Cardiac Geometry and Function in Diabetic or Prediabetic Adolescents and Young Adults

The Strong Heart Study

Marina De Marco, md[1]
Giovanni de Simone, md[1,2]
Mary J. Roman, md[2]
Marcello Chinali, md, phd[1]
Elisa T. Lee, phd[3]
Darren Calhoun, phd[4]
Barbara V. Howard, phd[4]
Richard B. Devereux, md[2]

OBJECTIVE—The aim of this study was to evaluate whether diabetes (DM) and impaired fasting glucose (IFG) were associated with early alterations in left ventricular geometry and function in a large population of adolescents and young adults independently of major confounders.

RESEARCH DESIGN AND METHODS—We analyzed echocardiographic data of 1,624 14- to 39-year-old participants (mean age 26.6 ± 7.7 years; 57% female) without prevalent cardiovascular disease from the fourth Strong Heart Study examination; 179 (11%) participants had DM and 299 (18%) had IFG.

RESULTS—Participants with DM and IFG were older and more often obese and hypertensive than participants with normal fasting glucose (NFG) (all $P < 0.05$). After adjustment for age, sex, systolic blood pressure, and body fat, diabetic and IFG participants had higher left ventricular mass index than those with NFG (41.5 ± 8.7 and 39.6 ± 9.2 vs. 35.6 ± 7.8 g/m$^{2.7}$) and reduced stress-corrected midwall shortening (98 ± 8.6 and 99 ± 7.5 vs. 101 ± 8.5%; all $P < 0.05$). The prevalence of left ventricular hypertrophy was higher in DM (20%) and IFG (17%) than in NFG participants (12%; $P < 0.05$). Compared with the other groups, DM was also associated with higher prevalence of inappropriate left ventricular mass, concentric geometry, and more diastolic abnormalities independently of covariates (all $P < 0.05$).

CONCLUSIONS—In a population of adolescents and young adults, DM is independently associated with early unfavorable cardiovascular phenotype characterized by increased left ventricular mass, concentric geometry, and early preclinical systolic and diastolic dysfunction; early cardiovascular alterations are also present in participants with prediabetes.

Diabetes Care 34:2300–2305, 2011

The prevalence of obesity and type 2 diabetes (DM) in youth has increased dramatically in the last decade, especially in minority populations (1,2). Early onset of type 2 DM is associated with increased risk of cardiovascular complications compared with usual onset of the disease (3). Part of the increased cardiovascular risk might be related to a direct adverse effect of DM on the heart, independently of coronary artery disease, that has been documented in adults (4–6). However, the impact of DM and prediabetes on cardiac geometry and function in youth has not been extensively characterized in large population-based samples. It is unknown whether in the youth there is an independent influence of DM on cardiovascular phenotype. Accordingly, the current study was undertaken to evaluate whether DM and prediabetes, as measured by impaired fasting glucose (IFG), are associated with cardiac alterations independently of major confounders in a population-based sample of adolescents and young adults.

RESEARCH DESIGN AND METHODS

The Strong Heart Study (SHS) is a longitudinal population-based survey of cardiovascular risk factors and disease in American Indians from 13 communities in Arizona, Oklahoma, and South and North Dakota (7). The fourth SHS examination, conducted between 2001 and 2003, enrolled members of large three-generation families (the Strong Heart Family Study) (8,9) including 1,944 under 40 years old. During this examination, all participants underwent transthoracic Doppler echocardiography. For the purposes of the current study, 33 participants were excluded because of prevalent cardiovascular disease: 2 with history of heart failure, 11 with prevalent coronary artery disease, 6 with previous stroke, 1 who had underwent previous valve replacement, and 13 with echocardiographic evidence of significant valve disease (aortic or mitral stenosis or regurgitation more than mild). In addition, 287 participants were also excluded because of missing information on DM status. Accordingly, we analyzed data from 1,624 adolescents and young-adult participants (57% female; age range 14–39 years, mean age 26.6 ± 7.7 years) free of prevalent cardiovascular disease. Participants (or a parent or guardian in the case of minors) gave written informed consent under protocols approved by all participating communities and institutional review boards.

Physical examination and classification of participants

Clinical examinations, including a personal interview, physical exam, and morning blood sample collection after a 12-h fast, were performed at local community settings and Indian Health Service clinics by the study staff. A detailed description of the study design and methods of the SHS have previously been reported (4,7–9).

From the [1]Department of Clinical and Experimental Disease, Federico II University Hospital, Naples, Italy; the [2]Division of Cardiology, Weill Cornell Medical College, New York, New York; the [3]Department of Biostatistics and Epidemiology, University of Oklahoma, Oklahoma City, Oklahoma; and the [4]Medstar Health Research Institute, Hyattsville, Maryland.
Corresponding author: Giovanni de Simone, simogi@unina.it.
Received 30 January 2011 and accepted 13 July 2011.
DOI: 10.2337/dc11-0191

Percent body fat was estimated by bioelectric impedance analysis (model B14101; RJL Equipment, Detroit, MI). BMI-for-age charts, developed by the National Center for Health Statistics, were used in participants <18 years old. Obesity was defined by the 95th percentile of the normal distribution (9,10). Guideline correction was applied (9,11,12) so that all participants with BMI ≥30 kg/m^2 were considered obese. Waist circumference and waist-to-hip ratio (WHR) were used as indicators of central adiposity (12). Brachial blood pressure was measured three consecutive times on seated participants using appropriately sized cuffs. The mean of the last two measurements was used. Arterial hypertension was defined as follows: use of antihypertension medications; systolic or diastolic blood pressure above the 95th percentile of the normal distribution for age, sex, and height in participants younger than 18 years old (13); and blood pressure ≥140/90 mmHg (or ≥130/80 mmHg in the presence of DM) in participants ≥18 years old (14). DM was defined by fasting glucose ≥126 mg/dL or by use of insulin or oral hypoglycemic therapy. IFG was defined by fasting glucose between 100 and 125 mg/dL (15). In DM, good DM control was defined as HbA_{1c} <7% (15). Glomerular filtration rate (GFR) was estimated by the simplified Modification of Diet in Renal Disease formula (16). Urinary albumin excretion was measured on a single spot urine sample and was expressed in relation to grams of urinary creatinine (uAlb/Crea). Albuminuria was defined as uAlb/Crea ≥30 mg/g (15,16).

Echocardiographic measures

Echocardiograms were performed in all participants by expert sonographers according to standardized methods and reviewed offline by two independent readers (4,9) following the American Society of Echocardiography recommendations (17). Left ventricular mass (LVM) was calculated by a necropsy-validated formula (18) and was normalized to height in meters to the power of 2.7 (LVMi) (19). Left ventricular hypertrophy (LVH) was defined using previous reported age- and sex-specific partition values (LVMi >38.5 g/m$^{2.7}$ for female and >40.7 g/m$^{2.7}$ for male participants up to 20 years old; LVMi >46.7 g/m$^{2.7}$ for women and >49.2 g/m$^{2.7}$ for men over 20 years old, respectively) (9,19). Relative wall thickness (RWT) was calculated as myocardial thickness (posterior wall plus septum) divided by left ventricular internal dimension and normalized for age ($_a$RWT) (20). Concentric left ventricular geometry was defined as $_a$RWT >0.40 (20). Stroke volume (SV) was computed as the difference between end diastolic and end systolic volumes by the *z*-derived method (21) and was normalized to height to the power of 2.04 (22). Ejection fraction (EF) was obtained by the ratio of SV to end diastolic volume. The ratio between pulse pressure and SV (PP/SV) was used as a raw indicator of total arterial stiffness. Stroke work, a measure of cardiac workload, was calculated multiplying systolic blood pressure (pressure load) × SV (volume load) × 0.014 (23). To establish whether increased LVM was compensatory for increased cardiac workload or, instead, was inappropriately high, we calculated the individual theoretical ideal value of LVM (LVMp), using age-specific equations generated by stroke work, sex, and height to the power of 2.7 (9,23). The value of LVM directly measured from echocardiograms was divided by LVMp and expressed as percent of predicted value (Δ%LVM). Inappropriately high LVM was defined as Δ%LVM >109% up to age 20 years and Δ%LVM >128% above age 20 years (9,23). To generate estimates of left ventricular systolic function independent of myocardial afterload, we evaluated left ventricular minor axis fractional shortening (FS) at either endocardial or midwall levels in relation to circumferential end systolic stress (stress-corrected endocardial FS [sc-eFS] and stress-corrected midwall FS [sc-mFS]). Sc-mFS is a measure of wall mechanics that reflects myocardial contractility independently of left ventricular geometry, whereas EF and sc-eFS are more influenced by left ventricular geometry (24). Left ventricular diastolic function was assessed by Doppler interrogation of transmitral velocity at early (E) and late (A) left ventricular filling, their ratio, the deceleration time (DT) of early diastolic left ventricular filling, and the atrial filling fraction. Isovolumic relaxation time (IVRT), a raw index of active left ventricular relaxation, was measured between aortic valve closure and mitral valve opening. Doppler measurements were obtained offline from an average of several cardiac cycles. Heart rate was measured simultaneously (8).

Statistical analysis

Data were analyzed using SPSS 12.0 software (SPSS, Chicago, IL) and expressed as means ± 1 SD. Variables without normal distribution are presented as median and interquartile range, and their logarithmic values were used for parametric statistics. Indicator variables were included in all multivariate analyses for the three different field centers (Arizona and Oklahoma vs. North/South Dakota). ANOVA (with Ryan-Einot-Gabriel-Welsch *F* post hoc test), and χ^2 statistics were used for descriptive statistics. Differences between groups were, therefore, assessed by binary logistic regression analysis or ANCOVA, adjusting for significant confounders (with Sidak correction of main effects). The impact of relatedness was considered by using standard kinship coefficients (0.25 for parent/offspring, 0.25 for full siblings, 0.125 for half siblings, and 0 for no consanguinity). In multiple linear regression analysis of echocardiographic parameters of left ventricular geometry and function, kinship coefficient was first entered together with filed center, age, and sex. In a second block, we included a stepwise selection of the following variables: systolic blood pressure, heart rate, percentage of body fat, HDL and LDL cholesterol, triglycerides, GFR, uAlb/Crea, and antihypertensive treatment with renin-angiotensin system antagonists (anti-RAS), including ACE inhibitors or AT1 receptor antagonists. DM status was, therefore, forced into the model to verify whether an independent effect remained on left ventricular geometry or function. Finally, in the last block, fasting plasma glucose was also forced into the model. Attention was paid to avoid substantial multicollinearity by setting the greatest tolerable variance inflation factor to 2.5. Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and metabolic characteristics

Among the 1,624 adolescents and young-adult participants without reported prevalent cardiovascular disease, 1,146 (71%) had NFG, 299 (18%) had IFG, and 179 (11%) had DM. Sixty-six percent were obese, and 19% had arterial hypertension.

Mean reported duration of DM was 4.7 years. Insulin treatment was reported in 43 DM participants (24%), while 95 participants (53%) were on oral antidiabetic therapy.

Table 1 shows that age, BMI, body fat, waist girth, and WHR progressively increased from NFG to DM. IFG and DM participants had similar prevalence of obesity and mean values of blood pressure, both of which were significantly higher than NFG. Prevalence of arterial

Table 1—*Clinical, anthropometric, and metabolic characteristics of participants with NFG, IFG, or DM*

	NFG	IFG	DM	*P*
N	1,146	299	179	
Age (years)	25.3 ± 7.4	28.6 ± 7.7*	32.1 ± 5.9*†	≤0.0001
Sex (% women)	60	47*	58†	≤0.0001
BMI (kg/m^2)	30.6 ± 8.0	35.9 ± 8.6*	38.1 ± 10.2*†	≤0.0001
Body fat (%)	36 ± 11	40 ± 11*	43 ± 9*†	≤0.0001
Waist circumference (cm)	98 ± 18	112 ± 19*	117 ± 19*†	≤0.0001
WHR	0.88 ± 0.08	0.92 ± 0.07*	0.95 ± 0.08*†	≤0.0001
Obesity (%)	61	78*	83*	≤0.0001
Systolic blood pressure (mmHg)	116 ± 12	121 ± 13*	122 ± 18*	≤0.0001
Diastolic blood pressure (mmHg)	73 ± 11	79 ± 11*	80 ± 11*	≤0.0001
Arterial hypertension (%)	11	25*	65*†	≤0.0001
Antihypertensive therapy (%)	2	6*	25*†	≤0.0001
Heart rate (bpm)	66 ± 11	67 ± 11	74 ± 12*†	≤0.0001
Smokers (%)	35	37	39	=0.441
Fasting glucose (mg/dL)	89 (84–94)	105 (102–112)*	182 (137–280)*†	≤0.0001
Triglycerides (mg/dL)	111 (82–158)	142 (103–197)*	196 (145–295)*†	≤0.0001
LDL cholesterol (mg/dL)	93 ± 27	98 ± 29*	109 ± 33*†	≤0.0001
HDL cholesterol (mg/dL)	51 ± 13	48 ± 13*	46 ± 13*	≤0.0001
Plasma creatinine (mg/dL)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.6(0.6–0.8)*†	≤0.0001
GFR (mL/min/1.73 m^2)	109 ± 23	109 ± 23	129 ± 34*†	≤0.0001
uAlb/Crea (mg/g)	6 (4–11)	7 (4–13)	17 (9–62)*†	≤0.0001
Albuminuria (%)	8	12*	41*†	≤0.0001

Data are means ± 1 SD or median (interquartile range) unless otherwise indicated. *P* for ANOVA, Ryan-Einot-Gabriel-Welsch *F* post hoc analysis. *$P < 0.05$ vs. NFG. †$P < 0.05$ vs. IFG.

hypertension and antihypertensive treatment progressively increased from NFG to DM. Participants with DM had a higher heart rate than the other groups (all $P < 0.05$). Prevalence of smokers was similar between groups. Fasting glucose, triglycerides, and LDL cholesterol progressively increased from NFG to DM, whereas participants with IFG and DM had lower HDL cholesterol compared with those with NFG. Participants with DM had significantly lower plasma creatinine and significantly higher GFR, uAlb/Crea, and albuminuria compared with the other groups (all $P < 0.0001$).

Cardiovascular phenotype

Left ventricular geometry. Table 2 shows comparisons of echocardiographic parameters by univariate and multivariate analyses. After adjustment for age, sex, kinship coefficient, field center, systolic blood pressure, and percent of body fat, there was no significant between-group difference in left atrial dimension or left ventricular chamber diameter. Participants with DM had higher $_a$RWT than both IFG and NFG participants independently of covariates. Concentric left ventricular geometry was more prevalent in participants with DM (7.3 vs. 3.7% NFG and 3.1% IFG; $P = 0.03$). After adjustment for covariates, odds of concentric left ventricular geometry were significantly greater in participants with, compared with those without, DM (odds ratio [OR] 2.15 [95% CI 1.06–4.36], $P = 0.03$). Table 2 shows that absolute and indexed values of LVM were progressively higher in participants with IFG or DM than in those with NFG independently of differences in potential confounders. The prevalence of clear-cut LVH was 17% in IFG and 20% in DM participants, both significantly higher compared with 12% in NFG participants ($P < 0.05$). The prevalence of LVM exceeding the individual age-specific value predicted by stroke work, sex, and height to the power of 2.7 (inappropriate LVM) was higher (25%) in participants with DM than in those without DM (13% in NFG and 17% in IFG participants; OR 1.63 [1.08–2.44], $P = 0.02$).

Left ventricular systolic and diastolic function and systemic hemodynamics. As shown in Table 2, after adjustment for age, sex, kinship coefficient, field center, systolic blood pressure, and percent of body fat, no significant differences were found for stroke index or PP/SV. EF was lower in participants with IFG, due to their greater wall stress, as shown by the normal sc-eFS. In contrast, sc-mFS (an afterload geometry-independent myocardial function parameter) was significantly lower in participants with DM and IFG than in NGT (all adjusted $P < 0.05$). All Doppler parameters of diastolic function differed significantly among groups in univariate analysis, showing a trend to abnormal relaxation associated with worsening of glycemic control (all $P < 0.05$). After adjustment for covariates, however, no significant differences were detected for mitral E velocity or DT. Mitral A wave velocity was progressively higher from NFG to DM. Compared with the other groups, participants with DM had lower E-to-A ratio, higher IVRT, and greater atrial filling fraction. Differences in Doppler diastolic parameters were confirmed also adjusting for heart rate.

Differences in echocardiographic parameters were not substantially altered after further control for plasma creatinine, uAlb/Crea, anti-RAS treatment, and duration of DM in addition to age, sex, kinship coefficient, field center, systolic blood pressure, and percent of body fat. No significant differences were found between DM participants on oral therapy and those on insulin treatment. In addition, all results reported in Table 2 were also confirmed after the exclusion of the 43 DM participants on insulin treatment. Finally, we did not detect any significant differences in echocardiographic parameters between DM participants with versus without good glycemic control (HbA_{1c} <7%).

Independent correlates of left ventricular geometry and function. Multiple linear regression analyses were performed to evaluate independent correlates of left ventricular geometry and function in the whole population. Table 3 shows multiple *R* values and standardized β coefficients of variables significantly associated with the most relevant echocardiographic parameters. As shown in Table 3, greater body fat was independently related to increased left ventricular mass index and RWT, reduced sc-mFS, and prolonged left ventricular relaxation (lower E-to-A ratio and longer IVRT). Among metabolic parameters, low HDL cholesterol was associated with increased LVMi and RWT and decreased sc-mFS, while high LDL was related to low E-to-A ratio. GFR was related to increased LVMi, RWT, and EF. Albuminuria was significantly related to

Table 2—*Left ventricular geometry and function in participants with NFG, IFG, or DM*

	NFG	IFG	DM	*P*	Adjusted *P*
N	1,146	299	179		
LA diameter (cm)	3.5 ± 0.4	3.7 ± 0.4	3.8 ± 0.4	≤0.0001	≤0.776
Left ventricular diameter (cm)	5.4 ± 0.4	5.4 ± 0.4	5.4 ± 0.5	≤0.0001	≤0.261
aRWT	0.31 ± 0.05	0.32 ± 0.04	0.34 ± 0.04*†	≤0.0001	≤0.003‡
Left ventricular mass (g)	145 ± 37	166 ± 41*	169 ± 43*	≤0.0001	≤0.009
Left ventricular mass index (g/m$^{2.7}$)	36 ± 8	39 ± 9*	41 ± 9*	≤0.0001	≤0.014
Stroke index (mL/m$^{2.04}$)	27 ± 4	28 ± 4	28 ± 4	≤0.001	≤0.919
PP/SV (mmHg/mL/beat)	0.55 ± 0.14	0.52 ± 0.14	0.52 ± 0.15	≤0.003	≤0.810§
EF (%)	62 ± 4	61 ± 4*	62 ± 4	≤0.001	≤0.022
sc-eFS (%)	99 ± 8	100 ± 8	100 ± 9	≤0.246	≤0.859§
sc-mFS (%)	101 ± 9	99 ± 8*	98 ± 9*	≤0.0001	≤0.003§
E velocity (cm/s)	92 ± 16	91 ± 16	89 ± 19	≤0.038	≤0.579
A velocity (cm/s)	54 ± 14	59 ± 14*	66 ± 16*†	≤0.0001	≤0.0001
E-to-A ratio	1.8 ± 0.5	1.6 ± 0.5	1.4 ± 0.4*†	≤0.0001	≤0.0001
Deceleration time (ms)	212 ± 36	219 ± 40	223 ± 38	≤0.0001	≤0.197
IVRT (ms)	76 ± 10	77 ± 11	81 ± 11*†	≤0.0001	≤0.012
Atrial filling fraction	0.24 ± 0.07	0.26 ± 0.07	0.31 ± 0.09*†	≤0.0001	≤0.0001

P for ANOVA. *P* adjusted by ANCOVA for age, sex, systolic blood pressure, body fat, field center, and kinship coefficients; Sidak post hoc analysis. **P* adjusted <0.05 vs. NFG. †*P* adjusted <0.05 vs. IFG. ‡Adjustment excluded age. §Adjustment excluded systolic blood pressure.

increased LVMi. No independent impact was detected for kinship coefficients, plasma triglycerides, or anti-RAS therapy (or total antihypertensive treatment). DM remained significantly associated with high left ventricular mass index, low EF, low sc-mFS, and prolonged IVRT, without significant correlation with RWT or E-to-A ratio (Table 3).

When fasting plasma glucose was forced into the model, a significant effect of DM remained only for LVMi ($\beta = 0.10$; $P < 0.05$), whereas high glucose was associated with low EF ($\beta = -0.13$; $P < 0.01$), low sc-mFS ($\beta = -0.10$; $P < 0.05$), and prolonged IVRT ($\beta = 0.12$; $P < 0.01$). In subanalyses performed selectively in participants without DM, high homeostasis model assessment index was independently related to high LVMi, increased RWT, and lower sc-mFS (all adjusted $P < 0.05$). In DM, HbA_{1c} and duration of DM were not independently related to left ventricular geometry and function.

Table 3—*Standardized β coefficients of multivariate correlates of left ventricular geometry and function*

	LVMi (g/m$^{2.7}$)	RWT	EF (%)	sc-mFS (%)	E-to-A ratio	IVRT (ms)
Age (years)	0.21*	0.23*	0.11*	−0.10*	−0.39*	0.27*
Sex (male vs. female)	0.22*	NS	−0.20*	−0.22*	NS	0.07†
Systolic blood pressure (mmHg)	0.19*	0.10*	NS	NS	−0.05†	NS
Heart rate (bpm)	−0.08‡	0.10*	−0.07†	−0.16*	−0.42*	−0.11*
Body fat (%)	0.38*	0.16*	NS	−0.14*	−0.08†	0.11‡
HDL cholesterol (mg/dL)	−0.08‡	−0.09†	NS	0.07‡	NS	NS
LDL cholesterol (mg/dL)	NS	NS	NS	NS	−0.06‡	0.08‡
Triglycerides (mg/dL)	NS	NS	NS	NS	NS	NS
GFR (mL/min/1.73 m^2)	0.10*	0.08‡	0.14*	NS	NS	NS
uAlb/Crea (mg/g)	0.08‡	NS	NS	NS	NS	NS
Anti-RAS therapy (yes vs. no)	NS	NS	NS	NS	NS	NS
DM (vs. NFG)	0.08‡	NS	−0.07†	−0.08‡	NS	0.08‡
Multiple *R*	0.55	0.40	0.28	0.32	0.66	0.37

Models adjusted also for field center and kinship coefficients. NS, not statistically significant (adjusted $P > 0.05$). †Adjusted $P < 0.05$. ‡Adjusted $P < 0.01$. *Adjusted $P < 0.0001$.

CONCLUSIONS—The increasing incidence of obesity and, subsequently, DM in youth in different countries represents a major public health concern because of the risk of cardiovascular complications (1,3). The current study provides the first comprehensive comparison of left ventricular structure and function between DM, prediabetic, and normoglycemic members of a large population-based sample of adolescents and young adults with high prevalence of obesity but free from prevalent cardiovascular disease. Our findings demonstrate that despite the young age, participants with DM exhibit features associated with increased cardiovascular risk, including LVH, concentric left ventricular geometry, and preclinical systolic and diastolic dysfunction. Moreover, participants with prediabetes (measured by IFG) also had a significantly higher prevalence of LVH than participants with NFG, reflecting important target organ damage already present at an early phase of alteration of glucose metabolism. This observation is important in view of the strong relation between LVH and adverse cardiovascular outcomes (25) and provides a strong rationale for targeting prevention strategies in this subpopulation. Although participants with DM and IFG were more often obese and hypertensive, these two conditions were not sufficient to explain the identified cardiovascular abnormalities associated with DM, which remained an independent correlate of increased left ventricular mass, reduced left ventricular systolic function, and abnormal left ventricular relaxation. Thus, our results suggest that DM augments the already demonstrated adverse impact of obesity and hypertension on cardiovascular phenotype in the young participants of the SHS (8,9). Accordingly, in DM, the level of increased LVM substantially exceeds the need to compensate for cardiac workload, resulting in a markedly higher prevalence of inappropriate LVM. This finding also reinforces the view that in DM, LVH may not only be a response to substantially increased hemodynamic load, related to obesity or hypertension, but may also reflect neurohormonal and metabolic stimuli to left ventricular growth.

Another characteristic of the emerging cardiovascular phenotype in DM in youth is the presence of geometry-related left ventricular functional alterations, also

identified in prediabetes. Early left ventricular systolic dysfunction, associated with DM and IFG, could be detected by sc-mFS but not by measures of left ventricular systolic function taken at the chamber level, substantially influenced by the abnormalities in left ventricular geometry, documented by the progressive increase in RWT (24). The slight reduction in EF found in IFG was not confirmed by sc-eFS, demonstrating an afterload mismatch (higher systolic blood pressure without adequate compensation in left ventricular geometry) in this subgroup. Abnormality in left ventricular filling, characterized by active, energy-consuming relaxation (low E-to-A ratio and prolonged IVRT), was also evident, independent of major covariates. These findings are particularly notable because these alterations might mediate, at least in part, the documented increased risk of heart failure associated with DM, also in the absence of myocardial infarction (6).

Thus, the cardiovascular phenotype emerging from our analysis is similar to that reported in the description of the so-called "diabetic cardiomyopathy" in elderly adults (4,5): increased left ventricular mass with tendency to concentric left ventricular geometry together with subtle systolic and diastolic dysfunction. We can hypothesize that several mechanisms related to DM (e.g., stress damage, interstitial accumulation of advanced glycated end products) might contribute to development and progression of these alterations. Exposure over time to high levels of insulin, related to increased central fat distribution, might also have an important pathophysiological role. Unfortunately, in this SHS cohort, HbA_{1c} was measured only in DM participants and could not be analyzed in the whole population. In the subanalyses performed in the DM participants, HbA_{1c} did not exhibit an independent impact. However, fasting plasma glucose could be used in the whole population as a surrogate of metabolic control of glucose homeostasis, providing a wider range of variability. Under this assumption, the final model of the multiple regression analysis strongly suggests that at least a part of the subtle left ventricular systolic and diastolic dysfunction detected in the young DM SHS participants is related to their metabolic control.

Despite their young age, DM participants exhibited dyslipidemia and kidney function alterations, including a tendency to glomerular hyperfiltration and early proteinuria. These metabolic alterations are independently associated with left ventricular geometry and function parameters and, thus, might also contribute to the adverse cardiovascular phenotype found in DM through mechanisms that might involve microvascular changes, inflammation, early atherosclerotic disease, and hormonal dysregulation.

Some limitations of this study merit consideration. Despite the high prevalence of obesity, the number of participants with DM is relatively small because of the young average age of this cohort. Incidence of DM, which requires a number of years of insulin resistance and resultant pancreatic overstimulation, peaks in the fourth decade of life in the SHS population (26). The SHS is a population of American Indians with high prevalence of obesity and DM that at the beginning of the study was greater than in the general U.S. population. However, results of the SHS are increasingly applicable to other populations of different ethnicities in which there are rising epidemics of obesity, DM, and other metabolic abnormalities (27).

American Indian participants of the SHS have been extensively documented to have high prevalence of obesity and type 2 DM, but we could not completely exclude possible misclassification of participants with type 1 DM and concomitant obesity because we did not measure antibodies or C-peptide levels. However, when we compared the 37 DM participants with reported insulin therapy with those without insulin treatment, we did not find any significant differences, and results of this study were all confirmed after exclusion of DM participants under insulin treatment.

In conclusion, we found that in a population-based cohort of adolescents and young adults, DM and IFG are associated with early signs of structural and functional left ventricular alterations. Early identification of myocardial manifestations of DM is of major importance because myocardial abnormalities predict cardiovascular disease. Further studies are warranted to elucidate pathophysiological mechanisms and to determine to what extent the early abnormalities we have identified in DM contribute to the risk of cardiovascular disease.

Acknowledgments—This work was supported by grants HL-41642, HL-41652, HL-41654, HL-65521, and M10-RR-0047-34 (GCRC) from the National Institutes of Health, Bethesda, MD. Views expressed in this article are those of the authors and do not necessarily reflect those of the Indian Health Service.

No potential conflicts of interest relevant to this article were reported.

M.D.M. conceived and designed the research project, was actively involved in the analyses and interpretation of data, and wrote the manuscript. G.d.S. conceived and designed the research project, was actively involved in the analyses and interpretation of data, and critically revised the manuscript. M.J.R. edited and critically revised the manuscript and gave important conceptual contributions to improvement of the work. M.C. was actively involved in the analyses and interpretation of data. E.T.L., D.C., and B.V.H. edited and critically revised the manuscript and gave important conceptual contributions to improvement of the work. R.B.D. participated in the conception and design of the project and critically revised the manuscript.

The authors thank the Indian Health Service, the SHS participants, the participating tribal communities, and the SHS Center coordinators for their help in the realization of this project.

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