EDITORIAL

"Longitudinal Changes in Risk Variables of Insulin Resistance Syndrome From Childhood to Young Adulthood in Offspring of Parents With Type 2 Diabetes: The Bogalusa Heart Study" by Srinivasan et al

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THE BOGALUSA HEART STUDY is a biracial (black and white) community-based investigation of the origins of cardiovascular disease which focuses on children, adolescents, and young adults using a multidisciplinary approach. This Study is a medical research treasure in which the investigators are systematically elucidating the origins of our country's major cause of death. Cardiovascular pathologists, clinicians, and epidemiologists have the overall goals to determine, at the earliest possible age, improved cardiovascular risk analyses, treatment paradigms, and, in the end, the prevention of cardiovascular diseases.

Srinivasan et al have presented an epidemiological assessment using a longitudinal design to evaluate cardiovascular risk factors among offspring from diabetic parents.[1] The offspring are repeatedly examined for a variety of risk variables related to the insulin resistance syndrome, which recently has been referred to as the "metabolic syndrome" in the National Cholesterol Education Program's Adult Treatment Panel III guidelines.[2] This linkage to new guidelines underscores the importance and relevance of the Study. Factors included in this syndrome are obesity, hypertension, dysglycemias (often referred to as impaired fasting glucose, impaired glucose tolerance or diabetes), and dyslipidemias (often referred to as the atherogenic lipid phenotype, eg, reduced levels of high-density lipoprotein cholesterol [HDLc] and elevated circulating levels of triglyceride and small, dense low-density lipoprotein cholesterol [LDLc]). Srinivasan and colleagues cast a broad net to include important components of the insulin resistance syndrome in the follow-up of these young subjects, who are divided into 2 groups as a function of parental diabetes or not. For example, obesity is evaluated by measurements of generalized and visceral obesity, hypertension by systolic and diastolic blood pressures, dysglycemias by fasting glucose and insulin levels, and a mathematical conversion of these two variables for assessment of insulin resistance (homeostasis model assessment or HOMA) and dyslipidemias by total LDLc, total HDLc, and triglycerides.

Admirably, this study departs from the more conventional cross-sectional evaluations by exploring risk variables as a longitudinal function of age. The main new observation, using multivariate analyses, is that parental diabetes is an independent predictor of longitudinal changes among the offspring for adiposity, insulin, glucose, the HOMA index of insulin resistance, systolic and diastolic blood pressure, and LDLc regardless of race and gender. Using differential prevalence of the risk variables during childhood, adolescence, and young adulthood, these offspring of diabetic parents display excess body fat beginning in childhood advancing to disorders of dysglycemias during adolescence and finally to dyslipidemias by young adulthood. These time points are especially important since this design *should* provide the database instructing pediatricians of the ages of onset for clinically detectable and thus treatable cardiovascular risk variables.

It is important to note that these studies were, in part, initiated as early as 1984. Unfortunately, since the origins of this study, there have been significant changes in our concepts regarding hypertension, dysglycemias, and dyslipidemias. A more current take of these data presented by Srinivasan et al indicates some future trends that should make similar longitudinal studies of cardiovascular risk variables more sensitive, thus permitting improved delineation of risks between childhood, adolescence, and young adulthood. Such refinement may give pediatricians and internists the possibility for definitive age delineation for early risk detection, treatment, and/or prevention strategies.

How is this study, and others as well, less than definitive? It is widely recognized among epidemiologists and clinicians that type 2 diabetes is preceded by a prediabetic stage characterized by a variety of metabolic abnormalities including dysglycemia. Despite this recognition many studies lack accurate ascertainment of type 2 diabetes or other dyglycemias because of substantial underestimates using current US diagnostic guidelines established in 1997 by the American Diabetes Association (ADA).[3] For example, in this Bogalusa Study, the authors describe parental ascertainment with regards to whether a person factually reports whether or not one knows they have diabetes. Approximately 30% of the American diabetic population does not recognize they have diabetes.[4] Thus these individuals would be assigned to the "nondiabetic" subgroup. The 30% figure may actually be higher in this cohort because of the enrichment of African Americans, the latter of which have a substantially higher prevalence of diabetes, and since there were no glucose tests performed on the parents. The authors correctly described these concerns and their impact on the temporal onset of risk variables.

There is an additional concern that is less commonly appreciated, which is the lack of ability for a physician or researcher to clinically diagnose diabetes. Thus a physician can obtain a

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fasting plasma glucose and tell the individual there is no diabetes present by ADA criteria, when in fact that subject can have diabetes by the World Health Organization (WHO) criteria using the 2-hour post oral glucose value. This concept represents an additional and substantial, up to 30% more, ascertainment bias.[5-8] Of the 1,439 parents evaluated in the Bogalusa Study, 303 reported that they had diabetes, which reflects a very high risk population that is enriched by a mechanism that is not described, but is probably related to selection processes. Using the US 30% unknown diabetes figure, at least 90 subjects in the 1,136 "nondiabetic" subgroup in fact have diabetes.[4] If the 1,136 were actually tested by fasting glucose levels using ADA criteria, which they were not, these 90 subjects should have been ascertained. Of the now 393 ascertained diabetic parents, 30% more could have diabetes by the WHO criteria, ie, another 117 individuals.[5-8] Thus for the risk variables examined, there may be a prevalence of up to 18% (90 + 117/1136) diabetic parents in the "nondiabetic" group.

It is also now well recognized that insulin resistance–associated risk variables are related to other dysglycemic syndromes, which represent a continuum from impaired fasting glucose (ADA term) and impaired glucose tolerance (WHO term) to diabetes. In general, 25% to 30% of individuals in Western populations are thought to have dysglycemias.[6,7] In the United States, this figure is about 15% due to reliance on ADA criteria.[4] Among high-risk groups, there may be as high as a 70% prevalence of dysglycemic syndromes, eg, impaired glucose tolerance or diabetes, even in subjects with normal fasting glucose levels by ADA criteria.[9] Thus up to 795 parents from the 1,136 "nondiabetic" subgroup in this Bogalusa Study could have the phenotype of dysglycemias that are strongly linked to the risk variables described by the authors except for LDLc. LDLc is not directly linked to the insulin resistance syndrome and is not a component of the atherogenic lipid phenotype.[10] Thus it was unusual to observe this variable in a report focused on the insulin resistance syndrome.

Although using prevalence statistics at various age groups apparently links obesity to childhood, glucose variables to adolescence and lipid abnormalities to young adulthood, these data are of concern due to the possibility of up to 18% diabetic or 25% to 70% dysglycemic individuals in the "nondiabetic" parental group. Glucose and lipid disturbances conceivably could also begin in childhood, but because of smaller differences between the groups, those risk variables may be indistinguishable at younger ages due to confounding and additive underestimates in group comparisons. Thus the more robust data, eg, obesity, may occur in all age groups, whereas the least robust data occur in older individuals. There are several data sets that suggest glucose and lipid disturbances also occur earlier than reported in the current study.

These current Bogalusa results are distinctly different from the longitudinal diabetic offspring data derived from Pima Indians. The latter studies use the WHO criteria (2-hour post oral glucose) for dysglycemic evaluation in *both* parents and offspring.[11] In the Pimas, offspring of diabetic parents have substantial abnormalities of glucose/insulin risk variables even in the 5- to 9- and 10- to 14-year-old groups, when compared to offspring of nondiabetic parents. Whether these marked differences are related to the methods of dyslipidemic ascertainment and/or to differences between Pima and Bogalusa community subjects is unclear.

Prior data from the Bogalusa Heart Study, unrelated to parental diabetes, also suggest that dysglycemic and dyslipidemic abnormalities are clearly advancing by childhood and early adolescence, whereas in the current Study, dyslipidemias appeared to have an onset in young adults. For example, by age 10 to 15 years, rather marked reductions (30%) in HDLc levels are described, especially in children and adolescents who have concomitant obesity or hyperinsulinemia, ie, risk variables of the insulin resistance syndrome.[12] Further evaluations comparing 5 to 10 year olds with 11 to 17 and with 18 to 37 year olds also show dysglycemic related variables and dyslipidemias clustering with other insulin resistance variables in all age groups, including the 5 to 10 year olds.[13] These large temporal differences were not observed in the current study, probably due to the dysglycemic ascertainment reasons described above. Further, these current offspring glucose data may represent a significant underestimate of the actual prevalence of dysglycemias, and may explain the lack of significance for impaired fasting glucose between the control, "nondiabetic" parental offspring and the experimental, diabetic parental offspring groups.

Blood pressure assessment in the current study among offspring may also be too insensitive to ascertain changes at younger ages since the criterion of 140/90 mm Hg was used. The Joint National Committee (JNC) on the Detection of Hypertension in Adults indicates an optimal blood pressure of less than 120/80, normal blood pressure less than 130/85, and 140/90 used in this Bogalusa Study is the JNC VI criteria for stage 1 hypertension in adults. Certainly the value of 140/90 in children and adolescents is too high for optimal sensitivity for distinguishing between offspring from diabetic and nondiabetic parents.

Finally, results from the Bogolusa Heart Study's cardiovascular pathologists show that virtually all children age 2 to 15 years have aortic fatty streaks.[14] Another 50% of children 2 to 15 years of age have fatty streaks in coronary vessels, of whom 8% have raised fibrous plaque. These anatomic observations in children strongly suggest a link to dyslipidemias, hypertension, and/or the dysglycemic syndromes. We wait with interest for the definitive temporal link between epidemiological and anatomic variables related to the insulin resistance syndrome and atherosclerosis in offspring of dysglycemic parents.

Each of these concerns described above are important points since this Study is being followed closely by the medical community, and it may encourage pediatricians caring for children and adolescence to be less attentive to glucose, lipid, or blood pressure disturbances in younger age groups. Because of the important nature of the Bogalusa Heart Study, and similar studies, there is strong encouragement for use of the WHO dysglycemic diagnostic criteria to become the standard as in other large epidemiologic studies, especially in studies exploring the insulin resistance syndrome and related disorders.[11]

In conclusion, the Bogalusa Heart Study undoubtedly will prove to be an important step in the early intervention and prevention of cardiovascular disease. Its main quality is the

focus on children, adolescents, and young adults. It is now well appreciated that among young people, there are substantial and alarming increases in the cardiovascular risk variable burden associated with the insulin resistance or metabolic syndrome. With such importance, timelessness, and relevance, the study designs must be most rigorous and robust. Once the temporal relationships of these risk factors are established, the Bogalusa Study investigators may wish to take on the challenge of how to overcome physician cognitive dissonance which is the major barrier to the effective diagnosis and treatment of the dysglycemias, dyslipidemias, and hypertension.[15-20]

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