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Jump Starting Shared Medical Appointments for Diabetes with Weight Management: Rationale and Design of a Randomized Controlled Trial

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Abstract

Background—Rates of glycemic control remain suboptimal nationwide. Medication intensification for diabetes can have undesirable side effects (weight gain, hypoglycemia), which offset the benefits of glycemic control. A Shared Medical Appointment (SMA) intervention for diabetes that emphasizes weight management could improve glycemic outcomes and reduce weight while simultaneously lowering diabetes medication needs, resulting in less hypoglycemia and better quality of life. We describe the rationale and design for a study evaluating a novel SMA intervention for diabetes that primarily emphasizes low-carbohydrate diet-focused weight management.

Methods—Jump Starting Shared Medical Appointments for Diabetes with Weight Management (Jump Start) is a randomized, controlled trial that is allocating overweight Veterans (body mass index ≥ 27 kg/m²) with type 2 diabetes into two arms: 1) a traditional SMA group focusing on medication management and self-management counseling; or 2) an SMA group that combines low-carbohydrate diet-focused weight management (WM/SMA) with medication management. Hemoglobin A1c reduction at 48 weeks is the primary outcome. Secondary outcomes include hypoglycemic events, diabetes medication use, weight, medication adherence, diabetes-related quality of life, and cost-effectiveness. We hypothesize that WM/SMA will be non-inferior to standard SMA for glycemic control, and will reduce hypoglycemia, diabetes medication use, and weight relative to standard SMA, while also improving quality of life and costs.

Conclusions—Jump Start targets two common problems that are closely related but infrequently managed together: diabetes and obesity. By focusing on diet and weight loss as the primary means to control diabetes, this intervention may improve several meaningful patient-centered outcomes related to diabetes.

Keywords

Diabetes; obesity; low-carbohydrate diet; shared medical appointments; comparative effectiveness; health services research

Introduction

As the primary risk factor for type 2 diabetes, obesity underlies the current diabetes epidemic; 80–90% of patients with type 2 diabetes are classified as overweight or obese.[1–3] In the United States, diabetes more than doubles the risk for death from heart disease or stroke, and is the leading cause of blindness, kidney failure, and non-traumatic lower-limb amputations.[1] Good glycemic control reduces the devastating complications of diabetes. Studies suggest that every 1% reduction in hemoglobin A1c (HbA1c) leads to risk reductions of 37% for microvascular complications, 18% for incident cardiovascular disease or stroke, and 14% for all-cause mortality.[4,5] Despite this knowledge, glycemic control remains widely suboptimal.[6,7]

Shared medical appointments (SMA) are a care delivery strategy with potential to enhance the quality of diabetes care. A subtype of group medical visits, SMA convene groups of patients to meet repeatedly over time for discussion, education, self-management support, and medication management. A recent review found that SMA lower HbA1c by 0.55% and systolic blood pressure (BP) by 5.2 mmHg among patients with diabetes.[8]

While SMA facilitate provision of education and self-management support, a central mechanism by which they improve HbA1c is medication intensification, which can have undesirable side effects including weight gain and hypoglycemia. These factors may offset the benefits of glycemic control.[9–11] SMA typically do not emphasize weight management as the primary means to control diabetes,[8] which is problematic because weight loss predicts improved glycemic control,[12–15] and may independently reduce diabetes complications even apart from its effect on glycemia.[16,17] Because weight loss can improve glycemic control while reducing diabetes medication needs, it may also lower hypoglycemia risk.[14,18,19] Reduced medication needs and weight loss may both contribute to improved quality of life.

Given these data, an SMA intervention that emphasizes weight management could improve diabetes control and lower weight, while simultaneously reducing diabetes medication requirements, hypoglycemia, and side effects. Low-carbohydrate diets may be a particularly effective approach for weight management and diabetes. Meta-analyses indicate that low-carbohydrate diets reduce weight and BP without causing disproportionate rates of serious adverse events.[20,21] In addition, a review by the American Diabetes Association found that low-carbohydrate diets improve glycemic parameters, and can lower medication

requirements relative to other diets.[22] Another meta-analysis showed that greater decreases in carbohydrate intake are associated with greater improvements in HbA1c.[23]

We are studying the effectiveness of low carbohydrate diet-focused weight management in the setting of an SMA intervention for diabetes and obesity. In Jump Starting Shared Medical Appointments for Diabetes with Weight Management (Jump Start), we are allocating overweight patients with type 2 diabetes into two arms: 1) a traditional SMA group focusing on general self-management counseling and medication management; or 2) an SMA group that primarily emphasizes low carbohydrate diet-focused weight management counseling for diabetes management (WM/SMA). We hypothesize that WM/SMA will be non-inferior to standard SMA for glycemic control, and more effective in reducing hypoglycemic events, diabetes medication requirements, weight, and costs, all while increasing diabetes-related quality of life.

Methods

Study design

Jump Start (ClinicalTrials.gov NCT01973972) is designed to examine whether WM/SMA is non-inferior to SMA with regard to diabetes management, while also exploring potential advantages of WM/SMA over SMA, such as reduction of diabetes medication requirements and hypoglycemic events, lower costs, and improved diabetes-related quality of life. We are currently randomizing Veterans into two active study arms. The SMA group receives general diabetes counseling and medication management for diabetes and hypertension, while the WM/SMA group primarily receives low-carbohydrate diet-focused weight management counseling, along with medication management for diabetes and hypertension. All participants are followed for 48 weeks. This study has been approved by the Durham Veterans Affairs (VA) Medical Center Institutional Review Board. The study is being conducted according to Good Clinical Practice guidelines, the U.S. Code of Federal Regulations (CFR) Title 21 CFR (Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards) and the Declaration of Helsinki.

Study population

Our recruitment goal is 308 subjects. Study inclusion criteria are: a diagnosis of type 2 diabetes (based on ICD-9 codes 250.x0 or 250.x2 or ICD-10 E11.xxx); hemoglobin A1c (HbA1c) >8.0% at the time of screening (7.5% if under age 50); body mass index (BMI) $\geq 27 \text{ kg/m}^2$; interest in losing weight; agreement to attend regular visits per study protocol; access to a telephone and reliable transportation; and assignment to a VA Medical Center (VAMC) primary care provider.

Exclusion criteria include: hemoglobinopathy that interferes with measurement of HbA1c; conditions that could increase the risk of study participation, including age ≥ 75 years old, type 1 diabetes, chronic kidney disease (serum creatinine $>1.5 \text{ mg/dL}$ in men, $>1.3 \text{ mg/dL}$ in women), current unstable coronary heart disease, BP $\geq 160/100 \text{ mm Hg}$, triglycerides $\geq 600 \text{ mg/dL}$, or serum low-density lipoprotein cholesterol (LDL-C) $\geq 190 \text{ mg/dL}$ at screening; pregnancy, breastfeeding, or lack of birth control if premenopausal (females only); dementia,

psychiatric illness, or substance abuse that may interfere with adherence; or enrollment in another weight loss program or research study that might affect the main outcomes of this study.

Study recruitment

We are recruiting patients from outpatient sites affiliated with the Durham VA Health Care System. After reviewing electronic health record (EHR) data to identify patients meeting our inclusion and exclusion criteria, we mail introductory letters to these potentially eligible patients. These letters provide basic information about the study, and offer patients the opportunity to opt out of the study by calling a toll-free number. Patients who do not opt out of participation are contacted by research staff after 5 days for further discussion about the study and, if appropriate, enrollment. Patient advertisements posted in patient areas are also used for recruitment. Clinicians are provided flyers with study information, and may refer participants via the EHR.

When potential participants are self-referred or referred by clinicians, research personnel review the EHR for eligibility prior to calling them. Potential participants are contacted by phone to address eligibility and schedule an in-person individual enrollment visit to confirm eligibility.

Study enrollment

Written informed consent is obtained at the beginning of the individual enrollment visit with each potential participant. After providing informed consent, potential participants complete a screening medical history, study questionnaire, vital sign assessment, and height and weight measurements to determine BMI. Participants also complete baseline laboratory testing, including HbA1c, serum creatinine, and a serum lipid profile. Final study eligibility is determined based on these assessments as per the inclusion/exclusion criteria listed above. Individuals deemed ineligible for the study are informed of other available VA weight loss and diabetes programs.

Randomization

Participants determined to be eligible for the study are randomized in equal numbers to either SMA or WM/SMA, with stratification by baseline HbA1c (7.5–8.9% versus ≥9%) and diabetes treatment regimen (no insulin or basal insulin alone versus basal plus prandial insulin). Baseline HbA1c and diabetes treatment regimen are known to correlate with our outcomes, we aimed to balance participants in these strata across treatment groups. Randomization is performed using a computerized random number generator in blocks of size <10 (all study personnel except the statisticians are blinded to block size).

Intervention assignment is not revealed to participants until their initial group visit to prevent initiation of behavior changes prior to the onset of the intervention at the first group visit. Participants are considered randomized when they learn of their assignment to either SMA or WM/SMA during the first group visit. Participants who drop out before the first visit and do not learn of their randomization assignment will not be included in data analysis.

Study interventions

Overview—Participants are divided into small groups (goal of 10–15 participants) within their randomly-assigned treatment arm (SMA or WM/SMA). Each group remains together throughout the study, and the same physician and staff members oversee all of a group's sessions. Groups meet independently according to a treatment arm-specific schedule (Table 1). Participants in the SMA groups meet every 4 weeks for 16 weeks, then every 8 weeks for 32 weeks, with content focusing on diabetes counseling and medication management. Participants in the WM/SMA groups meet every 2 weeks for 16 weeks to receive weight management counseling and medication management, followed by meetings every 8 weeks for 32 weeks for diabetes counseling, weight management counseling, and medication management. In both arms, each session lasts approximately 2 hours; session content is tailored within each intervention arm to ensure balance between arms regarding duration of the meetings. All of the group meetings and outcome assessments occur at clinics associated with our VA center.

Structure of group sessions—Group sessions in both study arms proceed in three distinct phases (Table 2): data gathering; data processing and synthesis; and medication management. During the 30 minute 'data gathering' phase, participants check in with study staff, undergo measurement of vital signs and weight, turn in their blood glucose logs, and complete questionnaires addressing current symptoms and recent hypoglycemic episodes. At outcome visits (weeks 0, 16, 32, and 48), participants additionally turn in diet logs and complete additional questionnaires for the purpose of study outcome assessment. Following data gathering, the 45–60 minute 'data processing and synthesis' phase begins. During this phase, participants have the opportunity to eat a healthy snack provided by study staff and socialize with other group members. A study nurse, dietitian, or certified diabetes educator (CDE) then delivers an educational talk to the group focusing on intervention arm-specific material. Talks are interactive, with questions permitted at any time. Concurrent with the talk, the study physician reviews logs and questionnaires provided by each participant and devises an initial medication management plan for the patient. Following data processing and synthesis, the 30–45 minute 'medication management' phase concludes the group session. During this phase, the study physician meets briefly with each individual participant to discuss intervention-arm specific medication adjustments, along with any possible adherence or medication procurement issues. The study physician and participant agree upon any medication changes, which are also communicated to the participant's primary care provider (PCP) via the EHR. Participants are given contact information for the study team; the study physician is available 24 hours a day.

SMA intervention—The SMA intervention was developed during a prior study,[24] with modifications based on a recent systematic review.[8] These modifications are designed to increase intervention potency, and include: 1) higher visit frequency to enhance understanding, adherence, and safety; and 2) fostering social support at home by allowing spouses/partners to attend meetings with participants. Of note, content from the SMA intervention is utilized in both arms. In the SMA arm, patients receive the full intervention dose (Table 1). In the WM/SMA arm, SMA content is included after week 16, but fewer

topics are covered (given the lower number of remaining sessions after week 16) and topics are abbreviated to allow time for continued weight management counseling.

The goal of each SMA session is to provide group-based diabetes counseling and to address participants' diabetes and hypertension medication management on an individualized basis. Educational counseling in the SMA intervention addresses specific aspects of diabetes care. Initial meetings include a brief group discussion designed to elicit the predisposing, enabling, and reinforcing factors common to the members of each individual group (e.g., fear of hypoglycemia, lack of knowledge of causes of complications of diabetes, and lack of knowledge of appropriate foot care). Subsequent sessions are tailored to the topics identified in the initial group session. Although the order in which topics are covered may vary by group, our comprehensive curriculum of diabetes counseling topics is covered in its entirety during the 48-week intervention (Appendix 1). Of note, SMA groups discuss healthful eating concepts, such as portion control, the effects of macronutrients on blood glucose, basic carbohydrate counting, and the positive impact of weight loss on glycemic control; however, SMA groups do not advocate a particular diet. Specifically, because the low-carbohydrate diet is not considered 'standard care' for the dietary management of diabetes, it is not taught to the SMA group.

The goal of medication management in the SMA arm is to intensify diabetes and antihypertensive therapy until blood glucose and blood pressure parameters are optimally controlled. Medication adjustment is addressed on an individualized basis by a study physician during group sessions, with guidance from shared algorithms for diabetes and hypertension (Appendix 2). Use of these medication management algorithms helps assure consistency in medication management between groups, and team case reviews are conducted periodically by the study physicians in order to assure algorithm adherence. Case review is also performed by physicians unaffiliated with the study in order to assess fidelity to our protocol (see 'Fidelity Assessment' section below for additional detail)

WM/SMA intervention—For the first 16 weeks of the WM/SMA intervention, group sessions focus on low-carbohydrate diet-based weight management counseling (Table 1). For the remaining 32 weeks, sessions focus on general diabetes counseling as per the SMA intervention section above, with incorporation of continued weight management counseling. Throughout the study, participants also receive individualized medication management as part of each session.

At the first group session, our team uses a low-carbohydrate diet book and handouts developed for previous studies to provide the group with general information on carbohydrate restriction, along with specific details on the induction phase of the low-carbohydrate diet.[25–27] Carbohydrate intake is initially restricted to 20–30 grams daily. Calorie intake is not restricted, as a low carbohydrate diet typically leads to spontaneous calorie reduction.[28,29] The diet allows unlimited amounts of animal foods (beef, chicken, turkey, other fowl, fish, shellfish, eggs) and limited amounts low-carbohydrate vegetables and hard cheese. Artificial sweeteners may be used, but caffeine and alcohol are avoided.

At subsequent WM/SMA sessions, participants receive continued dietary, behavioral, and supportive counseling from the study dietitian. Session topics include instruction regarding food choices, grocery shopping, restaurant eating, dealing with social situations, recipe makeovers, and mindful eating (Appendix 3), and often incorporate behavioral techniques to aid adherence. In later sessions, a greater emphasis is placed on physical activity and other strategies for maintaining weight loss (e.g., self-monitoring, eating breakfast). Because a participant's spouse or partner may shop and/or prepare food for the family, spouses/partners are also invited to attend group sessions.

Early in the study, WM/SMA participants set a weight loss goal for first 16 weeks with the help of study personnel. As weight loss approaches half of this goal, participants are instructed to add approximately 5 grams to the daily carbohydrate intake each week as long as weight loss continues. Should weight loss cease, participants are instructed to return to the daily carbohydrate intake from the previous week. When participants approach their goal weight, they again add approximately 5 grams to the daily carbohydrate intake every week until weight regain occurs, after which they return to the daily intake from the previous week. This becomes the participant's maintenance carbohydrate intake level. Added carbohydrates may include salad vegetables, low-carbohydrate vegetables, avocado, cheese, nuts, or lower carbohydrate fruit (e.g., berries). In addition, participants may try low-carbohydrate products such as snack bars and shakes. In our previous studies, good adherence to these instructions resulted in approximately 10% of daily calorie intake coming from carbohydrate.[27–29] Other strategies for maintenance of weight loss are also emphasized in latter sessions.

Medication management for WM/SMA participants is primarily aimed at preventing hypoglycemia and curtailing medications that can interfere with weight loss. Based on participants' baseline HbA1c level, diabetes agents (other than metformin) are decreased or discontinued at diet initiation. Adjustment of diabetes agents is addressed on an individualized basis by a study physician during group sessions, with guidance from a shared algorithm to help assure consistency in medication management between groups (Appendix 4). Because diuresis ensues during the first 2–4 weeks of low-carbohydrate diet initiation, diuretic doses are also modified using a shared algorithm, and magnesium and potassium are supplemented as needed. Following week 16, further medication adjustment is guided by the algorithms used for the SMA group (Appendix 1). As with the SMA groups, algorithms help assure between-group consistency; team case reviews are conducted periodically by the study physicians in order to assure algorithm adherence. Case review is also performed by physicians unaffiliated with the study in order to assess fidelity to our protocol (see 'Fidelity Assessment' section for additional detail).

Additional procedures common to intervention arms—All participants receive a pocket calorie, fat, and carbohydrate counting guide to aid with dietary changes.[30] Participants are encouraged to drink at least 8 glasses of water and to take a standard multivitamin daily. All are also advised of current recommendations to strive for 30 minutes of moderate-intensity aerobic physical activity 5 days per week.[31]. In both groups, we ask participants to sign attendance contracts at the first session.

Fidelity Assessment

In order to ensure that all critical components are covered during group sessions, study staff members monitor each session and complete checklists detailing content in both the WM/SMA and SMA arms. Additionally, as above, the study physicians conduct periodic team case reviews to assure algorithm adherence, and case reviews are performed by physicians unaffiliated with the study in order to assess fidelity to the medication management protocols.

Outcome Measures

All study measurements are performed by trained research personnel in an unblinded fashion. Measures are collected at parallel time points in both study arms (weeks 4, 8, 12, 16, 24, 32, 40, and 48); weight and hypoglycemic events are additionally assessed at weeks 2, 6, 10, and 14 in the WM/SMA arm, but these additional data are not used for formal outcome ascertainment. Participants who wish to discontinue the study are asked to return for outcome assessment at weeks 16, 32, and 48. Participants are compensated a total of \$125 for completion of outcome visits throughout the study. Table 3 summarizes the study measures and timing of outcome assessment, and measures are discussed in greater detail below.

Primary outcome—The primary outcome, HbA1c, is measured by the Durham VAMC Central Laboratory at baseline and every 16 weeks thereafter. The Central Laboratory assesses HbA1c via high performance liquid chromatography on a TOSOH G-7 (San Francisco, CA), certified by the National Glycohemoglobin Standardization Program and standardized to the Diabetes Control and Complications Trial assay.

Secondary outcomes—Hypoglycemic events are assessed following a procedure described in Zammitt et al.[32] Participants complete a hypoglycemic event form at each group visit. All participants are provided a handout that lists mild and severe hypoglycemic symptoms, and distinguishes between unassisted and assisted events. All hypoglycemic events are recorded by participants on standardized forms, including all events associated with a documented blood glucose <70 mg/dL and any additional occurrence of symptoms typical of hypoglycemia, as described by ADA Workgroup on Hypoglycemia.[33] Participants are additionally asked if they received medical attention for hypoglycemia since the last assessment, which allows for assessment of serious hypoglycemic events treated outside the VA.

We ascertain diabetes medication use with each participant at every visit. For all subjects, we identify changes to the total daily dose of each diabetes medication over the course of the study, and then compute the proportion of each study arm's participants that fall into each of the following categories: 1) diabetes medication increased from baseline, 2) diabetes medication unchanged from baseline, 3) diabetes medication decreased from baseline, and 4) diabetes medication eliminated. To summarize the changes in each participant's diabetes medication use, we use the medication effect score (MES) to evaluate the overall diabetes medication use for each participant. The MES was devised to reflect the overall intensity of

diabetes pharmacotherapy based on the potencies and dosages of the medications in a patient's regimen, allowing comparison of treatment intensity across different regimens.[34]

Body weight is measured by trained research personnel at every visit on a standardized digital scale, with participants wearing light clothing and shoes removed. The scale is calibrated annually. Weight measurements at weeks 2, 6, 10, and 14 in the WM/SMA group are not used for outcome ascertainment, but for patient feedback only.

We capture costs associated with the WM/SMA and SMA interventions for cost-effectiveness or cost-minimization analysis, including intervention-related costs and health care costs. Intervention-related costs include labor and capital costs. Labor includes interventionist time in both study arms, which we assess using VA Human Resources data for salaries and study data on time spent per task. Capital costs include the development and implementation of the interventions, overhead costs, office space, supply costs, and telephone services costs. Health care costs include expenditures VA incurs for hospital admissions, outpatient visits, laboratory tests, pharmacy fills, radiology tests, surgical procedures, nursing care, and all other care provided by VAMCs. VA cost data will be obtained from the patient treatment file data, Outpatient Care file, and VA Health Economic Research Center average unit cost estimates. Because prior studies have shown intensive lifestyle modification can reduce medication utilization and expenditures,[35] we will examine whether outpatient visit, outpatient medication, and inpatient expenditures differ between study arms.

In order to facilitate cost-effectiveness analyses, we collect the EuroQol-5D (EQ-5D).[36] The EQ-5D, a sensitive 5-item health utility measure used to construct quality-adjusted life-years (QALYs), has good performance in Veteran outpatient populations and assesses five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Additional outcomes—BP is measured every 4 weeks using an automatic sphygmomanometer. After a participant has been seated quietly for 5 minutes, an appropriately-sized cuff is applied to the right arm (left arm if the right arm is missing or unsuitable) and BP is measured twice, with a third measurement if the first 2 deviate more than 10%. An average of the two latter measurements is used for analyses.

Lipids are measured in the fasting state by the Durham VAMC Central Laboratory at baseline and every 16 weeks thereafter using the standard Central Laboratory assay, which includes direct measurement of LDL-C.

Trained personnel measure waist circumference every 16 weeks by placing a non-elastic tape measure on the skin in a horizontal plane around the abdomen at the level of the iliac crest.[37] An average of two measurements will be used for analyses.

We evaluate health-related quality of life (HRQOL) using the Problem Areas in Diabetes (PAID) Scale, a disease-specific HRQOL scale. PAID is a validated, 20-item measure used in many randomized trials, and is a sensitive measure of HRQOL in patients with diabetes. [38] PAID assesses emotional adjustment to life with diabetes and has demonstrated high internal reliability, sound concurrent validity with a number of theoretically related measures

(e.g., hypoglycemia fear), and evidence of predictive validity for adherence to treatment and blood glucose control. Patients rate the degree to which each item is currently problematic on a 5-point scale, from 0 (not a problem) to 4 (serious problem).

Dietary Adherence. Dietary adherence is assessed at baseline and every 16 weeks with a 3-day food record. Participants are mailed logs prior to each outcome visit, and instructed to document all food and drink consumed over 3 consecutive days including 1 weekend day. The study team teaches participants what details to document and how to accurately estimate quantities. From these diaries, a registered dietician uses Food Processor software (Version 10, ESHA Research, Salem, OR) to estimate calorie intake and the percentage of dietary intake from each of the macronutrients (i.e. protein, carbohydrate, and fat). If participants forget their food record, the study team conducts a 24 hour food recall at the outcome visit.

We assess daily physical activity with the International Physical Activity Questionnaire (IPAQ), which was developed and validated by an international team of physical activity experts for use in young and middle-aged adults (15–69 years).[39] We use the long version, which assesses activity over the past 7 days in six domains: occupational, transport, yard/garden, household, leisure, and sitting. The IPAQ provides estimates of metabolic equivalent tasks energy expenditure, which can be reported for each activity or as a total score.

Medication nonadherence is evaluated using a validated questionnaire containing 3 items that assess the extent to which participants have missed doses of their medications over the past 7 days.[40] Participants are instructed to consider nonadherence specifically to their diabetes medications.

Using a validated scale,[41] we examine group cohesion (interaction and communication among group members, member retention, decision-making, vulnerability among group members, and consistency between group and individual goals). A total group score is formed by averaging across all items. Group cohesion is not assessed at baseline because participants are meeting for the first time, but is measured every 16 weeks thereafter.

We also assess depressive symptoms, sleep, and pain interference at baseline and every 16 weeks. Depressive symptoms are assessed using the Patient Health Questionnaire-2 (PHQ-2), which consists of 2 items about depressed mood and anhedonia assessed over the past 2 weeks.[42] Sleep is assessed with the Medical Outcomes Study (MOS) 6-Item Sleep Scale Standard – Revised 2010 which consists of 6 items assessed over the past 4 weeks.[43] The pain scale is the PROMIS Pain Interference 8a, which consists of 8 items that assess pain interference in daily activities over the past 7 days using a 5-point scale.[44]

Adverse Events—A comprehensive checklist of symptoms is assessed at every visit using a standardized form. Anticipated adverse events and side effects for weight-reducing diets and/or medication intensification include hypoglycemia, hypotension, gallbladder disease, headache, weakness, muscle cramps, constipation, diarrhea, and dehydration. Many of these effects relate to dietary change and are transient or easily treated, and can be prevented with adequate hydration and sodium intake (via broth), which is emphasized in the dietary counseling. A study physician is on call at all times to manage adverse events felt to be

related to the study, and patients with unrelated adverse events are referred for appropriate health care. All adverse events are reported to the IRB according to local requirements and reviewed by an independent Data Monitoring Committee (DMC).

Statistical analysis

Our primary analysis and sample size calculations are based on a test of noninferiority.[45–47] The null hypothesis in our noninferiority framework is that WM/SMA will be less than 0.5% higher than in the SMA group at study end. All hypothesis testing will be conducted with two-sided p-values at the standard 0.05 level. Analyses will be performed using SAS for Windows (Version 9.4: SAS Institute, Cary, NC) and R (<http://www.R-project.org/>).

Primary analysis—Our primary outcome is HbA1c measured every 16 weeks for 48 weeks. We will use a linear mixed model (LMM) with an unstructured covariance matrix to address within-patient correlation between repeated measures over time. A random effect will be included to account for clustering of patients within small groups. We will test our noninferiority hypothesis by examining the estimate of the difference in HbA1c between WM/SMA and SMA at 48 weeks. Specifically, we will examine the 95% confidence interval (CI) of this estimated difference, and if the upper limit of the CI is less than the threshold value of 0.5%, we can conclude noninferiority of WM/SMA to SMA.[48] If we conclude noninferiority, we will then test for superiority of WMA/SMA to SMA at 48 weeks by examining the 95% CI for the difference in HbA1c between WM/SMA and SMA at 48 weeks for inclusion of 0. We plan to estimate the parameters in the model with a full-likelihood method using the SAS procedure MIXED (SAS Version 9, Cary, NC). Our model will also include randomization stratification variables baseline HbA1c (7.5–8.9% or 9%) and use of a complex (i.e., multiple types) insulin regimen or not.

Secondary Analyses—Like HbA1c, diabetes medication use (as indicated by MES) and weight are continuous, longitudinal secondary outcomes, so we will also use an approach similar to the primary analysis – however, because we have more time point assessments, time will be a continuous variable and will not be dummy coded. For these models, we will fit random intercepts and slopes for time and a random intercept for the clustering effect of the small groups, and will set up contrasts of model parameters to test the hypothesis that the outcome will be lower in the WM/SMA group versus the SMA group.

Hypoglycemic events will be calculated as the number of events per person-year in the 48 weeks following enrollment in the study. As this will be a count type variable, we will apply mixed-effects Poisson or Negative Binomial regression models adjusted for the clustering of patients within small groups;[49] we will test the hypothesis that WM/SMA participants will have fewer hypoglycemic events than those in the SMA arm.

To compare the WM/SMA intervention and the SMA intervention from a payer perspective, we will calculate an incremental cost-effectiveness ratio (ICER) that summarizes the relative costs and benefits of WM/SMA over SMA alone (if WM/SMA yields significantly greater quality improvements than SMA). Otherwise, we will conduct cost-minimization analysis.[50] The primary measure of effectiveness in this study is glycemic control, so we will estimate the ICER as the difference in the average cost per participant between study arms

divided by the difference in the average level of glycemic control between the two groups. We will also assess effectiveness on the basis of QALYs (derived from the EQ-5D). We will conduct a number of sensitivity analyses to assess the robustness of our base-case ICER results.

Additional Analyses—For our other continuous, longitudinal outcomes (blood pressure, lipids, waist circumference, diabetes specific HRQOL, dietary adherence, physical activity, medication non-adherence and health utility), we likewise will use similar models as described for the primary analysis. Tests for these secondary outcomes will be superiority tests.

Missing data—As in any longitudinal study, outcome values may be missing due to dropout, inability to reach the patient for follow-up, or item non-response. A thorough investigation of the mechanisms for any missing data will be conducted, including a description of missingness by intervention groups, the identification of missing data patterns, and which observed (baseline and time-varying) covariates predict missingness. Because the main predictors of interest for the primary analysis are collected at baseline, we do not anticipate missing data in these variables. Our primary analytic method handles dropout in a principled manner. This main analysis technique, LMM includes all available data on all subjects and implicitly accommodates missingness when the response is Missing At Random (i.e., when missingness is due either to treatment, prior outcome, or other baseline covariates included in the LMM).[51] Depending on the type and scope of missing data, we will also explore multiple imputation as a sensitivity analysis.[52] If the probability of dropout relates to unobservable quantities, additional methods such as selection and pattern mixture models may be used in sensitivity analyses.[53]

Intention-to-Treat Principle—In superiority trials, conducting primary and secondary analyses on an intent-to-treat basis where patients are analyzed in the arm to which they were randomized regardless of intervention adherence is standard practice. For a noninferiority trial, an intention-to-treat analysis would not be the conservative approach, therefore, we will perform our primary analysis on both an intent-to-treat and per-protocol basis.[47,48] Our secondary analyses are based on superiority tests and will be conducted on an intent-to-treat basis.

Sample size calculation—The sample size estimate of $n=154$ patients per arm (total $n=308$) is based on the primary noninferiority hypothesis that mean HbA1c in the WM/SMA group will be $<0.5\%$ higher (non-inferiority limit) than in the SMA group at 48 weeks. In our analysis, this involves using a two-sample t-test sample size calculation at the $\alpha=0.025$ level for the between-group HbA1c difference at the 48-week time point, multiplied by a factor reflecting the correlation between baseline and follow-up time point HbA1c measures.[54] The sample size is adjusted to reflect the clustering of patients within small groups,[55] and then inflated to compensate for potential missing observations due to attrition. Based on previous data, we assume a within-individual correlation of 0.5 between HbA1c at baseline and at 48 weeks, an SD for HbA1c of 1.5%, and an intraclass correlation coefficient of approximately 0.01 (accounts for clustering of individuals attending the same

groups over time).[24,56] Using these parameters and assuming a 20% attrition rate by 48 weeks, 154 patients per group need to be enrolled at baseline to identify a <0.5% between-group difference in HbA1c with 80% power and $\alpha=0.025$. If noninferiority is determined, this sample size will provide >80% power to detect 0.7% improvement in mean HbA1c in the WM/SMA group compared to SMA.

Discussion

This randomized trial uses an efficient SMA-based care delivery strategy to address an important question for patients with uncontrolled diabetes: what is the comparative effectiveness of a strategy primarily focusing on low-carbohydrate diet-based weight management versus a strategy focusing on standard self-management counseling and medication management? In addition to glycemic control, we consider several important patient-centered and diabetes-related outcomes including hypoglycemic events, medication requirements, weight, and quality of life. We also track a comprehensive list of symptoms to ascertain if either approach might have unforeseen effects on health. We are measuring dietary intake, physical activity, medication adherence, and group cohesion to help understand mediators of effects, as well as health care utilization and costs to examine whether one approach is more appealing from a health system perspective.

In addition to comparing the effectiveness of a low-carbohydrate diet-focused SMA to a standard SMA, a strength of this study is its focus on two common, related problems that are infrequently managed together: type 2 diabetes and obesity. Our multidisciplinary approach brings together the expertise necessary to manage both problems in one program, potentially improving several meaningful outcomes. Another strength is the interventions' SMA-based format, which can communicate common diabetes messages and deliver disease management to multiple patients in an efficient manner. Use of the SMA alone as an active control is another strength because it will help researchers and policy-makers understand how a low-carbohydrate diet-focused SMA intervention could fit into current and planned program offerings. Finally, if the WM/SMA strategy improves glycemic control with fewer hypoglycemic events and lower health care utilization, the study could potentially lead to the safe re-emphasis of lower glycemic targets that appear to reduce diabetes complications.

Limitations

Because one arm implements substantial dietary changes while the other does not, it is not possible to blind patients to their intervention assignment. We considered options for blinding outcome assessors and the physicians making medication adjustments but ultimately elected to forego blinding for several reasons. First, the risk of these staff members becoming unblinded is very high; while SMA participants generally increase their diabetes medication doses, most WM/SMA participants typically decrease their diabetes medications early in the study, and often lose weight to a noticeable degree. Second, several of the measures (e.g., hypoglycemic event logs, blood pressure measurement, symptom checklist) are needed by the study physician for clinical decision-making and counseling purposes. Third, the logistical difficulty of having additional blinded research staff and physicians meeting with participants separately from the SMA clinical

team made this option burdensome to the participant and more costly overall. In order to minimize bias, outcome measurements are collected as objectively as possible. The primary outcome, HbA1c, is processed by the Durham VAMC Central Laboratory along with the many other patient samples that are received daily at this large medical center. These staff are not involved in research and unlikely to be aware of the study, its hypotheses, or participant assignment. Weight and blood pressure are measured with automatic digital devices with strict protocols to minimize variability with the blood pressure measurement. Other measures are based on patient self-report; participants are advised to respond to the best of their ability and as completely as possible. Research staff are instructed not to influence responses.

Another limitation of our approach is that the WM/SMA intervention's high-intensity design precludes exploration of whether a less intensive weight management approach might improve HbA1c. We have attempted to balance efficiency and intensity by spacing out the visits in the latter portion of the study. The United States Preventative Services Task Force (USPSTF) has indicated, however, that lower intensity weight management interventions are not sufficiently effective to recommend.[57]

A related limitation is the two interventions' different meeting frequency during the first 16 weeks. We decided these differences are warranted because these two distinct approaches each require a unique meeting schedule. As discussed above, behavioral weight management interventions should meet frequently to be sufficiently effective.[57] The USPSTF defines high-intensity interventions as 12–26 sessions in a year; the WM/SMA intervention meets for 13 sessions over 48 weeks, which we reduced from 17 sessions in our previous weight management studies in order to make its frequency closer to the SMA intervention frequency. We also increased the frequency of the SMA alone intervention meetings, which in prior studies typically occurred every 2 months or less frequently. These differences in intervention meeting frequency may warrant consideration when interpreting our findings.

Conclusions

The Jump Start intervention uses a low-carbohydrate diet-based weight management approach to target two common problems that are closely related but infrequently managed together: diabetes and obesity. By primarily focusing on diet as the means to manage diabetes, this multidisciplinary intervention may improve several meaningful patient-centered outcomes related to diabetes.

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Abbreviations

BMI body mass index

BP	blood pressure
CDE	certified diabetes educator
DMC	Data Monitoring Committee
EHR	electronic health record
EQ-5D	EuroQol-5D
GCS-R	Group Cohesiveness Scale-Revised
HbA1c	hemoglobin A1c
HRQOL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPAQ	International Physical Activity Questionnaire
LDL-C	low-density lipoprotein cholesterol
LMM	linear mixed model
MES	Medication Effect Score
MNQ	Medication Non-adherence Questionnaire
MOS	Medical Outcomes Study
PAID	Problem Areas in Diabetes
PCP	primary care provider (PCP)
PHQ-2	Patient Health Questionnaire-2
QALYs	quality-adjusted life-years
SMA	shared medical appointment
USPSTF	United States Preventative Services Task Force
VA	Veterans Affairs
VAMC	VA Medical Center
WM/SMA	weight management shared medical appointment

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Appendix 1. Education topic schedule for the shared medical appointment (SMA) arm

Class	Week	Diabetes Topic
1	0	Introduction to diabetes/study overview (What is diabetes?; signs/symptoms of diabetes; glucometer teaching)
2	4	Understanding type 2 diabetes: definitions and principles
3	8 *	Signs and symptoms of hyper/hypoglycemia: what you need to know about high and low blood sugars
4	12 *	Hemoglobin A1c testing: what does your result mean and what are your risks for diabetes complications
5	16 *	Taking care of your diabetes everyday (following your meal plan/being physically active); food and exercise recommendations
6	24 *	Diabetes medications: how pills and insulin work to lower your blood sugar
7	32 *	Taking care of your diabetes at special times (sick days, time away from home)
8	40 *	Complications of diabetes: how diabetes affects your nerves, eyes, kidneys, heart and blood vessels

Class	Week	Diabetes Topic
9	48 *	Foot care tips: fighting diabetes foot problems

* For weeks 8 and beyond, topic is chosen from available topics in based on group members' majority vote – therefore, while all cohorts cover each topic in Appendix 1, order may vary.

Appendix 2. Medication Adjustment Algorithms for shared medical appointment (SMA) intervention, also used in weight management-SMA arm after weight management intervention

<i>a. Basal Insulin</i>	
Average of morning fasting BG values from preceding 7 days (mg/dL)	Change in basal insulin (glargine or NPH) dose
89 or lower	↓ by 10%
90–140	No change
141–169	↑ by 10%
170–199	↑ by 15%
200 or higher	↑ by 20%

References:

1. Riddle MC, Rosenstock J, et al. Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003; 26:3080–86.
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<i>b. Pre-prandial regular or rapid-acting insulin (titrate B, L, and D doses independently)</i>	
Average of pre-prandial BG values from the preceding 7 days (mg/dL)	Change in prandial insulin dose
99 or lower	↓ by 10%
100–150	No change
151–200	↑ by 5%
201–250	↑ by 10%
251–300	↑ by 15%
301 or higher	↑ by 25%

References:

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<i>c. Oral agents (not adjusted if insulin is adjusted at the specified visit)</i>	
Average of morning fasting BG values from the preceding 7 days (mg/dL)	Change in oral agent dose
89 or lower	↓ by 25–50%
90–140	No change

<i>c. Oral agents (not adjusted if insulin is adjusted at the specified visit)</i>	
Average of morning fasting BG values from the preceding 7 days (mg/dL)	Change in oral agent dose
141–169	↑ by 25%
170–199	↑ by 50%
200 or higher	↑ by 50–100%

Notes:

1. Discontinue agent for low BG if agent at lowest dose.
2. Add agent for high BG and current agent(s) at maximum dose.
3. Order of discontinuation of medication (opposite order for addition of medication):
 - a. First removed: insulin or secretagogues based on patient preference
 - b. Then: thiazolidinediones
 - c. Metformin and GLP-1 receptor agonists will be reduced only for hypoglycemic symptoms

<i>d. Blood Pressure Medication</i>		
Average of 2 blood pressure readings at visit		Change in one medication
Systolic	Diastolic	
99 or lower	NA	↓ by 25–50%
100–140	<90	No change
150–169	90–100	↑ by 25–50%
170 or greater	110 or greater	↑ by 50–100%

Notes:

1. Treat symptomatic orthostatic hypotension (dizziness or lightheadedness when changing from lying/sitting to standing position) like systolic blood pressure 99 or lower.
2. If at minimum dose, stop one medication.
3. If at maximum dose, start one medication.
4. Follow diabetes/coronary artery disease/congestive heart failure guidelines regarding choice of agents when starting or stopping medication

Appendix 3. Education topic schedule for the weight management-shared medical appointment (WM/SMA) arm

Class	Week	Diabetes Topic
1	0	Introduction to the low carbohydrate diet
2	2	Low carb concepts & label reading
3	4	Troubleshooting the low carb diet/food record discussion
4	6	Decoding a restaurant menu
5	8	Mindfulness-based approach to weight loss
6	10	Stocking a low carb kitchen
7	12	Low carb cooking video

Class	Week	Diabetes Topic
8	14	Phasing in additional carbs to the diet
9	16 *	Exercise recommendations/Introduction to diabetes
10	24 *	Food record review/shared medical appointment topic #2
11	32 *	Low carb show & tell/shared medical appointment topic #3
12	40 *	Travel tips on a low carb diet/shared medical appointment topic #4
13	48 *	Low carb resources/shared medical appointment topic #5

* For weeks 16 and beyond, WM/SMA groups cover both low-carb-focused content and an SMA topic. For weeks 24 and beyond, SMA topic is chosen based on group members' majority vote from topics in Appendix 1– therefore, order and specific SMA topics covered may vary between cohorts.

Appendix 4. Medication Adjustment Algorithms for WM/SMA Intervention

a. Initial Diabetes Medication Adjustment Prior to Weight Management Program (WM/SMA)

Additional points:

- Dec. = Decrease
- Alpha-glucosidase inhibitors will be stopped in all subjects for the duration of the WM/SMA intervention.
- Incretin agonists will be treated like metformin and not be adjusted initially.

Rationale:

- If glycemic control is only fair, then continue insulin sensitizers
- Decrease or discontinue secretagogues that increase the risk of hypoglycemia
- Reduce insulin because of reduced dietary carbohydrate and/or energy intake
- If fair/poor control and on no medication, start without medication and assess at 2 weeks

b. Diabetes Medication Adjustment for Hypoglycemia during Weight Management (WM/SMA)

Decrease medications as follows:

- Oral agents: 50% reduction in dose
- Insulin: 50% reduction in total daily dose
- Alpha-glucosidase inhibitors will be stopped in all subjects for the duration of the WM/SMA intervention.
- Incretin/amylin agonists will be treated like metformin and not be adjusted initially.

Order of discontinuation of medication:

- First removed: insulin or secretagogues based on patient preference
- Then: thiazolidinediones
- Metformin and incretin agonists will be reduced only for hypoglycemic symptoms

c. Diabetes Medication Adjustment For Hypoglycemia During Weight Management (WM/SMA) IF TAKING METFORMIN ONLY

Decrease metformin based on following sequence:

- 1000 mg am/1000 mg pm
- 1000 mg am/500 mg pm
- 500 mg bid

- 500 mg qd
- discontinue

d. Blood Pressure Medication Adjustment Prior to Weight Management Program (WM/SMA)

Table 1

Comparison of WM/SMA and SMA Arms

	WM/SMA	SMA
Week 0	<ul style="list-style-type: none"> • Measure weight, waist, BP, labs, all questionnaires • WM counseling • Medication adjustment 	<ul style="list-style-type: none"> • Measure weight, waist, BP, labs, all questionnaires • Diabetes counseling • Medication adjustment
Weeks 2, 6, 10, 14	<ul style="list-style-type: none"> • Measure weight • View SMBG and hypoglycemia logs • WM counseling 	<ul style="list-style-type: none"> • No visit
Weeks 4, 8, 12	<ul style="list-style-type: none"> • Measure weight and BP • Collect SMBG and hypoglycemia logs • WM counseling • Medication adjustment 	<ul style="list-style-type: none"> • Measure weight and BP • Collect SMBG and hypoglycemia logs • Diabetes counseling • Medication adjustment
Week 16	<ul style="list-style-type: none"> • Measure weight, waist, BP, labs, all questionnaires • Collect SMBG and hypoglycemia logs • Diabetes and WM counseling • Medication adjustment 	<ul style="list-style-type: none"> • Measure weight, waist, BP, labs, all questionnaires • Collect SMBG and hypoglycemia logs • Diabetes counseling • Medication adjustment
Weeks 24, 32, 40, 48	<ul style="list-style-type: none"> • Measure weight and BP • Measure waist, labs, all questionnaires at Weeks 32 and 48 only • Collect SMBG and hypoglycemia logs • Diabetes and WM counseling • Medication adjustment 	<ul style="list-style-type: none"> • Measure weight and BP • Measure waist, labs, all questionnaires at Weeks 32 and 48 only • Collect SMBG and hypoglycemia logs • Diabetes counseling • Medication adjustment

Abbreviations: WM=weight management; SMA=shared medical appointment; BP=blood pressure; SMBG=self-monitored blood glucose.

Table 2

Shared structure of group sessions for both study arms.

Phase	Patients	Study staff	RD/RN/CDE	Physician
Data gathering (30 minutes)	Turn in logs and questionnaires; BP and weight measurement	Collect logs and questionnaires; measure BP and weight		
Data processing and synthesis (45–60 minutes)	Socialize with group members and participate in education session	Enter data into database; alert physician to any urgent problems	Deliver arm-specific education session	Review BG/BP, draft medication management plan for each participant
Medication management (30–45 minutes)	Discuss any medication changes with physician	Generate graphs showing patients' progress on weight, diabetes, and BP control		Discuss plans with participants in individual sessions, address urgent problems, facilitate communication of plan to PCP

Abbreviations: BG=blood glucose; BP=blood pressure; CDE=certified diabetes educator; PCP=primary care providers; RD=registered dietitian; RN=registered nurse

Table 3

Summary and timing of outcome measures.

Outcome	Method	Baseline	Week 4, 8, 12	Week 16	Week 24	Week 32	Week 40	Week 48
Primary Outcome								
Diabetes control	Hemoglobin A1c	*		*		*		*
Secondary Outcomes								
Hypoglycemic events	Event log/ questionnaire [32]	*	* [†]	*	*	*	*	*
Diabetes medication use	Diabetes MES [34]	*	*	*	*	*	*	*
Weight	Calibrated digital scale	*	* [†]	*	*	*	*	*
Cost-effectiveness	Intervention costs, health care costs, EQ-5D[36]	*		*		*		*
Additional Outcomes								
Blood pressure	Automatic digital blood pressure cuff	*	*	*	*	*	*	*
Lipids	Lipid profile with direct LDL-C	*		*		*		*
Waist circumference	Non-elastic measuring tape	*		*		*		*
Diabetes-specific HRQOL	PAID Scale [38]	*		*		*		*
Dietary adherence	3-day food record pre-visit	*		*		*		*
Physical activity	IPAQ[39]	*		*		*		*
Medication nonadherence	Voils MNQ[40]	*		*		*		*
Group cohesion	GCS-R[41]			*		*		*
Depression	PHQ-2 [42]	*		*		*		*
Sleep quality	MOS Sleep Scale [43]	*		*		*		*
Pain	Pain Interference Scale [44]	*		*		*		*

Abbreviations: EQ-5D = EuroQol-5D; GCS-R = Group Cohesiveness Scale-Revised; HRQOL = health-related quality of life; IPAQ = International Physical Activity Questionnaire; LDL-C = low-density lipoprotein cholesterol; MES = Medication Effect Score; MNQ = Medication Non-adherence Questionnaire; MOS = Medical Outcomes Study; PAID = Problem Areas in Diabetes; PHQ-2 = Patient Health Questionnaire-2

[†] During the first 16 weeks of the intervention period, hypoglycemic events and weight are measured every 2 weeks in the WM/SMA arm; however, data collected at weeks 2, 6, 10, and 14 will be used for medication adjustment for safety only.