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

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The occurrence of metabolic abnormalities related to insulin resistance syndrome in nondiabetic offspring of type 2 diabetic parents is known. However, information is lacking on the timing and the course of development of the components of this syndrome from childhood to adulthood in the offspring of parents with diabetes. This aspect was examined in a community-based cohort with (n = 303) and without (n = 1,136) a parental history of type 2 diabetes followed longitudinally since childhood (ages 4 to 17 years; mean follow-up period, 15 years) by repeated surveys. Offspring with parental diabetes versus those without such history had significantly excess generalized and truncal adiposity as measured by body mass index (BMI) and subscapular skinfold beginning in childhood, higher levels of fasting insulin and glucose and homeostasis model assessment index of insulin resistance (HOMA-IR) from adolescence, and higher levels of low-density lipoprotein (LDL) cholesterol and triglycerides and lower levels of high-density lipoprotein (HDL) cholesterol in adulthood. Many of these risk variables changed adversely at an increased rate in offspring of diabetic parents. In a multivariate analysis, parental diabetes was an independent predictor of longitudinal changes in adiposity, glucose, insulin, HOM-IR, systolic and diastolic blood pressure, and LDL cholesterol in the offspring, regardless of race and gender. As young adults, the offspring of diabetic parents had a higher prevalence of generalized (BMI > 30, 36% *v* 16%, *P* = .0001) and visceral (waist > 100 cm, 15% *v* 6%, *P* = .0001) obesity, hyperinsulinemia indicative of insulin resistance (insulin > 18 μU/mL, 15% *v* 8%, *P* = .0001), hyperglycemia (≥110 mg/dL, 2% *v* 0.5%, *P* = .02), high LDL cholesterol (≥160 mg/dL, 11% *v* 7%, *P* = .02), low HDL cholesterol (<40 mg/dL for males and <50 mg/dL for females, 40% *v* 31%, *P* = .004), high triglycerides (≥150 mg/dL, 23% *v* 15%, *P* = .0001), and hypertension (>140/90 mm Hg, 11% *v* 6%, *P* = .004). Thus, the offspring of diabetic parents displayed excess body fatness beginning in childhood and accelerated progression of adverse risk profile characteristics of insulin resistance syndrome from childhood to young adulthood. These observations have important implications for early prevention and intervention.

TYPE 2 DIABETES has become one of the most commonly prevalent chronic diseases in the United States, with approximately 16 million people having clinical manifestations of the disease and another 13 million people having impaired fasting glucose (110 to 125 mg/dL).[1] In addition, there has been an increase in the prevalence of the disease over time.[1] Of concern is the increase in the incidence of type 2 diabetes among children and adolescents over the past decade.[2,3]

It is widely recognized that type 2 diabetes is preceded by a long prediabetes stage characterized by metabolic abnormalities.[4-10] Studies in this regard mainly involved ethnically distinct groups with a high prevalence of the disease.[5-7,10] Information is scant on the time-course of potential antecedent markers or risk factors for the disease at an early age in the US general population.

Because type 2 diabetes has a strong genetic and familial component,[11-13] a positive parental history is widely being used as a surrogate measure of risk to identify potential risk factors of the disease in the offspring.[4,14-18] A number of prospective population studies have shown that, besides positive family history, obesity and adverse levels of fasting and post-glucose plasma glucose and insulin are important risk factors of type 2 diabetes.[5-10,19] In addition, conventional risk factors of coronary heart disease (CHD) such as hypertension and dyslipidemia are also known to occur long before the onset of diabetes.[20-22] The risk factors of type 2 diabetes and CHD are recognized as components of insulin resistance syndrome (syndrome X), linked metabolically by a common pathophysiologic mechanism involving insulin resistance/hyperinsulinemia.[23-25]

Information on the timing and course of development of components of insulin resistance syndrome from childhood to young adulthood in persons at risk might be useful not only in assessing future risk but also in prevention and intervention algorithms. As part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of cardiovascular risk factors in children and young adults,[26] this study examines the longitudinal changes in risk variables of insulin resistance syndrome in a cohort of subjects with and without parental history of type 2 diabetes as they grew from childhood into young adulthood.

MATERIALS AND METHODS

Population

The Bogalusa Heart Study is conducted in the biracial (65% white, 35% black) community of Bogalusa, LA. Six cross-sectional surveys of children aged 4 to 17 years were conducted between 1973 and 1988. In addition, four cross-sectional surveys of young adults aged 18 to 32 years who had been previously examined as children and remained accessible were conducted between 1979 and 1991. The above panel design, based on repeated cross-sectional examinations, resulted in serial observations from childhood to young adulthood required for the longitudinal analysis. However, since this was not a prospective study

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by design, not every participant was examined in all surveys. The participation rate was approximately 80% for children and 60% for the young adult cohort. The study cohort (n = 1,439) was selected from 1,930 young adults who participated in the 1988 to 1991 survey and provided information on parental history of diabetes during this and the 1984 to1986 surveys.

Parental history of type 2 diabetes (onset after the age of 30) was obtained from the study cohort through a questionnaire as part of the examination. There were 303 subjects who reported father (42%), mother (54%), or both parents (4%) having diabetes either in both the 1984 to 1986 and the 1988 to 1991 surveys or in the 1988 to 1991 survey, and 1,136 subjects who reported consistently neither parents having diabetes in either survey. No data were collected to ascertain whether the offspring of diabetic mothers were in utero during gestational diabetes or before or after the mother had diabetes.

The study cohort consisted of 71% whites, 29% blacks, 61% females, and 39% males. The distributions of the study cohort by age at the 1988 to 1991 survey and number of screenings between childhood and adulthood are given in Table 1. Seventy-four percent of young adults were screened 4 times or more and only 10.3% were screened twice since childhood. The mean follow-up interval was 15 years.

The number of observations totaling 6,598 made on this 1,439–study cohort from childhood to young adulthood by age at the time of examination and status of parental diabetes is given in Table 2.

General Examination

All examinations followed the same protocols, described previously.[27] Subjects were instructed to fast for 12 hours prior to screening, and compliance was determined by interview on the morning of the examination. Anthropometric and blood pressure measurements were made in replicate and mean values were used in all analyses.

Height and weight were measured 2 times; subscapular skinfold thickness 3 times. The body mass index (BMI = weight in kilograms divided by the square of the height in meters) was used as a measure of overall adiposity; subscapular skinfold for truncal fatness. In the 1988 to 1991 survey, waist circumference, measured in triplicate, was used as an indicator of visceral fatness. The reproducibility in terms of intraclass (intra-observer) correlation coefficients was greater than 0.99 for weight and height, and greater than 0.97 for subscapular skinfold and waist circumference. Young adults were considered obese if their BMI was above 30 or waist circumference above 100 cm.

Blood pressure levels were measured in 6 replicates by 2 randomly assigned nurses on the right arm of subjects in a relaxed, sitting position. Young adults were classified as hypertensive if they had systolic blood pressure higher than 140 mm Hg, diastolic blood pressure higher than 90 mm Hg, or had been treated for hypertension.

Laboratory Analyses

From 1978 to 1986, cholesterol and triglyceride levels were measured using chemical procedures on Technicon Autoanalyzer II (Technicon Instrument, Tarrytown, NY) according to the Laboratory Manual of the Lipid Research Clinics Program.[28] Since then, these variables were determined by enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, North Chicago, IL). Serum lipoprotein cholesterols were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedure.[29] Both chemical and enzymatic procedures met the performance requirement of the Lipid Standardizations Program of the Centers for Disease Control and Prevention, Atlanta, GA. The laboratory has been monitored for precision and accuracy of lipid measurements by the agency's surveillance program since 1973. The intraclass correlation coefficients between the blind duplicate (10% random sample) values ranged from 0.87 to 0.99 for total cholesterol, 0.88 to 0.99 for triglycerides, 0.86 to 0.98 for low-density lipoprotein (LDL) cholesterol, and 0.86 to 0.98 for high-density lipoprotein (HDL) cholesterol. Based on the guidelines from the National Cholesterol Education Program Adult Treatment Panel III,[30] adult offspring were classified as dyslipidemic if they have adverse levels of LDL cholesterol (≥160 mg/dL), HDL cholesterol (<40 mg/dL for males and <50 mg/dL for females), or triglycerides (≥150 mg/dL), or if they were being treated for dyslipidemia.

Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). The high cross-reactivity (41%) of the assay with proinsulin should not affect the insulin measurements because proinsulin is secreted in very low amounts relative to insulin in individuals without diabetes. From 1978 to 1991, plasma glucose was measured by a glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Fullerton, CA). Since then, it has been measured enzymatically as part of a multichemistry profile. The intraclass correlation coefficients between the blind duplicate values ranged from 0.94 to 0.98 for insulin and 0.86 to 0.98 for glucose. For comparison between groups hyperinsulinemia was arbitrarily defined as fasting values above 18 μU/mL, values considered indicative of insulin resistance in normal subjects.[31] An index of insulin resistance was calculated according to the homeostasis model assessment formula[32]: HOMA-IR = fasting insulin (μU/mL) × fasting glucose (mmol/L) ÷ 22.5. This model is considered useful to assess insulin resistance in epidemiologic studies.[33] Based on American Diabetes Association criteria,[34] individuals were classified as having diabetes or impaired fasting glucose if their fasting glucose values were ≥ 126 mg/dL or 110 to 125 mg/dL, respectively.

Table 1. Distribution of Study Cohort by Age at Last Survey and Number of Screenings Between Childhood and Adulthood: The Bogalusa Heart Study

	No. of Screenings†						
Age* (yr)	2	3	4	5	6	7	Total
19-24	47	79	107	177	170	25	606
25-28	77	121	144	154	134	82	712
>28	23	26	19	18	16	19	121
Total	148	226	270	349	320	126	1,439

*Age at the last screening.
†Since childhood.

Table 2. Number of Observations on Study Cohort by Age and Parental Type 2 Diabetes: The Bogalusa Heart Study

	No. of Examinations*		
Age (yr)	With Parental Diabetes (n = 303)	Without Parental Diabetes (n = 1136)	Total (N = 1,439)
<7	28	157	185
7-8	59	315	374
9-10	105	459	564
11-12	138	526	664
13-14	188	668	856
15-16	179	613	792
17-18	137	527	664
19-20	99	399	498
21-22	98	432	530
23-24	95	395	490
25-26	89	293	382
27-28	79	242	321
>28	74	204	278
Total	1,368	5,230	6,598

*Values represent multiple observations made from childhood to adulthood on individuals with and without parental diabetes.

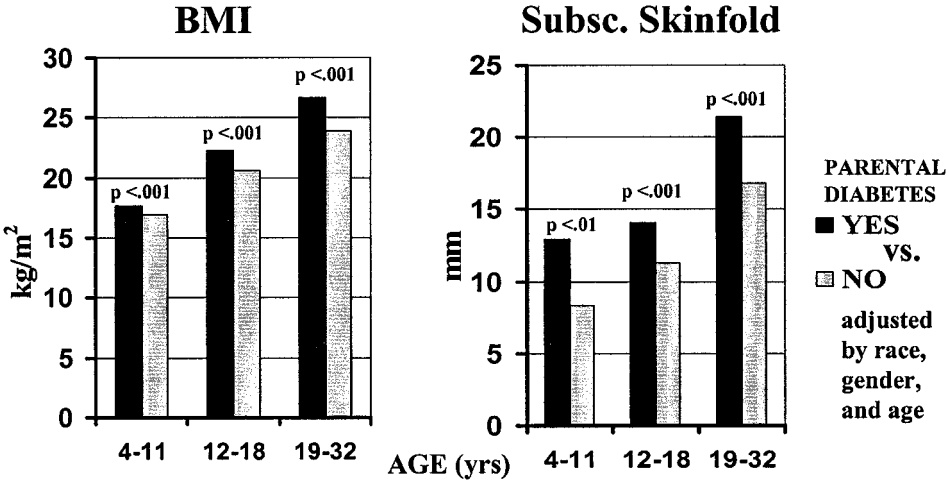

Fig 1. Mean levels of BMI and subscapular skinfold thickness in offspring by parental history of diabetes and age group corresponding to childhood, adolescence, and young adulthood. The Bogalusa Heart Study.

Statistical Analyses

For tests of significance insulin glucose and triglycerides were logarithmically transformed to approach normality. Mean levels of risk variables by age groups 4 to 11, 12 to 18, and 19 to 32 years corresponding to childhood, adolescence, and young adulthood periods were compared between groups with and without parental diabetes in a general linear model using age, race, and gender as covariates and single measurement per subject in each age group. Using data from the last survey, the prevalence of risk factors related to insulin resistance syndrome in young adults was compared between those with and without parental diabetes in a chi-square analysis.

To evaluate the longitudinal rates of change in different risk variables and the association between parental history of diabetes and the longitudinal changes in risk variables in the offspring from childhood to young adulthood, generalized estimating equations (GEE) analysis was used.[35] GEE analysis adjusts for the correlation between observations taken on the same individuals repeatedly. Further, GEE analysis is suitable for longitudinal data on individuals with varying number and unequal spacing of observations. For each risk variable, a univariate regression model with age as predictor was used to describe the rate of change with age in each parental history group. Since the main objective was to evaluate the effect of parental diabetes on the longitudinal changes of risk variables in the offspring, parental history of diabetes was used as the main predictor variable in the regression model. Age, age^2, race, and gender and their interactions with the main predictor variable were always included in the full model. In addition, BMI, glucose, insulin, and HOMA-IR index were included in the model as applicable. For example, when BMI was a dependent variable, glucose, insulin, and HOMA-IR index were used as covariates. Nonsignificant terms ($P > .05$) were removed from the full model by backward stepwise procedure. Other obesity measures such as subscapular skinfold and waist circumference were not included in the multivariable model because of their high correlation with BMI.

RESULTS

Mean levels of risk variables of insulin resistance syndrome in childhood (4 to 11 years), adolescence (12 to 18 years), and young adulthood (19 to 32 years) are shown in Figs 1 through 4 by parental history of diabetes. Single measurement per subject was used in each age group. Comparisons were made after adjusting for age, race, and gender. Offspring with parental diabetes versus those without such history displayed significantly higher levels of BMI and subscapular skinfold beginning in childhood (Fig 1); higher levels of fasting insulin and glucose and HOMA-IR index beginning in adolescence (Fig 2); and higher levels of triglycerides and LDL cholesterol and lower levels of HDL cholesterol in adulthood (Fig 3). Systolic

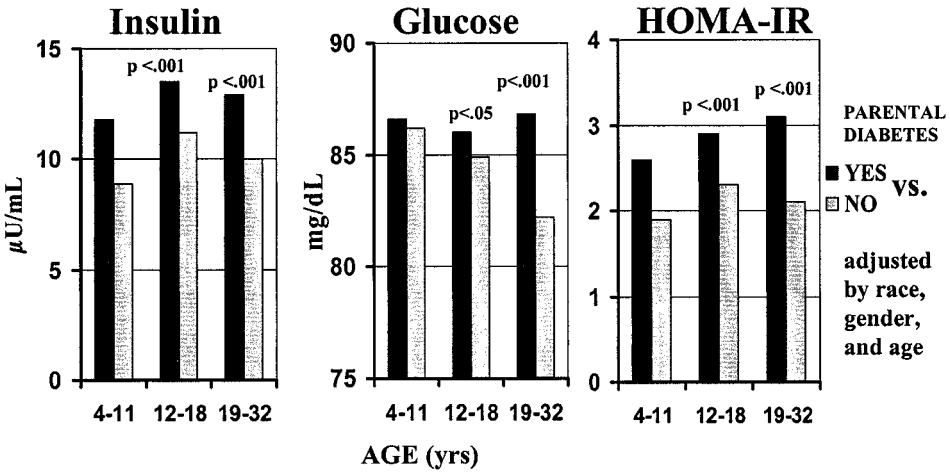

Fig 2. Mean levels of fasting insulin and glucose and HOMA-IR index in offspring by parental history of diabetes and age group corresponding to childhood, adolescence, and young adulthood. The Bogalusa Heart Study.

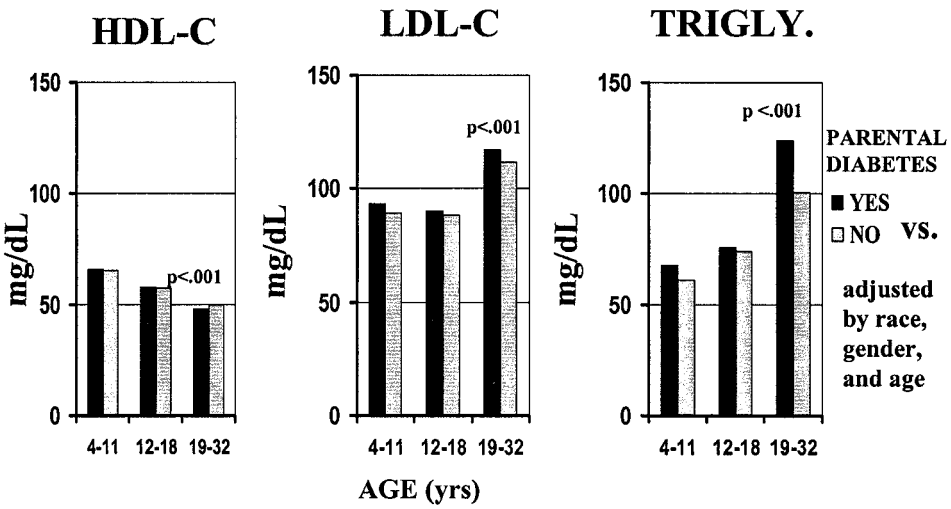

Fig 3. Mean levels of LDL cholesterol, HDL cholesterol, and triglycerides in offspring by parental diabetes and age group corresponding to childhood, adolescence, and young adulthood. The Bogalusa Heart Study.

and diastolic blood pressure levels remained similar between the 2 groups during these periods, except that the systolic blood pressure of offspring of diabetic parents was higher in childhood (Fig 4).

Longitudinal rates of change in risk variables obtained by a univariate regression model are presented in Table 3. The rates of increase in BMI, subscapular skinfold, triglycerides, LDL cholesterol and systolic blood pressure were significantly higher in the offspring with parental diabetes versus those without parental diabetes. The rate of decrease in glucose was significantly lower in offspring with parental diabetes. Parental diabetes was marginally ($P = .08$) associated with higher rate of increase in HOMA index of insulin resistance in the offspring.

In a multivariate analysis, parental diabetes history was independently associated with adverse longitudinal changes in BMI, fasting insulin and glucose, HOMA-IR, systolic and diastolic blood pressure, and LDL cholesterol in the offspring, regardless of race and gender (Table 4). There was a significant interaction between parental diabetes and age of the offspring in predicting adverse changes in BMI. This interaction with age, when viewed in conjunction with data shown in Fig 1 and Table 3, indicated that BMI was not only consistently higher from childhood to young adulthood, but also increased faster with age among those with parental diabetes than those without such a parental history. The adjusted rate of change in BMI per year in offspring of diabetic parents (1.42 kg/m^2/yr; 95% confidence interval [CI], 0.98 to 1.85) was higher than in offspring of non-diabetic parents (0.59 kg/m^2/yr; 95% CI, 0.35 to 0.46). Further, an interaction between parental diabetes and gender was noted for systolic and diastolic blood pressure, indicating that adverse changes in these variables occur relatively more in males than in females (4.82 mm Hg/yr [95% CI, 2.33 to 7.32] *v* 4.20 mm Hg/yr [95% CI, 1.25 to 7.73]) for systolic blood pressure and 0.97 mm Hg/yr [95% CI, 0.07 to 1.86] *v* 0.68 mm Hg/yr [95% CI, 0.43 to 1.79] for diastolic blood pressure). Although parental diabetes was not an independent predictor of adverse changes in triglycerides and HDL cholesterol in the offspring, BMI, insulin, HOMA-IR, and glucose (triglycerides

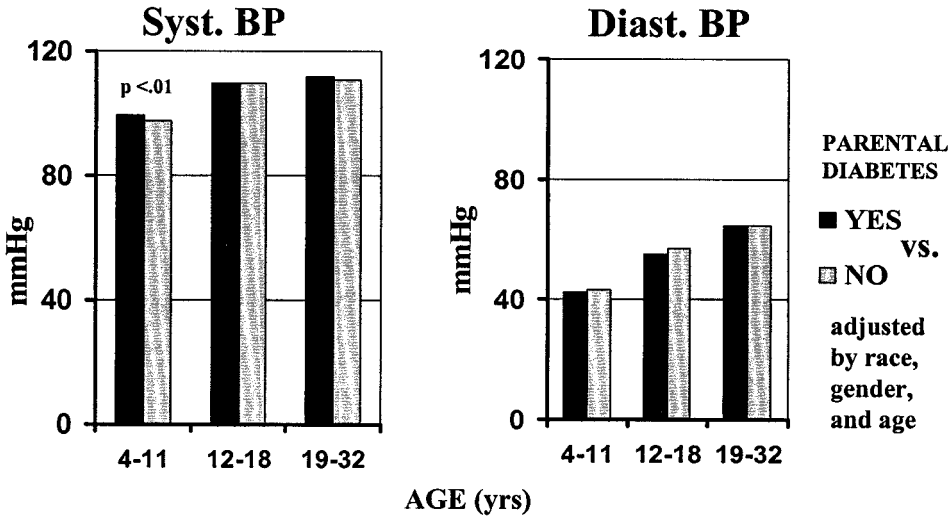

Fig 4. Mean levels of systolic and diastolic blood pressure in offspring by parental history of diabetes and age group corresponding to childhood, adolescence, and young adulthood. The Bogalusa Heart Study.

Table 3. Longitudinal Rates of Change in Risk Variables of Insulin Resistance Syndrome in the Study Cohort by Parental History of Diabetes: The Bogalusa Heart Study

Risk Variable	Parental Diabetes		Yes *v* No *P* Value
	Yes	No	
BMI (kg/m^2/yr)	0.53 (0.49-0.57)*	0.45 (0.43-0.47)	.000
Subscapular skinfold (mm/yr)	0.70 (0.60-0.80)	0.57 (0.53-0.62)	.02
Insulin (μU/mL/yr)†	−0.05 (−0.19-0.10)	−0.10 (−0.16-−0.06)	.45
HOMA-IR/yr	0.005 (−0.02-0.01)	−0.03 (−0.08-0.02)	.08
Glucose (mg/dL/yr)†	−0.005 (−0.01-−0.001)	−0.41 (−0.47-−0.35)	.01
Triglycerides (mg/dL/yr)†	4.34 (2.71-5.96)	2.41 (2.11-2.71)	.02
LDL cholesterol (mg/dL/yr)	2.14 (1.92-2.37)	1.82 (1.72-1.93)	.02
HDL cholesterol (mg/dL/yr)	−0.99 (−1.12-−0.86)	−0.94 (−1.02-−0.87)	.50
Systolic blood pressure (mm Hg/yr)	0.69 (0.65-0.73)	0.58 (0.50-0.67)	.03
Diastolic blood pressure (mm Hg/yr)	0.53 (0.49-0.64)	0.61 (0.57-0.64)	.32

*Values are univariate regression slope (GEE) (95% CI) with respect to age in years.
†Fasting subjects only

only) were associated independently with these 2 variables (data not shown).

To test whether paternal or maternal history of diabetes makes a difference in the prediction of adverse longitudinal changes in risk variables in the offspring, the above multivariate analysis was performed separately for maternal and paternal diabetes (data not shown). The results including BMI and HOMA-IR index were similar to that shown in Table 4, except with respect to insulin (maternal diabetes, $P = .04$; paternal diabetes $P = .20$) and to glucose (maternal diabetes, $P = .03$; paternal, $P = .13$). The relatively smaller sample size might have contributed to the observed differences in insulin and glucose.

The prevalence of risk factors characteristic of insulin resistance syndrome in young adult subjects at the last survey is shown in Table 5 by parental diabetes history. Obesity in terms of excess generalized adiposity (BMI) or visceral adiposity (waist circumference), hyperinsulinemia indicative of insulin resistance, hyperglycemia, hypertension, and high risk levels of LDL cholesterol, HDL cholesterol, and triglycerides were all significantly more prevalent among the offspring of diabetic parents. Within the hyperglycemia category, the prevalence of hyperglycemia indicative of impaired fasting glucose (110 to 125 mg/dL) was marginally ($P = .08$) higher, and hyperglycemia (≥126 mg/dL) indicative of clinical diabetes significantly higher among those with parental diabetes.

DISCUSSION

Little information is available at a community level in the US general population on the longitudinal changes in risk variables of insulin resistance syndrome measured simultaneously from childhood to young adulthood in subjects at risk for developing type 2 diabetes. The present community-based study shows that offspring of parents with type 2 diabetes developed excess generalized and truncal adiposity beginning in childhood, higher levels of fasting insulin and glucose and HOMA-IR index from adolescence, and adverse levels of triglycerides, LDL cholesterol, and HDL cholesterol in adulthood. Many of these risk variables changed adversely at a greater rate from childhood to adulthood in offspring of diabetic parents. These observations provide further evidence that risk factors of type 2 diabetes are found at relatively young age in those with parental diabetes.[6,10,14,17] Whether intrauterine imprinting enunciated by the fetal-origin or thrifty phenotype hypothesis,[36] besides genetics,[11-13] also contributed to the observed adverse changes in the offspring is not clear.

Table 4. Parental Diabetes as a Predictor of Adverse Longitudinal Changes in Risk Variables of Insulin Resistance Syndrome in the Study Cohort: The Bogalusa Heart Study

Risk Variables	Parental Diabetes	Interaction of Parental Diabetes and		
		Age	Race	Gender
BMI (kg/m^2)	0.17*†	0.07†	—	—
Insulin (μU/mL)	1.03†	—§	—	—
HOMA-IR	0.27‡	—	—	—
Glucose (mg/dL)	1.33†	—	—	—
Systolic blood pressure (mm Hg)	3.20†	—	—	2.79‡
Diastolic blood pressure (mm Hg)	2.24†	—	—	1.99‡
Triglycerides (mg/dL)	0.02	—	—	—
LDL cholesterol (mg/dL)	0.09‡	—	—	—
HDL cholesterol (mg/dL)	0.02	—	—	—

*GEE regression coefficient. The model included parental diabetes as the main predictor along with age, age^2, race, and gender, and their interaction with the main effect; and BMI, glucose, insulin, and HOMA-IR as applicable.
†$P < .05$; ‡$P < .001$.
§— indicates no significant interaction.

Table 5. Prevalence of Risk Factors Characteristic of Insulin Resistance Syndrome in Young Adult Offspring by Parental Diabetes: The Bogalusa Heart Study

Risk factor	Parental Diabetes		*P* Value
	Yes (n = 303)	No (n = 1136)	
Obesity			
BMI (kg/m^2) > 30	36.3*	16.3	.000
Waist > 100 cm	14.8	6.2	.000
Hyperinsulinemia†			
>18 μU/mL	15.1	7.5	.000
Hyperglycemia†			
≥110 mg/dL	2.0	0.5	.02
110-125 mg/dL	1.3	0.4	.08
≥126 mg/dL	0.7	0.1	.05
Dyslipidemia			
LDL cholesterol ≥ 160 mg/dL	11.2	7.1	.02
HDL cholesterol (males: <40 mg/dL; females: <50 mg/dL)	39.6	30.8	.004
Triglycerides ≥ 150 mg/dL†	23.4	14.7	.000
Hypertension			
> 140/90 mm Hg or Rx	11.2	6.3	.004

*Prevalence (%) at the last survey
†Fasting subjects only
Abbreviation: Rx, under antihypertensive medication.

With respect to longitudinal changes in measures of obesity and glucose homeostasis in the current study cohort, parental diabetes was an independent predictor of adverse changes in adiposity, fasting insulin and glucose, and HOMA-IR index, regardless of race or gender. Of note, the adverse association between body fatness and parental diabetes was influenced by age in that the body fatness increased faster with age, probably reflecting the burden of interaction between genetic and lifestyle-related factors with age. Earlier studies have shown an independent association between the development of diabetes and baseline obesity.[5,9,10,13,19,37] Of relevance to the present finding is an earlier study in Pima Indians showing childhood and adolescence obesity in those with diabetic parents as a strong predictor of subsequent diabetes.[10]

Earlier studies have shown that insulin resistance and the compensatory hyperinsulinemia predate the development of type 2 diabetes.[4-9] The observed independent association between parental diabetes and adverse longitudinal changes in basal insulin and HOMA-IR index in the offspring suggests that these individuals may be at increased risk for developing diabetes in the future. In addition to impaired insulin sensitivity, a defect in insulin-independent glucose utilization (glucose effectiveness) is considered an important trait for developing diabetes.[38] In an earlier study, we found that parental diabetes was independently associated with incremental glucose response, but not with insulin response, during a 1-hour oral glucose load in both black and white young offspring.[17] The current finding of adverse longitudinal profiles of basal insulin and HOMA-IR index in conjunction with increased basal glucose also suggests slow glucose removal and diabetes susceptibility in the offspring of diabetic parents.

Although excess prevalence of type 2 diabetes in blacks versus whites is well established among middle-aged older US adults,[1,39,40] the longitudinal trends of risk variables in the offspring of diabetic parents remained the same in both races in this study of youth. It has been suggested that black-white differences in the established risk factors of type 2 diabetes, especially obesity and its differential effects on diabetes risk among blacks and whites,[39-41] may account for this excess. Long-term follow-up of the study cohort is needed to ascertain the link between the observed adverse longitudinal trends of risk variables in the black and white offspring of diabetic parents and development of diabetes later in life.

The link between obesity and insulin resistance, the two major risk factors for type 2 diabetes, is well known. However, the question remains whether obesity proceeds or follows, insulin resistance/hyperinsulinemia in the general population. Conceptually, potential mechanisms have been proposed to explain the causality either way.[42,43] It is of interest that offspring of diabetic parents in this study developed excess generalized and truncal adiposity beginning in childhood, while elevated levels of insulin and HOMA-IR index became apparent beginning in adolescence. This is consistent with earlier observations, including our own, showing temporal association between the degree of baseline adiposity and incidence of hyperinsulinemia in children, adolescents, and young adults alike, independent of baseline insulin level[44]; and childhood obesity as a powerful predictor for developing insulin resistance syndrome in young adulthood.[45,46] With respect to temporal sequence of development of type 2 diabetes, a longitudinal study in Pima Indians found that the transition from normal glucose tolerance to impaired glucose tolerance was associated with a marked weight gain and decreases in insulin action and acute insulin secretory response to glucose; the progression from impaired glucose tolerance to diabetes was associated with further adverse changes in these risk variables and an increase in basal endogenous glucose output.[47] Further, longitudinal studies in rhesus monkeys, a nonhuman primate experimental model known to spontaneously develop obesity and, later, type 2 diabetes showed that the onset of diabetes can be prevented by prevention of obesity.[48]

The present study also demonstrates that parental diabetes was independently associated with adverse longitudinal changes in CHD risk variables such as systolic and diastolic blood pressure, and LDL cholesterol. Although parental diabetes was not an independent predictor of adverse changes in triglycerides and HDL cholesterol in the offspring, measures of obesity and glucose homeostasis were associated independently with these variables. This suggests that parental diabetes may adversely affect triglycerides and HDL cholesterol indirectly in the offspring through its effect on measures of obesity and glucose homeostasis. Of note, as young adults the offspring of diabetic parents in this study already showed increased prevalence of multiple risk factors for both diabetes and CHD such as generalized and visceral obesity, hyperinsulinemia/insulin resistance, hyperglycemia, hypertension, and dyslipidemia, characteristic features of insulin resistance syndrome. Earlier studies have found that prediabetic individuals display an atherogenic profile of lipoproteins and blood pressure, possibly induced by obesity and insulin resistance/hyperinsulinemia, which may be present long before the development of diabetes and may contribute to the risk of macrovascular disease.[20-22]

The community-based nature of this study, with risk vari-

ables measured from childhood to adulthood, adds strength to the current findings. However, the present study has certain limitations. The major limitation being the lack of verification of diabetes status of the parents, including those with undiagnosed condition. Others have found 78% to 81% of self-reported information to be valid.[49,50] The reliability of our questionnaire could, in part, be estimated based on consistency in reporting from the last 2 surveys. Concordance was identified if reported negative parental history at the last survey or positive parental history at the previous survey agreed with the information provided in the other survey. Accordingly, there was 89% concordance in the reporting between the 2 surveys. In terms of negative parental history, many parents may not recognize that they do have diabetes or they may be still too young to manifest the clinical disease. However, the inherent difficulties associated with negative parental history would most likely result in an underestimation of the strength of the association between parental diabetes and risk variables in the offspring during childhood, adolescence, and adulthood, especially when the differences in risk variables were smaller. It is also conceivable that the observed gradation of adverse levels of obesity variables in childhood versus insulin resistance parameters in adolescence versus lipid variables in young adulthood may be due to the fact that the most robust variable may occur in all age groups, whereas the least robust variable may occur in older age groups. This study also lacks serial measurements of glucose tolerance and in vivo insulin action and secretion used in clinical and etiological studies. Instead, we used risk variables that are relatively easily measured and applicable at a population level. Finally, although some, but not all, family history studies have suggested an excess of maternal transmission of type 2 diabetes,[51-53] the current study lacks the statistical power to adequately address the issue.

In summary, our study shows that offspring of parents with type 2 diabetes developed an adverse risk profile characteristic of insulin resistance syndrome from childhood to young adulthood at an increased rate. Both genetic predisposition and environment are important in this regard. Importantly, parental diabetes was associated with excess generalized and truncal adiposity, a modifiable risk factor, beginning in childhood. These results when viewed in the context of an increasing incidence of type 2 diabetes among adolescents[2,3] accompanying the upward secular trend in obesity in American youth[54,55] underscores the importance of control of obesity through prudent diet and exercise early in life to prevent or temper the onset of the disease, especially among high-risk ethnic/racial groups. Of note, regular exercise as a preventive measure can also stimulate non–insulin-mediated glucose uptake by muscle and decrease the risk of type 2 diabetes in subjects who are at high risk for the disease.[56]

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REFERENCES

1. Harris MI, Flegal K, Cowie C, et al: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: The Third National Health and Nutrition Examination Survey 1988-1994. Diabetes Care 21:518-524, 1998

2. Pinkas-Hamiel D, Dolan LM, Daniels SR, et al: Increased incidence of non-insulin-dependent diabetes mellitus, among adolescents. J Pediatr 128:608-615, 1996

3. Fagot-Campagna AF, Pettitt DJ, Engelgau MM, et al: Type 2 diabetes among North American children and adolescents: An epidemiologic review and a public health perspective. J Pediatr 136:664-672, 2000

4. Warram JH, Martin BC, Krolewski AS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 113:909-915, 1990

5. Haffner SM, Stern MP, Mitchell BD, et al: Incidence of type 2 diabetes in Mexican American predicted by fasting insulin and glucose levels, obesity, and body-fat distributions. Diabetes 39:283-288, 1990

6. Zimmet PZ, Collins VR, Dowse GK, et al: Hyperinsulinemia in youth is a predictor of type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 35:534-554, 1992

7. Saad MF, Knowler WC, Pettitt DJ, et al: A two-step model for development of non-insulin-dependent diabetes. Am J Med 90:229-235, 1991

8. Charles MA, Fontbonne A, Thibult N, et al: Risk factors for NIDDM in white population. Paris Prospective Study. Diabetes 40: 706-710, 1991

9. Skarfors ET, Selinus KI, Lithell HO: Risk factors for developing non-insulin-dependent diabetes: A 10 year follow-up of men in Uppsala. Br Med J 303:755-760, 1991

10. McCance DR, Pettitt DJ, Hanson RL, et al: Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. Diabetologia 37:617-623, 1994

11. Barnett AH, Eff C, Leslie DG, et al: Diabetes in identical twins: A study of 200 pairs. Diabetologia 20:87-93, 1981

12. Newman B, Selby JV, King MC, et al: Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. Diabetologia 30:763-768, 1987

13. Knowler WC, Pettitt DJ, Savage PJ, et al: Diabetes incidence in Pima Indians: Contributions of obesity and parental diabetes. Am J Epidemiol 113:144-156, 1981

14. Leslie RDG, Volkmann HP, Poncher M, et al: Metabolic abnormalities in children of non-insulin dependent diabetics. Br Med J 293:840-842, 1986

15. Haffner SM, Stern MP, Hazuda HP, et al: Increased insulin concentrations in non-diabetic offspring of diabetic parents. N Engl J Med 319:1297-1301, 1988

16. Laws A, Stefanik ML, Reaven GM: Insulin resistance and hypertriglyceridemia in non-diabetic relatives of patients with non-insulin dependent diabetes mellitus. J Clin Endocrinol Metab 69:2343-2347, 1989

17. Srinivasan SR, Elkasabany A, Dalferes ER Jr, et al: Characteristics of young offspring of type 2 diabetic parents in a biracial (black-white) community-based sample: The Bogalusa Heart Study. Metbolism 47:998-1004, 1998

18. McClain MR, Srinivasan SR, Chen W, et al: Risk of type 2 diabetes mellitus in young adults from a biracial community: The Bogalusa Heart Study. Prev Med 31:1-7, 2000

19. Shaten BJ, Smith GD, Kuller LH, et al: Risk factors for the development of type II diabetes among men enrolled in the usual care group of the Multiple Risk Factor Intervention Trial. Diabetes Care 16:1331-1339, 1993

20. Haffner SM, Stern MP, Hazuda HP, et al: Cardiovascular risk factors in confirmed prediabetic individuals: Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 263:2893-2398, 1990

21. McPhillips JB, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin dependent diabetes in a community of older adults. Am J Epidemiol 131:443-453, 1990

22. Sarlund H, Pyörälä K, Penttilä I, et al: Early abnormalities in coronary heart disease risk factors in relatives of subjects with non-insulin-dependent diabetes. Arterioscler Thromb 12:657-663, 1992

23. Reaven GM: Role of insulin resistance in human disease: Banting Lecture 1988. Diabetes 37:1595-1607, 1988

24. DeFronzo RA, Ferannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetic Care 14:173-194, 1991

25. Liese AD, Mayer-Davis EJ, Haffner SM: Development of the multiple metabolic syndrome: An epidemiologic perspective. Epidemiol Rev 20:157-172, 1998

26. The Bogalusa Heart Study 20th Anniversary Symposium. Am J Med Sci 310:S1-S138, 1995 (suppl 1)

27. Berenson GS, McMahan CA, Voors AW, et al: Cardiovascular Risk Factors in Children—The Early Natural History of Atherosclerosis and Essential Hypertension. New York, NY, Oxford University Press, 1980

28. Lipid Research Clinics Program: Manual of Laboratory Operations. Vol 1: Lipids and Lipoprotein Analysis. Washington, DC, National Institutes of Health, 1974 (DHEW Publication No. [NIH] 75-628)

29. Srinivasan SR, Berenson GS: Serum lipoproteins in children and methods for study, in Lewis RA (ed): CRC Handbook of Electrophoresis, vol 3: Lipoprotein Methodology and Human Studies. Boca Raton, FL, CRC, 1983, pp 185-203

30. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 285:2486-2496, 2001

31. Laakso M: How good a marker is insulin level for insulin resistance? Am J Epidemiol 137:959-965, 1993

32. Mathews DR, Hosker JP, Rudenski AS, et al: Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412-419, 1985

33. Haffner SM, Miettinen H, Stern MP: The homeostasis model in the San Antonio Heart Study. Diabetes Care 20:1087-1092, 1997

34. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20:1183-1197, 1997

35. Diggle PJ, Liang KY, Zeger SL: Analysis of Longitudinal Data. New York, NY, Oxford University Press, 1994

36. Hales CN, Barker DJ: Type 2 (non-insulin-dependent) diabetes mellitus: The thrifty phenotype hypothesis. Diabetologia 35:595-601, 1992

37. Edelstein SL, Knowler WC, Bain RP, et al: Predictors of progression from impaired glucose tolerance to NIDDM: An analysis of six prospective studies. Diabetes 46:701-710, 1997

38. Martin BC, Warram JH, Krolewski AS, et al: Role of glucose and insulin resistance in development of type 2 diabetes mellitus: Results of a 25-year follow-up study. Lancet 340:925-929, 1992

39. Resnick HE, Valsania P, Halter JB, et al: Differential effects of BMI on diabetes risk among black and white Americans. Diabetes Care 21:1828-1835, 1998

40. Brancati FL, Kao WH, Folsom AR, et al: Incident type 2 diabetes mellitus in African American and white adults. The Atherosclerosis Risk in Communities Studies. JAMA 283:2253-2259, 2000

41. Cowie CC, Harris MI, Silverman RE, Johnson EW, et al: Effect of multiple risk factors on differences between blacks and whites in the prevalence of non-insulin-dependent diabetes mellitus in the United States. Am J Epidemiol 137:719-732, 1993

42. Ravussin E, Swinburn BA: Insulin resistance is a result, not cause of obesity. Socratic debate: The pro side, in Angel A, Anderson H, Bouchard C (eds): Progress in Obesity Research Seventh International Congress on Obesity. London, UK, Libby, 1996, pp 173-178

43. Sims EAH: Insulin resistance is a result, not a cause of obesity. Socratic debate: The con side, in Angel A, Anderson H, Bouchard C (eds): Progress in Obesity Research. Seventh International Congress on Obesity. London, UK, Libby, 1996, pp 587-592

44. Srinivasan SR, Myers L, Berenson GS: Temporal association between obesity and hyperinsulinemia in children, adolescents, and young adults: The Bogalusa Heart Study. Metabolism 48:928-934, 1999

45. Sinaiko A, Donahue RP, Jacobs DR, et al: Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults. The Minneapolis Children Blood Pressure Study. Circulation 99:1471-1476, 1999

46. Srinivasan SR, Myers L, Berenson GS: Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood. The Bogalusa Heart Study. Diabetes 51:204-209, 2002

47. Weyer C, Bogardus C, Mott DM, et al: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 104:787-794, 1999

48. Hansen BC, Bodkin NL: Primary prevention of diabetes mellitus by prevention of obesity in monkeys. Diabetes 42:1809-1814, 1993

49. Napier JA, Metzner H, Johnson BC: Limitations of morbidity and mortality data obtained from family histories—A report from the Tecumseh community health study. Am J Public Health 62:30-35, 1972

50. Tretli S, Lund-Larsen PH, Foss OP: Reliability of questionnaire information of cardiovascular disease and diabetes: Cardiovascular disease study in Finnmark County. J Epidemiol Community Health 36:269-273, 1982

51. Alcolado JC, Alcolado R: Importance of maternal history of non-insulin-dependent diabetic patients. BMJ 302:1178-1180, 1991

52. Thomas F, Balkau B, Vauzelle-Kervroedan F, et al: Maternal effects and familial aggregation in NIDDM. Diabetes 43:63-67, 1994

53. Mitchell BD, Kammerer CM, Reinhart LJ, et al: Is there an excess in maternal transmission of NIDDM? Diabetologia 38:314-317, 1995

54. Freedman DS, Srinivasan SR, Valdez RA, et al: Secular increases in relative weight and adiposity among children over two decades: The Bogalusa Heart Study. Pediatrics 99:420-426, 1997

55. Mokdad AH, Serdula MK, Dietz WH, et al: The spread of obesity epidemic in the United States, 1991-1998. JAMA 282:1519-1522, 1999

56. Goodyear LJ, Kahn BB: Exercise, glucose transport and insulin sensitivity. Ann Rev Med 49:235-261, 1998