

# Increased Fasting Triglyceride Levels Are Associated With Hepatic Insulin Resistance in Caucasian but Not African-American Adolescents

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Increased lipid levels are related to insulin resistance in children and adults (1–3). Insulin resistance occurs due to an inability to suppress hepatic glucose production (HGP) or to stimulate peripheral glucose uptake. It is not clear whether hyperlipidemia primarily affects hepatic or peripheral insulin sensitivity. In this study, the stable-labeled, frequently sampled intravenous glucose tolerance test (4–7) was used to measure total-body insulin sensitivity ( $S_i$ ), peripheral insulin sensitivity ( $S_i^*$ ) (5), and hepatic insulin resistance (HIR) (8) in African-American and Caucasian adolescents.

## RESEARCH DESIGN AND METHODS

Healthy, Tanner stage 1–5, Caucasian ( $n = 18$ , age  $14.0 \pm 2.6$  years, BMI  $23.0 \pm 3.2$  kg/m<sup>2</sup>) and African-American ( $n = 10$ , age  $14.1 \pm 2.3$ , BMI  $25.6 \pm 5.1$ ) subjects were studied. Informed written consent and assent were obtained. The protocol was approved by The Ohio State University Office of Responsible Research.

Studies were performed in the Clinical Research Center of The Ohio State University after overnight fasting. Intravenous catheters were placed in the antecubital fossa of each arm. A bolus of 25% dextrose in water with ~13% [6-6]D<sub>2</sub> glucose (Cambridge Isotopes, Cambridge, MA) was given over 1 min (4,7,9). The total dose was 250 mg/kg. Blood samples were taken at –10, 0, 2, 4, 6, 8, 12, 14, 16, 19, 22, 27, 32, 42, 52, 62, 72, 82,

92, 102, 122, 142, 162, and 182 min relative to the bolus for measurement of glucose and insulin concentrations in the CORE laboratory of the Clinical Research Center. Fasting plasma lipid levels were measured before dextrose bolus in the clinical laboratory of The Ohio State University Hospital. LDL cholesterol was calculated in the usual manner. Mole percent excess of [6-6]D<sub>2</sub> glucose was measured by Metabolic Solutions (Cambridge, MA).

$S_i$  and  $S_i^*$  were calculated from total and labeled glucose concentrations, respectively, using the computer program Minmod (version 6.01; Minmod, Los Angeles, CA).  $S_i^*$  was assumed to be due to peripheral glucose uptake (9). HGP was calculated over the last hour of the study when the system had returned to a quasi-steady state through the use of Steele's equations. To adjust for differing insulin levels when HGP was determined, HIR was calculated by multiplying HGP by the mean insulin level over the same hour (4,7).

Unpaired  $t$  tests were used for comparisons between groups. Pearson's correlation coefficients were used to assess relationships between lipid levels and  $S_i$ ,  $S_i^*$ , and HIR. Data (mean  $\pm$  SE) were log normalized, where necessary.

**RESULTS** — In all subjects, log  $S_i$  decreased as log triglycerides increased ( $r = -0.50$ ,  $P = 0.008$ ). There was a positive relationship between log TGs and log HIR ( $r = 0.48$ ,  $P = 0.025$ ).  $S_i^*$  and TGs were

not related. Total, HDL, and LDL cholesterol levels were not related to  $S_i$ ,  $S_i^*$ , or HIR. Log  $S_i$  ( $P = 0.054$ ) and  $S_i^*$  ( $P = 0.092$ ) tended to decrease and log HIR ( $P = 0.051$ ) to increase as BMI increased. Log HIR correlated with total cholesterol levels ( $r = 0.52$ ,  $P = 0.013$ ).

Mean TG, total and HDL cholesterol, fasting total plasma glucose and insulin concentrations,  $S_i$ ,  $S_i^*$ , and HIR did not differ between African-American and Caucasian adolescents. LDL cholesterol levels tended to be higher in African-American ( $109 \pm 7$  mg/dl) than in Caucasian ( $93 \pm 5$ ) adolescents ( $P = 0.071$ ).

Relationships between plasma lipid levels and  $S_i$ ,  $S_i^*$ , and HIR differed between races. In Caucasians, log  $S_i$  negatively correlated with log plasma TG ( $r = -0.63$ ,  $P = 0.007$ ) and BMI ( $r = -0.55$ ,  $P = 0.022$ ); log HIR (Fig. 1) was positively related to plasma TG ( $P = 0.012$ ) and total ( $P = 0.011$ ) and LDL ( $P = 0.011$ ) cholesterol levels and tended to positively correlate with BMI ( $P = 0.078$ ), and  $S_i^*$  negatively correlated to BMI ( $r = -0.54$ ,  $P = 0.022$ ). No relationships were found in the African-American subjects or between  $S_i^*$  and lipid levels in either group.

**CONCLUSIONS** — These results demonstrate three important findings. First, they confirm the negative relationship between surrogate markers of insulin sensitivity and plasma TGs in children and adolescents reported by Weiss et al. (2) and Dwyer et al. (3), using the more rigorous frequently sampled intravenous glucose tolerance test and minimal model. This, is in contrast to Gower et al. (10), who found no relationship in a mixed-race group, although they studied only prepubertal children who would be expected to be more insulin sensitive than the current study's pubertal and postpubertal subjects.

Second, the results indicate that the relationship between TG levels and insulin resistance is primarily due to a positive relationship to basal HIR and not peripheral insulin sensitivity. This is in contrast

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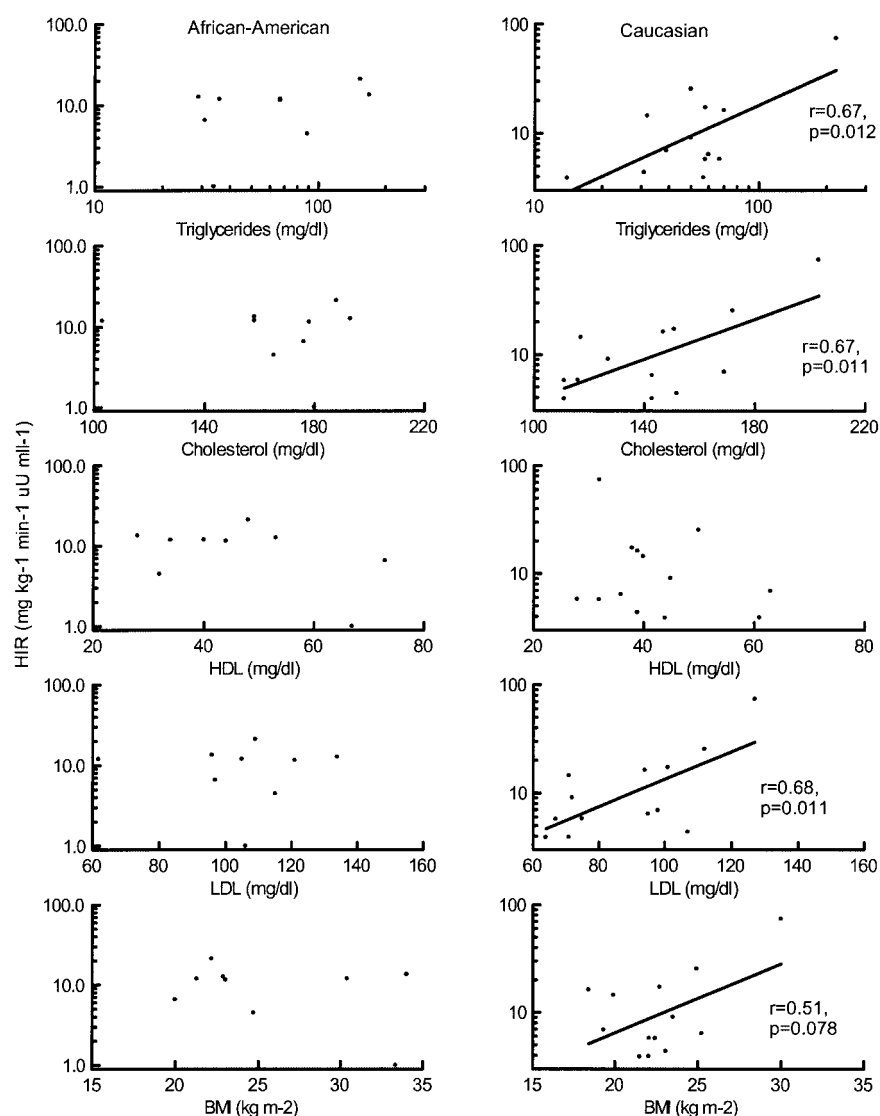
**Abbreviations:** HGP, hepatic glucose production; HIR, hepatic insulin resistance; TG, triglyceride.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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**Figure 1**—Relationship of HIR to fasting plasma lipid levels and BMI in African-American and Caucasian adolescents.

to most, but not all, studies in animals and humans where TG infusion acutely decreases glucose uptake and increases HGP during insulin infusion (11–15). The lack of relationship between TGs and peripheral insulin sensitivity in the current study may be due to the fact that the fasting TG levels measured were lower than those generated by TG infusions. At lower levels, TGs may influence HIR, while at higher levels, both hepatic and peripheral effects occur.

Third, the results indicate differences in the relationships of lipid levels to insulin sensitivity between African-American and Caucasian adolescents. Sumner et al. (16) demonstrated similar findings in adults. Specifically, HIR is positively correlated with TG and LDL cholesterol levels in Caucasians but not African

Americans. There are marked differences in mortality and morbidity between African-American and Caucasian adults for many of the diseases associated with the metabolic syndrome (17–20). Furthermore, African-American adolescents are usually more insulin resistant than Caucasian adolescents (21–23) and have lower TG levels (2). Neither of these differences was significant in the current study due to the small number of subjects. The differing relationships between plasma lipids and HIR suggest that future preventative strategies for the development of insulin resistance will need to target different parts of the metabolic syndrome in the two races. The data suggest that lowering TGs, and possibly other lipid levels, is likely an important target in Caucasian adolescents.

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