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The rationale, design, and baseline characteristics of PREVENT-DM: A community-based comparative effectiveness trial of lifestyle intervention and metformin among Latinas with prediabetes

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ABSTRACT

Promotora Effectiveness Versus Metformin Trial (PREVENT-DM) is a randomized comparative effectiveness trial of a lifestyle intervention based on the Diabetes Prevention Program delivered by community health workers (or promotoras), metformin, and standard care. Eligibility criteria are Hispanic ethnicity, female sex, age ≥ 20 years, fluent Spanish-speaking status, BMI ≥23 kg/m^2, and prediabetes. We enrolled 92 participants and randomized them to one of the following three groups: standard care, DPP-based lifestyle intervention, or metformin. The primary outcome of the trial is the 12-month difference in weight between groups. Secondary outcomes include the following cardiometabolic markers: BMI, waist circumference, blood pressure, and fasting plasma glucose, hemoglobin A1C (HbA1c), total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, and insulin. PREVENT-DM participants are socioeconomically disadvantaged Latinas with a mean annual household income of $15,527 ± 9922 and educational attainment of 9.7 ± 3.6 years. Eighty-six percent of participants are foreign born, 20% have a prior history of gestational diabetes, and 71% have a first-degree relative with diagnosed diabetes. At baseline, PREVENT-DM participants had a mean age of 45.1 ± 12.5 years, weight of 178.8 ± 39.3 lbs, BMI of 33.3 ± 6.5 kg/m^2, HbA1c of 5.9 ± 0.2%, and waist circumference of 97.4 ± 11.1 cm. Mean baseline levels of other cardiometabolic markers were normal. The PREVENT-DM study successfully recruited and randomized an understudied population of Latinas with prediabetes. This trial will be the first U.S. study to test the comparative effectiveness of metformin and lifestyle intervention versus standard care among prediabetic adults in a "real-world" setting.

1. Introduction

Type 2 diabetes affects 28.9 million adults in the United States; and 86 million Americans are estimated to have prediabetes, a high-risk state for developing diabetes [1]. Previous research has reported that 25 to 50% of individuals with prediabetes will develop type 2 diabetes within 5 years [2]. The prevalence of diabetes is higher among U.S. Latinos (20.1%) than whites (11.0%) [3], and the lifetime risk of developing diabetes is highest among Latinos [4], suggesting that diabetes disparities may worsen as this population continues to grow [5]. Among Latinos, Hispanic women (hereafter called Latinas) have a higher lifetime diabetes risk (52%) than males (45%) [4]. These data underscore the importance of developing effective interventions to prevent diabetes among all Latinos, and especially Latinas.

The U.S. Diabetes Prevention Program (DPP) clinical trial demonstrated that intensive lifestyle intervention and metformin are both effective treatments to prevent or delay the onset of type 2 diabetes in adults with prediabetes [6]. Similar to other efficacious lifestyle interventions [7,8], the DPP lifestyle intervention consisted of a structured diet and physical activity program with 2 principal goals: 1) performing at least 150 min per week of moderate-intensity physical activity; and 2) achieving at least 7% weight loss from baseline. DPP participants were randomized to receive either the intensive lifestyle intervention, metformin 850 mg or placebo twice daily. Relative to placebo, the reduction in diabetes incidence was 58% for the lifestyle intervention and 31% for metformin [6].

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A large body of translational research has adapted and tested the DPP lifestyle intervention in "real-world" settings, demonstrating that this program is effective when delivered by interventionists with various training backgrounds in diverse target populations [9]. Despite the reported efficacy of metformin in the original DPP trial, there has been much less focus on disseminating and studying the effectiveness of this diabetes prevention treatment in pragmatic settings. Only one published study, which was conducted in India, included a metformin arm compared to a DPP-based lifestyle intervention, the two treatments combined, or placebo [10]. Therefore, the existing literature provides little evidence to guide the choice of diabetes prevention treatments by at-risk individuals and their healthcare providers in the U.S.

The trial protocol described here aims to determine, in a "real-world" setting, the comparative effectiveness of metformin and a DPP-based lifestyle intervention, compared to standard care among Latinas with prediabetes. Based on our pilot data and findings from DPP [6,11], we hypothesize that both the lifestyle intervention and metformin will result in significant weight loss relative to standard care. We chose Latinas as the target population because: 1) they have the highest risk of developing diabetes relative to Hispanic men and other demographic groups; 2) their culturally-shaped influence on family members' lifestyle behaviors may result in a multiplying effect of the study interventions; [12–14] and 3) previous DPP translation studies across all racial/ethnic groups have included mostly women, while citing challenges to engaging men [9]. This paper presents the rationale, design, and baseline characteristics of this novel comparative effectiveness study, called the Promotora Effectiveness Versus Metformin Trial (PREVENT-DM).

2. Materials and methods

2.1. Study design and participants

PREVENT-DM is a three-arm randomized controlled trial with a parallel group design, comparing standard care to metformin or a group-based adaptation of the DPP lifestyle intervention delivered by community health workers. This protocol has been approved by the Temple University and Northwestern University Institutional Review Boards, and is recorded in the National Clinical Trials Registry (NCT02088034).

The inclusion and exclusion criteria for PREVENT-DM are listed in Table 1. Participants are women of self-reported Latina ethnicity, who are fluent Spanish speakers and at least 20 years old. In addition, participants must have a BMI ≥23 kg/m [2] and prediabetes defined according to the most recent American Diabetes Association criteria: fasting plasma glucose concentration of 100–125 mg/dL and/or hemoglobin A1C from 5.7–6.4% [15]. This BMI cutoff was selected because of the high prevalence of prediabetes among normal-weight Latinas [16]. Potential participants were excluded if they met any of following criteria: current or planned pregnancy during the study period; diabetes at baseline; current participation in a supervised weight loss program; chronic conditions that could affect their ability to participate; medical comorbidities that could influence body weight; medications that could affect weight or glucose metabolism; or contraindication to metformin.

Table 1
PREVENT-DM inclusion and exclusion criteria.

Inclusion criteria
Sociodemographic
Women
Latino ethnicity
Fluent Spanish speaker
Age ≥ 20 years
Anthropomorphic and glycemic measures[a]
Body mass index ≥ 23 kg/m^2
Fasting plasma glucose 100–125 mg/dL
Hemoglobin A1C 5.7–6.4%
Exclusion Criteria
Current participation in a supervised weight loss program
Diabetes
Current or planned pregnancy
Medical conditions that could affect participation
Cardiovascular event or angina in prior 6 months
Uncontrolled hypertension (≥160/100 mmHg)
Pulmonary disease with oxygen requirement
Orthopedic conditions limiting regular activities
Severe psychiatric illness[b]
Medical conditions that could affect outcomes
HIV
Cancer requiring treatment in past 5 years[c]
Uncontrolled thyroid disease[d]
Medications affecting outcomes[e]
Contraindications to metformin
Hypersensitivity to metformin
Serum creatinine ≥ 1.4 mg/dL

[a] Participants were eligible based on meeting the BMI criterion and at least one of the glycemic criteria listed.
[b] Psychiatric illnesses excluded were depression with suicidal ideation, bipolar disorder, schizophrenia, or substance abuse.
[c] Participants were not excluded based on a history of non-melanoma skin cancer.
[d] Uncontrolled thyroid disease was defined as the presence of hypothyroidism with a thyroid stimulating hormone level outside the therapeutic range within the last 6 months.
[e] Medications that could impact weight or glucose metabolism were considered exclusions (e.g. systemic corticosteroids, topiramate, and bupropion).

2.2. Rationale and description of the metformin intervention

Metformin is a biguanide agent that has been extensively studied as a treatment for type 2 diabetes in seminal clinical trials demonstrating its long-term safety and effectiveness for this indication [17,18]. More recent trials have tested the efficacy of metformin as a treatment to prevent or delay the onset of diabetes among high-risk individuals. The multi-site U.S. Diabetes Prevention Program clinical trial was one of the largest such studies with a total of 3234 participants with prediabetes, 10.5% of whom were Latinas. The DPP demonstrated a 31% reduction in diabetes incidence with metformin treatment relative to placebo [6]. This relative risk reduction remained at 25% after participants stopped taking metformin for 1–2 weeks [19]. Other clinical trials studying metformin in those at high risk for diabetes have reported comparable relative risk reductions [20].

Metformin has also been found to induce modest weight loss among individuals with prediabetes, which is considered the primary mechanism explaining its efficacy in preventing or delaying the onset of type 2 diabetes [21]. In the DPP, participants randomized to the metformin arm lost 5.6 lbs. at 12 months, corresponding to 2.7% of their initial body weight. [22] The only DPP translational trial to study metformin found no weight loss among those receiving this medication, lifestyle intervention, or both treatments combined [10]. However, the dosage of metformin administered in this trial was lower than in DPP, and this study enrolled South Asian participants with a lower mean BMI (25.8) than DPP participants (34.0) [6]. Clinical trials examining metformin treatment among women with polycystic ovarian syndrome, overweight/obesity, and insulin resistance have demonstrated statistically significant reductions in weight compared to placebo [23,24]. A meta-analysis including all randomized controlled trials of metformin in those at-risk for diabetes reported a statistically significant pooled weight loss relative to placebo or no treatment [20].

In the current study, we chose to use metformin 850 mg twice daily because this dose has been most widely used in the diabetes prevention literature [20], thereby facilitating comparisons with earlier efficacy trials including the DPP. Participants receiving metformin in the current trial start at a dose of 850 mg daily for one month and take 850 mg twice daily thereafter. For patients who experience gastrointestinal side effects, the metformin dose is reduced by half for one month before resuming the previous dose. If side effects recur, metformin is stopped