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The Importance of Age and Obesity on the Relation Between Diabetes and Left Ventricular Mass

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OBJECTIVES The study investigated the relation of age with diabetes, obesity and hypertension on left ventricular mass (LVM).

BACKGROUND Epidemiological studies demonstrate a general rise of LVM with aging, but whether this phenomenon is independent or a function of coexisting diseases that accompany the aging process is unclear. Although obesity, hypertension and diabetes often coexist and increase in prevalence with age, studies of LVM in diabetics have been reported in mostly nonobese populations, and with little regard to the age-hypertension-obesity interactions and effects on LVM.

METHODS We prospectively measured LVM in 875 consecutive, mostly obese individuals (673 men, 202 women). Clinical data were obtained by chart review and clinical history. Echocardiographic measurements of LVM (American Society of Echocardiography criteria) were calculated using the Devereux formula and corrected for height$^{2.7}$ (LVM/Ht).

RESULTS Mean age was 49.3 ± 12.3 years, body mass index 33.3 ± 8.0 kg/m^2, and LVM/Ht$^{2.7}$ 41.7 ± 13.4 g/m$^{2.7}$. Of the total cohort, 673 patients were men, 519 obese, 228 hypertensive, and 52 diabetic. Of the 519 obese, 183 were hypertensive and 44 were diabetic (22 of those were hypertensive). Of the 228 hypertensives, 183 were obese and 26 were diabetic. On multivariate analysis, obesity ($p = 0.0001$), age ($p = 0.0001$), hypertension ($p = 0.0003$) and diabetes ($p = 0.02$) were all independently associated with LVM/Ht$^{2.7}$. Obesity was the most potent independent predictor of LVM/Ht$^{2.7}$, associated with an increase of 8.1 g/m$^{2.7}$ in LVM/Ht$^{2.7}$. In diabetics, obesity had a synergistic effect on LVM/Ht$^{2.7}$ ($p = 0.006$), which was further amplified by age ($p = 0.03$).

CONCLUSIONS Age, obesity, hypertension and diabetes are all independent determinants of LVM. The magnitude of the effect of diabetes on LVM is mainly consequent to a significant interaction of diabetes with obesity and age. (J Am Coll Cardiol 2001;37:1957–62) © 2001 by the American College of Cardiology

Left ventricular mass (LVM) is a strong predictor of cardiovascular morbidity and mortality (1). Epidemiological studies demonstrate a general rise in LVM with advancing age, but whether this phenomenon is independent (i.e., part and parcel of the aging process) or a function of coexisting disease states that accompany the aging process is not clear (2–7). Obesity and hypertension, two major determinants of LVM, tend to increase with age and, when combined, are characterized by a high prevalence of diabetes (8), which in itself has been independently linked to left ventricular hypertrophy (LVH) (9). Pathological and echocardiographic studies of LVM in diabetics, who tend to be older, obese and often hypertensive (10), to date have been reported in mostly nonobese populations (11–13), with little attention to the potential age-hypertension-obesity interactions and effects on LVM.

Because some of these factors are modifiable and potentially influence morbidity and mortality, we planned this study to evaluate the contribution of these factors and their potential interactions on LVM in a large cohort of mostly obese patients with a wide age range, high prevalence of hypertension and a substantial number of diabetics. We hypothesized that there is a significant interaction among these factors, and specifically, that the effects of diabetes on LVM may be related to aging and to the presence of hypertension and obesity.

METHODS

The study population consisted of 953 consecutive patients from the metropolitan Toronto area referred for echocardiography as part of cardiopulmonary investigation for further evaluation of dyspnea and fatigue. From this total, 875 (91.2%) patients, 673 men and 202 women, aged 49.3 ± 12.3 years, mean body mass index (BMI) 33.3 ± 8.0 kg/m^2, had satisfactory echocardiographic images and were included in the study.

Diabetes was defined according to the American Diabetes Association guidelines at the time of the study (fasting glucose of >7.8 mmol/liter) and treated by the primary care physician. No data are available regarding the degree of glycemic control.

Hypertension was defined and treated by the primary care

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Abbreviations and Acronyms

ASE	= American Society of Echocardiography
BMI	= body mass index
CAD	= coronary artery disease
DM	= diabetes mellitus
IVS	= interventricular septum
LVEDD	= left ventricular end diastolic dimension
LVH	= left ventricular hypertrophy
LVM	= left ventricular mass
$LVM/Ht^{2.7}$	= left ventricular mass corrected for $height^{2.7}$
PW	= posterior wall

physician in accordance with the Fifth Joint National Committee (resting blood pressure >160/90), the accepted guidelines at the time of the study. Coronary artery disease (CAD) was defined clinically by a known history of angina or myocardial infarction and by chart review. In addition, weight and height were measured, and BMI calculated in every patient. As widely accepted, patients with BMI >30 kg/m^2 were classified as obese (14,15).

Echocardiographic methods. Echocardiographic studies were performed at rest with the patient at steady state in the left lateral position, using commercially available Hewlett-Packard 1000 or newer systems with 2.5-MHz transducers and reviewed by two experienced readers. Two-dimensional guided M-mode measurements of left ventricular end diastolic dimension (LVEDD), interventricular septal thickness and posterior wall (PW) thickness were measured at the left ventricular (LV) minor axis at the level of the chordae tendinae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography (ASE) (16). Every effort was made to obtain optimal echocardiographic images, with the M-mode cursor perpendicular to the LV long axis.

The LVM was calculated using measurements of LVEDD, interventricular septum (IVS) and PW thickness, made according to the standard ASE leading-edge-to-leading-edge methodology, at the onset of the QRS complex on a simultaneously acquired electrocardiogram. The LVM was calculated using the corrected ASE formula described by Devereux et al. (17): $LVM\ (g) = 0.80\ [1.04 \times (LVEDD + IVS + PW)^3 - LVDD^3] + 0.6$. The LVM was corrected for $height^{2.7}$ ($LVM/m^{2.7}$) by dividing it by $height^{2.7}$ as previously reported (18) and expressed in units of grams per $meter^{2.7}$ ($g/m^{2.7}$). Thus, LVH was defined as $LVM/Ht^{2.7}$ >47 $g/m^{2.7}$ for women and >50 $g/m^{2.7}$ for men (18). Echocardiographic parameters were measured by consensus by two experienced observers, blinded to the clinical and metabolic data. Interobserver variability of LVM assessment in the obese population in our laboratory has been previously published (19).

Statistical analysis. All values for quantitative measures are expressed as the mean ± 1 SD. Categorical variables are presented as percent. Comparisons across groups were performed by using the two-tailed Student *t* test when comparing continuous variables and chi-square test when comparing categorical variables.

The contribution of the different risk factors (including gender, age, BMI, CAD, hypertension and diabetes) to the $LVM/Ht^{2.7}$ was determined by a multivariate linear regression. Only the interaction terms that were statistically significant were retained in the final models. Plots were made to show the predicted $LVM/Ht^{2.7}$ for varying BMI and age and interactions with diabetes. Additional models, evaluating the contribution of the different predictors on LVM in men and women separately as well as excluding the patients with CAD, were also calculated. All statistical significance was assessed at the 0.05 level. Statistical analysis was performed utilizing the SAS statistical package, version 6.12 (SAS Institute, Cary, North Carolina).

RESULTS

The average age of the study population was 49.3 ± 12.3 years, BMI 33.3 ± 8.0 kg/m^2 and $LVM/Ht^{2.7}$ (41.7 ± 13.4 $g/m^{2.7}$. Of the 875 patients, 673 (77%) were men, 519 (59.3%) were obese, 228 (26%) were hypertensive, and 52 (6.0%) were diabetic. Of the 519 obese patients, 183 (35.3%) were hypertensive and 44 (8.5%) were diabetic (22 of those were hypertensive). Of the 228 hypertensives, 183 (82.6%) were obese and 26 (11.4%) were diabetic (22 of those were obese). One hundred and thirty (57%) of the hypertensive patients were on antihypertensive therapy, and the remaining 98 were managed with diet and lifestyle modification. Fifty-two patients (31 men) were diabetic, 26 of which (50%) were hypertensive (22 of those were obese). Twenty-seven (51.9%) of the diabetics were on hypoglycemic medications and 25 were diet controlled.

Baseline characteristics of the overall study population and according to the presence of obesity are described in Table 1.

Results of the multivariate linear regression analysis are summarized in Table 2. Several predictors demonstrated an independent and additive effect on LVM. Obesity was found to be the strongest correlate of $LVM/Ht^{2.7}$ followed by CAD, hypertension, and age.

Multivariate predictors of $LVM/Ht^{2.7}$. **GENDER.** There were no significant gender-based differences in $LVM/Ht^{2.7}$ ($p = 0.9$).

CAD. This was an independent predictor of $LVM/Ht^{2.7}$ ($p = 0.02$), associated with an increase of 4.1 $g/m^{2.7}$ in $LVM/Ht^{2.7}$.

HYPERTENSION. Hypertension was an independent predictor of $LVM/Ht^{2.7}$, associated with an increase of 3.6 $g/m^{2.7}$ on $LVM/Ht^{2.7}$.

OBESITY. Obesity was the most potent independent predictor of $LVM/Ht^{2.7}$ ($p = 0.0001$), associated with an increase of 8.1 $g/m^{2.7}$ in $LVM/Ht^{2.7}$. When using BMI as a continuous variable, every 4 kg/m^2 increase in BMI was associated with a 2.94 $g/m^{2.7}$ increase in $LVM/Ht^{2.7}$.

Table 1. Clinical Characteristics of the Study Population

	Obese (n = 519)	Nonobese (n = 356)	p Value	All (n = 875)
Age (yrs)	49.5 ± 12.4	48.9 ± 12.1	0.4*	49.3 ± 12.3
Men	383 (73.8%)	290 (81.5%)	0.008†	673 (77%)
BMI (kg/m^2)	38.1 ± 6.9	26.3 ± 2.6	0.0001*	33.3 ± 8.0
Hypertension	183 (35.3%)	45 (12.6%)	0.001†	228 (26%)
CAD	46 (8.9%)	11 (3.1%)	0.001†	57 (6.5%)
Diabetes	44 (8.5%)	8 (2.3%)	0.001†	52 (6%)
LVM/$Ht^{2.7}$ ($g/m^{2.7}$)	45.9 ± 14.3	35.2 ± 8.3	0.0001*	41.7 ± 13.4

*Two-sample *t* test. †Chi-square test.
BMI = body mass index; CAD = coronary artery disease; LVM/$Ht^{2.7}$ = left ventricular mass corrected for $height^{2.7}$.

AGE. Age was a significant predictor of LVM/$Ht^{2.7}$ (p = 0.0001), associated with a 1.4 $g/m^{2.7}$ increase in LVM/$Ht^{2.7}$ for every 10-year increase in age.

DIABETES. Diabetes was a significant predictor of LVM/$Ht^{2.7}$ (p = 0.02), with its major impact expressed through significant interactions with age and obesity. For example, in a 49-year-old patient with BMI of 33 kg/m^2 (mean age and BMI in our study population), diabetes is associated with an increase of 0.24 $g/m^{2.7}$ in LVM/$Ht^{2.7}$, whereas in a patient with the same age, but with a BMI of 40 kg/m^2, diabetes is associated with an increase of 3.49 $g/m^{2.7}$ in LVM/$Ht^{2.7}$.

Interaction among age, diabetes, and obesity on LVM. The effect of the age and obesity on LVM/$Ht^{2.7}$ in the study population is shown in Table 2. A strong interaction existed between obesity and diabetes on LVM/$Ht^{2.7}$ (p = 0.006), which was further amplified by the age (p = 0.03), as seen in Figure 1.

When analyzing men and women separately, the effect of age and obesity as strong independent predictors of LVM/$Ht^{2.7}$ was again demonstrated, but their interaction with diabetes appeared to be more gender based. As all diabetic women in this study were obese, an interaction between BMI (as a continuous measure of severity of obesity) and diabetes was evaluated in this subgroup. In women, a significant interaction between BMI and diabetes on LVM/$Ht^{2.7}$ (p = 0.003) was present and was amplified by age (p = 0.005). In men, a strong interaction between diabetes and obesity was again demonstrated (p = 0.0001), but not with age. We found no further significant interactions between the other analyzed variables on LVM.

Model excluding patients with CAD. Excluding all the patients with CAD from the analysis did not significantly modify the results. Hypertension (p = 0.0003), obesity (p = 0.0001) and age (p = 0.0001) were all significant determinants of LVM/$Ht^{2.7}$ with a persistent significant interaction between diabetes and obesity on LVM/$Ht^{2.7}$ (Table 3, Fig. 2).

Table 2. Multiple Linear Regression Analysis: Determinants of LVM/$Ht^{2.7}$ (n = 875)

	Estimate	SE	95% CI	p Value
Intercept	28.2	13.8	26.1, 30.4	0.0001
Obesity	8.1	0.87	7.2, 9.0	0.0001
Gender	−0.1	0.97	−1.1, 0.9	0.9
Age	0.14	0.03	0.11, 0.18	0.0001
HTN	3.6	0.99	2.6, 4.7	0.0003
CAD	4.1	1.7	2.3, 5.9	0.02
Diabetes	−20.6	9.2	−30.4, −10.9	0.02
Age-DM*	0.31	0.14	0.16, 0.46	0.03
DM-Obesity*	12.9	4.7	7.9, 17.9	0.006

*Interaction.
CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; LVM/$Ht^{2.7}$ = left ventricular mass corrected for $height^{2.7}$; SE = standard error.

DISCUSSION

In this study we analyzed the impact of age, obesity, hypertension, CAD, and diabetes mellitus (DM) on LVM in a large cohort of a mainly obese patient population. Obesity was the strongest predictor of LVM in this population, and its effects on LVM were additional to the clear and independent effects of age, CAD, and hypertension. Diabetes is an independent predictor of LVM, but its effects are magnified through significant interactions with obesity and increasing age.

The present study results differ in several respects from previous studies that have shown the association between LVM and DM, the most important of which is the inclusion of a large number of obese and hypertensive subjects, allowing an analysis of the effects of DM on LVM in relation to these most common associated factors. The results indicate that in addition to the independent effects of obesity, hypertension, age, CAD, and DM on LVM/$Ht^{2.7}$, the increased LVM found in diabetics is mainly consequent to the interaction of diabetes with obesity, which is amplified by the aging process.

Table 3. Multiple Linear Regression Analysis: Determinants of LVM/$Ht^{2.7}$ excluding CAD (n = 818)

	Estimate	SE	95% CI	p Value
Intercept	27.3	1.8	25.4, 29.2	0.0001
Obesity	8.2	0.9	7.3, 9.1	0.0001
Age	0.16	0.03	0.12, 0.20	0.0001
Hypertension	3.7	1.01	2.6, 4.8	0.0003
DM-Obesity*	8.4	2.1	6.2, 10.6	0.0001

*Interaction.
CAD = coronary artery disease; CI = confidence interval; DM = diabetes mellitus; LVM/$Ht^{2.7}$ = left ventricular mass corrected for $height^{2.7}$; SE = standard error.

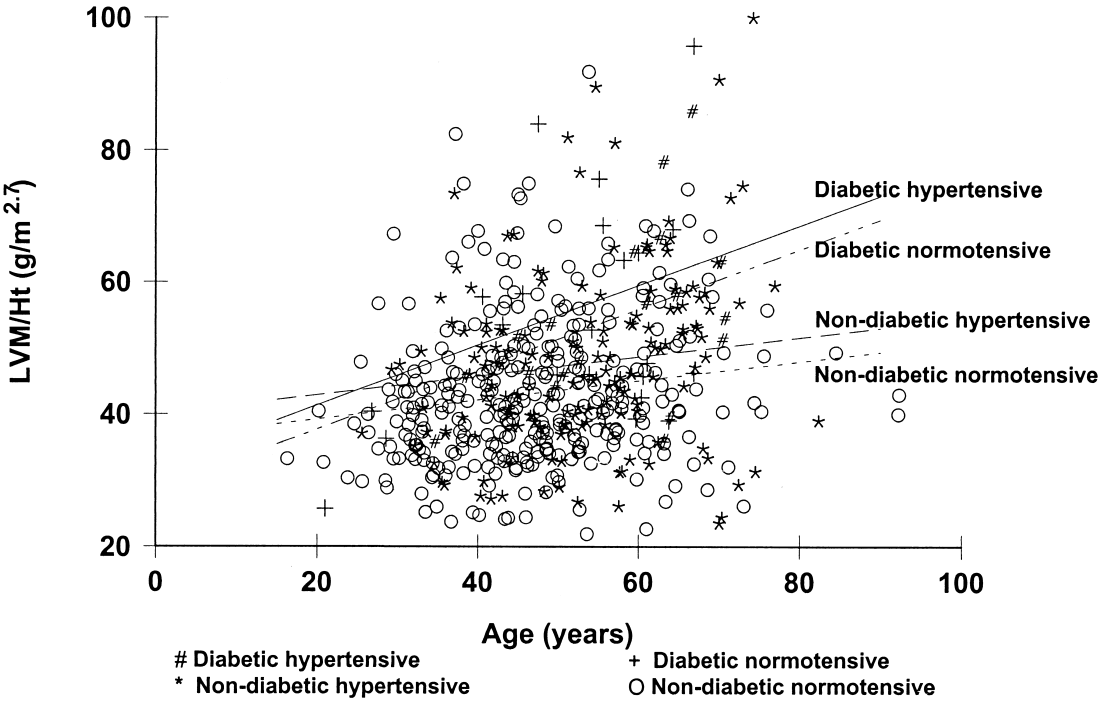

Figure 1. Interaction of age with diabetes on left ventricular mass corrected for height$^{2.7}$ (LVM/Ht$^{2.7}$) in the presence of obesity (n = 875).

Obesity, hypertension and LV mass. The prevalence of hypertension in North America varies from 4% in the 18 to 24-year-old group to as high as 60% in the 65 to 74-year-old group (2). Obesity, a condition that affects one-third of the North American population (20), magnifies the risk of hypertension by a factor of 1.9 to 5.6 and much more so in patients with android or central body obesity (21).

In the Framingham Heart Study, obesity was an independent predictor of echocardiographic LVH (2), with a 51% increase in the risk of LVH in women and a 47% increase in men for every 2 kg/m^2 increment in BMI. More important was the additive effect of obesity and hypertension, which resulted in a 17-fold increase in LVH from the group with low pressure and normal weight to the group with higher pressure and highest BMI. Our study supports these findings, with an overall prevalence of LVH of 23.5%, which is dependent on BMI and hypertension, ranging from 3.6% in the healthy lean individuals to 54.5% in diabetic obese hypertensives (Fig. 3).

Pathological examination of the gross and microscopic anatomy of hearts of patients with marked chronic obesity showed the heart weight to be considerably greater than predicted by extrapolation from ideal body weight, with LV dilation and hypertrophy and occasionally right ventricular hypertrophy (22). This increase was due mostly to myocardial hypertrophy, occasionally associated with myocardial

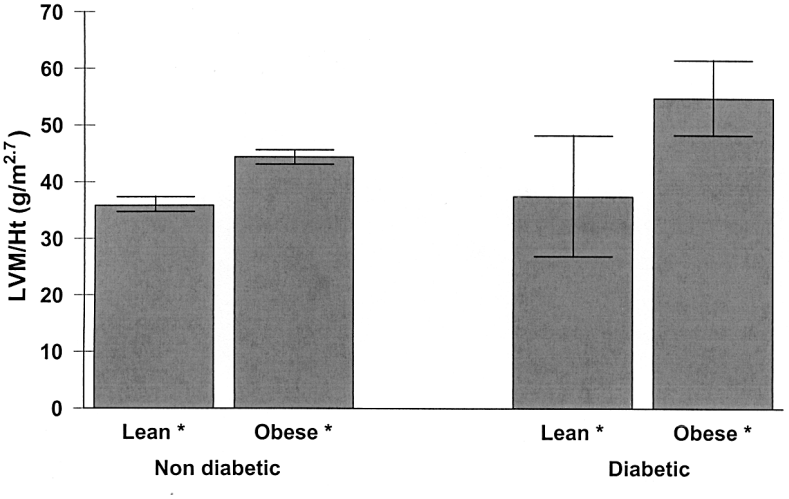

Figure 2. Interaction of obesity with diabetes on left ventricular mass corrected for height$^{2.7}$ (LVM/Ht$^{2.7}$), excluding coronary artery disease patients (n = 818).

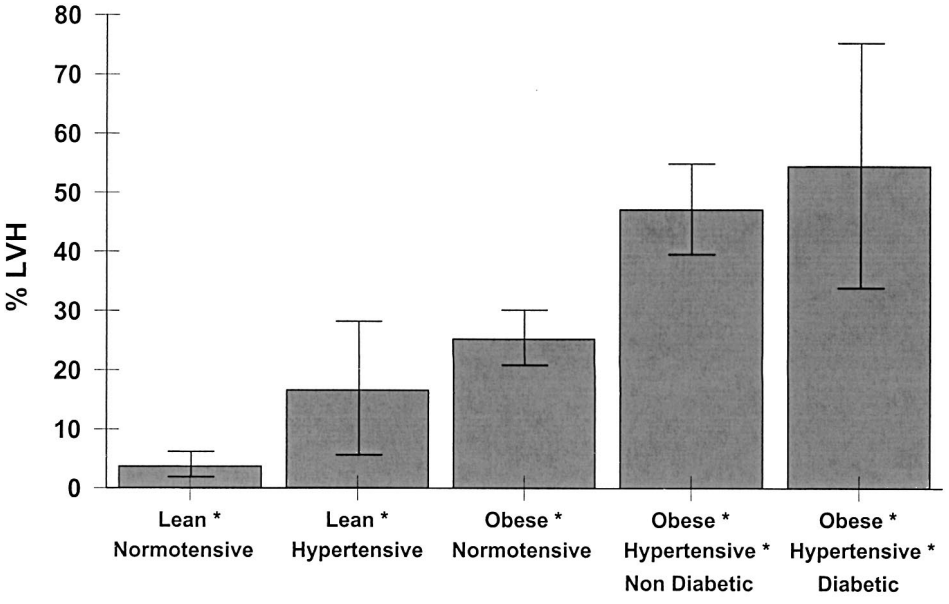

Figure 3. Prevalence of left ventricular hypertrophy (LVH) according to obesity, hypertension, and diabetes (n = 875).

fibrosis, and not to excess epicardial fat or fatty infiltration of the myocardium, previously thought to be principal features of the obese heart (23).

Diabetes, hypertension and LVM. The overall prevalence of DM in the North American adult population is 6.6%, most of whom are obese (10,24), and hypertension is twice as frequent in people with diabetes as it is in those without (25). An association between diabetes and LVM was previously reported by Galderisi et al. (9), but no further data on BMI, the prevalence or severity of obesity in the diabetic population, were presented.

The association of DM and hypertension with LVH had been previously studied, but not in relation to obesity. Grossman et al. (12) studied 25 diabetic hypertensives and found that septal and PW thickness and consequently LVMI (LVM indexed to body surface area) were increased in diabetic hypertensives in comparison to matched nondiabetic hypertensives and to normal controls. Average age was 59 ± 10 years, but the mean BMI of 28.7 ± 5.5 kg/m^2 among the diabetic hypertensives was much lower than in our study (40.2 ± 9.4 kg/m^2), and the prevalence of obesity was not reported.

In a study by Van Hoeven and Factor (11) of patients who died from congestive heart failure, the cardiac pathologic features found at autopsy in diabetics were compared to those seen in patients with either diabetes with hypertension or hypertension alone. Patients with both diabetes and hypertension were found to have greater LV wall thickness and the heaviest hearts, suggesting additive effects or possibly an interaction. Body mass index was not described, and the impact of obesity on LVM in these patients was not assessed. Our results further extend these previous findings by demonstrating the role of obesity as an amplifier of the effects of DM on LVM.

Age and LVM. Previous studies have reported discrepant findings on the relation between age and LVM. Although the effects are modest, our findings support those of Levy et al. (2) and Koren et al. (3), who described a progressive increase in LVM with increasing age, which was independent of BMI and hypertension.

Additionally, our results confirm the findings by Galderisi et al. (9) of an interaction between age and diabetes on LVM in women, but importantly we relate it to the coexistence of obesity. The reason for the significant effects of age on LVM in obese diabetic women is still unknown, but is consistent with previous findings of a higher cardiovascular morbidity and mortality in this population (26,27).

Study limitations. This cross-sectional study is limited by design to observational differences between groups. More than 90% of the patients studied were Caucasians, and our findings cannot be extrapolated to African-Americans, a population with a high prevalence of obesity-diabetes-hypertension. Additionally, this was a referred population with dyspnea and fatigue, and although a selection bias cannot be excluded, the large number of patients included in the study—all with normal LV function—and the high prevalence of dyspnea and fatigue of undefined etiology among the general obese population lend further validity to these findings. Effect of severity of hypertension and pharmacologic therapy on LV mass in the various subgroups could not be measured, as these data were not available. In addition, as 87% of the hypertensive women were obese and as obesity is a more potent predictor of LVM, the modest effects of hypertension on LVM were relatively minimized by the effects of obesity, rendering them statistically insignificant in this subgroup.

Finally, the prevalence of diabetes in this study was very low, even among the obese. Although not well evaluated,

this is likely explained by a lower prevalence in our population of some of the correlates of DM in the obese, including duration and severity of obesity (28,29), distribution of obesity (30), family history (31), ethnic background (32) and older age (33).

CONCLUSIONS

Our results confirm the independent association of age, CAD, hypertension, obesity, and DM with LVM. Obesity, a preventable disorder and a current epidemic, is the strongest determinant of LVM, and its effects on LVM are additive to those of age, hypertension, and diabetes.

The magnitude of the effects of diabetes on LVM is mainly consequent to the interaction of diabetes with obesity and aging. As diabetic subjects are usually older and obese, these interactions explain most of the increase in LVM in this population.

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