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Beyond fasting plasma glucose: The association between coronary heart disease risk and postprandial glucose, postprandial insulin and insulin resistance in healthy, nondiabetic adults☆,☆☆

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ABSTRACT

Objective. Prediabetes is defined by elevations of plasma glucose concentration, and is aimed at identifying individuals at increased risk of type 2 diabetes and coronary heart disease (CHD). However, since these individuals are also insulin resistant and hyperinsulinemic, we evaluated the association between several facets of carbohydrate metabolism and CHD risk profile in apparently healthy, nondiabetic individuals.

Methods. Plasma glucose and insulin concentrations were measured before and at hourly intervals for eight hours after two test meals in 281 nondiabetic individuals. Insulin action was quantified by determining the steady-state plasma glucose (SSPG) concentration during the insulin suppression test. CHD risk was assessed by measurements of blood pressure and fasting lipoprotein profile.

Results. For purposes of analysis, the population was divided into tertiles, and the results demonstrated that the greater the 1) fasting plasma glucose (FPG) concentration, 2) incremental plasma insulin response to meals, and 3) SSPG concentration, the more adverse the CHD risk profile ($p < 0.05$). In contrast, the CHD risk profile did not significantly worsen with increases in the incremental plasma glucose response to meals.

Conclusions. In nondiabetic individuals, higher FPG concentrations, accentuated daylong incremental insulin responses to meals, and greater degrees of insulin resistance are each associated with worse CHD risk profile (higher blood pressures, higher triglycerides, and lower high density lipoprotein cholesterol concentrations). Interventional efforts aimed at decreasing CHD in such individuals should take these abnormalities into consideration.

Abbreviations: CHD, Coronary Heart Disease; FPG, Fasting Plasma Glucose; HDL-C, High-Density Lipoprotein-Cholesterol; LDL-C, Low-Density Lipoprotein-Cholesterol; SSPG, Steady State Plasma Glucose.

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1. Introduction

Prediabetes consists of "individuals whose glucose levels do not meet criteria for diabetes yet are higher than those considered normal" [1]. The simplest definition of prediabetes is based on FPG concentration. However, individuals with elevated FPG commonly have a number of other abnormalities including postprandial hyperglycemia, insulin resistance, daylong hyperinsulinemia, high triglyceride concentration, low HDL-C concentration, and elevated blood pressure [1–6].

Although past studies have focused on the associations between FPG and CHD risk, it has been suggested that postprandial glucose may be a better predictor of risk [7,8]. However, quantification of postprandial glucose concentrations has relied on measurement of the plasma glucose response to a 75 g oral glucose challenge, and has not taken into account differences following ingestion of mixed meals [9]. Furthermore, few studies [10] have evaluated the possible role of insulin resistance, a common finding in individuals with prediabetes [4], as a possible mediator of CHD risk.

This study aims to evaluate the association between conventional CHD risk factors and four variables (FPG, daylong glucose and insulin responses to mixed-meals, and insulin resistance) in a large population of individuals without diabetes.

2. Methods

The experimental population included 175 women and 106 men who had responded to newspaper advertisements describing our studies on the role of insulin resistance in human disease between 1996 and 2008. Majority (72%) were of non-Hispanic white ethnicity. Volunteers were excluded if they had diabetes or took medications known to affect carbohydrate metabolism. Of the total population, 132 individuals (47%) had normal fasting glucose and 149 individuals (53%) had prediabetes (FPG 5.6–6.9 mmol/L) [1]. Participants were not further subdivided into the four sub-categories defined by the American Diabetes Association [1]. Exclusions also included anemia, cardiac, liver or kidney disease. Stanford University's Institutional Review Board approved the study protocols, and individuals gave written informed consent.

Meal profile tests were performed by measuring plasma glucose and insulin concentrations after an overnight fast and before and at four hourly intervals after breakfast (20% of daily calories at 0800) and lunch (40% of daily calories at 1200) [11]. Each meal contained, as percentage of daily calories, 15% protein, 43% carbohydrate, and 42% fat. Daylong incremental increases in postprandial glucose and insulin concentrations were calculated by determining the area under the curve over the eight-hour observation period, subtracting the area under the FPG and fasting plasma insulin concentrations respectively.

Insulin-mediated glucose uptake was quantified by a modified version [12] of the insulin suppression test [13,14]. Following an overnight fast, an intravenous catheter was placed in one arm for a 180-min infusion of octreotide (0.27 μg/m^2/min), insulin (32 mU/m^2/min), and glucose (267 mg/m^2/min). A second intravenous catheter was placed in the other arm to draw blood for measurement of plasma glucose and insulin concentrations at 150, 160, 170, and 180 min after the start of the infusion, and averaged to obtain the SSPG and steady-state plasma insulin concentration. Since steady-state plasma insulin concentrations were comparable among individuals, and the glucose infusion identical, SSPG concentration provides an estimate of insulin action—the higher the SSPG concentration, the more insulin resistant the individual [14,15].

Blood pressure was measured using Dinamap automatic blood pressure recorder (GE HealthCare, Tampa, FL) after participants had been seated quietly for five minutes. Three measurements were taken at one-minute intervals and averaged. Plasma lipid and lipoprotein concentrations were collected after an overnight fast and measured in the Clinical Laboratory at Stanford University Medical Center.

Statistical analyses were performed using SPSS Version 19 (SPSS, Chicago, IL). Nonparametric variables (triglyceride, postprandial glucose and postprandial insulin) were log-transformed prior to analyses. Multivariate-adjusted linear models were used to compare tertiles of FPG, daylong incremental postprandial glucose and insulin concentrations, and SSPG. Models were adjusted for age, sex, ethnicity and BMI.

3. Results

Supplemental Table S1 shows the relationship between FPG tertile and CHD risk factors. The higher the FPG tertile, the more adverse the CHD risk profile, with the exception of LDL-C and HDL-C. In contrast, Table 1 shows that increases in postprandial hyperglycemia were only associated with SSPG and FPG concentration, and showed no relationship with other CHD risk factors.

Increases in daylong incremental postprandial insulin were associated with a lower HDL-C and SSPG concentrations, but not with LDL-C concentration, triglyceride concentration, systolic blood pressure, or diastolic blood pressure (Supplemental Table S2). It should be noted that the increment in SSPG concentration was 5.9 mmol/L between individuals in the lowest and highest tertile of daylong incremental postprandial insulin response, as compared to the 1.4 mmol/L difference between those with the lowest and highest third of daylong incremental glucose response. Table 2 demonstrates that SSPG concentration was most closely associated with all CHD risk factors, except for systolic blood pressure.

4. Discussion

The category of prediabetes was introduced to identify apparently healthy individuals at increased risk of developing type 2 diabetes and/or CHD [1]. Our results show a significant association between conventional CHD risk factors and three out of four metabolic characteristics of type 2 diabetes (namely FPG concentration, post-meal increases in plasma insulin concentration, and SSPG concentration [Supplementary Tables 1a, 2a and 2]). A recent study by Faerch and associates concluded that in nondiabetic individuals "the association between plasma glucose levels and