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Methods

Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides × glucose versus triglyceride/high-density lipoprotein cholesterol

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ABSTRACT

The objective was to compare relationships between insulin-mediated glucose uptake and surrogate estimates of insulin action, particularly those using fasting triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations. Insulin-mediated glucose uptake was quantified by determining the steady-state plasma glucose (SSPG) concentration during the insulin suppression test in 455 nondiabetic subjects. Fasting TG, HDL-C, glucose, and insulin concentrations were measured; and calculations were made of the following: (1) plasma concentration ratio of TG/HDL-C, (2) TG × fasting glucose (TyG index), (3) homeostasis model assessment of insulin resistance, and (4) insulin area under the curve (insulin-AUC) during a glucose tolerance test. Insulin-AUC correlated most closely with SSPG ($r \sim 0.75$, $P < .001$), with lesser but comparable correlations between SSPG and TG/HDL-C ratio, TyG index, homeostasis model assessment of insulin resistance, and fasting TG and insulin ($r \sim 0.60$, $P < .001$). Calculations of TG/HDL-C ratio and TyG index correlated with SSPG concentration to a similar degree, and the relationships were comparable to estimates using fasting insulin. The strongest relationship was between SSPG and insulin-AUC.

1. Introduction

A high plasma triglyceride (TG) and a low high-density lipoprotein cholesterol (HDL-C) concentration are the characteristic dyslipidemia of insulin-resistant individuals [1,2], and the plasma concentration ratio of TG/HDL-C has been suggested as a useful surrogate estimate of insulin action [3]. More recently, Guerrero-Romero et al [4] proposed that the product of plasma TG and glucose concentrations could serve as a useful surrogate estimate of insulin resistance. However, because the number of subjects studied by these authors was relatively small (n = 99) and approximately one third had type 2 diabetes mellitus, we believed that it is important to compare these 2 approaches to identify insulin-resistant individuals in a relatively large number of nondiabetic subjects.

Author contributions: FA and GMR designed the study, interpreted the data, and wrote the manuscript; FA collected the data and performed statistical analysis.

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2. Research design and methods

The study sample consisted of 455 nondiabetic individuals (245 women and 210 men) whose mean ± SD age was 48 ± 13 years and body mass index was 26.4 ± 4.5 kg/m^2. Subjects were divided into normal fasting glucose (NFG) and impaired fasting glucose (IFG) groups [5]. The study was approved by Stanford University's Institutional Review Board, and all study subjects signed an informed consent before admission to the Research Center.

After an overnight fast, an oral glucose tolerance test was performed. Plasma glucose and insulin concentrations were measured before and 30, 60, 120, and 180 minutes after ingestion of 75 g of glucose. The total integrated insulin response was quantified by calculating the insulin area under the curve (insulin-AUC) using the trapezoidal method.

On a different day, insulin-mediated glucose uptake (IMGU) was measured by a modification [6] of the insulin suppression test (IST) as introduced and validated by our laboratory [7,8]. After an overnight fast, a continuous 180-minute infusion of octreotide acetate (0.27 μg/[m^2 min]), insulin (32 mU/[m^2 min]), and glucose (267 mg/[m^2 min]) was given. Venous blood samples were obtained every 10 minutes during the last 30 minutes of the infusion for measurement of steady-state plasma glucose (SSPG) and insulin concentrations. As steady-state plasma insulin concentrations (mean ± SD) were similar among individuals (52 ± 15 μU/mL), SSPG concentrations provided a direct estimate of IMGU; the higher the SSPG, the more insulin resistant the individual. Measurements of IMGU with the IST are highly correlated ($r > 0.9$) with the hyperinsulinemic-euglycemic clamp technique [8].

Measurements were made of fasting plasma glucose, insulin, TG, and HDL-C concentrations as described previously [3,6-8]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the HOMA calculator software available on the Web site of Diabetes Trials Unit at the University of Oxford (http://www.dtu.ox.ac.uk/homacalculator). Triglyceride × fasting glucose (TyG) index was calculated as the natural logarithm (Ln) of [TG (milligrams per deciliter) * glucose (milligrams per deciliter)/2] [4].

Triglyceride/HDL-C concentration ratio, TG, fasting insulin, HOMA-IR, and insulin-AUC were log-transformed for statistical analyses. Pearson correlation coefficients and their 95% confidence intervals were calculated among variables of interest. The significance of difference between 2 correlation coefficients was determined in the entire sample by the Meng-Rosenthal-Rubin test for correlated correlations [9] and between the NFG and IFG groups by the Cohen test for independent correlations [10]. Both tests involved converting each correlation coefficient into a z score to stabilize the variance of the transformed correlation and to make it more normally distributed. Statistical analyses were performed using the statistical package R version 2.10.1 (The R Foundation for Statistical Computing).

3. Results

Fig. 1 displays the relationship between SSPG concentrations and the 2 fasting TG-based indices of insulin action in the entire sample. It can be seen that the r values for TyG index (panel A) and TG/HDL-C ratio (panel B) were comparable and accounted for approximately 35% variance in insulin action. Furthermore, in the whole group, SSPG concentration significantly ($P < .001$) correlated (r and 95% confidence interval) with TG ($r = 0.57$; 0.51-0.63), fasting insulin ($r = 0.61$; 0.55-0.66), fasting glucose ($r = 0.37$; 0.29-0.45), HOMA-IR ($r = 0.63$; 0.57-0.68), and insulin-AUC ($r = 0.77$; 0.73-0.80).

On comparison of correlation coefficients, the magnitude of the correlation between SSPG concentration and TG/HDL-C ratio was not significantly different than that between SSPG and TyG index ($P = .16$) or HOMA-IR ($P = .38$). The correlation of SSPG with insulin-AUC was significantly stronger ($P < .001$) than the correlations of SSPG with TyG index, TG/HDL-C ratio, TG, fasting insulin, fasting glucose, and HOMA-IR. On the other hand, the correlation of SSPG with fasting glucose was significantly weaker ($P < .001$) than the correlations of SSPG with TyG index, TG/HDL-C ratio, TG, fasting insulin, HOMA-IR, and insulin-AUC.

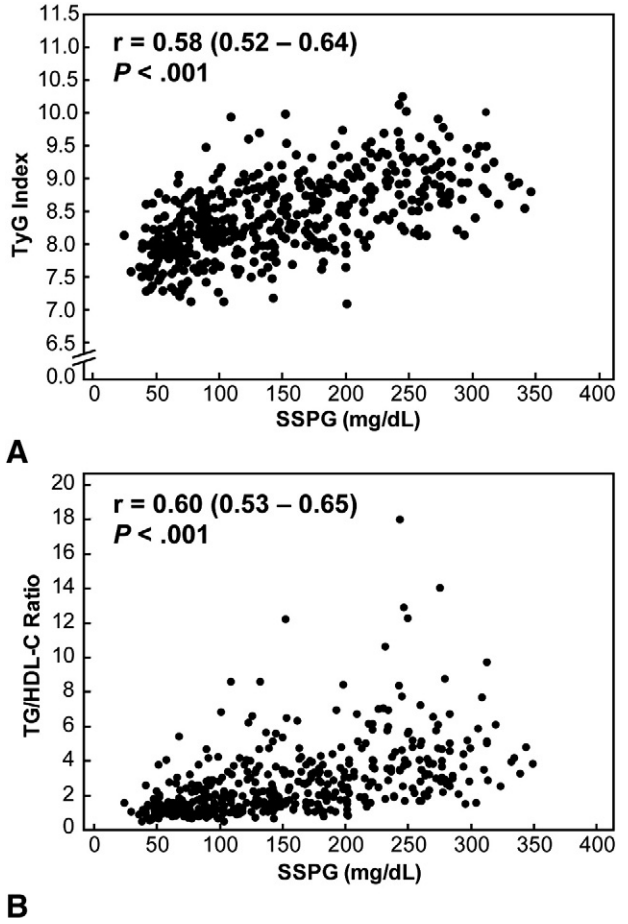

Fig. 1 – Relationship of SSPG concentration with TyG index (A) and TG/HDL-C ratio (B) in 455 nondiabetic individuals. Footnote in each graph: *r* value is the Pearson correlation coefficient with its 95% confidence interval in parenthesis. The median (25th, 75th percentiles) plasma glucose was 91 (84, 98) mg/dL; TG, 101 (72, 148) mg/dL; HDL-C, 48 (41, 58) mg/dL; TyG index, 8.40 (8.02, 8.86); TG/HDL-C ratio, 2.1 (1.3, 3.5); and SSPG, 140 (85, 212) mg/dL.