Cardiovascular Characteristics in Subjects With Increasing Levels of Abnormal Glucose Regulation

The Strong Heart Study

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OBJECTIVE—To evaluate whether impaired fasting glucose (IFG) or the combination of IFG and impaired glucose tolerance (IGT) is associated with progressive abnormalities of cardiac geometry and function.

RESEARCH DESIGN AND METHODS—We studied 562 nondiabetic (311 women), nonhypertensive participants of the second Strong Heart Study exam, without prevalent cardiovascular (CV) disease and with estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 (age 46–65 years, 198 with isolated IFG [35%], and 132 with combined IFG and IGT [23%]). Anthropometric parameters, insulin resistance, fibrinogen, C-reactive protein (CRP), lipid profile, blood pressure (BP), and echocardiographic parameters were compared with 232 participants with normal glucose tolerance (NGT).

RESULTS—BMI, prevalence of central obesity, homeostatic model assessment index of insulin resistance, plasma triglycerides, fibrinogen, and CRP increased progressively across categories of glucose intolerance ($P < 0.0001$), with the IFG+IGT group having higher values than those with isolated IFG ($0.05 < P < 0.0001$). Compared with NGT, both IFG and IFG+IGT exhibited greater left ventricular (LV) mass ($P < 0.0001$) and lower Doppler early peak rapid filling velocity to peak atrial filling velocity ratio ($P < 0.005$), without differences in LV systolic function. The odds of LV hypertrophy (LV mass index >46.7 in women or >49.2 g/$m^{2.7}$ in men) was 3.5 in IFG participants (95% CI 0.68–17.76; P = NS) and 9.76 (2.03–46.79; $P = 0.004$) in IFG+IGT, compared with NGT, after adjustment for age, sex, heart rate, systolic BP, and waist circumference (WC). In the overall sample, LV mass index was associated with WC ($P = 0.033$), CRP ($P = 0.027$), and 2-h oral glucose tolerance test ($P = 0.001$) independently of confounders.

CONCLUSIONS—Cardiometabolic profile and markers of inflammation are more severely altered in men and women with both IFG and IGT compared with those with IFG alone. These individuals, in the absence of hypertension, have a 10-fold greater probability of preclinical CV disease (LV hypertrophy).

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Diabetes increases the risk of cardiovascular (CV) disease and mortality (1), an association that is independent of other CV risk factors (2). Evidence has also emerged of an increased CV risk in individuals with abnormal glucose regulation (3,4). Both states of abnormal glucose regulation (i.e., impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) are reported to be associated with excess body weight and increased levels of CV risk factors, morbidity, and mortality (5–7), although these associations are not universally recognized (8,9).

Whether increased plasma glucose above the normal range but below that of clinical diabetes has an impact on cardiac geometry and function is little explored. Cohort studies in communities have shown increased left ventricular (LV) mass and remodeling in individuals with prediabetes (10–12), which appear to be mediated by insulin resistance and body fat distribution (11). However, there are limited clinical or population studies examining CV phenotype in individuals with IGT (13,14), and they included participants with hypertension and/or CV disease, making it difficult to evaluate the role of abnormal glucose levels.

Glucose dysregulation is a continuum from elevation of either fasting or postprandial glucose concentration to impairment of both and, eventually, to type 2 diabetes. This progression is associated with worsening CV risk profile, and individuals with both IFG and IGT have more severe metabolic abnormalities and a greater risk of conversion to type 2 diabetes than those with isolated IFG or IGT (5). Thus, it is plausible that CV phenotype also may worsen in parallel with more severe glucose impairment. Accordingly, in the population of the Strong Heart Study (SHS), we compared the metabolic and echocardiographic features of nondiabetic participants who had either IFG or IFG and IGT combined from the second exam; we hypothesized that the combination of IFG and IGT is associated with more severe abnormalities of cardiac geometry and function than isolated IFG.

RESEARCH DESIGN AND METHODS

Study population

The SHS is a longitudinal, population-based study designed to estimate CV risk

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factors and disease in American Indians 45–74 years of age from 13 communities in Arizona, Oklahoma, and South and North Dakota. During the second SHS examination (1993–1995), participants underwent transthoracic echocardiogram using phased-array commercial echocardiographs with M-mode and two-dimensional and Doppler capabilities as previously reported (15). In addition, all participants without known diabetes (ongoing hypoglycemic treatment or history of diabetes indicated via questionnaire) had a standardized oral glucose tolerance test. For the current study, we selected participants who fulfilled the following inclusion criteria: age <65 years, estimated glomerular filtration rate (eGFR) >60 mL/min, fasting triglycerides <750 mg/dL, no hypertension (defined as systolic blood pressure [BP] ≥140 mmHg, diastolic BP ≥90 mmHg, or self-report of using antihypertensive medication), no prevalent CV disease (stroke, coronary heart disease, congestive heart failure), adjudicated by the SHS Mortality and Morbidity Committees, according to published criteria (16). Institutional review boards of the participating institutions and the participating tribes approved the study.

Measurements

Clinical examinations and collection of blood samples after a 12-h fasting were performed in the morning at local Indian Health Service facilities by the study staff. Laboratory tests were performed by standard methods. Plasma fibrinogen and C-reactive protein (CRP) were determined by validated methods, as reported elsewhere (17,18). Percentage of body fat was measured by bioelectric impedance analysis. Homeostatic model assessment index was used to estimate insulin resistance (HOMA-IR) by the following formula: HOMA-IR: (insulinemia [mU/L] × glycemia [mmol/L])/22.5.

Echocardiography

Echocardiograms were performed using phased-array commercial echocardiographs with M mode, two-dimensional and Doppler capabilities, and reviewed offline by two independent readers as previously reported (19). LV mass was obtained by an anatomically validated formula and normalized for body height (in $m^{2.7}$) (20). Standard methods were used to calculate relative wall thickness, as a measure of LV geometry, ejection fraction (21), as a measure of LV systolic chamber function, and midwall fractional shortening, as a measure of wall mechanics. Measurement of diastolic transmitral blood flow was performed as previously described (22). Mitral early (E) and late (A) velocity were recorded at the annular level and used to calculate the early peak rapid filling velocity to peak atrial filling velocity ratio (E/A ratio). E-deceleration time was also measured. LV hypertrophy (LVH) was defined by sex-specific partition values >46.7 g/$m^{2.7}$ for women and >49.2 g/$m^{2.7}$ for men.

Definitions

American Diabetes Association diagnostic criteria were used to classify participants by category of glucose profile. Normal glucose tolerance (NGT) was defined as fasting plasma glucose (FPG) <100 mg/dL, 2-h plasma glucose (PG) <140 mg/dL; IFG was defined by FPG ≥100 but <126 mg/dL; IGT was defined by 2-h PG ≥140 mg/dL but 2-h PG <200 mg/dL. Obesity was defined by BMI ≥30 kg/m^2.

Statistical analysis

Data are expressed as mean ± SD or proportion (%). Indicator variables were included in all analyses for the three field centers: Arizona, South/North Dakota, and Oklahoma. SPSS 16.0 (SPSS, Chicago, IL) software was used for data management and statistical analysis. Comparisons among the groups were performed using χ^2 and ANOVA with Ryan-Einot-Gabriel-Welsch (REGW) post hoc test. Nonnormally distributed variables (triglycerides, HOMA-IR, CRP, and fibrinogen) were log-transformed for statistical analysis and back-transformed to natural units for presentation in the text and tables. Differences in echocardiographic variables were tested by ANCOVA, adjusting for field centers and sex. Between-groups differences were evaluated by estimating simple main effects of adjusted means with Sidak correction for multiple comparisons. The odds of LVH in categories of impaired glucose regulation, compared with NGT, were analyzed by binary multivariate logistic regression analysis using a hierarchical procedure with priority enter of demographic variables, systolic BP, heart rate, and waist circumference (WC). Two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and metabolic characteristics

Among the 562 participants without hypertension, renal disease, diabetes, and CV disease (age 46–65 years, 311 women), 232 (41%) had NGT, 198 (35%) had IFG, and 132 (24%) had IFG and IGT combined.

Table 1 shows the anthropometric and clinical features of the population by categories of glucose status. Mean age was similar among groups, whereas there was a higher proportion of women in the NGT (58%) and IFG+IGT group (67%) compared with IFG (44%) ($P < 0.0001$). BMI, WC, prevalence of central obesity, fasting insulin, HOMA-IR, and fasting triglycerides increased progressively, and HDL-cholesterol decreased across categories of glucose status ($P < 0.0001$); there were significant differences between IFG and IFG and IGT combined in post hoc analysis ($0.05 < P < 0.0001$). No difference was found in total cholesterol and eGFR values. Also, fibrinogen and CRP were progressively higher in the categories of abnormal glucose status ($P < 0.0001$), with a significant difference between IFG and IFG and IGT combined ($P < 0.05$–0.001). Systolic and diastolic BP were higher in both prediabetic groups than in NGT individuals (both $P < 0.001$), without differences between IFG and IFG and IGT combined.

Echocardiographic data. Table 2 shows echocardiographic findings in the participants. A statistically significant difference across glucose categories was found in heart rate, LV mass, LV mass index, relative wall thickness, and E/A ratio ($0.05 < P < 0.0001$). Specifically, heart rate and LV mass index were significantly higher in individuals with IFG and IGT combined than in those with isolated IFG, also after adjusting for sex. However, most of the difference among groups was due to substantially greater differences in women (35 ± 7 g/$m^{2.7}$ in NGT, 39 ± 8 g/$m^{2.7}$ in IFG, and 42 ± 8 g/$m^{2.7}$ in IFG and IGT combined; $P < 0.0001$) than in men (35 ± 6 g/$m^{2.7}$ in NGT, 37 ± 8 g/$m^{2.7}$ in IFG, and 37 ± 8 g/$m^{2.7}$ in IFG and IGT combined; $P = 0.13$). No difference was detected in ejection fraction or midwall shortening. The prevalence of LVH was 1% in participants with NGT, 4% in IFG, and 10% in IFG and IGT combined ($P < 0.0001$). This progression was almost identical in both sexes. In logistic regression analysis (Table 3), both IFG and IFG and IGT combined exhibited a greater probability of LVH compared with NGT ($P < 0.05$ and $P < 0.001$, respectively). In the overall study population, LV mass index was correlated with greater WC, higher CRP, and higher 2-h glucose

Table 1—*Clinical and metabolic characteristics of study participants*

	NGT	IFG	IFG+IGT	IFG vs. NGT	IFG+IGT vs. NGT	IFG+IGT vs. IFG
n = 562	*n* = 232	*n* = 198	*n* = 132			
Age (years)	54 ± 5	55 ± 5	55 ± 5	—	—	—
Women (%)†	134 (58)	88 (44)	89 (67)	0.01	NS	0.001
Obesity (%)†	62 (27)	100 (50)	83 (63)	0.001	0.001	0.05
High WC (%)†	119 (51)	132 (67)	107 (81)	0.01	0.001	0.01
BMI (kg/m^2)†	27 ± 5	31 ± 6	32 ± 5	0.001	0.001	0.05
WC (cm)†	95 ± 12	104 ± 14	108 ± 13	0.0001	0.0001	0.05
Waist/hip ratio†	0.92 ± 0.07	0.96 ± 0.07	0.96 ± 0.05	0.0001	0.0001	NS
HbA_{1c} (%)†	5.2 ± 0.9	5.3 ± 1.0	5.4 ± 1.1	0.05	0.05	NS
HOMA-IR†	2.1 ± 1.6	4.4 ± 3.6	5.8 ± 2.9	0.0001	0.0001	0.0001
Cholesterol (mg/dL)	197 ± 37	190 ± 38	194 ± 37	—	—	—
Triglycerides (mg/dL)†	116 ± 68	132 ± 68	161 ± 101	0.0001	0.0001	0.005
HDL-C (mg/dL)†	47 ± 15	41 ± 13	40 ± 11	0.0001	0.0001	NS
eGFR (mL/min/1.73 m^2)	89 ± 27	88 ± 22	88 ± 21	—	—	—
CRP (mg/L)†	3.7 ± 4.2	4.9 ± 8.7	7.6 ± 11.6	NS	0.0001	0.0001
Fibrinogen (mg/dL)†	315 ± 56	332 ± 58	350 ± 75	0.0001	0.0001	0.05
Systolic BP (mmHg)†	114 ± 12	119 ± 12	117 ± 11	0.0001	0.0001	NS
Diastolic BP (mmHg)†	71 ± 8	74 ± 9	72 ± 7	0.0005	0.0005	NS

Data are expressed as mean ± SD or *n* (%). ANOVA trend: †$0.05 < P < 0.0001$. HDL-C, HDL-cholesterol.

independent of age, heart rate, fasting glucose, HOMA-IR, and lipids. After adjustment for age, WC, heart rate, and systolic BP, only participants with IFG and IGT combined retained an independent, 10-fold greater probability of LVH (odds ratio 9.76 [95% CI 2.03–46.79]) compared with NGT (Table 4).

CONCLUSIONS—This study demonstrates that progressive impairment of glucose metabolism in individuals without diabetes is associated with a progressive deterioration of CV phenotype, characterized by BP-independent LVH; this accompanies progressively severe metabolic abnormalities: central obesity, insulin resistance, proatherogenic lipid profile, and increased inflammatory markers. Participants with alterations of both fasting and 2-h postglucose load exhibit higher LV mass than those with isolated IFG, a finding never previously recognized. In particular, participants with both IFG and IGT have a 10-fold higher probability of LVH compared with NGT, independent of confounders including older age, higher heart rate, BP, and WC.

Previous studies examining the pathophysiological mechanisms underlying the different stages of progression toward type 2 diabetes have already shown that individuals with combined IFG and IGT have greater impairment of insulin action and insulin secretion as well as more severe metabolic derangement than individuals with either IGT or IFG (23). In addition, worsened CV risk profile and carotid subclinical atherosclerosis have been reported in the category of IFG and IGT combined compared with isolated IGT or IFG (5). Based on these observations, the hypothesis that cardiac structure and function may also worsen with deterioration of glucose metabolism is well-founded.

Previous studies evaluating CV burden in prediabetes have produced inconsistent results. In a young cohort from the Strong Heart Family Study (24), a greater prevalence of LVH was shown in obese adolescents with IFG than in those with normal glucose profile, suggesting a role of insulin resistance in LV remodeling. In a large sample of the Framingham Heart Study, Rutter et al. (11) reported increasing LV mass with worsening glucose tolerance

Table 2—*Echocardiographic characteristics*

	NGT	IFG	IFG+IGT	IFG vs. NGT	IFG+IGT vs. NGT	IFG+IGT vs. IFG
n = 562	*n* = 232	*n* = 198	*n* = 132			
HR (beats/min)†	69 ± 11	71 ± 10	73 ± 11	NS	0.005	0.05
LVIDD (mm)	49 ± 5	50 ± 5	50 ± 5	—	—	—
LVM (g)†	140 ± 32	155 ± 34	157 ± 36	0.001	0.001	0.05
LVM index (g/m$^{2.7}$)†	35 ± 7	38 ± 8	40 ± 8	0.0001	0.0001	0.001
RWT†	0.33 ± 0.04	0.34 ± 0.04	0.34 ± 0.05	0.05	0.05	NS
Ejection fraction (%)	65 ± 5	65 ± 6	65 ± 6	—	—	—
Midwall shortening	18 ± 2	18 ± 2	18 ± 2	—	—	—
E/A ratio†	1.07 ± 0.28	1.01 ± 0.22	1.00 ± 0.26	0.005	0.005	NS
Deceleration time (msec)	209 ± 31	215 ± 35	215 ± 35	—	—	—

Data are expressed as mean ± SD. HR, heart rate; LVIDD, LV internal diastolic diameter; LVM, LV mass; RWT, relative wall thickness. ANOVA trend: †$0.05 < P < 0.0001$.

Table 3—*Odds ratio and 95% CIs of LVH in participants with prediabetes*

	NGT	IFG	*P* value	IFG+IGT	*P* value
Model 1^	1.00	4.99 (1.04–23.83)	0.044	14.4 (3.17–65.45)	0.001
Model 2^^	1.00	3.47 (0.68–17.76)	0.135	9.76 (2.03–46.79)	0.004

^Unadjusted. ^^Adjusted by age, WC, heart rate, and systolic BP.

in women but not in men, but this relation was largely accounted for by obesity. Subsequently, Velagaleti et al. (12) found a positive relation of either high fasting glucose or insulin to LV mass/LV end diastolic dimension evaluated by nuclear magnetic resonance in men but not women. However, they could not find any relation between categories of prediabetes and LV mass indexed for height$^{2.7}$ when BMI was included into the model. Equally uncertain are the data regarding individuals with IGT because of small samples and presence of several confounding variables (13,14).

To date, no information was available on cardiac structure and function in individuals with combined IFG and IGT, a condition characterized by profound metabolic alterations that rapidly progress to diabetes. Our data show that IFG and IGT combined is associated with a very high odds of LVH compared with isolated IFG and NGT, also independent of measures of obesity, a relevant finding, especially considering the strict selection of a healthy normotensive population sample with relatively normal renal function. Most of these differences were in women, who were 67% of the IFG+IGT subgroup. In general, in the SHS cohort women exhibit higher values of LV mass index than men (25). There is evidence that LV adaptation to obesity and hypertension is more severe in women than in men (26). The evidence of more severe increase in LV mass index in women with combined IFG and IGT is consistent with the evidence that components of metabolic syndrome are independently associated with greater LV mass index in hypertensive women but not in hypertensive men, in whom there was no effect beyond the one attributable to hypertension (27). A number of mechanisms have been proposed to explain these sex differences (25).

Table 4—*Independent predictors of LV mass index among participants with NGT, IFG, or IFG and IGT*

Variables	Exp (B) (95% CI)	*P* value^
WC	1.04 (1.00–1.09)	0.033
CRP	2.04 (1.08–3.84)	0.027
2-h plasma glucose	1.03 (1.01–1.05)	0.001

^Independently by age, heart rate, FPG, HOMA-IR, triglycerides, HDL-cholesterol, and systolic BP. Exp (B), exponentiation of the B coefficient.

In isolated IFG, the increase in LV mass is substantially due to insulin resistance and its associated abnormalities, namely central fat distribution and prehypertension, consistent with our previous findings in specific analyses (20,24). In combined IFG and IGT, the elevation of 2-h postglucose load, a surrogate of postprandial glucose levels, emerges as an independent correlate of LV mass, together with visceral adiposity and inflammation, consistent with the evidence that, compared with fasting glucose levels, postprandial hyperglycemia prolongs the adverse effect of hyperglycemia (28). In addition, postprandial blood glucose is associated with fluctuations in glucose concentrations, which further increase vascular damage, potentially affecting LV geometry (29). Our finding is also consistent with previous reports that 2-h postload glucose is a stronger risk predictor of CV disease and mortality than FPG (30). Interestingly, it has been recently reported that even within the normoglycemic range, 2-h postload glucose is associated with increased CV mortality (31).

Another potential mechanism that is revealed by our study is the independent association of CRP with more accentuated LV mass growth. CRP was particularly elevated in the group with IFG and IGT combined. An increase in CRP has been repeatedly demonstrated in prediabetic individuals (32–34) and ascribed to accumulation of visceral fat (another independent correlate of elevated LV mass), which is known to release proinflammatory cytokines (35). Previous studies have reported correlations between markers of inflammation and measures of LV structure and function (20,36). More recently, the Multiethnic Study of Atherosclerosis confirmed a close association of LV mass with markers of inflammation, including fibrinogen, CRP, interleukin-6, and von Willebrand factor, but also noted that the association between CRP and LV mass was entirely accounted for by obesity (36). Our study demonstrates that in the context of more advanced prediabetes (such as the combination of IFG and IGT), the association between CRP and LV mass is at least partially independent of visceral obesity. The inflammatory state may promote LV remodeling via multiple mechanisms, including activation of pathways promoting cardiomyocyte growth but also through alterations of extracellular matrix and deposition of abnormal collagen (37). However, the finding that visceral fat, 2-h blood glucose, and CRP were all independent correlates of increased LVH does not exclude that these factors may act synergistically in promoting myocardial growth by a more complex interplay of mechanisms.

The strength of our study includes a carefully selected cohort without CV disease or hypertension to isolate the effects of glucose abnormalities. The presence of mild renal dysfunction in some participants could have influenced LV mass because previous studies demonstrated that renal function may impact LV mass growth (38); however, eGFR values were similar in the three groups, making it unlikely that in the present analysis, renal function could mediate even in part the relation between increasing LV mass and worsening glucose metabolism. Unfortunately, our design is observational and cross-sectional, which prevents conclusions about causal relationships between degrees of abnormal glucose regulation and increase in LV mass. In addition, our data refer to a specific ethnic cohort, which may limit generalizability to prediabetic individuals from different ethnicities; in contrast, this cohort has served well as a model for many populations with high rates of obesity and diabetes. Finally, due to the high prevalence of obesity in our participants, it is possible that undetected obstructive sleep apnea may have contributed to impair ventricular geometry, as demonstrated in previous studies (39).

In conclusion, men and women with prediabetes have worsening cardiometabolic and proinflammatory profiles and multiple abnormalities in cardiac structure and function with increasing deterioration of glucose tolerance. The condition of combined IFG and IGT in the absence of hypertension and in the presence of relatively normal kidney function is associated with a

10-fold greater probability of LVH, a strong independent predictor of CV events. Thus, there is a need for early identification of individuals with glucose dysregulation to adopt appropriate preventive strategies to reduce CV risk. Promoting lifestyle intervention to reduce weight and increase muscle mass is the most effective measure to improve metabolic status, reduce progression to diabetes, and induce a favorable ventricular remodeling (40). In addition, careful attention to BP and lipid treatment and smoking cessation should be a priority for these individuals. Direct treatment of insulin resistance might be considered, but appropriate trials should be designed to confirm this suggestion.

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B.C., P.D.B., and G.d.S. conceived and designed the project. B.C., P.D.B., M.I., and G.d.S. analyzed and interpreted data. B.C. and G.d.S. wrote the first draft of the manuscript. M.J.R., E.T.L., R.B.D., G.R., and B.V.H. critically revised the manuscript and gave substantial conceptual contributions to improvement of the work. G.d.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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