

Why Test the Children?

Understanding insulin resistance, its complications, and its progression

In this issue of *Diabetes Care*, Goran et al. (1) review the results of their study of insulin resistance and the compensatory responses to it in 57 early pubertal children of different racial/ethnic backgrounds. They utilized the frequently sampled intravenous glucose tolerance test (GTT) to assess insulin sensitivity (S_i), acute insulin response (AIR), and also calculated insulin secretion, hepatic insulin extraction, and insulin clearance. In these children, they found that S_i , independent of adiposity, was greater in the Caucasian children than in those of African and Hispanic heritage, confirming the observations of others (2–4). They also discovered differences in the compensatory responses of Hispanic and African-American subjects, which they hypothesized would be similar. The Hispanic subjects had higher first- and second-phase insulin secretion. The African-American subjects showed a higher AIR and lower hepatic insulin extraction, with first- and second-phase insulin secretion closer to those of the Caucasian children.

Such studies are important, but one could ask, “Why perform them in children?” Certainly type 2 diabetes and obesity are major and emerging problems in the young (5,6), and we are not yet certain that the pathogenesis of insulin resistance and type 2 diabetes are the same in children as in adults, especially those who are elderly. The potential, catastrophic complications of these disorders in this young population has been predicted (7), and the first evidence of its reality was presented at the 62nd Scientific Sessions of the American Diabetes Association this past summer in San Francisco (8). Goran et al. also point out that, in these young subjects, the potentially complicating factors of “smoking, alcohol, aging, and menopausal status” are absent. Also absent are the effects of living for decades with insulin resistance and its complications. It is important, however, to remember that features of insulin resistance develop early, can be documented by age

11, and, by that age, are segregating on the basis of ethnicity (9).

As our knowledge about the effects of insulin resistance and the metabolic syndrome grows, it is becoming important to understand its progression and all of its attendant complications (10) through the course of human development. Although the debate over the relative importance of genetic and environmental factors in the etiology of type 2 diabetes continues, it is clear that prenatal and early postnatal factors are important contributors (11,12), as is puberty when the disorder develops in childhood (13,14). If we are to effectively intervene to prevent diabetes and reverse the current trend of increasing prevalence, we will need to know not only how to do so, but when. The how may well vary with the developmental stage when the intervention occurs. If successful early strategies to prevent insulin resistance and diabetes are to be devised, they will almost certainly be different for the intrauterine environment, for the period of infancy and early childhood, and for puberty.

A second issue addressed by the authors is the significance of their study “relating to the treatment and prevention of type 2 diabetes across different ethnic groups.” Implicit in their discussion is the idea that it may become increasingly important to consider the “translational” potential of new physiologic information as we now do, almost routinely, with molecular discoveries. As our therapeutic armamentarium for diabetes management grows, the more we learn about specific metabolic “lesions,” the more accurately and effectively we will be able to attack them. If these lesions sort out along racial/ethnic lines, our drug design and trials could be more directly targeted and resultant data could be more clearly interpreted. If trials are not designed to allow analysis by subgroups, differential effects may be missed. Consistent documentation of racial/ethnic differences in insulin resistance and insulin secretion, coupled with discovery of the mechanisms of these

differences, could establish new therapeutic and preventive strategies.

The continuing subdivision of “non-insulin-dependent diabetes” into states as diverse as latent autoimmune diabetes in adults (LADA), maturity-onset diabetes of the young (MODY), Flatbush diabetes, and mitochondrial diabetes suggest that more is to come. The fact that these individual forms of diabetes occur primarily in different racial/ethnic groups, coupled with suggestions that long-term complications of insulin resistance and type 2 diabetes may also differ with race/ethnicity, suggest that this is a fertile field of investigation. As the study by Goran et al. is not the first of its kind, we can be assured that it will not be the last.

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References

1. Goran MI, Bergman RN, Cruz ML, Watanabe R: Insulin resistance and associated compensatory responses in African-American and Hispanic children. *Diabetes Care* 25:2184–2190, 2002
2. Arslanian S, Suprasongsin C: Difference in the in vivo secretion and sensitivity of healthy black versus white adolescents. *J Pediatr* 129:440–443, 1996
3. Osei K, Schuster DP: Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. *Diabet Med* 11:755–762, 1994
4. Osei K, Schuster DP, Owusu SK, Amoah AG: Race and ethnicity determine serum insulin and C-peptide concentrations and hepatic insulin extraction and insulin clearance: comparative studies of three populations of West African ancestry and white Americans. *Metabolism* 46:53–58, 1997
5. Rosenbloom AL, Joe JR, Young RS, Winter

- WE: Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 22:345–354, 1999
6. Fagot-Campagna A, Pettitt DJ, Engelgau MM, Burrows NR, Geiss LS, Valdez R, Beckles GL, Saaddine J, Gregg EW, Williamson DF, Narayan KM: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136: 664–672, 2000
 7. American Diabetes Association: Type 2 diabetes in children and adolescents (Consensus Statement). *Diabetes Care* 23: 381–389, 2000
 8. Dean H, Flett B: The natural history of type 2 diabetes diagnosed in childhood: long term followup in young adult years (Abstract). *Diabetes* 51 (Suppl. 2):A24, 2002
 9. Reaven P, Nader PR, Berry C, Hoy T: Cardiovascular disease insulin risk in Mexican-American and Anglo-American children and mothers. *Pediatrics* 101:E12, 1999
 10. Reaven GM: Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease: syndrome X revisited. In *Handbook of Physiology, Section 7. The Endocrine System, Vol. II. The Endocrine Pancreas and Regulation of Metabolism*. Jefferson LS, Cherrington AD, Eds. New York, Oxford University Press, 2001, p. 1167–1197
 11. Dabelea D, Pettitt DJ: Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. *J Pediatr Endocrinol Metab* 14:1085–1091, 2001
 12. Osmond C, Barker DJ: Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect* 3:545–553, 2000
 13. Arslanian S: Type 2 diabetes in children: clinical aspects and risk factors. *Horm Res* 57 (Suppl. 1):19–28, 2002
 14. Goran MI, Gowan BA: Longitudinal study of pubertal insulin resistance. *Diabetes* 50: 2444–2450, 2001