

## Surveillance of Insulin Resistance in Children

Recent case-series studies and smaller cross-sectional samples have reported alarming observations among youth: once a disease of middle age and older adulthood, type 2 diabetes now represents nearly one-half of newly diagnosed diabetes cases in some obese adolescent African-American and Hispanic populations (1). Furthermore, the metabolic syndrome, also known as syndrome X or the insulin resistance syndrome, has recently been documented in youth (2). The cornerstone of this syndrome is obesity and insulin resistance, giving rise to a plethora of risk factors for type 2 diabetes and cardiovascular disease, including impaired glucose tolerance, dyslipidemia, hypertension, impaired fibrinolytic activity, and a heightened state of systemic inflammation (3).

In this issue of the journal, Allard et al. (4) describe fasting blood concentrations of glucose, insulin, and free fatty acids (FFAs) in children and adolescents. These timely data, from a carefully conducted population-based study in Quebec, Canada, contribute to our understanding of the potential public health impact of the pediatric obesity epidemic. As expected for a typical population of youth, the distribution of fasting glucose was quite narrow, whereas that of fasting insulin was quite broad. The difference between the 5th and 95th percentiles for fasting insulin (~390%) was ~15 times greater than that of fasting glucose (~25%). Concentrations of fasting glucose were somewhat higher for boys than for girls, whereas fasting insulin concentrations were somewhat higher for girls than for boys. As such, the homeostasis model of insulin resistance (HOMA), the product of glucose and insulin, was comparable between the genders.

Allard et al. (4) raised two important questions. First, does the product of glucose and insulin, the HOMA, provide a superior predictor of insulin resistance than either fasting glucose or insulin alone? Second, to what degree do circulating FFAs play a role in the pathophysiology of insulin resistance?

The challenge of evaluating the comparative utility of fasting glucose, insulin, and HOMA in this study is that no gold standard comparison, such as the euglycemic hyperinsulinemic clamp measure, was available. It therefore is not possible to address the first of these questions directly from the present data. The investigators reported that the correlation between fasting insulin and HOMA was >0.99 among all age-gender strata. Although not reported, the correlation between glucose and HOMA was presumably weak or nonexistent because of the very limited range of glucose relative to insulin. It has previously been established that fasting insulin, particularly in populations with normal glucose tolerance, is a very good predictor of insulin sensitivity (5–7). Sinaiko et al. (7) conducted euglycemic hyperinsulinemic clamps in a representative sample of 357 middle school students in Minneapolis, Minnesota. Inverse correlations between the concentration of fasting insulin and insulin sensitivity from the clamp tests were found in both boys ( $r = -0.42$ ;

$P = 0.0001$ ) and girls ( $r = -0.41$ ;  $P = 0.0001$ ). Among populations with little or no impaired fasting glucose, fasting glucose and HOMA appear to contribute little to the prediction of insulin sensitivity beyond that explained by fasting insulin (5, 6). Although the glucose concentration in the postprandial period appears to be a good marker of insulin sensitivity in such populations (6), oral glucose tolerance tests are prohibitively time-consuming for population-based surveillance systems. It is therefore prudent to include fasting insulin measures in future pediatric surveillance for the purposes of monitoring the population burden of insulin resistance and targeting high-risk subgroups. Indeed, the presence of high fasting insulin and excessive body weight may occur with either normal or impaired fasting glucose. Primary prevention would be warranted in either case.

Fasting glucose distribution would be expected to be broadest among high-risk populations, most significantly the obese (8, 9). For this reason, it would be useful to examine the distribution of fasting glucose concentrations stratified by body mass index categories. Especially among the overweight and obese, measurement of fasting glucose can be justified because it is easy, inexpensive, and useful in screening for impaired fasting glucose and possible type 2 diabetes because of standardized criteria. Moreover, the emergence of type 2 diabetes among North American youth (1) supports the hypothesis described by Allard et al. (4) of a rightward shift in the distribution of fasting glucose as a result of the obesity epidemic.

FFAs were inversely associated with insulin and HOMA in the younger children, whereas no association was observed in the older children and adolescents, suggesting that increased FFAs do not promote insulin resistance in this population. The authors suggest that the inverse association in the younger age groups can be explained by known age-related differences in metabolic fuel use. However, several methodologic issues regarding FFAs need to be considered. The degree to which FFAs contribute to insulin resistance may depend on the type (saturation and chain length) and source (subcutaneous vs visceral adipose tissue) of FFAs (10, 11). Furthermore, among healthy young populations, the association between FFAs and study endpoints may be nonlinear; simple correlations may mask important physiologic relationships, especially if only a small number of individuals have very high FFA concentrations and insulin resistance (e.g., the obese). Although high FFA concentrations in late adolescence and young adulthood may exacerbate insulin resistance, elucidation of these issues will likely require both prospective observational analyses and well-controlled physiologic studies.

The authors state that the distributions of glucose, insulin, and HOMA did not appear to vary by ethnicity, although they do report some significant differences among 13-year-old boys for FFAs and 16-year-old boys for insulin. Other studies have clearly shown that race/

ethnicity, for a variety of genetic and environmental reasons, is an important determinant of insulin resistance and risk of type 2 diabetes (6, 12). Among 403 school children of the Corpus Christi Study, Batey et al. (12) reported that components of the insulin resistance syndrome were considerably more prominent among Mexican Americans than among non-Hispanic whites. For these reasons, it is useful to stratify results by ethnicity even when such stratification may not be warranted by the results of preliminary statistical tests.

The underlying causes of insulin resistance and obesity involve the interaction of many genes with physical inactivity and dietary patterns. Because the obesity epidemic has occurred over a period of genetic stability, ~20 years, and has afflicted every major racial and ethnic group, the challenge to public health lies on the environmental side of the interaction. Pediatric data sources have revealed striking statistics in physical inactivity and dietary patterns. Between 1988 and 1994, two of three US children reported at least 2 h of television viewing per day and one of four children reported at least 4 h per day (13). Consumption of soft drinks (14) and fast food (15) has increased steadily between the 1970s and 1990s, the same time period within which the obesity epidemic has unfolded. Milk intake in youth has decreased precipitously during this same time period (14), whereas intake of fruits, nonstarchy vegetables, and whole grain foods continues to fall far short of recommended amounts (16). Systematic assessment of these and other relevant lifestyle patterns and environmental factors are necessary to advance knowledge of the critical factors involved in the evolution of insulin resistance and obesity. The ideal surveillance system would therefore include the full range of known etiologic factors, including physiologic, behavioral, and environmental components.

#### References

- Ludwig DS, Ebbeling CB. Type 2 diabetes mellitus in children: public health and primary care considerations [Review]. *JAMA* 2001;286:1427–30.
- Young-Hyman D, Schlundt DG, Herman L, De Luca F, Counts D. Evaluation of the insulin resistance syndrome in 5- to 10-year-old overweight/obese African American children. *Diabetes Care* 2001;24:1359–64.
- Reaven GM. Role of insulin resistance in human disease (syndrome X): and expanded definition [Review]. *Annu Rev Med* 1993;121–31.
- Allard P, Delvin EE, Paradis G, Hanley JA, O'Loughlin J, Lavallée C, et al. Distribution of fasting plasma insulin, free fatty acids, and glucose concentrations and of homeostasis model assessment of insulin resistance in a representative sample of Quebec children and adolescents. *Clin Chem* 2003;49:644–9.
- Laakso M. How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 1993;137:959–65.
- Dickinson S, Colagiuri S, Faramus E, Petocz E, Brand-Miller JC. Postprandial hyperglycemia and insulin sensitivity differ among lean young adults of different ethnicities. *J Nutr* 2002;132:2575–9.
- Sinaiko AR, Jacobs DR Jr, Steinberger J, Moran A, Luepker R, Rocchini AP, et al. Insulin resistance syndrome in childhood: associations of the euglycemic insulin clamp and fasting insulin with fatness and other risk factors. *J Pediatr* 2001;139:700–7.
- Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med* 2002;346:802–10.
- Kriska AM, Pereira MA, Hanson RL, de Courten MP, Zimmet PZ, Alberti KGMM, et al. Association of physical activity and plasma insulin concentrations in two populations at high risk for type 2 diabetes but differing by body mass index. *Diabetes Care* 2001;24:1175–80.
- Louheranta AM, Sarkkinen ES, Vidgren HM, Schwab US, Uusitupa MJ. Association of the fatty acid profile of serum lipids with glucose and insulin metabolism during 2 fat-modified diets in subjects with impaired glucose tolerance. *Am J Clin Nutr* 2002;76:331–7.
- Bergman RN, Van Citters GW, Mittelman SD, Dea MK, Hamilton-Wessler M, Kim SP, et al. Central role of the adipocyte in the metabolic syndrome. *J Invest Med* 2001;49:119–26.
- Batey LS, Goff DC Jr, Tortolero SR, Nichaman MZ, Chan W, Chan FA, et al. Summary measures of the insulin resistance syndrome are adverse among Mexican-American versus non-Hispanic white children: the Corpus Christi Child Heart Study. *Circulation* 1997;96:4319–25.
- Andersen RE, Crespo CJ, Bartlett SJ, Cheskin LJ, Pratt M. Relationship of physical activity and television watching with body weight and level of fatness among children. Results from the Third National Health and Nutrition Examination Survey. *JAMA* 1998;279:938–42.
- Cavadini C, Siega-Riz AM, Popkin BM. US adolescent food intake trends from 1965 to 1996. *Arch Dis Child* 2000;83:18–24.
- Guthrie JF, Lin B-H, Frazao E. Role of food prepared away from home in the American diet, 1977–78 versus 1994–96: changes and consequences. *J Nutr Educ Behav* 2002;34:140–50.
- Crane NT, Hubbard VS, Lewis CJ. National nutrition objectives and the Dietary Guidelines for Americans [Review]. *Nutrition Today* 1998;33:49–58.

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