Insulin Resistance Is an Important Determinant of Left Ventricular Mass in the Obese

Zion Sasson, MD; Yosef Rasooly, MD; Teosar Bhesania, MD; Iris Rasooly, MD, MPH

Background. Obesity in adults is associated with increased left ventricular (LV) mass. The mechanism for this is unclear, however. We tested the hypothesis that insulin resistance is an important independent contributing factor to LV mass in the healthy obese population.

Methods and Results. The study population consisted of 40 normotensive, nondiabetic, otherwise healthy obese subjects with body mass index (BMI) >25 kg/m². LV mass was echocardiographically determined according to the Penn convention, using the formula of Devereux and Reichek. Insulin resistance was assessed using indices derived from Intravenous Glucose Tolerance Test (IVGTT): insulin level at baseline, insulin level at 90 minutes of IVGTT (insulin-90), insulin integration over 90 minutes of IVGTT, and rate of glucose disposal (k value). Insulin-90 (r=.61, P=.0001), k value (r=.55, P=.003), insulin integration over 90 minutes (r=.46, P=.003), basal insulin (r=.44, P=.005), and BMI (r=.59, P=.0001) were all strongly correlated with LV mass by univariate analysis. No significant correlation was found with blood pressure or age. In multivariate regression analysis, only insulin-90 and k value correlated significantly with LV mass (P=.03, P=.02, respectively), accounting for 50% of the variance of LV mass, whereas the association with BMI became insignificant (P=.2).

Conclusions. LV mass in the normotensive nondiabetic obese population is strongly associated with, and may be mediated by, the degree of insulin resistance and its associated hyperinsulinemia, independent of BMI and blood pressure. (Circulation. 1993;88[part 1]:1431-1436.)

Key Words • obesity • left ventricle • hypertrophy • myocardium • echocardiography • insulin

Obesity in adults is associated with increased left ventricular (LV) mass,1-3 a powerful independent predictor of cardiovascular morbidity and mortality.4 The mechanism for this increase in LV mass in the obese is not clearly understood. Although hypertension, a common cause of LV hypertrophy, is frequent in obesity, recent data from the Framingham Heart Study demonstrated that the increased LV mass in the obese occurs independently of hypertension.1 The obese state is also characterized by insulin resistance and compensatory hyperinsulinemia,5,7 which may directly promote myocardial hypertrophy through the insulin-like growth factor-1 receptors (IGF-1).8 This hypothesis has been advanced as a potential pathogenetic mechanism for LV hypertrophy in other hyperinsulinemic states9 and is supported by the presence of abundant IGF-1 receptors in the myocardium.10 The role and possible relation of the insulin-resistant state with LV mass in the otherwise healthy obese has not been investigated. The present study examines this relation using echocardiographically determined LV mass and indices of insulin resistance derived from the Intravenous Glucose Tolerance Test (IVGTT). The study population consists of subjects with varying degrees of obesity who were otherwise healthy and free of diabetes and high blood pressure.

Methods

Study Population

The study population consisted of healthy, normotensive, obese adults who were recruited through the media in the metropolitan Toronto area. Obesity was defined as body mass index (BMI) >25 kg/m², corresponding to over 110% of ideal body weight.11 Exclusion criteria were (1) history of hypertension or systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg measured in either of two separate visits, (2) history or clinical evidence of ischemic heart disease (myocardial infarction or angina pectoris), congestive heart failure, valvular heart disease, or chronic pulmonary disease, (3) ECG tracing showing rhythm other than sinus or evidence of myocardial infarction or ischemia (patients with nonspecific ST-T abnormalities or electrocardiographic criteria for LV hypertrophy were not excluded), (4) history of diabetes mellitus, (5) treatment with any of the following medications known to affect glucose tolerance or LV mass: corticosteroids, β-blockers, thiazide diuretics, vasodilators, calcium antagonists, and angiotensin converting enzyme inhibitors, and (6) pregnancy. All subjects had a stable weight (<5% variability for the preceding year). None had limitations in their daily activities and none were involved in a regular exercise program. To determine eligibility for the study, participants underwent a struc-
tured clinical interview and a detailed physical examination. Of the first 60 obese responders, 12 were excluded for the following medical conditions: 3 for ischemic heart disease, 2 for diabetes mellitus, and 7 for hypertension.

The 48 subjects who met the above criteria underwent, on the same day, a detailed echocardiographic examination and an IVGTT. Based on the results, 8 subjects were excluded from the analysis for the following reasons: 5 were found to have abnormal IVGTT (k value ≤0.9%/min) indicating impaired glucose tolerance and probably inadequate insulin secretion; 2 had technically inadequate echocardiographic study for analysis; and 1 subject was excluded because of inadequate blood sampling. The findings of the remaining 40 patients were analyzed. All these patients were healthy and normotensive, with normal glucose tolerance tests. All had normal echo-Doppler study with normal LV systolic function and no structural abnormalities except for minimal mitral or tricuspid regurgitation, increased LV mass, or LV hypertrophy in some subjects.

Informed consent was obtained from all participants after the nature and purpose of the study were fully explained. The study protocol was approved by the Ethics Committee on Human Research at the University of Toronto.

Weight, Height, and Blood Pressure Measurements

Weight (kilograms) and height (meters) were measured conventionally. BMI (kilograms per square meter) was calculated and used as an index of obesity. Mild/moderate obesity is generally defined as BMI of 25 to 31 kg/m² and severe obesity as BMI >31 kg/m². These categories correspond to 110% to 140% and >140% of ideal body weight, respectively, as defined by the Metropolitan Life Insurance Co tables. Arterial blood pressure was measured in the left arm using the first and fifth phases of the Korotkoff sounds by mercury column sphygmomanometer after 10 minutes of rest in the supine position. A large cuff was used in patients with a large arm circumference. The average of three consecutive blood pressure measurements, taken before the metabolic investigations, was used for analysis.

Echocardiographic Methods

All echocardiographic studies were performed using a commercially available ATL Ultramark 8 system with 2.25- and 3.0-MHz transducers. Echocardiograms were obtained at rest with the patient at steady state in the left lateral position. Two-dimensional guided M-mode measurements of LV end-diastolic dimension (LVDD), interventricular septum thickness (IVS), and posterior wall thickness (PW) were measured at the left ventricular minor axis at the level of the chordae tendinae just beyond the mitral leaflet tips, as recommended by the American Society of Echocardiography. Every effort was made to obtain optimal echocardiographic images, with the M-mode cursor perpendicular to the LV long axis.

LV mass was calculated using measurements of LVDD, IVS, and PW, made according to the Penn convention at the onset of the QRS complex on a simultaneously recorded ECG. The average of two cardiac cycles was used for data analysis. LV mass was calculated using the formula of Devereux and Reichek: \[ \text{LV mass (g)} = 1.04 \times [(\text{LVDD} + \text{IVS} + \text{PW})^3 - (\text{LVDD})^3] - 13.6. \] LV mass was corrected for height (meters) by dividing it by height (LV mass/height) as previously reported and expressed in units of grams per meter.

Echocardiographic parameters were measured by consensus of two experienced observers, blinded to the clinical and metabolic data. Interobserver variability of LV mass assessed by repeat measurements of a random sample of 15 study patients was small, with coefficient of variation of 5.3% and correlation coefficient (r) of .92 (P<.0001).

Metabolic Investigations

The insulin and glucose response to the IVGTT was evaluated as previously described. Each participant was instructed to adhere to a diet rich in carbohydrates (at least 250 g daily) and to refrain from extreme physical exercise or inactivity for at least 5 days before the investigation. Patients were admitted to the Clinical Investigations Unit at the Wellesley Hospital on the morning of the study after an overnight fast (10 to 12 hours). The IVGTT was performed with a bolus injection of 300 mg of glucose per kilogram of body weight (in a 50% solution). The glucose bolus was given within 1.5 minutes. Venous blood samples for glucose and insulin levels were drawn at -10, -5, 2, 4, 6, 8, and 10 minutes from the glucose injection and then every 10 minutes up to 90 minutes. Plasma glucose (millimoles per liter) was measured by the glucose oxidase method using a Beckman glucose analyzer (Beckman Instruments, Fullerton, Calif). Plasma insulin (picomoles per liter) was measured by radioimmunoassay using a Pharmacia insulin kit (Uppsala, Sweden). Baseline fasting insulin and glucose levels were defined as the average of the two samples taken at -10 and -5 minutes. The following metabolic indices were used to quantify the degree of insulin resistance: insulin level at baseline (fasting) and at 90 minutes of IVGTT (insulin-90), insulin integration over 90 minutes of IVGTT, and the \( k \) value, a quantitative measure of the rate of glucose disposal.

The \( k \) value was calculated from the formula: \( k = 100 \ln \frac{t_2}{t_2-t_1} \), where \( t_1 \) is the elapsed time (in minutes) by which the glucose concentration declined to one half of its peak level. All assays and above calculations were performed at the Banting and Best Diabetes Center Core Research Laboratory, University of Toronto.

Statistical Analysis

All statistical analyses were conducted using the STATVIEW II statistical package (MacIntosh). Summary data are expressed as mean±1 SD and range (minimum to maximum) when appropriate. A two-tailed unpaired Student's \( t \) test was used to compare LV mass of subjects with insulin resistance indices above the median with those with values below the median. Linear univariate regression analysis was used to estimate the strength of association between LV mass and the following variables: BMI, indices of insulin resistance, age, and blood pressure. Multivariate analysis was used to determine which of the important univariate variables were significant independent predictors of LV mass and the strength of these associations.
TABLE 1. Clinical, Echocardiographic, and Metabolic Characteristics of the Study Group (n=40)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±1 SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical/demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>48±13</td>
<td>27-71</td>
</tr>
<tr>
<td>Men</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89.9±16.7</td>
<td>67.2-128.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168±9</td>
<td>152-196</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.6±5.4</td>
<td>25-44.6</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124±11</td>
<td>104-140</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>77±8</td>
<td>60-90</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass, g</td>
<td>180±42</td>
<td>108-274</td>
</tr>
<tr>
<td>LV mass/height, g/m</td>
<td>109±25</td>
<td>67-169</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal insulin, pmol/L</td>
<td>77±39</td>
<td>30-174</td>
</tr>
<tr>
<td>Insulin-90, pmol/L</td>
<td>131±142</td>
<td>25-672</td>
</tr>
<tr>
<td>Insulin integration, pmol/L per minute×10⁸</td>
<td>18.2±12.5</td>
<td>6.3-62.0</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>5.1±0.4</td>
<td>4.4-6.0</td>
</tr>
<tr>
<td>k value, %/min</td>
<td>1.5±0.4</td>
<td>0.9-2.53</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; LV, left ventricular; insulin-90, insulin level at 90 minutes of Intravenous Glucose Tolerance Test (IVGTT); insulin level, integration, integration of insulin above zero over 90 minutes of IVGTT; and k value, rate of glucose disposal derived from IVGTT.

Results

Study Population

The study population consisted of 40 healthy, normotensive, nondiabetic subjects (18 men and 22 women) with mean age of 48±13 years and varying degrees of obesity (BMI, 31.6±5.4; range, 25.0 to 44.6 kg/m²). The clinical, echocardiographic, and metabolic characteristics of the study group are presented in Table 1. There were no significant differences between men and women with respect to BMI (31.1±5.9 and 32.5±2.9 kg/m², respectively; P=.6), LV mass/height (110±26 and 107±24 g/m, P=.4), and metabolic parameters (insulin levels at baseline and 90 minutes and insulin integration over 90 minutes of IVGTT as well as k value).

Univariate Correlates of LV Mass

Linear regression analysis was performed to define the strength of the correlation between LV mass and BMI, blood pressure, age, and indices of insulin resistance (Table 2). LV mass was strongly correlated with BMI (r=.59, P=.0001), insulin-90 (r=.61, P=.0001), and k value (r=.55, P=.003) and less strongly with basal insulin and insulin integration over 90 minutes of IVGTT (r=.44, P=.005 and r=.46, P=.003, respectively). Age and blood pressure showed a weak and nonsignificant correlation with LV mass. Similar results for univariate correlates of LV mass were obtained when analyzing the men and women separately (for BMI, r=.66 and .54, respectively; for insulin-90, r=.56 and .66; and for k value, r=.67 and .44; P<.05 for all these analyses). Dividing the study population into two equal subgroups according to the median value for each of the metabolic parameters (above and below the median) revealed that those with higher insulin levels (baseline level >65 pmol/L, 90-minute level >75 pmol/L, and insulin integration over 90 minutes >14 pmol/L per minute×10³) and similarly, those with decreased glucose disposal rate (k value <1.4), had significantly greater LV mass/height compared with those with lower insulin levels and higher glucose disposal rate. No significant differences in the male/female ratio was found among those subgroups (Figure).

Multivariate Analyses of LV Mass Correlates

The various metabolic indices of insulin resistance were significantly intercorrelated, with correlation coefficients ranging from r=.38 to .88. To determine which of these indices were truly independent (of the other metabolic indices) in predicting LV mass, a multivariate analysis was constructed specifically to control for this strong intercorrelation. After inclusion of all the metabolic variables in this model, insulin-90 and k value were found to be the only significant independent predictors of LV mass (P=.03 and P=.04, respectively).

Multivariate regression analysis was then performed to determine the relative contribution of insulin-90, k value, and BMI (the only other variable associated with LV mass by univariate analysis) to LV mass (Table 3). The multiple r for the model was .72. Both insulin-90 and k value were found to be significant and independent predictors of LV mass (P=.03 and P=.02, respectively), whereas the association of BMI to LV mass became insignificant (P=.2). When age was added to this model, it was not significantly associated with LV mass, and the significant association between LV mass and insulin-90 persisted (P=.01) independently of BMI and age. In a separate stepwise multiple regression model of insulin-90, k value, and BMI (in that order), insulin-90 accounted for 37.0% of the total variance in LV mass and, when combined with k value, for 49.4% of
the variance. In this model, the addition of BMI accounted for only an additional 2.3% increment (to a total of 51.7%) to the variance in LV mass. Adding age and blood pressure (although controlled for by the inclusion criteria) to the above variables in the model did not significantly improve the prediction of LV mass. Similar results were obtained when analyzing the men and women separately.

Discussion

In this study we examined the impact of insulin resistance on LV mass in 40 healthy, nondiabetic, normotensive subjects with varying degrees of obesity. The major finding was that LV mass was strongly related to the degree of insulin resistance, specifically to the hyperinsulinemic response to glucose challenge. This relation was independent of body weight, age, and blood pressure. Although BMI and insulin resistance were both found to be strong univariate predictors of LV mass, insulin resistance remained the only independent predictor of LV mass in multivariate analysis, accounting for 50% of the variance in LV mass. These findings suggest that the increased LV mass of obesity may be mediated in large part through its associated insulin resistance and compensatory hyperinsulinemia.

The metabolic characteristics and distribution of increased LV mass in our study group are similar to other obese populations reported in the literature. The findings of a strong association between the degree of obesity and severity of insulin resistance and between obesity and LV mass are concordant with previous reports in larger study populations and are typical of the general obese population. In particular, the recent report from the Framingham Heart Study demonstrated in 3922 healthy normotensive participants that obesity of even mild to moderate degree was strongly correlated with increased LV mass independently of age and blood pressure. The unique contri-

**TABLE 3. Multivariate Predictors of Left Ventricular Mass (n=40)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>.96</td>
<td>.74</td>
<td>1.67</td>
<td>.204</td>
</tr>
<tr>
<td>Insulin-90</td>
<td>0.06</td>
<td>.03</td>
<td>5.06</td>
<td>.030</td>
</tr>
<tr>
<td>k Value</td>
<td>-18.95</td>
<td>7.55</td>
<td>6.30</td>
<td>.016</td>
</tr>
<tr>
<td>Intercept</td>
<td>98.47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple r</td>
<td>.72</td>
<td></td>
<td></td>
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</tbody>
</table>

BMI indicates body mass index (kg/m²); insulin-90, insulin levels at 90 minutes of Intravenous Glucose Tolerance Test (IVGTT); k value, rate of glucose disposal derived from IVGTT; multiple r, multiple correlation coefficient; SE, standard error.
bution of our study to this literature is that, to the best of our knowledge, it is the first to examine and to demonstrate that LV mass in these patients is related more to the metabolic abnormalities associated with obesity, namely, insulin resistance, than to the obesity itself as expressed by the BMI. The similarity in our study population between men and women, with regard to BMI, LV mass/height, and the metabolic parameters for insulin resistance as well as the similar results obtained in the sex-specific analyses, suggest that our conclusions are applicable to both men and women.

The association of increased LV mass with insulin resistance and hyperinsulinemia has been described previously in several rare genetic disorders such as leprechaunism and total lipodystrophy as well as in other metabolic diseases such as acromegaly and hypothyroidism. It also has been demonstrated in infants of diabetic mothers and in infants with nesidioblastosis, both conditions characterized by intratropical hyperinsulinemia. The findings of our study extend this possible causal relation between hyperinsulinemia and LV mass to obesity, an extremely common condition and, in all likelihood, the most common hyperinsulinemic state.

One possible mechanism by which hyperinsulinemia might induce myocardial hypertrophy is through its growth-stimulating/anabolic effect. Insulin may stimulate growth by binding to either the insulin receptors or the IGF-1 receptors due to its structural similarity to the IGF-1 polypeptide. Activation of the IGF-1 receptors by insulin has been demonstrated in increased insulin concentrations similar to those found in our obese population and has been shown to result in increased DNA synthesis, protein synthesis, and cell proliferation in various tissue cultures. In particular, Banskota et al have demonstrated this effect of insulin in a human vascular smooth muscle preparation. Ito et al recently expanded on these observations and demonstrated in a rat myocardial preparation that activation of the IGF-1 receptor did in fact lead to hypertrophy of the cardiomyocytes by increasing mRNA levels for muscle-specific genes (myosin light chain 2, α-actin, and troponin I) and stimulating protein synthesis.

A second mechanism by which hyperinsulinemia might lead to myocardial hypertrophy in the obese is by increasing blood volume via its effect on sodium reabsorption in the kidney. Hyperinsulinemia leads to increased sodium reabsorption by the kidney in both obese and nonobese subjects under euglycemic conditions. This may be due to a direct renal effect of insulin or to indirect effect(s) through stimulation of the sympathetic nervous system or impairment of atrial natriuretic peptide activity. It is of interest that obese subjects with hyperinsulinemia maintain normal sensitivity to the sodium-retaining effect of insulin despite their insulin resistance with respect to carbohydrate metabolism. The increase in sodium reabsorption probably accounts for the expanded extracellular fluid, blood volume, and increased cardiac output demonstrated in the obese. These changes in blood volume and cardiac output may lead, over time, to an adaptive increase in LV mass.

Our study has several limitations, some of which are addressed below. First, insulin resistance was assessed indirectly with IVGTT-derived metabolic indices, using insulin and glucose levels at baseline and after glucose challenge. This method provides an accurate and reliable measurement of insulin resistance in subjects with normal or high basal insulin levels and intact insulin response to glucose challenge. It becomes inaccurate in those subjects with inadequate insulin secretion, in which a more direct measurement of insulin resistance such as the glucose clamp or minimal model technique may be required. However, as we excluded subjects with diabetes or impaired glucose tolerance and as our study population had higher than normal insulin secretion rates, we feel confident that insulin resistance has been adequately demonstrated by the method used. This is further supported by the strong correlation found in our study between the degree of obesity and the IVGTT-derived metabolic parameters, which is in accordance with the well-established association between obesity and insulin resistance.

Second, a possible limitation of this study is the lack of control groups. These would ideally consist of subjects with similar degrees of obesity but normal insulin sensitivity or, conversely, of subjects with normal body weight but with insulin resistance. Such control groups would have isolated insulin resistance and body weight, respectively, as the specific variables under study and thus would allow a more specific evaluation of their intercorrelation and contribution to LV mass. However, these are largely hypothetical control groups that would be inappropriate for the study. The first (obese subjects with normal insulin sensitivity) is highly unusual, as obesity and insulin resistance are strongly correlated and, therefore, even if found, would not be representative of any easily identifiable patient population. The second (normal-weight subjects with insulin resistance) would mostly consist of certain hypertensive and diabetic patients who would have multiple confounding effects on LV mass (hypertension) and measurements of insulin resistance (diabetes). It would therefore seem that, in the absence of appropriate control groups, that controlling the various variables can be adequately achieved statistically by multivariate analysis, as used in this study. The appropriateness of this method was ensured by the wide range of degrees of obesity and insulin resistance in our study population, which allowed for the assessment of the relative contribution of each to LV mass.

Third, the observations and conclusions of this study do not apply to obese subjects who are hypertensive, as hypertension was controlled for by exclusion in the study design. In this regard, it is interesting to note that hypertension itself has been shown to be an insulin-resistant state, independent of obesity, and that hypertensive obese subjects have higher insulin levels than normotensive obese subjects. Thus, hypertension might provide an additional mechanism by which insulin could induce increased LV mass in the obese. Further studies are needed to clarify the relative effect of insulin on the LV mass in obese subjects with hypertension.

We conclude that the variation in LV mass in the normotensive, nondiabetic, obese population may be mediated primarily through the degree of insulin resistance and its compensatory hyperinsulinemia independent of the degree of obesity and blood pressure. Further longitudinal studies would be required to establish a causal relation between increased LV mass in
the obese and insulin resistance and hyperinsulinemia. When considered in conjunction with recent reports that insulin resistance can be modified by pharmacological and nonpharmacological means, these results should stimulate further research to assess the effect of such interventions on LV mass and the morbidity and mortality associated with it in the obese.

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