Decreased Glucose Tolerance, Not Decreased Insulin Sensitivity, Is a Maturational Abnormality in the Male Offspring of a Parent With Early Coronary Artery Disease

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We investigated whether the male offspring of a parent with early coronary artery disease (before the age of 60; n = 61) exhibit decreased insulin sensitivity compared with controls matched for age and body mass index (BMI) (n = 39). The insulin sensitivity index (S_I) was determined by the minimal modeling method of Bergman from a frequently sampled intravenous glucose tolerance test with intravenous tolbutamide. Offspring and controls had a similar S_I, insulin-independent glucose utilization (S_G), first-phase insulin response (AIR_G), and area under the glucose curve. When subjects were separated into two age groups, younger subjects aged 15 to 30 years and older subjects aged 31 to 45 years, important differences were seen. S_G was significantly increased in younger offspring compared with controls (22.8 ± 2.3 *v* $16.8 \pm 2.3 \times 10^{-3} \cdot min^{-1}$, $P < .05$). Older offspring had a significantly increased area under the glucose curve compared with controls (18,250 ± 322 *v* 17,225 ± 347 mg/dL $\cdot min^{-1}$, $P < .05$). Older offspring also had decreased S_I compared with younger offspring (5.0 ± 0.4 *v* $6.6 \pm 0.9 \times 10^{-4} \cdot min^{-1} \cdot \mu$ U/mL, $P < .05$), but this difference was eliminated after adjusting for BMI and waist to hip ratio (5.5 ± 0.4 *v* $5.8 \pm 0.9 \times 10^{-3} \cdot min^{-1}$, nonsignificant). This study does not support the concept that insulin resistance is an early atherogenic risk factor in offspring at risk for coronary disease because of their family history. However, it does point to the importance of maturational changes in glucose homeostasis in these offspring.

THERE IS CONSIDERABLE evidence implicating hyperinsulinemia and insulin resistance in the etiology of coronary artery disease. Fasting and post–oral glucose load insulin levels are increased in patients with coronary disease.[1] Young et al[2] demonstrated glucose intolerance, hyperinsulinemia following an intravenous glucose load, and resistance to insulin-mediated glucose uptake in 20 male patients with coronary artery disease. Impaired insulin-mediated glucose metabolism was noted by Shinozaki et al[3] in 19 patients with documented coronary artery disease and normal or impaired glucose tolerance. Laakso et al[4] found decreased insulin sensitivity in 30 middle-aged non-obese subjects with asymptomatic atherosclerosis of the femoral or carotid arteries. Insulin resistance is also thought to have a major role in the regulation of lipid metabolism, and is associated with many of the dyslipidemic changes commonly seen in patients with atherosclerosis.[5] These include fasting hypertriglyceridemia,[6] hypoalphalipoproteinemia,[7] postprandial lipemia,[8,9] and dense low-density lipoprotein (LDL) particles.[10,11]

However, from prospective epidemiological studies, a different picture emerges.[12] An independent role for insulinemia in atherogenesis was implied by three early prospective studies, namely the Paris Prospective Study,[13] the Busselton Study from Western Australia,[14] and the prospective Helsinki study,[15] which found fasting or post–glucose challenge insulin levels to be independent predictors of coronary disease morbidity. However, a 15-year follow-up report from the Paris Prospective Study noted that fasting insulin and 2-hour postload insulin levels were no longer independent predictors of coronary morbidity when expressed as continuous variables, although a 2-hour postload insulin level remained a significant independent predictor as a categorical variable.[16] Only the Busselton Study included both sexes, and only in men was there a relationship after 12 years between postchallenge insulin levels and coronary morbidity.[14] However, follow-up data from this study after 13 years have been equivocal.[17] Other prospective studies have also been unable to implicate hyperinsulinemia as an independent risk factor for coronary disease.[18-23]

To investigate this issue, we examined whether decreased insulin sensitivity is present in the male offspring of parents with early coronary artery disease. Because of the possibility that decreased insulin sensitivity is a maturational abnormality developing over time, we also examined these offspring at two age ranges: 15 to 30 years and 31 to 45 years.

SUBJECTS AND METHODS

Subjects

Subjects were male offspring of a parent with documented evidence of major coronary artery disease before age 60. All parents had a history of either coronary angioplasty, coronary bypass surgery, or myocardial infarction (including fatal myocardial infarction). Exclusion criteria for the parents were an LDL cholesterol level and family history suggestive of familial hypercholesterolemia, and treatment for diabetes mellitus with an oral hypoglycemic agent or insulin within 1 year of diagnosis of coronary disease. Offspring and controls were recruited into two groups by age: 20 offspring aged 15 to 30 years (younger subjects) and 41 offspring aged 31 to 45 years (older subjects). Nine offspring were younger than 20 years of age, as were seven controls. All adolescents were at Tanner stage V of pubertal development, with a testicular length of 4 cm or greater. Subjects were recruited into the study irrespective of previously known lipid values. Body weight was not an exclusion criterion, although none of the subjects were morbidly obese. All subjects were healthy without evidence of gastrointestinal, renal, cardiac, endocrine, or other significant chronic disease. All but one

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subject had a normal fasting plasma glucose level of less than 115 mg/dL, with one older offspring having a fasting plasma glucose of 116.7 mg/dL. Offspring were matched to controls by age and body mass index (BMI), with 19 controls in the younger age group and 20 controls in the older age group. All controls met the following criteria: (1) absence of a history of parental coronary disease; (2) absence of a history in the grandparents suggestive of coronary artery disease if either of the subject's parents were less than 60 years of age at the time of study; and (3) absence of parental diabetes. All but three offspring had familial coronary artery disease, with a history of coronary disease in both a parent and a grandparent. All offspring and controls were white.

Study Protocol

This study was approved by the Institutional Review Board of the Medical College of Wisconsin. Informed consent was obtained from the subject, and parental consent was also obtained if the subject was less than 18 years of age. The subject's height, weight, and blood pressure were measured at a preliminary examination. The blood pressure recorded was the average of three readings from the right arm after the subject had rested for 10 minutes in the supine position. The waist to hip ratio was the ratio of a waist measurement at the level of the umbilicus and hip measurement at the level of the greater trochanter. Smoking and alcohol intake were recorded from a life-style questionnaire. Dietary composition was analyzed by means of either a 1-day (at the beginning of the study) or 3-day food diary and food frequency records. Values recorded were the mean of the food recall and food frequency values. Lipoprotein concentrations were measured after a 12-hour overnight fast. For each subject, the number of close relatives (ie, parents, siblings, grandparents, aunts, and uncles) with non–insulin-dependent diabetes, coronary artery disease, and hypertension was extracted from a family history questionnaire. No attempt was made to independently verify this information.

Measurement of Insulin Sensitivity and Glucose Utilization

Subjects were admitted to the Clinical Research Center at the Medical College of Wisconsin for a frequently sampled intravenous glucose tolerance test with intravenous tolbutamide. Three days before the test, they were placed on a weight-maintaining diet containing at least 150 g carbohydrate. Alcohol was not permitted during this time. Following a 12-hour fast, during which time no smoking was permitted, intravenous catheters were inserted in both arms. Three baseline samples were taken for determination of serum insulin and plasma glucose at −20, −15, and −10 minutes. At time zero, 0.3 gm/kg 50% glucose was injected over 1 minute. Blood was taken from the contralateral arm at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 minutes. At 20 minutes, 300 mg tolbutamide diluted in 10 mL sterile water was injected over 20 seconds. For adolescents younger than 17 years, the dose of tolbutamide was 5 mg/kg, to a maximum dose of 300 mg, and the test was terminated at the 90-minute specimen. Each blood sample was centrifuged and stored at −20°C.

Analysis of glucose and insulin values was performed by the modified minimal modeling method of Bergman et al.[24] The model assumes that injected glucose is distributed rapidly into a single compartment and that plasma glucose decreases by two components: a component that is independent of the incremental insulin response, and a second component that is dependent on insulin. The glucose effectiveness index (S_G) is a measure of the effect of glucose to enhance its own disappearance at basal insulin, and the insulin sensitivity index (S_I) is a measure of the ability of insulin to diminish endogenous glucose production and to augment glucose utilization.[25] First-phase insulin response (AIR_G) was calculated by the trapezoid method as the area under the incremental insulin curve from 0 to 10 minutes after administration of intravenous glucose. The area under the absolute glucose curve was also determined by the trapezoid method. In instances in which the tolerance test was terminated before the 180-minute sample either because of the age of the subject or because of hypoglycemia, values were extrapolated to 180 minutes. The peak glucose concentration was the highest glucose level recorded during the intravenous glucose tolerance test, and was invariably within 10 minutes of administration of intravenous glucose.

Laboratory Procedures

Fasting lipoproteins were separated by sequential flotation ultracentrifugation into very–low-density lipoprotein (VLDL) ($d < 1.006$ g/mL), LDL ($d = 1.006$ to 1.063 g/mL), and high-density lipoprotein ($d > 1.063$ g/mL) as described by Schumaker and Puppione.[26] Cholesterol level was measured using a commercial kit (Boehringer, Mannheim, Germany). Interassay and intraassay coefficients of variation for cholesterol measurement were 3.8% and 3.2%, respectively. Triglyceride level was measured using a commercial kit (Stanbio Laboratory, San Antonio, TX) with interassay and intraassay coefficients of variation of 3.2% and 2%, respectively. Plasma glucose was assayed enzymatically using a Beckman Glucose Analyzer 2 (Beckman, Fullerton, CA). The interassay coefficient of variation for glucose measurement was 5.4% and intraassay coefficient of variation 1.3%. Insulin level was measured by radioimmunoassay using a commercial kit (Incstar, Stillwater, MN). Interassay and intraassay coefficients of variation for insulin measurement were 5.4% and 5.8%, respectively.

Data Analysis and Statistics

Offspring and controls were compared using a 2 × 2 factorial ANOVA. The factors were age group, and offspring versus controls. Comparison of means adjusted for BMI or waist to hip ratio used an analysis of covariance within the same 2 × 2 factorial structure.[27] Statistical analyses were performed using the Minitab statistical package (Minitab, State College, PA). Values recorded are the mean ± SEM.

RESULTS

Comparison Between Offspring and Controls in Characteristics, Lipoprotein Concentrations, and Family History

Characteristics and fasting lipid values of offspring and controls are shown in Table 1. Offspring were similar to controls in terms of age, BMI, waist to hip ratio, systolic blood pressure, triglyceride, VLDL cholesterol, VLDL triglyceride, and HDL cholesterol, but offspring had significantly higher diastolic blood pressure (80.5 ± 1.6 *v* 73.8 ± 1.9 mm Hg, $P < .01$) and LDL cholesterol (98.9 ± 3.5 *v* 84.7 ± 3.8 mg/dL, $P < .01$).

Analyzed by age group, younger offspring were similar to controls in terms of BMI, waist to hip ratio, systolic blood pressure, fasting triglyceride, VLDL cholesterol, VLDL triglyceride, and HDL cholesterol, but offspring had significantly higher diastolic blood pressure (73.6 ± 3.0 *v* 67.4 ± 2.6 mm Hg, $P < .05$) and LDL cholesterol (93.9 ± 6.7 *v* 81.2 ± 4.2 mg/dL, $P < .05$). Older offspring were similar to controls in terms of BMI, diastolic blood pressure, systolic blood pressure, triglyceride, VLDL cholesterol, VLDL triglyceride, and HDL cholesterol, but had a significantly higher waist to hip ratio (0.937 ± 0.008 *v* 0.913 ± 0.014, $P < .05$) and LDL cholesterol (101.3 ± 4.2 *v* 88.0 ± 6.4 mg/dL, $P < .05$).

Comparisons were also made between younger and older offspring and younger and older controls. There were significant differences between younger and older offspring in terms of

Table 1. Characteristics and Fasting Lipoprotein Concentrations of Offspring and Controls

Characteristic	All Offspring	All Controls	Younger Offspring	Younger Controls	Older Offspring	Older Controls
No. of subjects	61	39	20	19	41	20
Age (yr)	32.7 ± 1.1	30.5 ± 1.5	21.9 ± 1.0‖	22.0 ± 0.9‖	38.6 ± 0.7‖	38.3 ± 1.0‖
BMI (kg/m^2)	25.5 ± 0.5	24.7 ± 0.5	23.4 ± 0.7§	23.3 ± 0.5§	26.6 ± 0.5§	26.0 ± 0.8§
Waist to hip ratio	0.907 ± 0.009	0.889 ± 0.010	0.845 ± 0.011‖	0.864 ± 0.014§	0.937 ± 0.008*‖	0.913 ± 0.014*§
Diastolic BP (mm Hg)	80.5 ± 1.6†	73.8 ± 1.9†	73.6 ± 3.0*§	67.4 ± 2.6*§	83.9 ± 1.6§	79.9 ± 2.1§
Systolic BP (mm Hg)	127.4 ± 1.9	126.3 ± 1.9	125.6 ± 3.4	127.8 ± 2.6	128.2 ± 2.3	124.8 ± 2.7
LDL cholesterol (mg/dL)	98.9 ± 3.5†	84.7 ± 3.8†	93.9 ± 6.7*	81.2 ± 4.2*	101.3 ± 4.2*	88.0 ± 6.4*
Triglyceride (mg/dL)	112.1 ± 8.6	102.5 ± 8.8	82.9 ± 15.8‡	99.4 ± 8.3	126.7 ± 9.6‡	105.4 ± 15.6
VLDL cholesterol (mg/dL)	22.3 ± 1.8	18.3 ± 1.8	15.8 ± 1.8‡	14.3 ± 1.6‡	25.4 ± 2.4‡	22.0 ± 3.0‡
VLDL triglyceride (mg/dL)	63.6 ± 5.7	60.7 ± 6.6	53.6 ± 13.1	55.4 ± 5.8	68.5 ± 5.6	65.7 ± 11.8
HDL cholesterol (mg/dL)	45.6 ± 1.4	46.5 ± 2.3	46.9 ± 2.5	42.8 ± 2.5‡	45.0 ± 1.7	49.9 ± 3.7‡

NOTE. Younger subjects were aged 15 to 30 years and older subjects 31 to 45 years. Results are the mean ± SEM. Comparisons were made between each group of offspring and the aged-matched control group.

*$P < .05$.

†$P < .01$.

‡$P < .05$, §$P < .01$, ‖$P < .001$: younger *v* older offspring and younger *v* older controls.

BMI (23.4 ± 0.7 *v* 26.6 ± 0.5 kg/m^2, $P < .01$), waist to hip ratio (0.845 ± 0.011 *v* 0.937 ± 0.008, $P < .001$), diastolic blood pressure (73.6 ± 3.0 *v* 83.9 ± 1.6 mm Hg, $P < .01$), triglyceride concentration (82.9 ± 15.8 *v* 126.7 ± 9.6 mg/dL, $P < .05$), and VLDL cholesterol concentration (15.8 ± 1.8 *v* 25.4 ± 2.4 mg/dL, $P < .05$). There were also significant differences between younger and older controls in terms of BMI (23.3 ± 0.5 *v* 26.0 ± 0.8 kg/m^2, $P < .01$), waist to hip ratio (0.864 ± 0.014 *v* 0.913 ± 0.014, $P < .01$), diastolic blood pressure (67.4 ± 2.6 *v* 79.9 ± 2.1 mm Hg, $P < .01$), VLDL cholesterol (14.3 ± 1.6 *v* 22.0 ± 3.0 mg/dL, $P < .05$), and HDL cholesterol (42.8 ± 2.5 *v* 49.9 ± 3.7 mg/dL, $P < .05$).

Offspring and controls were on similar diets (Table 2). There were also no differences in the number of alcoholic drinks taken per day and number of smokers in each group. However, differences were apparent when comparisons were made by age group. Compared with controls, younger offspring were eating significantly less total fat (28.8% ± 1.5% *v* 32.2% ± 1.5% of total calories, $P < .05$), less protein (15.3% ± 0.6% *v* 17.3% ± 0.5% of total calories, $P < .05$), less cholesterol (286.6 ± 19.8 *v* 413.4 ± 33.2 mg/d, $P < .01$), and more total carbohydrate (54.2% ± 2.1% *v* 50.1% ± 1.7% of total calories, $P < .05$). Older offspring were eating less simple carbohydrate than their controls (18.4% ± 1.1% *v* 24.2% ± 1.5%, $P < .05$), but ate more cholesterol (326.2 ± 24.1 *v* 267.1 ± 28.4 mg/d, $P < .05$) and had more alcoholic drinks per day (4.5 ± 0.8 *v* 2.5 ± 0.8, $P < .05$). The diet of younger offspring was also different from that of older offspring in terms of total fat (28.8% ± 1.5% *v* 33.3% ± 1.0% of total calories, $P < .05$), simple carbohydrate (24.7% ± 1.7% *v* 18.4% ± 1.1% of total calories, $P < .01$), and alcohol consumed (2.1 ± 0.8 *v* 4.5 ± 0.8 alcoholic drinks per day, $P < .05$).

The offspring had a significantly increased number of close family members (siblings, parents, grandparents, aunts, and uncles) with non–insulin-dependent diabetes ($P < .01$), hypertension ($P < .01$), and coronary artery disease ($P < .001$) (Fig 1). Seven of 61 offspring (11.5%) had a parent with non–insulin-dependent diabetes, but none of the controls. This had developed at least 1 year after diagnosis of the parent's coronary disease, often many years after. Twenty-three offspring (37.7%) had at least one grandparent with the diagnosis of non–insulin-dependent diabetes, compared with five controls (12.2%).

Table 2. Dietary Composition, Alcohol Intake, and Number of Smokers for Offspring and Controls

Parameter	All Offspring	All Controls	Younger Offspring	Younger Controls	Older Offspring	Older Controls
No. of subjects	61	39	20	19	41	20
Fat (%)	31.8 ± 0.8	32.1 ± 1.1	28.8 ± 1.5*‡	32.2 ± 1.5*	33.3 ± 1.0‡	32.0 ± 1.6
Saturated fat (%)	10.9 ± 0.4	11.0 ± 0.5	10.7 ± 0.8	11.5 ± 0.8	11.1 ± 0.4	10.5 ± 0.8
Carbohydrate (%)	51.3 ± 1.0	50.9 ± 1.2	54.2 ± 2.1*	50.1 ± 1.7*	49.9 ± 1.1	51.7 ± 1.7
Simple carbohydrate (%)	20.4 ± 1.0	23.0 ± 1.2	24.7 ± 1.7§	21.7 ± 1.9	18.4 ± 1.1†§	24.2 ± 1.5†
Complex carbohydrate (%)	28.8 ± 1.1	28.3 ± 1.0	29.6 ± 1.9	28.4 ± 1.6	28.4 ± 1.4	28.2 ± 1.2
Protein (%)	15.7 ± 0.4	16.7 ± 0.5	15.3 ± 0.6*	17.3 ± 0.5*	15.9 ± 0.5	16.2 ± 0.8
Fiber (g/d)	22.6 ± 1.3	21.2 ± 1.2	19.4 ± 1.7‡	21.0 ± 2.2	24.1 ± 1.8‡	21.4 ± 1.3
Cholesterol (mg/d)	313.2 ± 17.5	338.4 ± 25.0	286.6 ± 19.8†	413.4 ± 33.2†§	326.2 ± 24.1*	267.1 ± 28.4*§
Alcoholic drinks per day (n)	3.7 ± 0.6	2.6 ± 0.5	2.1 ± 0.8‡	2.6 ± 0.8	4.5 ± 0.8*‡	2.5 ± 0.8*
Smokers (n)	0.15 ± 0.05	0.13 ± 0.05	0.10 ± 0.07	0.11 ± 0.07	0.17 ± 0.06	0.15 ± 0.08

NOTE. Younger subjects were aged 15 to 30 years and older subjects 31 to 45 years. Results are the mean ± SEM. Comparisons were made between each group of offspring and the aged-matched control group.

*$P < .05$.

†$P < .01$.

‡$P < .05$, §$P < .01$: younger *v* older offspring and younger *v* older controls.

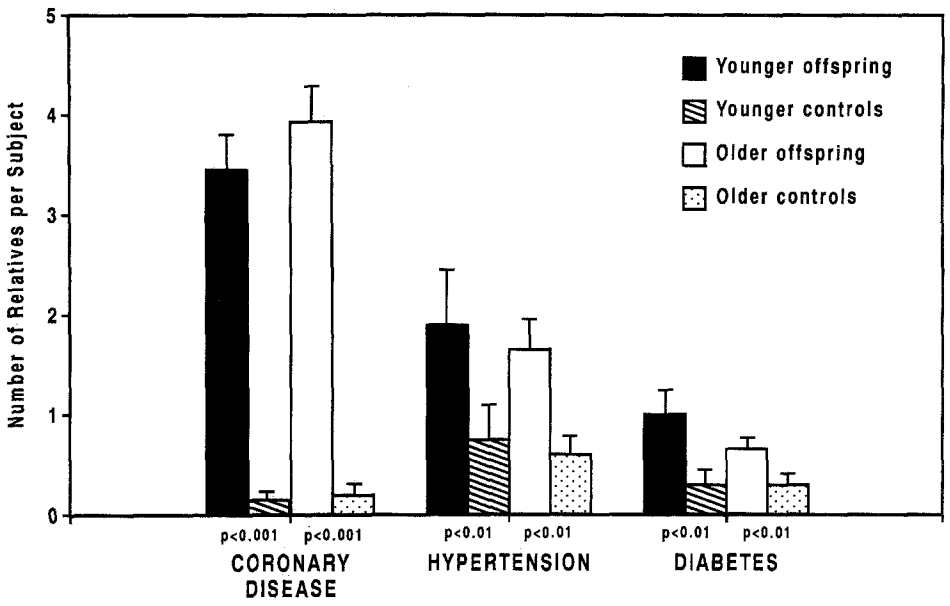

Fig 1. Number of close relatives per subject with coronary artery disease, hypertension, and non-insulin-dependent diabetes. Each subject was questioned about the number of parents, siblings, grandparents, uncles, and aunts with these conditions.

Twenty-eight offspring (46%) had a parent on treatment for hypertension, compared with seven controls (17.9%).

Comparison of Values From the Frequently Sampled Intravenous Glucose Tolerance Test and Modeling

Offspring and controls showed similar values for S_I (5.5 ± 0.4 *v* 6.0 ± 0.4, NS), S_G, AIR_G, fasting glucose, peak glucose, and area under the glucose curve (Table 3). The glucose and insulin curves are shown in Figs 2 and 3.

However, comparison of offspring and controls by age group showed significant differences. Younger offspring had values similar to control values for S_I (6.6 ± 0.9 *v* 6.2 ± 0.5 × 10^{-4} · min^{-1} · μU/mL), AIR_G, fasting glucose, and area under the glucose curve, but a significantly higher value for S_G (22.8 ± 2.3 *v* 16.8 ± 2.3 × 10^{-3} · min^{-1}, $P < .05$) and significantly lower peak glucose concentrations (232.7 ± 7.8 *v* 260.9 ± 10.7 mg/dL, $P < .05$). Older offspring had values similar to control values for S_I (5.0 ± 0.4 *v* 5.8 ± 0.7, NS), S_G, AIR_G, and fasting glucose, but a significantly increased area under the glucose curve (18,250 ± 322 *v* 17,225 ± 347 mg/dL · min, $P < .05$) and peak glucose concentration (287.5 ± 9.3 *v* 252.0 ± 14.2 mg/dL, $P < .05$). The difference in area under the glucose curve remained significant after correcting for BMI and waist to hip ratio (18,035 ± 322 mg/dL · min in older offspring *v* 17,134 ± 347 in controls, $P < .05$).

Comparing younger and older offspring, younger offspring had significantly higher values for S_I (6.6 ± 0.9 *v* 5.0 ± 0.4 × 10^{-4} · min^{-1} · μU/mL, $P < .05$) and S_G (22.8 ± 2.3 *v* 18.6 ± 1.0 × 10^{-3} · min^{-1}, $P < .05$), and lower values for area under the glucose curve (17,016 ± 451 *v* 18,250 ± 322 mg/dL · min, $P < .05$) and peak glucose concentration (232.7 ± 7.8 *v* 287.5 ± 9.3 mg/dL, $P < .01$). The difference in S_I between younger and older offspring was no longer significant after adjusting for BMI and waist to hip ratio (5.9 ± 0.9 *v* 5.5 ± 0.4 × 10^{-3} · min^{-1}, NS).

DISCUSSION

We were unable to demonstrate a decrease in insulin sensitivity in the male offspring of parents with early coronary artery disease. This study therefore provides no support to the notion that decreased insulin sensitivity is an early atherogenic risk factor in offspring at risk for coronary disease because of their family history.

How can one reconcile the results from our study with equally good evidence that insulin sensitivity is decreased in coronary disease survivors? A possible solution relates to

Table 3. Insulin and Glucose Kinetic Parameters and Glucose Levels Derived From the Frequently Sampled Intravenous Glucose Tolerance Test

Parameter	All Offspring	All Controls	Younger Offspring	Younger Controls	Older Offspring	Older Controls
No. of subjects	61	39	20	19	41	20
S_I (×10^{-4} · min^{-1} · μU/mL)	5.5 ± 0.4	6.0 ± 0.4	6.6 ± 0.9†	6.2 ± 0.5	5.0 ± 0.4†	5.8 ± 0.7
S_G (×10^{-3} · min^{-1})	20.0 ± 1.0	18.1 ± 1.4	22.8 ± 2.3*†	16.8 ± 2.3*	18.6 ± 1.0†	19.5 ± 1.6
AIR_G (μU/mL · min)	360.5 ± 36.7	339.3 ± 43.0	379.6 ± 72.5	275.1 ± 26.8	351.2 ± 42.3	400.2 ± 78.7
Area under the glucose curve (mg/dL · min)	17,845 ± 272	17,429 ± 243	17,016 ± 451†	17,644 ± 308	18,250 ± 322*†	17,225 ± 347*
Fasting glucose (mg/dL)	89.2 ± 1.0	88.3 ± 1.1	84.5 ± 1.5	85.9 ± 1.4†	91.5 ± 1.1	90.8 ± 1.4†
Peak glucose (mg/dL)	269.5 ± 58.8	256.3 ± 8.8	232.7 ± 7.8*‡	260.9 ± 10.7*	287.5 ± 9.3*‡	252.0 ± 14.2*

NOTE. Results are the mean ± SEM. Comparisons were made between each group of offspring and the aged-matched control group.

*$P < .05$.

†$P < .05$, ‡$P < .01$: younger *v* older offspring and younger *v* older controls.

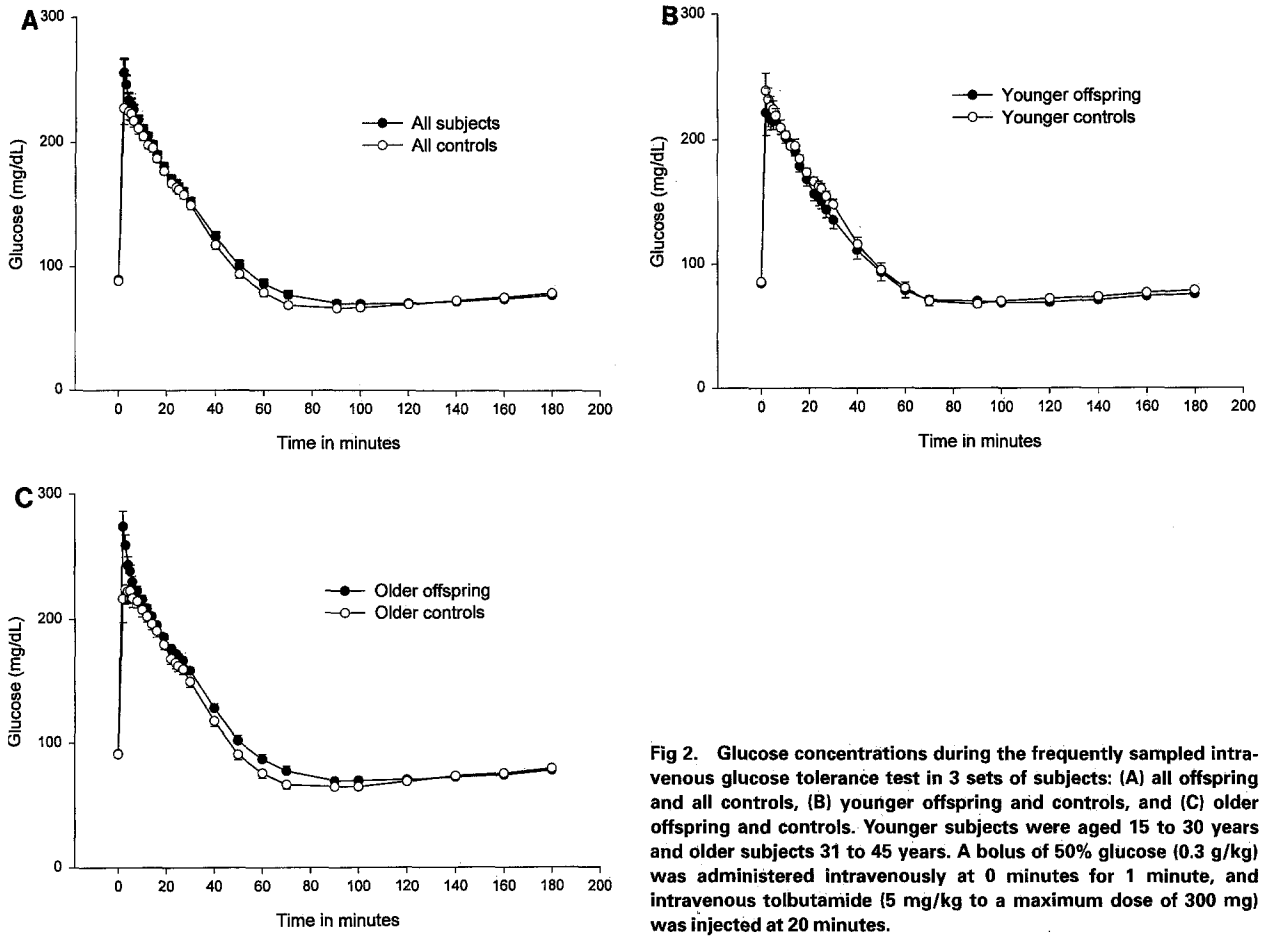

Fig 2. Glucose concentrations during the frequently sampled intravenous glucose tolerance test in 3 sets of subjects: (A) all offspring and all controls, (B) younger offspring and controls, and (C) older offspring and controls. Younger subjects were aged 15 to 30 years and older subjects 31 to 45 years. A bolus of 50% glucose (0.3 g/kg) was administered intravenously at 0 minutes for 1 minute, and intravenous tolbutamide (5 mg/kg to a maximum dose of 300 mg) was injected at 20 minutes.

visceral fat accumulation. Patients with coronary disease have a greater amount of visceral fat than controls, and this is true even in the non-obese.[28] In men undergoing coronary angiography, an increased waist to hip ratio is a significant indicator for risk of coronary artery disease.[29] In prospective studies, there is a strong association between the ratio of abdominal to subcutaneous thigh fat and the 12- and 13-year incidence of myocardial infarction, angina pectoris, stroke, and death.[30,31] Intraabdominal fat is also a strong determinant of hyperinsulinemia and insulin resistance.[32-35] It is therefore likely that in the main, hyperinsulinemia and insulin resistance are not primary abnormalities, but secondary phenomena related to the accumulation of adipose tissue, in particular adipose tissue surrounding the omentum and viscera.[36-38] Furthermore, because the accumulation of visceral fat is age-related,[39-41] it may take many years for the fullest expression of the "visceral fat syndrome" to develop.[42]

Of relevance to this issue is the role of insulin sensitivity in non–insulin-dependent diabetes and essential hypertension. Both conditions are associated with increased coronary risk and frequently cluster together with visceral obesity.[43,44] Decreased insulin sensitivity has been noted in a number of studies of first-degree relatives and offspring of non–insulin-dependent diabetics.[45-53] However, reduced insulin sensitivity has not been a uniform finding, and some investigators have found abnormal β-cell function, not reduced insulin sensitivity, to be the major abnormality in potentially prediabetic offspring.[54-58] Others suggest that the primary defect in non–insulin-dependent diabetes involves the interrelationship between insulin sensitivity and β-cell function.[59-62] However, it should be noted that non–insulin-dependent diabetes is frequently associated with increased visceral fat,[63-66] and the insulin resistance of the prediabetic state may well be inseparable from the effects of body fat.

The presence of insulin resistance independent of body weight or visceral fat seems much clearer for hypertension. Several studies have demonstrated decreased insulin sensitivity in relatives of hypertensives, the majority of whom were non-obese.[67-74] Alleman et al[73] found normal body fat distribution in addition to decreased insulin sensitivity in lean offspring of hypertensive parents. However, body fat distribution was assessed by means of dual-energy x-ray absorptiometry, which provides a measure of upper- and lower-body fat rather than absolute visceral fat. Nevertheless, in total, these studies suggest that reduced insulin sensitivity is an early primary abnormality in prehypertensives.

A significant abnormality detected in our older offspring was an increase in area under the glucose curve. Similar findings were obtained by Abel and Ledingham[74] in newly diagnosed nondiabetic hypertensives. In their study, the decrease in glucose tolerance was related to impaired insulin release. Insulin release was quantified by kinetic parameters derived from the minimal model, and a reduction in second-phase β-cell responsivity was demonstrated. By contrast, we found no abnormality in insulin secretion in our offspring.

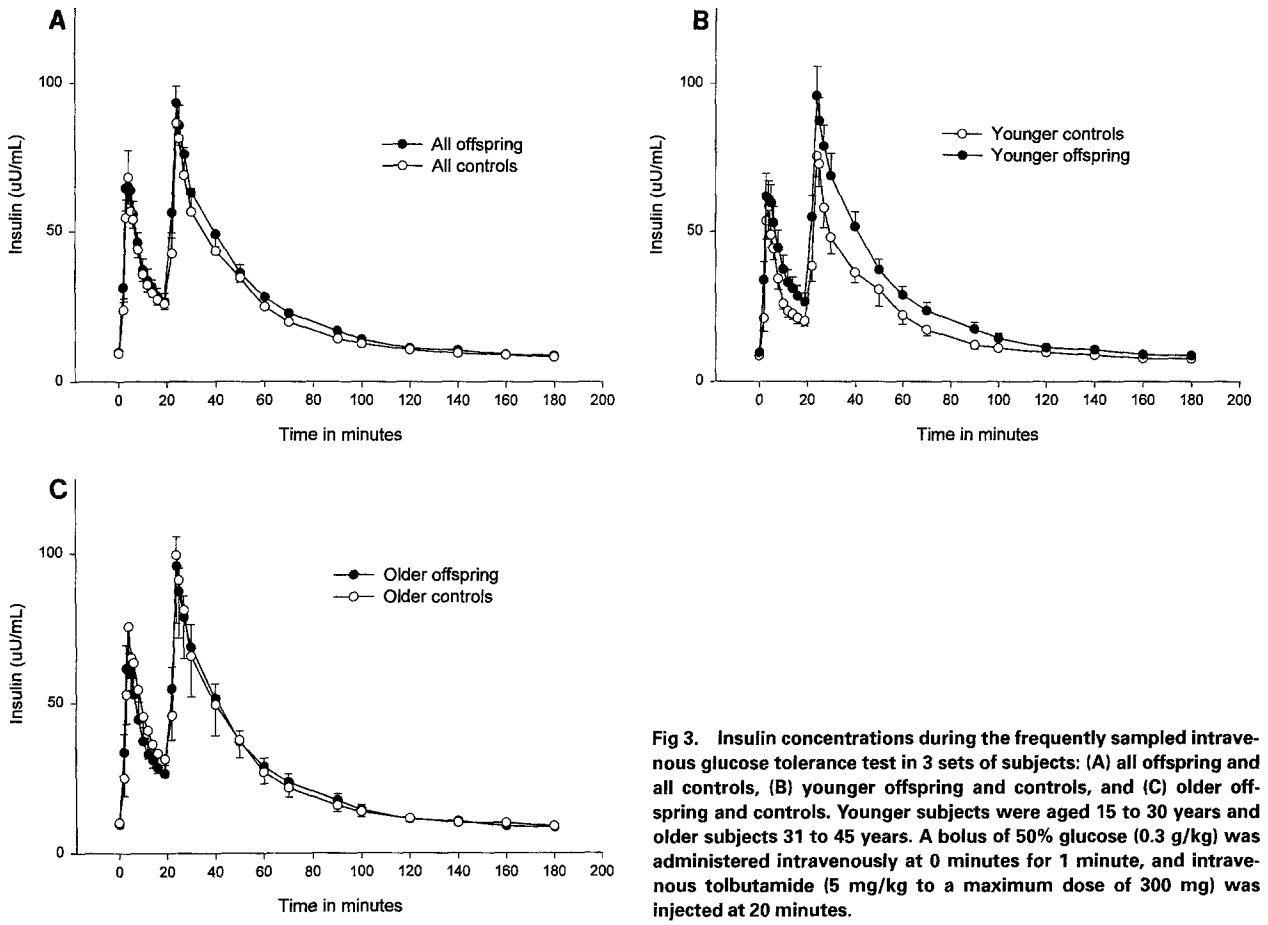

Fig 3. Insulin concentrations during the frequently sampled intravenous glucose tolerance test in 3 sets of subjects: (A) all offspring and all controls, (B) younger offspring and controls, and (C) older offspring and controls. Younger subjects were aged 15 to 30 years and older subjects 31 to 45 years. A bolus of 50% glucose (0.3 g/kg) was administered intravenously at 0 minutes for 1 minute, and intravenous tolbutamide (5 mg/kg to a maximum dose of 300 mg) was injected at 20 minutes.

It should be noted that an increased waist to hip ratio was present in our older offspring, suggesting the presence of increased visceral fat. An association between increased visceral fat and decreased glucose tolerance is now well established.[75-78] However, the increase in area under the glucose curve in our study remained significant after correcting for BMI and waist to hip ratio, suggesting that this increase was unrelated to body fat or body fat distribution. It would appear therefore that an increase in area under the glucose curve after a bolus of intravenous glucose is a significant maturational abnormality in the offspring of parents with early coronary artery disease.

Another abnormality noted, exclusive to the younger offspring, was an enhanced S_G. S_G is a measure of the effect of glucose to enhance its own disappearance at basal insulin levels.[25] An increase in S_G has been noted once previously in an offspring study by Henriksen et al[53] in first-degree relatives of non–insulin-dependent diabetic patients (mean age, 29.4 years). However, in their study, offspring had reduced insulin sensitivity, and it was postulated that the increased S_G represented a compensatory mechanism to preserve normal glucose tolerance. It is possible that some form of compensatory mechanism accounts for the increased S_G in our study. Alternatively, although we believe it to be a less likely possibility, the increased S_G may be the result of extrinsic factors. We found that younger offspring were poorly matched to controls in terms of diet, in that the offspring were consuming significantly less fat and protein and more carbohydrate than controls. However, to our knowledge, increased insulin-independent fractional glucose disappearance has not been described in the context of high-carbohydrate diets.

We also found that younger offspring were significantly more insulin-sensitive than older offspring. However, after correcting for BMI and waist to hip ratio, this difference was no longer apparent, suggesting an effect of adiposity. Using the minimal modeling method in healthy non-obese males aged 60 to 80 years and subjects aged 23 to 29 years, Pacini et al[79] found that age had no effect on insulin sensitivity or β-cell activity. However, this is not the consensus, and it is generally accepted that aging is associated with a decrease in insulin sensitivity, probably on the basis of a postreceptor defect.[80-84] Fink et al[84] found similar insulin sensitivity in subjects aged 20 to 39 and 40 to 59 years but decreased insulin sensitivity in subjects over the age of 60, suggesting that decreased insulin sensitivity is confined to the very old. By contrast, our data suggest that age has an effect on insulin sensitivity in early adulthood and middle age.

In conclusion, our results failed to support the hypothesis that insulin resistance is an early abnormality in the offspring of parents with coronary artery disease. This study therefore provides no support to the concept that insulin resistance is an early independent risk factor for atherogenesis. This accords with much prospective epidemiological data. However, we did demonstrate an enhanced insulin-independent glucose utiliza-

tion in the younger offspring and an increase in area under the glucose curve in older offspring. Younger offspring were also more insulin-sensitive than older offspring, an effect that seems related to increased adiposity.

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