Protocol Revised 11/03/2014

Overview

The rise in diabetes and pre-diabetes parallels the increasing rates of obesity among adults over the past two decades.[15] Overweight and weight gain have been shown to prospectively predict the onset of type 2 diabetes (T2D).[16,17] Moreover, the risk of developing T2D is 3.9-fold and 12.4-fold greater among overweight and obese women, respectively, compared to normal-weight women.[18] This close relationship between obesity and diabetes is not surprising given the impairments in glucose removal and insulin resistance seen at obesity onset.[19]

Two large behavioral weight loss trials with overweight and obese pre-diabetic patients in the US and Finland found that a weight loss of 4 to 7 kg reduced the incidence of diabetes by 50% or more over 2 to 3 years.[20,21] Participants in the weight-loss interventions had decreases in waist circumference, blood pressure, and triglycerides, and a non-significant increase in HDL-cholesterol.[20,22] These studies are highly promising; however, they were carried out in highly controlled environments, with strict selection criteria. We do not know how well these interventions work in real world settings, under real life conditions, and with more complex or non-mainstream patients. Affordable and effective interventions for specific at-risk populations remain imperative.

Obesity and diabetes are major problems in the Hispanic population.

Prevalence rates of overweight and obesity are significantly higher among Hispanics than non-Hispanic whites,[23] as are rates of pre-diabetes,[1] T2D,[1,24] and risk for cardiovascular disease.[1,24-26] In the US, while the estimated lifetime risk for developing T2D for non-Hispanic white women born in 2000 is approximately 31%, the risk for Hispanic women is conservatively estimated at 52%.[27] In fact, *Hispanic women have the highest estimated lifetime risk of developing diabetes of all ethnic/gender groups*.[27] If T2D is diagnosed at age 40, Hispanic women are projected to lose 12.4 life-years and 21.5 quality-adjusted life-years.[27]

Need for diabetes-risk interventions targeting Hispanic populations

While there is compelling evidence demonstrating the benefits of weight-loss interventions for both diabetic and pre-diabetic individuals, Hispanic participants typically lose less weight than non-Hispanic white participants, even in successful trials. Furthermore, most large randomized trials have selected only adherent individuals, using strict filtering criteria that screen out individuals generally considered poor candidates for retention.[46-49] Many of the successful interventions tested in clinical trials may be too resource-intensive for implementation in community settings[40] and often include costly incentives, meal replacement products[40] or home visits.[50]

The current study will be implemented in a federally qualified health center (the Virginia Garcia Memorial Health Center, VGMHC) primarily serving low-income Hispanic patients. We will compare the efficacy of a culturally competent group intervention targeting Hispanic women with impaired glucose regulation (diabetic and prediabetic patients), contrasting it with a usual care control condition. The intervention we will be testing is modeled on an intervention program for obese Mexican-American women we previously conducted at KPNW CHR.[14] Our study will assess the cost of the intervention within the context of the clinical trial, and will assess the feasibility and cost of implementation in the absence of research support.

To ensure that this intervention is viable, sustainable, and able to be disseminated, and not merely a one-time research project, the program will be conducted by Virginia Garcia clinic staff, with training, supervision and support, and a minimum of “scaffolding” provided by the research team. Following the clinical trial, and at the request of VGMHC we will assess the sustainability and cost of the intervention as delivered by the interventionists without support from research staff.

Aims

1. Assess short (6-month) and long-term (12- and 18-month) changes in body weight and waist circumference in women in the intervention group compared to an enhanced usual-care control group
2. Compare the effects of the intervention vs. enhanced usual-care control on secondary outcomes, including short- and long-term changes in diabetes and prediabetes-related outcomes of metabolic markers of glycemic control (a) hemoglobin A1c, and (b) fasting glucose; cardiovascular disease risk factors: (c) fasting lipid profile; and lifestyle outcomes: (d) dietary intake (total energy, simple carbohydrates, saturated fat, number of servings of fruits and vegetables, dietary fibers, and whole grains), and physical activity.
3. Determine the implementation cost of delivering this weight-loss intervention at a Federally Qualified Health Center in the context of a pragmatic clinical trial.

Research Design

This will be a randomized clinical trial testing a weight-loss lifestyle intervention for obese Hispanic women with prediabetes or T2D. The primary aims of the intervention will be to reduce body weight and waist circumference at 6, 12, and 18 months. Secondary aims will be to improve levels of HbA1c, markers of glycemic control (fasting glucose in addition to HbA1c) and cardiovascular disease risk (serum lipid profile), diet, and physical activity. We will also determine the implementation cost for delivering the trial intervention in a federally qualified health center. Following the clinical trial, through a 2-cohort phase, we will assess the sustainability and cost of delivering the intervention as part of regular patient care at the clinic in the absence of research support.

Trial participants will be randomly assigned to one of two conditions: 1) Enhanced usual care control, or 2) a culturally tailored behavioral intervention. Outcome assessments will be conducted at 6, 12, and 18 months. Recruitment will be conducted in seven cohorts of approximately 30 randomized participants each.

Each participant will receive a $25 gift card at the completion of the 6-month visit, $30 at 12-month and $35 at 18-month data collection points.

Eligibility

We will enroll 200 obese Hispanic women in this weight-loss intervention trial.

Inclusion criteria.

- All participants will be patients who receive their primary medical care at the Virginia Garcia Memorial Health Center (VGMHC)
- Self-identified as Spanish-speaking Latina or Hispanic
- Female
- Age 18 and older
- BMI greater than or equal to 27kg/m^2
- Classified as diabetic or prediabetic in the electronic medical record by *at least one* of the following:
    - Fasting plasma glucose ≥ 100
    - 2-h post glucose level on the 75-g oral glucose tolerance test ≥ 140-199 mg/dL (7.8-11.0 mmol/L)
    - Hemoglobin HBA1c ≥ 5.7
    - Diagnosis of diabetes in patient's medical chart

    - Diagnosis of prediabetes in patient's medical chart

- Residing in the Portland metropolitan area, and having no plans to leave the area in the next 18 months.
- Willing and able to attend the 26-weekly group meetings and 6 monthly group meetings.
- Willing to accept random assignment to the active intervention or enhanced usual care control.
- Clearance by the patient's VGMHC primary care physician to participate in the intervention.

Exclusion criteria

- Treatment for cancer in the past two years (excluding non-melanoma skin cancers).
- Having conditions that require limitation of physical activity or that would be contraindicated for the DASH diet patterns.
- Taking weight-loss medication currently or within the past 6 months.
- Current or recent ($\leq$ 12 months) pregnancy, breastfeeding, or planning pregnancy in the next 18 months.

Recruitment

After attending an explanatory session as part of the informed consent process, each participant will sign the IRB-approved, written, bilingual, study consent prior to being enrolled in the study. The consent form will describe the purpose of the study, the requirements for participation, and the potential benefits and risks. It will also document that participation is voluntary, that it may be terminated by the participant at any time, and that decision to participate will not affect the clinical care received at VGMHC.

Potentially eligible patients from VGMHC will be identified through a review of the electronic medical record and through direct physician referral. Potentially eligible patients will be mailed a written description of the study and a consent form to review. Recruitment materials will be provided in both Spanish and English. Interested women will be invited to call the research center for more information, and those who are not interested in participating will be able to decline by telephone or by mail. Those who do not respond to the mailing may be called by a bilingual project staff member and asked about their interest in the study.

When contacting potential participants, project staff will use an IRB-approved telephone guide for describing the study, and potential participants will be encouraged to ask questions about the project. After doing so, interested participants will be asked for verbal consent to complete a brief screening interview to confirm eligibility. Those who appear to be eligible and who state their desire to learn more about the study, will be invited to attend an explanatory session at VGMHC and will be mailed a detailed description of the study.

The explanatory session will be conducted in two parts: Upon arrival, Dr. Lindberg will conduct a group meeting where she will provide attendees with information about the study and the nature of the interventions, and will encourage attendees to ask questions. Attendees will be advised that their decision about study participation in no way will affect their clinical care at VGMHC, and that they may withdraw from the study at any time.

During the second part of the explanatory session, after having an opportunity to ask questions in a one-on-one setting, interested women will be asked to sign the study consent form. Questions will be answered by Dr. Lindberg and study staff using IRB-approved study conversation guides. After signing the consent, the consented volunteers will be measured for height and weight to determine BMI. Women who are BMI-eligible will then be scheduled for a baseline telephone interview that will take place during the following 2 weeks. This telephone

interview (which will be conducted in Spanish or English, by participant preference) will be conducted by the Center for Health Research staff, and will include a food frequency questionnaire and a physical activity questionnaire., Questions about acculturation, quality of life, and literacy/numeracy will be obtained at the baseline visit.. Following completion of the telephone interviews, participants will be scheduled for an individual randomization visit at the VGMHC. During this visit, a female bilingual VGMHC staff member will measure weight, waist circumference, and will take a fasting blood sample using a point-of-care device. Participants will then receive their study materials and treatment assignment from an intervention staff member. Data collection staff will be masked from participant group assignment.

Participants assigned to the usual care control condition will receive printed materials (in English and/or Spanish) developed by the NHLBI on how to improve weight-related behaviors ("*Steps to Lose Weight," "ChooseMyPlate," "Nutrition and Finding Your Way to a Healthier You*"). We recognize that literacy limitations will reduce the usefulness of these materials for some of our participants, but providing this type of printed materials is our approximation of the best "usual care" practices currently available at VGMHC. Participants in both the intervention and the enhanced usual care control arms will receive a bathroom scale, a set of measuring cups and spoons, and a pedometer (with printed instructions and tips for increasing physical activity).

Follow-up data for all randomized participants will be collected at 6, 12 and 18 months following randomization. Physical data collection (height, weight, waist circumference, blood draws) will be completed at the VGMHC clinic; all other data collection will be done by telephone interview. All data-collection staff will be female and bilingual, and masked to participant treatment assignment.

Explanatory Session and Consent Visit

Explanatory sessions will be conducted by a bilingual study staff member who will provide a thorough overview of the study, including the intervention, design, and requirements for weekly group meetings, planned data collection, and duration of follow up. Attendees will be encouraged to ask questions. Then, the study consent will be discussed, and women interested in enrolling in the study will meet individually with study staff to address additional questions, confirm eligibility, and sign the consent form. Those who consent will be measured for height and weight, and will be scheduled for baseline bilingual assessment interviews conducted by telephone in the next 2 weeks. The telephone baseline assessment will include a food frequency questionnaire and physical activity questionnaire.

Participants may take their consent home to return at a later time but must return to the VGMHC with their consent form, to be witnessed and signed, and have their baseline measurements taken.

We have revised the consent to include sharing of participants PHI with Arizona Sate University. PhD candidate students in the Department of Nutrition will conduct the follow up SW FFQ interviews and, if needed due to literacy issues, conduct the Follow Up visit questionnaire by phone.

The change in consent will affect about 90 participants. Participants in the intervention groups will receive their new consent at one of the sessions. Usual care participants will receive a phone call from Dr. Lindberg alerting them to watch for the form in the andif desired discuss the change in the consent.

Prior to randomization, participants will be required to obtain medical clearance for participation from their VGMHC health care provider.

Baseline Data Collection and Randomization

After completing the baseline telephone assessments, participants will be scheduled for a randomization visit at VGMHC. During this visit we will collect baseline measurement of fasting lipids, glucose, and HbA1c as they are done in the course of clinic operations at VGMHC, by

finger-stick using point-of-care devices. Participants will then receive their treatment assignments using a computerized block randomization scheme provided by the study statistician. Randomization will be stratified by baseline BMI (27-34, 35-39, 40 or more) and age (18-45, 46 and above). To ensure equal balance in the two arms, randomization will occur in block sizes of 4. Participants will be informed of their randomization assignments by intervention staff members. Data collection staff will be masked to treatment assignments.

Enhanced Usual Care Control

We considered using a no-treatment control condition, but our community clinic partners requested that we provide the same information to participants in both conditions. This strategy insures that all participants get something they value as part of their involvement in the study, and also provides a comparison of the lifestyle intervention program to a very low-cost and easy to deliver information-only program.

Weight Management Tools for All Trial Participants

So that all randomized participants receive the same basic information, those assigned to the enhanced usual care control condition will receive bilingual printed materials on how to improve weight-related behaviors: copies of the NHLBI "Steps to Lose Weight," "ChooseMyPlate," and "Nutrition and Finding Your Way to a Healthier You." We recognize that literacy limitations may be an issue for some participants, but providing this type of printed material is our approximation of the best current "usual care" practice. In addition to this written material, all participants in both arms of the trial will receive:

Bathroom Scale: As found in other studies, [38] our research experience has been that few Hispanic women self-weigh regularly, and most do not own a scale. To aid in self-monitoring, all participants will be provided with a digital bathroom scale.

Pedometer: A pedometer and printed bilingual instructions for its use and tips for increasing PA will be provided to help participants monitor daily steps. We will not use pedometers for outcome data collection.

Measuring cups and spoons: Our pilot work has shown that many Hispanic women are unfamiliar with Anglo-American food measurements.[14] Traditional Latin American cooking practices rarely use measuring cups and spoons. To help participants measure their food, all participants will be provided with a set of measuring cups and spoons, along with a printed equivalence table (Anglo-American measuring units and metric units).

Retention

To maximize participant retention, during the screening process will we provide oral and written information about study expectations, time commitment, schedule and length of intervention group sessions, and potential benefits and risks. To enhance completion of the assessment visits, we will use appointment reminders (letters and phone), and schedule visits at times as convenient as possible to the participant.

Weight Loss Intervention

The initial intervention will consist of weekly meetings for 6 months, as recommended by Wadden.[93] The meetings will be structured to be very interactive, involve participant input and group activities, foster problem solving, support, and program ownership. We are planning for approximately 15 participants per group; groups of similar size have been shown to be quite effective in previous weight-loss studies.[3,25]

Each session will have a similar structure with 6 main components:

1. Social support/group sharing
2. Review of each individual's progress since the last session
3. Main content area (e.g., meal patterns, calories)
4. Behavioral skills training
5. Goal setting and action plans (in small groups)
6. Plans of self-monitoring activity

After the completion of the first six months of weekly intervention sessions, participants will attend monthly group sessions and will also interact with each other weekly by telephone. The monthly group sessions and weekly telephone contacts constitute a weight-maintenance phase which will help maintain self-management behaviors started during the initial intervention. The self-management behaviors include setting weekly behavioral goals and developing specific action plans to achieve those goals, social disclosure of these goals and plans, and scheduled accountability for evaluating the outcomes of these plans.

The structure of these monthly, one hour and-a-half group sessions of the maintenance phase will be similar to the initial weight loss sessions, starting with a weigh-in and reporting to the group regarding the outcome of their weight management efforts since the last group session. The session leaders will then lead a discussion focused on a selected self-management strategy such as environmental modification, stimulus control, or social contracting, with illustrations taken from the participants' experience. There will also be a presentation on a topic recommended by participants at previous meetings, emphasizing managing ongoing challenges of making appropriate food choices and managing total energy intake, motivation, and resistance training.

Motivation for attending the monthly group sessions are social support from other group members, new information on nutrition presented by group leaders, and advice from peers and group leaders. The importance of attending the monthly maintenance meetings will be emphasized during the final 4 weekly weight-loss sessions with encouragement for participants to make a commitment to the group to return to the monthly meetings.

Participants will be asked to establish a telephone support net for which each participant will call one other participant between group meetings. This telephone contact, which will be promoted as a transition aide and as an essential part of the weight-loss maintenance program, will be introduced 2 weeks before the end of the weekly sessions. Participants will be encouraged to contact each other according to a mutually agreed upon schedule for brief (5-10 minute) supportive telephone conversations. The network will provide ongoing social support between the monthly group sessions.

Dietary, Exercise and Behavioral Recommendations

The weight loss program is designed to achieve weight loss through dietary calorie reduction, increased energy expenditure through physical activity, and improved self-efficacy through behavioral self-management.

Dietary recommendations:

1. Consume ~500 fewer calories per day to achieve ½-2 lb weight loss per week.
2. Eat a healthy dietary pattern (i.e., the DASH eating style and WLM program, a diet rich in fruits, vegetables, and low-fat dairy foods, and low in fat).
3. Limit alcohol consumption to no more than one drink per day.

Physical activity recommendations:

4. In addition to normal daily activities, exercise at moderate intensity most days per week.
5. Progress gradually to 30-60 minutes/day to a weekly target of at least 180 minutes.

Behavioral recommendations:

6. Record daily food intake and physical activity.
7. Set short-term goals and create action plans.
8. Be an active study participant by attending intervention group sessions.

Measures

Weight will be measured with participants in light indoor clothes without shoes, and determined to the nearest 0.1 kg by a calibrated digital scale.

Height will be measured at enrollment to the nearest 0.1 cm using a calibrated, wall-mounted stadiometer.

Waist circumference will be measured at the midpoint between the lower rib and the iliac crest. We will record this to the nearest 0.5 cm. Measurement will be done with a Linen non-stretch tape measure with a tension device to provide a constant tension during measurement.

HbA1c and fasting lipids, and glucose will be collected in the course of patient care, using point-of-care devices to facilitate data collection by VGMHC staff members. Data will be collected for all trial participants at baseline, 6-, 12-, and 18-months post randomization. For participants that are unable to come to the clinic for the blood draw, we will do a home outreach and collect the sample at their homes.

Fasting lipids (total cholesterol, HDL-cholesterol, and triglycerides) will be measured enzymatically (Lipid Panel Plus Reagent Disc; Henry Schein, Inc, Melville, NY) in whole blood using a Piccolo Blood Chemistry Analyzer (Abaxis Inc., Union City, CA). LDL-cholesterol will be calculated using the Friedewald equation.[96] Fasting glucose will be measured using a OneTouch Ultra blood glucose monitoring system (LifeScan, Inc. Milipitas, CA). HbA1c will be measured from capillary blood using an A1cNow+ device (Bayer HealthCare LLC, Sunnyvale, CA), and FDA-approved and National Glycohemoglobin Standardization Program certified instrument that accurately measures HbA1c in point-of-care and home settings.

Table 5 Data collection schedule

	Baseline	6 mos	12 mos	18 mos
Weight	X	X	X	X
Height	X			
Waist circumference	X	X	X	X
24-hr food recalls	X	X	X	X
Glucose, HbA1c and lipid profile	X	X	X	X
7-Day Physical Activity Recall	X		X	X
Quality of life MOS SF-36	X	X	X	X
Satisfaction questionnaire		X	X	X
Demographics, numeracy, literacy, acculturation	X			

Dietary data will be collected using SW Food Frequency Questionnaire at each data collection time point.,

Data will be collected by telephone interview by bilingual interviewers from Center for Health Research staff Physical activity. We will assess physical activity through National Health Survey- General Practice Physical Activity Questionnaire

Participant and staff satisfaction with the intervention will be assessed with the Client Satisfaction Questionnaire (CSQ-8).[106] The CSQ-8 is a well-validated, 8-item Likert-type questionnaire that has been widely used in studies of physical and mental health[107] among Spanish-speaking and Hispanic individuals.[108]

Quality of life will be assessed with the MOS SF-36 (Medical Outcomes Study Short Form Health Survey), available in Spanish and English.[109,110] This widely used 36-item instrument assesses physical functioning, role functioning-physical, role functioning-emotional, bodily pain, general health, social function and psychological wellbeing/mental health, and vitality. The Spanish version of this standardized instrument has good internal consistency and concurrent validity, with coefficient alpha higher than .7 for all dimensions.[110,111]

Participants will receive a

25 for the 6-month visit, $30 for the 12-month visit, and $35 for the 18-month visit.

Adverse Event information will be collected at 6, 12 and 18 months

Data Management

Assessment data will come from questionnaires (all administered as interviews), staff-generated documents, and measured weight and waist circumference. The Kaiser Permanente Center for Health Research (CHR) data center staff are trained and certified in data management procedures: data entry, data flow, quality control, editing, reporting, and storage. The

department maintains CHR's data management hardware, software, security, storage, and networking resources. Standard data management procedures include Manuals of Operations, logging of forms, and work performance and quality control functions. Data management protocols include creation of a detailed plan for each instrument covering design, coding, pre-testing, preparation, administration, entry, verification, data set cleaning, and basic descriptive statistics. Procedures for data editing, entry, verification, and summarization are well-established at CHR. Dr. Lindberg, the study statistician, and the project manager will work closely to establish and monitor the data management procedures for this study. The study statistician will perform or directly oversee all data analyses.

Statistical Analysis

Before any analyses are carried out, the data will be audited for quality, completeness, and evaluation of distributions with reference to planned analysis models. The evaluation of distributions will include the detection of outliers in quantitative data and checking distributions of variables to ensure that they meet the assumptions of planned analyses. Whenever possible we will use analytical techniques that allow us to keep the natural distribution of the variables, but will consider transformation if necessary.

The main analysis will be based on intention-to-treat principles. To test the effect of the intervention on the short term outcomes at 6 months, we will use a residualized change score to determine whether the intervention and control groups differ in change in outcome (e.g., weight and HbA1c) from baseline, controlling for baseline values. The analysis uses regression with the dependent variable being the change in weight (or HbA1c) at 6 months and the independent variables are baseline weight (or HbA1c) and a dummy variable for study arm (intervention versus control). To examine the long-term effect of the intervention we will use multilevel modeling to examine the trajectory of the outcomes across baseline, 6, 12, and 18 months. Weight (or HbA1c) is the dependent variable; time, study arm, and the time by study arm interaction are the independent variables. Quadratic models will be fit to the data, as it is anticipated that the change over time will not be linear throughout the 18 month period. These approaches will also be used for the analysis of the short-term and long-term effects of the intervention on other outcomes: waist circumference, fasting glucose, serum lipid profile, dietary intake (total energy, simple carbohydrates, saturated fat, number of servings of fruits and vegetables, dietary fiber and whole grains), and PA.

Assessment of success in sustainability phase

To evaluate the success of the implementation of the intervention into clinical practice at VGMHC, the average percentage of behavioral strategies, participant objectives, session content completed across sessions, average number of participants recruited, average participant satisfaction, percent of sessions attended in each phase, and average weight change will be reported. These numbers will be compared to the benchmark numbers established during the clinical trial phase of the study.

Additional Analyses

We will also examine health literacy and numeracy and acculturation as potential moderators of the impact of the intervention by including interaction terms in the residualized change and multilevel models. Acculturation and health literacy and numeracy will be added to the models as main effects along with the interaction of these variables and the study arm. A significant interaction would signify that the effect of the intervention varies by the level of the moderator. Since these analyses may not be sufficiently powered, effect sizes as well as statistical significance will be of interest. We will also explore the effect of the intervention on quality of life over the 18 month period using the multilevel approach outlined above.