Glycemic excursion minimization in the management of type 2 diabetes: a novel intervention tested in a randomized clinical trial

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ABSTRACT

Introduction This study of adults with type 2 diabetes employed a non-inferiority hypothesis to investigate whether an innovative lifestyle focused on minimizing postnutrient blood glucose (BG) excursions (glycemic excursion minimization (GEM)) would be equivalent or superior to conventional weight loss (WL) therapy in regard to reducing HbA1c, and superior to WL when investigating physical, behavioral and psychological secondary outcomes. The impact of BG feedback on GEM efficacy was also investigated.

Research design and methods 178 adults with type 2 diabetes for ≤10 years, HbA1c ≥6.8%, and not using insulin were randomized to WL (n=40) or one of three versions of GEM. Didactic (GEM-D, n=39) taught participants to choose low-glycemic load foods, reduce sedentary time and increase moderate routine physical activity. GEM-S (n=51) received GEM-D and systematically measured BG before and after meals and physical activity to educate and motivate food and activity choices. GEM-C (n=48) received GEM-D with continuous glucose monitoring feedback. All participants received 6 hours of group training and BG and activity monitors. Before and 3 months after treatment, participants were assessed for HbA1c, lipids, weight, routine physical activity, nutrition, depression, diabetes empowerment and distress.

Results GEM versions did not differ in primary or secondary outcomes, so they were combined for analyses. While WL reduced body mass index (BMI) (p=0.005), GEM demonstrated a greater reduction in HbA1c (p=0.005), BMI (p=0.013), carbohydrate intake (p=0.001), BG response to a glucose challenge (p=0.02), and cardiovascular risk (p=0.003). Only GEM participants significantly improved diabetes empowerment, diabetes distress, depressive symptoms, steps/day, and active hours and reduced calories/day. Neither intervention had negative side effects.

Conclusions GEM is an effective alternative to WL with respect to physical, behavioral and psychosocial outcomes.

Trial registration number NCT03196895.

Significance of this study

What is already known about this subject?
► Weight loss therapy is the conventional and effective lifestyle intervention for adults with type 2 diabetes.

What are the new findings?
► An alternative lifestyle intervention, focused on reducing postnutrient glucose excursions through diet and exercise, resulted in a greater improvement in HbA1c and secondary benefits compared with weight loss therapy.

How might these results change the focus of research or clinical practice?
► These findings suggest that clinicians and patients have a new additional lifestyle intervention option that focuses on reducing postnutrient excursions rather than reducing weight.

(T2D).[1] From a clinician's perspective, this approach may be difficult for some patients to achieve and maintain. Alternative lifestyle approaches for managing T2D could be beneficial. Recently, the American Diabetes Association concluded: 'Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns.'[2] This study investigates an alternative T2D management program based on reducing postprandial glucose excursions through reducing carbohydrate ingestion and increasing routine physical activity.

Pharmacological treatment of T2D uses medications having several different modes of action, which provides more tools for treating the disease. Similarly, a variety of useful lifestyle interventions may help improve glucose outcomes. Postprandial glucose often
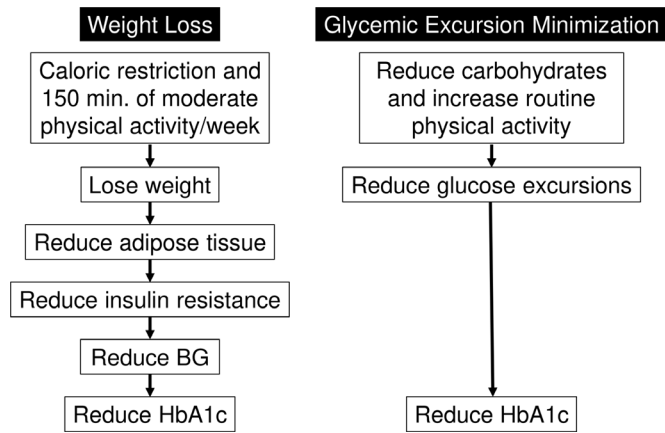
INTRODUCTION

Weight loss (WL) lifestyle interventions based on caloric restriction are frequently recommended for individuals with type 2 diabetes

Figure 1 The different mechanisms of action for weight loss (WL) and glycemic excursion minimization (GEM). BG, blood glucose.

represents the highest levels of hyperglycemia reached in many patients with T2D. Glycemic excursion minimization (GEM) focuses on reducing these extremes from meals, snacks and drinks by moderating carbohydrates (which drive hyperglycemia) and increasing routine physical activity after meals (to hasten blood glucose (BG) recovery by using glucose and reducing insulin resistance).[3]

Postprandial glucose excursions are a major contributor to HbA1c and may also independently contribute to diabetes complications.[4 5] Our preliminary studies suggested that GEM can reduce both HbA1c and cardiovascular risk.[6 7] However, that version of the GEM intervention focused on three specific *procedures*: (1) replacing high with low <u>G</u>lycemic load foods to diminish BG rises, (2) increasing moderate to vigorous <u>E</u>xercise to hasten BG recovery, and (3) <u>M</u>onitoring BG to learn what impacts BG change. The current GEM intervention focuses on the *process* of GEM through a variety of procedures not limited to glycemic load, moderate to vigorous exercise, and BG feedback. This study also investigated the contribution of BG monitoring as a feedback procedure, given its cost, inconvenience and past literature indicating minimal efficacy with T2D.[8]

WL and GEM interventions are based on different presumed underlying mechanisms (figure 1). WL interventions reduce HbA1c through a cascade of events where restricting calories (or radically reducing carbohydrates to produce ketones) leads to WL, reduces visceral adipose tissue (a major source of insulin resistance), leads to more efficient insulin action and BG uptake, lowers BG levels, and in turn lowers HbA1c. This chain of processes contrasts with GEM, which directly diminishes BG excursions through reducing carbohydrates and increasing physical activity, subsequently reducing HbA1c. This direct mechanism might produce BG results more quickly, making it evident and encouraging to patients.

Further, reducing glycemic excursions may reduce glucose toxicity and insulin resistance. The term 'glucose toxicity' was originally described as a mixture of insulin resistance due to chronic hyperglycemia and hyperglycemia-induced dysfunction of normal beta cell insulin secretion.[9] This may occur in a relatively short time (days) although most often it is discussed as a chronic dysfunction contributing to hyperglycemia through multiple mechanisms.[10 11]

Therefore, we hypothesized that GEM would improve the primary outcome variable (HbA1c) and be equivalent or superior (non-inferiority) to an equivalent dose (6 hours of group contact) of conventional WL intervention, but superior to WL in regard to secondary variables (cardiovascular risk and psychological functioning). Since these interventions are based on different underlying mechanisms, we hypothesized that WL would reduce body mass index (BMI) and calorie ingestion more, while GEM would reduce carbohydrate ingestion and increase physical activity and BG monitoring more. Given the concerns that reducing carbohydrates might result in consuming more fats and worsening lipids, we hypothesized that GEM, compared with WL, would not increase hyperlipidemia.[12]

BG feedback can educate individuals about the effects of their food and activity choices. It may also motivate them to repeat choices that lead to desirable BG levels. It can also serve as a negative feedback loop to activate choices that can correct out-of-control BG levels.[13] Thus, we hypothesized that increasing the quality and quantity of BG feedback would improve GEM's effectiveness.

MATERIALS AND METHODS
Participants
Two hundred and six adults were recruited through radio and print advertisements and the University of Virginia Hospital patient registry. Twenty-seven failed inclusion/exclusion criteria and one declined to participate (online supplemental table 1). Participants were 30–80 years old, had T2D for ≤10 years, and had HbA1c ≥6.8%. Insulin usage was an exclusion criterion since GEM had the potential to significantly lower BG. Box 1 lists all exclusion criteria. Incentives to participate were free intervention, blood tests, BG meters and supplies (Bayer Contour), activity monitors (Fitbit Charge 2), and $100 on completion of the 3-month follow-up assessment. Participants in the different interventions did not differ on any demographic variables (table 1).

Procedures
Assessments
After being thoroughly informed, participants signed a consent form approved by the University of Virginia Institutional Review Board for Health Sciences Research. Next, they participated in a pretreatment assessment including a brief physical, blood tests for HbA1c and lipids, routine consumption of carbohydrates (Carbohydrate Routine Consumption scale (CRC)), psychological questionnaires to assess attitudes towards glucose monitoring,

Box 1   Exclusion criteria

- ► Between the ages of 30 and 80 years.
- ► Type 2 diabetes for 10 years or less.
- ► HbA1c ≥6.8%.
- ► Takes insulin. Participants may start insulin during the course of the study if clinically indicated.
- ► Has taken medications that impede weight loss (eg, prednisone) within the last 3 months.
- ► Currently pregnant or contemplating pregnancy within the next 14 months.
- ► Has conditions that preclude increasing physical activity (eg, severe neuropathy cardiovascular disease, chronic obstructive pulmonary disease/emphysema, osteoarthritis, stroke, or severe mental disease like manic depressive illness, severe depression, active substance abuse).
- ► Has conditions that restrict diet, such as severe gastroparesis, ulcers, or food allergies.
- ► Is undergoing treatment for cancer.
- ► Has a history of lactic acidosis.
- ► Has ever had diabetic ketoacidosis.
- ► Has marked renal impairment (estimated glomerular filtration rate <45; chronic kidney disease stage 3b).
- ► Takes psychotropic medications that raise blood glucose (eg, atypical antipsychotics).
- ► Cannot read English.
- ► Blindness.
- ► Has cognitive impairment.

diabetes empowerment, diabetes distress (Emotional and Regimen subscales), depressive symptoms, and diabetes knowledge as it relates to GEM principles.[6 14–18] Using the Medication Effect Score (MES), a participant's diabetes medications and doses were converted to a common metric, their HbA1c lowering potential, and these were summed across the participant's diabetes medications.[19]

The MES is a way of comparing the wide range of diabetes regimens and doses that participants were using. Participants also completed a mixed meal tolerance test (MMTT). This involved measuring BG following an overnight fast, drinking a 237 mL Boost Original nutrition drink (41 g carbohydrates, 4 g fat and 10 g protein), and measuring BG again 60 min later. The MMTT was intended to document any reduction to a BG challenge following the different interventions.

The following week, all participants wore a blinded activity monitor to quantify baseline sedentary behavior (hours active) and overall activity (total steps). They were also interviewed by telephone on two workdays and one weekend day for the researcher to complete the Automated Self-Administered 24-hour (ASA24) dietary recall to quantify daily consumption of carbohydrates, fats and proteins.[20] The ASA24 is a computer-driven interview that documents all nutrients consumed, their volume and preparation method to provide detailed micronutrient analyses of that day's intake. This assessment was repeated 3 months after the conclusion of treatment (follow-up), as shown in figure 2.

Treatment

Following the pretreatment assessment, blocks of 10 participants were randomized to WL or one of three versions of GEM by using a minimization method that matched interventions on baseline HbA1c, MES and disease duration.[21]

Participants met in groups of 8–11 people for 6 hours over a 2-month period. GEM participants met for four 90 min sessions, with 1 week between sessions 1 and 2, and 3 weeks between sessions 2–3 and 3–4. This was intended to diminish reliance on group support and encourage autonomy. Because nutritionists wanted more frequent

Table 1 Demographic variables comparing WL and the three versions of GEM		WL	GEM-D	GEM-S	GEM-C	P value
Started treatment	(n)	40	36	50	46	
Completed 3-month follow-up	(n)	36	33	47	43	
Age (years)	(Mean/SD)	58.3±10.9	54.7±11.7	54.8±11.6	58.2±11.9	0.301
Education (years)	(Mean/SD)	15.3±2.6	16.8±3.2	15.9±2.5	15.8±3.6	0.23
Female	(%)	55.6	69.7	63.8	51.2	0.353
Black	(%)	19.4	18.2	21.3	16.3	0.924
White	(%)	72.2	75.8	74.5	81.4	
BMI	(Mean/SD)	34.9±7.1	34.9±6.5	35.6±6.6	34.0±4.7	0.681
Weight (kg)	(Mean/SD)	100.1±20.3	99.1±20.2	102.2±21.8	95.9±16.7	0.512
Years with diabetes	(Mean/SD)	5.5±3.0	6.1±3.1	4.8±3.2	5.7±3.2	0.278
HbA1c, pre (mmol/mol)	(Mean/SD)	67±11	68±13	65±12	71±18	0.229
HbA1c, pre (%)	(Mean/SD)	8.2±1.0	8.4±1.2	8.1±1.1	8.6±1.6	
MES, pre	(Mean/SD)	1.06±0.74	1.36±0.82	1.13±0.80	1.13±0.81	0.43
MES, post	(Mean/SD)	1.17±0.9	1.31±0.76	1.13±0.77	1.13±0.87	0.76
Hypoglycemia, self-reported incidence of levels 1–3 (normalized to occurrences/year)	(Mean/SD)	2.0±6.2	2.6±6.1	0.9±3.0	3.6±9.2	0.26

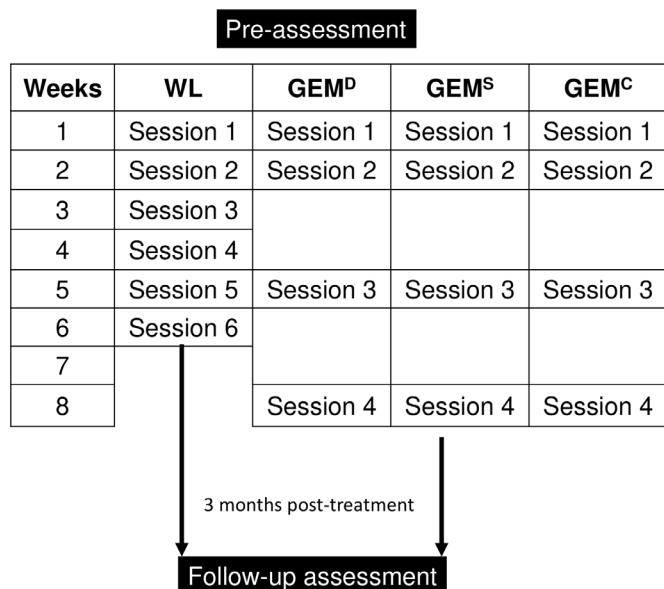BMI, body mass index; GEM, glycemic excursion minimization; MES, Medication Effect Score; WL, weight loss.

Pre-assessment

Weeks	WL	GEM^D	GEM^S	GEM^C
1	Session 1	Session 1	Session 1	Session 1
2	Session 2	Session 2	Session 2	Session 2
3	Session 3			
4	Session 4			
5	Session 5	Session 3	Session 3	Session 3
6	Session 6			
7				
8		Session 4	Session 4	Session 4

3 months post-treatment

Follow-up assessment

Figure 2 Flow chart illustrating participants' matriculation through the study. GEM, glycemic excursion minimization; WL, weight loss.

contact for WL treatment, WL participants met weekly for six 60 min sessions (figure 2).

All participants received a manual and homework diary (available on request). The manuals for the three GEM versions differed only regarding the inclusion of BG monitoring. GEM-S participants were instructed to measure their BG before and 2 hours after nutrient intake, and before and 30 min following more than 10 min of sustained physical activity to learn how these choices impacted their BG. This feedback was also intended to motivate participants to repeat food and activity choices that resulted in desired BG change. GEM-C participants used their continuous glucose monitor (CGM) readouts for similar purposes but noted BG peaks and their duration from such choices. They used the High BG alert to notify them when their BG went above their target and the DexCom Clarity app to review their data. They inserted one 7-day Dexcom G5 sensor at each treatment session, and another 8 weeks after the last treatment session. After the sensors inserted between classes 2–3 and 3–4 expired, participants were encouraged to rely on BG monitoring to note changes in their BG. This was done to promote independence from CGM.

To ensure integrity of the three GEM groups, the diabetes nurse educator (AD) used version-specific instructor's guides and participants used version-specific manuals and diaries. Group sessions comprised participants from the same GEM group. The GEM manual and sessions involved the following four units:

1. Identifying personal motivation to improve metabolic control and educating participants on how their routine choices concerning types and amounts of food and physical activity might affect their BG and their personal goals. In the week following session 1, participants monitored their routine BG-relevant choices in their diary. If assigned to GEM-S or GEM-C, they noted the impact these choices had on their BG.
2. Reducing common high net carbohydrate foods through replacement and substitution. In the 3 weeks following session 2, participants read nutrition labels and recorded choices involving high versus low net carbohydrate foods in their diary. If assigned to GEM-S or GEM-C, they learnt the effect these had on their BG. Participants strove to keep their BG from rising more than 20 mg (1.665 mmol/L) from premeal levels at 2 hours after ingestion.
3. Increasing mild and moderate physical activity, especially postprandially, to increase direct glucose utilization and enhance insulin sensitivity. In the 3 weeks following session 3, participants used the Fitbit Charge 2 and recorded its feedback in their diary in regard to hours active and total steps. Participants assigned to GEM-S or GEM-C recorded the impact of exercise on their BG.
4. Discussing ways to continue and optimize food and activity choices over a lifetime, to manage relapses, and to thank significant others for their support in making and sustaining their behavior change.

This version of GEM differed from that of an earlier intervention, in that it was group based rather than one on one, did not have a specific fifth unit on BG monitoring, had multiple versions of GEM instead of only GEM-S, and had updated content in the manual.[6]

The WL intervention was led by a registered dietitian/ nutritionist and a certified diabetes educator. It consisted of six, weekly 60 min group sessions, individualized to accommodate participants' lifestyle and preferences. The goal was to reduce daily calorie intake by 250–500 g through healthy eating, physical activity, and establishing individualized behavioral goals for eating and activity. The eating plan consisted of healthy carbohydrates (eg, whole grains, fruits, vegetables), lean protein (eg, fish, chicken, legumes), and healthy fats (emphasis on monounsaturated fat). Each week, participants were asked to log their food intake and physical activity in their diary. The dietitian provided feedback on the logs to help participants achieve their goals. The six-chapter manual was adapted from lessons in the Centers for Disease Control and Prevention curriculum: Prevent T2[22], and the chapters focused on:

1. eating well and tracking food, with an emphasis on the plate method and basic carbohydrate counting with strategies for tracking intake.
2. getting active and healthy shopping and cooking.
3. burning more calories than are taken in.
4. keeping the heart healthy and managing stress.
5. coping with triggers and taking charge of one's thoughts.
6. eating well away from home and getting support.

WL class activities focused on lessons learnt from the previous week's activities and content from the new chapter.[23]

At the beginning of each session, participants in all groups used a standardized questionnaire to report perceived symptoms of all the level 1–3 hypoglycemic experiences they had since the previous session. These were defined as: level 1 (low enough for treatment), level 2 (sufficiently low to indicate serious, clinically important hypoglycemia) and level 3 (associated with severe cognitive impairment requiring external assistance for recovery).[18]

Statistical methods

The sample size was calculated to provide sufficient power for comparing the primary outcome: change in HbA1c from pre to follow-up, with contrasts used to test specific hypotheses among interventions. Two previous studies of lifestyle intervention in patients with diabetes provided estimates of variation for the calculations.[6 24] Allowing for 20% dropout, a sample of 50 participants per intervention provided 91% power for the contrast comparing WL and GEM interventions, when the mean HbA1c difference is 0.4%. The sample size also provides 82% power for comparing the three GEM versions, assuming the difference between the means in the version with the greatest reduction and the version with the least reduction is 0.7%.

Intent-to-treat analyses were performed using SAS V.9.4. A one-way analysis of variance compared changes in HbA1c among the four interventions. Orthogonal contrasts were used to divide the treatment sum of squares, with 3 df, to make specific comparisons among the interventions. One contrast (1 df) was used to compare the WL and GEM interventions. The F-test for a second contrast (2 df) was used to compare the three GEM versions regarding changes in HbA1c, followed by pairwise comparisons among GEM versions. χ^2 tests were used to compare categorical outcomes among the interventions. Two-tailed probabilities were used to interpret all results. To address possible alpha error from multiple comparisons, the Benjamini-Hochberg procedure was employed.[25]

RESULTS

Primary outcome variable

At follow-up, the mean and SD of the HbA1c reduction for GEM-D, GEM-S, and GEM-C was −0.8±1.5%, −1.1±1.1%, and −0.9±1.0%, F=0.50, p=0.61 (online supplemental table 3). Another way of calculating clinical significance is to compare the proportion of participants who lowered their HbA1c below 7.0%.[18] After removing four participants whose baseline HbA1c was less than 7.0%, 50% of GEM-D, 50% of GEM-S, and 34% of GEM-C achieved this criterion (χ^2=2.52, p=0.284). Yet another way of contrasting groups is to compare them in regard to the percent responders—those who reduced HbA1c ≥0.5%. GEM-D, GEM-S and GEM-C had 64%, 72%, and 67% who achieved this criterion, respectively (χ^2=0.7, p=0.71). Furthermore, when the three versions

of GEM were compared on secondary variables, they only differed in the frequency of BG monitoring during the third month of follow-up (p=0.001), where GEM-D participants measured BG less frequently (online supplemental table 3). As shown in table 1, the GEM groups did not differ in either occurrence of hypoglycemia during the treatment phase or diabetes medications at baseline and follow-up. Consequently, contrasts were used to compare WL participants to all GEM participants combined.

Table 2 displays pre and follow-up means and SDs for the WL and GEM versions, followed by p levels comparing WL to GEM and pre to follow-up differences for WL and GEM participants. Within each set of contrasts, the error rates are controlled for multiple comparisons using the Benjamini-Hochberg procedure false discovery rate of 0.05.[25]

Online supplemental table 2 displays pre to follow-up change scores and corresponding F statistics. Online supplemental figure 1 displays SD differences between the groups.

The mean pre to follow-up reduction of HbA1c was significantly different between GEM and WL: −0.95% and −0.35%, respectively (F=8.17, p=0.005, table 2). At follow-up, a significantly greater proportion of GEM than WL subjects had HbA1c <7.0%: 40% and 23%, respectively (χ^2=5.255, p=0.022). However, GEM did not differ from WL in regard to the percentage of responders; 68% vs 53%, respectively (χ^2=3.8, p=0.15).

Secondary outcome variables

When comparing pre-to-post changes, GEM reduced cardiovascular risk based on the United Kingdom Prospective Diabetes Study Outcomes Model 2 (UKPDS-OM2)[26] algorithm significantly more than WL (p=0.003, table 2). When comparing pre-to-post changes separately for the GEM and WL groups, only GEM increased empowerment (p<0.001), decreased diabetes distress on both the Emotional and Regimen subscales (p=0.002 and p<0.001, respectively), and reduced depressive symptoms on the Patient Health Questionnaire-9 (p=0.038).

Side effect variables

Neither WL nor GEM significantly increased consumption of fat or protein or increased low-density lipoprotein, triglycerides or total cholesterol. However, when comparing pre-to-post changes for the GEM and WL groups separately, both WL and GEM significantly increased high-density lipoprotein (HDL) (p=0.002 and p<0.001, respectively; table 2). The groups did not differ in their diabetes medication regimens, either at baseline or at follow-up (see tables 1 and 2). Over the course of treatment, no episodes of level 3 hypoglycemia and few episodes of level 1 and 2 hypoglycemia were self-reported, so these were combined for analysis. Extrapolating to an annual event rate, WL and GEM participants reported the equivalent of 2.0 and 2.3 events/year (t=−0.264, p=0.79).

Table 2 Pre and follow-up assessment scores and statistical significance of between (groups) and within (pre, follow-up) with a false discovery rate of 0.05[25]

Variables	WL Mean (SD)		GEM Mean (SD)		P value		
	Pre	Follow-up	Pre	Follow-up	WL to GEM	WL	GEM
Primary outcome variable							
HbA1c (%)	8.24 (0.99)	7.93 (1.39)	8.36 (1.33)	7.39 (1.31)	0.005*	0.055	<0.001*
Secondary benefit variables							
Cardiovascular risk (United Kingdom Prospective Diabetes Study Outcomes Model 2, UKPDS-OM2) (%)	15 (11)	14 (10)	14 (12)	11 (8)	0.003*	0.171	<0.001*
Diabetes empowerment	30.6 (3.8)	31.7 (4.8)	30.0 (4.6)	33.1 (4.9)	0.073	0.096	<0.001*
Diabetes distress (Emotional)	2.26 (1.05)	2.14 (1.04)	2.35 (1.11)	2.12 (1.10)	0.629	0.303	0.002
Diabetes distress (Regimen)	3.14 (1.11)	2.79 (1.24)	3.07 (1.35)	2.48 (1.27)	0.175	0.078	<0.001*
PHQ-9 (depression symptoms)	4.61 (4.28)	4.10 (4.76)	4.38 (4.75)	3.62 (4.81)	0.683	0.541	0.038*
Side effect variables							
LDL (mmol/L)	5.74 (1.88)	5.57 (1.65)	5.63 (2.06)	5.70 (2.00)	0.335	0.427	0.579
HDL (mmol/L)	2.37 (0.48)	2.43 (0.48)	2.39 (0.56)	2.54 (0.68)	0.528	0.002*	<0.001*
Triglycerides (mmol/L)	7.99 (5.72)	7.22 (3.05)	9.99 (7.94)	8.27 (4.55)	0.513	0.383	0.816
Total cholesterol (mmol/L)	9.34 (1.96)	9.18 (1.80)	9.62 (2.42)	9.58 (2.37)	0.403	0.402	0.832
Total fats/day (g) (ASA24)	105.8 (41.2)	101.9 (42.2)	83.3 (29.3)	85.1 (31.7)	0.598	0.664	0.741
Proteins (g) (ASA24)	104.2 (29.6)	97.1 (29.1)	83.9 (26.0)	85.4 (28.0)	0.335	0.427	0.579
Mechanism variables							
Diabetes knowledge	14.2 (2.7)	14.5 (3.7)	14.6 (3.0)	17.2 (2.9)	<0.001*	0.690	<0.001*
BMI	34.9 (7.1)	34.2 (6.8)	34.9 (6.0)	33.6 (6.1)	0.013	0.005*	<0.001*
Carbohydrates (serving) (CRC)	32.5 (14.3)	29.0 (12.1)	34.9 (16.7)	18.2 (14.8)	<0.001	0.050	<0.001*
Carbohydrates/day (g)(ASA24)	236 (66)	208 (68)	214 (80)	148 (67.9)	0.001	0.178	<0.001*
Calories/day (ASA24)	2292 (580)	2111 (617)	1953 (595)	1710 (561)	0.061	0.756	<0.001*
Steps/day (Fitbit)	7438 (3434)	7669 (3455)	6599 (2961)	7156 (3392)	0.698	0.368	0.012*
Hours active (Fitbit)	7.14 (2.82)	7.50 (2.65)	7.62 (2.51)	8.31 (2.71)	0.538	0.041	0.006*
ΔBG from MMTT (0–60 min) (mmol/L)	4.66 (1.57)	5.04 (1.79)	4.42 (1.73)	4.18 (1.73)	0.021	0.082	0.090
Self-monitoring of blood glucose (SMBG): Count in past 30 days	15.4 (22.6)	18.7 (20.0)	10.1 (18.4)	28.5 (29.2)	0.056	0.143	<0.001*
Glucose monitoring satisfaction	3.32 (0.47)	3.60 (0.62)	3.36 (0.52)	3.73 (0.51)	0.267	0.003	<0.001*
Medication Effect Score	1.06 (0.74)	1.17 (0.90)	1.19 (0.81)	1.18 (0.80)	0.227	0.223	0.768

*Significant with a false discovery rate of 0.05.[25]
ASA24, Automated Self-Administered 24-hour dietary recall; BG, blood glucose; BMI, body mass index; CRC, Carbohydrate Routine Consumption scale; GEM, glycemic excursion minimization; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MMTT, mixed meal tolerance test; PHQ-9, Patient Health Questionnaire-9; WL, weight loss.

Mechanism variables

At follow-up, compared with WL, GEM participants demonstrated a greater reduction in BMI (p=0.013) and carbohydrate ingestion on both the CRC and ASA24 (respectively p<0.001 and p=0.001), a smaller BG response to Boost (p=0.021), and an increase in GEM-specific diabetes knowledge (p<0.001, table 2). When comparing pre-to-post changes separately for the GEM and WL groups, both WL and GEM participants significantly reduced BMI (respectively p=0.005 and p<0.001) and improved Glucose Monitoring Satisfaction Scale scores (respectively p=0.003 and p<0.001). Only GEM participants increased their use of self-monitoring of blood glucose (SMBG, p<0.001), reduced calories ingested per day on the ASA24 (p<0.001), and increased steps/day (p=0.012) and hours active (p=0.006). Groups did not differ in regard to their diabetes medication regimen (MES), both before and after treatment (tables 1 and 2).

DISCUSSION

This study investigated whether a novel treatment program focused on reducing postnutrient glucose excursions was equal or superior to conventional WL therapy when equating dosage (contact hours). Across primary, secondary and side effect variables, WL was never superior to GEM. This indicates that targeting the reduction of postnutrient BG is a legitimate treatment option for clinicians and patients alike, and may be especially appropriate to consider for those patients who do not need, want, or are unable to achieve and maintain WL.

Both interventions significantly reduced BMI, while increasing HDL and improving attitudes towards BG monitoring. Compared with WL, GEM was significantly better at improving HbA1c, carbohydrate ingestion, BMI, GEM-relevant knowledge, and cardiovascular risk. Further, only GEM significantly improved psychological functioning (greater empowerment, lower diabetes distress, and fewer depressive symptoms), reduced calories, increased physical activity and increased frequency of BG monitoring. Nevertheless, many WL participants did benefit, with 23% reducing their HbA1c below 7% and 53% being classified as responders. The benefits of both interventions and the differences between groups cannot be attributed to change in diabetes medication regimen, as their MES did not change.

The objective of GEM is to empower individuals with the knowledge and skills to make choices that reduce carbohydrate intake and increase routine physical activity. GEM achieved these goals by significantly increasing relevant knowledge, decreasing carbohydrate consumption (as defined by both the CRC questionnaire and the 24-hour dietary recall), and increasing routine physical activity (total steps and hours active) and empowerment. It is important to note that this involved only modest behavior change, with a mean reduction in carbohydrate ingestion of 31% (follow-up mean consumption of 148±68 g of carbohydrates/day), reduced sedentary behavior and increased steps/day, but no increase in moderate to vigorous activity (Fitbit active minutes). Further, these gains were achieved after only four group sessions combined with educational materials (GEM manual and daily diaries). Additionally, GEM does not involve hunger or restricted calorie intake, and can provide BG feedback within 30–120 min of glycemic-relevant choices.

The empowerment aspect of GEM was hypothesized to reduce depressive symptoms, but this could have also been attributed to the physiological consequences of lowering HbA1c.[27] An exploratory analysis of GEM participants demonstrated that a reduction in depressive symptoms significantly correlated with reductions in HbA1c (r=0.21) and diabetes distress (Regimen subscale: r=0.43, Emotional subscale: r=0.35), and with an increase in diabetes empowerment (r=−0.42). Stepwise regression indicated that only improvements in diabetes empowerment and the diabetes distress regimen uniquely predicted the reduction in depressive symptoms (R^2=0.25). This suggests that improvement in generic depressive symptoms in patients with T2D may be driven by improvement in diabetes-specific psychological functioning.

There were two unanticipated outcomes. First, while the lack of a significant benefit of BG monitoring among adults with T2D is consistent with some studies, the potential role of BG monitoring to educate, motivate and activate patient choices was anticipated to be beneficial.[27] The most parsimonious explanation is that the education, exercise, and behavioral feedback from self-monitoring and keeping a diary were powerful enough that glucose monitoring did not add an additional benefit.

A randomized clinical trial methodology may have been inappropriate when comparing different active lifestyle interventions. In this study, participants were randomized to interventions relying on BG monitoring (GEM-S and GEM-C) or not relying on monitoring (WL and GEM-D). This means that some people who wanted BG monitoring did not receive it and might have been frustrated, while others who did not want BG monitoring because of needle or blood phobias, apprehension about sensors under their skin, or the technical challenges of BG monitoring received what they did not want. Likewise, it may be that some people who had tried, failed and rejected WL in the past were randomly assigned to WL. An alternative and possibly more appropriate methodology may be the partially randomized preference design.[28] This allows patients with strong preferences to select their preferred treatment and randomizes participants with no strong preference to one of the treatment arms. Support for this speculation comes from a small study that the investigators recently conducted where adults were recruited to participate in GEM-C and randomized to that or routine care.[29] In that study, where everyone who received GEM-C wanted it, the mean HbA1c reduction at the 3-month follow-up was −1.3%. Further studies will be needed to confirm this.

The second unanticipated outcome was that GEM participants lost more weight than WL participants.

WL participants reduced their mean intake of carbohydrates, fats and proteins, but these were not significant, and it did not lead to a significant reduction of calories at the 3-month follow-up. In contrast, GEM significantly lowered calorie intake by significantly reducing carbohydrate intake and increasing caloric expenditure through routine physical activity. It may be that focusing on reducing carbohydrates, rather than reducing calories, is a more effective or palatable way to lose weight.[2]

A methodological limitation was providing GEM-D participants with BG meters and unlimited supplies. When these participants asked how often they should measure their BG, they were instructed to follow their primary care physician's recommendations. However, some GEM-D participants used the free SMBG supplies liberally, possibly making them functionally equivalent to GEM-S. Another possible limitation is that our WL intervention was too brief. Despite increasing the number of WL treatment sessions from four to six, we strove to equate doses by giving both interventions 6 hours of group involvement.

Given that GEM and WL were delivered by different clinicians, this could possibly account for differences between the interventions. However, in a program evaluation at follow-up, WL and GEM participants rated how helpful they found listening to the group leader, and hearing from and talking to other participants on a 5-point scale ('Not helpful at all' to 'Extremely helpful'). The respective mean ratings for the WL and GEM interventions on these two questions were 4.4 vs 4.5 (p=0.603) and 4.1 vs 4.1 (p=0.845). Further, group attendance was the same for the two interventions, with attendance rates being 80% and 75%, respectively, for WL and GEM (p=0.34). These data suggest that the GEM and WL interventions were similar in perceived quality.

Future investigations into the role of BG feedback in GEM should not provide BG monitoring supplies to the equivalent of GEM-D, but should provide regular CGM access to GEM-C participants and employ a partially randomized preference trial design. For greater external validity, it will be important to replicate these findings at other sites and with less restrictive inclusion criteria. It will also be important to identify those individuals who will respond optimally to WL or to GEM to promote treatment efficacy, reduce patient frustration, and reduce healthcare expenditures.

Despite these limitations, the GEM intervention is a novel and effective treatment for adults with T2D that should be considered as an option for patients who do not want or are unable to lose weight and who are willing to reduce their carbohydrate intake and increase their routine physical activity.

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