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# Hypertriglyceridemia: A simple approach to identify insulin resistance and enhanced cardio-metabolic risk in patients with prediabetes

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ABSTRACT

*Aims:* Prediabetes (PreDM) is a metabolically heterogeneous condition, differing in degree of insulin resistance and risk of type 2 diabetes mellitus and coronary heart disease (CHD). This study was initiated to evaluate the hypothesis that a fasting plasma triglyceride (TG) concentration $\geqslant$1.7 mmol/L can aid in identifying the subset of individuals with PreDM who are most insulin resistant and at greatest risk to develop CHD as well as type 2 diabetes mellitus.

*Methods:* In this cross-sectional study, measurements were made of: (1) steady-state plasma glucose (SSPG) concentration during the insulin suppression test to ascertain degree of insulin resistance and (2) conventional CHD risk factors in 587 apparently healthy individuals with normal fasting plasma glucose (NFG, $n = 370$) or PreDM ($n = 217$).

*Results:* Subjects with PreDM were significantly ($P < 0.001$) more insulin resistant (higher SSPG concentrations) and had a more adverse CHD risk profile than those with NFG. A TG concentration $\geqslant$1.7 mmol/L identified a subset of individuals with PreDM (38%) who had a higher mean SSPG concentration (11.3 ± 3.5 mmol/L vs. 9.3 ± 3.9 mmol/L, $P < 0.001$), were more likely to be insulin resistant (66% vs. 39%, $P < 0.001$), and had a more adverse CHD risk factor profile.

*Conclusions:* Measurement of fasting TG concentration in individuals with PreDM may provide a simple clinical approach to identify those who are insulin resistant, at enhanced risk of CHD, and more likely to develop type 2 diabetes mellitus.



## 1. Introduction

The American Diabetes Association (ADA) defines prediabetes (PreDM) as an "intermediate group of individuals whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal [1]." Thus, the ADA does not consider PreDM to be a clinical entity in its own right, but as a means to identify individuals at increased risk to develop diabetes as well as coronary heart disease (CHD). Although there appears to be general agreement that

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PreDM is a significant predictor of incident type 2 diabetes, the relationship between PreDM and CHD is not as clear [2]. For example, a recent analysis by the United States Preventive Services Task Force concluded that in the absence of manifest diabetes "no study consistently found that elevated fasting glucose level could predict CHD events [3]". Similarly, results of a population-based prospective study [4] found that hazard ratios for CHD risk "were generally modest and nonsignificant across tenths of glucose values below 7.0 mmol/l." Perhaps of most relevance to our study are the results of the Emerging Risk Factors Collaboration analysis of studies that indicated that vascular disease was increased when fasting plasma glucose (FPG) concentration was ⩾5.6 mmol/L (100 mg/dl) [5]. However, they concluded that in people "without a history of diabetes, information about fasting blood glucose concentration or impaired fasting glucose status did not significantly improve metrics of vascular disease prediction when added to information about several conventional risk factors." Since patients with PreDM as a group tend to be insulin resistant, with associated increases in several CHD risk factors [6–8], it could be argued that this cluster of abnormalities not glycemia, *per se*, is responsible for the increased CHD risk in PreDM. In support of this speculation are the findings by Faerch and colleagues [9] showing that insulin resistance, as quantified by the hyperinsulinemic, euglycemic clamp, was independently related to Framingham risk score in nondiabetic individuals. This relationship was not seen with either fasting or post-oral glucose challenge glucose concentrations, resulting in their conclusion that "the association between plasma glucose levels and CVD risk is mainly explained by insulin resistance."

If insulin resistance is the fundamental defect leading to increased CHD in patients with PreDM, why do questions remain concerning the existence of this relationship in view of the increased prevalence of insulin resistance in PreDM? One possible explanation is that patients who meet the diagnostic criteria of PreDM are metabolically heterogeneous; they are not all insulin resistant, nor have the same cardiometabolic risk factor profile [6–8]. In this context, we have recently shown that a plasma triglyceride (TG) concentration ⩾1.7 mmol/L (⩾150 mg/dl) identified insulin resistance and associated cardio-metabolic risk in hypercholesterolemic individuals who did not have diabetes [10]. The current analysis was undertaken to see if the same approach would be useful in separating persons with PreDM into subgroups differing in terms of insulin resistance and cardio-metabolic risk. If so, it would provide a relatively simple clinical tool to identify the subgroup of patients with PreDM who were at greatest risk of type 2 diabetes and CHD, enabling the thoughtful implementation of more aggressive efforts to overcome excess adiposity and encourage more physical activity.

## 2. Methods

### 2.1. Study subjects

The experimental sample included 587 individuals who had volunteered to participate in our research studies from 1996 to 2014. All volunteers had provided informed consent and the study protocols were approved by Stanford's Institutional Review Board. Subjects were all in good general health and without history of cardiovascular, kidney, or liver diseases. Individuals were excluded from this analysis if they were taking medicines to lower lipids or treat diabetes or had a FPG ⩾7.0 mmol/L. Volunteers were classified [1] as having either normal fasting glucose (NFG; FPG concentration < 5.6 mmol/L, $n = 370$) or PreDM (FPG concentration ⩾5.6 mmol/L and <7.0 mmol/L, $n = 217$).

### 2.2. Clinical and metabolic measurements

Race and ethnicity were determined during a medical history. Weight and height were measured while individuals were wearing light clothing and no shoes. Body mass index (BMI) was calculated by dividing weight in kilograms by height metered squared. Blood pressure was measured using an automatic blood pressure recorder. Prior to these measurements, subjects were seated quietly for 5 min in a chair with feet on the floor and arm supported at heart level. Using an appropriately sized cuff, 3 blood pressure readings were taken at 1-min intervals and averaged.

All metabolic tests were performed at the General Clinical Research Center of Stanford University Medical Center after an overnight fast. Lipid and lipoprotein concentrations were assayed in the core laboratory at Stanford University Medical Center by standardized methods approved by the Centers for Disease Control and Prevention.

Insulin-mediated glucose disposal was quantified with the modified version [11] of the insulin suppression test as introduced and validated by our research group [12–14]. Briefly, after an overnight fast, an intravenous catheter was placed in each of the subjects' arms. One arm was used for the administration of 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); the other arm was used for collecting blood samples. Blood was drawn at 10-min intervals from 150 to 180 min of the infusion to determine the steady-state plasma glucose (SSPG) and insulin concentrations. Because steady-state plasma insulin concentrations are similar in all subjects, the SSPG concentration provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; therefore, the higher the SSPG concentration, the more insulin resistant the individual. It should be noted that insulin-mediated glucose disposal as determined by the insulin suppression test is closely correlated with that obtained with the euglycemic, hyperinsulinemic clamp technique [13,14].

Individuals in the NFG and PreDM groups were divided into those with a fasting plasma TG concentration < 1.7 mmol/L or ⩾1.7 mmol/L, thus creating 4 subgroups: (1) NFG, TG < 1.7 mmol/L; (2) NFG, TG ⩾1.7 mmol/L; (3) PreDM, TG < 1.7 mmol/L; and (4) PreDM, TG ⩾1.7 mmol/L. Based upon the results of prospective studies, the third of a nondiabetic population that is most insulin resistant (highest SSPG concentrations) is at significantly greater risk to develop the adverse clinical syndromes associated with insulin resistance [15,16]. In our study a SSPG concentration ⩾10.8 mmol/L defined the one-third of the experimental sample with the highest SSPG concentration, and this value was used as the criterion to classify an individual as being insulin resistant.