Left ventricular structure and function in prediabetic adults:Relationship with insulin resistance

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ABSTRACT

Introduction: Several studies have shown that ventricular dysfunction is increased in individuals with diabetes. Insulin resistance (IR) may precede type 2 diabetes, and is a pathogenic factor for it. Furthermore, IR has been shown to be an independent predictor of cardiovascular disease in diabetes. Given that glucose intolerance and IR precede the development of overt diabetes, these factors would be associated with abnormal myocardial performance. **Aim of the Work:** To evaluate the state of left ventricular structure and function in prediabetic adults in relation with IR. **Patients and Methods:** A case–control study was performed. One hundred and twenty-one consecutive adults with prediabetes were enrolled for the study. Forty-two of the adults had IR (group A) and 79 had insulin sensitivity (group B). Forty-three healthy (with normal blood glucose) adults matched for age and gender were considered as a control group. All groups were subjected to full medical history and clinical examination and biochemical and echocardiographic studies. **Results:** There were no statistically significant differences between the insulin-sensitive prediabetic group and the control group in all parameters of left ventricular structure and systolic and diastolic functions. Significant differences were observed between group A and control group in the parameters of left ventricular diastolic function (both isovolumetric relaxation time and E/A ratio). Regarding correlation between the parameters of diastolic function and different variables of IR prediabetic group, there was a statistically significant coefficient correlation with HOMA IR, waist circumference and triglycerides. No correlation was observed with fasting glucose, Hb A1c, body mass index, blood pressure (BP) and total lipids. **Conclusion:** In prediabetic adults, IR is associated with impaired left ventricular diastolic function, and this association appears to be independent of BP, ventricular geometry, glucose tolerance status, total plasma lipids and obesity.

Key words: Insulin resistance, prediabetes, ventricular function

INTRODUCTION

Diabetes mellitus, hypertension, dyslipidemia, obesity and aging are associated with a high risk of cardiovascular disease (CVD) as well as other clinical conditions.[1] The mechanisms through which cardiovascular risk is increased are partially understood. Several distinct pathologic processes may initiate myocyte injury, ventricular dilatation and myocardial dysfunction in patients with diabetes. The common pathways involve neurohumoral, cytokines, immune factors, oxidative stress and the accumulation of advanced glycosylation end products (AGE) leading to protein cross-linking.[2-4]

Echocardiography has introduced the possibility to evaluate not only systolic but also diastolic function. Left ventricular systolic dysfunction reduces the ejection fraction and ejection time and prolongs the isovolumetric contraction time. On the other hand, left ventricular diastolic dysfunction increases the isovolumetric relaxation

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time and modifies the timing of diastolic filling.[5,6]

Several studies have shown that ventricular dysfunction is increased in individuals with type 2 diabetes. Insulin resistance (IR) may precede diabetes by a decade or more, and is a pathogenic factor for it.[7] Furthermore, IR has been shown to be an independent predictor of CVD in diabetes.[8]

Given that glucose intolerance and IR precede the development of overt diabetes, these factors would be associated with abnormal myocardial performance. To investigate this hypothesis, the current study was undertaken to evaluate the state of left ventricular structure and function in prediabetic adults in relation with IR.

PATIENTS AND METHODS

Patient selection

A case–control study was performed. One hundred twenty-one consecutive adults with prediabetes were enrolled for the study. All the patients were recruited from the outpatient diabetes and general medicine clinics of Suez Canal University Hospital from February 2009 to May 2010. Forty-three healthy (with normal blood glucose) adults matched for age and gender were considered as the control group.

Exclusion criteria included the following: hypertension, diabetes mellitus, chronic kidney disease, CVD, severe obesity (body mass index [BMI] >40 kg/m^2), heavy smokers and aged adults (over 60 years old).

All groups were subjected to full medical history and clinical examination, including blood pressure (BP), BMI, systemic examination and biochemical and echocardiographic studies. The BMI was calculated as weight/height^2 (kg/m^2) and was used as an estimate of the overall adiposity.[9] Waist circumference, a validated estimate of visceral adiposity, was measured to the nearest 0.5 cm. Central obesity is defined as waist circumference >102 cm in males and >88 cm in females.[10]

Diabetes was diagnosed according to the American Diabetes Association (ADA) criteria. Blood was drawn after fasting for 8 h. A fasting blood sugar (FBG) level below 100 mg/dL or glycosylated hemoglobin (Hb A1c) <5.7% is considered normal. A FBG level between 100 and 126 mg/dL or Hb A1c 5.7–6.5% confirms the presence of prediabetes and FBG more than 126 mg/dL or Hb A1c >6.5% confirms the presence of diabetes in two separate occasions.[11] A Homeostasis model of insulin resistance (HOMA IR) was used as a measure of IR. It was assessed according to the level of fasting glucose and insulin, which were measured with a dextran–charcoal radioimmunoassay. Serum intact pro-insulin was measured by using a highly specific, two-site monoclonal antibody-based immunoradiometric assay.[12]

The formula for the HOMA IR model is as follows:

HOMA IR = (Fasting insulin mU/mL X Fasting glucose mmol/L) / 22.5

Prediabetic adults were divided by their IR status at baseline (HOMA IR above and below a median of 2.7) to IR (group A) and insulin sensitive (group B), respectively. The median was based on the overall nondiabetic control group at baseline.

Echocardiographic studies were performed with a Hewlett-Packard phased array (Sonos 1800, USA made, model: DR 53 15) ultrasonoscope using a 2.5 and 3.5 MHz transducer. Measurements of ventricular septum, posterior wall and left ventricular cavity were performed according to the American Society of Echocardiography criteria. Left ventricular mass was calculated from the left ventricular end-diastolic cavity and septal and posterior wall thickness were calculated using the Penn convention and the American Society of Echocardiography guidelines. Left ventricular mass index (LVMI) was determined as the ratio of left ventricular mass in grams to the body surface area in square meters. The relative wall thickness (RWT) was measured at the end-diastole as the ratio of posterior wall thickness plus septal thickness divided by left ventricular internal dimension. The transmitral flow velocity profile was recorded from the apical four-chamber view with the pulsed wave Doppler sample volume positioned at the tips of mitral leaflets during diastole. The left ventricular outflow velocity pattern was recorded from the apical long axis view, with the pulsed wave Doppler sample volume positioned just below the aortic valve. Five consecutive beats were measured and averaged for each measurement. From the mitral inflow signal, we measured the E velocity (E), the A velocity (A) and the E/A ratio. The isovolumetric relaxation time (IVRT) was measured with the pulsed wave sample volume placed between the mitral inflow and the left ventricular outflow tract.[13-15]

Ethical consideration: Informed consent was obtained from all the adults. The aim and the value of the work were explained in a simplified manner for them. No harm was inflicted on them. On the contrary, all had benefits of the

follow-up and the final results of the study.

Statistical analysis

The data were coded and organized. The final study results were stated using the SPSS program version 14. Results were presented through tables. Student-*t*, correlation coefficient and Chi-square tests were used to evaluate the results. Chi-square test was used for qualitative variables while independent *t*-test was used for quantitative variables. Correlation analysis was performed using Pearson's test. Statistical significance was considered at a *P*-value <0.05 and highly significant at a *P*-value <0.001.

RESULTS

The baseline characteristics of 121 (65 males and 56 females) prediabetic adults, mean age 47.8 years, with and without IR versus 43 controls (23 males and 20 females), mean age 48.6 years, are shown in Table 1. 34.7% of the prediabetic adults had IR (group A) and 65.3% had insulin sensitivity (group B). No significant differences were observed between both the prediabetic adult and the control groups regarding BMI, waist circumference, BP and plasma lipids. Except waist circumference, all the mentioned parameters were nearly similar in both the male and the female prediabetic adults.

Echocardiographic and Doppler examination is shown in Table 2. There were no statistically significant differences between the insulin-sensitive prediabetic and control groups in all parameters of left ventricular structure and systolic and diastolic functions. On the other hand, significant differences were observed between the group with IR and the control group in the parameters of left ventricular diastolic function (both IVRT and E/A ratio). Comparing echo parameters between groups A and B, no significant differences were observed except in the E/A ratio.

Correlation between the parameters of diastolic function and different variables of IR prediabetic group is shown in Table 3. There was a statistically significant coefficient correlation with HOMA IR, waist circumference and triglycerides. No correlation was observed with FBG, Hb A1c, BMI, BP and total lipids.

DISCUSSION

Several studies have demonstrated left ventricular diastolic dysfunction to represent the first manifestation of myocardial involvement in diabetes. The dysfunction represents the earliest pre-clinical manifestation of diabetic cardiomyopathy, preceding systolic dysfunction.[16,17] Furthermore, the dysfunction can precede the development of diabetes,[18] suggesting that it is not exclusively a complication of diabetes but rather a coexisting condition. The development of diabetic

Table 1: Clinical and biochemical studies (mean values) of both the case and the control groups

Variables	Control group N = 43	Prediabetic (case)			*P*-value		
		All N = 121	Group A N = 42	Group B N = 79	*P*	*P**	*P***
Age (years)	48.6 ± 8.3	47.8 ± 8.3	49.5 ± 7.4	47.3 ± 6.9	n.s	n.s	n.s
Gender							
Male	23 (53%)	65 (54%)	24 (57%)	41 (52%)	n s	n.s	n.s
Fem ale	20 (47%)	56 (46%)	18 (43%)	38 (48%)	n.s	n.s	n.s
SBP (mmHg)	122.3 ± 9.2	121.4 ± 6.5	123.5 ± 4.7	121.6 ± 5.7	n.s	n.s	n.s
DBP (mmHg)	75.5 ± 3.2	78.4 ± 4.8	79.3 ± 6.2	77.4 ± 4.9	n.s	n.s	n.s
BMI (%)	26.2 ± 5.4	28.6 ± 5.6	29.4 ± 6.9	27.1 ± 4.6	n.s	n.s	n.s
W. circum. (cm)	98.4 ± 2.7	103.3 ± 4.5	107.6 ± 3.9	101.4 ± 3.7	<0.01	n.s	<0.05
Total lipids (mg/dL)	489.7 ± 36.3	509.3 ± 44.2	520.7 ± 38.4	501.5 ± 28.8	n.s	n.s	n.s
Triglyceride (mg/dL)	145.9 ± 18.4	189.6 ± 16.6	193.2 ± 13.4	186.3 ± 17.2	<0.01	<0.05	<0.05
HDL-c (mg/dL)	48.5 ± 2.8	47.2 ± 2.2	45.3 ± 2.9	47.9 ± 4.2	n.s	n.s	n.s
LDL-c (mg/dL)	121.9 ± 16.3	132.1 ± 17.2	136.3 ± 18.2	131.1 ± 13.9	n.s	n.s	n.s
FBG (mg/dL)	83.9 ± 11.2	117.8 ± 6.6	119.1 ± 3.2	110.9 ± 11.2	<0.01	<0.01	<0.01
Hb A1c (%)	4.9 ± 0.9	6.1 ± 0.2	6.2 ± 2.1	5.9 ± 0.3	<0.05	<0.05	<0.05
HOMA IR	2.7 ± 0.1	3.9 ± 1.9	5.3 ± 1.9	2.5 ± 1.4	<0.01	n.s	<0.05

Group A = Prediabetic adult with insulin resistance, Group B = Prediabetic adult with insulin sensitive, BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic BP, N = Number of cases, n.s. = Non significant, FBS = Fasting blood glucose, W. circum. = Waist circumference, HDL-c = High-density lipoprotein cholesterol, LDL-c = Low-density lipoprotein cholesterol, Hb A1c = Glycosylated hemoglobin, P = Comparison between group A and control. P = Comparison between group B and control, P** = Comparison between all prediabetic adults and control group.*

Table 2: Echocardiographic mean values in both the case and the control groups

Variables	Control group	Prediabetic (case)			*P*-value		
	N = 43	All	Group A	Group B	*P*	*P**	*P***
		N = 121	N = 42	N = 79			
End SD (mm)	27.9 ± 1.5	28.2 ± 1.5	28.5 ± 1.3	27.9 ± 1.9	n.s.	n.s.	n.s.
End DD (mm)	48.4 ± 3.9	49.1 ± 2.9	49.3 ± 2.1	48.2 ± 3.1	n.s.	n.s.	n.s.
EF%	63.8 ± 7.1	62.4 ± 6.2	61.6 ± 4.2	64.1 ± 6.9	n.s.	n.s.	n.s.
IVS thickness (mm)	8.2 ± 0.7	8.1 ± 0.5	80.2 ± 0.8	82.1 ± 0.3	n.s.	n.s.	n.s.
PW thickness (mm)	8.1 ± 0.9	8.2 ± 0.7	8.8 ± 0.3	7.9 ± 0.2	n.s.	n.s.	n.s.
RWT%	35.3 ± 3.4	34.9 ± 4.1	36.1 ± 2.8	33.9 ± 2.8	n.s.	n.s.	n.s.
LVMI (gm/m^2)	89.9 ± 7.2	91.2 ± 6.9	92.2 ± 8.1	89.2 ± 0.9	n.s.	n.s.	n.s.
IVRT (ms)	91.3 ± 11.2	96.2 ± 9.1	99.9 ± 4.2	92.1 ± 8.4	<0.01	n.s.	n.s.
E/A ratio	1.5 ± 0.6	1.4 ± 0.7	1.2 ± 0.2	1.5 ± 0.8	<0.01	n.s.	n.s.

Group A = Prediabetic adults with insulin resistance, Group B = Prediabetic adult, SD = Systolic diameter, DD = Diastolic diameter, EF = Ejection fraction, IVS = Interventricular septum, PW = Posterior wall, RWT = Relative wall thickness, LVMI = Left ventricular mass index, E = E velocity, A = A velocity, E/A = E/A ratio, IVRT = Isovolumetric relaxation time, N = Number of cases, n.s. = Non significant, P = Comparison between group A and control, P = Comparison between group B and control, P** = Comparison between group A and B*

Table 3: Correlation coefficient between diastolic function parameters and different variables in group A

	IVRT		E/A ratio	
Variables	r value	*P*-value	r value	*P*-value
Age (years)	0.23	n.s.	0.32	n.s.
SBP (mmHg)	0.34	n.s.	0.29	n.s.
DBP (mmHg)	0.41	n.s.	0.43	n.s.
Total lipid (mg/dL)	0.51	n.s.	0.53	n.s.
HDL-c (mg/dL)	0.21	n.s.	0.22	n.s.
LDL-c (mg/dL)	0.28	n.s.	0.25	n.s.
Triglycerides (mg/dL)	0.71	<0.01	0.75	<0.01
BMI%	0.38	n.s.	0.42	n.s.
W. circum. (cm)	0.72	<0.01	0.75	<0.01
FBG (mg/dL)	0.33	n.s.	0.46	n.s.
Hb A1c%	0.42	n.s.	0.41	n.s.
HOMA IR	0.83	<0.001	0.82	<0.001

Group A = Prediabetic adult with insulin resistance, E = E velocity, A = A velocity, E/A = E/A ratio, IVRT = Isovolumetric relaxation time, BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic BP, N = Number of cases, n.s. = Non significant, FBS = Fasting blood glucose, W. circum. = Waist circumference HDL-c = High-density lipoprotein cholesterol, LDL-c = Low-density lipoprotein cholesterol, Hb A1c = Glycosylated hemoglobin

myocardial dysfunction is likely multifactorial, with putative mechanisms including metabolic disturbance, changes in the extracellular matrix components, small vessel disease, autonomic dysfunction and IR. Due to cardio-metabolic repercussions of hyperglycemia, a detailed evaluation of cardiovascular changes in prediabetic and diabetic patients is recommended. Furthermore, two recent studies, the "ADVANCE" trial[19-20] and the "ACCORD" trial,[21,22] reported no significant benefit from intensive HbA1c lowering in terms of cardiovascular outcomes in subjects with long-standing diabetes. Therefore, we speculate that an early intervention is necessary. To our knowledge, the state of myocardial performance in prediabetes has received little attention. We therefore studied prediabetic normotensive adults in whom the prevalence of IR and impaired glucose tolerance is high to test the hypotheses that IR is associated with impaired cardiac function and that this relationship is dependent or independent of glucose tolerance status.

The main finding of the current study is that IR is associated with impaired left ventricular diastolic function and that the association appears to be independent of BP, ventricular geometry, glucose tolerance status, total plasma lipids and obesity.

The E/A ratio exhibited a stepwise decrease from the control to the prediabetic to the IR groups, primarily a result of increased A-wave velocity. The isovolumic relaxation time was significantly longer in the IR group. These findings suggest that there is a progressive impairment in left ventricular relaxation depending on the insulin sensitivity and increasing burden of IR on myocardial function. Our results are consistent with that of a recently published study in patients without overt type 2 diabetes.[23] In addition, the diastolic changes were

associated with an unaltered geometric pattern and a non-significant depressed systolic function in all groups. These different findings indicate that the functional changes are independent and precede the systolic and structural changes. Our observation is consistent with those of prior studies in the fields of obesity,[24] metabolic syndrome[25] and diabetes.[26]

The mechanism underlying the relationship between IR and myocardial performance is not clear, and the current cross-sectional study cannot identify the causative factor. Studies have shown that IR states are associated with decreased endothelium-dependent vasodilation.[27,28] In addition, insulin has been shown to induce vascular smooth muscle proliferation and migration in cell culture.[29] Hyperglycemia has been shown to lead to the formation of AGEs. Therefore, It has been suggested that individuals with prediabetes may have decreased ventricular function due to prolonged exposure to elevated glucose levels.[3,18] Results from the present study did not identify impaired left ventricular performance among individuals with insulin-sensitive prediabetes. Furthermore, no correlation was found between the performance and either fasting glucose or Hb A1c measurements. Our data suggest that IR may be more important in the development of diastolic dysfunction than accumulation of AGEs.

Previous studies have shown that visceral fat in healthy individuals is associated with impaired left ventricular function.[24,30] The present study confirms this association. In agreement with a recent study by Wilfried *et al*.,[23] we observed that abdominal adiposity, as measured by waist circumference, was significantly and adversely associated with diastolic function, whereas BMI as a measure of general adiposity was not. In addition, we found that IR appears to be more strongly associated with dysfunction than with measures of obesity. These results suggest that the obesity–diastolic dysfunction relationship may be mediated in part through increasing IR. Obesity, especially central abdominal obesity, is associated with the secretion of inflammatory cytokines and proteins.[31] Another study demonstrated an association between inflammatory markers and functional cardiac outcomes in patients with a first uncomplicated myocardial infarction. Stress hyperglycemia amplifies the inflammatory immune reaction and worsens the functional cardiac outcomes.[32] In general, adipocytes, in particular from the visceral abdominal regions, produce several bioactive peptides that in turn impact on vascular structure and function.[33,34]

However, increased BP tends to reduce the myocardial performance.[1,27,35] Nevertheless, in our study, as all subjects were normotensive, such an association was not found.

We should point out that the total lipids had an insignificant correlation with ventricular dysfunction. When the components of the lipids were considered separately, diastolic dysfunction showed direct associations only with triglycerides. These results are consistent with those of Lisa *et al*. They reported that triglycerides are independently associated with the E/A ratio.[36]

In conclusion, we have shown that prediabetic subjects have an impaired left ventricular diastolic function, which represent a major pattern of CVD, and these changes are predominantly observed in prediabetic subjects with increased HOMA IR and visceral obesity. None of the studied prediabetic adults had history of cardiac complications. Subsequently, the data of the current study suggest that as changes can be detected before the appearance of clinically apparent heart failure, echocardiographic assessment for all prediabetics, especially those with IR or those who are obese, is recommended as the primary prevention for the development of future CVD. Because the functional changes in the prediabetic state are limited to subjects with IR, the use of insulin-sensitizing agents to prevent diabetes could have a beneficial effect on CVD. It is likely that over the next few years, the measurement of IR will become an increasingly important part of the process of risk assessment, and may possibly also improve the monitoring of therapy. Additional studies will be needed to assess the impact of IR on ventricular elasticity and the effect of an improvement in insulin sensitivity to improve myocardial performance.

It is imperative to note several limitations in this study design. First, the relatively small sample size. Second, this study enrolled individuals carefully screened to exclude diabetes and hypertension. Further research will be needed to confirm whether these results generalize to the general population, more insulin-sensitive individuals and those with hypertension through a large community-based study.

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