1). His thyroid stimulating hormone was normal at 1.33 µIU/mL (reference

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Table 1. Serial laboratory results.

Lab test	October 2014	May 2015	October 2016	October 2017	April 2018	April 2019	August 2020	September 2022
Prolactin (2.64–13.13 ng/dL)	4130 ng/dL	290.40 ng/dL	60.76 ng/dL	22.82 ng/dL	12.68 ng/dL	8.87 ng/dL	2.09 ng/dL	0.64 ng/dL
FSH (1.27–19.26 mIU/mL)	5.06 mIU/mL	1.49 mIU/mL	3.41 mIU/mL	—	4.68 mIU/mL	—	3.64 mIU/mL	1.93 mIU/mL
Testosterone (260.0–1000.0 ng/dL)	28.9 ng/dL	15.1 ng/dL	53.6 ng/dL	69.3 ng/dL	86.6 ng/dL	166.1 ng/dL	304.1 ng/dL	269.5 ng/dL
ACTH (7–69 pg/mL)	<5 pg/mL	—	<5 pg/mL	—	<5 pg/mL	8 pg/mL	3.7 pg/mL	20 pg/mL
Cortisol (AM: 5–23 µg/dL)	0.6 µg/dL	—	—	—	—	—	3.4 µg/mL	7.2 µg/mL
TSH (0.34–5.60 µIU/mL)	1.33 µIU/mL	0.12 µIU/mL	0.12 µIU/mL	0.02 µIU/mL	<0.02 µIU/mL	<0.02 µIU/mL	<0.02 µIU/mL	7.56 µIU/mL
Free T4 (0.58–1.64 ng/dL)	0.54 ng/dL	1.35 ng/dL	1.22 ng/dL	1.29 ng/dL	1.27 ng/dL	1.44 ng/dL	1.33 ng/dL	0.55 ng/dL
IGF-1 (90–262 ng/mL)	160 ng/mL	163.2 ng/mL	—	—	302 ng/mL	320 ng/mL	281 ng/mL	199 ng/mL

FSH: follicle-stimulating hormone; ACTH: adrenocorticotropic hormone; TSH: thyroid stimulating hormone; Free T4: free thyroxine; IGF-1: insulin-like growth factor-1.
Lab results over an 8-year follow-up after the pituitary adenoma resection. There is normalization of the prolactin level, resolution of the hypogonadotropic hypogonadism, and normalization of the ACTH over serial follow-up. Persistence of central hypothyroidism is noted on the most recent labs. IGF-1 level was normal postoperatively, showed a transient rise around the time that the prolactin level normalized in April 2018, and then returned to baseline by September 2022. "—" Indicates that the data are unavailable.

range: 0.34–5.60 µIU/mL) with low free T4 of 0.54 ng/dL (reference range: 0.58–1.64 ng/dL), consistent with central hypothyroidism. His follicle-stimulating hormone was inappropriately normal at 5.06 mIU/mL (reference range: 1.27–19.26 mIU/mL) with a low LH of 0.74 mIU/mL (reference range: 1.24–8.62 mIU/mL) and low total testosterone of 28.9 (reference range: 260.0–1000.0 ng/dL). A random cortisol level was low at 0.6 µg/dL, but this was after the patient had received dexamethasone 8 mg IV. The insulin-like growth factor-1 level was in the normal range at 160 ng/mL (reference range: 155–432 ng/mL). He was diagnosed with prolactinoma and presumed panhypopituitarism. He was started on treatment with cabergoline 0.25 mg twice a week, hydrocortisone 20 mg twice a day, and levothyroxine 200 mcg daily. Magnetic resonance imaging (MRI) of the brain showed a 5.3 cm sellar mass with an upward deviation of the optic chiasm and effacement of the ventricles without obvious hydrocephalus (Figure 1). There was a fluid-fluid level consistent with hemorrhage (Figure 2). Humphrey Visual Field test by ophthalmology showed bitemporal hemianopsia with left inferior nasal quadrantanopia. He was evaluated by neurosurgery, which cleared the patient for discharge with plans for surgical resection on an urgent basis.

One week later, the patient underwent right frontal supraorbital craniotomy for drainage of the suprasellar hemorrhage and decompression of the optic chiasm. He was given hydrocortisone 100 mg IV (Intravenous) prior to the surgery and the postoperative day 1 AM cortisol was 2.1 mcg/mL (reference range: 5–23 mcg/mL). Pathology revealed a

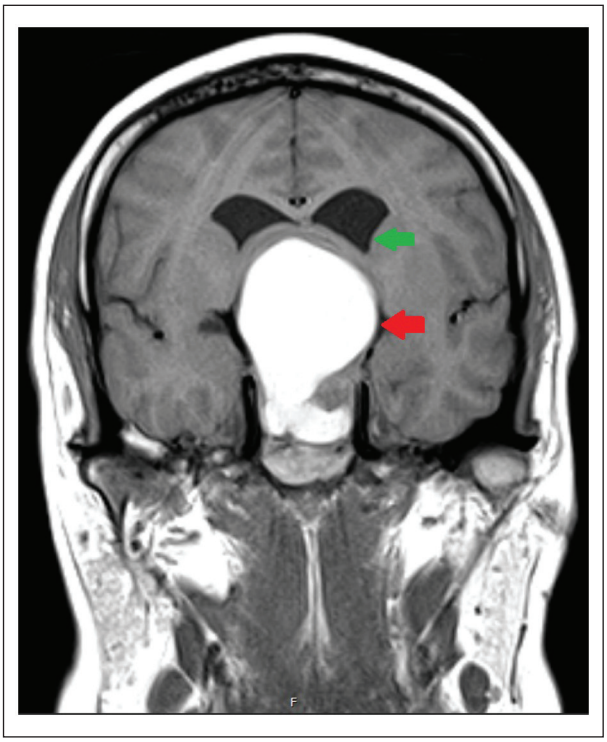

Figure 1. Preoperative MRI pituitary showed a large precontrast T1 hyperintense sellar-suprasellar cystic and solid mass lesion causing mass effect (red arrow) and upward deviation of the optic chiasm. There is effacement of the lateral ventricles without obvious hydrocephalus (green arrow).
MRI: magnetic resonance imaging.

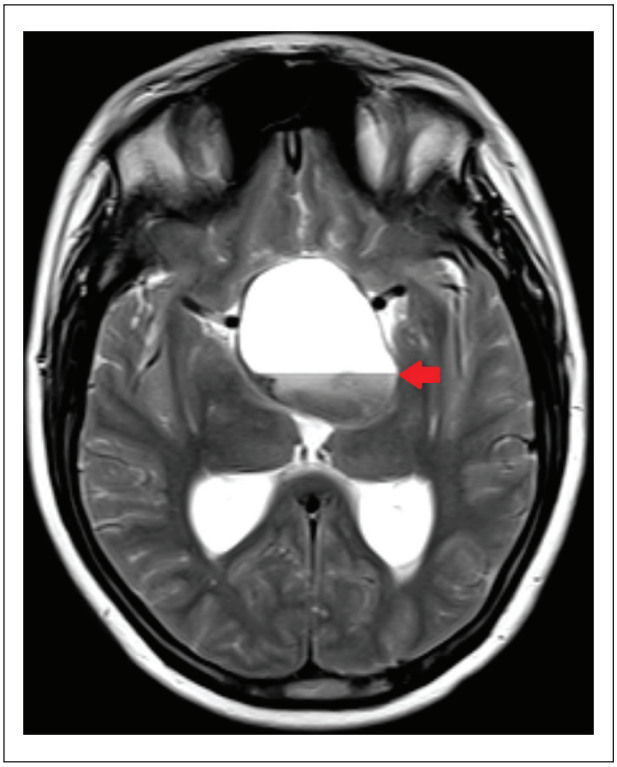

Figure 2. The cystic component of the sellar-suprasellar mass demonstrated a fluid-fluid level (red arrow) with a homogenously hyperintense material on T2, layering over a less intense dependent fluid component.

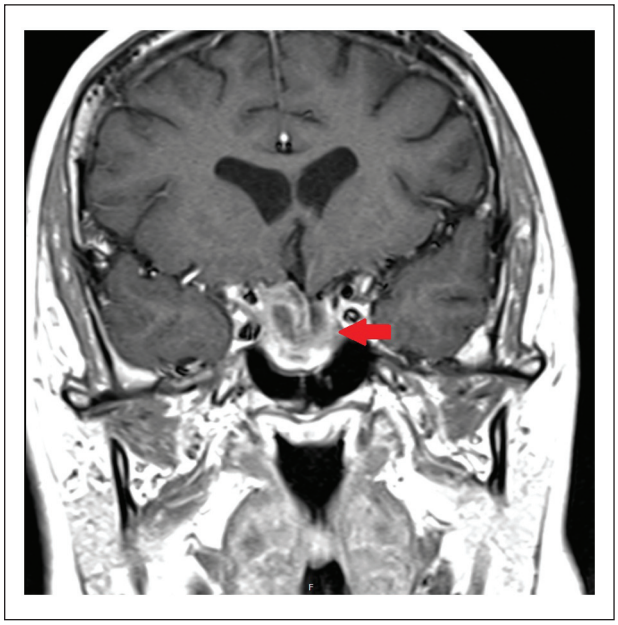

Figure 3. Residual mass lesion within the sellar and suprasellar region (red arrow). The center of the lesion is cystic, and the periphery shows nodular enhancement. The optic chiasm is elevated, and the mass lesion reaches up to the floor of the third ventricle.

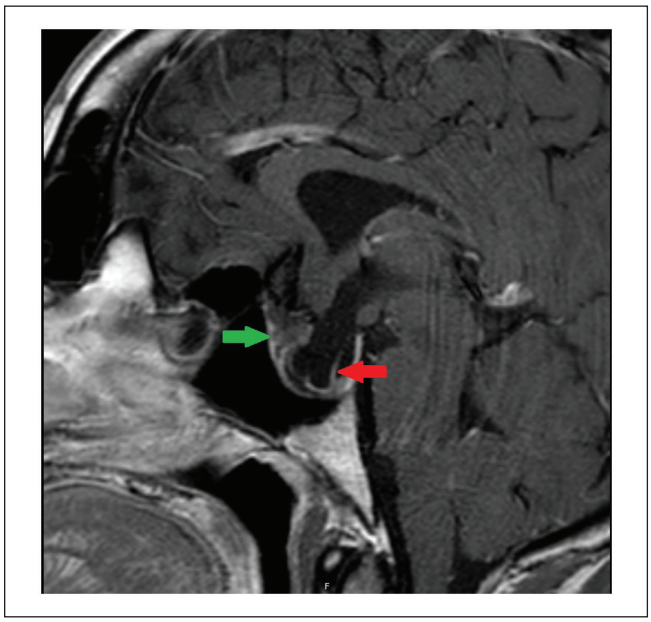

Figure 4. The sella is expanded and there is herniation of the floor of the third ventricle into the floor of the sella (red arrow). A 1 cm soft tissue is noted along the right anterior superior sella which represents the residual pituitary tissue (green arrow).

pituitary adenoma that was diffusely positive for prolactin and had an extensive hemorrhage. Scant mitotic figures were present. The gross specimen consisted of multiple fragments that measured $3.5 \times 3.0 \times 0.8$ cm in aggregate. The cabergoline, levothyroxine, and hydrocortisone were continued at their previous doses on discharge.

On his first clinic follow-up after 3 months, he was noted to have an improvement in the prolactin level to 946.60 ng/mL, and cabergoline was continued. His hydrocortisone was reduced to 15 mg in the morning and 10 mg in the afternoon to provide more physiological dosing. His levothyroxine dose was left unchanged at 200 mcg per day given that his free T4 level was 1.22 ng/dL. His total testosterone was low at 31 ng/dL. Testosterone replacement therapy was not initiated due to the anticipated improvement in testosterone levels with the control of hyperprolactinemia. The initial postoperative MRI showed a residual mass lesion within the sellar and suprasellar region that measured 2.4×1.8 cm in size and caused elevation of the optic chiasm (Figure 3). There was a significant decrease in the hemorrhage and the bilateral cavernous sinuses did not show the presence of any mass lesion. The patient did not tolerate dose escalation of the cabergoline beyond 0.5 mg two times a week due to which he was maintained on cabergoline 0.5 mg two times a week over the long-term. Annual pituitary MRIs were obtained over the next 6 years which showed resolution of the pituitary hemorrhage and stable expansion of the sella. On the MRI obtained 2.5 years post-surgery, no residual tumor was seen. The residual pituitary tissue measured 1 cm in size and was located along the right anterior superior sella (Figure 4). Annual visual field tests were obtained which

showed resolution of the left inferior nasal quadrantanopsia but he had persistent bitemporal hemianopsia.

His prolactin level normalized 3.5 years after the pituitary surgery but his testosterone level remained low at 86.6 ng/mL (Table 1). He was offered testosterone replacement therapy but refused due to the cost of the medication. His testosterone level displayed progressive improvement and he had normalization of the testosterone level 16 months after he was first noted to have a normal prolactin level. The adrenocorticotrophic hormone (ACTH) level was low at 3.7 pg/mL with concurrent cortisol of 3.4 mcg/mL which was indicative of ongoing secondary adrenal insufficiency. He displayed an increase in facial and body hair, regression of the gynecomastia, and had gained 1 inch in height. He did not consent to a repeat genital examination due to which Tanner's stage could not be reassessed.

The patient was then lost to follow-up for 2 years. He then returned to the endocrinology clinic and was noted to have discontinued his prescription medications without any apparent symptoms or signs of adrenal insufficiency. The reason for discontinuation of medications was a lack of insurance and financial difficulties. Labs showed normal prolactin level, normal testosterone, normal ACTH, and an appropriate rise of cortisol to 18 mcg/dL following a cosyntropin stimulation test (a normal response is peak cortisol of 18 mcg/dL or higher).[4] Central hypothyroidism persisted due to which levothyroxine 75 mcg daily was restarted. MRI pituitary did not reveal a recurrence of the pituitary adenoma. Cabergoline was not resumed but he continued to maintain normal prolactin and testosterone levels on serial observation.

Discussion

Our case highlights that pituitary hormone deficits that develop in patients with prolactinoma can resolve over long-term follow-up. Our patient's prolactin level normalized 3.5 years after starting cabergoline therapy followed by a resolution of hypogonadotropic hypogonadism after an additional 16 months. He was noted to have a resolution of secondary adrenal insufficiency 8 years after his pituitary surgery as evidenced by a normal ACTH level and normal cosyntropin stimulation test. Although his central hypothyroidism persisted, he displayed a reduction in his levothyroxine dose requirement from 200 mcg daily at the initial visit to 75 mcg daily at the last appointment.

Giant prolactinomas are defined as pituitary tumors more than 4 cm in diameter with significant suprasellar extension and prolactin elevation above 1000 mcg/L with no co-secretion of growth hormone or ACTH.[4] These are rare tumors, accounting for 2–3% of all prolactinomas, and display a male predominance.[5,6] Cabergoline is the first-line treatment option in these tumors and can lead to the normalization of prolactin in 60% of patients. Tumor response, defined as a $>$30% decrease in tumor diameter or $>$65% reduction in tumor volume, was seen in 74% of patients.[5] This means that a decrease in the tumor size can occur even in patients whose prolactin level does not normalize with treatment. Our patient underwent decompression of the tumor to preserve his vision. Residual pituitary tumor was left behind after surgery which responded to treatment with cabergoline.

The hormone deficiencies that result from prolactinomas include hypogonadotropic hypogonadism, central hypothyroidism, secondary adrenal insufficiency, and growth hormone deficiency. The presence of three or more pituitary hormone deficits constitutes panhypopituitarism. Pituitary hormone deficits are noted at diagnosis in around 74% of patients with giant prolactinomas.[7] The most common hormone deficit is hypogonadotropic hypogonadism, which can occur by two mechanisms. The first mechanism is the inhibitory effect of prolactin on the pulsatile secretion of follicle-stimulating hormone and luteinizing hormone, in which case the correction of hyperprolactinemia leads to the resolution of the hypogonadism.[8] The second mechanism is the destruction of gonadotroph cells by pressure atrophy from the tumor, in which case the hypogonadism is permanent. Resolution of hypogonadotropic hypogonadism following treatment with cabergoline occurred in 58–67% of men with giant prolactinomas.[7,9] Studies rarely reported the resolution of the other pituitary hormone deficits. This is in contrast to our patient who also had a resolution of secondary adrenal insufficiency.

There is no consensus on the timing of instituting testosterone therapy in patients with prolactinoma who have hypogonadotropic hypogonadism. Italian Association of Clinical Endocrinologists and the International Chapter of Clinical Endocrinology released a position statement that recommends the institution of testosterone therapy within 3–6 months of starting dopamine agonists for the treatment of hypogonadism in men with prolactinoma as long as the prolactin level is decreasing with treatment.[10] Testosterone replacement-induced hyperprolactinemia and tumor growth have been reported. The hypothesis is that the exogenous testosterone is aromatized to estradiol which stimulated the release of prolactin by the anterior pituitary.[11] This hypothesis is supported by the fact that there are case reports that show that treatment with aromatase inhibitors leads to a decrease in the prolactin level and a decrease in the tumor size.[12]

Our patient had radiological evidence of pituitary hemorrhage at the time of the initial presentation. Patients with pituitary hemorrhage may be asymptomatic, report chronic headaches or present with classical features of PA. Pituitary hormone deficits are common in PA and can occur from the destruction of anterior pituitary endocrine cells or the impaired release of pituitary hormones due to the increased intrasellar pressure exerted by the tumor. Secondary adrenal insufficiency is the most common hormone deficit in PA with an incidence of 50–80%, followed by gonadotropin deficiency at 40–75%, and thyrotropin deficiency at 30–70%.[13] One retrospective study that followed patients with PA for a mean duration of 3.7 years revealed that 79% of

patients required long-term glucocorticoid replacement compared to 50% at presentation.[14] Long-term levothyroxine requirement was 67% compared to 50% at presentation. There were no statistically significant differences in the rates of adrenal insufficiency, hypothyroidism, or hypogonadism among the patients who underwent surgery or conservative management of PA.

Our case report has some limitations. The secondary adrenal insufficiency was not confirmed at the initial diagnosis due to the recent administration of dexamethasone. However, the finding of suppressed ACTH on follow-up while the patient was taking a physiological dose of hydrocortisone supported this diagnosis. The patient continues to have central hypothyroidism, so complete recovery of pituitary function has not yet occurred. Delaying testosterone replacement may not be appropriate in patients who are severely symptomatic from hypogonadism. In addition, these findings may not be generalizable to patients who have undergone more extensive pituitary surgery and do not have residual healthy pituitary tissue left behind. Prospective studies looking into the long-term follow-up of patients with prolactinoma are necessary to assess the odds of recovery of pituitary function.

Conclusion

This case highlights the importance of periodic monitoring of pituitary labs to assess for the recovery of pituitary function in patients with panhypopituitarism as a result of hemorrhage into a prolactinoma. Correction of the hyperprolactinemia can lead to the completion of puberty and normalization of the testosterone level in patients who present with stalled puberty in the setting of a prolactinoma.

Author contributions

L.P.M. drafted the first version of the article and was part of the team that took care of the patient. D.E. participated in drafting the article and editing the final version.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Consent

Written consent was obtained from the patient for the publication of this case report.

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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Case Report

Mixed Corticomedullary Tumor of the Adrenal Gland: A Case Report and Literature Review

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Abstract: Adrenal mixed corticomedullary tumors (MCMTs) are composed of an admixture of cortical and medullary cells. Owing to the presence of two distinct components of different embryonic lineage, these tumors are extremely rare. Less than 30 tumors of this type have been reported to date. MCMTs have varied presentation including hypertension, Cushing syndrome or even as adrenal incidentalomas. Also noted is a slightly higher female preponderance. We report a case of a 26-year-old female who was evaluated for uncontrolled hypertension. A renal ultrasound followed by MRI abdomen revealed a 9.3 × 8.1 × 7.0 cm partially cystic, partially solid enhancing mass in the region of/replacing the left adrenal gland. Hormonal work-up was significant for elevated catecholamines concerning pheochromocytoma. She underwent laparoscopic left adrenalectomy, with adequate pre-operative adrenergic blockade. Histology and immunochemical testing were consistent with a mixed corticomedullary tumor. She was monitored annually for recurrence of the tumor. We also performed a comprehensive review of literature of the cases published so far to the best of our knowledge.

Keywords: mixedcorticomedullary tumor; adrenal tumor; pheochromocytoma; Cushing's syndrome

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1. Introduction

The adrenal cortex is derived from the dorsal mesentery, which is mesodermal in origin, and the medulla from cells that have migrated from the neural crest, which are ectodermal in origin [1]. Most adrenal neoplasms that arise from the adrenal glands are of a single embryonic lineage. Composite or mixed adrenal tumors are very rare, with mixed corticomedullary tumors being the rarest. Mixed corticomedullary tumors comprise a closely intermingled population of adrenal cortical cells and pheochromocytes, each showing distinct histological features of their respective neoplasms. Mixed corticomedullary tumors were first described by Mathison et al. in 1969 in a patient who presented with Cushing's syndrome and hypertensive crisis during surgery [2]. There was a pre-operative elevation of cortisol and urinary catecholamines with a histopathological exam disclosing mixed adrenal cortical and medullary cells.

We describe a distinctive case of a young woman who presented with uncontrolled hypertension and had markedly elevated urinary and plasma metanephrines. Imaging revealed a large left adrenal mass, which, following resection, revealed a mixed corticomedullary tumor on histopathological analysis.

2. Case

A 27-year-old asymptomatic woman was incidentally found to have a blood pressure of 163/114 mm Hg during a regular office visit. Repeat measurements confirmed a persistently high blood pressure at 183/129 mm Hg, which triggered treatment initially with lisinopril followed by the addition of hydrochlorothiazide by her primary care physician. Her past medical history was significant for an uneventful pregnancy four years prior to presentation. Her family history was negative for endocrine tumors or syndromes. On examination, vitals including temperature, heart rate, and respiratory rate were normal except for the elevated blood pressure; physical examination revealed no abdominal masses. Laboratory data showed leukocytosis (16,000/μL) and a normal basic metabolic panel. A renal artery ultrasound, ordered as an initial work up for secondary hypertension, showed a mass adjacent to the spleen and left kidney with an echogenic, homogeneous texture and a hypoechoic, cystic interior. The entire mass measured 9.7 cm × 7.5 cm × 7.5 cm, with the cystic portion measuring 6.2 cm × 5.8 cm × 5.5 cm. Within 2 weeks of initial presentation, the patient developed episodic dizziness, flushing, palpitations and left flank pain. Her blood pressure continued to be uncontrolled and labetalol was added. An MRI of the abdomen and pelvis revealed a 9.3 × 8.1 × 7.0 cm partially cystic, partially solid enhancing mass with T2 hyperintensity in the region of/replacing the left adrenal gland (Figure 1). Endocrinological work-up revealed strikingly elevated 24 h urine metanephrine, 631 mcg (25–222 mcg), and normetanephrine, 27,047 mcg (40–412 mcg), which was supported by high plasma metanephrine, 105 pg/mL (0–62 pg/mL), and normetanephrine, 11,987 pg/mL (0–145 pg/mL), levels. Regretfully, adrenocortical hyperfunctioning was not tested, as she had no clinical manifestations of Cushing's syndrome or hyperandrogenism. The aldosterone to renin ratio was also not measured. Her serum calcitonin levels, thyroid hormone levels and thyroid ultrasound were normal.

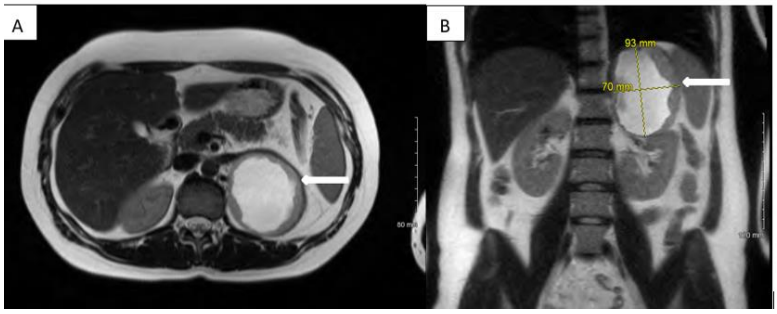


Figure 1. MRI. Axial (**A**) and coronal (**B**) T2 MRI image showing a large hyperintense mass in the region of left adrenal gland.

Taking her clinical presentation and laboratory findings into consideration, a provisional diagnosis of pheochromocytoma was made, and she was initially treated with phenoxybenzamine for adequate alpha adrenergic blockade and metoprolol was later added two days prior to surgery. A left adrenalectomy was performed laparoscopically. Histopathological examination demonstrated predominantly large epithelioid or polygonal cells with amphophilic cytoplasm and mildly atypical vesicular nuclei, focally arranged in nests, suggestive of pheochromocytes. Admixed with this were nests and cords of more uniformly rounded epithelial cells with granular eosinophilic cytoplasm and smaller, more uniform vesicular nuclei indicative of cortical adenoma cells (Figure 2). While the bulk of the lesion was diffusely stained positive for chromogranin (negative for synaptophysin) correlating with medulla [Figure 3A], the cords and strands of more eosinophilic epithelioid cells were stained positive for inhibin, MART-1 (Figure 3B) and SF-1, concurring with the cortical component of the adenoma. These findings were consistent with the diagnosis of an adrenal mixed corticomedullary tumor. The postoperative period was uneventful. A month later the patient's blood pressure normalized without any anti-hypertensive medication. Her plasma metanephrine (<10 pg/mL), normetanephrine (39 pg/mL) and chromogranin

A (<1 nmol/L) also normalized. Genetic testing was negative for VHL, RET oncogene and SDHB gene mutations. Other genes were not tested because of lack of insurance approval. Five months post-surgery, she had a recurrence of symptoms with headaches, visual changes and occasional palpitations for a week. Repeat plasma normetanephrine was slightly elevated (274 pg/mL) but plasma metanephrine (25 pg/mL) and chromogranin A (2 nmol/L) were normal. CT of the chest, abdomen and pelvis, however, showed no significant residual tumor. A PET scan and MIBG scan was considered, keeping the possibility of an additional extra-adrenal tumor in mind but could not be performed because of lack of insurance approval. Her symptoms gradually resolved. As the patient was not on any medications/herbs/supplements that can lead to false-positive results, we attributed the mild elevation of normetanephrine to a laboratory error. Continued surveillance revealed normal metanephrine and chromogranin levels. The patient conceived a year later and had an uneventful pregnancy and delivery. She remains asymptomatic and has normal serum metanephrine levels 2½ years after her initial surgery.

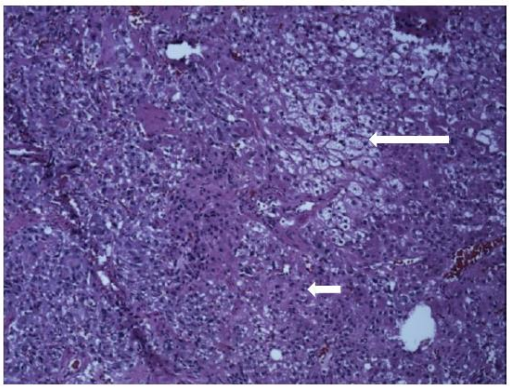
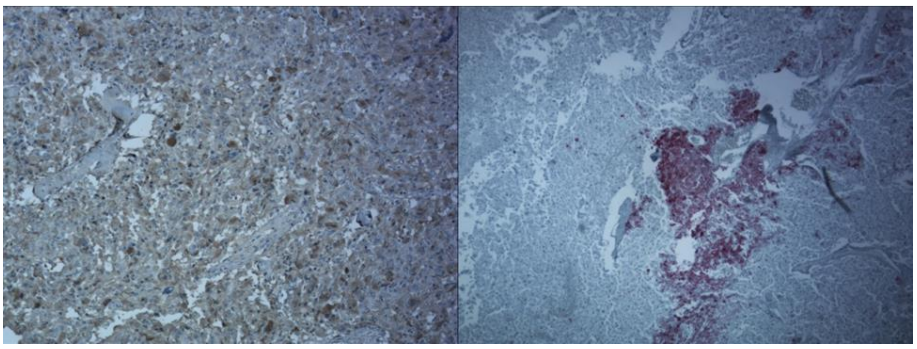


Figure 2. Histology.



(**A**) (**B**)

Figure 3. Chromogranin staining.

3. Discussion

As the two components of the adrenal gland have different embryological origins, it is not surprising that mixed corticomedullary tumors are rare. A total of twenty eight patients with adrenal mixed corticomedullary tumors have been described [2–24]. Of these, only three had malignant mixed corticomedullary tumors [16,23,24] and one [16] among those succumbed rapidly to their disease. With that exception, the prognosis of mixed corticomedullary tumors appears to be good [5,16].

The pathogenesis of mixed corticomedullary tumors is poorly understood. Several hypotheses have been proposed. One of these known as the 'collision theory,' proposed a separate embryological origin of the two components of the tumor, with the cortical cells arising from the mesoderm and the pheochromocytes from the neural crest and then fusing to form the tumor [5,16]. Another theory suggested that a mutation in the intra-adrenal

portal system leads to proliferation of adrenocortical cells with excessive secretion of cortisol, which eventually stimulates the hyperplasia of pheochromocytes [9]. Additionally, it has been proposed that genetic mutations in stem cells can lead to these tumors [18]. Excess secretion of cortisol from cortical tumors has been thought to induce a rate limiting enzyme in catecholamine synthesis which in turn mediates medullary hyperplasia [18]. Finally, the disruption of normal cortico–chromaffin cell interactions by unknown mechanisms could result in a trophic stimulation of both cell lineages [13]. It is interesting to note that the genes involved in tumor formation of the adrenal medullary cells have a minimal or no role in the formation of adrenal cortical tumors [13]. Genetic mutations are common in pheochromocytoma paraganglioma syndromes [25] and more so in young subjects with a positive family history, large extra-adrenal tumors and those with multiple tumors. Pheochromocytoma paraganglioma syndromes are categorized into three clusters based on genetic mutations and pathogenic pathways. Cluster 1 includes mutations in the overexpression of vascular endothelial growth factor gene (VEGF). Cluster 2 includes activating mutations of the WNT signaling pathway. Cluster 3 includes abnormal mutations of the tyrosine kinase pathway. Similarly, there are three biochemical phenotypes—Dopaminergic, noradrenergic, and adrenergic phenotypes—which are defined through significant productions of, respectively, 3-methoxytyramine, normetanephrine, and metanephrine relative to the combined production of all three metabolites. Our patient had a predominantly noradrenergic secreting adrenal tumor which typically occurs with genetic mutations of Von Hippel-Lindau (VHL), succinate dehydrogenase iron sulfur subunit B (SDHB), succinate dehydrogenase complex flavoprotein subunit A (SDHA), succinate dehydrogenase complex subunit C integral membrane protein 15 kDa (SDHC), succinate dehydrogenase complex subunit D integral membrane protein (SDHD) and Fumarate hydratase (FH) genes. Genetic mutations involved in adrenergic secreting adrenal tumors include rearranged during transfection (RET), transmembrane protein 127 (TMEM 127) and myc-associated factor X (MAX) genes. Genetic mutations involved in dopaminergic secreting adrenal tumors include succinate dehydrogenase complex subunit D integral membrane protein (SDHD), succinate dehydrogenase iron sulfur subunit B (SDHB) and succinate dehydrogenase complex subunit C integral membrane protein 15 kDa (SDHC). The biochemical distinction could be due to promoter hypermethylation of the Phenylethanolamine N-methyl Transferase (PNMT) gene which converts norepinephrine to epinephrine. Due to lack of insurance approval, complete genetic testing could not be performed in this patient. Noradrenergic tumors (those predominantly releasing norepinephrine) usually are described as having more continuous symptoms as the secretory pathways are less mature compared to those releasing epinephrine. Thus, noradrenergic tumors often continuously release norepinephrine while adrenergic (epinephrine predominant) tumors more often release epinephrine in paroxysms. Clinical presentations of mixed corticomedullary tumors have varied from subclinical to florid Cushing's syndrome [3,9,13,17,19,20,22], hypertension [2,3,9,10,13,19–21,23,24,26] and diabetes [2,3,13,21] to psychic irritability [3,19] and weight loss [2,3,23]. There is clearly a female preponderance, as is illustrated in Table 1. A total of 74% of the patients presented with hypertension while 39% had Cushing's syndrome. Our patient developed typical paroxysmal symptoms and uncontrolled hypertension, suggestive of pheochromocytoma. Preoperative treatment to control hypertension is extremely essential due to the high risk of intra-operative hypertensive crisis and malignant arrhythmias. Multiple methods were implemented to achieve pre-operative control of blood pressure with the most widely practiced method being initial alpha-blockade at least 10 to 14 days before surgery and beta blockers added on at least 3 to 4 days after adequate alpha blockade. Some centers use calcium channel blockers as an add on to alpha blockade, while very few centers use metyrosine which inhibits catecholamine synthesis by blocking the enzyme tyrosine hydroxylase. Post-operative biochemical surveillance using the same laboratory tests that were obtained pre-operatively is recommended to confirm a surgical cure of the catecholamine-producing tumor. The risk of recurrent disease following resection of a benign pheochromocytoma or paraganglioma is around 15% [27]. Recurrent disease has not been reported among

patients who present with a benign mixed corticomedullary tumor. We have included a review of the literature published so far to the best of our knowledge and availability in Table 1. Given the varied presentation of mixed corticomedullary tumors, a complete work up of adrenal incidentaloma with measurement of both cortical and medullary hormones is recommended to prevent missing a diagnosis of subclinical Cushing's syndrome, pheochromocytoma or primary aldosteronism.

Table 1. Review. This table includes a comprehensive review of literature published on various presentations of mixed corticomedullary tumors.

Year	Age	Gender	Presenting Symptoms	Tumor Size (cm)	Cystic Component	Hormones
1969 [2]	39	F	Intraoperative hypertensive crisis, Cushing's syndrome	4	N/R	Cortisol, catecholamines (both nor-met and met)
1993 [3]	61	F	Hypertension, hyperglycemia	3.5	N/A	Cortisol, catecholamines (nor-met predominant)
1995 [28]	32	M	Cushing's syndrome	4.5	N/A	Cortisol
1996 [4]	56	F	Cushing's syndrome, paroxysmal hypertension	8	No	Cortisol, aldosterone, catecholamines (epinephrine predominant)
1996 [4]	32	F	Cushing's syndrome, Paroxysmal hypertension	9	No	Cortisol, aldosterone, catecholamines (epinephrine predominant)
2001 [5]	34	F	Hypertension, hair loss and amenorrhea	4.5	No	Cortisol
2001 [5]	52	F	Flank pain	2.5	No	None
2002 [6]	N/A	N/A	Hypertension	N/A	N/A	Catecholamines
2002 [6]	N/A	N/A	hypertension	N/A	N/A	Aldosterone
2002 [6]	N/A	N/A	hypertension	N/A	N/A	Aldosterone
2002 [6]	N/A	N/A	hypertension	N/A	N/A	Aldosterone
2003 [7]	55	F	Mild Cushing's syndrome and hyperglycemia	2.5	No	Cortisol
2007 [8]	41	F	Cushing's syndrome, intra-operative hypertension	4	No	Cortisol (catecholamines not tested)
2008 [9]	25	F	Gestational diabetes, paroxysmal hypertension, Cushing's syndrome	3.2	No	Cortisol, catecholamines (Nor-met predmoninant)
2009 [10]	54	F	Mild hypertension, diabetes	4.9	No	Cortisol, Catecholamines (Nor-met predominant)
2009 [11]	66	F	Subclinical Cushing's syndrome	4.2	Yes	Cortisol

Table 1. *Cont.*

Year	Age	Gender	Presenting Symptoms	Tumor Size (cm)	Cystic Component	Hormones
2010 [12]	48	F	Abdominal distension, pedal edema, breathlessness	8	No	Catecholamines (Urinary VMA)
2011 [13]	64	F	hypertension	3.6	No	Catecholamines (metanephrines)
2012 [14]	78	F	Hypertensive urgency	10	No	Catecholamines (dopamine)
2013 [15]	53	M	Incidental finding of left adrenal mass	5.5	No	Cortisol and catecholamines (NSE and chromogranin A)
2013 [16]	63	M	Right upper quadrant palpable mass	8	No	Cortisol
2016 [17]	48	M	Cushing's syndrome, hypertension	3.9	No	Cortisol, catecholamines (metanephrine)
2017 [18]	58	M	Fluctuant blood glucose levels, paroxysmal hypertension	3	No	Cortisol, Catecholamines (Urinary VMA)
2020 [19]	31	F	Gestational hypertension, psychiatric disturbances persistent to postpartum	3.8	No	Cortisol, Catecholamines (Normetanephrine predominant)
2022 [20]	52	F	Palpitations, weight gain, anxiety	4.1	No	Cortisol, Catecholamines (both met and nor-met)

4. Conclusions

1. This case illustrates a rare case of mixed corticomedullary tumor of the adrenal gland that are composed of an admixture of cortical and medullary cells.
2. Owing to the presence of two distinct components of different embryonic lineage, these tumors are extremely rare. Less than 30 tumors of this type have been reported to date.
3. Patients may present with Cushing's syndrome, hypertension or non-specific symptoms like weight loss.
4. A high degree of suspicion is required to avoid a hypertensive crisis during surgery. For this reason, clinicians should be aware of this entity.

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Ectopic Adrenocorticotropic Hormone-Producing Metastatic Gastrinoma: A Case Report

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Abstract

Pancreatic neuroendocrine tumors secreting gastrin and adrenocorticotropic hormone (ACTH) are rare. The presentation of the cases can be varied, making the diagnosis challenging and often delayed. Here, we present a patient who presented with severe hypokalemia and was found to have ectopic Cushing's syndrome. An abdominal CT scan showed a pancreatic lesion with metastatic liver disease. A biopsy of the liver lesion confirmed a metastatic neuroendocrine tumor. The final diagnosis was ectopic ACTH-producing metastatic gastrinoma. Twenty-four-hour urinary cortisol was significantly elevated at 9,790 mcg/24 hours. The excess hormonal secretion was successfully treated with ketoconazole and somatostatin analogs. She was further started on chemotherapy with capecitabine plus temozolomide, which has become the preferred chemotherapy treatment after the results of the recently completed trial. She also received Y90 therapy for metastatic liver disease. The prognosis of metastatic pancreatic neuroendocrine tumors is poor. Multidisciplinary combined therapies can help control disease and improve prognosis. We present an 18-month-long patient follow-up and a literature review of ectopic ACTH-producing metastatic gastrinomas.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Oncology
Keywords: somatostatin analogs, capecitabine and temozolomide, ketoconazole, pancreatic neuroendocrine tumor, ectopic cushing syndrome, metastatic gastrinoma, gastrinoma

Introduction

Neuroendocrine neoplasms (NENs) are rare neoplasms arising from neuroendocrine cells. Gastrinomas, secreting gastrin, are one of the most common functional pancreatic neuroendocrine tumors (pNETs) [1]. If not diagnosed early, it can lead to advanced disease and poor prognosis in many cases. The secretion of gastrin and adrenocorticotropic hormone (ACTH) by a neuroendocrine tumor is relatively rare. The incidence of Cushing syndrome (CS) affects less than 1% of patients with Zollinger-Ellison syndrome (ZES) [2]. Its clinical presentation varies and tends to be misdiagnosed. Liver metastasis and ACTH production in gastrinomas are associated with a worse prognosis [3]. Treatment is multidisciplinary and aimed at decreasing hormonal secretion and controlling tumor growth. Experience with systemic chemotherapy for metastatic gastrinoma with/without ACTH production is limited. We present a case of ectopic ACTH production from a metastatic gastrinoma with an 18-month-long treatment course. We discuss the challenges for early diagnosis, management of hormonal over-secretion, and tumor growth management. We will also provide a literature review on ectopic ACTH-producing metastatic gastrinomas.

Case Presentation

A pleasant 61-year-old female initially presented to her primary care physician (PCP) with symptoms of fatigue and generalized swelling. She was doing well at her last PCP visit, about five months ago, which was a routine annual visit. Over the last three to four months, she noted worsening symptoms of fatigue, generalized swelling, 6-7 lb weight gain, weakness, lately struggling to walk up two flights of stairs, and mild worsening of her acid reflux symptoms. She has a past medical history of hypertension, treated with hydrochlorothiazide and gastroesophageal reflux disease (GERD), diagnosed about five years ago. She was initially started on H2 blocker, famotidine 40 mg bid for GERD, and later switched to proton pump inhibitor (PPI), omeprazole 20 mg daily.

Her examination on presentation showed 2+ lower extremity edema. She had a chemistry panel done and was referred to cardiology for edema and decreased exercise tolerance. Helicobacter pylori testing was ordered given her worsening acid reflux symptoms despite the use of a PPI. Initial lab work revealed hypokalemia 2.7 mmol/L (3.6-5.2 mmol/L), random blood sugar 224 mg/dl, and elevated ALT 79 U/L (7-56 U/L). Her PCP recommended starting potassium chloride 20 mEq bid and ordered HbA1c, liver ultrasound, and hepatitis panel. HbA1c was elevated at 7.3%, repeated potassium level was 2.6 mmol/L, and the right upper quadrant ultrasound revealed several lesions in the liver suspicious for metastatic disease.

She was admitted to the hospital for severe hypokalemia and a liver biopsy. On admission, her potassium

level was 1.9 m/L. She was aggressively treated for hypokalemia with potassium replacement (required more than 200 mEq of potassium supplementation daily, amiloride, and spironolactone). With severe hypokalemia and clinical presentation of generalized edema, CS was considered one of the differentials. Labs showed significantly elevated cortisol at 126.1 mcg/dl (2.3-19.4 mcg/dl), ACTH was elevated at 272 pg/ml (7.2-63.3 pg/ml), and non-suppressed dehydroepiandrosterone sulfate (DHEAS) at 113 mcg/dl (29.4-220.5 mcg/dl). Diagnosis of ACTH-dependent CS was made. She had an abdominal CT, which revealed multiple hepatic lesions suggesting primary hepatocellular carcinoma versus hepatic metastases. Additionally, a 9-mm pancreatic nodule within the distal pancreatic tail was noted (Figure *1*).

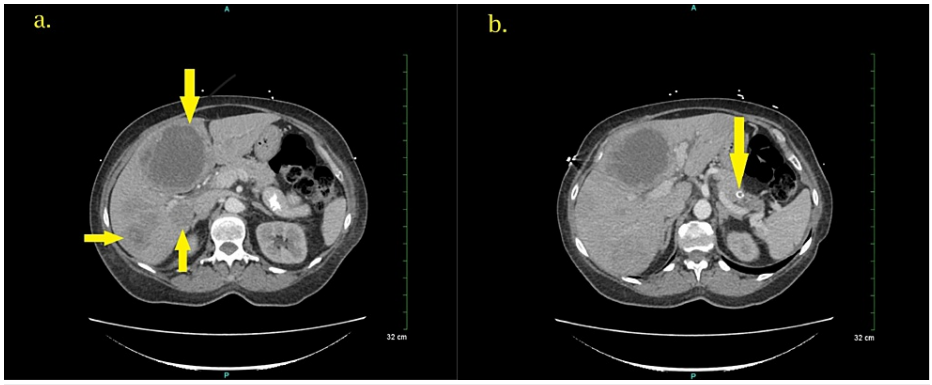

FIGURE 1: CT scan images of the abdomen with contrast: Multiple hepatic lesions measuring up to 8.2 cm are seen in the image on the left (a), and a 9 mm nodule is identified in the pancreatic tail with a rim seen in the image on the right (b).

She underwent a biopsy of the liver nodule, which was positive for a neuroendocrine tumor. Given the staining with CDX2 and the lack of reactivity with TTF-1, the site of origin was most likely the GI tract. The final pathology diagnosis was malignant NET, grade 2, Ki-67 10.05% positive. With the lesion in the pancreas and liver biopsy positive for neuroendocrine tumor, a diagnosis of pNET with liver metastasis was made. She had a pituitary-dedicated brain MRI, which showed a normal pituitary and no other significant abnormal findings. On further questioning, she also mentioned that she had diarrhea, which had improved after starting acid reflux medication. Additional labs revealed that the fasting gastrin level was significantly elevated at 1,065 pg/ml (<100 pg/ml), elevated chromogranin A at 1,149 ng/ml (<311 ng/ml), pancreatic polypeptide of 126 pg/ml (56-480 pg/ml), VIP 50 of pg/ml (<78 pg/ml), insulin of 5.1 uIU/mL (<19.6 uIU/ml), prolactin of 14.7 ng/ml (<25 mg/ml), PTH of 34 pg/ml (10-65 pg/ml), and serum calcium within normal limits. Additionally, 24-hour urinary cortisol was significantly elevated at 9,790 mcg/24 hours (4-45 mcg/24 hours).

The concern was her significant hypercortisolemia and the need to rapidly control it to reduce morbidity/mortality. Metyrapone and mitotane were unavailable in the hospital pharmacy and would have needed more time to procure. She was started on ketoconazole at a high dose of 400 mg orally, three times a day. Liver function tests were closely monitored, and they remained stable. She was also started on octreotide 150 mcg subcutaneously, three times daily. Surgery was consulted for the potential need for bilateral adrenalectomy if medical therapy was not adequate or not tolerated. Cortisol level at the time of diagnosis was 126.1 mcg/dl; after starting ketoconazole and octreotide, cortisol level on day one was 89.1 mcg/dl, on day two was 61.5 mcg/dl, on day three was 53.5 mcg/dl, on day four was 30.2 mcg/dl, and on day five was 18.1 mcg/dl. She responded well with decreasing cortisol levels and decreased requirements of potassium supplements. She initially required close to 200 mEq/day of potassium chloride; however, at the time of discharge, she did not need any potassium supplements and was off spironolactone and amiloride, and her cortisol level was less than 20. She had a new onset of diabetes contributed by significant hypercortisolemia; she was initially treated with insulin to control her blood sugar levels and was discharged on low-dose basal and prandial insulin. At the time of discharge from the hospital, she was symptomatically better.

In the outpatient setting, she is being followed by endocrinology and oncology. She continues on ketoconazole; the dose has been titrated to maintain eucortisolemia, and the latest dose is 100 mg, two times a day. Octreotide was discontinued, and she was started on once-a-month lanreotide. She was started on capecitabine and temozolomide chemotherapy. HbA1c level decreased from 7.8% initially using insulin therapy to 5.5% in six months; insulin was subsequently discontinued, and she is currently taking metformin 500 mg XR twice daily. Her blood sugar continues to be well controlled. Her generalized edema and other symptoms have subsided. Her genetic testing for multiple endocrine neoplasia type 1 (MEN 1) was negative. Her initial gastrin level, which was significantly elevated at 1,065 pg/ml (<100), decreased to 280

pg/mL in six months. Serum ACTH and cortisol levels have been in the normal range. Her latest ACTH was 30 pg/ml, AM cortisol was 10.2 mcg/dl, and DHEAS was 10 mcg/dl. Further, 24-hour urinary cortisol, which initially was 9,790 mcg/24 hours, decreased to 13.9 mcg/24 hours in six months.

She also received Y90 treatment (image-guided hepatic arterial radioembolization). She continues on PPIs, ketoconazole, lanreotide, and chemotherapy. Her latest repeat imaging at her oncology office showed a decrease/stability in the hepatic lesion size for most lesions. She has been stable for nearly 18 months without serious complications.

Discussion

Neuroendocrine neoplasms (NENs) are rare. They arise from neuroendocrine cells and include both benign and malignant tumors. Gastroenteropancreatic NENs are NENs found in the gastrointestinal system and can be well-differentiated neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs). The pNETs that produce hormones (insulin, gastrin, ACTH, CRH, growth hormone, parathyroid hormone, and calcitonin) are called functional NETs. They also produce other vasoactive substances such as chromogranin A, pancreastatin, and pancreatic polypeptide.

Gastrinomas, which secrete gastrin and cause ZES, are one of the most common functional pNETs. Specifically, 20-60% of gastrinomas arise in the pancreas, and 60-90% are malignant [1]. The annual incidence of gastrinomas is 0.5-21.5 per million population [4]. Additionally, 13-53% (mean 34%) of pancreatic gastrinomas have metastasized to the liver at the time of diagnosis, which is one of the determinants of long-term survival and hence has a worse prognosis [1]. In our patient, the tumor had metastasized to the liver at the time of diagnosis.

The diagnosis of ZES can be challenging, and there could be a lag of a few years from the onset of symptoms until the diagnosis of gastrinoma is made. The average time from onset of symptoms to diagnosis of gastrinoma is about six years [5]. One of the reasons is that the symptoms (peptic ulcer disease, heartburn, diarrhea, weight loss, and acid hypersecretion complications such as bleeding, stricture, and perforation) can be nonspecific and masked by PPI use, which is likely what happened in our patient. She had symptoms of acid reflux and diarrhea about five years ago and was initially treated with H2 blockers and later switched to PPI with an improvement of her symptoms. The diagnosis of gastrinoma only came about after the workup detected the consequences of ectopic ACTH hypersecretion.

Moreover, 20-25% of gastrinomas are associated with MEN 1 [4]. MEN 1 testing should be considered, especially in individuals with a family history of MEN 1, young adults, suspicious clinical or laboratory findings (e.g., renal colic or nephrolithiasis, history of hypercalcemia, elevated prolactin), or multiple MEN1 tumor types (parathyroid gland, anterior pituitary, and enteropancreatic). In our patient, MEN 1 genetic testing was negative.

Ectopic ACTH production by an islet cell tumor of the pancreas is a relatively rare cause of hypercortisolism, accounting for less than 1% of all patients with CS [6]. The excess cortisol production in these patients results in high morbidity and mortality seen. Achieving control of excessive cortisol secretion is crucial in the management of patients. Diagnosis may be challenging as, with the relatively short duration of exposure to a high level of cortisol secondary to ACTH-dependent CS from an ectopic source, patients may not develop all the clinical features of cortisol excess. In the series of 90 patients from NIH with ectopic ACTH secretion, 74% of patients were hypokalemic [7]. The presentation can be varied, such as weight gain and loss, menstrual irregularities, fractures, cognitive and psychiatric disorders, hypertension, elevated blood sugars, infections, weakness, and bruising. Physicians of many specialties often evaluated these patients before the clinical diagnosis was entertained. Once considered, urinary free cortisols (UFCs) were more than 10 times the upper end of normal in more than half of the patients [7]. Our patient presented with severe hypokalemia, weight gain, weakness, and new-onset diabetes. Her UFC was 9,790 mcg/24 hours, significantly elevated.

The secretion of gastrin and ACTH by a NET is relatively rare. The incidence of CS affects less than 1% of patients with ZES [2]. Its clinical presentation varies and tends to be misdiagnosed. In terms of presentation, the simultaneous occurrence of ZES and CS is usually not seen. ZES preceding CS has been reported in multiple cases. Maragliano et al. reported that, in 71% of the gastrin and ACTH-secreting pNETs, the symptoms of gastrinoma preceded those of ectopic ACTH production on an average of 33 months [8]. With the progression of the disease/liver metastasis, it is likely that some transformation in the histopathological and endocrinological nature of the pancreatic islet tumor cells occurs, and neoplastic cells acquire the ability to secrete ACTH [8]. In our patient, the symptoms of CS appeared much later than her initial symptoms of GERD and diarrhea. ACTH production is likely a sign of gastrinomas becoming malignant/metastatic, thus making a strong case for considering surgical therapy in gastrinomas that may otherwise appear to be benign. This makes it important to screen early for CS in ZES patients for early detection of this aggressive disease.

The treatment goals of patients with the secretion of gastrin and ACTH include 1) rapid control of ectopic

ACTH production/adrenal cortisol over secretion; 2) treatment of the consequences of hormonal excess such as hypokalemia, high blood sugars, and acid hypersecretion; and 3) management of the tumor/metastasis secreting gastrin and ACTH.

In patients with ZES, even in the absence of tumor progression, CS can be fatal due to complications of hypercortisolemia [9]. Promptly controlling excess ACTH/cortisol production is crucial in managing the patients. If the source of ACTH overproduction is uncertain or inoperable, rescue treatment with medications or bilateral adrenalectomy is needed. The optimal therapy for the ectopic ACTH syndrome is surgical excision of the tumor, which may not be possible in metastatic tumors [7]. For patients with nonresectable tumors, hypercortisolism can be controlled with adrenal enzyme inhibitors, such as ketoconazole, metyrapone, and etomidate, and can be continued for a prolonged period. Of the 90 patients with ectopic ACTH secretion in the NIH series, 62 received medical therapy, and 20 received ketoconazole alone [7]. There was a report that the somatostatin analog effectively reduced ACTH levels in an ectopic ACTH-secreting patient [10]. Pharmacological treatment with ketoconazole and somatostatin analog, octreotide, was promptly initiated in our patient. Metyrapone or mitotane was unavailable at the pharmacy. Surgery was consulted for bilateral adrenalectomy if the cortisol levels did not rapidly improve with medical therapy. The patient responded well to ketoconazole, and reduction of the cortisol level was achieved in a short period, and it has persisted for more than a year follow-up course. The dose of ketoconazole was titrated to maintain cortisol levels in a normal range.

In gastrinoma, medical and surgical approaches are usually complementary. For most patients with ZES associated with MEN 1, medical therapy is the preferred treatment. Surgical intervention for patients with sporadic tumors without evidence of metastasis can be considered, which can reduce the risk of eventual morbidity and risk of metastatic spread of the tumor [1]. Medical management with PPIs controls hydrochloric acid hypersecretion, thus relieving symptoms and preventing complications. When PPIs cannot control gastric acid secretion, somatostatin analogs such as octreotide and lanreotide can inhibit the secretion of gastrin and cause apoptosis induction and tumor growth suppression [11-13]. Our patient was on PPI for a few years and continued it. During hospitalization, she initially received octreotide and later switched to once-a-month lanreotide (20 mg/month) to decrease ectopic hormone production and stabilize tumor cell growth.

Experience with systemic chemotherapy for metastatic gastrinoma with/without ACTH production is limited. In a recent randomized trial in pNETs, capecitabine plus temozolomide, compared with temozolomide alone, resulted in similar response rates in both groups (approximately 30%). However, the median progression-free survival was longer in the combination arm (22.7 months vs. 14.4 months, hazard ratio (HR)=0.58, p=0.023) [14]. For the capecitabine plus temozolomide group, the median overall survival was 58.7 months compared to 53.8 months for temozolomide alone (HR=0.82, p=0.42). In randomized controlled trials for pNETs, the combination therapy response rate and median progress-free survival rate are the highest reported so far [14]. Based on the trial, in advanced pNETs, capecitabine plus temozolomide chemotherapy, is the preferred regimen. Our patient is followed by the oncology team and is on the combination chemotherapy of capecitabine and temozolomide.

For metastatic disease, liver-directed therapy includes resection, radiofrequency ablation, hepatic artery embolization, cryoablation, and liver transplantation. Radioembolization with selective internal radiation therapy using Yttrium microspheres is also used, although prospective studies are yet to be completed comparing one type of embolization with another [15]. Our patient underwent Y90 therapy.

The prognosis of patients with ZES and ectopic ACTH production is poor [3]. Liver metastasis and ACTH production in gastrinomas are associated with a worse prognosis [1,3]. In one of the largest gastrinoma series of about 212 patients from NIH, Yu et al. reported that the survival rate in gastrinoma patients after ectopic ACTH secretion diagnosis averages 1.7 years [3]. In our patient, with the treatment she received so far, we did not observe disease progression after more than 18 months since the onset of CS. Mortality related to gastrinoma mostly depends upon the benign vs. malignant nature of the tumor and on the extent of the disease involvement. As earlier discussed, in patients with ZES, even in the absence of tumor progression, CS can be fatal due to complications of hypercortisolemia [9]. For pNETs, routine use of chromogranin A for diagnosis, post-treatment surveillance, or assessing therapy response is not recommended due to limited sensitivity and specificity [16].

For patients with pNETs, G1 and G2 stage with distant organ metastasis, the median survival time was 33 months, while that of G3 stage disease patients was only five months [17]. Our patient had a G2-stage tumor. The risk of recurrence could be higher in specific subgroups of patients. Patients with tumors having a Ki-67 proliferative index greater than 5%, at least in the initial period after surgery, may need more frequent surveillance. In patients with a Ki-67 proliferative index greater than 5%, as seen in our patient, Commonwealth Neuroendocrine Tumor Research Collaborative guidelines for surveillance suggest imaging frequency to be every six to 12 months for the first three years and then every one to two years for at least 10 years [18].

Conclusions

Evaluating patients for CS should be considered when presenting with new onset or poorly controlled diabetes, weakness, and hypokalemia, even in the absence of typical stigmata. Control of excess cortisol is crucial in managing ectopic ACTH-secreting malignant tumors and can be achieved either by medications or bilateral adrenalectomy. Gastrinomas can be difficult to diagnose due to nonspecific symptoms, but early diagnosis can potentially reduce further comorbidities and improve prognosis. Somatostatin analogs can reduce hormonal secretion as well as tumor control. Capecitabine and temozolomide combination chemotherapy is the preferred regimen for malignant NETs. Treatment for patients with metastatic NETs will have to be individualized. With combination therapy of steroidogenesis inhibitors, somatostatin analogs, chemotherapy, and hepatic radioembolization, our patient remains stable at 18 months follow-up.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Shrikant Tamhane, Lakshmi P. Menon, Dinesh Edem

Acquisition, analysis, or interpretation of data: Shrikant Tamhane, Lakshmi P. Menon, Dinesh Edem, Pranjali Sharma, Jhansi Maradana

Drafting of the manuscript: Shrikant Tamhane

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Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. University of Arkansas for Medical Sciences issued approval NA. Our institution does not require IRB or ethics committee approval for case reports. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Factors Associated with Online Patient Portal Utilization Experience in an Arkansas Phone Survey

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Abstract

Introduction: *Accessing electronic health record information through a patient portal is associated with numerous benefits to both health care providers and patients. However, patient portal utilization remains low. Little is known about the factors associated with patient portal utilization following the onset of the COVID-19 pandemic.*

Methods: *In March 2022, we conducted a random digit dial phone survey of both cell phones and landlines of adults living in Arkansas that asked numerous demographic and health-related measures, including patient portal utilization in the past 12 months. A total of 2,201 adult Arkansans completed the survey between March 1 and March 28, 2022. Weighted estimates were generated using rank ratio estimation to approximate the 2019 American Community Survey 1-year Arkansas estimates for race/ethnicity (72% White, 15% Black/African American, 7.8% Hispanic, 4.9% other race/ethnicity), age (73% 18–39, 32% 40–59, and 31% 60+), and gender (49% male, 51% female). We fit the data to a logistic regression model.*

Results: *We found that education, employment, prior telehealth experience, having a check-up in the past 2 years, and having a primary care provider were all positively associated with patient portal utilization. We also found that non-Hispanic Black/African-American respondents were less likely to access a patient portal relative to non-Hispanic White respondents.*

Discussion: *Patient portal utilization is related to several demographic and health-related factors among an adult population in Arkansas. Given that the documented benefits of patient portal utilization are broad, under-utilization by groups that already experience relatively worse health outcomes could reproduce or even exacerbate existing health disparities. Additional research is needed to further investigate what barriers to patient portal utilization remain for these populations.*

Keywords: *telehealth*, *telemedicine*, *EHR*, *patient portal*, *survey*

Introduction

An electronic health record (EHR) is the electronic compilation of a patient's medical information, including all patient-provider interactions, immunizations, and laboratory tests, accessible to both patients and providers through a patient portal. The patient portal provides a secure platform for information in the EHR to be shared between patients and providers.[1]

EHR and patient portals provide all parties involved in patient care with the most updated and accurate information. EHR has become especially important in the United States (U.S.), as many patients seek the care of multiple physicians due to comorbidities.[2] Be it routine clinic visits, surgeries, or

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emergency or urgent care visits, EHR provides up-to-date and immediate patient medical information.[1,2]

The implementation of EHR has resulted in efficient and well-informed clinical decisions, reduced medical errors, decreased costs due to reduced repeated testing and efficient billing, and overall improved patient satisfaction and health outcomes.[3–5] A recent systematic review documented numerous benefits to patient portal utilization, including improved patient outcomes, medication adherence, perceived relationship with the provider, and patient engagement.[6] Although providers may play a role in the EHR-associated patient benefits, these benefits are also largely dependent on patient utilization of EHR information through a patient portal.

Patient portal utilization has been low despite implementation efforts such as the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009,[7] with estimates ranging between 27% and 37% of all patients having accessed their EHR information through a patient portal in the past year.[8–10] However, an increasing number of patients have started to access their health information online, as evidenced by a 5.8% increase in patient portal utilization in the U.S. between 2014 and 2018.[11,12]

Yet, patient portal utilization has been unevenly adopted across demographic groups, according to a study that investigated patient portal use from the Health International Trend Survey (HINTS).[11] According to this study, access to high-speed internet, previous online patient-provider communication, and trust in the protection of medical records have been closely associated with patient portal use.[11]

In addition, patient portal utilization has been higher among females, White populations, and those with higher levels of education.[11,13] Patients who are more likely to access their patient portal are those with a poor self-rated health status, those who view the portal as beneficial, those who are highly invested their self-care, and those with access to technology.[13]

Other positive predictors of patient portal utilization include willingness to communicate with health care providers electronically and the belief that they should be able to access their own medical information online.[14] In contrast, people without a primary care provider (PCP) are less likely to interact with patient portals, as they may not be offered access to, or instructed on the use of, patient portals.[15]

In older populations, reluctance to engage with digital health technologies, such as a patient portal, may be due to lower levels of digital and general health literacy, lack of familiarity with technology, and concerns with privacy and security.[16–18] In addition, patient portal utilization is lower among Hispanic patients, non-Hispanic Black/African-American patients, and older patients.[19–22] Previous research has found that patient portal utilization is also less common in some areas of the country, such as the South and the Northeast. Patients from these regions are less likely to be offered patient portal access by their health care providers.[8]

Although previous studies have evaluated the relationship between patient demographic characteristics and patient portal utilization, most studies involve pre-COVID-19 pandemic data. Since the onset of the pandemic, telehealth has led to increased patient portal use among both providers and patients, and the change in telehealth usage could have an additional effect on patient portal adoption.[23]

Recent evidence suggests that this expansion has not been equitable across all populations, both for telehealth services broadly[24,25] and for patient portal utilization specifically.[26] This recent study utilized a sample from a national survey conducted in early 2020 and found lower patient portal utilization among males, Hispanic patients, those with good or better general health, those with less education, those with Medicaid health insurance, those without a regular health care provider, and those who did not use the internet.[26]

However, due to the rapid changes in the expansion of telehealth and policies governing telehealth during this period, there is a need to examine whether these and other health-related factors are associated with patient portal utilization in later stages of the COVID-19 public health emergency (PHE) to inform how to address current potential barriers to patient portal utilization.

The current study addresses these gaps in existing research by evaluating patient portal utilization in adults living in Arkansas in 2022 using data collected via a random digit dial phone survey. We included sociodemographic characteristics as predictors of patient portal utilization in our model; however, we also incorporated prior telehealth experiences and measures of health care access—such as having a PCP and having recent general wellness exams—as potential factors of patient portal utilization.

Arkansas ranks 48th in overall population health, 44th in percentage of active physicians per 100,000 people,[27,28] and among the lowest five states in the nation for percentages of households with a computer (48th), percentage of households with a broadband internet subscription (46th), and the availability of high-speed internet (48th).[29,30]

To our knowledge, this study is the first to evaluate the factors associated with patient portal utilization among adult patients in Arkansas. Identifying factors associated with patient portal initialization in Arkansas could assist in

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eventually targeting specific subpopulations to increase patient portal access and improve health outcomes in Arkansas and in other rural states.

Methods

PARTICIPANTS

A total of 2,201 adult Arkansans completed the survey between March 1 and March 28, 2022. Eligibility criteria included being an adult (age 18 or older) and an Arkansas resident.

PROCEDURES

Arkansas residents were contacted using random digit dialing of both landline and cell phones (see *Fig. 1* for geographical distribution of participants). Individuals who met the eligibility criteria were provided information regarding participation in the study, including the estimated time, potential risks and benefits, the voluntary nature of participation, and confidentiality of responses; consent was indicated by respondents agreeing to participate. The average length of interview was 17 min.

Study procedures were approved by the institutional review board for the protection of human subjects at the University of Arkansas for Medical Sciences. We oversampled Black/African-American and Hispanic residents to ensure adequate representation. Trained interviewers administered the survey via computer-assisted telephone interviews, and the survey was administered in the participants' language of choice (English or Spanish).

DEPENDENT VARIABLE

The outcome measure of interest was patient portal utilization and was assessed using the survey item, "In the past 12 months, have you used your online medical record to securely message healthcare providers and staff (e.g., e-mail)?," from the HINTS Survey Cycle 5 (2020).[31] Participants who responded "yes" to this item were identified as patient portal utilizers, and those who responded "no" were identified as patient portal non-utilizers. Respondents who answered "don't know/not sure" or who refused to respond were excluded from analysis.

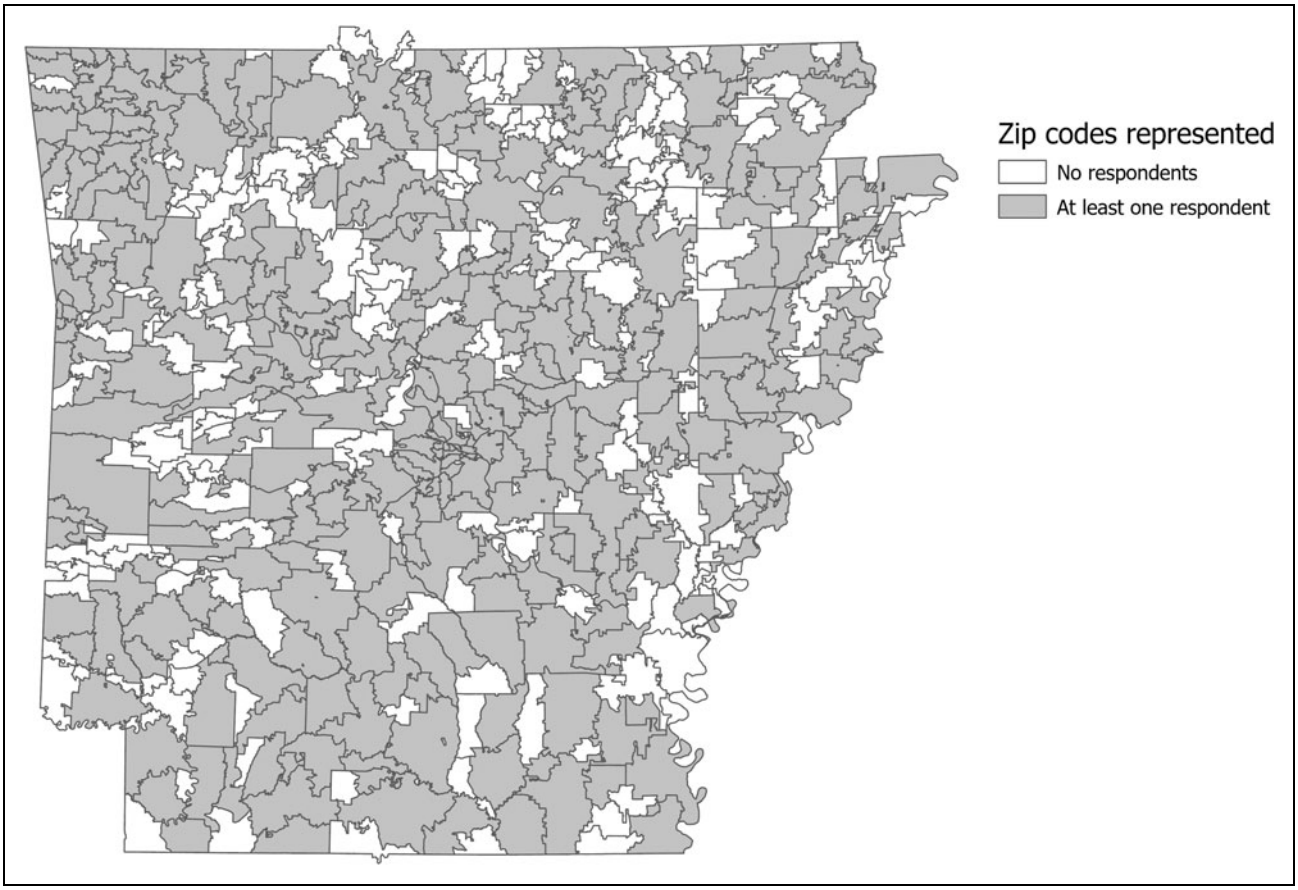

Fig. 1. Map of Arkansas zip codes shaded to represent areas with at least one survey respondent.

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CO-VARIATES

Co-variates in the model included several sociodemographic factors as well as health status and behaviors. Sociodemographic factors were adapted from the Behavioral Risk Factor Surveillance System survey.[32] Race was categorized into four groups: non-Hispanic White, non-Hispanic Black/African-American, Hispanic, and non-Hispanic other/multiple races, due to small numbers of participants in other self-reported race/ethnicity categories.

Age was categorized into three groups: young adults (ages 18–39), middle-aged adults (ages 40–59), and older adults (aged 60 or older). Subjective social status was a continuous variable assessed using the MacArthur Subjective Social Status scale,[33] with responses ranging from 1 to 10. Gender was dichotomized to male/female. Marital status was dichotomized into single (never married, separated, divorced, widowed) and partnered (married, a member of an unmarried couple).

Employment was dichotomized to employed (employed for wages, self-employed), retired/homemaker/student, and unemployed (out of work for 1 year or more, out of work for <1 year, unable to work). Highest level of educational attainment was categorized into three groups: high school degree or less, some college/associate degree, and bachelor's degree or higher. U.S. nativity was determined using yes/no responses to the survey item, "Were you born in the United States or a U.S. territory?"

Health status and health behaviors were assessed using items adapted from the National Health Interview Survey[34] and the Behavioral Risk Factor Surveillance System survey,[32] and included having a PCP, deferring health care due to cost, and having a recent check-up. Having a PCP was determined using the survey item, "Do you have one person you think of as your personal doctor or health care provider?" and dichotomized into yes (yes, one person; yes, more than one person)/no.

Deferring health care due to cost was determined by "yes" and "no" response to the survey item, "Was there a time in the past 12 months when you needed a doctor but could not see one because of the cost?" Having a recent check-up was determined using the survey item, "About how long has it been since you last visited a doctor for a routine checkup?"

Responses were grouped into two categories: within the past 2 years (within the past year [anytime <12 months ago], within the past 2 years [1 year but <2 years ago]), and 2 years ago or more (within the past 5 years [2 years but <5 years ago], 5 or more years ago, never). Self-rated health was dichotomized from the survey item, "Would you say that in general your health is…," with excellent, very good, and good serving as one group and fair and poor as the other.

STATISTICAL ANALYSIS

Weighted estimates were generated using rank ratio estimation to approximate the 2019 American Community Survey 1-year Arkansas estimates for race/ethnicity, age, and gender. Chi-squared tests for categorical variables and *t*-tests for continuous variables among patient portal utilizers and non-utilizers were calculated for demographic and self-reported health information.

Due to the binary nature of the study outcome measure (i.e., patient portal utilization), data were fit to a logistic regression model to generate odds ratios (OR) and confidence intervals (CI), with an alpha value of 0.05 set *a priori*. Analyses were conducted using R version 4.2.1.[35]

Results

Descriptive statistics for the characteristics of the sample among patient portal utilizers and non-utilizers can be found in *Table 1*.

We observed group differences between patient portal utilizers and non-utilizers for age, social ladder, marital status, educational attainment, having a PCP, having a check-up in the past 2 years, and having previously utilized telehealth. The largest age group among patient portal utilizers was 40–59 years of age ($n = 243$, 38%) and 18–39 years of age among non-utilizers ($n = 591$, 39%; $p = 0.019$).

Patient portal utilizers self-reported their subjective social status (mean = 5.96, standard deviation [SD] = 2.24) as higher than non-utilizers (mean = 5.74, SD = 2.34; $p = 0.046$). The most common response options among patient portal utilizers for the highest level of educational attainment was a Bachelor's degree or higher ($n = 261$, 40%), but high school or less for patient portal non-utilizers ($n = 558$; 36%; $p < 0.001$).

A larger proportion of patient portal utilizers reported having a PCP (utilizers: $n = 598$, 93%; non-utilizers: 1,210, 79%; $p < 0.001$), check-ups within the past 2 years (utilizers: $n = 603$, 93%; non-utilizers: $n = 1{,}196$, 78%; $p < 0.001$), and previous experience with telehealth (utilizers: $n = 478$, 74%; non-utilizers: $n = 599$, 39%; $p < 0.001$) than patient portal non-utilizers.

Results from the logistic regression using weights can be found in *Table 2*.

Relative to non-Hispanic White respondents, non-Hispanic Black/African-American respondents were less likely to have utilized an online patient portal (OR = 0.72; 95% CI [0.53–0.98]; $p = 0.04$). Respondents with some college, technical school, or an associate degree were more likely to be patient portal utilizers than those who had attended only high school or less (OR = 1.42; 95% CI [1.01–2.01]; $p = 0.044$), as were respondents with a bachelor's degree or higher (OR = 1.61; 95% CI [1.12–2.30]; $p = 0.010$).

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Table 1. Weighted Descriptive Statistics for Demographic Characteristics of the Survey Sample (Weighted Overall *N* = 2,181) by Patient Portal Utilizers (Weighted *n* = 1,534, 69.7%) and Non-Utilizers (Weighted *n* = 647, 29.4%)

CHARACTERISTIC	OVERALL (*N* = 2,181)[a]	PATIENT PORTAL NON-UTILIZERS (*N* = 1,534)[a]	PATIENT PORTAL UTILIZERS (*N* = 647)[a]	*p*[b]
Race/ethnicity				
Non-Hispanic White	1,562 (72%)	1,081 (71%)	481 (75%)	0.074
Non-Hispanic Black/African-American	333 (15%)	240 (16%)	93 (15%)	
Hispanic	169 (7.8%)	129 (8.4%)	39 (6.2%)	
Non-Hispanic other race(s)	105 (4.9%)	78 (5.1%)	27 (4.2%)	
Missing	12	5	6	
Age				
Age 18–39	807 (37%)	591 (39%)	216 (33%)	**0.019**
Age 40–59	701 (32%)	458 (30%)	243 (38%)	
Age 60+	672 (31%)	484 (32%)	188 (29%)	
Subjective social status (1–10)	5.80 (2.31)	5.74 (2.34)	5.96 (2.24)	**0.046**
Missing	127	93	34	
Gender				
Male	1,067 (49%)	775 (51%)	292 (45%)	0.073
Female	1,114 (51%)	759 (49%)	355 (55%)	
Marital status				
Single	997 (46%)	732 (48%)	265 (41%)	**0.019**
Partnered	1,176 (54%)	795 (52%)	381 (59%)	
Missing	7	6	1	
Educational attainment				
High school or less	704 (32%)	558 (36%)	145 (22%)	**<0.001**
Some college/associate degree	773 (36%)	533 (35%)	241 (37%)	
Bachelor's degree or higher	700 (32%)	439 (29%)	261 (40%)	
Missing	3	3	0	
Employment status				
Unemployed	323 (15%)	241 (16%)	81 (13%)	0.062
Retired/homemaker/student	618 (28%)	449 (29%)	169 (26%)	
Employed	1,232 (57%)	837 (55%)	396 (61%)	
Missing	7	7	0	
Born in the United States				
Not born in the United States	93 (4.3%)	68 (4.5%)	24 (3.8%)	0.4
Born in the United States	2,076 (96%)	1,454 (96%)	621 (96%)	
Missing	12	11	1	
Self-rated health				
Fair/poor	515 (24%)	352 (23%)	162 (25%)	0.4
Excellent/very good/good	1,661 (76%)	1,177 (77%)	484 (75%)	
Missing	4	4	0	

continued →

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Table 1. Weighted Descriptive Statistics for Demographic Characteristics of the Survey Sample (Weighted Overall $N = 2,181$) by Patient Portal Utilizers (Weighted $n = 1,534$, 69.7%) and Non-Utilizers (Weighted $n = 647$, 29.4%) *continued*

CHARACTERISTIC	OVERALL ($N = 2,181$)[a]	PATIENT PORTAL NON-UTILIZERS ($N = 1,534$)[a]	PATIENT PORTAL UTILIZERS ($N = 647$)[a]	p[b]
Have a PCP				
No	368 (17%)	320 (21%)	48 (7.4%)	**<0.001**
Yes	1,808 (83%)	1,210 (79%)	598 (93%)	
Missing	4	3	1	
Deferred health care due to cost in the past 12 months				
No	1,898 (87%)	1,337 (87%)	562 (87%)	0.8
Yes	278 (13%)	193 (13%)	85 (13%)	
Missing	3	3	0	
Had check-up within the past 2 years				
No	376 (17%)	334 (22%)	42 (6.5%)	**<0.001**
Yes	1,799 (83%)	1,196 (78%)	603 (93%)	
Missing	5	3	2	
Previously utilized telehealth				
No	1,091 (50%)	924 (61%)	167 (26%)	**<0.001**
Yes	1,077 (50%)	599 (39%)	478 (74%)	
Missing	12	10	1	

Bold values indicate statistical significance at the 0.05 level.

[a] *n* (%); mean (SD).

[b] Chi-squared test with Rao and Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

PCP, primary care provider; SD, standard deviation.

Respondents who were employed were more likely than unemployed respondents to have patient portal experience (OR = 1.90; 95% CI [1.21–2.98]; $p = 0.005$). In addition, respondents who had a PCP (OR = 2.20; 95% CI [1.35–3.57]; $p = 0.002$), had a check-up within the past 2 years (OR = 3.28; 95% CI [1.90–5.66]; $p < 0.001$), and had prior telehealth experience (OR = 3.95; 95% CI [2.99–5.21]; $p < 0.001$) were all more likely than those without to have utilized a patient portal.

Discussion

Our study found that patient portal utilization among Arkansan adults was positively associated with previous telehealth utilization, having a PCP, and having had a check-up in the past 2 years. These findings align with the prior literature, where digital access and prior experience with digital health care (e.g., telemedicine) have been found to be associated with patient portal utilization.[14]

However, unlike previous findings in which self-reported health status was negatively associated with patient portal utilization, we found no association between self-reported health status and odds of utilizing a patient portal.[14,26] These results could be due to a difference in barriers to digital health care access specific to the study population; however, it may be due to a shift in digital health attitudes and behaviors following the COVID-19 PHE, which provided an opportunity for telehealth and other digital health options to become more widespread.

Additional research is needed to further investigate the effect of COVID-19 on barriers to access, adoption, and utilization of digital health technologies, including patient portal utilization.

We also found positive associations between patient portal utilization and employment, as well as higher levels of education, which aligns with several previous studies.[36] including at least one study conducted following the COVID-19 PHE.[37] Our study also corroborated a disparity in patient portal access among non-Hispanic Black/African-Americans, but not among any other racial/ethnic groups, such as Hispanic patients.[19,26,38]

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Table 2. Adjusted Odds Ratios and Confidence Intervals from the Logistic Regression Model Using Weights for Utilizing Electronic Health Record

CHARACTERISTIC	aOR	95% CI	*p*
Race/ethnicity			
Non-Hispanic White	–	–	
Non-Hispanic Black/African-American	0.72	0.53–0.98	**0.040**
Hispanic	0.84	0.55–1.28	0.4
Non-Hispanic other race(s)	0.95	0.62–1.48	0.8
Age			
Age 18–39	–	–	
Age 40–59	1.31	0.91–1.88	0.2
Age 60+	1.01	0.67–1.51	>0.9
Subjective social status	0.99	0.94–1.05	0.8
Gender			
Male	–	–	
Female	1.03	0.78–1.34	0.8
Marital status			
Single	–	–	
Partnered	1.19	0.91–1.57	0.2
Educational attainment			
High school or less	–	–	
Some college/associate degree	1.42	1.01–2.01	**0.044**
Bachelor's degree or higher	1.61	1.12–2.30	**0.010**
Employment status			
Unemployed	–	–	
Retired/homemaker/student	1.47	0.92–2.33	0.10
Employed	1.90	1.21–2.98	**0.005**
Born in the United States			
Not born in the United States	–	–	
Born in the United States	0.81	0.43–1.51	0.5
Self-rated health			
Fair/poor	–	–	
Excellent/very good/good	0.83	0.59–1.17	0.3
Have a PCP			
No	–	–	
Yes	2.20	1.35–3.57	**0.002**
Deferred health care due to cost in the past 12 months			
No	–	–	
Yes	1.40	0.91–2.13	0.12
Had check-up within the past 2 years			
No	–	–	
Yes	3.28	1.90–5.66	**<0.001**
Previously utilized telehealth			
No	–	–	
Yes	3.95	2.99–5.21	**<0.001**

Bold values indicate statistical significance at the 0.05 level.

aOR, adjusted odds ratio; CI, confidence interval; EHR, Electronic Health Record.

Results from other studies examining digital health interventions during the COVID-19 PHE have also found evidence for disparate rates in access and utilization among underserved populations, such as rural, older, and racial/ethnic minority patients.[26,39] In addition, we found no evidence of age being associated with patient portal utilization, unlike results from similar prior studies.[36,38]

However, the results of our study support a recent finding using data collected in 2020 that found no differences in patient portal utilization among age groups.[26] In addition, a recent systematic review of factors related to patient portal utilization also noted that evidence supporting the relationship between ethnicity, age, and patient portal utilization is mixed.[40] Additional research is needed to more definitively identify how age and race/ethnicity are related to utilization of online patient portals—particularly following the onset of the COVID-19 pandemic—and what moderating factors may influence this relationship.

To our knowledge, this is the first study of the factors associated with patient portal utilization among adult patients in Arkansas, a state with poor computer and high-speed internet access and poor health outcomes.[29,30] Among this population, we found similar sociodemographic and health-related factors that were associated with patient portal utilization as has been reported in previous related studies in the U.S.

Our results underscore the need for additional outreach and interventions to increase engagement among populations in Arkansas who face the greatest health disparities, including non-Hispanic Black/African-American patients, patients with lower education, unemployed patients, and patients with lower health care engagement. Health care organizations may benefit from more aggressive promotion of patient portals, as well as providing additional education to patients regarding the use of the portal.

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LIMITATIONS

Our study is not without limitations. Although our study team oversampled Black/African-American and Hispanic residents to ensure adequate representation and implemented survey weights to approximate the demographics of Arkansas, participant non-response bias may have had an influence on our findings. In addition, our only metric of patient portal utilization came from a single survey item asking about any patient portal access specifically with regard to sending secure messages to a health care provider in the past 12 months.

Additional research is needed to more fully understanding how the factors identified in the current study are associated with health care provider types (e.g., primary care, specialty care), type (e.g., messaging, lab results, completing forms, etc.), and frequency of patient portal utilization.

Finally, within the scope of the present study, we are unable to examine the factors associated with being offered patient portal access, only actual patient portal utilization. Future work is needed to investigate whether the same characteristics are associated with patients utilizing patient portals as well as those of patients being offered use of a patient portal several years following the onset of the COVID-19 pandemic.

Conclusions

In a sample of adult Arkansans in 2022, we found evidence that higher education, employment, having a recent primary care visit, and prior telehealth utilization were all associated with increased likelihood of patient portal utilization in the past 12 months. We also found that non-Hispanic Black/African-American respondents were less likely to have utilized a patient portal than non-Hispanic White respondents.

Additional research is needed to further examine how patient portal health care specialty, as well as type and frequency of portal engagement, are related to these characteristics. Given that the documented benefits of patient portal utilization are broad (e.g., medication adherence, patient outcomes, patient/provider relationship, patient engagement), underutilization by groups that already experience relatively worse health outcomes could reproduce or even exacerbate existing health disparities. Conversely, improving utilization among these groups offers an opportunity to potentially narrow those disparities.

Authors' Contributions

C.A.B.: Methodology, Validation, Formal Analysis, Data Curation, Writing—Original Draft, and Writing—Review and Editing. J.A.A.: Conceptualization, Methodology, Writing—Original Draft, and Writing—Review and Editing. S.E.: Writing—Original Draft, Writing—Review and Editing. D.E.W.: Conceptualization, Methodology, Validation, Writing—Review and Editing, and Project Administration. D.E.: Writing—Review and Editing. P.A.M.: Writing—Conceptualization, Writing—Review and Editing, Supervision, and Funding Acquisition.

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Disclosure Statement

No competing financial interests exist.

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Assessment of diabetes self-care behaviors and knowledge among Marshallese adults with type 2 diabetes in the Republic of the Marshall Islands

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ABSTRACT

Aims: The aim of this study is to assess and document engagement in type 2 diabetes mellitus (T2DM) self-care behaviors and self-reported diabetes knowledge among Marshallese adults living in the Republic of the Marshall Islands (RMI).

Methods: The study uses data from a T2DM health screening study completed in the RMI; survey and biometric data were captured as part of the health screenings. Study objectives were examined using descriptive statistics to describe the characteristics of the participants, their diabetes self-care behaviors, and their levels of self-reported diabetes knowledge.

Results: Results indicate many Marshallese diagnosed with T2DM did not engage in adequate self-care behaviors, including blood sugar checks and foot examinations. Participants reported having forgone needed medical care and medication due to issues with cost and/or access, and participants reported low levels of diabetes knowledge.

Conclusions: The results demonstrate the need for further work in improving engagement in diabetes self-care by Marshallese living in the RMI. Increased engagement in self-care and diabetes education programs may help Marshallese with T2DM to improve control of their glucose and avoid long-term health complications, as well as reduce costs to the healthcare system.

1. Introduction

The Republic of the Marshall Islands (RMI) is a small grouping of atolls located between Hawai'i and New Zealand with a population of approximately 58,000 people. The Marshallese population experiences extremely high prevalence of overweight and obesity-related illness, particularly type 2 diabetes mellitus (T2DM); the RMI has the highest age-adjusted T2DM prevalence in the world (30.5%), compared to the United States (US) (13.3%) and globally (9.3%) [1–5].

The health disparities experienced by Marshallese are related to historical trauma resulting from extensive nuclear weapons testing conducted by the US government. From 1946–1958, the US military conducted more than 60 nuclear tests in the RMI [6]. The resulting nuclear fallout dramatically altered the Marshallese lifestyle [7,8]. Before the nuclear testing, inhabitants of the RMI relied on a traditional diet of fresh fruits, vegetables, and fish sourced from the local agricultural systems, which required high levels of physical activity to acquire. Nuclear radiation from the explosions contaminated the local food ecosystems that were central to the sustenance farming lifestyle of the Marshallese people. As a result, inhabitants of the RMI involuntarily

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shifted their diet to one reliant on high-carbohydrate commodity foods imported by the US, and physical activity related to food acquisition was greatly reduced [6,8–11]. The high prevalence of T2DM in the Marshallese population is likely attributable to this sudden shift in nutrition and physical activity.

In addition to healthy diet and regular exercise, proper management of T2DM requires numerous self-care behaviors that should be integrated into an individual's daily routine, including monitoring glucose levels, managing stress, regularly taking medications, and routinely seeing a doctor [12,13]. If unmanaged, T2DM can lead to life-threatening irreversible health complications like cardiovascular diseases, stroke, nephropathy, neuropathy, retinopathy, and amputation [14,15]. Studies have found that Marshallese individuals experience socioeconomic barriers to engagement in self-care behaviors, particularly cost-related medication non-adherence and forgoing medical care due to cost [13,16]. The minimum wage in the RMI is extremely low and is currently set at $3 per hour [17]. Due to the low minimum wage, healthcare is not always affordable. All Marshallese citizens carry basic insurance under the national healthcare plan; however, under this plan, they pay $5 for a full outpatient visit including laboratory, diagnostics, and pharmacy, $17 for an Emergency Room visit, and $10 per hospital admission [18]. Public transportation costs range between $1 and $5 each way [18].

Engagement with diabetes self-care behaviors has been documented among Marshallese populations living in the US and among other racial and ethnic minorities [13,19]. However, few studies have examined engagement in self-care behaviors among Marshallese populations living in the RMI. The current study seeks to fill this gap in the literature by examining self-reported diabetes self-care behaviors and diabetes self-management knowledge among Marshallese adults living in the RMI. Understanding diabetes self-care behaviors and diabetes self-management knowledge may help to inform future interventions and programs to overcome barriers to appropriate T2DM management in the RMI.

2. Materials and methods

2.1. Community-based participatory research

This study utilized a community-based participatory research (CBPR)[20–23] approach, the use of which is important given the historical trauma experienced by the Marshallese people [6]. CBPR engages community partners, honors their unique contributions at all stages of research, and ensures Marshallese cultural knowledge informs the process [20–22]. The study team worked closely with the RMI Ministry of Health and Human Services (MOHHS), the Marshallese Educational Initiative, Kora In Jiban Lolorjake Ejmour, and a community advisory board (CAB) to develop the study protocol and activities. A more detailed description of the study development and protocol can be found elsewhere [23].

2.2. Study population

The study uses primary data from a health screening study completed in the RMI. Individuals who met the inclusion criteria and consented to participate in the study provided survey and biometric data. Participant inclusion criteria included: (1) self-identified as Marshallese and (2) over 18 years of age. The CBPR partners recommended verbal consent with a written document outlining the study information. Previous work with the Marshallese community has highlighted participants' desire for a verbal discussion of study requirements and a simplified consent process [24,25]. Therefore, a waiver of consent documentation was granted by the Institutional Review Board (IRB #262557) and approved by the RMI MOHHS, and verbal consent was utilized.

Community health workers and CAB members assisted with recruiting churches to participate in the screenings. Recruitment efforts also included announcements on the local radio station, through text messaging, and through invitations extended to non-participating churches who inquired about participation after hearing of the health screenings taking place elsewhere. Once a church agreed to participate, town hall-style question and answer sessions were conducted to inform and recruit individual participants. Additionally, the health screenings were advertised via postings on local websites, social media, and study flyers.

At the health screening events, participants were provided a study information sheet in Marshallese and were allowed time to read and review the information sheet with a community health worker. Participants were encouraged to ask any questions they may have had before verbally acknowledging consent to participate in the study. Participants received a copy of the study information sheet in Marshallese for their records, and those who consented to the study were given $10 as compensation for their participation. All participants received counseling regarding their results at the health screenings.

2.3. Measures

Survey and biometric data were captured as part of the health screenings. All staff had previous experience with the collection of biometric and survey data in the RMI and had completed human subjects, ethics, research privacy and confidentiality, blood-borne pathogen, biometric data collection, and study-specific trainings. Study instruments were chosen collaboratively with Marshallese stakeholders, translated into Marshallese, and validated with Marshallese participants. The data collection methods and survey items have been utilized in prior studies with Marshallese participants [26–31].

Sex, educational attainment, and age of the participant were collected via self-report. Biometric measures collected included weight and height (to calculate body mass index [BMI]) and glycated hemoglobin (HbA1c). Participants' weight (without shoes) was measured to the nearest 0.5 pound using a calibrated digital scale. Height (without shoes) was measured to the nearest 0.25 in. using a stadiometer. BMI was calculated using collected height and weight [(weight in pounds/height in inches^2) X 703]. HbA1c was collected via finger prick using aseptic techniques and analyzed using PTS Diagnostic's A1CNOW+ point-of-care tests. HbA1c was recorded as percent of glycated hemoglobin (NGSP %). HbA1c was categorized as controlled if the participant's HbA1c was less than 9.0% and uncontrolled if their HbA1c was 9.0% or greater.

To determine the extent of the participants' diabetes knowledge and to document participants' diabetes self-care behaviors and ability to access healthcare services, participants completed a survey instrument adapted from the Behavioral Risk Factor Surveillance System (BRFSS) survey's Diabetes and Healthcare Access Modules [32] and the validated Michigan Diabetes Care Profile [33]. All responses were self-reported. The Diabetes and Healthcare Access Modules of the BRFSS include standardized questions for sociodemographic information, when the participant last saw a healthcare provider, forgoing care due to cost, the frequencies of blood sugar monitoring, and the frequencies of feet checks. The Diabetes Care Profile [33] module called "Understanding" was used, which asks participants about their knowledge/understanding of diabetes and diabetes care. Questions were translated into Marshallese and edited as needed to fit within the context of the RMI.

2.4. Analysis

Study objectives were examined using descriptive statistics to describe the participants, their self-reported diabetes self-care behaviors, and their self-reported level of diabetes knowledge. Analysis was performed using STATA SE v17 (Statacorp, LLC., College Station, TX) [34].

3. Results

3.1. Demographics

Five hundred and twenty eight (528) Marshallese adults from 20 churches located on Majuro Atoll participated in the health screenings. Of the 528 participants who participated in the health screenings, 152 indicated they had a previous diagnosis of T2DM by responding yes to the question, "Has a doctor, nurse, or other health professional EVER told you that you had diabetes?" Individuals with a previous diagnosis of T2DM were administered an additional survey which asked participants about their knowledge of diabetes and their diabetes-related self-care behaviors. The 152 participants who completed this survey were included in the analysis.

Table 1
Participant Demographics, Biometrics, and Engagement in Self-Care Behaviors.

	Obs	N (Mean ± SD)	% of Sample	Range
Sex	152			
Female		103	67.8	
Male		49	32.2	
Education	152			
Never attended or elementary education		34	22.4	
Some high school		58	38.2	
High school graduate or GED		31	20.4	
Some college or technical school		23	15.1	
College graduate		6	4.0	
Age (continuous)	152	52.8 ± 11.7	–	23–77
Age (categorical)	152			
18–24		2	1.3	
25–44		35	23.0	
45–64		90	59.2	
> 65		25	16.5	
BMI[1]	150			
Normal weight		20	13.3	
Overweight		53	35.3	
Obese		77	51.3	
Blood sugar control[2]	140			
Controlled (HbA1c < 9.0%)		55	39.3	
Uncontrolled (HbA1c > 9.0%)		85	60.7	
Number of times per day checked glucose	133			
Zero		28	21.1	
Once		76	57.1	
Twice		20	15.0	
Three or more times		9	6.8	
Number of days checked feet	151			
Less than 7 days per week		102	67.6	
Seven days per week		49	32.5	
Number of days checked shoes				
Less than 7 days per week		83	55.0	
Seven days per week		68	45.0	
Last visit with a doctor, nurse, or health professional	152			
Within the past 6 months		114	75.0	
More than a year ago		22	14.5	
More than 2 years ago		7	4.6	
None		4	2.6	
Don't know/not sure		5	3.3	
Forgone medical care	152			
No		42	27.6	
Yes		110	72.4	
Forgone medication	152			
No		87	57.2	
Yes		65	42.8	

Notes: Only valid percentages shown. Percentages may not total 100 due to rounding.
SD, standard deviation; GED, graduate equivalency degree; BMI, body mass index; HbA1c, hemoglobin A1c
[1]Missing data due to participant limitations
[2]Missing data due to supply chain issues obtaining HbA1c test kits

Table 1 provides the descriptive statistics of the participants' demographic characteristics and self-care behaviors. Participants were predominately female (67.8%) and between the ages of 45 and 64 (59.2%), with a mean age of 52.8 years (± 11.7 years). Two-thirds of the participants had completed some high school (38.2%) or an elementary-level (22.4%) education. The majority of the participants were overweight (35.3%) or obese (51.3%) and had an HbA1c indicative of uncontrolled T2DM (60.7%).

3.2. Self-care behaviors

Slightly more than half of participants reported checking their glucose levels once per day (57.1%), followed by zero times per day (21.1%) and twice per day (15.0%). The majority of participants did not check their feet (67.6%) or their shoes (55.0%) every day as recommended.

3.3. Healthcare access

Three-fourths of participants (75.0%) stated they had seen a physician or other healthcare provider within the past six months, 14.5% stated it had been more than a year, and 4.6% reported seeing a physician or other healthcare provider more than two years ago. A small number of participants stated they had never seen a physician or other healthcare provider (2.6%) or they did not know the last time they had seen a provider (3.3%). Nearly three-fourths (72.4%) of participants reported having forgone medical care, and 42.8% had forgone needed medications due to cost or lack of access (e.g., no transportation, out of stock, closed/no staff available).

3.4. Diabetes knowledge

Table 2 reports the descriptive results of participants' diabetes knowledge. Overall, the mean score for diabetes knowledge was 17.3 (± 7.3) with a range of 0–26. More than half of participants stated they knew 'a lot' about taking medications correctly (60.5%), taking care of their feet (55.9%), the benefits of improving blood sugar control (55.9%), the role of exercise in diabetes (51.3%), and how to prevent and treat low blood sugar (51.3%). Areas where less than half of participants reported knowing 'a lot' were regarding how to manage pregnancy and diabetes (36.2%), how to use the results of blood sugar monitoring (45.4%), and how to eat for blood sugar control (46.7%).

4. Discussion

Marshallese living in the RMI experience extremely high prevalence of T2DM [1–5]. To assist Marshallese individuals in managing the effects of an existing T2DM diagnosis, it is important to understand their T2DM-related self-care behaviors and the knowledge Marshallese patients with T2DM have of managing the disease. The current study sought to understand self-care behaviors and self-reported diabetes knowledge among a sample of Marshallese adults living in the RMI.

Overall, our results show many Marshallese previously diagnosed with T2DM did not engage in adequate self-care behaviors, including checking their blood sugar and examining their feet. These findings are similar to studies done previously in the US and the RMI, which showed low engagement with self-care activities [29,35]. For example, one study assessing self-care behaviors among 111 Marshallese adults living in the US found low engagement in diabetes-related self-care behaviors. Among the seven self-care activities examined (maintaining a normal weight, exercising regularly, checking glucose daily, having a biennial eye exam, taking a diabetes course, having an annual foot exam, and having an annual doctor visit), Marshallese participants integrated less than an average of four behaviors into their routine [35]. This is particularly concerning given the high percentage of participants in the present study with an HbA1c indicative of uncontrolled diabetes. Almost

Table 2
Participant Perceived Diabetes Knowledge by Category (n = 152).

How well do you understand…	N (Mean ± SD)	%	Range
Diabetes knowledge scale score	17.3 ± 7.3		0–26
How to manage your diabetes?			
Not at all	24	15.8	
A little	52	34.2	
A lot	76	50.0	
How to manage your stress?			
Not at all	26	17.1	
A little	50	32.9	
A lot	76	50.0	
How to eat for blood sugar control?			
Not at all	23	15.1	
A little	58	38.2	
A lot	71	46.7	
The role of exercise in diabetes?			
Not at all	21	13.8	
A little	53	34.9	
A lot	78	51.3	
How to take your medications correctly?			
Not at all	20	13.2	
A little	40	26.3	
A lot	92	60.5	
How to use the results of blood sugar monitoring?			
Not at all	39	25.7	
A little	44	29.0	
A lot	69	45.4	
How diet, exercise, and medicines affect blood sugar levels?			
Not at all	22	14.5	
A little	54	35.5	
A lot	76	50.0	
How to prevent and treat high blood sugar?			
Not at all	27	17.8	
A little	55	36.2	
A lot	70	46.1	
How to prevent and treat low blood sugar?			
Not at all	21	13.8	
A little	53	34.9	
A lot	78	51.3	
How to prevent long-term complications of diabetes?			
Not at all	24	15.8	
A little	53	34.9	
A lot	75	49.3	
How to take care of your feet?			
Not at all	18	11.8	
A little	49	32.2	
A lot	85	55.9	
The benefits of improving blood sugar control?			
Not at all	18	11.8	
A little	49	32.2	
A lot	85	55.9	
How to manage pregnancy and diabetes?			
Not at all	51	33.6	
A little	46	30.3	
A lot	55	36.2	

SD, standard deviation

two-thirds of the participants had an HbA1c greater than 9.0%; by comparison, 50% of US adults with uncontrolled T2DM have an HbA1c greater than 9.0% [36].

Additionally, participants reported having forgone needed medical care and medication due to issues with cost and/or access. Healthcare is remote and underfunded in the RMI, and in combination with a high unemployment rate and low minimum wage, many Marshallese face difficulties in accessing and paying for medical care and supplies [7,37]. Transportation is also an issue, as many healthcare providers are not located within walking distance and many Marshallese do not own/are unable to access personal transportation [38,39]. These findings are similar to studies assessing barriers to medical care access and medication adherence in the US and in the RMI, highlighting the importance of addressing financial and transportation-related barriers to care [16,29,40–43].

Further, many participants reported low levels of diabetes self-management knowledge. However, the results do show some higher levels of self-reported diabetes self-management knowledge when compared to a previous study done in the RMI [29]. The results provide evidence of the work being done in the RMI to educate Marshallese on diabetes self-management [27]. Although an improvement, the combination of a high proportion of individuals with uncontrolled T2DM, inadequate self-care, insufficient knowledge about diabetes self-management, and barriers to healthcare does place the participants at a greater risk of life-threatening irreversible health complications, such as cardiovascular diseases, stroke, nephropathy, retinopathy, neuropathy, and infections leading to amputations [14,15]. Further, the expense of uncontrolled diabetes affects the economy of the RMI; in 2017, healthcare expenditures were 16.34% of the RMI's gross domestic product, similar to the US [44]. More work is needed to educate Marshallese communities in the RMI on the importance of diabetes self-management and increase engagement in diabetes self-management behaviors, both to improve the health of Marshallese living in the RMI and to lower government healthcare spending.

4.1. Limitations

There are several limitations to the results presented here. The convenience sample limits the ability to generalize the results to broader Marshallese and Pacific Islander communities, and the sampling method limits comparisons to other studies. Further, diabetes self-care behaviors and diabetes self-management knowledge are self-reported by the participant. Self-reports do carry a risk of bias, including the adjustment of participant responses to be more socially desirable [45] if the interviewer knows the participant, as is often the case with CBPR [46]. Although social desirability may play a role in the responses, prior work has shown the effect is limited even for sensitive questions (e.g., substance use) [46].

5. Conclusion

The findings are a valuable addition to the literature on diabetes self-care behaviors and diabetes self-management knowledge among Marshallese living in the RMI. The results demonstrate the need for further work in improving engagement in diabetes self-care by Marshallese living in the RMI. It is important to consider the evidence of gains in diabetes self-management knowledge by additional resources to individuals with T2DM in an effort to increase engagement in self-care behaviors. Increased engagement in self-care may help Marshallese with T2DM to improve control of their T2DM and avoid long-term health complications.

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Declaration of Competing Interest

The authors declared no competing interests.

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Endocrinology, Diabetes & Metabolism CASE REPORTS

L Menon and others

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New-onset primary adrenal insufficiency in pregnancy associated with a unilateral adrenal infarction: a case report

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Summary

New-onset primary adrenal insufficiency is rare in pregnancy. The symptoms of adrenal insufficiency such as nausea, vomiting and dizziness may be attributed to the pregnancy itself, which can lead to a delay in the diagnosis. The presence of hypotension, hypoglycemia or hyperkalemia should raise the suspicion for adrenal insufficiency. We report the case of a 25-year-old woman who presented with tachycardia, left flank pain and vomiting at 36 weeks' gestation. She was found to have primary adrenal insufficiency and started on hydrocortisone and fludrocortisone with resolution of the vomiting and tachycardia. MRI of the abdomen revealed an acute nonhemorrhagic infarct of the left adrenal gland. The contralateral adrenal gland was normal. Autoimmune and infectious etiologies of primary adrenal insufficiency were ruled out and the adrenal insufficiency was attributed to the unilateral adrenal infarction. Adrenal insufficiency persisted after delivery and then resolved at approximately 16 months post partum. This case highlights the need to test women with unilateral adrenal infarction in pregnancy for the presence of primary adrenal insufficiency.

Learning points

- Adrenal insufficiency should be considered when a pregnant woman develops nausea, vomiting and dizziness in association with hypotension or hypoglycemia. Hypovolemic hyponatremia related to vomiting can occur in pregnancy, but the failure to correct hyponatremia despite adequate IV hydration should raise the suspicion for adrenal insufficiency.
- Adrenal infarction should be in the differential diagnosis for unilateral flank pain in pregnancy. Other common etiologies for flank pain in pregnancy include nephrolithiasis, pyelonephritis and acute cholecystitis.
- Unilateral adrenal infarction in pregnancy can lead to the development of primary adrenal insufficiency. Following delivery, these patients need to be monitored for the resolution of the adrenal insufficiency.

Introduction

Adrenal insufficiency (AI) is characterized by deficient or absent cortisol production. It is classified as primary AI when there is destruction of the adrenal cortex or defects in adrenal steroidogenesis and secondary AI when damage occurs at the level of the pituitary gland or hypothalamus. AI can be insidious in onset and lead to symptoms such as fatigue, anorexia, nausea, vomiting and unintentional weight loss or it may present

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acutely as an adrenal crisis (1). The symptoms and signs of adrenal crisis include hypotension, tachycardia, impaired cognitive function and abdominal pain. Hyponatremia, hyperkalemia and hypoglycemia are frequently noted during an adrenal crisis (2). AI is rare in pregnancy with a prevalence of 5.5/100 000 (3). Pregnant women with AI are at increased risk of preterm delivery and delivery by cesarean section (3, 4). The patients included in these studies had AI that preceded the pregnancy. It is unclear whether these risks also apply to patients who develop new-onset AI in pregnancy.

We present the case of a 25-year-old woman who developed new-onset primary AI during pregnancy leading to the development of an adrenal crisis. Investigation into the etiology of the AI led to the finding of a subacute non-hemorrhagic infarct of the left adrenal gland (NHAI). No alternative etiologies for the primary AI were found. This case highlights the need to consider AI in pregnant women who present with a unilateral adrenal infarction.

Case presentation

A 25-year-old woman, who was at 36 weeks' gestation of her second pregnancy, presented to labor and delivery triage with a 2-day history of left flank pain and 1-day history of nausea, vomiting and dizziness. The flank pain radiated to the front of her abdomen and was 7/10 in severity. She denied dysuria, vaginal bleeding, contractions and decrease in fetal movement. She had no past medical history and her first pregnancy resulted in an uncompleted spontaneous vaginal delivery 18 months ago. There was no history of aspirin, anti-coagulant or illicit drug use. Vital signs showed a blood pressure of 111/65 mm Hg, heart rate of 129 bpm, respiratory rate of 24/min, SpO_2 of 100% and temperature of 98.3°F. She had tenderness of the left flank. Her abdomen was gravid and there was no abdominal tenderness or contractions. Her cervix was closed, thick and high. No cutaneous or mucosal hyperpigmentation was noted.

Investigation

Initial laboratory investigation revealed hyponatremia to 125 mmol/L (reference range: 135–145 mmol/L), hypoglycemia to 54 mg/dL and low serum bicarbonate of 14 mmol/L (reference range: 22–32 mmol/L) (Table 1). Her potassium and creatinine were in the normal range. Thyroid hormone level was in the normal range with a TSH of 2.51 µIU/mL (reference range: 0.34–5.60 µIU/mL) and free T4 of 1.13 ng/dL (reference range: 0.58–1.64 ng/dL). Urinalysis showed moderate leukocyte esterase and three to five white blood cells per high power field (WBC/HPF).

A CT chest with pulmonary embolism (PE) protocol was obtained due to the tachycardia and tachypnea which showed no central or segmental PE. An indeterminate 1.9 cm left adrenal mass was incidentally noted (Fig. 1). As part of the workup for the incidentally noted adrenal mass, adrenocorticotropic hormone (ACTH) level was obtained which was elevated at 220.8 pg/mL (reference range: 7.2–63.3 pg/mL) and the AM cortisol was low for pregnancy at 7.7 µg/dL (non-pregnancy reference range: 5–23 µg/dL). A cosyntropin stimulation test was not done. MRI of the abdomen with and without contrast was obtained 15 days later following delivery which showed that the left adrenal gland had a central T2 hyperintensity with a rim of T2 hypointensity and was nonenhancing (Fig. 2). The findings were reported to be consistent with subacute NHAI. The right adrenal gland appeared normal. The 21-hydroxylase antibody, T-spot tuberculosis test and urinary *Histoplasma* antigen were negative.

Table 1 Serial laboratory data during hospitalization.

Laboratory test (normal reference range)	**At admission**	**Day 2 of hospitalization**	**Day 3 of hospitalization**
Sodium (135–145 mmol/L)	**125 mmol/L**	**133 mmol/L**	136 mmol/L
Potassium (3.5–5.1 mmol/L)	3.8 mmol/L	3.9 mmol/L	3.6 mmol/L
Chloride (98–107 mmol/L)	102 mmol/L	106 mmol/L	110 mmol/L
Bicarbonate (22–32 mmol/L)	**14 mmol/L**	**12 mmol/L**	**17 mmol/L**
Glucose (70–110 mg/dL)	**54 mg/dL**	**48 mg/dL**	152 mg/dL
ACTH (7.2–63.3 pg/mL)		**220.8 pg/mL**	
Cortisol (5–23 µg/dL)		**7.7 µg/dL**	

Hyponatremia and hypoglycemia were noted at admission which persisted despite IV hydration. Her hyponatremia and hypoglycemia were corrected after the administration of stress dose hydrocortisone. Bold text indicates lab results that are outside the normal range.
ACTH, adrenocorticotropic hormone.

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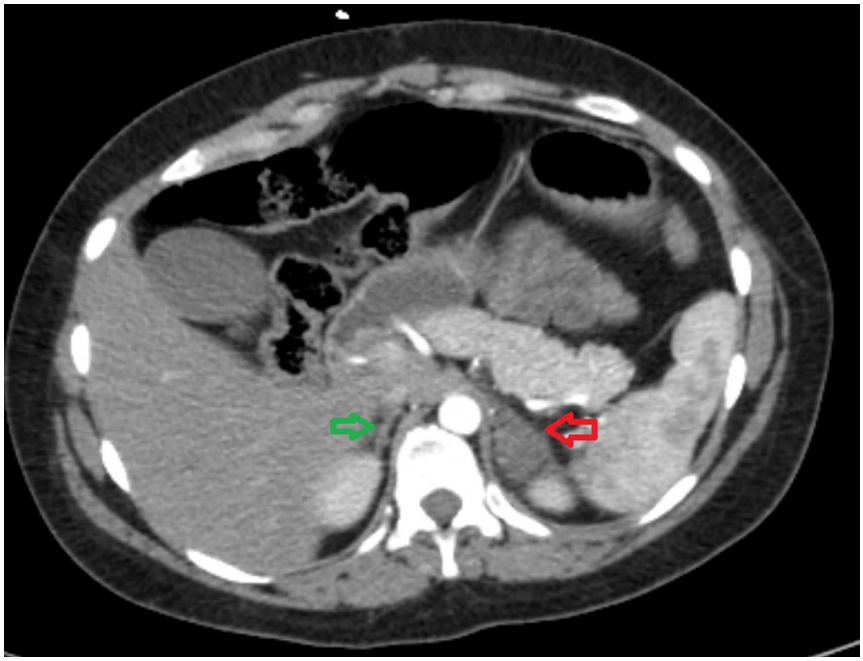

Figure 1
CT chest with PE protocol showing the incidental finding of a 1.9 cm left adrenal hypodensity (red arrow). The green arrow shows the right adrenal gland which is normal in morphology.

Treatment

She was started on normal saline infusion at 125 mL/h for IV hydration and ondansetron 4 mg q6h for nausea. One injection of 12.5 mg 50% dextrose was given IV for the hypoglycemia. The patient was then able to tolerate the intake of clear liquids but had intermittent vomiting and continued to experience hypoglycemia. Her IV fluids were changed to 5% dextrose with ½ normal saline at 125 mL/h. She had persistent hypotension despite the IV hydration with the lowest BP reading of 88/59 mm Hg due to which she received an additional 1 L normal saline bolus with a transient improvement in BP. Cephalexin 2 gram q24h was started as empiric treatment for a urinary tract infection (UTI).

Following the finding of elevated ACTH on the second day of hospitalization, hydrocortisone 100 mg IV q8h was started. Her hypotension resolved after the initiation of steroids and there was resolution of her nausea and vomiting over the subsequent 24-h period. The hydrocortisone dose was weaned to 20 mg in the morning and 10 mg in the afternoon over the

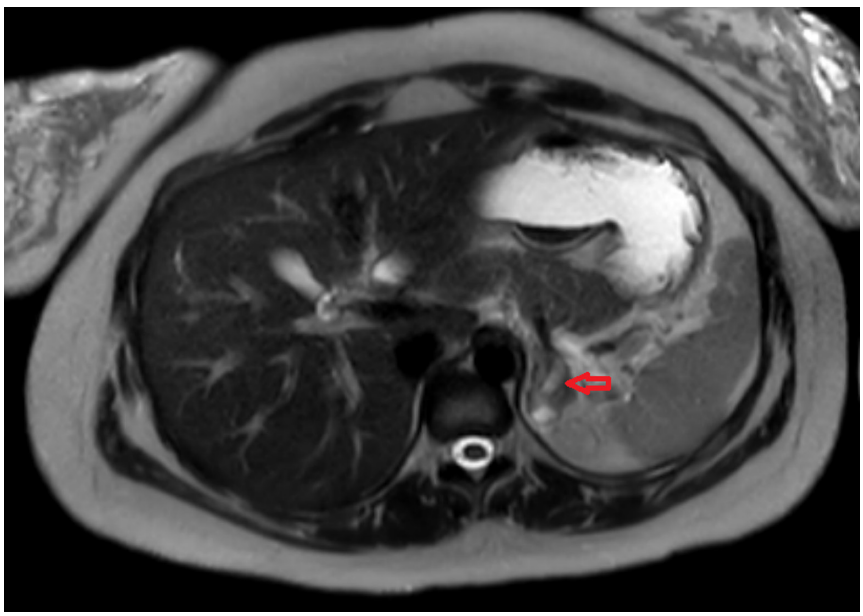

Figure 2
MRI abdomen showing T2 hyperintensity in the left adrenal gland with a hypoechoic rim. The red arrow shows the left adrenal gland.

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following 2 days and she was also started on fludrocortisone 0.05 mg daily. The patient was discharged home on this regimen on the fourth day of hospitalization.

Outcome and follow-up

The patient had a scheduled induction of labor at 38+5 weeks' gestation. Hydrocortisone 100 mg IV q8h was administered during labor. She had an uncomplicated vaginal delivery and the infant was healthy. Hydrocortisone and Fludrocortisone were continued after discharge.

She had her first appointment in the endocrinology clinic 2 months after delivery at which time the hydrocortisone dose was lowered to 15 mg in the morning and 5 mg in the afternoon and the fludrocortisone 0.05 mg daily was continued. Labs showed persistent elevation of ACTH to 151.9 pg/mL along with a low dehydroepiandrosterone sulfate (DHEAS) of 9 µg/dL (reference range: 65–380 µg/dL), which was evidence of ongoing adrenal insufficiency. The patient discontinued the fludrocortisone on her own after this appointment and denied the development of dizziness following discontinuation. She was normotensive with normal renin activity of 2.9 ng/mL/h (reference range: 0.5–4.0 ng/mL/h) and normal potassium level due to which the fludrocortisone was not resumed. Serial ACTH and DHEAS were obtained which showed elevated ACTH and low DHEAS.

The ACTH level was noted to have normalized 16 months after delivery but the DHEAS level remained persistently low. The patient felt well and was eager to stop the hydrocortisone because she felt that the hydrocortisone was making it difficult for her to lose weight. A cosyntropin stimulation test was then obtained which showed a peak post-cosyntropin cortisol level of 14. 5 µg/dL using the Access cortisol immunoassay. This was considered an adequate response given the lower cutoff for newer cortisol assays (5). Following shared decision-making, the decision was made to stop hydrocortisone. The patient was educated about the possible symptoms of recurrence of adrenal insufficiency. The patient did well after stopping the hydrocortisone and did not have recurrence of nausea, vomiting or dizziness.

Discussion

Pregnancy is associated with activation of the hypothalamic–pituitary–adrenal axis. There is increase in the plasma total cortisol due to the increased hepatic production of cortisol-binding globulin (CBG) under the effect of estrogen and increased free cortisol due to the displacement of cortisol from CBG by progesterone (6). The plasma total cortisol level rises in parallel to gestation and ranges from 16.3–55 µg/dL in the third trimester (7). Our patient's cortisol level was low for the third trimester at 7.7 µg/dL. Given that the patient was critically ill, we favored giving stress dose of hydrocortisone immediately over performing a cosyntropin stimulation test. The placenta is a source of ACTH and the ACTH level rises through pregnancy (7). In one study, a 3-fold elevation in the ACTH level was found in the third trimester compared to the first trimester (8). The ACTH level reaches a peak during delivery and normalized by 24 h after delivery (8). In our patient, the ACTH level was almost 4-fold elevated in the third trimester and remained elevated for over a year post partum. This supports the diagnosis of primary AI.

The most common etiology of primary AI is autoimmune adrenalitis (Addison's disease). Elevated levels of 21-hydroxylase antibody are highly specific for the diagnosis of Addison's disease and are found in over 90% of individuals with this diagnosis (9). Infectious etiologies of primary AI include tuberculosis, fungal infections and HIV. Infiltration of the adrenal glands by metastatic cancers, primary adrenal lymphoma, sarcoidosis or amyloidosis can lead to primary AI, which can be apparent on imaging (10, 11, 12, 13). Bilateral adrenal hemorrhage can lead to the development of new-onset primary AI in pregnancy (14). The adrenal glands are each drained by a single adrenal vein, and venous congestion associated with pregnancy can be a risk factor for the development of adrenal hemorrhage and infarction. The hypercoagulable state associated with pregnancy is also a risk factor for the development of NHAI (15).

In one retrospective study, NHAI was present in 1.3% of abdominal MRIs obtained in pregnant women for the evaluation of abdominal or flank pain (16). MRI features of NHAI include unilateral adrenal enlargement, increased T2 signal intensity without T1 hyperintensity and retroperitoneal edema near the affected adrenal gland. CT findings of NHAI consist of enlargement and hypoenhancement of the adrenal gland (17). Urinary tract calculi should be considered in the differential diagnosis for acute flank pain in pregnancy. In one study, urinary calculi was diagnosed in 13 out of 20 pregnant women who underwent CT of the

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Table 2 Literature review of case reports of unilateral NHAI in pregnancy.

Number	Author (year of publication)	Age (years)	Gestational age (weeks)	Presenting symptoms	Imaging modality	Laterality	Adrenal function status	Pregnancy and neonatal outcome
1	Ornaghi *et al.* (2023) (19)	21	32	Right upper quadrant and flank pain, nausea and vomiting	CT with contrast	Right	Normal	Uncomplicated delivery, healthy neonate
2	Shah *et al.* (2022) (20)	25	32	Left flank pain, vomiting	CT with contrast	Left	Adrenal insufficiency diagnosed post-partum	Preterm spontaneous rupture of membranes, neonate had breathing difficulties but made a full recovery
3	Warda *et al.* (2021) (21)	24	30	Left upper quadrant abdominal pain radiating to the back	MRI without contrast	Left	Adrenal insufficiency diagnosed based on suboptimal response on cosyntropin stimulation test	Uncomplicated delivery, viable neonate
4	Jerbaka *et al.* (2021) (22)	36	36	Left abdominal pain	CT with contrast	Left	Normal	Oligohydramnios, healthy neonate
5	Padilla *et al.* (2021) (23)	25	Second trimester	Right upper quadrant abdominal pain, nausea	MRI without contrast	Right	Not reported	Not reported
6	Chasseloup *et al.* (2019) (24)	30	32	Right abdominal pain	CT with contrast	Right	Normal	Preterm labor, healthy neonate
7	Hynes *et al.* (2019) (25)	21	29	Right upper quadrant abdominal pain, nausea, vomiting	MRI without contrast and CT with contrast	Right	Not reported	Uncomplicated pregnancy, neonatal outcome not mentioned
8	Aljenaee *et al.* (2017) (26)	29	24	Right upper quadrant abdominal pain	CT with contrast	Right	Not reported	Uncomplicated delivery, neonatal outcome not mentioned
9	Reichman *et al.* (2016) (27)	28	38	Right upper quadrant and flank pain	MRI without contrast	Right	Normal	Not reported
10	Sormunen-Harju *et al.* (2016) (28)	31	38	Right upper abdominal pain	CT with contrast	Right	Normal	Uncomplicated delivery, healthy neonate
11	Green *et al.* (2013) (29)	25	28	Right upper quadrant abdominal pain, nausea, vomiting	CT with contrast	Right	Normal	Preterm labor, healthy neonate
12	Schmitt *et al.* (2010) (30)	29	36	Right upper quadrant and flank pain	CT with contrast	Right	Normal	Emergency cesarean section for uncontrolled pain, neonate with moderate respiratory distress

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abdomen and pelvis for the evaluation of acute, refractory flank pain (18).

Unilateral NHAI typically does not lead to AI if the contralateral adrenal gland is healthy (19). The possible underlying pathophysiologic mechanism for the development of AI in our patient is that the healthy adrenal gland could not keep up with the demand for increased cortisol production in pregnancy. A literature review of all published cases reports of unilateral NHAI in pregnancy is provided in Table 2. The majority of cases of NHAI in pregnancy presented in the third trimester, with abdominal or flank pain and vomiting being the most common presenting symptoms. The right adrenal gland was more commonly affected. Only two previous cases of unilateral NHAI in pregnancy leading to AI were noted (20, 21). The left adrenal gland was involved in both cases, similar to our patient. Flank pain was the presenting clinic manifestation in both cases, but in neither of the two cases did the patient have hypotension or hypoglycemia. The first patient had spontaneous rupture of membranes during day 2 of admission and the AI was diagnosed post-partum based on a low random serum cortisol (20). In contrast to our patient, she did not develop adrenal crisis and only required oral hydrocortisone replacement. The second patient was diagnosed with AI based on a cosyntropin stimulation test that showed a mid-normal ACTH level and peak cortisol of 11 µg/dL (21). That patient stopped the hydrocortisone during pregnancy but went on to have a spontaneous vaginal delivery at 39 weeks and was given stress dose IV hydrocortisone during labor. Our patient is unique in having developed adrenal crisis as a result of the NHAI. Recovery of adrenal function occurred around 9 months post partum in the first patient, whereas the second case report did not provide information about the assessment of adrenal function following delivery. The longer duration required for recovery of adrenal function in our patient is likely related to having had a more extensive infarction.

The cornerstone for the management of primary AI is adequate glucocorticoid and mineralocorticoid replacement. The Endocrine Society guidelines suggest using hydrocortisone over other formulations of glucocorticoids such as prednisone (31). The typical pre-pregnancy hydrocortisone dose is 15–25 mg per day in two to three divided doses. The hydrocortisone dose is typically increased by about 20–40% beginning from the 24th week onward to mimic the physiological increase in free cortisol during pregnancy. Our patient was given a total daily hydrocortisone dose of 30 mg to reflect the increased hydrocortisone dose used during pregnancy. Mineralocorticoid replacement is done using fludrocortisone. The typical dose of fludrocortisone is 0.05–0.1 µg per day. The dose is adjusted based on the blood pressure and serum potassium level. Progesterone exerts an anti-mineralocorticoid effect due to which the fludrocortisone dose may need to be increased in late pregnancy if the patient develops orthostatic hypotension and hyperkalemia.

Our patient presented with hypotension, intractable vomiting, hyponatremia and hypoglycemia which was consistent with a diagnosis of adrenal crisis. The subacute adrenal infarction coupled with a UTI likely triggered the adrenal crisis. The incidence of adrenal crisis in patients with preexisting AI in pregnancy is around 7% (32). The incidence of adrenal crisis in pregnancy without a history of prepregnancy AI has not been reported in the literature. The treatment of adrenal crisis in pregnancy consists of prompt administration of stress dose IV hydrocortisone 100 mg every 6–8 h (7). Normal saline is administered to correct the hypotension. Five percent dextrose is added to the IV fluids in case of hypoglycemia. Fludrocortisone is not administered during an adrenal crisis because high dose hydrocortisone itself exerts a mineralocorticoid effect. Stress dose IV hydrocortisone is also administered at the onset of the second stage of labor and the dose is repeated every 6–8 h until delivery.

Our patient's AI persisted after delivery but later resolved at approximately 16 months post partum. The likely underlying mechanism behind the recovery of adrenal function is that the elevated ACTH level led to the hyperplasia of the contralateral adrenal gland which was then able to produce sufficient cortisol. Animal models have shown that unilateral adrenalectomy leads to increase in weight of the residual adrenal gland and that proliferation of cells occurs primarily in the zona fasciculata (33). Our case highlights that recovery of adrenal function is possible in the case of AI secondary to unilateral adrenal infarction in pregnancy.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the case study reported.

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Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement

LM participated in the treatment of the patient and drafting the manuscript. DE, JM, PS and SS participated in literature review, reviewing and revising the manuscript. All authors have read and approved the final draft of the manuscript.

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Diabetes And Glucose Metabolism

SAT173

Insulin Autoimmune Syndrome: A Rare Diagnosis With Unique Features

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Introduction: Insulin Autoimmune Syndrome [IAS], or Hirata's disease, is a rare cause of hypoglycemia. It is characterized by positive insulin autoantibodies in an insulin naïve patient and should be considered in the differential for post-prandial hypoglycemia. **Case:** A 48-year-old male presented with postprandial tremors, sweating, palpitations and episodes of incoherent speech and loss of consciousness at least 6 months prior to his presentation. He had no history of diabetes, however, was found to have severe symptomatic documented hypoglycemic episodes, with resolution of hypoglycemic symptoms upon treatment; fulfilling the Whipple's triad. Outpatient workup for causes of his hypoglycemia ruled out insulinoma, use of diabetes medications or insulin, adrenal insufficiency, severe illness, infections, thyroid, liver or kidney dysfunction. He never had gastrointestinal or bariatric surgery. Given his symptoms and severity of hypoglycemic episodes, he was admitted for observation and 72 hour fast. Lab work during hypoglycemic episode revealed inappropriately elevated insulin and low to normal c-peptide levels, undetectable proinsulin, elevated beta-hydroxybutyrate, normal IGF-1, IGF-2, and a negative sulfonylurea screen. Importantly, his insulin: c-peptide ratio was more than 1 and his insulin antibodies were elevated, consistent with IAS. He denied any history of autoimmune disorders or use of any medications with sulfhydryl group. CGM sensor clearly showed the relationship between high glycemic index foods, glucose spikes, and drops in his blood glucose several hours later. Dietary counselling was provided, without much improvement. Trials of Acarbose and Octreotide were not tolerated due to side effects like rash. Prednisone 20 mg bid was started; Diazoxide was titrated to 200 mg tid with much improvement. He has been followed by our clinic, and tapered to prednisone 10 mg bid and Nifedipine 30 mg daily with resolution of his symptoms. **Conclusions:** Severe hypoglycemia in non-diabetic patients requires investigation utilizing a broad differential diagnosis and biochemical evaluation. The findings of post-prandial hypoglycemia and inappropriately high insulin, with low to normal c-peptide and proinsulin levels with an insulin: C-peptide [ICP] ratio >1 in a non-diabetic patient is consistent with IAS. An ICP ratio >1 is a clue that the half-life of insulin has been increased by circulating antibodies. Mechanistically, post-prandial hyperglycemia cause insulin secretion, however, circulating insulin antibodies neutralize its effect. Ongoing hyperglycemia leads to further high levels of insulin, followed by intermittent spontaneous decoupling of insulin-antibody complex and subsequent post-prandial hypoglycemia. IAS may spontaneously resolve over time but may require indefinite length of treatment and dietary modification until this occurs.

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Recurrent Graves' Disease Following Near-Total Thyroidectomy: A Case Report and Literature Review

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Abstract

Recurrent Graves' disease due to regrowth of thyroid tissue is a rare complication of near-total thyroidectomy, which can be challenging to recognize and manage. Here, we present the case of a 30-year-old woman with Graves' disease and thyroid eye disease who underwent near-total thyroidectomy with resultant hypothyroidism. Her levothyroxine dose requirement gradually decreased and thyroglobulin level increased, which led to the diagnosis of recurrent Graves' disease. A neck ultrasound showed regrowth of thyroid tissue. The treatment options in such cases are repeat thyroid surgery and radioactive iodine ablation. The patient had moderate-severe active thyroid eye disease, so radioactive iodine ablation was contraindicated. Repeat surgery was deemed high risk due to the location of the residual thyroid tissue near the recurrent laryngeal nerve. Watchful waiting with serial thyrotropin (TSH) receptor antibody monitoring was chosen, and her levothyroxine dose was adjusted based on her thyroid function tests. There was a normalization of her TSH receptor antibody level over the next two and half years and stabilization of levothyroxine dose requirement. Recurrent Graves' disease must be considered when there is an ongoing decrease in the levothyroxine dose requirement associated with a rise in the serum thyroglobulin level following near-total thyroidectomy. Conservative management with medical therapy can induce remission in the case of recurrent Graves' disease following near-total thyroidectomy, without the need for radioactive iodine ablation or repeat thyroid surgery.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine
Keywords: graves’ disease, thyroglobulin, tsh receptor antibody, thyroid eye disease, thyroid surgery

Introduction

Graves’ disease is an autoimmune disorder in which there are antibodies directly against the thyroid follicular cells. The main autoantigen in Graves’ disease is the thyroid-stimulating hormone receptor antibody (TRAb), which binds to the thyrotropin receptor. TRAb generally has a stimulatory effect and leads to the oversecretion of thyroid hormones and proliferation of thyrocytes, resulting in hyperthyroidism [1]. Graves’ disease can be diagnosed by the finding of elevated TRAb in a patient with hyperthyroidism or by the presence of a diffusely increased uptake on a thyroid uptake and scan [2]. The treatment options for Graves’ hyperthyroidism include antithyroid medications (ATDs), radioactive iodine ablation (RAI), and total or near-total thyroidectomy [2]. Treatment with antithyroid medications can induce remission in around 50% of cases [3]. Both RAI and total thyroidectomy usually lead to the development of hypothyroidism requiring lifelong levothyroxine replacement to maintain euthyroidism.

In this context, we present a case of a 30-year-old woman with Graves’ disease who underwent near-total thyroidectomy that was complicated by the regrowth of thyroid tissue due to a TRAb stimulation. She had progressive reduction in the levothyroxine dose requirement leading to the diagnosis of recurrent Graves’ disease.

Case Presentation

A 30-year-old woman with a past medical history of depression, anxiety, and Crohn’s disease presented to the ER in October 2019 with a four-month history of palpitations, weight loss despite increased appetite, shortness of breath, worsening anxiety, diplopia, and prominence of eyes. She was seven months postpartum at that time and had initially attributed her symptoms to being postpartum. On physical examination, her heart rate was 123, respiratory rate was 26, and her BMI was 38.70 kg/m^2. She had a diffusely enlarged tender goiter, tachycardia, and fine tremors. The estimated thyroid size was 60 grams. Eye exam revealed lid lag, periorbital edema, proptosis, and chemosis, consistent with thyroid eye disease (TED). Labs revealed that the TSH was suppressed at <0.02 ng/dL (0.58-1.64 ng/dL), free T4 was elevated to 2.76 mg/dL (0.58-1.64 ng/dL), and total T3 elevated to 4.0ng/mL (0.7-2.0 ng/mL). The TRAb was elevated at 2.76 ng/dL (<1.75 IU/L), and thyroid-stimulating immunoglobulin (TSI) was elevated at >500% (<=122%), diagnostic of Graves’ disease. Thyroid ultrasound showed thyromegaly with the right lobe measuring 7.1 x 3.2 x 3.5 cm and the left lobe measuring 6.9 x 3.2 x 2.8 cm. No nodules were noted. Methimazole 20 mg twice

daily, propranolol 40 mg four times a day, and prednisone 60 mg daily were started. She reported chronic tobacco use and was counselled about smoking cessation.

Over the next two months, she developed worsening neck swelling and new onset dysphagia. Thyroid examination revealed an increase in the size of the goiter with an estimated thyroid size of 90 grams. She was referred to ENT who performed a total thyroidectomy in December 2019. The surgery was complicated by the high vascularity of the gland, due to which residual tissue was left behind near the recurrent laryngeal nerve. Pathology showed a 7.8 x 4.5 x 4.2 cm right lobe, 2.0 x 1.4 cm isthmus, and 6.2 x 3.6 x 3.2 cm left lobe, and the capsule was predominantly intact. Diffuse papillary hyperplasia was noted, consistent with the diagnosis of Graves' disease. A 0.4 cm focus of papillary thyroid cancer was noted on the left lobe (Figure *1A*, *1B*).

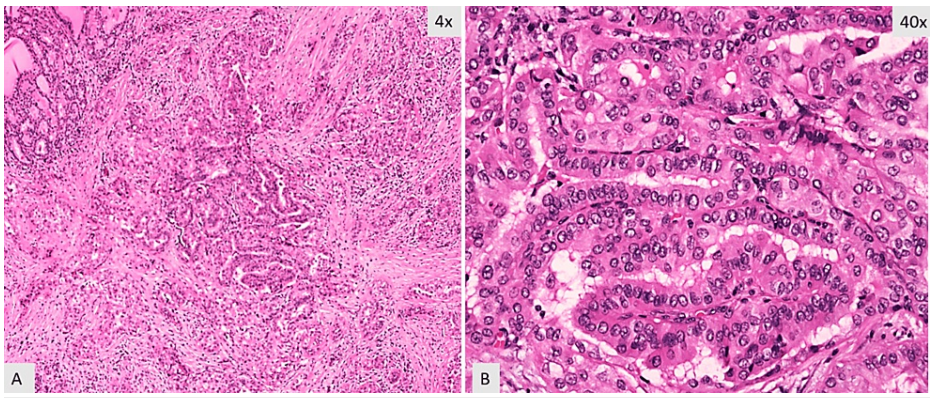

FIGURE 1: Histology from the total thyroidectomy showing the focus of the papillary thyroid carcinoma

A. Papillary thyroid thyroid carcinoma, classic variant in the background of papillary hyperplasia (hematoxylin & eosin stain, 4X magnification). B. Papillary thyroid carcinoma with nuclear enlargement and overlapping. Optically clear nuclei with thick nuclear membrane (hematoxylin & eosin stain, 40X magnification).

Given that the micro-papillary thyroid carcinoma was staged at pT1aNxMx, no further surveillance or RAI ablation was performed. The staging of pT1aNxMx denotes that the primary tumor was less than 1 cm in size and limited to the thyroid and regional lymph nodes or the presence of distant metastasis was not assessed on this pathology specimen.

She was started on levothyroxine 200 mcg daily following near-total thyroidectomy. TSI (>500%, normal value <122%) and TRAb (>18.44IU/L, normal value <=1.75IU/L) remained high one month after the surgery. The post-operative thyroglobulin was 0.5 ng/mL, which indicated that minimal residual thyroid tissue was left behind during the surgery. Serial labs showed persistent hyperthyroidism due to which her levothyroxine dose was gradually lowered until she reached a nadir dose of levothyroxine 50 mcg daily at one year after her near-total thyroidectomy (Figure *2*). Of note, her weight based levothyroxine requirement was 212 mcg daily at that time. Her thyroglobulin level increased from 0.5 ng/mL two months after the surgery to 19.9 ng/mL one year later.

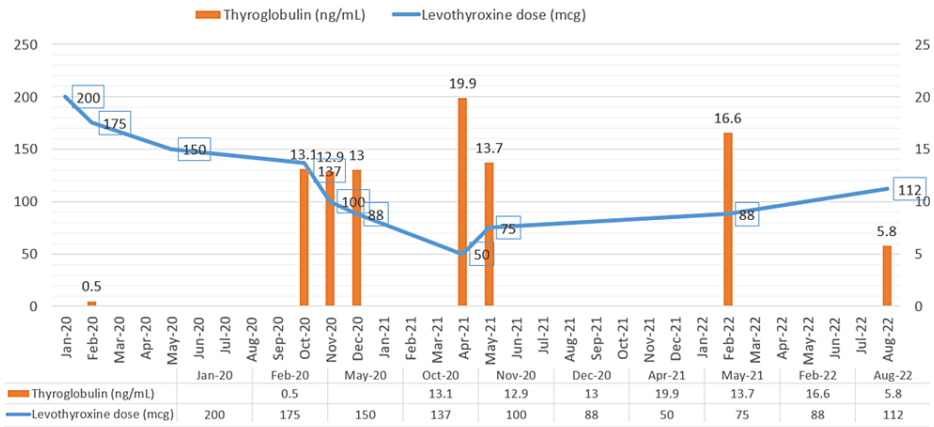

FIGURE 2: Relationship between the thyroglobulin level, TRAb, and levothyroxine dosage

In September 2020, she went to the ER for throat pain following ingestion of a pizza roll and concern for food getting stuck in her throat. CT neck soft tissue with contrast was obtained, which showed a hyperdense nodule in the region of the right thyroid lobe measuring 2.5 x 1.9 x 1.9 cm, concerning for the regrowth of thyroid issue. A neck ultrasound was obtained, which confirmed this finding (Figure *3*).

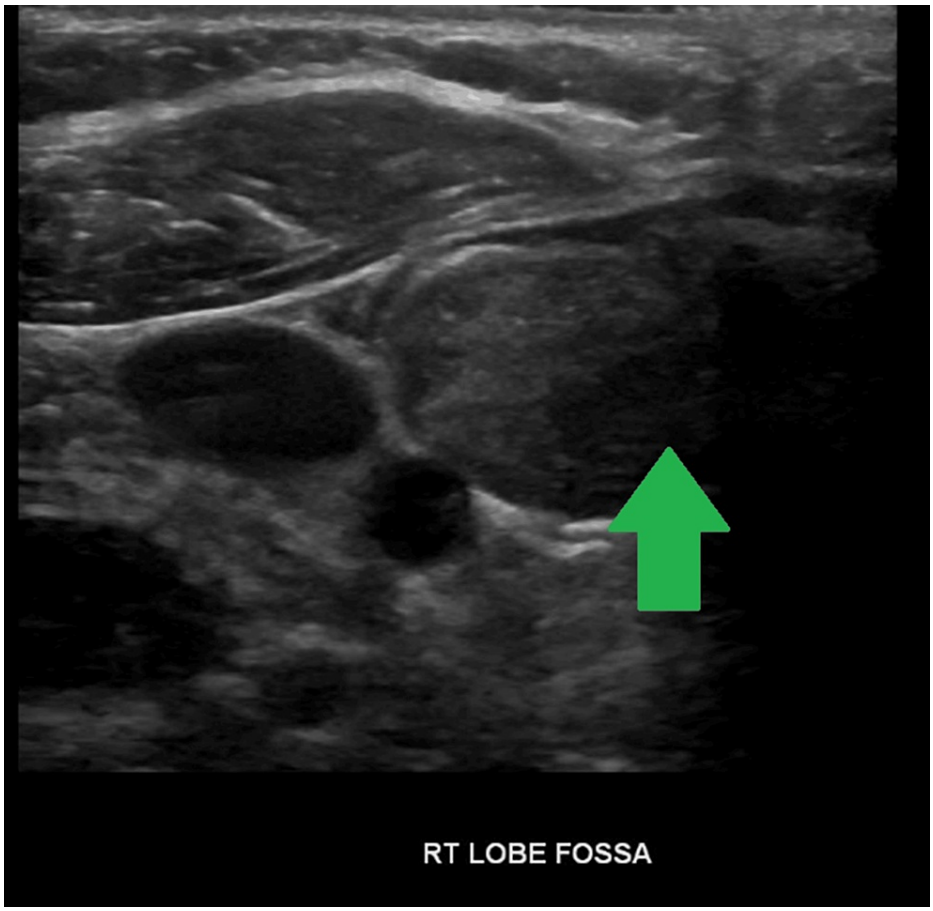

FIGURE 3: Neck ultrasound showing regrowth of thyroid tissue

The recurrence of micro-papillary thyroid cancer was unlikely because the tumor was present on the left lobe at the initial surgery. Thyroid uptake and scan was not obtained since the ultrasound finding was consistent with the regrowth of thyroid tissue. She was seen by surgery who deemed her a poor candidate for repeat surgery due to the location of the thyroid tissue in close proximity to the recurrent laryngeal nerve placing her at high risk for recurrent laryngeal nerve injury. RAI was contraindicated due to the presence of

moderate-severe active thyroid eye disease. Following a multidisciplinary discussion with endocrinology, surgery, and ophthalmology, the decision was made to continue conservative management.

On follow-up visit in May 2021, her TSH was elevated to 4.71, due to which her levothyroxine dose was increased to 75 mcg. She displayed a gradual increase in her levothyroxine dosage requirement over the next year along with a slow decline in her thyroglobulin level (Figure *3*).

At her most recent clinic visit in August 2022, she was maintained on levothyroxine 112 mcg daily. Her TRAb has declined into the normal range at 1.65 IU/L, and her thyroglobulin has decreased to 5.8 ng/mL, consistent with reduced endogenous thyroid hormone production. Neck ultrasound in July 2022 showed a decrease in the size of the residual thyroid tissue, which now measures 2.5 x 1.2 x 1.6 cm. This decrease in the size of the thyroid tissue is secondary to the decreased stimulation of the thyrocytes due to the normalization of TRAb and implied that there would be no further increase in thyroid hormone production from the residual thyroid tissue.

She was found to have active TED with a clinical activity score (CAS) of 3 immediately prior to her near-total thyroidectomy. CT of the orbits showed bilateral proptosis with enlarged extraocular muscles with mild to moderate crowding at the bilateral orbital apex. She displayed a worsening of her TED after total thyroidectomy with an increase in CAS to 7 in May 2020 despite a course of oral prednisone 40 mg daily. In addition, she displayed a worsening of her mood disorder due to the use of high-dose glucocorticoids due to which IV pulse methylprednisolone was not administered. She was subsequently started on teprotumumab every three weeks and completed a total of seven doses. Teprotumumab is a monoclonal antibody that acts as an antagonist at the insulin-like growth factor-1 receptor and attenuates the inflammatory response in TED. Her CAS improved to 2. At her most recent visit, her TED was inactive, but she had residual proptosis. Ophthalmology plans to see her in clinic every six months to monitor for signs of recurrence of active TED. They plan to perform orbital decompression to treat the proptosis if there is no recurrence of active TED.

Discussion

This case highlights a rare complication of near-total thyroidectomy for the treatment of Graves' disease and provides an overview of its diagnosis and treatment. The patient had a progressive decrease in her levothyroxine dose post near-total thyroidectomy, which raised the concern for regrowth of residual functional thyroid tissue. Imaging studies were consistent with regrowth of thyroid tissue. This case also highlights the utility of serum thyroglobulin for serving as a marker for thyroid hormone synthesis in the case of a benign thyroid disorder.

Thyroidectomy is the preferred treatment for Graves' disease under certain select situations, such as the presence of large thyroid nodules, thyromegaly with compressive symptoms, suspected or confirmed malignancy, or coexisting primary hyperparathyroidism [2]. Thyroidectomy can also be performed for treating Graves' disease in the presence of moderate-severe active TED. A prospective study showed that both subtotal and total thyroidectomy lead to an improvement in CAS in patients with moderate-severe active TED [4].

The optimum extend of thyroid surgery in Graves' disease has been a matter of debate historically. Bilateral subtotal thyroidectomy, which involves leaving a 2-4 gram remnant of thyroid tissue bilaterally was initially favored because of the aim of avoiding surgical hypoparathyroidism and recurrent laryngeal nerve injury [5]. This approach carries the risk of causing recurrent hyperthyroidism, especially if a large thyroid remnant was left behind or if the TSH receptor antibody titer is high. The risk of persistent hyperthyroidism is around 30%, with permanent hypothyroidism in 60% and long-term euthyroidism in only 10% of the patients [6]. Unilateral subtotal thyroidectomy with contralateral hemithyroidectomy (Dunhill procedure) involves leaving a 4-7 gram remnant on the side of the recurrent laryngeal nerve and macroscopic resection of the entire thyroid tissue on the contralateral side. Total thyroidectomy involves resection of all visible thyroid tissue bilaterally. It reliably induces hypothyroidism and carries a lower risk of recurrent hyperthyroidism than subtotal thyroidectomy. The risks of surgical complications, including permanent hypoparathyroidism and recurrent laryngeal nerve injury, are similar between subtotal thyroidectomy and total thyroidectomy when performed by a high-volume thyroid surgeon.

A prospective, single-center study of patients with Graves' disease who were randomized to bilateral subtotal thyroidectomy, Dunhill procedure, and total thyroidectomy showed that the TRAb titer decreased in all three groups equally and reverted into the normal range by the end of the study period in 76% of the study population [7]. There was an improvement in eye symptoms following surgery in 74% of the patients, no change in 21% of the patients, and worsening in 5% of the patients with no between-group differences. The post-operative complication rates of laryngeal nerve paralysis, bleeding, and permanent hypoparathyroidism did not show statistical significant differences between the three groups. The American Thyroid Association guidelines recommend total or near-total thyroidectomy as the procedure of choice for the surgical management of Graves' disease [2].

Near-total thyroidectomy involves the removal of the entire thyroid gland except for a unilateral or bilateral

remnant of less than 1 gram. A systematic review of total versus near-total thyroidectomy in Graves' disease showed that near-total thyroidectomy was associated with a lower risk of hypoparathyroidism [8]. There was no increased risk of recurrent hyperthyroidism with near-total thyroidectomy as compared to total thyroidectomy.

The initial post-operative levothyroxine dose following total thyroidectomy is determined by the formula 1.6 mcg/kg body weight per day, which provides the full replacement dose [2]. This formula has been reported to overestimate the levothyroxine dose requirement in obese individuals because the levothyroxine dose requirement is mainly a function of the lean body mass. In one retrospective cohort study that looked into weight-based levothyroxine dose requirement in patients who underwent total thyroidectomy, the levothyroxine dose required to achieve euthyroidism was 1.28 mcg/Kg for BMI > 40 kg/m^2 [9]. Our patient weighed 133.7 kg at the time of surgery with a BMI of 46.17 kg/m^2 due to which her levothyroxine dose was estimated at 212 mcg daily (based on the formulate 1.6 mcg/Kg), and she was started on levothyroxine 200 mcg daily. The levothyroxine dose was gradually lowered based on persistent hyperthyroidism until she reached a nadir dose of 50 mcg daily (corresponding to 0.32 mcg/kg). The dose requirement is lower in individuals with hypothyroidism who have a partially preserved thyroid function, such as some individuals with Hashimoto's thyroiditis [10]. The patient's decreased need for levothyroxine relative to her body weight was indicative of persistent endogenous thyroid hormone production, and this was confirmed by the finding of the elevated thyroglobulin level.

The role of serum thyroglobulin to serve as a marker for biochemically recurrence of papillary thyroid cancer following total thyroidectomy is well established [11]. Our case demonstrates that the serum thyroglobulin is helpful in tracking the endogenous thyroid hormone production when there is evidence of recurrent Graves' disease following total thyroidectomy. The level of thyroglobulin rose with the decrease in the levothyroxine dose requirement and subsequently declined when there was a normalization of the TSH receptor antibody level and increase in the levothyroxine dose requirement.

A neck ultrasound helps locate the site of the regrowth of thyroid tissue in the case of suspected recurrent or residual Graves' disease. If the neck ultrasound does not show evidence of thyroid tissue, a thyroid uptake and scan should be obtained to evaluate for the presence of ectopic thyroid tissue. Recurrent or residual Graves' disease and hyperthyroidism following thyroidectomy has been reported in ectopic thyroid tissue sites, namely, mediastinum [12,13], infrahyoid [14], thyroglossal duct remnants [15], lateral neck [16,17], or regrowth of thyroid tissue in the thyroid bed [18]. Therapeutic options include lowering the levothyroxine dosage, initiating ATDs [12,14], RAI ablation [12,14], or repeat surgery [14,15,16,17].

In our case, RAI ablation was contraindicated given the moderate-severe active TED. Repeat surgery for the resection of the residual thyroid tissue is associated with the risk of wound infection, laryngeal nerve paralysis, and hypocalcemia. We chose a conservative approach of a watchful observation with the lowering of the levothyroxine dose, monitoring TRAb and thyroglobulin levels. As the levels of TRAb improved to the normal range, the thyroglobulin level also reduced and levothyroxine requirements went up, without any additional therapy like ATDs, RAI, or repeat surgery. There was a resolution of the active TED along this time frame, which was attributed to the decrease in the TRAb level. TRAb binds to the TSH receptors on the orbital soft tissue and stimulates the release of pro-inflammatory cytokines. TRAb titers correlate with the disease severity in TED [19]. Hence, a decrease in the TRAb titer can lead to an improvement in TED.

Conclusions

Recurrent Graves' disease is a rare complication of near-total thyroidectomy for Graves' disease, which should be suspected when there is a progressive decrease in the levothyroxine dose requirement along with a rise in the thyroglobulin level. A high preoperative TRAb titer is a risk factor for recurrent Graves' disease by stimulating the proliferation of thyrocytes after near-total thyroidectomy. Conservative management with medical therapy can induce remission in the case of recurrent Graves' disease following near-total thyroidectomy. Our case illustrates the importance of a watchful observation along with surveillance of TRAb and thyroglobulin levels in diagnosing and treating this condition. Total thyroidectomy should be preferred over near-total thyroidectomy to reduce the risk of developing recurrent Graves' disease due to regrowth of thyroid tissue.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Lakshmi P. Menon, Jhansi Maradana

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Critical review of the manuscript for important intellectual content: Lakshmi P. Menon, Jhansi Maradana, Dinesh Edem

Drafting of the manuscript: Syeda Naqvi, Dinesh Edem

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Persistent Insulin Autoimmune Syndrome in a Caucasian Male in the Absence of Triggers

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Abstract

Insulin autoimmune syndrome (IAS) or Hirata disease is a rare condition presenting as recurrent hypoglycemia, and associated with elevated insulin levels in the presence of insulin autoantibodies (IAAs) in patients who were never exposed to exogenous insulin and with no evidence of pancreatic abnormalities. IAS is much more frequent in East Asians, especially the Japanese population, compared to the lower incidence in Caucasians. However, it can be associated with other autoimmune diseases or drug use like methimazole and alpha-lipoic acid (ALA).

We report a case of a 47-year-old Caucasian male presenting with a 12-month history of worsening episodes of fasting and post-prandial hypoglycemia associated with symptoms of dizziness, tremors, palpitations, and unconsciousness associated with hypoglycemia. Symptoms resolved with the administration of carbohydrate-containing foods, establishing Whipple's triad. At an outside facility, he had initial labs that showed elevated insulin levels (141 µU/ml) with normal glucose, C-peptide, and proinsulin levels, but there was no availability of an IAA lab assay. Given his symptoms, severity, and frequency of hypoglycemia, he was admitted to the hospital for a 72-hour fast, which showed the lowest glucose level of 64 mg/dl with inappropriately high insulin of 22.2 µU/ml, low C-peptide of 0.57 ng/ml, and undetectable proinsulin of <1.6 pmol/L, but with IAA being >50 U/ml (0.0-0.4 U/ml). He was treated with intensive dietary counseling with a low-carbohydrate diet and prednisone 20 mg twice daily initially. Additionally, he could not tolerate octreotide, diazoxide, and acarbose due to side effects. He is currently on prednisone 10 mg daily and nifedipine with no further hypoglycemic episodes, but still has a high IAA of >50 U/ml and serum insulin levels of 70-112 µU/ml.

Our case highlights the importance of recognizing hypoglycemia and checking for IAA levels as first-line diagnostic tests, in the absence of which there could be a delay in diagnosis and leading to unnecessary lab and imaging testing. Our case is unique since it happened in a Caucasian without any prior exposure to a triggering factor and has not undergone self-remission yet, which happens in most of IAS cases.

Categories: Endocrinology/Diabetes/Metabolism, Family/General Practice, Internal Medicine
Keywords: low carb diet, insulin autoimmune syndrome, postprandial hypoglycemia, hirata's disease, autoimmune hypoglycemia, high serum insulin, insulin antibodies

Introduction

Hypoglycemia is a condition in which plasma glucose is low enough to cause adrenergic and/or neuroglycopenic symptoms and signs. Hypoglycemia is confirmed by Whipple's triad, where all three criteria must be met, namely, symptoms or signs consistent with hypoglycemia, a low plasma glucose concentration, and resolution of symptoms or signs after plasma glucose is raised [1]. Insulin autoimmune syndrome (IAS), or Hirata's disease, is a rare condition presenting as recurrent spontaneous hyperinsulinemic hypoglycemia, which was described by Hirata et al. in 1970 [2,3]. IAS is associated with markedly elevated insulin levels in the presence of insulin autoantibodies (IAAs) in patients who were never exposed to exogenous insulin and had no evidence of pathologic pancreatic abnormalities [4]. Hypoglycemia is most likely post-prandial and/or fasting and could also occur after physical exertion [4,5].

IAS appears to be a form of type VII hypersensitivity that can be associated with certain human leukocyte antigens (HLAs), especially HLA DRB1*0406, which is more frequent in East Asians; hence, IAS was the third most common cause of hypoglycemia in Japan [6]. However, IAS in Caucasians appears to be associated with HLA DRB1*0403, which has a much lower incidence overall [3,5]. IAS can either be idiopathic or can be associated with other autoimmune diseases such as Graves' disease, systemic lupus erythematosus, rheumatoid arthritis, or monoclonal gammopathy or with certain drugs such as methimazole, carbimazole, and alpha lipoid acid (ALA) [3,5]. Due to its rare occurrence in Caucasians and the lack of IAA assays in some labs, IAS could often go undiagnosed for a significant period of time, with several unnecessary lab and imaging tests, resulting in significant morbidity for the patients. IAS is mostly a self-remitting disease but

can be challenging if it becomes persistent, with treatment being stopping the offending drugs, low-carbohydrate meal plan, glucocorticoids, alpha-glucosidase inhibitors, immunosuppressant or even plasma exchange [3-5,7,8]. There is no clear consensus on treatment guidelines, except for case reports or review papers.

We present a case of persistent IAS with delayed diagnosis in a Caucasian male without self-remission, being treated with dietary changes, glucocorticoids, and nifedipine.

Case Presentation

A 47-year-old male with no history of diabetes presented to our endocrine clinic for evaluation of fasting and post-prandial hypoglycemia with episodes of dizziness, tremors, palpitations, and unconsciousness associated with low blood glucose (BG) for the past 12 months. He was doing well until one year ago, when he noted feeling dizzy and lightheaded while driving, leading to an episode of disordered driving, which improved after eating a carbohydrate-containing food. Five months later, he had another episode where he lost control of the car, went completely quiet, and spoke incoherent sentences, which improved after eating. Over the past six months, he has had worsening and increasingly frequent episodes of dizziness, tremors, palpitations, speaking in incoherent sentences, and unconsciousness associated with a low plasma BG of <70 mg/dl. Symptoms resolved with the administration of carbohydrate-containing foods, fulfilling Whipple's triad. He has noted night-time fasting and post-meal symptoms. He endorsed 20 lbs. of weight gain in the last year due to eating foods constantly to keep his glucose in the normal range.

His past medical history was significant for obesity, and he was not on any medications. He never had gastrointestinal or bariatric surgery. Vital signs were normal, except for a BMI of 32. Apart from abdominal adiposity, the physical examination was unremarkable. Fasting outpatient workup revealed insulin levels of 86.1-141 µU/ml (2.6-24.9 µU/ml), plasma glucose of 90-140 mg/dl (70-105 mg/dl), C-peptide of 1.3-4.1 ng/ml (1.1-4.4 ng/ml), and proinsulin of 1.6-2.5 pmol/L (0.0-10.9 pmol/L). Other causes of hypoglycemia, like surreptitious diabetic medications, exogenous insulin, adrenal insufficiency, infections, severe illness, thyroid, liver, and kidney dysfunction, were ruled out. Given his endogenous hyperinsulinemia, he had an abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen, all of which did not reveal a pancreatic mass.

Labs	Results
HbA1c (4.8%–6.4%)	5.4
Fasting BG (70–105 mg/dl)	97
Fasting insulin (2.6–24.9 µU/ml)	86
Fasting C-peptide (1.1–4.4 ng/ml)	1.3
Proinsulin (0.0–10.9 pmol/L)	1.6
Sulfonylurea screen	Negative
TSH (0.34–5.60 µIU/ml)	0.91
Cortisol (6.2–19.4 µg/dl)	10.1
ACTH (7.2–63.3 pg/ml)	23

TABLE 1: Initial outpatient labs before the endocrinology visit. Elevated insulin levels with normal glucose levels suggest insulin binding with its autoantibodies.

BG: blood glucose, HbA1c: hemoglobin A1c, TSH: thyroid-stimulating hormone, ACTH: adrenocorticotropic hormone.

Given his symptoms, their severity, and frequency, he was admitted to the hospital for a 72-hour fast. Lab work during a hypoglycemic episode showed plasma glucose of 64 mg/dl, with inappropriately high insulin of 22.2 µU/ml, low C-peptide of 0.57 ng/ml, with undetectable proinsulin of <1.6 pmol/L, negative sulfonylurea and meglitinide screen, normal ACTH, cortisol and insulin-like growth factor-1 (IGF-1). Beta-hydroxybutyrate was elevated at 3.69 mmol/L (<0.27 mmol/L), and the response to the glucagon stimulation test was <25 mg/dl in 30 minutes, indicative of depletion of glycogen reserves. His insulin auto-antibodies were high at >50 U/ml (0.0-0.4 U/ml), suggesting insulin autoimmune syndrome (IAS). Continuous glucose monitor (CGM) sensor BG checks showed a clear relationship between high-glycemic foods with resultant glucose spikes with subsequent hypoglycemia two to four hours later.

72-hour fasting labs	Day 1	Day 3
Blood glucose (70–105 mg/dl)	115 (H)	63 (L)
Insulin (2.6–24.9 µU/ml)	92.3 (H)	20.4
C-peptide (1.1–4.4 ng/ml)	2.22	0.52 (L)
Proinsulin (0.0–10.9 pmol/L)	<1.6	<1.6
Beta-hydroxybutyrate (≤0.27 mmol/L)	0.92 (H)	3.69 (H)
Insulin antibody (0.0–0.4 U/ml)	>50.0 (H)	>50.0 (H)

TABLE 2: Labs at the beginning of the 72-hour fasting and before the end of the fast.

The patient didn't have any hypoglycemic symptoms with a glucose of 63; hence, it was an inconclusive test. Elevated insulin autoantibody results returned post-discharge, at which point he was started on treatment for IAS. IAS: insulin autoimmune syndrome.

Dietary counseling was provided to lower carbohydrates and increase protein, fats, and fiber-containing foods without much improvement. He was started on prednisone 20 mg twice daily, and octreotide 200 mcg three times daily, which could not be continued due to GI side effects. He was discharged home on prednisone and increasing doses of diazoxide with much improvement in BGs and symptoms. He had significant edema and weight gain with diazoxide 50 mg three times daily, resulting in stopping the medication. He was then switched to acarbose, which worked well but caused extensive rashes with the subsequent discontinuation of medication. He was then changed to prednisone 10 mg twice daily and nifedipine 60 mg ER daily, which he has tolerated for more than six months. Fifteen months after the diagnosis, he has been maintained on a low-carb diet, prednisone 10 mg once daily, and nifedipine 60 mg ER daily. He has lost 20 lbs. in the past year, now with a BMI of 29. He has significant and frequent hypoglycemic episodes whenever he stops taking prednisone or nifedipine. He continues to have insulin antibodies >50 U/ml and insulin levels ranging from 70 to 112 µU/ml; however, on his current regimen, his hypoglycemic episodes, as reported in the CGM, are very rare but tolerable.

Discussion

Our patient's case is unique, as there was a delay in the diagnosis of his insulin autoimmune syndrome (IAS), and he had no history of prior exposure to any triggering factor and no spontaneous self-remission.

IAS is a rare cause of spontaneous hyperinsulinemic hypoglycemia, initially described by Hirata et al. in 1970, which is characterized by markedly elevated insulin levels due to the presence of insulin autoantibodies (IAA), especially in patients with no prior exogenous insulin use or any pancreatic abnormality [4]. IAS can manifest either as post-prandial and/or fasting hypoglycemia, where insulin is bound to its autoantibodies, which have a high binding capacity to insulin and low affinity in nature. Post-prandially, carbohydrates in the meals result in pancreatic insulin secretion, but the insulin is strongly bound to the IAA, causing insulin-IAA complexes, resulting in post-prandial hyperglycemia and even higher insulin release. When the binding capacity is exceeded, the insulin dissociates from IAA and now causes significant post-prandial hypoglycemia two to five hours after a meal [9,10]. CGM studies have shown IAS to be associated with alternating post-prandial hyperglycemia followed by hypoglycemia [7,11]. Symptoms are initially adrenergic/autonomic (tremors, anxiety, hunger, and sweating), followed by neuroglycopenia (irritability, behavior change, confusion, loss of consciousness, or seizures). Weight gain has also been associated with elevated insulin levels and the need to eat constantly to avoid post-prandial hypoglycemia [1].

IAS has been classified as either idiopathic or drug-related, especially sulfhydryl-containing medications, namely methimazole [12], carbimazole, sulfonylureas, or ALA [3,13]. Sulfhydryl-containing medications bind and reduce disulfide bonds linking two insulin chains, making them more immunogenic to the antigen-presenting cells, resulting in the development of IAA [5]. IAS has also been associated with other autoimmune disorders in at least half of the cases in the Asian population. Oest et al. and Wammer et al. mention two distinct subtypes of IAS in East Asian and Caucasian populations [5,14]. It is postulated that IAS in East Asians is more drug-induced, has higher rates of self-remission, and is more associated with HLA subtype DRB1*0406, whereas the IAAs are polyclonal [15]. In contrast, IAS in Caucasians are more idiopathic with lesser rates of self-remission, association with HLA subtype DRB1*0403 and the IAA's being more monoclonal [3]. IAS is still a rare disease entity, except in Japan, where it's the third most common cause of hypoglycemia; however, worldwide prevalence is increasing given higher rates of offending drug/supplement use, greater clinical awareness, and routine checking of IAA's [4].

The first step in diagnosing the etiology of hypoglycemia would be to confirm hypoglycemia by documenting

Whipple's triad. In patients who fulfill Whipple's triad and do not have an obvious etiology for hypoglycemia, the next step is to proceed to the 72-hour fast to diagnose hyperinsulinemic hypoglycemia. Diagnosis of hypoglycemia includes insulinoma vs nesidioblastosis vs post-bariatric hypoglycemia vs exogenous insulin use vs use of hypoglycemic drugs. Oftentimes, cases of IAS are mislabeled as insulinoma, leading to inappropriate and expensive lab and diagnostic tests, which mostly occur due to a lack of clinician awareness of this disease entity. The gold standard for diagnosis of IAS involves elevated levels of insulin and IAA's. In the absence of exogenous insulin use, another giveaway is the presence of markedly elevated insulin levels compared to C-peptide levels, resulting in an insulin: C-peptide ratio of >1, which is typically <1 in insulinoma and other hyperinsulinemic states [3,9].

There are no definitive guidelines or consensus on the therapies for IAS. Most of the therapies are from case reports or case series with no comparison studies [3,4]. IAS is usually a self-remitting disease in three to six months, with offending drug withdrawal being the best initial step [9]. Management should be aimed at preventing the post-prandial glucose spike with a low-carbohydrate meal plan [16], with frequent small meals low in simple sugars resulting in lower rates of post-prandial hypoglycemia. Along similar lines, alpha-glucosidase inhibitors like acarbose [9] or voglibose reduce the breakdown of disaccharides to monosaccharides, preventing post-prandial hyperglycemia and hypoglycemia. Tapering doses of glucocorticoids have been successfully used to help with the remission or control of hypoglycemia. Other immunosuppressants, like azathioprine [17] and rituximab [7], have been used in various case reports with good success. Other treatments like octreotide [9], diazoxide [18], and partial pancreatectomy have been less commonly used. Plasmapheresis [8] has been successfully used as a last resort in emergencies. Calcium channel blockers (CCBs) like nifedipine and verapamil have been shown to reduce insulin secretion through inhibition of voltage-gated calcium channels on pancreatic β-cells [19]. There have been case reports [20] that have shown the effectiveness of nifedipine in cases of hyperinsulinemic hypoglycemia, especially in infants and post-bariatric hypoglycemia.

Our patient had a prolonged taper of glucocorticoids with a recurrence of hypoglycemic symptoms whenever his prednisone or nifedipine was tapered. He continues to have elevated IAA but significantly reduced hypoglycemic episodes on prednisone and nifedipine.

Conclusions

Hypoglycemia can cause significant morbidity and a structured diagnostic approach should be undertaken to discern its causes. IAS should be considered in the differential diagnosis of hyperinsulinemic hypoglycemia, which can be diagnosed by measuring IAAs in the setting of elevated insulin levels. Given the easier availability of medications and supplements that can contribute to the development of IAS, it is imperative to be aware of this disease entity, to prevent further unnecessary diagnostic testing. There is no definitive pharmacotherapy and further research is needed. First-line treatment involves stopping the offending drug and initiating low-carbohydrate meal plans, steroids, or other immunosuppressants. However, this is a mostly self-remitting disease with a good prognosis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Dinesh Edem, Lakshmi Menon, Jhansi Maradana, Priyanka Majety, Mc Anto Antony

Acquisition, analysis, or interpretation of data: Dinesh Edem

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Disclosures

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SAT-P65

Insulin Autoimmune Syndrome: A Rare Diagnosis With Unique Features

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ABSTRACT

Introduction:
Insulin Autoimmune Syndrome [IAS], or Hirata's disease, is a rare cause of hypoglycemia. It is characterized by positive insulin autoantibodies in an insulin naïve patient and should be considered in the differential for post-prandial hypoglycemia.
Case: A 48-year-old male presented with postprandial tremors, sweating, palpitations and episodes of incoherent speech, and loss of consciousness at least 6 months prior to his presentation. He had no history of diabetes, however, was found to have severe symptomatic documented hypoglycemic episodes, with a resolution of hypoglycemic symptoms upon treatment, fulfilling the Whipple's triad. Outpatient workup for causes of his hypoglycemia ruled out insulinoma, use of diabetes medications or insulin, adrenal insufficiency, severe illness, infections, thyroid, liver, or kidney dysfunction. He never had gastrointestinal or bariatric surgery. Given his symptoms and severity of hypoglycemic episodes, he was admitted for observation and 72 hours fast. Lab work during hypoglycemic episode revealed inappropriately elevated insulin and inappropriately normal c-peptide levels, undetectable proinsulin, elevated beta-hydroxybutyrate, normal IGF-1, IGF-2, and a negative sulfonylurea screen. Importantly, his insulin: c-peptide ratio was more than 1 and his insulin antibodies were elevated, consistent with IAS. He denied any history of autoimmune disorders or the use of any medications with a sulfhydryl group. CGM sensor clearly showed the relationship between high glycemic index foods, glucose spikes, and drops in his blood sugar several hours later. Dietary counseling was provided, without much improvement. Trials of Acarbose and Octreotide were not tolerated due to side effects like a rash. Prednisone 20 mg bid was started; Diazoxide was titrated to 200 mg tid with much improvement. He has been followed by our clinic and tapered to prednisone 10 mg bid and Nifedipine 30 mg daily with a resolution of his symptoms.
Discussion: Severe hypoglycemia in non-diabetic patients requires investigation utilizing a broad differential diagnosis and biochemical evaluation. The findings of post-prandial hypoglycemia and inappropriately high insulin, with low to normal c-peptide and proinsulin levels with insulin: C-peptide [ICP] ratio >1 in a non-diabetic patient is consistent with IAS. An ICP ratio >1 is a clue that the half-life of insulin has been increased by circulating antibodies. Mechanistically, post-prandial hyperglycemia cause insulin secretion, however, circulating insulin antibodies neutralize its effect. Ongoing hyperglycemia leads to further high levels of insulin, followed by intermittent spontaneous decoupling of insulin-antibody complex and subsequent post-prandial hypoglycemia. IAS may spontaneously resolve over time but may require an indefinite length of treatment and dietary modification until this occurs.

INTRODUCTION

- Insulin Autoimmune Syndrome [IAS], or Hirata's disease, is a rare cause of hypoglycemia, mediated by the presence of high titers of Insulin Auto-antibodies [IAA] in an insulin naïve patient[1].
- Diagnosis of IAS is challenging, requiring careful workup to rule out other causes of hyperinsulinemic hypoglycemia.
- It should always be considered in the differential for postprandial hypoglycemia.

Cause	Insulin	C-peptide	Proinsulin	Ratio of Insulin to C-peptide
IAS	↑↑	↑↑	↑↑	**> 1**
Insulinoma	↑	↑	↑	< 1
Exogenous Insulin	↑	↓	↓	> 1
Beta cell Hypertrophy	↑	↑	↑	< 1
Secretagogues	↑	↑	↑	< 1

Table 1[2]: Patterns of increase in levels of Insulin, C peptide, and proinsulin and ratios of ICP during hypoglycemic events according to cause

Labs	Results
Glucose	100
Insulin	132 [H]
C-Peptide	2.8
Proinsulin	2.5
IAA	> 625 [H]
SU panel	Negative

Labs	Results
Glucose	92
Insulin	71 [H]
C-Peptide	1.08
Proinsulin	< 1.6

Table 2: Lab results at 1st visit, 1 year ago
Table 3: Labs results after 1 year of diagnosis

CASE PRESENTATION

A 48-year-old Caucasian male presented with episodes of postprandial tremors, sweating, palpitations, and episodes of incoherent speech and loss of consciousness over the last 6 months. He had no history of diabetes or any autoimmune disorder. He was found to have severe symptomatic documented hypoglycemic episodes, with a resolution of hypoglycemic symptoms upon treatment, fulfilling Whipple's triad.

Outpatient workup for causes of his hypoglycemia ruled out insulinoma, use of diabetes medications or insulin, adrenal insufficiency, severe illness, infections, thyroid, liver, or kidney dysfunction. He never had gastrointestinal or bariatric surgery. Given his symptoms and the severity of hypoglycemic episodes, he underwent a 72-hour fast.

Lab work revealed inappropriately elevated insulin and normal c-peptide levels, undetectable proinsulin, elevated beta-hydroxybutyrate, normal IGF-1, IGF-2, and negative sulfonylurea screen. His insulin: C-peptide ratio was more than 1 and his insulin antibodies were elevated, consistent with IAS.

Dietary counseling was provided, without much improvement. Trials of Acarbose and Octreotide were not tolerated due to side effects like a rash. Prednisone 20 mg bid and diazoxide titrated to 200mg three times a day improved symptoms. He has been followed by our clinic and tapered to prednisone 10 mg daily, and Nifedipine 30 mg ER daily with a resolution of his symptoms.

DISCUSSION

- Severe Hypoglycemia in non-diabetic patients requires thorough biochemical investigation by utilizing a broad differential diagnosis.
- Findings of Post-Prandial Hypoglycemia [PPH] and inappropriately high insulin, with low to normal C-peptide and proinsulin levels with an Insulin:C-Peptide [ICP] ratio > 1 in a non-diabetic patient is consistent with IAS.
- In IAS, Post-prandial hyperglycemia causes insulin secretion, however, the circulating IAA neutralizes the insulin effect. Ongoing hyperglycemia leads to further higher levels of insulin release, followed by intermittent spontaneous decoupling of Insulin-antibody complex and subsequent hypoglycemia.
- IAS is a self-remitting disease, though management is mostly supportive, including dietary modifications with a low-carbohydrate, high-fiber, high-protein, and fat diet to prevent the development of PPH.
- Pharmacologic therapies include drugs that reduce pancreatic secretion [octreotide, diazoxide, or nifedipine], and immunosuppressive agents [glucocorticoids, azathioprine, and rituximab]

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QI Project to Improve Confidence Among Residents in Managing Inpatient Hyperglycemia

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Insulin Cheat Sheet for Management of Inpatient Hyperglycemia

Hyperglycemia in hospitalized patients is defined as blood glucose levels >140 mg/dL, although current guidelines recommend glycemic targets of BG levels between 140 to 180 mg/dL for most patients.[1]

For patients with inpatient hyperglycemia, please follow these steps:

Step 1: Assess home BG control.

- Does the patient have diabetes? What type? Type 1 or 2 or ketosis prone?
- What is the outpatient regimen? Oral meds or insulin ?
- Is outpatient BG controlled or not? (Any hypo or hyperglycemia, BG monitoring, complications, Check HbA1C, order one if not documented in the last 3 months) [A1c unreliable in anemia]

Step 2: Assess factors affecting current BG reading.

- ↑ BG: Stress, illness, steroids, Pressors, noncompliance, withholding diabetes medications.
- ↓ BG: low PO intake, illness, significant wt loss, inconsistent carbohydrate intake.

Step 3: Choose frequency of Gluco-checks.

- QAC, HS for patients eating consistent meals.
- Q4-6 in patients who are NPO, receiving continuous TPN or tube feeds.
- Add a 3 AM check if there is a high risk of nocturnal hypoglycemia.

Step 4: Consider treatment options.

1. **Oral and non-insulin injectable agents**
   - **Insulin is mainstay of inpatient diabetes management. Do not use oral meds while inpatient !!!**
   - **Metformin** should be avoided in AKI and eGFR <30, iodinated contrast, due to risk of lactic acidosis.
   - **Sulfonylureas** have a risk of hypoglycemia and weight gain.
   - **Thiazolidinediones** (-glitazones) have risk of fluid retention, wt gain, and contraindicated in CHF.
   - **SGLT2i** have risk of euglycemic DKA, must be held 3 days preoperatively.[2]
   - **GLP1-RA** have risk of gastrointestinal side effects.

2. **Insulin treatment**
   - **Insulin** is mainstay of inpatient diabetes management, for treatment of persistent hyperglycemia >180.
   - Has 3 components:
     - ✓ **Basal insulin: Long-acting insulin (once daily)** or rarely intermediate acting NPH - required in all type 1 DM patients and many type 2 DM patients.
     - ✓ **Nutritional / Bolus insulin: Rapid [analog]** or short acting insulin (regular) - Rapid insulin should be given within 15 minutes within a meal, Regular insulin should be given 30 minutes before a meal.
     - ✓ **Correctional insulin (SSI):** Rapid or short acting insulin - **Never appropriate as a monotherapy for patients with type 1 DM. Not appropriate as monotherapy > 24-48 hrs for most patients.**
   - Refer to the table at the end of the sheet for a summary of the different types of insulin and oral meds

Step 5: Choosing a diet: Choose 'diabetic diet' around max of 45 gms carbs per each meal

Step 6: Choosing an insulin regimen.

1. **If the patient on a home insulin regimen:** resume current home regimen considering home blood glucose control or inpatient factors that may affect control and require altering the regimen (→ step 2)
2. **Type 2 diabetes**
   a. **Mild hyperglycemia** (glucoses ≤ 200, diabetes controlled on oral meds at home, or insulin naive) - Give SSI. Can consider low-dose basal insulin.
   b. **Moderate hyperglycemia** (glucoses are running 201-300) - start basal insulin 0.2 units/day with SSI.
   c. **Severe hyperglycemia** (blood glucoses are running >300)- start TDD insulin 0.3 units/kg/day with half as basal and half as short-acting insulin divided between meals with SSI.
3. **Type 1 diabetes** - will likely have a home insulin regimen, if not start TDD insulin 0.3 units/kg/day with 50% as basal and 50% as short acting insulin divided between meals with SSI.
4. **Calculate Total Daily Dose: Give 50 as BASAL, and 50% as BOLUS/short acting insulin.**

If patient on insulin at home: consider changing TDD based on Step 1 and Step 2	
On Correction Insulin	Add total amount of correction insulin over the prior 24 hrs.
Lean body/ Renal insufficiency	0.2 – 0.3 units/kg
Obese	Calculate 0.4 U/kgs for Bgs 140-200 Calculate 0.5 U/kg for Bgs > 200

Step 6: Adjusting insulin regimen.
***Based on BG levels:**

1. **Basal insulin -** If fasting morning BG is consistently out of range adjust basal insulin. There is a risk of overbasalization (treating inappropriately with basal insulin when mealtime may be necessary). **Consider overbasalization** if: basal dose is >0.5units/kg or bedtime (HS) BG is >50mg/dl greater than morning BG, if hypoglycemia occurs, of if BG levels are highly variable during the day. [1]
2. **Meal-time insulin -** if bedtime or pre-meal readings are consistently out of range, consider adjusting meal-time insulin or starting meal-time insulin if not on it
3. **Choosing Sliding scale insulin [SSI] -**
   a. **Low dose:** if patients are type 1, very lean, Basal insulin dose < 20 U/day, have severe renal impairment or if very insulin sensitive based on readings
   b. **Moderate dose:** usual dose, basal dose is > 30 units/day
   c. **High dose:** Patients that have very high insulin requirements such as more than >100 units of insulin per day, or basal dose is > 50 units/day.

***If the patient is made NPO:**

- Basal insulin should be decreased to 50%-70% of home basal insulin.
- Hold meal-time insulin (if the patient is on it) and continue SSI.
- If full dose insulin is already given and the patient is made NPO (or enteral nutrition is held) initiate D5 or D10 IVF for duration of insulin action.

***If the patient is on continuous tube feeds:**

- Basal insulin: 50% of TDD (Detemir or Glargine once daily, or NPH twice daily).
- Nutritional/bolus insulin: 50% of TDD (Regular insulin Q6 hrs –preferred or aspart/lispro Q4h.)
- Additional correctional insulin can be added (also can be regular or rapid acting insulin, but similar to the type of nutritional insulin).

***Transitioning from IV insulin to subcutaneous insulin: [2]**

- Consider clinical factors that may affect insulin dose: nutrition (e.g., TF, poor PO intake), steroids, kidney function, patients without pre-existing diabetes require less basal insulin.
- At least a 2 hour-overlap is recommended between basal and IV insulin.
- Can use previous 6h, 8h, or 12 h of IV insulin to extrapolate a daily dose (i.e., insulin received in 6h x 4 = total daily dose) then utilize 50% to 80% of daily dose as basal for transition.
- Alternatively, you can use weight-based dosing: i.e., 0.25 units/kg as TDD.

***Converting non-formulary insulin to formulary insulin:**

- Do not use insulin U-500 for inpatients. Patients already on U-500 insulin at home, can anecdotally be managed on less insulin inpatient than on at home.
- Regular insulin has 1:1 dose conversion to Aspart/Lispro but will have longer duration of action (6 hours instead of 4 hours) and therefore longer between doses.
- Detemir[20-22 hr duration] has 1:1 conversion with Glargine[22-24 hr duration]
- Converting from 70/30 or premixed insulin to Glargine-Aspart regimen: Calculate total daily dose of insulin from 70/30. Give 40% of TDD as basal. Rest 60% to be split over meal-time rapid acting insulin.

Step 7: Discharge planning.

- Assess the need for **diabetic education,** especially if discharging on insulin as a new medication.
- Discharge can be an opportunity for improved glycemic control. Below is a general guide but consider clinical scenarios including risk of hypoglycemia, medication induced hypoglycemia, new diagnosis, etc. that would need adjustment:
  - **For patients with A1C <7%**, continue pre-admission regimen.
  - **If A1c is between 7%-9%**, consider adding small basal insulin dose or intensification of home regimen.
  - **If A1c is >9%,** use combination of oral meds and insulin at 80% of hospital requirements.[3]

Note: an endocrine consult is recommended for but not limited to:

1. Uncontrolled hyperglycemia despite using usual insulin regimens.
2. Frequent, severe, or unexplained hypoglycemia.
3. Type 1 Diabetes if labile glucoses.
4. If the patient uses an insulin pump at home.
5. Patient has labile blood sugar readings (Brittle diabetes).

OBJECTIVE

Hyperglycemia is a common inpatient finding among patients both with and without diabetes (according to the Arkansas Department of Health more than 1 in 9 adults in Arkansas had diabetes in 2014). The management of hyperglycemia is important in the inpatient setting because both hyperglycemia and hypoglycemia can be associated with adverse outcomes for patients. Despite the frequency of encountering hyperglycemia inpatient, residents rotating on UAMS Internal Medicine services often have questions about it's management.

METHODS

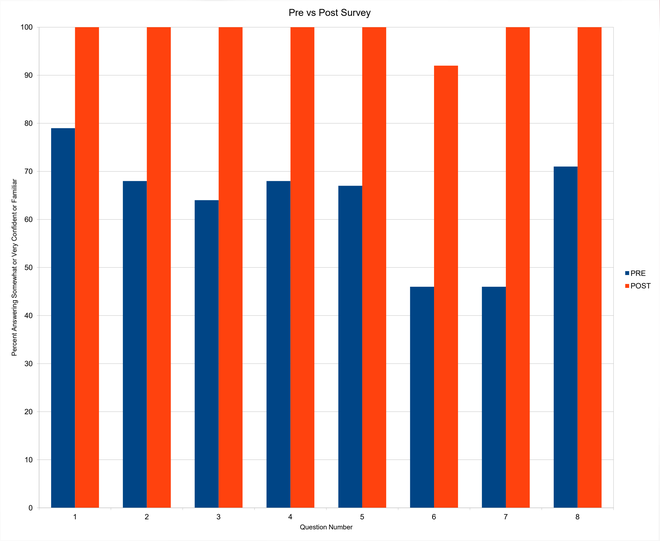
A survey was sent out to residents at UAMS assessing confidence regarding several common topics in inpatient hyperglycemia and diabetes management

→ A handout that is intended to serve as a quick reference to improve confidence was then provided

→ A post survey was sent out to assess improvement in confidence as well as to identify future areas of improvement

RESULTS

28 resident's complete the pre-survey before the handout was sent out and 12 residents completed the post-survey. The raw proportion of respondent's answering somewhat or very confident or somewhat or very familiar increased as seen in the chart below after the handout was distributed. To the question "Do you know when an Endocrine consult is recommended in management of inpatient hyperglycemia?" 46% of responses were "No" on the presurvey which decreased to 0% on the post survey.



CONCLUSIONS

An educational handout was able to increase the raw proportion of residents responding somewhat or very confident or somewhat or very familiar to questionnaire about common topics in inpatient hypoglycemia.

QUESTION REFERENCE

1. How confident are you in managing inpatients with hyperglycemia ?
2. How confident are you adjusting insulin in diabetic inpatients with uncontrolled blood glucose levels?
3. How confident are you starting insulin on insulin naïve patients?
4. How confident are you adding bolus insulin to basal insulin for better glycemic control in diabetic patients?
5. How confident are you adjusting insulin in diabetic inpatients who are NPO or on tube feeds?
6. How confident are you in using the various kinds of insulin given for glucose control?
7. How familiar are you with the uses and side effects of non-insulin hypoglycemic medications?
8. How confident are you with managing patients' diabetic medications at time of discharge?

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Ectopic Cushing's Syndrome Presenting As Refractory Hypokalemia

Program: Abstracts - Orals, Featured Poster Presentations, and Posters
Session: SUN 29-49-Congenital Adrenal Hyperplasia & Ectopic Cushing's Clinical

Sunday, June 16, 2013: 1:45 PM-3:45 PM
Expo Halls ABC (Moscone Center)

Poster Board SUN-45

Dinesh Edem*[*1]*, Priyanka Iyer[1], Katherine Fallano[1] and Esther Irina Krug[2]*
[1]Johns Hopkins University/ Sinai Hospital of Baltimore, Baltimore, MD, [2]Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD

Introduction: Ectopic ACTH production represents approximately 10% of the total cases of Cushing's Syndrome (1); with <1% caused by pancreatic neuroendocrine tumors (pNET). Optimal approach to diagnosis and management of these tumors is not well defined.

Case: An 82 yr old previously asymptomatic woman with known osteoporosis presented with a cervical spine fracture after sustaining a fall. On exam she had no cushingoid features except for mild plethora. Laboratory studies were notable for persistent hypokalemia (K=2.8 mmol/L) despite aggressive replacement, new onset hyperglycemia and metabolic alkalosis. Cortisol and ACTH levels were elevated at 71.9 mcg/dl and 187 pg/ml respectively. Cortisol level after 8 mg overnight dexamethasone suppression was 123 mcg/dL. CT scan of the abdomen revealed a 6 cm x 5 cm pancreatic mass and several liver lesions. An octreotide scan showed intense uptake in the pancreas and liver. Liver biopsy revealed metastatic small cell carcinoma with histopathologic staining and tumor markers suggestive of a pNET. She was felt not to be a candidate for surgical resection. Treatment with ketoconazole (400mg TID) initially resulted in decrease in cortisol levels and improvement of hypokalemia and hyperglycemia. Refractory hypercortisolemia recurred within several days despite ongoing treatment. Octreotide LAR (40 mg IM) was administered with no clinical response. She received one dose of mifepristone but was unable to continue due to inability to swallow whole tablets. As her condition declined, her family decided to pursue comfort care only and the patient died after 1 month of hospital stay.

Discussion: Pancreatic Neuroendocrine tumors can cause severe ectopic Cushing's Syndrome. Since cushingoid features are usually absent, its prevalence may be underestimated. Refractory hypokalemia may point towards diagnosis. In patients with unresectable tumors response to currently available medical therapies remains poor. Optimal treatment strategy and role of glucocorticoid receptor antagonists and its effects on morbidity and mortality requires further study.

(1) Ilias et al. 2005 Cushing's syndrome Due to Ectopic Corticotropin Secretion: Twenty Years' Experience at the National Institutes ofHealth. J Clin Endocrinol Metab 90(8): 4955.

Nothing to Disclose: DE, PI, KF, EIK

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Sacral osteomyelitis caused by klebsiella pneumoniae carbapenemase-producing klebsiella pneumoniae

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SINAI HOSPITAL
a LifeBridge Health center

Introduction

The last 17 years have seen the emergence of enterobacteriaceae strains, most notably Klebsiella pneumoniae (Kp), that produce Kp carbapenemases (KPC) and are resistant to virtually all beta lactam agents. Although endemic to various parts of the world, including the Northeastern United States (figure 1), infections caused by KPC-producing organisms have only sporadically been reported in Maryland[2]. KPC producers are most commonly found in the bloostreamt (figure 2), and only one case of KPC osteomyelitis has been described to date[4]. Here we present a case of KPC-producing Kp causing sacral osteomyelitis.

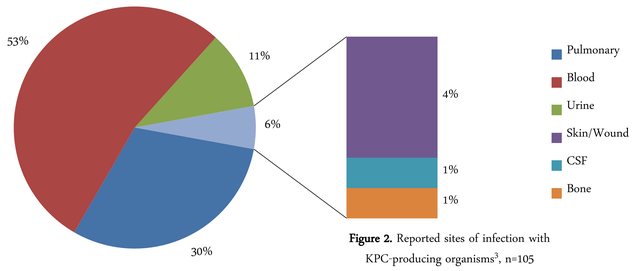

Figure 2. Reported sites of infection with KPC-producing organisms[3], n=105

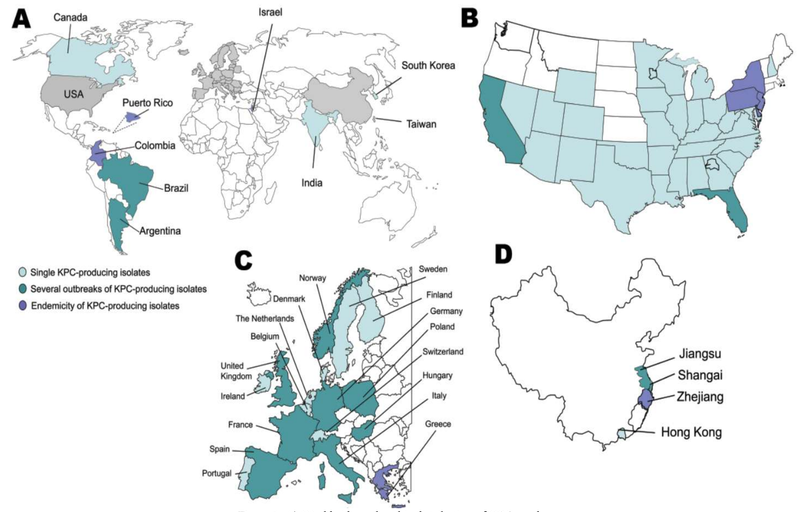

Figure 1. A) Worldwide geohraphic distribution of KPC producers; B) distribution in the United States; C) distribution in Europe; D) distribution in China[1]

Case Description

A 76-year-old woman with end-stage renal disease and paroxysmal atrial fibrillation was brought to the emergency room (ER) from a subacute rehabilitation facility (SAR) after becoming lethargic and developing a fever. Three months prior she had been living independently in the community, until an admission to an outside hospital for pulmonary edema due to hypertensive emergency, requiring intubation and an admission to the intensive care unit (ICU). During her three-week hospital stay she received one dose of ceftriaxone and a two-day course of cefazolin for empiric treatment of a urinary tract infection (UTI). She was discharged on a 14-day course of intravenous vancomycin for left arm cellulitis, as shown in figure 3. Two blood cultures and a urine culture had no growth. During her subsequent two-month stay in SAR she developed a sacral decubitus ulcer and received empiric ciprofloxacin for another UTI.

On presentation to our ER, she was noted to be hypotensive, tachycardic and tachypneic, and was intubated for impending cardiorespiratory failure. Vancomycin and piperacillin-tazobactam were started empirically, and she was admitted to the ICU. One of the two blood cultures drawn on admission grew Bacteroides sp, and the therapy was de-escalated to metronidazole three days after admission. Surgical debridement of the decubitus ulcer was performed. Preliminary results from soft tissue cultures identified vancomycin-resistant Enterococcus for which ampicillin was started. Subsequently, both soft tissue cultures and a bone culture grew KPC-producing Klebsiella pneumoniae, with sensitivities as shown in table 1. All antibiotics were discontinued and empiric tigecycline was started while additional antibiotic sensitivities were sent to the Mayo Clinic. Those revealed the organism to be sensitive to tigecycline and colistin. She was discharged to SAR on an 8-week course of i.v. tigecycline for KPC osteomyelitis.

Antibiotic	MDIL	MINT
Amikacin	≥64	R
Ampicillin	≥32	R
Ampicillin/Sulbactam	≥32	R
Cefazolin	≥64	R
Cefepime		R
Ceftazidime	≥64	R
Ceftriaxone		R
Ciprofloxacin	≥4	R
Gentamicin	≥16	R
Imipenem		R
Levofloxacin	≥8	R
Meropenem	≥16	R
Piperacillin	≥128	R
Trimethoprim/Sulfa	≥320	R
Tobramycin	≥16	R

Table 1. Antibiogram of the *Klebsiella pneumoniae* bone culture isolate

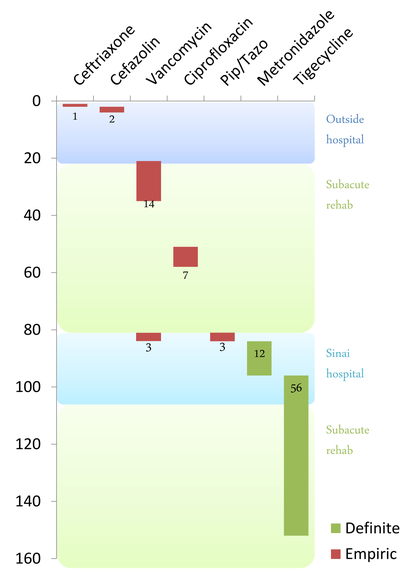

Figure 3. Antibiotics administered since initial admission to the outside hospital

Discussion

This is to our knowledge only the second case of KPC osteomyelitis reported in the literature. Our patient had several risk factors that predisposed her to colonization and subsequent infection by a KPC-produsing organism (table 2), most notably prior antibiotic therapy and multiple ICU adissions with intubations.

Bloodstream infections with KPC-producing organisms carry mortality rates as high as 50%, and is 100% in cases or resistance to the two mainstays of therapy—Tigecyclin and Polymixin B/Colistin[3]. Even short courses of these antibioitcs can promote resistance, and the first "pan-resistant" KPC organism has already been described[8]. This has raised concerns of overtreatment[9] in cases of colonization without signs of infection. The emergence of KPC osteomyelitis, a very real infection that requires a prolonged course of antibiotics, is therefore a cause for concern.

Risk factor	Colonization [5,6]	Infection [7]
Prior antimicrobial use	+	+
ICU admission	+	+
Respiratory insufficiency at ICU admission	+	
Central venous catheter (CVC) use		+
Duration of CVC use (>14 days)		+
Urinary catheter use	+	
Number of comorbidities	+	

Table 2. Risk factors associated with colonization or infection by KPC-producing organisms

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COMMUNITY ASSOCIATED METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (CA-MRSA) CAUSING SEVERE NECROTIZING PNEUMONIA WITH LOCULATED EMPYEMA IN AN ADULT

Radhika Parikh, M.B.B.S. (Associate); Dinesh Edem, M.B.B.S. (Associate); Patricia Tellez Watson (Associate); Marianne Cunanan-Bush M.D.; JHU/Sinai Hospital of Baltimore

Case Description: 47 year old Caucasian housewife admitted with shortness of breath, cough, and fever. She recently completed five days of azithromycin, but subsequently was sent to the Emergency Room for worsening cough and shortness of breath by Primary Care Physician. Past history significant for benign breast mass, however the patient was placed on Tamoxifen for reasons unknown to us. Two weeks PTA, she had shingles, but denied any recent hospitalization. She reported sick contacts including her children having a viral upper respiratory tract illness about a week prior to onset of symptoms. On admission she was tachycardic, tachypneic, and febrile but saturating over 95% on room air. On examination, breath sounds were reduced in left posterior lung zone. A 2 view chest X-ray and lateral decubitus film showed moderate size infiltrates in the lingula and left lower lobe of the lung with a moderate size free flowing left-sided pleural effusion. The laboratory findings showed leukocytosis and transaminitis. She was placed on Avelox for presumed CAP without improvement in symptoms, thus a Pulmonary consult was called for a diagnostic thoracentesis which was suggestive of empyema. CT thorax showed large left empyema with extensive consolidation of the left lower lobe. Thoracic surgery was called and performed a VATS procedure with chest tube placement. ID consult recommended intravenous (IV) Vancomycin as pleural fluid cultures grew MRSA. Her HIV antibody was negative. The patient was sent home as she clinically improved with a portable chest tube and a PICC line to complete a total of at least a 4 week IV Vancomycin course with close follow up with CT surgeon.

Discussion: In 2005, approximately 94,000 individuals developed their first invasive /serious MRSA infection, of which approximately 19,000 died. Of these individuals about 14% were community-associated. There are studies on risk factors for MRSA soft tissue and skin infections. MRSA prevalence is high in patients with HIV. There are not many studies linking higher incidence of invasive community acquired MRSA infection to immunocompromised states or hormonal treatment. Predictors of death include older age, residence in a nursing home, severe bacteremia, and organ impairment. Consultation with an ID specialist was associated with lower risk for death.

Conclusion: More studies need to be done on incidence of MRSA in patients on chemotherapy, with HIV and other immunocompromised states. A high suspicion for CA MRSA pneumonia in patients with recent immunosuppression, early diagnosis, and timely treatment play a key role in reducing morbidity and mortality.

Title: Lessons Learned from the Pilot Family Model of Diabetes Self-Management Intervention in the Republic of the Marshall Islands.

Introduction

Nearly one-third of Marshallese living in the Republic of the Marshall Islands (RMI) report having been diagnosed with type 2 diabetes mellitus (T2DM), a disparity likely to be related to historical trauma surrounding nuclear testing by the US in the mid-20th century, which significantly altered the Marshallese diet and lifestyle. Diabetes self-management education and support (DSMES) is an evidence-based intervention critical for persons to effectively manage diabetes and reduce the risk of complications. However, distrust of the medical community and socioecological factors in the RMI make the management of diabetes more difficult. Therefore, it is of critical importance to create an effective, culturally adapted family model of diabetes self-management education and support (F-DSMES), which addresses diabetes management through motivational family interviewing, goal-setting, and education on supportive behaviors, while focusing on behavioral changes in the family context.

In order to further improve F-DSMES interventions in the RMI and to inform work with similarly disadvantaged people in low-to-middle income countries, we report the results of the 12-month post-intervention data analysis, as well as an evaluation of the lessons learned during the implementation of a culturally adapted F-DSMES intervention.

Methods

Recruitment took place in four churches in Majuro and included 10 hours of content delivered over 8-10 weeks. Forty-one individuals with T2DM were included. As part of the adaptation of F-DSMES, an additional fifty-six family members, who live in the same household as those with T2DM participated F-DSMES education courses. We measured glycemic control by change in HbA1c and conducted interviews with eight participants to document participant-reported barriers encountered during the F-DSMES intervention.

Results

Participants showed statistically significant improvement in five measures of diabetes knowledge and family support. Participants also identified five barriers encountered during the intervention: 1) recruitment, retention, and attendance; 2) accessing physicians and/or medical counseling; 3) adhering to diet recommendations; 4) getting exercise; and 5) lack of detail/explanation within lessons.

Conclusions

Valuable information was gained to improve the development of larger-scale trials. The results provide evidence of the need for these trials and the desire of those with diabetes and their family members to participate in diabetes management programs. While improvements in diabetes knowledge and family support typically improve biometric measures, socioecological barriers in the RMI may make the knowledge more difficult to apply. Unemployment is high, minimum wage is low, and fruits and vegetables are difficult to obtain, so Marshallese in the RMI rely on cheap, filling options like rice and processed foods. Similarly, the lack of healthcare resources for people in the RMI is a barrier that is challenging to overcome. Cultural expectations surrounding food and mealtime may also require additional consideration in order to develop an effective, culturally-adapted F-DSMES. Those doing similar work in other low-to-middle income countries will need to take into consideration the potential barriers and facilitators within participants' social and physical environment. This intervention is aligned with the goals of transcultural nursing because it is designed improve cultural congruence, competence, education, and research surrounding the delivery of DSMES.

Risk of Hypoglycemia associated with U-500 Insulin Therapy in Markedly Insulin Resistant Diabetes (MIRD)

Sat-405-P

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Division of Endocrinology, VA Pittsburgh Healthcare System[1] & Division of Endocrinology, University of Pittsburgh Medical Center[2]

INTRODUCTION

- Insulin Resistance is the link between the epidemics of obesity and Type 2 DM
- MIRD, which requires >200 units/day of insulin, is the clinical manifestation of that link and the reason for the recent sharp increase in U-500 insulin use
- U-500 insulin improves HbA1C in MIRD, requires fewer injections of lower volumes, and improves patient satisfaction and quality of life[1,2,3]
- The prevalence of hypoglycemia on U-500 insulin is unclear; 4 studies show higher incidence, but 15 others show no change vs U100 insulin; however, all are based on symptom recall, patient questionnaires, or ICD-9 Codes, without SMBG verification, and are associated with significant ascertainment and recall biases, resulting in under-reporting of hypoglycemia
- Home Telehealth, in widespread use at VAPHS, involves automatic downloads to a central server of meter data in real time, and provides BG data that are accurate (data-driven), reliable (free of recall bias) and authentic (independent of patient bias)[4]

OBJECTIVES

To determine whether the hypoglycemia rates are increased during outpatient therapy with U-500 insulin compared to U-100 Insulin.

METHODS

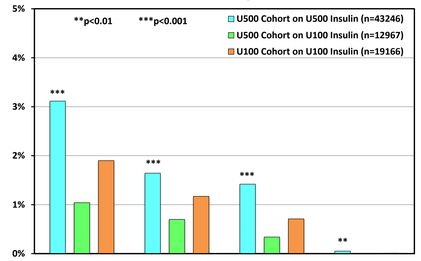
- Retrospective chart review of MIRD patients identified by VA pharmacy
  1. **U500 Cohort:** 221 patients converted to U500 insulin from U100 insulin
  2. **U100 Cohort:** 197 patients maintained on U100 insulin only
- 12 months of SMBG data were extracted over a 3 year period, and differentiated based on patient self documentation (SD) or Home Telehealth (HT)
- Prevalence rates of hypoglycemia were determined in both cohorts, plus the U500 cohort before conversion (on U100 insulin), and classified as Any (<70mg/dl), Mild (60-69 mg/dl), Moderate (40-59 mg/dl), and Severe (<40 mg/dl) Hypoglycemia
- Prevalence rates of hypoglycemia were calculated as:
  - ✓ Percentage of blood glucose measurements
  - ✓ Percentage of patients with ≥1 episode of hypoglycemia
  - ✓ Percentage of patients with >10 episodes over 12 months of monitoring
  - ✓ Percentage of BGs <70mg/dl, corrected for monitoring days
- Cohort Comparisons were made by χ^2 test
  - ✓ Comparing hypoglycemia in the U500 cohort on U500 insulin, U500 cohort on U100 insulin, and U100 cohort on U100 insulin
  - ✓ Comparing hypoglycemia rates on HT and SD
  - ✓ Comparing the frequency of Hypoglycemic readings/100 monitoring days
  - ✓ Comparing frequency of repetitive hypoglycemia (>10 episodes in 12 months)

RESULTS

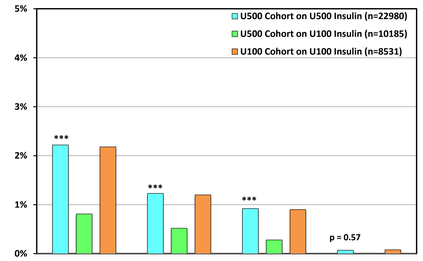
Patient characteristics

	U500 Cohort on U500 insulin (n=221)	U500 Cohort on u100 insulin (n=72)	U100 cohort on U100 insulin (n= 197)
Total # of BG values	66226	23152	27697
Total # of days BG's monitored	23707	8296	10298
Mean SMBG's/day	2.8/day	2.8/day	2.7/day
Patients checking BG's	201/221 (91%)	72/72 (100%)	111/197 (56.3%)
Pts using Home Telehealth (HT)	111/221 (50.2%)	38/72 (52.8%)	65/197 (33%)
Pts using Self Documentation (SD)	90/221 (40.7%)	34/72 (47.2%)	46/197 (23.6%)
Pts not checking BG	20/221 (9%)	0/72 (0%)	86/197 (43.7%)

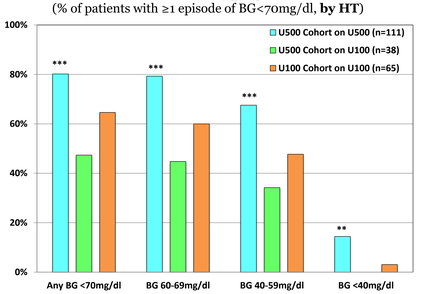
Prevalence of Hypoglycemia
(% of BG values <70mg/dl, by **HT**)



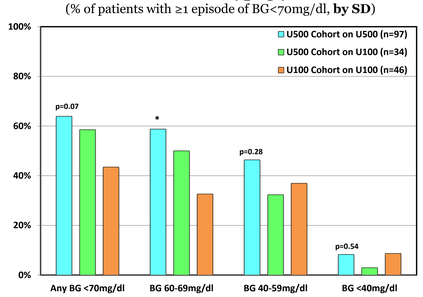
Prevalence of Hypoglycemia
(% of BG values <70mg/dl, **by SD**)



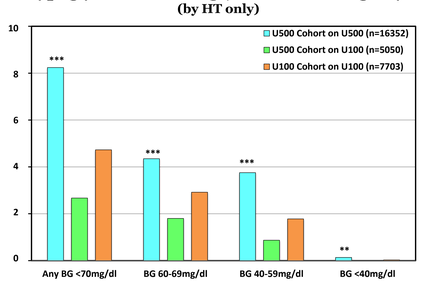
Prevalence of Hypoglycemia
(% of patients with ≥1 episode of BG<70mg/dl, **by HT**)



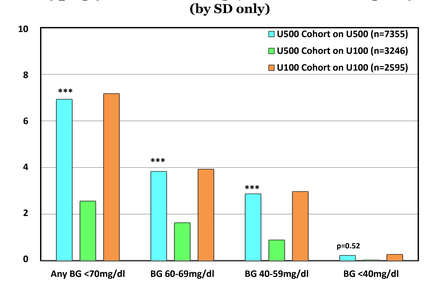
Prevalence of Hypoglycemia
(% of patients with ≥1 episode of BG<70mg/dl, **by SD**)



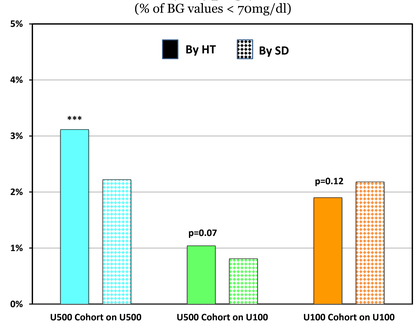
Hypoglycemic Readings/100 Monitoring Days
(by HT only)



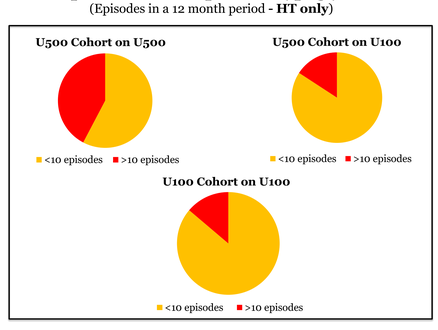
Hypoglycemic Readings/100 Monitoring Days
(by SD only)



Prevalence of Any Hypoglycemia, HT vs SD
(% of BG values < 70mg/dl)



% of patients with repetitive hypoglycemia
(Episodes in a 12 month period - **HT only**)



SUMMARY

- The **U-500 Cohort** was more likely to
  - Check BG more frequently
  - Use HT, which was more reliable than SD for documenting hypoglycemia
- **U-500 Cohort** had
  - More frequent episodes of hypoglycemia (mild, moderate, and severe)
  - More patients with at least 1 episode of hypoglycemia
  - More patients with repetitive hypoglycemia (>10 episodes/12 months)
  - Higher prevalence of hypoglycemic readings/100 monitoring days
- **Caveats**
  - Ascertainment bias: SD is subject to lack of reliability, and cannot be assumed that true prevalence of hypoglycemia is reflected by SD
  - Selection bias: The U-100 HT subset included only 33% of the U-100 cohort who diligently monitored BG, and may not be representative of the entire U-100 cohort

CONCLUSIONS

- U500 Insulin therapy is associated with mild, moderate and severe hypoglycemia, but whether or not it is commensurate with A1c reduction is yet to be demonstrated
- This is the first study to report reliable BG data from Home Telehealth (direct meter downloads) during U-500 therapy
- HT, or any other method involving direct meter downloads, provides the only reliable estimate of hypoglycemia prevalence, eliminating the recall bias associated with self documentation (SD)

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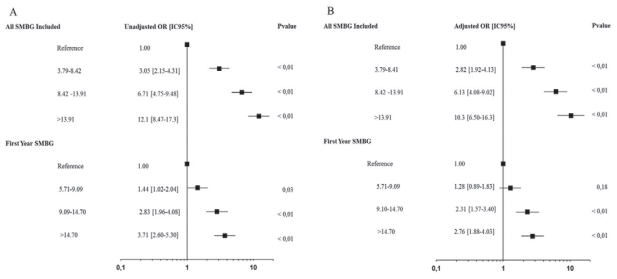
The above does not represent the views of the Department of Veterans Affairs or US Government

Figure.



403-P

Clinical Correlates of Predictors of Hypoglycemia over Four Years in 2,729 People with Type 2 Diabetes Starting Insulin

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We aimed to identify factors associated with documented symptomatic hypoglycemia (DH), and severe hypoglycemia (SH), in people starting insulin therapy in the CREDIT study, an international prospective observational study. Data was collected from routine care semi-annually over 4 years; 2,729 and 2,271 people had data from the last 6 months of years 1 and 4. Multivariable logistic regression selected factors associated with DH - the models were then applied to SH. Participants with ≥1 DH event (excluding SH) were 18.5% and 16.6% in years 1 and 4, 24.6% and 18.3% if achieving HbA1c <7.0% (SH 3.0% and 4.6%), and 16.5% and 16.2% if not (SH 1.5% and 1.1%). On multivariable analysis, baseline variables associated with DH at year 1 were lower body mass index, more physical activity, and no oral agents vs. sulfonylurea, with lower HbA1c, higher total insulin dose, and sulfonylurea use at year end. In year 4, baseline variables were lower body mass index, higher diastolic blood pressure (BP), lower HbA1c, macrovascular disease, and more physical activity, and explanatory variables higher systolic BP, lower HbA1c, and higher insulin dose. Insulin regimen was a univariate associate, weaker at year 4 than year 1, and not retained on multivariate analysis. The models developed for DH predicted SH. Thus the results confirm that thinner, active people, taking oral agents and having better glucose control with higher insulin doses have more DH in the years after starting insulin. Predictor and explanatory variables developed for DH can be extended to SH. The suggestion from intensive control studies that DH/SH is more of a problem at higher HbA1c is not supported in routine care. Hypoglycaemia (DH and SH) occur at significant but not high rates after starting insulin therapy, but with active management rates are stable over 4 years despite increased insulin dosage. The association with insulin regimen and with oral agent use declines from year 1 to year 4 with active clinical management.

Supported By: Sanofi

404-P

Within-Day Variability Based on 9-Point Profiles Correlates with Risk of Overall and Nocturnal Hypoglycemia in Adults with Type 1 (T1D) and Type 2 Diabetes (T2D)

TIMOTHY S. BAILEY, ANUJ BHARGAVA, J. HANS DEVRIES, GREGG GERETY, JANUSZ GUMPRECHT, WENDY S. LANE, CAROL H. WYSHAM, BRITTA ANKER BAK, CHARLOTTE THIM HANSEN, ATHENA PHILIS-TSIMIKAS, *Escondido, CA, Des Moines, IA, Amsterdam, Netherlands, Albany, NY, Katowice, Poland, Asheville, NC, Spokane, WA, Søborg, Denmark, San Diego, CA*

Higher glycemic variability has previously been linked to an increased risk of hypoglycemia. The correlation between within-day variability, based on 9-point profiles, and hypoglycemia was investigated in two double-blind, treat-to-target, crossover trials comparing insulin degludec once daily (OD) with insulin glargine U100 OD in adults with T1D (SWITCH 1, n=501) or insulin-experienced adults with T2D (SWITCH 2, n=721). Within-day glycemic variability was calculated as the relative fluctuation of the 9-point profile, defined through the integrated absolute distance from the mean within-day variability. Variabilities were subsequently categorized into low, medium and high tertiles based on the geometric mean. Hypoglycemia was defined as overall symptomatic (severe or blood glucose [<56 mg/dL] confirmed), nocturnal symptomatic (00:01-05:59) and severe (requiring third-party assistance and confirmed by a blinded adjudication committee) events. This analysis showed that an increase in within-day variability has a significant correlation with an increasing risk of overall and nocturnal hypoglycemia (Table). However, no correlation was found for severe hypoglycemia in this dataset.

In conclusion, within-day glycemic variability is associated with a risk of overall and nocturnal hypoglycemia.

Table. Effect of Within-Day Variability (9-Point Profile) on Hypoglycemia in SWITCH 1 and 2: Low and High Tertiles Compared with Medium Tertile.

Hypoglycemia	Variability tertiles	SWITCH 1			SWITCH 2		
		Events	Estimate [95% CI]	*p*-value	Events	Estimate [95% CI]	*p*-value
Overall	Low	1318	0.92 [0.82; 1.03]		140	0.79 [0.61; 1.03]	
	Medium	1675	1.00	*p*=0.0008	258	1.00	*p*<0.0001
	High	2234	1.15 [1.04; 1.27]		430	1.49 [1.20; 1.86]	
Nocturnal	Low	166	0.76 [0.59; 0.97]		44	0.76 [0.49; 1.20]	
	Medium	247	1.00	*p*<0.0001	79	1.00	*p*=0.0002
	High	365	1.45 [1.14; 1.84]		149	1.72 [1.22; 2.41]	
Severe	Low	54	0.78 [0.49; 1.25]		8	1.46 [0.52; 4.13]	
	Medium	55	1.00	*p*=0.5388	9	1.00	*p*=0.7756
	High	53	0.81 [0.50; 1.31]		10	1.18 [0.45; 3.08]	

SWITCH 1: NCT02034513; SWITCH 2: NCT02030600
CI, confidence interval

Supported By: Novo Nordisk A/S

405-P

Accurate Assessment of Hypoglycemia Risk with U500 Insulin in Markedly Insulin Resistant Diabetes (MIRD) from Direct Meter Downloads via Home Telehealth (HT)

DINESH EDEM, MICHAEL GRIMES, RONALD CODARIO, R. HARSHA RAO, *Pittsburgh, PA*

Introduction: Five-fold concentrated (U500) insulin is a viable therapeutic option in MIRD (Total daily dose of insulin ≥200 units/d), with well-documented glycemic efficacy but uncertain hypoglycemia risk. Studies report conflicting data, with both higher and unchanged hypoglycemia risk, but the methods used to assess hypoglycemia, such as diagnosis codes, questionnaires, and blood glucose [BG] logs, are unreliable and known to under-report hypoglycemia.

Objective: To assess the true risk of hypoglycemia in MIRD patients taking U500 insulin.

Methods: Retrospective chart reviews of MIRD patients being treated with either U500 (n=221) or U100 insulin (n=199), to determine the fraction of BG values <70 mg/dl and number of hypoglycemic episodes over a year, using BG data derived from meter downloads via HT or self-documented (SD) patient BG logs.

Results: The U500 cohort was more likely to check BG (199/221 [90%] vs. U-100 113/199 [57%], p<0.001), use HT (99/221 [45%] vs. 47/199 [24%], p<0.001), and maintain lower A1c (8.1±0.1% vs. 8.7±0.1%, p<0.01). U-500 patients also documented more BG values <70mg/dl (1362/50013 [3%] vs. 456/23714 [2%], p<0.001), and more experienced hypoglycemic episodes (143/199 [72%] vs. 62/113 [55%], p<0.01). However, the increase was limited to mild (BG 60-69 mg/dl; 128/199 [64%] vs. 52/113 [46%], p<0.01) or moderate hypoglycemia (BG 40-59 mg/dl; 107/199 [54%] vs. 45/113 [40%], p<0.05), not severe hypoglycemia (BG <40mg/dl; 20/199 [20%], vs. 7/113 [6%], p=0.3), and only evident by HT (948/31021 [3%] vs. 205/12518 [2%], p<0.001), not SD (414/18992 [2%] vs. 251/11196 [2%], p=0.7).

Conclusions: U500 insulin therapy improves glycemic control, but increases the risk of mild and moderate, but not severe hypoglycemia. However, higher hypoglycemic risk is seen only in verified BG data from direct meter downloads by HT, not in self-documented BG logs, indicating a significant recall bias in reporting hypoglycemia.

406-P

Hypoglycemia Rates in Type 2 Diabetes Mellitus: Results of the Population-Based InHypo-DM Study (Canada)

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A thorough understanding of medication-related hypoglycemia incidence is important to the therapeutic optimization of type 2 diabetes (T2DM). This study aimed to substantiate the population-based effect of insulin and/or sulphonylureas (SUs) on the rate of hypoglycemia.

All data were obtained from the InHypo-DM cross-sectional cohort study, Canada's largest hypoglycemia-related survey to date. Negative binomial

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Glycemic Excursions and Bolus frequency with Insulin Pump Therapy

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[1]Division of Diabetes, Endocrinology and Metabolism, UPMC

Introduction

- **Insulin Pump Therapy (IPT)** is one of the most effective means of optimizing glycemic control in patients with Type 1 (T1DM) and insulin requiring Type 2 Diabetes (T2DM).
- **Advantages** of IPT include better glycemic control, improved quality of life, and flexibility of insulin administration.
- **Limitations** of IPT include increased costs, risk of DKA, infusion site infections, and a need for higher degree of technical ability.
- Potential adverse effects of IPT include **hypoglycemia** due to excessive or frequent administration of insulin boluses (i.e. insulin stacking), and **hyperglycemia** due to inappropriate basal insulin infusion rates, or errors in carbohydrate counting or correction bolus administration.
- The frequency of hypo- and hyperglycemia and their relation to bolus frequency with IPT has not been previously investigated.

Objectives

- To identify patient practice patterns with IPT.
- To compare HbA1c, frequency and severity of hypo- and hyperglycemia, and glycemic variability (GV) between patients using IPT who bolus <5 vs ≥5 times daily.

Methods

- **Inclusion Criteria:** Patients > 18 yrs with T1DM or T2DM.
- Retrospective chart review of 100 consecutive patients using Medtronic® (Fridley, Minnesota) IPT, attending a University based specialty diabetes center.
- 2 weeks of de-identified insulin pump data was downloaded and grouped according to bolus frequency of <5 (**Group 1**: n = 45) and ≥5 (**Group 2**: n = 55) times/day.

Results

Table 1: Demographics

	<5 Bolus/day (n=45)	≥5 Bolus/day (n =55)	p value (t test)
Age (Mean)	44.6 ± 16.5	44.3 ± 15	0.93
Gender (% female)	64 %	62%	0.79
Race (% Caucasians)	98%	96%	0.68
Type of diabetes (T1DM)	96%	95%	0.83
Duration of diabetes (yrs)	27.3 ± 14.6	25.5 ± 11.6	0.49
Weight (Kg)	80.4 ± 14.7	78.6 ± 20.3	0.62
BMI (kg/m^2)	28.2 ± 4.9	27.3 ± 5.2	0.36
Creatinine (mg/dl)	0.93 ± 0.28	0.87 ± 0.2	0.31

Table 2: Patient practices

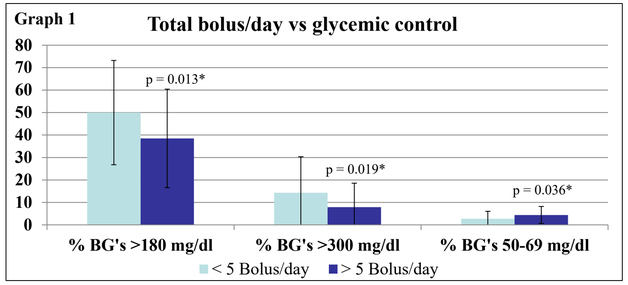
	<5 Bolus/day	≥5 Bolus/day	p value
Average BG reads/day	4.5 ± 4.4	5.8 ± 3.0	0.091
# of Total bolus/day	3.7 ± 0.8	7.32 ± 2.1	**<0.001**
# of Manual bolus/day	0.3 ± 0.5	1.24 ± 2.4	**0.012**
# of Wizard bolus/day	3.4 ± 1	6.09 ± 2.5	**<0.001**
# of Bolus with food/day	2.5 ± 1.0	3.95 ± 1.8	**<0.001**
# of Bolus with correction/day	2.3 ± 0.8	3.4 ± 1.6	**<0.001**
# Bolus overrides/day	0.6 ± 0.8	1.1 ± 1.4	**0.018**
Average suspend duration/day (min)	14.5 ± 26.7	19.6 ± 44.9	0.503
Total daily dose (TDD) insulin (Units)	47.5 ± 17.7	47.8 ± 26.5	0.94
TDD insulin (Units/kg)	0.6 ± 0.2	0.6 ± 0.2	0.980
% of TDD as bolus insulin	44 ± 13.9	50.9 ± 10	**0.005**
# of site changes/14 days	4.1 ± 1.1	4.5 ± 1.5	0.091

Table 3: Glycemic measure outcomes

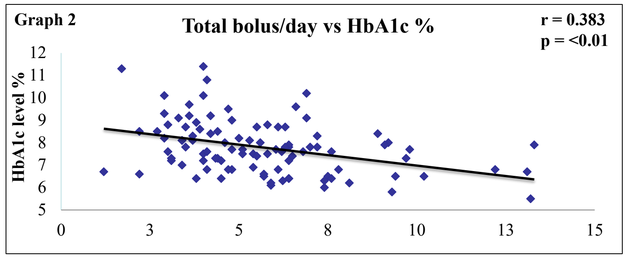
	<5 Bolus/day	≥5 Bolus/day	p value
HbA1c (%)	8.3 ± 1.3	7.4 ± 1	**<0.001**
Mean BG/14 days (mg/dl)	200.6 ± 49.5	175.8 ± 44.3	**0.01**
Coefficient of BG variability	39.3 ± 11.9	40.1 ± 9.4	0.669
% BG's <50 mg/dl	0.5 ± 1.3	0.7 ± 1.5	0.434
% BG's <40 mg/dl	0.1 ± 0.4	0.9 ± 0.5	0.242

Table 1, 2, 3: Data presented as Mean ± Standard Deviation.
p value significant at $p < 0.05$

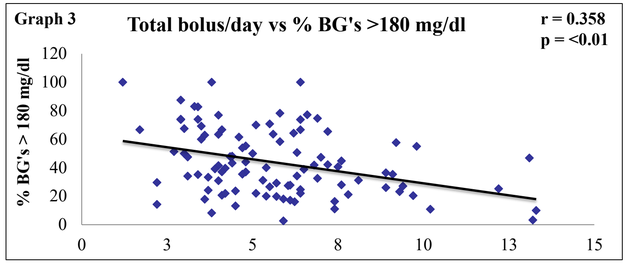
Graph 1



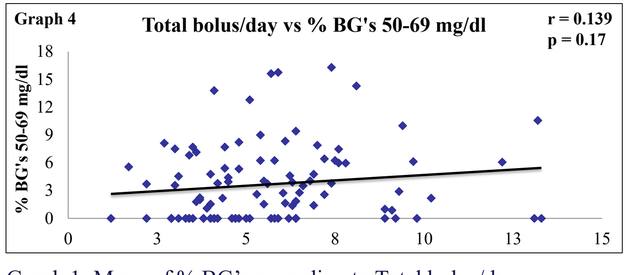
Graph 2



Graph 3



Graph 4



Graph 1: Mean of % BG's according to Total bolus/day
Graph 2, 3, 4: Scatterplots of Total bolus/day vs glycemic measures

Summary

- No group differences were observed for age, gender, DM duration, weight, BMI, serum creatinine or total daily dose (TDD) of insulin.
- The % TDD as bolus insulin was higher in Group 2.
- Group 2 administered more meal related, and correctional boluses than Group 1.
- Group 2 administered more wizard boluses, and were more likely to override wizard bolus calculations.
- Group 2 had lower A1C and mean BG; experienced less hyperglycemia and more mild hypoglycemia without any increase in severe hypoglycemia.
- GV was similar between both the groups.

Conclusions

- This is the first report demonstrating that patients using IPT who bolus more frequently had better glycemic control at the expense of more mild hypoglycemia.
- Future developments in IPT and glucose sensor technology that guide more frequent adjustments of basal insulin may result in improved glycemic control with lower risk for hypoglycemia.

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(BG>180 mg/dl) compared to using just an average patient and daytime specific setting in the bolus calculator (avg. time in hypoglycemia: from 24.7% to 22.6%, p=0.003). Time in hypoglycemia (BG<70 mg/dl) on the other hand remains virtually unchanged (avg. time in hypoglycemia: 1.7% vs. 1.8%, p=0.91).

Supported By: Linz Center of Mechatronics; Roche Diabetes Care

1039-P

Assessing Artificial Pancreas Performance in T2DM

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Introduction: Advanced insulin dosing options have been extensively studied for T1D, but little effort has been made for T2D, although closed loop insulin delivery has been shown to be feasible also for this group of patients.

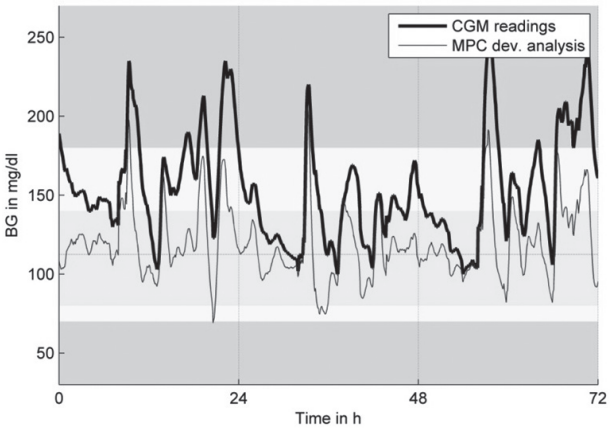
Methods: A deviation based method is used to evaluate the performance of an artificial pancreas with model predictive control (MPC) algorithm for T2D patients in silico. This method takes CGM data from a real clinical trial and estimates the effect of an alternative insulin dosing.

Results: The procedure is tested for four patients with T2D, currently using multiple daily injections. It can be seen that slightly higher insulin doses are used by the MPC algorithm and that time in range can be increased drastically. Time above 180 mg/dl can also be improved by the controller, only times below 70 mg/dl is slightly increased, but stays at a low level.

Table. Performance Measures of BG Control.

	TDD	BG<70mg/dl	80<BG<140mg/dl	BG>180mg/dl
Original	53.3 ± 12 U	0.9 ± 1.0%	35.4 ± 5.0%	25.5 ± 7.6%
MPC	59.8 ± 15 U	2.4 ± 0.8%	64.3 ± 10%	14.9 ± 9.3%

Figure.



Supported By: Linz Center of Mechatronics

1040-P

Change in the Usage of Pump Features Predicts Improvement of Glycemic Control

DOMINIC EHRMANN, BERNHARD KULZER, MELANIE SCHIPFER, NORBERT HERMANNS, *Bad Mergentheim, Germany*

Insulin pumps offer a wide range of technical features designed to help patients with achieving optimal glycemic control. However, many patients do not achieve better glycemic control despite CSII therapy. In this study, we analyzed whether a change in using pump features was associated with an improvement in glycemic control. 197 patients with CSII treatment were analyzed at baseline and 12-weeks later (age 42.2 ± 14.3 yrs.; 59% female; diabetes duration 22.2 ± 11.9 yrs.; duration of CSII 9.4 ± 7.3 yrs.; baseline A1c 8.3 ± 0.9%). Change in using pump features (Table) were the independent variables of interest in a linear regression analysis on the difference in HbA1c (follow-up - baseline). The analysis was controlled for demographic (age, gender, BMI, education) and medical variables (diabetes duration, duration of CSII, use of CGM/FGM, complications, SMBG).

Table. Linear Regression Analysis on the Difference in HbA1c (Follow-Up Baseline).

Increased use of pump features	Standardized beta	p
Temporary basal rates	-0.16	.027
Different basal rate profiles	-0.09	.219
Bolus options	0.16	.031
Bolus calculators	0.02	.790
Analysis software	-0.16	.025
CGM linking	-0.23	.002

An increased use of temporary basal rates as well as using analysis software more often predicted an improvement in HbA1c (Table). Linking a CGM system to the insulin pump was the strongest predictor of better glycemic control. In clinical practice, patients with CSII therapy should be educated how to make use of their pump features and should be encouraged to do so.

Supported By: Berlin-Chemie AG

1041-P

Glycemic Excursions and Bolus Frequency with Insulin Pump Therapy

DINESH EDEM, MAJA STEFANOVIC, PATRICK MCCARTHY, MARY T. KORYTKOWSKI, *Pittsburgh, PA*

Insulin pump therapy (IPT) is an effective method for achieving glycemic control in people with insulin requiring diabetes. IPT allows flexibility in the frequency and timing of bolus insulin doses that may lead to insulin stacking with risk for untoward glycemic excursions in some patients.

The goal of this study was to compare HbA1c and frequency and severity of hypo-/hyperglycemia in adults attending an academic diabetes center according to bolus frequency of <5 (Group 1: n = 38) and ≥5 (Group 2: n = 49) times/day using 2 weeks of de-identified downloaded pump data.

No differences were observed for age (Group 1 vs. 2: 47.4 vs. 43.9 y), gender (42% vs. 39% male), DM duration (29.2 vs. 25.2 y), weight (82.2 vs. 77.2 kg), BMI (28.7 vs. 26.8 kg/m2) or creatinine (both 0.9 mg/dl). Total daily insulin dose (49.1 ± 18.2 vs. 45.8 ± 24.4 units) was similar, but the percentage as bolus insulin was higher in Group 2 (43.8 ± 15.3 vs. 50.4 ± 10.4%, p = 0.019). Group 2 administered more food, correction and wizard override boluses; monitored BG more frequently; had lower A1c and mean BG; and experienced less hyper- and more hypoglycemia, with similar glycemic variability.

This is the first report demonstrating that patients using IPT who bolused more frequently had better glycemic control at the expense of more hypoglycemia. Future developments in IPT and glucose sensor technology may guide more frequent adjustments of insulin with an improved safety profile.

Table.

	< 5 Boluses/day Mean ± SD	≥ 5 Boluses/day Mean ± SD	p Value
Total no. of Bolus/day	3.5 ± 0.9	7.5 ± 2.8	0.0001
Total no. of BG Reads	3.8 ± 2.1	5.8 ± 3.0	0.0007
Average BG	200.3 ± 49.8	176.1 ± 43.8	0.0184
HbA1c (%)	8.1 ± 1.2	7.4 ± 1.0	0.0039
% of BG > 180 mg/dl	49.6 ± 23.6	39.0 ± 22.0	0.0326
% of BG > 300 mg/dl	14.4 ± 16.7	7.7 ± 9.9	0.0214
% of BG's < 70 mg/dl	3.0 ± 4.0	5.1 ± 5.2	0.0427

1042-P

Assessment of the Safety of SAR342434 and Humalog® when Administered through Insulin Pump: Pilot Study

SATISH K. GARG, HOWARD SURKS, IRENE NOWOTNY, BAERBEL ROTTHAEUSER, KARIN WERNICKE-PANTEN, JAMES THRASHER, *Aurora, CO, Bridgewater, NJ, Frankfurt, Germany, Little Rock, AR*

SAR342434 (SAR) and Humalog® (U100; LIS) contain insulin lispro with identical amino acid sequence. Similar PK/PD between the two products has been demonstrated in a clamp study. This pilot insulin pump study was designed to assess the safety of SAR and LIS when used in pumps (CSII) in terms of infusion set occlusions (ISO). This was a randomized, open-label, 2x4 week, 2 arm crossover study in 27 T1D patients (NCT02603510). The main objective was to assess the safety of SAR and LIS when used in CSII in terms of the incidence of ISO that was defined as failure to correct hyperglycemia (plasma glucose ≥300 mg/dL) by insulin bolus via the pump. Secondary objectives included intervals for infusion set changes, incidence of pump

For author disclosure information, see page A751.

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A Case Report of Symptomatic Hypophosphatemia Secondary to Elevated FGF-23 from Parenteral Ferric Carboxymaltose Treatment for Iron Deficiency Anemia

Saturday, April 1, 2017
01:00 PM - 03:00 PM
OCCC - West Hall B (EXPO Hall)

Poster Number

SAT 314

Introduction: Diagnosis of hypophosphatemia is often missed due to non specific symptoms, but it can cause considerable morbidity. Causes of hypophosphatemia include decreased intestinal absorption, internal redistribution, or increased renal excretion. FGF-23 is an osteocyte - derived hormone that maintains normal phosphate levels by decreasing both phosphate reabsorption and plasma calcitriol levels. We present a case of FGF-23 mediated hypophosphatemia caused by treatment with IV Ferric Carboxymaltose (FCM), resulting in severe muscle weakness.

Case: An 81 yr old male with a history of gastric bypass surgery 32 yrs previously, was admitted for evaluation after a 14-month history of progressive back pain, muscle weakness, frequent falls and inability to ambulate coinciding with onset of monthly IV FCM for Iron deficiency anemia. FCM was last given 1 week before admission. Physical exam revealed a wheelchair-bound obese male, L3-L5 point tenderness, decreased motor strength of 4/5 in lower extremities, and difficulty ambulating. CT revealed diffuse osteopenia and compression deformities of L1, L2 and L3. He was found to have a low phosphorus (Phos) level of 1.4 mg/dl (2.5-4.5). Phos was normal at 2.9, 3 yrs before. Further workup revealed elevated urine fractional excretion of phosphate (UFE Phos) of 49% (5-20%), inappropriately normal (nl) 24 hr urine Phos of 540 mg/D (400-1300), nl corrected Ca of 10.0, nl Mg of 1.7, elevated PTH of 194 pg/ml(15-65), nl 25- OH Vitamin (Vit.) D level of 33 ng/ml, and a low 1, 25 OH Vit. D level of 11 pg/ml (18-72). His FGF-23 level was elevated at 269 RU/ml (n<180). Markers of bone resorption were elevated: Alk Phos at 276 IU/L (38-126), Urine NTX at 118 nmol BCG/mmol Cr (9-60), and CTX at 1711 pg/ml (87-345). He was treated with oral Calcitriol 0.25mcg BID, oral 25-OH Vit. D 2000 IU QD, and oral K-Phos 1500 mg TID. IV FCM injections were changed to iron Dextran(DXN). Improvement in muscle weakness correlated with normalization of his Phos levels. Calcitriol and oral Phos supplementation were stopped after discharge at 4 weeks and 10 weeks, respectively. At 2 months after discharge, his FGF-23 level and 1,25 OH Vit. D normalized at 110 and 30, respectively. At 5 months follow-up, he was able to ambulate with use of a cane.

Discussion: Our case is similar to prior reports, indicating that IV iron preparations with carbohydrate moieties like FCM, lead to increased FGF-23 levels and cause hypophosphatemia, low 1,25 OH Vit-D and increased UFE Phos [1-4]. In contrast to FCM, IV iron DXN was not associated with elevated FGF-23 or low Phos in a prospective study which compared the two forms of iron [2]. Similarly, our patient maintained a normal Phos after switching to iron DXN treatment. Parenteral iron formulations are increasingly prescribed, hence clinicians should be aware of the risk of significant, symptomatic hypophosphatemia that is a consequence of FCM infusions.

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(1) Imel et al. Approach to the Hypophosphatemic Patient. JCEM. March 2012; 97(3): 696–706 (2) Wolf, et al. Effects of Iron def anemia and its Treatment on Fibroblast Growth Factor-23 and phosphate homeostasis in women. JBMR, Vol 28, No. 8, August 2013, pp 1793-1803 (3) Schouten BJ et al. FGF-23 Elevation and Hypophosphatemia after IV Iron

Polymaltose: A prospective Study. JCEM, July 2009, 94(7):2332-2337 (4) Hardy et al. IV Iron Administration and Hypophosphatemia in Clinical Practice. Int Journal of Pheumatology. Volume 2015, Article ID 468675, 6 pages.

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Disclosure

Nothing to Disclose: DE, HL, SMC

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THE ENDOCRINE SOCIETY'S 97TH ANNUAL MEETING & EXPO
ENDOCRINE SOCIETY
MARCH 5-8 SAN DIEGO, CALIFORNIA

Difficult to Control Hypothyroidism Despite Good Compliance

Program: Abstracts - Orals, Poster Previews, and Posters
Session: THR 001-023-Clinical and Translational Thyroid and Thyroid Autoimmunity Clinical/Translational

Thursday, March 5, 2015: 1:00 PM-3:00 PM
Hall D-F, Thyroid (San Diego Convention Center)

Poster Board THR-001

*Dinesh Edem, MBBS[1] and **Esther Irina Krug, MD**[2]*
[1]Sinai Hospital of Baltimore, Baltimore, MD, [2]Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD

Introduction: Hashimoto's thyroiditis (HT) is frequently associated with other autoimmune endocrine diseases as a part of autoimmune polyglandular syndrome 2 (APS2). Prevalence of pernicious anemia (PA) and autoimmune gastritis (AIG) is between 4- 12% in patients with HT[1]. AIG is characterized by atrophy of gastric mucosa and achlorhydria. Vitamin B_{12}deficiency and AIG frequently escape timely diagnosis due to non-specific symptoms, and may lead to gastric cancer, neurologic complications or anemia. Difficult to control hypothyroidism may present a clue leading to early diagnosis of AIG and PA. We present a case series of 3 patients with HT who were found to have AIG and severe vitamin B12 deficiency.

Case: Case 1: 50 year old man with 7 year history of HT presented with complaints of fatigue and memory problems. Over the course of treatment his TSH levels fluctuated widely requiring frequent Levothyroxine (LT4) dose adjustments despite excellent adherence and use of the same brand of LT4. **Case 2:** 66 year old woman with 25 year history of HT presented with fatigue and worsening depression. Over last 6 years her LT4 requirements increased from 88 mcg to 125 mcg/day. She had elevated TSH despite good compliance and use of the same brand of LT4. **Case 3:**65 year old woman with a 4 year history of HT presented with worsening anxiety, fatigue and constipation. Due to her fluctuating TSH level despite good compliance with same brand of LT4, her LT4 dose required frequent adjustments.

Clinical evaluation:LT4 malabsorption was suspected. Laboratory testing revealed positive anti-parietal cell antibodies (PCA), intrinsic factor (IF) antibodies, low vitamin B12 levels and elevated gastrin levels. None of the patients had anemia, and 2 out of 3 patients had no overt macrocytosis.

Management: Patients were switched to LT4 gel capsules, resulting in normalization in TSH levels in 3 months without additional dose increases. Intramuscular cyanocobalamin replacement normalized vitamin B12 levels and improved most of neurologic symptoms. Patients were also referred to gastroenterology for EGD to rule out gastric cancer.

Discussion: AIG and PA should be considered in patients with difficult to control HT. Timely recognition and treatment may help avoid adverse health outcomes. Treatment of hypothyroidism in such patients is challenging due to achlorhydria. Levothyroxine tablets require liquification in acidic environment for absorption and as a result are malabsorped in patients with AIG resulting in fluctuating thyroid hormone levels and frequent LT4 dose adjustments to maintain euthyroidism. LT4 gel capsule based liquid formulation of LT4 has shown consistent dissolution with variable gastric pH[2] resulting in steady absorption. Our patients were able to achieve improved control of HT using LT4 gel capsules.

Nothing to Disclose: DE, EIK

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MARCH 5-8 SAN DIEGO, CALIFORNIA

Recognition and Management of Osteoporosis in Patients Presenting with Acute Fragility Fractures

Program: Abstracts - Orals, Poster Previews, and Posters
Session: FRI 248-266-Osteoporosis
Clinical

Friday, March 6, 2015: 1:00 PM-3:00 PM
Hall D-F, Bone & Calciotropic Hormones (San Diego Convention Center)

Poster Board FRI-253

Dinesh Edem, MBBS[1], Shruti Bhandari, M.D.[2] and ***Esther Irina Krug, MD[3]***
[1]Sinai Hospital of Baltimore, Baltimore, MD, [2]Sinai Hospital of Baltimore, [3]Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD

Introduction: Osteoporosis (OP) is a systemic skeletal disease characterized by enhanced bone fragility leading to an increased risk of fractures. Roughly 10 million Americans over age of 50 have osteoporosis, and an additional 43.4 million suffering from osteopenia; with an incidence of 2 million fractures incurring a cost of $17 billion annually. History of prior osteoporotic fracture is an important risk factor for recurrent fragility fractures. Horizon recurrent fracture trial[1] in 2007 demonstrated that, annual infusion of Zoledronic acid (ZA) showed a 28% relative reduction in mortality and 32% RR in clinical fractures in the ZA group[2]. This study evaluates current rate of recognition and management of underlying osteoporosis in patients presenting with fragility fractures to a large teaching hospital.

Methods: Adult patients between the age of 60-85, who were admitted with acute fragility fracture of humerus, femur/hip or vertebrae to a large teaching hospital between Jan 2010 and Jan 2013, were identified. Retrospective chart review was done to obtain information regarding calcium (Ca), albumin, Vitamin D (Vit D) levels at admission, discharge instructions, Ca and Vit D supplementation, prescription for anti-resorptive therapy, referral for DEXA scan and follow up of osteoporosis care. Patients with traumatic fractures, secondary causes of OP and those who were already on anti-resoptive therapy were excluded from the study.

Results: 462 patients had fractures and 201 patients were included in the study. There were 137 (68 %) women and 64 (32%) men. There were 87(43%) patients above age 80, 69 (35%) above age 70, and 45 (22%) below age 70. Among the fractures, 57 (28%) were vertebral, 26 (13%) humeral, and 118 (59%) were femoral. Only 24 (12%) of patients already had a diagnosis of OP. During their inpatient stay, Vit D levels were checked only in 21 (10%) of patients, 43 (22%) of patients were already on either Ca or Vit D supplementation prior to admission. All the patients received discharge instructions for PT, OT and weight bearing, but only 87(43%) were asked to follow up with their PCP. 89(45%) of these patients were given either Ca or Vit D recommendations on discharge, only 6 (3%) of patients were given instructions to start anti-resorptive medication, and 4 (2%) of patients received a specialty referral. None of the patients were scheduled for a DXA scan.

Discussion: Our findings confirm available data[2] suggesting that patients with osteoporosis do not get adequate discharge instructions, BMD measurement, Ca and Vit D supplementation, recommendation for anti-resorptive therapy, or specialty referral. Considering a unique opportunity to improve long-term outcomes in patients with acute fragility fractures, introduction of a standardized electronic order set addressing post-fracture osteoporosis care could result in major improvements in outcomes locally and nationally.

(1) Boonen S. et al. for the HORIZON Recurrent Fracture trial. Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture. NEJM 2007; 357: nihpa40967.(2) Jennings LA, Auerbach AD, Maselli J, Pekow PS, Lindenauer PK, Lee SJ . Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture . J Am Geriatr Soc. 2010 Apr; 58(4):650– 7.

Nothing to Disclose: DE, SB, EIK

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Natural History of Untreated Insulinoma over a Course of 7 Years

Program: Abstracts - Orals, Poster Previews, and Posters
Session: THR 312-340-Endocrine Neoplasia: Tumorigenesis and Therapeutics Clinical/Translational

Thursday, March 5, 2015: 1:00 PM-3:00 PM
Hall D-F, Tumor Biology (San Diego Convention Center)

Poster Board THR-316

*Esther Irina Krug, MD[1], **Shruti Bhandari, M.D.**[2] and Dinesh Edem, MBBS[2]*
[1]Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD, [2]Sinai Hospital of Baltimore, Baltimore, MD

Introduction: Insulinoma is a rare neuroendocrine tumor characterized by autonomous insulin secretion and fasting hypoglycemia. Average duration of symptoms prior to diagnosis is less than 1.5 years (1). Change in size of the mass and symptoms severity over time is not well described in sporadic insulinomas. We are presenting a case of a patient with confirmed insulinoma with duration of symptoms of 7 years prior to resection.

Case: 44 year old women presented to our clinic with 3-year history of diaphoresis, confusion, tremors, palpitations and anxiety associated with documented fasting hypoglycemia with blood glucose <40 mg/dL. During in-patient fast study she became severely hypoglycemic in 8 hours. Laboratory studies revealed insulin 10.9 uIU/mL, blood glucose 28 mg/dL, C--peptide 2 ng/mL, pro-insulin 254.2 pmol/L, and negative hypoglycemic drug screen. Endoscopic ultrasound (EUS) and MRI were negative. We referred the patient to NIH for tumor localization and surgery, but she elected not to undergo further work-up and treatment at that time. She returned to our clinic 4 years later due to progression in frequency and severity of hypoglycemia, occurring after 2-3 hours of fasting, forcing her to wake up every 2 hours nightly and consume concentrated sweets to prevent hypoglycemia. She was admitted and started on D10 drip of 75 cc/hr, with blood glucose in 50-120 mg/dL range. During fast study she developed symptomatic hypoglycemia after 3 hrs of fasting. Labs revealed insulin 9.8 uIU/mL, blood glucose 43 mg/dL, C-peptide 1.8 ng/mL, pro-insulin 93.9 pmol/L and beta-hydroxybutyrate 1.3 mg/dL. Repeat EUS, done by the same gastroenterologist on the same equipment, revealed a 8x7mm hypoechoic irregular mass in the tail of pancreas. EUS-guided FNA revealed well differentiated pancreatic neuroendocrine neoplasm. Selective arterial calcium stimulation (SACS) localized insulinoma to the tail of pancreas. She had laparoscopic enucleation of 6 mm Insulinoma from the tail of pancreas. The patient has remained euglycemic and asymptomatic following surgery.

Discussion: Our findings suggest positive relationship between tumor growth and progression in frequency of hypoglycemia despite overall small tumor size. Considering reported threshold of detectability on EUS (2), we presume that during initial work-up tumor size had been less than 5 mm. EUS sensitivity for detection of lesions in tail of pancreas was reported to be as low as 40% (2). In some cases SACS, that was reported to have detection rate of 89% (3), may be the only option for pre-operative localization. In our case we observed excellent correlation between EUS and SACS in tumor localization.

(1). Grant CS. "Best Practice and research clinical gastroenterology" Vol 19, No 5, pp 783798, 2005 (2). Sotoudehmanesh R, et. al. "Endoscopic ultrasonography (EUS) in the localization of insulinoma". Endocrine. 2007 Jun;31(3):23841. (3). Won JG et al. Intra-arterial calcium stimulation test for detection of insulinomas: detection rate, responses of pancreatic peptides, and its relationship to differentiation of tumor cells. Metabolism. 2003 Oct;52(10):1320-9

Nothing to Disclose: EIK, SB, DE

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A Case of Intractable Recurrent Vomiting in a Young Patient with Type 1 Diabetes. an Unusual Presentation of Graves' Disease

Program: Abstracts - Orals, Poster Preview Presentations, and Posters
Session: MON 0463-0543-Non-Neoplastic Thyroid Disorders-Clinical and Case Reports Clinical/Translational

Monday, June 23, 2014: 1:00 PM-3:00 PM
Hall F (McCormick Place West Building)

Poster Board MON-0542

*Dinesh Edem, MBBS[1], **Esther Irina Krug, MD**[2], Rahul Gosain, MBBS[1] and Amitoj Gill, MBBS[1]*
[1]Johns Hopkins University/Sinai Hospital of Baltimore, Baltimore, MD, [2]Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD

Introduction: Hyperthyroidism (HT) associated with Graves' disease leads to a hypermetabolic state with sympathetic activation. Gastrointestinal symptoms of HT usually include weight loss despite good appetite and diarrhea or increased frequency of bowel movements. Persistent intermittent vomiting is rare and potentially misleading presentation of hyperthyroidism. It may lead to delay in diagnosis or misdiagnosis and inappropriate treatment, causing significant morbidity and distress to the patient.

Case: A 25 year old man with a 10 year history of Type1 Diabetes Mellitus (DM1) and hypertension diagnosed 6 months ago was admitted with intractable vomiting and a 4 kg weight loss. Patient had multiple previous admissions for similar complaints of recurrent vomiting over the past 2 years. Vomiting episodes tended to start in the morning prior to meals. Vomitus content was clear liquid. Once vomiting episode started the patient was unable to retain any fluids or food. He would typically present with significant hyperglycemia since he was afraid to administer insulin in the absence of meaningful food intake. In the interim his blood glucose was well controlled. Home medications also included glargine, aspart, pantoprazole. Physical Exam revealed a thin man in moderate distress vomiting clear liquids that he had swallowed just a few minutes ago. He had heart rate of 115-120 beats per minute. There was no lid lag, stare or proptosis. Thyroid was easily palpable but not overtly enlarged. There was no tremor noted. Initial labs revealed TSH of <0.009 uIU/mL (0.5 - 5.0), elevated free T4 - 2.13 ng/dL (0.8-1.8), Free T3 - 4.7pg/mL (1.8 - 4.2), TSI titer 566% (n < 130). HbA1c was 8.7%. Ultrasound revealed a diffusely heterogenous thyroid with increased Doppler flow, EGD revealed severe reflux esophagitis and gastric emptying study showed no significant gastroparesis. Patient was started on methimazole 10 mg BID, and propranolol 40mg Q12H which led to cessation of nausea and vomiting within 24 hours. In follow-up the patient has remained symptom free off pro-kinetic agents, with good glycemic control and improved thyroid function on methimazole.

Conclusion: This case illustrates severe recurrent vomiting as a highly unusual presenting symptom of relatively mild hyperthyroidism. Pre-existing DM1 made the correct diagnosis especially challenging. Absence of response to pro-kinetic agents and lack of severe gastroparesis may provide a diagnostic clue. Etiology of thyrotoxic vomiting is not well understood. Proposed mechanisms include increase in β-adrenergic activity, delayed gastric emptying or direct activity of thyroid hormones on the chemical trigger zone. Treatment includes administration of antithyroid agents and β-blockers.

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Nothing to Disclose: DE, EIK, RG, AG

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Size of Cortisol-Secreting Adrenal Adenoma, Clinical Symptoms and Severity of Hypercortisolism: Case Study of Two Patients

Program: Abstracts - Orals, Poster Preview Presentations, and Posters
Session: SUN 0773-0794-Adrenal Case Reports 3 - Cushing's, Conn's, Pheo Clinical

Sunday, June 22, 2014: 1:00 PM-3:00 PM
Hall F (McCormick Place West Building)

Poster Board SUN-0788

Dinesh Edem, MBBS[1], *Esther Irina Krug, MD*[2], *Ivana Milojevic, MD*[1] *and Amitoj Gill, MBBS*[1]
[1]*Johns Hopkins University/Sinai Hospital of Baltimore, Baltimore, MD,* [2]*Johns Hopkins University/ Sinai Hosp of Baltimore, Baltimore, MD*

Introduction: Cushings Syndrome (CS) is a rare disorder caused by prolonged exposure to endogenous or exogenous glucocorticoids. Incidence of CS ranges from 0.7 to 2.4 per million(1). Symptoms of CS including obesity, diabetes, hypertension, bone loss and depression are common in the population, making the diagnosis of CS extremely difficult. We present a case study of 2 patients with CS due to adrenal adenoma and analysis of correlation between severity of symptoms, tumor size and degree of hypercortisolism.

Case 1: A 56 year old woman with T2DM, hypertension and hirsutism returns for follow-up with complaints of gradual weight gain, increasing abdominal girth and leg cramps. She has family history of T2DM, osteoporosis and diabetes. Physical exam is notable for abdominal obesity,plethora, round facies, and supraclavicular fat pads. Serial 11 PM salivary cortisol ranged between 4 - 7.1 ng/mL(n <4.3), an overnight DST revealed a cortisol of 7.8 mcg/dL(n < 5), random ACTH level was < 0.5 pg/mL(6-50) with corresponding cortisol of 18.2 mcg/dL. CT scan of the abdomen revealed a 5.5 X 4.7 cm right adrenal adenoma which was subsequently resected. Patient had an uneventful postoperative course with no evidence of adrenal insufficiency. In follow-up her weight decreased by 10 lbs and diabetes improved. Repeat testing a year later showed ACTH of 28, and DST showed cortisol of 0.5.

Case 2 : A 74 year old woman with postmenopausal osteoporosis, hypothyroidism, T2DM on metformin returns to clinic with a 3 month onset of increasing abdominal girth, weight gain, worsening fatigue, proximal muscle weakness of her extremities and poor blood pressure control. DXA revealed significant bone loss despite ongoing treatment with Denosumab. Exam revealed normal BMI, increased abdominal girdth and muscle weakness, but no moon facies, plethora or striae. Serial 11 PM salivary cortisol ranged from 7.2 to 13.6 ng/mL(n <4.3), UFC of 162 mcg/24h (0-50), ACTH level < 5 pg/mL with corresponding cortisol level of 19mcg/dL . CT of the abdomen revealed a 4.5 X 2.1 cm left adrenal mass. Patient subsequently underwent a resection of a benign left adrenal cortical adenoma. Postoperatively on day 2, patient developed symptoms of adrenal insufficiency. Hydrocortisone therapy resulted in resolution of symptoms. Her AI gradually improved after several months of glucocorticoid replacement.

Discussion: These cases illustrate that in patients with CS due to cortisol secreting adrenal adenoma, clinical symptoms and tumor size may not correlate with severity of hypercortisolism and risk of post-operative adrenal suppression. Our patients had adrenal adenomas of almost the same size, but had varied clinical and biochemical picture. Risk of postoperative adrenal insufficiency appears to correlate with the preoperative severity of hypercortisolism.

(1)

Newell-Price J., Bertagna X., Grossman AB., Nieman LK. Cushing's syndrome. 2006 May 13; 367(9522):1605-17.

Nothing to Disclose: DE, EIK, IM, AG

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