Feasibility Study of a Low-Carbohydrate/ Time-Restricted Eating Protocol for Insulin-Using Type 2 Diabetic Patients

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ABSTRACT

Introduction: Low-carbohydrate diets and time-restricted eating are methods to improve hemoglobin A1C in patients with type 2 diabetes. However, insulin-using patients are often counseled against these practices due to hypoglycemia concerns. This observational study evaluated a protocol utilizing both methods coupled with proactive insulin titration.

Objectives: To evaluate the safety and feasibility of a timed eating protocol for insulin-using patients and to assess its impact on outcomes, including insulin use and hemoglobin A1C.

Methods: Participants included insulin-using adults ages 49 to 77 years with type 2 diabetes. They were counseled to eat 2 meals per day in a 6- to 8-hour window of their choosing, with a goal intake of ≤30 grams of carbohydrates per day. Glucose was closely monitored, and insulin was adjusted per study protocol. Primary outcomes included hypoglycemic events and compliance with timed eating. Insulin use, hemoglobin A1C, body mass index, blood pressure, and quality of life also were measured.

Results: Nineteen of the 20 participants completed the 6-month study. No hypoglycemic events requiring urgent medical care occurred. Symptomatic episodes with glucose between 47 and 80 mg/dl were reported by 37% (7/19) of participants. Average daily insulin use decreased by 62.2 U ($P < 0.001$) and insulin was discontinued for 14 participants. Average hemoglobin A1C remained unchanged. Average body mass index decreased by 4.0 ($P = 0.01$), systolic blood pressure decreased by 9.9 mm Hg ($P = 0.02$), and diabetes-related quality-of-life metrics improved significantly.

Conclusions: These results demonstrate that a time-restricted eating protocol is feasible and safe for insulin-using patients with type 2 diabetes when paired with a proactive insulin titration.

INTRODUCTION

Type 2 diabetes is a major contributor to morbidity and mortality in the United States.1 Its pathophysiology is interwoven with obesity and contributes to comorbidities, including vision loss, kidney failure, lower extremity amputation, and cardiovascular disease.2 Major improvements in type 2 diabetes treatment have occurred over the past 2 decades, including novel pharmaceuticals such as sodium-glucose transport protein 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists. However, incidence has continued to increase, and over 37 million American adults currently live with this disease.3 The combination of rising incidence and increasingly expensive medication continues to accelerate type 2 diabetes-related health care expenditures.4 The prevailing paradigm of type 2 diabetes care does not appear to offer the potential for reversing these trends in costs or disease burden. However, development of more effective lifestyle interventions potentially could make an impact.

Observations from routine clinical practice show that periods of fasting tend to lower blood sugar and insulin requirements. Patients with type 2 diabetes who are required to fast for common medical procedures, such as colonoscopy, require substantial insulin reductions to maintain euglycemia during the periprocedural period. A dietary routine can be organized around such fasting intervals with the goal of reducing insulin requirements. This practice is often referred to as "time

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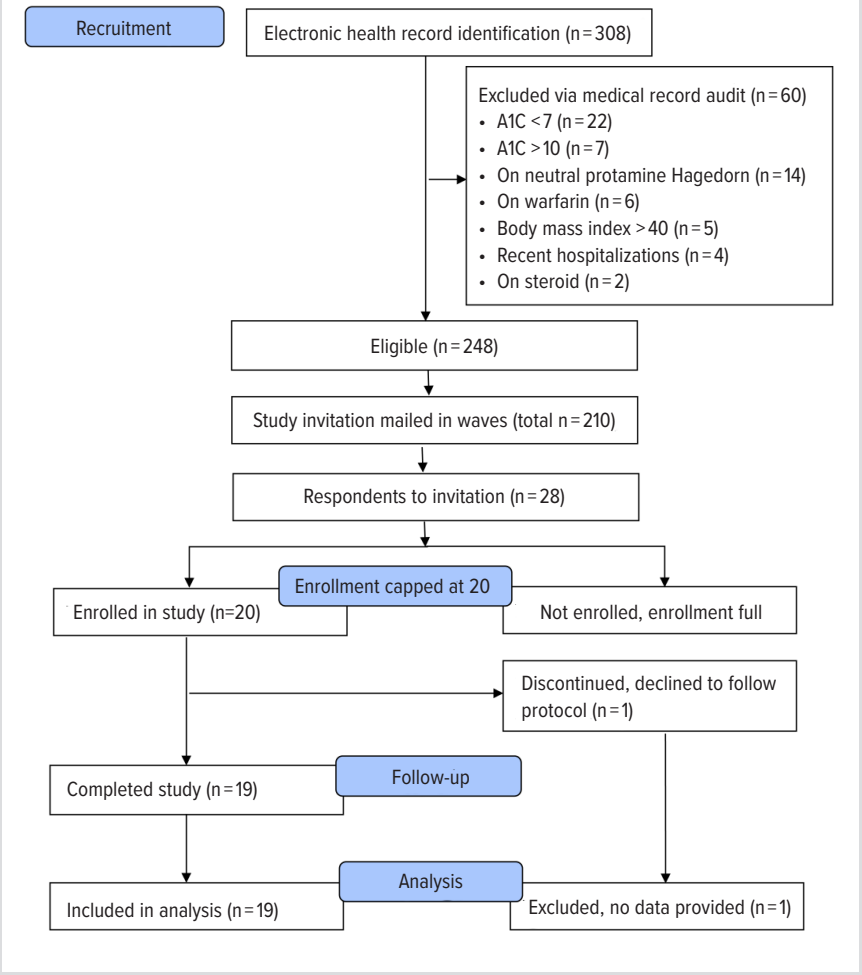
restricted eating" (TRE) and usually consists of a window of 6 to 10 hours where food is consumed followed by a 14- to 18-hour food-free interval.

Multiple studies report improved insulin sensitivity in nondiabetic populations who practice TRE compared to standard meal timing.[5-7] Further, TRE increases insulin sensitivity in non-insulin-using patients with type 2 diabetes[8] and improves insulin sensitivity in patients with prediabetes independent of weight loss.[9] There is also evidence that lower-carbohydrate diets can improve insulin sensitivity with superior hemoglobin A1C control compared to a low-fat diet.[10]

Although lower-carbohydrate (LC) diets and TRE have been shown independently to have positive effects on insulin sensitivity, no studies have been reported that combined these modalities to treat insulin-using patients with type 2 diabetes as part of a comprehensive insulin reduction program. Indeed, insulin-using patients often are counseled to refrain from these practices out of concern for hypoglycemia. We performed a study of a LC/TRE regimen with patients who have type 2 diabetes and use insulin to determine whether this population could safely use these methods when paired with a proactive insulin titration. We also sought to assess the regimen's impact on their insulin needs, hemoglobin A1C, body mass index (BMI), blood pressure, and quality of life.

Figure 1. CONSORT Flow Diagram



METHODS

This prospective cohort study evaluated the feasibility, safety, and efficacy of a LC/TRE protocol for patients with type 2 diabetes who use insulin. The study took place from February 2021 through January 2022 at 3 university-based general internal medicine clinics. Participants were followed for 6 months. The study was approved by the university's Institutional Review Board.

Participants

An electronic health record (EHR) data tool identified 308 insulin-using patients with type 2 diabetes who were medically homed at 3 general internal medicine clinics; 248 patients met inclusion and exclusion criteria. Letters were sent to 210 individuals in rolling fashion until the goal of 20 participants was met (Figure 1). Patients provided written informed consent at their first study visit. The initial recruitment plan called for flyers to be posted in study clinics, but COVID protocols halted clinic visits for routine care. This initiated the switch to direct mail. Participants were offered up to $285 for completing all study procedures.

Inclusion criteria included type 2 diabetes diagnosis, using once daily basal insulin, age 18 to 80 years, self-administering insulin, most recent A1C of 7% to 10%, stable diabetes medication regimen for > 3 months, demonstrated reliability with glucose monitoring and A1C checks, and BMI of 25 to 40.

Exclusion criteria included type 1 diabetes, using concentrated insulin or neutral protamine Hagedorn (NPH), living in a skilled nursing facility, unwilling or unable to do blood glucose checks 3 times per day, estimated glomerular filtration rate (eGFR) < 30 mL/min, taking steroids or warfarin, hospitalized within the past 3 months, symptomatic heart failure, weight loss > 10% in last 6 months, history of organ transplantation, pregnant or trying to become pregnant, and breastfeeding.

Study Visits

The protocol included 5 in-person visits over the course of 6 months. Participants met with the study physician at study initia-

tion, the start of month 4, and the 6-month conclusion. Intervening visits with the registered dietician occurred at the beginning of months 2 and 5 (Appendix).

Physician Visit 1 at Study Initiation: Participants were counseled to consume all calories in 2 meals within a 6- to 8-hour window of their choosing and educated on a lower carbohydrate diet with a goal intake of ≤30g of carbohydrates per day. Recommended meal plans featured meats, eggs, nuts, seeds, vegetables, and berries. Participants were encouraged to complete a food log and walk at least 20 minutes daily. They also received instructions on the insulin titration protocol and safety procedures, including a discussion of hypoglycemia symptoms and management.

Registered Nurse (RN) Phone Protocol: Participants started the protocol on a Monday to facilitate easy contact over a full 5-day work week. Daily contact continued until a stable insulin dose was reached. RN communications were reduced to weekly thereafter if the participant was still taking insulin or monthly once insulin was discontinued. Formal nurse calls also were scheduled at the beginning of months 3 and 6.

Registered Dietitian Visits 1 and 2 at Months 2 and 5: In-depth dietary counseling included a discussion of meal planning and expanded lower carbohydrate food options. A 3-day carbohydrate consumption food inventory was completed at each visit.

Figure 2. Total Insulin Use (Units/Day)

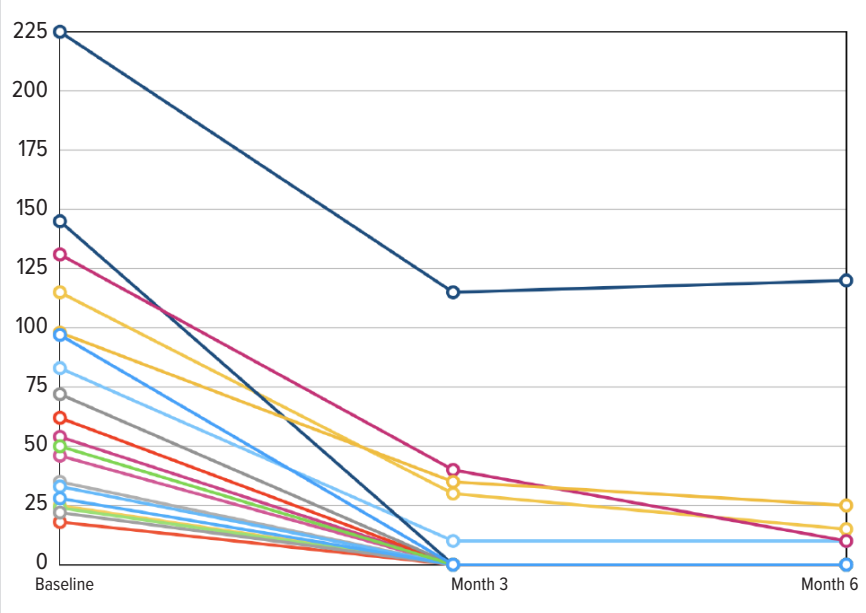


Table 1. Patient Characteristics and Outcomes (n = 19)

	Baseline	3 months	6 months	*P* value
Age, mean (SD), years	64.7 (8.3)			
Sex, N (%)				
Male	10 (52.6)			
Female	9 (47.4)			
Weight, mean (SD), pounds	227.7 (42.3)	205.7 (39.9)	201.2 (39.5)	0.11
Body mass index, mean (SD), kg/m^2	34.5 (4.30)	31.2 (4.27)	30.5 (4.17)	0.01[a]
Diastolic blood pressure, mean (SD), mmHg	80.5 (6.95)	77.7 (5.00)	72.8 (7.10)	0.002[a]
Systolic blood pressure, mean (SD), mmHg	134.5 (14.58)	129.1 (7.89)	124.6 (7.14)	0.02[a]
Hemoglobin A1C, mean % (SD)	7.8 (1.01)	7.9 (1.46)	7.8 (1.16)	0.99
Average time on insulin, years	9			
Short-acting insulin, mean (SD), units[a]	30.9 (37.63)	8.4 (20.62)	4.7 (12.18)	0.006[a]
Long-acting insulin, mean (SD), units[a]	40.8 (22.37)	3.68 (11.03)	5.0 (16.75)	<0.001[a]
Total insulin, mean (SD), units[a]	71.7 (53.66)	12.1 (28.15)	9.5 (27.63)	<0.001[a]

[a]Mean includes all study participants whether on insulin or not at that time point.

Physician Visit 2 at Month 4: Food logs, insulin use, blood sugar readings, and dietitian assessments were reviewed. Depending on insulin status, the discussion focused on either areas to improve adherence with the regimen or maintenance.

Physician Visit 3 After 6 Months: Protocol results were reviewed and final insulin and dietary recommendations were provided. The study physician communicated with each participant's primary physician regarding the participant's study progress and current medications.

Outcome Measures

At physician visits 1, 2, and 3, participant weight, height, and blood pressure were recorded. Diabetic medications were documented by the study physician, and hemoglobin A1Cs were drawn. Participants completed the 7-item Appraisal of Diabetes Scale (ADS) assessing psychological well-being, social well-being, role activities, and personal constructs on a 5-point Likert-like scale (Appendix). ADS scores can range from 7 to 35; a lower score corresponds with improved quality of life and decreased impact from diabetes.[11]

At physician visits 1 and 2, participants were given three monthly food logs (Appendix) to record the time of first and last eating each day and symptoms of hypoglycemia. These were returned by mail monthly to study personnel or brought to the next visit. Participants also received instructions regarding comple-

Table 2. Patient Compliance with Time-Restricted Eating (n = 19)

	Month 1, N = 16 (480 log entries[a])	Month 2, N = 16 (480 log entries[a])	Month 3, N = 16 (458 log entries[a])	Month 4, N = 13 (390 log entries[a])	Month 5, N = 13 (373 log entries[a])	Month 6, N = 11 (298 log entries[a])
Average time of eating (SD), hours	5.76 (1.9)	5.58 (1.9)	5.89 (2.0)	5.45 (2.2)	5.54 (2.0)	5.48 (2.2)
Range	0.15 – 13.3	0.1 – 13.3	0.3 – 2.4	0.2 – 13.3	0.2 – 11.0	0.0 – 14.0
< 8 hours 100% of time (%)	75%	56.3%	43.8%	30.8%	46.2%	54.5%
< 8 hours > 90% of time (%)	93.8%	100%	68.8%	84.6%	76.9%	72.7%
< 8 hours > 75% of time (%)	93.8%	100%	93.8%	100%	84.6%	92.3%
< 8 hours > 50% of time (%)	100%	100%	100%	100%	100%	100%[a]

[a]Entries = Monthly total of daily entries in subjects' food tracking logs.

tion of a 3-day food inventory documenting exact carbohydrate intake for all food consumed over a 3-day period.

At physician visits 2 and 3, participants were given a satisfaction survey where they rated, on a scale of 1=not at all to 5 = extremely, the likelihood of continuing the feeding protocol after study completion.

At registered dietitian visits 1 and 2, the 3-day food inventory was reviewed and carbohydrate counts were calculated. Incomplete data were discussed and food modeling provided best estimates of carbohydrate intake. This information was entered into the EHR. Food inventories have been shown to be an accurate assessment of patient food intake.[12]

Hypoglycemia Mitigation Protocol

Basal insulin was reduced by 50% on the day prior to protocol initiation and all short-acting doses were eliminated during the fasting interval. The 2 remaining short-acting insulin doses were left unchanged at study start for the 11 patients using mealtime insulin. Further insulin adjustments were made on a daily basis based on a predetermined titration protocol that reduced the insulin dose any time glucose dropped under 120 mg/dL (Appendix). This protocol preferentially titrated off long-acting insulin first to minimize its effect during the fasting window. Transient hyperglycemia up to 300 was tolerated during the first week in order to further minimize hypoglycemic risk. Participants were told to immediately inform study personnel of any severe hypoglycemic episodes defined as glucose < 50 and/or requiring medical assistance. Mild hypoglycemic episodes were recorded on the monthly food logs.

Data Collection

Participant sociodemographic data, A1C, weight, BMI, insulin dose, and average carbohydrate counts were extracted from the EHR by a member of the study team and entered in an Excel (Microsoft Corporation, 2018) spreadsheet on the study's secure server. Paper food logs and ADS results were copied into an Excel spreadsheet.

Statistical Methodology

We compared differences between the 3 different survey periods (baseline, 3 months, 6 months) using chi-square tests for categorical variables and the analysis of variance (ANOVA) for continuous variables. Similarly, we compared differences between the baseline and 6-month periods using a paired t test. Likert scale responses were examined individually using Fisher exact tests. Overall ADS scoring was assessed using a general linear mixed model analysis. We used a logistic regression model to find the odds of discontinuing insulin and 95% confidence intervals. All P values ≤ 0.05 were considered statistically significant. We conducted these analyses using SAS version 9.4M7 (SAS Institute Inc, Cary, North Carolina, 2020) and STATA version 17 (STATACorp LP, College Station, Texas, 2021).

Table 3. Appraisal of Diabetes Scale Results

Time Administered	Mean Score	Mean Difference (CI) vs Baseline	*P* value (from baseline)
Baseline	18.42		
3 months	15.68	-2.74 (-4.26 to -1.21)	< 0.001
6 months	15.42	-3.00 (-4.53 to -1.47)	< 0.001

No statistically significant difference between months 3 and 6.

RESULTS

Twenty participants were recruited and 19 completed the study. One declined further participation shortly after enrollment and provided no data to include in the analyses. The average age was 64.7, and nearly half of the participants were female (47.4%). The mean BMI was 34.5, and the average duration of insulin use was 9 years. All 19 participants attended the 3 physician visits and 15 completed both of the registered dietician visits (4 missed the second registered dietician visit).

Safety

Participants made no emergency or urgent care visits related to hypoglycemia over the course of the study. Symptomatic hypoglycemic episodes with readings between 47 and 80 were reported by 37% (7/19) of participants in 12 separate occurrences. Five of these episodes occurred within the first month of the study. Two participants experienced hypoglycemia in the third and fourth month. In all occurrences, hypoglycemia was associated with insu-

lin use. No participants experienced hypoglycemia once their insulin was stopped.

Insulin Use and Glycemic Control

Insulin use was stopped in 14 of the 19 (74%) participants by the end of the study (Figure 2). The titration process took less than 2 weeks for 12 of these. The other two stopped at 3 and 6 weeks, respectively. Five patients also stopped or reduced non-insulin diabetes medications outside of our protocol. The 5 participants who continued to use insulin were able to reduce their total insulin dose by 72%. Four of the 5 participants who continued basal insulin also continued short-acting insulin. Importantly, participants were able to achieve these changes in medication without worsening their A1C. Average A1C was 7.8% at the beginning and end of the study (Table 1).

BMI and Blood Pressure

Participants experienced statistically significant and clinically relevant improvements in both BMI and blood pressure (Table 1). Average BMI dropped from 34.5 at the beginning of the study to 30.5 by study end. This corresponded with an average weight loss of 26.5 pounds. Participants also experienced improvements in both systolic and diastolic blood pressure control. Average systolic pressure dropped from 134.5 mm Hg to 124.6 mm Hg. Three participants discontinued antihypertensive medications during the study due to significantly improved readings.

TRE and Carbohydrate Compliance

Most participants had a high degree of compliance with TRE (Table 2). Eleven of 19 provided the full 6 months of monthly food logs, 5 provided at least 3 months of data, and 3 did not provide any dietary data. The average time of documented eating was consistently under 6 hours throughout the study.

Carbohydrate counts performed during the dietitian appointments revealed that, in general, adherence was better for TRE than for carbohydrate restriction: 36.8% of participants were compliant with the <30g carbohydrate restriction at the 2-month mark, and this dropped to 26.7% by month 5 (Appendix). Additional participants met the less stringent 30 g to 60 g secondary target. At the time of the second dietitian appointment, the average carbohydrate intake per day was 61.7 g. Eight of the participants were in the > 60 g category; the top 3 reported carbohydrate intake values in this latter group were 90, 100, and 125 g per day. Of note, these are significantly lower than the recommended standard dietary intake of 225-325 g carbohydrates per day for a person who consumes 2000 calories daily.[13]

We had intended to perform a multivariate analysis to gain insight into whether compliance with TRE or the carbohydrate restriction predicted participants' ability to get off insulin. However, univariate analysis of the data did not find compliance with the discrete measures themselves to be independently predictive (Appendix).

Quality of Life and Satisfaction with the Study

Participants reported statistically significant improvements in their quality of life as measured by the ADS (Table 3). Scores improved significantly over the first 3 months, then continued to improve until study end. All areas assessed by the screening tool showed improvement; the most substantial changes resulted from improved coping with the diagnosis of type 2 diabetes and a decrease in type 2 diabetes impeding their life goals (Appendix).

At 6 months, participants were asked to respond to a question querying their intent to continue the LC/TRE protocol after conclusion of the study. The average response was 4.47 on a scale of 1 to 5. Thus, most participants reported a strong desire to continue.

DISCUSSION

We conducted a prospective study of a LC/TRE protocol with a cohort of insulin-using individuals with type 2 diabetes. Our results demonstrate that this protocol can be safely implemented in a primary care setting if it is done in concert with a proactive insulin titration. We also showed significant reductions in insulin use, weight, and blood pressure with these methods. These were accomplished while maintaining hemoglobin A1C. The overall improvement in quality-of-life scores demonstrates the potential of this protocol to improve an important outcome: helping participants feel in control of their type 2 diabetes management.

While the average hemoglobin A1C was still above goal in the setting of significant weight loss, this is not surprising since the mean daily insulin dose decreased by 62 units and no other medications were added. Our goal was to stop insulin, and we did not attempt to address non-insulin type 2 diabetes medications during the study as we wanted to isolate the effect on insulin use. An A1C of 7.8%, while unchanged, could still be improved. Clinically, participants could be further optimized on non-insulin-based treatments while working on further weight loss. Future studies could implement non-insulin medication titration along with this protocol.

This study builds upon previous research into the impact of TRE and LC regimens on type 2 diabetes in a novel way by combining the two methods and implementing them in an insulin-using population. Our results are congruent with glucose control findings from a randomized controlled trial by Che et al that was conducted in a population with obesity and type 2 diabetes.[14] Che found improvements in blood sugar control and weight loss with a 10-hour TRE regimen without carbohydrate restriction. They also documented significant reduction in diabetic medication use in the intervention group; however, they prioritized elimination of oral hypoglycemics over changes in insulin.

Our weight loss findings are also consistent with randomized controlled trial results from Jamshed et al.[15] They demonstrated that an eating window of less than 8 hours was superior for weight loss compared to a ≥12-hour window for patients without dia-

betes. Our time restriction was narrower and our study participants consumed significantly fewer carbohydrates on average (62 g v 135 g), potentially contributing to the greater weight loss we observed.

The specific intake of food within the TRE window is an additional difference in our approach. Most TRE-based interventions utilize an ad libitum food intake during the time-restricted period, and some have shown negative results.[16-17] We specifically gave directions for 2 discrete meals per day and advised against snacking unless necessary for hypoglycemia mitigation. This created a hypocaloric regimen on its own, eliminating most of the need for calorie-specific counseling. Perhaps more importantly, it created a consistency for participants that allowed all food intake to be appropriately covered with short-acting insulin around mealtime. Consistency can improve the ability to predict blood sugars in the short-term, allowing for a smoother insulin titration. It also helps establish a routine, which is essential for a process to feel normal and thus sustainable.

Many studies have focused on early TRE protocols, suggesting that early food intake has preferential metabolic effects compared to eating later in the day.[18] Although this may well be the case, we chose to explain the rationale for early TRE to our participants but made no effort to convince them to follow it. We instead encouraged them to choose a TRE window that felt most comfortable for them with the hope they would continue it in the long term. All 19 participants, left to their own choice, chose a late TRE window with food consumed at lunch/brunch and dinner. We observed that people value a structure that allows them to eat normal meals at socially conforming times and hypothesized that doing so would facilitate longer-term satisfaction.

Limitations

This was a small study without a control group, and we cannot be sure what the natural history of disease would have been for these participants. However, they were taking insulin for an average of 9 years prior to study initiation and there is little reason to expect that they would have been able to stop or decrease insulin use without this protocol. Only 3 clinical providers were involved in this study (1 physician, 1 registered dietician, and 1 registered nurse) and participants were seen in a single medical clinic. This limits generalizability as clinician qualities may have had a major role in the success of the protocol. Participant compliance with tracking daily food intake times fell to 58% in the final month of the study, so we do not have a complete picture of compliance across the entire study period. Additionally, the study duration of 6 months does not allow assessment of participants' ability to maintain this practice long term.

CONCLUSIONS

Fasting-based and carbohydrate-restricted diets have traditionally been viewed as a liability for insulin-using patients with type 2 diabetes due to fears of hypoglycemia. However, insulin-using patients may have the most to gain from these methods. This study demonstrated the potential of a LC/TRE protocol to safely lower insulin requirements. Randomized controlled trials are needed to compare this process to the current standard of care and to identify which components of this protocol are most important.

Funding/Support: This work was supported by a University of Wisconsin-Madison Division of General Internal Medicine Pilot Grant Award.

Financial Disclosures: None declared.

Acknowledgements: The authors wish to acknowledge Alisa Sunness, RD, CD, CDE, and Schyler Arthur, RN whose contributions made this study feasible.

Appendix: Available at www.wmjonline.org.

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