Sex-Specific Determinants of Left Ventricular Mass in Pre-Diabetic and Type 2 Diabetic Subjects

The Augsburg Diabetes Family Study

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OBJECTIVE — Obesity and hypertension are regarded as the most important determinants of left ventricular mass in the community. Little is known about sex-specific influences of obesity, hypertension, and other risk factors on left ventricular mass in pre-diabetic or diabetic subjects.

RESEARCH DESIGN AND METHODS — We examined how body composition, blood pressure, and other factors are related to left ventricular structure in elderly subjects (mean age 62 years, 88% of women postmenopausal) with pre-diabetes (impaired fasting glucose or impaired glucose tolerance; $n = 112$) and diabetes with ($n = 181$) and without ($n = 213$) overt cardiovascular disease (CVD).

RESULTS — Neither microalbuminuria nor physical activity was significantly associated with left ventricular mass. In pre-diabetic as well as diabetic subjects with CVD, mainly BMI and fat mass, particularly in women, were correlated with left ventricular mass. In the diabetic group without overt CVD, fat mass was only slightly correlated with left ventricular mass. In the latter group waist-to-hip-ratio, and, only in men, systolic blood pressure, glucose, and A1C were moderately correlated with left ventricular mass. Multiregression analysis over all groups again revealed fat mass as the main determinant of left ventricular mass in women. In women but not men obesity was associated with a significantly increased prevalence of concentric left ventricular hypertrophy.

CONCLUSIONS — In pre-diabetic and diabetic elderly subjects fat mass is the major determinant of left ventricular mass in women but not in men. These results may partly explain sex differences in CVD mortality in obese elderly diabetic subjects and underscore the need for activities focused on weight reduction.

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Left ventricular hypertrophy is independently associated with congestive heart failure and cardiovascular mortality (1–3). Diabetes is also known as an important risk factor for cardiovascular morbidity and mortality, and this association is partly mediated by its effect on left ventricular structure. Traditionally, hypertension and obesity have been regarded as the most important etiological factors in the development of left ventricular hypertrophy in the community (4–8). Diabetes and impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), the latter being regarded as a preclinical stage of diabetes, are also recognized as independent risk factors for the development of left ventricular hypertrophy (9–11). However, the role of the traditional etiological risk factors in pre-diabetic or diabetic subjects is unknown. In patients with more advanced stages of diabetes, in particular, it has been speculated that the traditional risk factors for left ventricular hypertrophy may have a lesser influence on left ventricular mass because of other mechanisms that may become more important (12). Furthermore, although it is known that in the general population cardiac adaptations to obesity and hypertension are sex-specific (7,8) and, in addition, influences of diabetes on left ventricular structure are reported to be different by sex (13), to our knowledge no data as yet exist about differential impacts of known etiological risk factors on left ventricular structure in subjects with pre-diabetes or subjects with established diabetes with or without concomitant cardiovascular disease (CVD).

The aim of this study was to examine how body composition, blood pressure, metabolic factors, and other factors are related to left ventricular mass and geometry in elderly men and women with pre-diabetes and diabetes with and without overt CVD.

RESEARCH DESIGN AND METHODS

— The present study was part of the Augsburg Diabetes Family Study, which was conducted in 2001–2002 with the primary goal of enrolling families to investigate the role of genes as well as environmental factors in the development of type 2 diabetes (14). The present investigation was organized as an echocardiographic substudy with 870 probands included. Of those, a total of

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Abbreviations: CVD, cardiovascular disease; FFM, free fat mass; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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800 individuals agreed to be examined by echocardiography (92%). For the present study, only subjects with impaired glucose metabolism were included (accordingly, $n = 164$ subjects with normal glucose tolerance were excluded). After further exclusion of patients with suboptimal echocardiographic readings (the latter had only slightly higher mean BMI than those with adequate echocardiographic readings, with no significant differences in mean age or diastolic blood pressure), significant valvular heart disease, and participants undergoing dialysis, 506 subjects remained for further analysis. All participants gave their informed consent, and the study was approved by the ethics committee of the Bavarian Medical Association.

Anthropometric data and blood pressure were measured under standardized conditions as described previously (14,15). Three weight groups, normal weight, overweight, and obesity, were defined as BMI <25, 25–29.9, and ≥30 kg/m^2, respectively (16).

Fat-free mass (FFM) was determined by measuring bioelectrical impedance as reported in detail previously (17,18). Body fat mass was calculated after subtraction of FFM from total body weight in kilograms.

Physical activity level was estimated by interview questions as reported in detail previously (19). For the present study, three groups were classified: no activity (−), low to moderate activity (+), and high activity (++).

Laboratory procedures were done under standardized conditions and were described in detail previously (14). Echocardiography was performed by two expert sonographers using the Sonos 3500 (Hewlett Packard, Palo Alto, CA). Left ventricular mass was derived from the widely applied formula described by Devereux et al. and others (20–22). The rank correlation for left ventricular mass in 30 duplicate measurements of the two sonographers was 0.89, and there was a mean difference between both observers of 8.3 g with a SD of 13 g (14). For estimation of the prevalence of left ventricular hypertrophy, body surface area was used as an index method; the respective cut points and criteria for geometric left ventricular patterns were used as described before (14,23,24).

All subjects without known diabetes had an oral glucose tolerance test after an overnight fast. Type 2 diabetes, IGT, and IFG were diagnosed according to the 1999 criteria of the World Health Organization (25). Because IGT and IFG are regarded as preclinical stages of diabetes, subjects showing one of those metabolic disturbances and having no history of CVD were combined to a group named "pre-diabetic subjects" ($n = 112$) (25).

Subjects with type 2 diabetes were divided into those with and without a presence of overt CVD. A presence of overt CVD was defined in patients with a history of myocardial infarction, coronary artery disease, heart surgery, cerebrovascular disease, or congestive heart failure or in patients with complaints of angina pectoris or claudicatio intermittens (14). This group consisted of 181 subjects (diabetic subjects with CVD). The remaining diabetic subjects ($n = 213$) were classified as diabetic subjects without overt CVD.

Statistical analyses

Means and prevalences of baseline characteristics were calculated for female versus male participants. Statistical significance was assessed by a two-way ANOVA for continuous variables and by χ^2 tests for prevalences. Univariate relations were assessed by Pearson's product-moment correlation, and ANCOVA was applied to calculate mean values of left ventricular parameters across the groups of subjects with albuminuria and physical activity. A variable originally incorporated in the multivariate models controlling for familiar interaction showed no significant effect and, therefore, was excluded from the final models. Forward stepwise multiple regression analysis was used to select variables independently related to left ventricular mass. To avoid disregarding of potential left ventricular mass determinants because of low numbers, a significance level of 0.1 in the univariate correlation analysis was allowed for entering the final multivariate models; otherwise $P < 0.05$ was considered to be significant. Prevalence differences in geometric types of left ventricular hypertrophy between the subgroups of normal weight, overweight, and obesity were tested by logistic regression analysis. All analyses were carried out with SAS for Windows (release 6.11).

RESULTS — Table 1 shows the characteristics of the study groups with respect to sex. Whereas in all groups there were highly significant sex differences in anthropometric data such as height, FFM, and fat mass as well as unadjusted left ventricular mass and creatinine, there were only minor or no sex differences in age, serum glucose, A1C, blood pressure, and antihypertensive medication use. In addition, there were no significant sex differences in left ventricular hypertrophy in the respective groups. Across all diabetic and pre-diabetic groups, subjects with macroalbuminuria ($n = 29$) had significantly higher left ventricular mass than those without albuminuria (207 vs. 160 g, $P < 0.01$). However, subjects with microalbuminuria had only slightly, although insignificantly, higher left ventricular mass compared with nonalbuminuric subjects (Table 2). The level of physical activity had no significant impact on left ventricular mass in the pre-diabetic nor in the diabetic group (Table 2). In pre-diabetic subjects, mainly BMI and fat mass, and to a lesser extent FFM, were correlated with left ventricular mass, particularly in women. Of interest, those variables were also the main correlates of left ventricular mass in the group of diabetic subjects with CVD, which was again more pronounced in women, whereas in the diabetic group without overt CVD, fat mass as well as FFM were only slightly correlated with left ventricular mass in women. In the latter group waist-to-hip ratio (WHR) and, only in men, systolic blood pressure, glucose, and A1C were moderately correlated with left ventricular mass (Table 2). Forward stepwise multiple regression analysis confirmed fat mass as the main determinant of left ventricular mass, explaining 25% of left ventricular mass variability in pre-diabetic women and 15% in pre-diabetic men. In the group of diabetic subjects without known CVD, the variability of left ventricular mass was less well explained by the usual determinants (Table 3). However, in diabetic patients with CVD, fat mass was the main determinant of left ventricular mass in women but not in men.

Taking all groups together and incorporating the absence or presence of CVD in the final multiregression model revealed fat mass again as the main determinant of left ventricular mass in women, whereas the presence of CVD in women played no and in men only a small role in this setting (Table 3). The use of antihypertensive agents in women was also a small contributor to the explanation of left ventricular mass variability. Similarly, creatinine, height, age, and FFM were small, although significant, contributors to the explanation of left ventricular mass in men. The results of the multiregression models were nearly the same when BMI

Table 1—*Clinical characteristics of the study population*

	LV mass					
	Pre-diabetic subjects		Diabetic subjects without CVD		Diabetic subjects with CVD	
	Men	Women	Men	Women	Men	Women
n	59	52	101	112	119	62
Age (years)	61 ± 9	62 ± 10	60 ± 11	64 ± 7*	63 ± 8	66 ± 11†
Systolic BP (mmHg)	138 ± 21	133 ± 23	142 ± 20	140 ± 23	141 ± 19	140 ± 22
Diastolic BP (mmHg)	82 ± 10	77 ± 9*	83 ± 11	79 ± 10†	80 ± 11	78 ± 11
Height (m)	1.73 ± 0.05	1.61 ± 0.06†	1.73 ± 0.06	1.59 ± 0.07†	1.72 ± 0.07	1.59 ± 0.07†
BMI (kg/m^2)	28.6 ± 3.4	29.8 ± 4.8	29.8 ± 4.3	31.0 ± 5	29.3 ± 3.7	32.1 ± 5†
WHR	0.96 ± 0.04	0.86 ± 0.05†	0.97 ± 0.04	0.88 ± 0.05†	0.98 ± 0.05	0.89 ± 0.05†
FFM (kg)	59.8 ± 5	44.5 ± 6†	61.2 ± 7	44.8 ± 6†	59.8 ± 7	45.0 ± 6†
Fat mass (kg)	26.5 ± 7	32.5 ± 9*	27.8 ± 8	34.3 ± 10†	27.6 ± 8	35.7 ± 10†
Creatinine (mg/dl)	1.0 ± 0.13	0.86 ± 0.13†	1.1 ± 0.33	0.87 ± 0.16†	1.2 ± 0.38	0.98 ± 0.29†
Serum glucose (mg/dl)	111 ± 6	108 ± 7*	165 ± 61	162 ± 57	167 ± 57	159 ± 66
A1C (%)	5.8 ± 0.3	6.0 ± 0.4	7.4 ± 1.3	7.4 ± 1.3	7.3 ± 1.2	7.4 ± 1.2
LV mass (g)	177 ± 81	140 ± 67*	162 ± 63	136 ± 58*	205 ± 96	150 ± 58†
LV hypertrophy	30	31	31	32	41	43
Antihypertensive medication	47	55	51	66*	87	85

Data are means ± SD or %. *$P < 0.05$ for men vs. women; †$P < 0.001$. BP, blood pressure; LV, left ventricular.

was substituted for FFM and fat mass, revealing nearly identical partial R^2 values for BMI.

Figure 1 shows the respective geometric left ventricular patterns with respect to normal or overweight stages. Whereas in men obesity was only mildly associated with abnormal left ventricular geometry (only eccentric hypertrophy was more prevalent in obese compared with normal-weight men, 16 vs. 4%; $P = 0.23$), in women obesity was strongly associated with abnormal left ventricular geometry (the prevalence of normal left ventricular pattern was 34% in obese vs. 56% in normal-weight women, $P < 0.05$). This difference was mostly explained by the higher prevalence of concentric left ventricular hypertrophy in obese women (31 vs. 7%; $P < 0.05$). This difference remained significant after con-

Table 2—*Correlation of left ventricular mass (r) with baseline variables and mean left ventricular mass with respect to microalbuminuria or physical activity*

	LV mass					
	Pre-diabetic subjects		Diabetic subjects without CVD		Diabetic subjects with CVD	
	Men	Women	Men	Women	Men	Women
n	59	53	101	112	119	62
Age (years)	0.02	−0.04	0.28*	0.14	0.07	−0.06
Systolic BP (mmHg)	0.13	0.13	0.13	0.24*	0.07	−0.13
Diastolic BP (mmHg)	0.10	0.10	−0.07	0.05	−0.04	−0.02
Height (m)	0.01	0.19	0.08	0.08	0.21*	0.06
BMI (kg/m^2)	0.36†	0.50†	−0.03	0.14	0.13	0.53†
WHR	0.22	0.26	0.20†	0.25†	0.10	0.04
FFM (kg)	0.22	0.40*	−0.03	0.06	0.24*	0.40*
Fat mass (kg)	0.38*	0.51†	0.03	0.17*	0.14	0.51†
Creatinine (mg/dl)	−0.19	−0.19	0.18	0.01	0.26*	−0.18
Serum glucose (mg/dl)	−0.04	0.06	0.23*	0.16	−0.03	−0.04
A1C (%)	−0.09	−0.16	0.29*	−0.08	0.00	0.03
Left ventricular mass						
Microalbuminuria −	157 (51)	134 (42)	159 (68)	132 (81)	202 (73)	146 (41)
Microalbuminuria +	178 (7)	171 (10)	166 (24)	148 (28)	200 (28)	152 (19)
Physical activity ++	167 (13)	148 (6)	170 (25)	135 (23)	192 (33)	126 (4)
Physical activity +	175 (20)	132 (23)	157 (40)	131 (40)	204 (44)	155 (24)
Physical activity −	182 (26)	146 (24)	163 (36)	140 (50)	216 (47)	151 (36)

Data are *r* or mean (*n*). *$P < 0.05$; †$P < 0.001$. BP, blood pressure.

Table 3—*Regression coefficients (β) and partial R^2 values of factors related to left ventricular mass in the final model after a forward stepwise procedure in the respective pre-diabetic and diabetic groups and in all subjects together*

	Men			Women		
	β	Partial R^2	*P*	β	Partial R^2	*P*
Pre-diabetic subjects						
Fat mass (kg)	3.5	0.15	0.005	3.12	0.25	0.0002
Antihypertensives (yes/no)	—	—	—	36.2	0.06	0.05
Diabetic subjects without CVD						
Systolic blood pressure (mmHg)	—	—	—	0.60	0.08	0.003
WHR	—	—	—	274.6	0.06	0.007
Antihypertensives (yes/no)	—	—	—	25.6	0.04	0.02
Age (years)	1.5	0.08	0.004	—	—	—
A1C (%)	10.1	0.05	0.02	—	—	—
Diabetic subjects with CVD						
Creatinine (mg/dl)	71.9	0.05	0.01	—	—	—
FFM (kg)	327.6	0.05	0.01	—	—	—
Fat mass (kg)	—	—	—	2.7	0.19	0.0005
All subjects together						
Creatinine (mg/dl)	34.8	0.04	0.0005	—	—	—
CVD (yes/no)	26.8	0.03	0.005	—	—	—
Height (m)	112.6	0.03	0.006	—	—	—
Age (years)	1.67	0.02	0.02	—	—	—
FFM (kg)	2.8	0.01	0.04			
Fat mass (kg)	—	—	—	1.92	0.14	0.0001
Antihypertensives (yes/no)	—	—	—	27.9	0.04	0.002

trolling for potential confounding factors such as systolic blood pressure, antihypertensive medication, and the presence of CVD in the multivariate logistic regression model.

CONCLUSIONS — The present study showed that there exist sex-specific differences in the determinants of left ventricular mass and left ventricular geometry in pre-diabetic and type 2 diabetic subjects, with women shown to be significantly more susceptible to increased fat mass than men.

Contrary to former studies, we decided not to exclude patients with already established CVD because we also intended to analyze the determinants of left ventricular structure in diabetic patients with more severe states of diabetes who would have been mostly missed by excluding those with established CVD (12).

Whereas hypertension and obesity explain most of left ventricular mass variations in the general population (24,26), the role of these risk factors in diabetic subjects is less well known. Blood pressure was hardly associated with left ventricular mass in our study participants. It has been speculated that in patients with more advanced stages of diabetes, blood pressure did not add markedly to the development of left ventricular hypertrophy because insulin resistance itself stimulates left ventricular mass growth (12,13). In the present study, insulin resistance was not directly measured. However, it could be shown that fat mass was a major determinant of left ventricular mass, especially in women. Of interest, in the Framingham study, insulin resistance was significantly more related to left ventricular mass in women than in men. This association was considerably attenuated after controlling for obesity (13), suggesting that obesity itself is a major determinant of insulin resistance. Adipose mass alone or BMI, rather than a commonly used surrogate of central obesity, namely WHR, was the main determinant of left ventricular mass in the present population. Accordingly, it must be speculated that mechanisms other than insulin resistance alone, which is strongly associated with central adiposity, may be responsible for this observation. Among the diabetic group without overt CVD, WHR, but not fat mass, was moderately associated with left ventricular mass in women in the multivariable analysis. Why the traditional determinants of left ventricular mass contributed less to the variability of left ventricular mass in the latter group remains to be explained. In general, in the present study, FFM correlated less strongly with left ventricular mass than fat mass compared with other studies (27). On the other hand, in a study of a general population from the same community (17) as well as in another Caucasian population (28), fat mass was at least as strongly correlated with left ventricular mass as FFM. In accordance with earlier studies in men, except for age, only A1C contributed significantly to the variance in left ventricular mass (29). Thus, other mechanisms may contribute to the left ventricular mass variability in that group of diabetic subjects (30). However, in the group of diabetic patients with overt CVD, again fat mass was the major determinant of left ventricular mass in women, whereas in men creatinine and FFM had less influence. Our findings are in accordance with another study in which obesity in particular in patients with diabetes and hypertension were associated with altered left ventricular geometry. However, sex-specific analyses were not presented in this study (31). Whereas macroalbuminuria was associated with left ventricular mass, microalbuminuria had no significant effect on left ventricular structure in the present study. Microalbuminuria seems to have significant effects in nondiabetic hypertensive populations (32), but studies in diabetic subjects showed inconsistent results (33). Contrary to other populations (34), in our

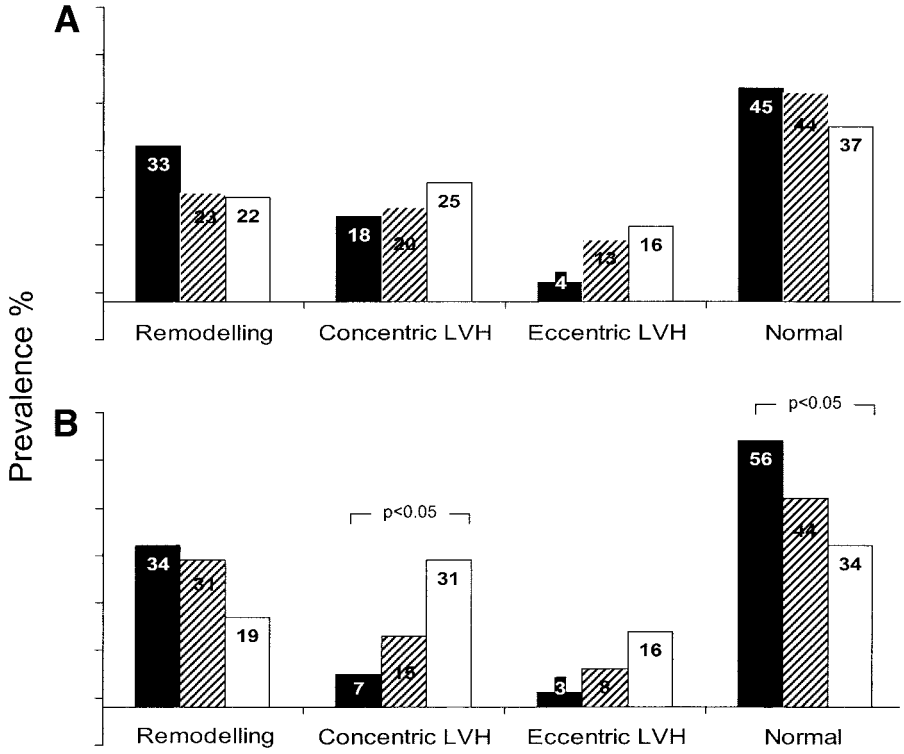

Figure 1—*Prevalence of left ventricular geometric patterns according to weight status in all subjects.* A*, men;* B*, women.* ■*, normal weight;* ▨*, overweight;* □*, obese.*

study, the level of physical activity had no impact on left ventricular mass, but to our knowledge it still has not been investigated in larger populations of pre-diabetic or diabetic subjects.

In our multivariate model, we could show that fat mass in women but not in men mostly and even more effectively than the presence of CVD explained the variability in left ventricular mass. When BMI was substituted for FFM and fat mass in the multivariate model, the results were nearly the same, suggesting that the overall excess body fat (FFM is also increased in obese subjects [18]) in diabetic and pre-diabetic women is responsible for the increased risk of left ventricular hypertrophy. Of interest, the risk of concentric left ventricular hypertrophy in particular increased with higher BMI in women, although obesity, because of its induced volume overload, is commonly thought to be associated with eccentric hypertrophy (6,7). Again, the obesity-associated insulin resistance may, more than obesity itself (35), be responsible for this effect. Insulin resistance, because of its trophic stimulating effect, has been thought to lead to increases in wall thicknesses and less often to increases in left ventricular dimensions (36). It has also been speculated that, independently from insulin, adipose tissue is an active endocrine gland contributing to the tendency for concentric cardiac hypertrophy (28). However, we do not know why the observed associations between obesity and left ventricular geometry are more pronounced in women than in men. In the general population, a significantly greater effect on left ventricular mass among women with obesity and hypertension has already been shown by our group as well as by others (7,8). It has been hypothesized that the postmenopausal hormonal changes render the female heart highly susceptible to hypertrophic stimuli (37). As with the concurrence of obesity and hypertension, a similar mechanism may play a role when diabetes or pre-diabetes concurs with postmenopause (only 12% of women in our elderly study group were premenopausal) because it has been shown that decreasing levels of estradiol may be responsible for increased left ventricular hypertrophy prevalence in postmenopausal women and that hormone replacement therapy may prevent an increase in left ventricular mass (38). However, only 14% of postmenopausal women in the present study were taking hormone replacement therapy with no significant differences in left ventricular mass. Accordingly, it could be speculated that the presumably low levels of endogenous estradiol in our female and the presumably low levels of testosterone in our mainly elderly male study population may be partly responsible for the observed higher susceptibility of female hearts for hypertrophic stimuli, i.e., adiposity. Additional explanatory effects could be interactions between the signaling effects of estrogen and aldosterone receptors (39,40); however, in the largest study, sex-related differences of serum aldosterone on left ventricular geometry were independent of menopausal status and BMI (41).

Data from other studies showed more pronounced cardiac growth effects in diabetic and prediabetic metabolic states in women compared with men (9,12,28, 42,43). However, whether this was due to a specific sensibility of female diabetic hearts to other left ventricular hypertrophy stimuli such as increased fat mass, which may be suggested from our data, was not investigated.

The greater impact of obesity on left ventricular structure in women may partly explain the increased relative risk for women to develop heart failure and CVD-associated mortality (44,45) because diabetic women are more often obese than are diabetic men (46) and, therefore, may be more prone to development of the prognostically more unfavorable concentric hypertrophy (47).

Study limitations

Because of the cross-sectional nature of our data, strong causal inferences could not be made. Although the size of our study population was greater than that of several previous studies investigating prediabetic and diabetic populations echocardiographically, we cannot exclude the possibility that the power was too low to reveal significant associations with left ventricular mass, for example, in the case of physical activity or microalbuminuria. Furthermore, we did not measure plasma insulin levels or directly estimated insulin resistance to account for the effects of insulin resistance independently or in addition to the effects of adiposity, although previous studies showed that at least in nondiabetic populations the effects of insulin seemed to be mostly mediated by adiposity (48).

In summary, we suggest that the impact of specific determinants of left ventricular structure in elderly subjects with type 2 diabetes or pre-diabetes differs from that in the general population because fat mass in particular was a major

determinant in these mostly postmenopausal women, but not in men. Our study thus indicates potential explanations for the risk differences between men and women for cardiac morbidity and mortality associated with diabetes and underscores the need for activities focused on weight reduction in those with prediabetes and diabetes.

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