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A prospective study of low fasting glucose with cardiovascular disease events and all-cause mortality: The Women's Health Initiative

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ABSTRACT

Background. While there is increasing recognition of the risks associated with hypoglycemia in patients with diabetes, few studies have investigated incident cause-specific cardiovascular outcomes with regard to low fasting glucose in the general population.

Objective. We hypothesized that low fasting glucose would be associated with cardiovascular disease risk and all-cause mortality in postmenopausal women.

Methods. To test our hypothesis, we used both continuous incidence rates and Cox proportional hazards models in 17,287 participants from the Women's Health Initiative with fasting glucose measured at baseline. Participants were separated into groups based on fasting glucose level: low (<80 mg/dL), normal/reference (80–99 mg/dL), impaired (100–125 mg/dL), and diabetic (≥126 mg/dL).

Results. Participants were free of cardiovascular disease at enrollment, had mean age of 62 years, and were 52% Caucasian, 24% African American, 8% Asian, and 12% Hispanic. Median follow-up was 15 years. Graphs of continuous incidence rates compared to fasting glucose distribution exhibited evidence of a weak J-shaped association with heart failure and mortality that was predominantly due to participants with treated diabetes. Impaired and diabetic fasting glucose were positively associated with all outcomes. Associations for low fasting glucose differed, with coronary heart disease (HR = 0.64 (0.42, 0.98)) significantly inverse; stroke (0.73 (0.48, 1.13)), combined cardiovascular disease (0.91 (0.73, 1.14)), and all-cause mortality (0.97 (0.79, 1.20)) null or inverse and not significant; and heart failure (1.27 (0.80, 2.02)) positive and not significant.

Conclusions. Fasting glucose at the upper range, but not the lower range, was significantly associated with incident cardiovascular disease and all-cause mortality.

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1. Introduction

In spite of the wealth of literature on the health effects of glycemic levels and diabetes, little evidence exists for the health effects of low blood sugar outside of the context of clinical hypoglycemia. It is well-recognized that elevated fasting glucose both in the diabetic range (≥126 mg/dL), as well as in the impaired or "pre-diabetes" range (100–125 mg/dL) confers increased cardiometabolic risk [1]. At the other end of the spectrum, subclinical hypoglycemia (<80 mg/dL) could also be indicative of metabolic dysregulation. Individuals with fasting glucose below or in the lower range of normal might have difficulty maintaining stable glucose levels, either through dysfunctional counter-regulatory mechanisms or other co-morbidities that may increase their risk for cardiovascular diseases and early mortality.

There is increasing concern about the relationship between low fasting glucose and the combined outcomes of cardiovascular disease (CVD) or all-cause mortality [2–4]. This concern is further supported by studies showing a J-shaped relationship for hemoglobin A1c (HbA1c) with cardiovascular disease and mortality [5–7], as well as by evidence from the ACCORD Trial showing specifically that intensive therapy for glycemic control in patients with diabetes is associated with increased mortality [8]. Despite this concern, only a few studies have investigated incident cardiovascular disease or cause-specific cardiovascular outcomes with regard to low fasting glucose in the general population [2–4,9,10]. To our knowledge, there have also been no studies that determined if these more specific relationships differ by race.

We hypothesized that participants in the Women's Health Initiative (WHI) with low fasting glucose would be at increased risk of incident CVD and all-cause mortality compared to women with fasting glucose in the normal range. Based on prior work by Park et al., the meta-analysis by The Emerging Risk Factors Collaboration, and the results of the ACCORD Trial [3,4,11], we further hypothesized that these associations would be stronger in those younger than 70 years compared to older individuals. Similarly, we hypothesized a stronger relationship in those receiving treatment for type 2 diabetes, based on the known hypoglycemic risk of glucose lowering medications and the results of the ACCORD Trial [8]. Finally, to investigate these relationships in different racial groups, we hypothesized that there would be significant heterogeneity by race.

2. Methods

2.1. Study Population

The Women's Health Initiative cohort includes 161,808 postmenopausal women age 50–79 who enrolled in one or more of the WHI Clinical Trials or the Observational Study between 1993 and 1998 [12]. This study includes a stratified sample of participants from the WHI that had fasting glucose measured at baseline and were free of CVD at enrollment (n = 17,287). Fasting glucose measurements are available from a stratified random sample of WHI participants from the following WHI components: 8.6% of participants in the hormone trials, 1% of the observational study, and 4.5% of the Diet Modification Trial, as well as 1584 cases of treated type 2 diabetes and 2198 controls from an ancillary case–control study [13]. Minorities were specifically oversampled to approximate distributions in the general population [14]. The WHI protocol was approved by institutional review boards at all participating study sites and all participants provided written informed consent.

2.2. Study Measures

Fasting serum glucose was measured using the hexokinase method on the Hitachi 747 [15]. For our primary analysis, we grouped participants according to fasting glucose level into four categories: low glucose (<80 mg/dL), normal glucose (80–99 mg/dL), impaired fasting glucose (100–125 mg/dL), and diabetes (≥126 mg/dL or diabetes diagnosis or diabetes medication use).

Participants were followed for incident coronary heart disease, stroke, heart failure, and all-cause mortality through September 30, 2014 and these events were adjudicated by local and central physician adjudicators [16]. For this study, specific CVD events were analyzed separately and as a combined CVD outcome. Some participants were censored because they did not consent to the extension studies [14].

Socioeconomic factors, smoking status, medical history, and physical activity were self-reported at baseline. Other covariates including BMI and blood pressure were measured at baseline using a standardized assessment protocol and cholesterol was assayed from fasting blood. Full documentation on data collection and variable definitions can be found on the WHI website: https://www.whi.org/researchers/data/Pages/Available%20Data.aspx.

2.3. Statistical Analysis

We calculated the means and standard deviations of baseline characteristics by glucose category and used non-parametric tests for trend to determine if there were significant differences across the levels of fasting glucose.

We investigated the continuous associations of fasting glucose with CVD events and all-cause mortality incidence rates using Poisson regression with linear spline terms and 3 knots at the cut-points for the fasting glucose categories. We calculated Kaplan–Meier survival curves and 95% confidence bands for CVD events and all-cause mortality by fasting glucose categories. We then used Cox proportional hazards models to determine hazard ratios and 95% confidence intervals for CVD events and all-cause mortality by fasting glucose categories using normal glucose as the reference. We included as confounders baseline demographic and socioeconomic factors of age, race, income, and education, as well as clinical CVD risk factors of total cholesterol, blood pressure, smoking, and body mass index (BMI). We also adjusted for diabetes treatment to account for confounding by indication.

Based on our a priori hypotheses that these associations would be stronger in those younger than 70 and that they would differ by race, we formally tested for differences by age and race. Finally, we performed a number of subgroup