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Original Article

The relationship between left ventricular mass and insulin resistance in obese patients☆

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ABSTRACT

Objective: In this study, we investigated the relationship between left ventricular mass and insulin resistance in obese patients.

Methods: A total of 90 subjects, 66 women, and 24 men, with an age range from 24 to 56 years, were enrolled in the study. Forty-nine patients were in the obesity group whose body mass index (BMI) was >29.9 kg/m^2 and 41 subjects were in the control group with a BMI <25 kg/m^2. All of them were normotensive, nondiabetic, and did not have any cardiovascular disease. They were not taking any medication. Weight, height, and waist circumference were measured and BMI was calculated. Plasma glucose, insulin, serum total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglyceride levels were measured, and insulin resistance was calculated via homeostasis model of assessment-estimated insulin resistance (HOMA-IR). Subjects were examined by echocardiography and left ventricular mass (LVM) and index (LVMI) were calculated with Devereux formula.

Results: Insulin levels, HOMA-IR, LVM, and LVMI were significantly higher in obesity group ($p < 0.01$). Fasting glucose, triglyceride, fasting insulin levels, and waist circumference did not correlate with LVMI.

Conclusion: In conclusion, though findings of the present study suggest increased left ventricular hypertrophy (LVH) in obese subjects compared to controls, it appears that the increased LVM or LVH is not linked to BMI and insulin resistance in this study population.

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1. Introduction

Cardiovascular disease (CVD) constitutes one of the major causes of deaths and disabilities, globally claiming 17.3 million lives a year. Incidence of CVD is expected to rise to 25 million by 2030.[1] In 2008, 30% of all global deaths is attributed to CVD. Death caused by cardiovascular diseases is also higher in low- and middle-income countries, as over 80% of all global deaths caused by cardiovascular diseases occurred in those countries.[2–4] Changes in the left ventricular structure increase the risk of cardiovascular diseases and death.[5] The risk of acute myocardial infarction, congestive heart failure, sudden death, ventricular ectopy, serious arrhythmias, and other cardiovascular events increases sixfold to eightfold with the occurrence of left ventricular hypertrophy (LVH).[6,7]

☆ This work was carried out at the Okmeydani Training and Research Hospital, Istanbul, Turkey.

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LVH, which leads to increase in left ventricular mass (LVM), poses a serious risk for an increase in cardiovascular diseases and deaths caused by them.[8] LVH can be prevented by eliminating the factors leading to increased LVM, but the nature of the factors that cause an increase in LVM is yet to be completely understood among normotensive and even among hypertensive individuals.[9,10] A prior study reports that no change in the LVM was observed in 25–30% of individuals with high blood pressure. These observations support the views that there are other metabolic and genetic factors effective in cardiac mass increase.[11]

Obese patients have persistent myocardial wall stress because of an increase in circulatory volume and minute volume.[12] There are studies suggesting a relationship between obesity and cardiac mass increase as well.[13,14] Duration of obesity is significantly correlated with LVH.[15] In vivo studies have shown that insulin resistance (IR) and hyperinsulinemia have effects on LVM.[16,17] Additionally, in vitro studies have shown that with the IR-associated hyperinsulinemia impact, an increase is observed in sympathetic stimulation, peripheral vascular resistance, renal sodium retention, cardiac workload, and the anabolic effect on cardiac proteins.[17,18] Some studies have determined an independent relationship between insulin level and cardiac mass.[18,19] However, it has not been completely proven that IR is an independent indicator of the LVM increase.[20]

According to the TEKHARF and the TURDEP I studies conducted in Turkey, prevalence of obesity was 28% and 32%, respectively.[21,22] TURDEP II study reported that obesity in Turkey increased by 40% compared to that reported in 1998, and that overweight and obese patients constitute 2/3 of the Turkish population.[22] Therefore, the aim of our study was to investigate the relationship between obesity, a significant health issue in Turkey, and IR, hyperinsulinemia, blood lipid level disorders, and LVM, which are commonly associated with obesity.

2. Materials and methods

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from each subject following a detailed explanation of the protocol of the study. All study procedures were conducted in accordance with the ethical principles stated in the ''Declaration of Helsinki''.

The study included 49 obese patients whose body mass indices (BMI) were equal to or greater than 30 kg/m^2 and 41 healthy subjects with BMI < 25 kg/m^2. The participants included in the study did not have history of hypertension, diabetes (familial or self), or drug therapy. Patients with blood pressure over 140/90 mmHg[23] and fasting plasma glucose level over 100 mg/dl were excluded from the study. The thyroid function tests, urea, and creatinine levels of the patients were within the normal range. There was no history of smoking in either patient or control groups. Atrial fibrillation, presence of intraventricular electrodes, ischemic heart disease, hypertrophic cardiomyopathy, congenital heart disease, valve prostheses, chemotherapy, pericarditis, intracardiac masses or thrombi, moderate or severe valvular stenosis or regurgitation, cor pulmonale, pulmonary thromboembolism, or heart failure were excluded from study.

Age and gender information of all individuals were recorded. Weight measurements were made with thin clothing and no shoes on the same scale (Arzum Peso Model AR535, China, 2008). Height measurements were made bare foot. BMI was calculated with the weight (kg)/height^2 (m) formula. Waist circumference (WC) was measured with a measuring tape at the level of the umbilicus. Blood pressure of the patients was measured from both arms after a rest of at least 15 min using a sphygmomanometer (Erka).

Glucose, total, very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL)-cholesterol, triglyceride, and insulin levels of the patients were measured in the venous blood sample drawn after 12-h fasting by a clinical biochemistry otoanalyzer (Olympus AU2700). Low-density lipoprotein (LDL)-cholesterol value was calculated using the Fridewalt formula.[24]

Insulin levels were measured via chemiluminescence method via Beckman Coulter DXİ 800 (Miami, USA 2006) device in the serum sample obtained from venous blood after 10 min of centrifugation at 3000 rpm. In each subject, the degree of IR was estimated at the baseline by homeostasis model of assessment (HOMA) method described by Matthews et al.[25] In particular, a homeostasis model of assessment-estimated insulin resistance (HOMA-IR) score was computed with the formula of ''fasting plasma glucose (mmol/L) $\times$ fasting serum insulin (mU/L) divided by 22.59''.[25]

All of the patient and control group participants received echocardiography (GE Vivid 3 pro, Indiana, USA). In case of 10 or more cycles, left ventricular diastolic diameters and thickness of posterior wall and septum in diastole in 2D parasternal long-axis position were measured by using 2.5 MHerz probes in the left lateral decubitus position.

LVM was calculated via Devereux formula.[26] LVM index (LVMI) was calculated as LVM divided by the body surface area. Males with LVMI >134 g/m^2 and females with LVMI >110 g/m^2 were considered to have LVH.[26]

Statistical analyses were conducted using the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software packages (UTAH, USA). Unpaired t test and Mann–Whitney U test was used for comparisons based on the distribution pattern of the numerical data. Chi-square test was used to compare categorical data. Associations between the parameters were evaluated with the Pearson and Spearman's correlation analyses where appropriate. The results were evaluated as significant when $p < 0.05$ within a 95% confidence interval.

3. Results

3.1. *Baseline characteristics*

The mean age of the obese group was 36.9 $\pm$ 7.61 years (range 25–56 years) and of the control group was 34.17 $\pm$ 7.77 years (range 24–56 years), with no significant difference between groups ($p = 0.097$). There were 40 (81.6%) females and 9 (18.4%) males in the obese group; and 26 (63.4%) females and 15 (36.6%) males in the control group. The groups did not differ significantly in terms of gender distribution ($p = 0.052$).

Table 1 – Blood biochemistry findings in obesity and control groups.

	Control group ($n = 41$) Mean ± SD (median)	Obesity group ($n = 49$) Mean ± SD (median)	p value
Glucose (mg/dl)	82.07 ± 9.33	87.84 ± 8.69	0.003
Total cholesterol (mg/dl)[a]	178.39 ± 30.73	197.39 ± 36.98	0.01
LDL (mg/dl)[a]	98.95 ± 24.79	115.73 ± 33.75	0.01
VLDL (mg/dl)[b]	18.12 ± 12.86 (13)	28.98 ± 13.93 (26)	0.0001
HDL (mg/dl)[a]	64.59 ± 17.07	50.98 ± 8.54	0.0001
Triglyceride (mg/dl)[b]	81.76 ± 46.91 (62)	144.49 ± 69.02 (137)	0.0001
Insulin (μU/mL)[b]	5.82 ± 2.75 (5.6)	12.95 ± 8.05 (10.95)	0.0001
HOMA-IR[b]	21.26 ± 11.55 (20.93)	50.75 ± 32.13 (41.76)	0.0001

SD: standard deviation; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis model of assessment-estimated insulin resistance.
[a] Student t test.
[b] Mann–Whitney U test.

The mean BMI of the obese cases was 37.63 ± 5.43 kg/m^2 for females and 37.76 ± 7.96 kg/m^2 for males; and the waist circumference of females was 112.35 ± 10.87 cm and of males was 117.22 ± 18.08 cm. These values in the control group were 20.97 ± 1.76 kg/m^2, 21.85 ± 1.90 kg/m^2, 72.15 ± 5.72 cm, and 81.86 ± 9.96 cm, respectively. The control group and the obesity group were significantly different in terms of their BMI and WC values ($p = 0.0001$; $p = 0.0001$; $p = 0.0001$; $p = 0.0001$, respectively).

The mean BMI of the overall study population was 30.2 ± 9.34 kg/m^2 for all cases, 37.66 ± 5.88 kg/m^2 for obesity group and 21.29 ± 1.84 kg/m^2 control group; and the waist circumference of all cases was 96.14 ± 21.71 cm, of obesity group was 113.24 ± 12.42 cm, and of control group was 75.71 ± 8.81 cm. The control group and the obesity group were significantly different in terms of their BMI and WC values ($p = 0.0001$; $p = 0.0001$, respectively).

3.2. *Blood biochemistry findings*

Plasma glucose, total, LDL and VLDL cholesterol, and triglyceride levels of the control and the obesity groups were compared, which yielded that these levels were higher among the obese patients with a statistically significant difference (Table 1). HDL level was found lower in obesity group than control group ($p = 0.0001$). The mean plasma insulin level of all cases was 9.7 ± 7.15 μU/mL, and was 12.95 ± 8.05 μU/mL and 5.82 ± 2.75 μU/mL for the obesity and control groups, respectively. The difference between the insulin levels of the obese and the control groups was statistically significant ($p = 0.0001$). The mean HOMA-IR level of all cases was 37.32 ± 28.89, which was found to be 50.75 ± 32.13 in the obesity group and 21.26 ± 11.55 in the control group. The difference between the two groups was statistically significant ($p = 0.0001$) (Table 1).

3.3. *Echocardiographic findings*

The obesity group's interventricular septal and left ventricular posterior wall thicknesses (IVST and LVPWT), and left ventricular internal diameter at diastole (LVID) were compared to the control group, and all values were found to be significantly higher (Table 2). The mean LVM of all cases was 160.85 ± 50.73 g, 191.82 ± 44.15 g in the obesity group and 123.84 ± 28.42 g in the control group. The obesity and control groups differed significantly in terms of mean LVM ($p = 0.0001$) (Table 2). LVMI of all cases was 85.88 ± 19.22 g/m^2, while it was 95.31 ± 17.83 g/m^2 and 74.6 ± 14.19 g/m^2 in the obesity and the control groups, respectively. The difference between the two groups was statistically significant ($p = 0.0001$) (Table 2).

3.4. *Correlation of BMI with glycemic parameters*

A positive significant correlation of BMI with insulin ($r = 0.386$, $p = 0.013$ and $r = 0.317$, $p = 0.027$; respectively) and HOMA IR ($r = 0.324$, $p = 0.023$ and 0.346, $p = 0.027$, respectively) was noted in control and obesity groups.

3.5. *Correlation of LVMI with laboratory and anthropometric parameters*

No significant association of LVMI values was noted with glycemic and lipid parameters as well as with waist circumference in control and obese groups, while in the overall population, LVMI was positively correlated with waist circumference ($r = 0.527$, $p < 0.001$), BMI ($r = 0.513$, $p < 0.001$), triglyceride ($r = 0.311$, $p = 0.003$), insulin ($r = 0.340$, $p = 0.001$), and HOMA-IR ($r = 0.314$, $p = 0.003$) levels (Table 3).

Table 2 – The echocardiographic findings in obesity and control groups.

Echocardiographic findings	Control group ($n = 41$) Mean ± SD	Obesity group ($n = 49$) Mean ± SD	p value
IVST	0.88 ± 0.11	1.05 ± 0.14	0.0001
LVID	4.39 ± 0.54	4.92 ± 0.49	0.0001
LPWT	0.86 ± 0.14	1.02 ± 0.17	0.0001
LVM	123.84 ± 28.42	191.82 ± 44.15	0.0001
LVMI	74.6 ± 14.19	95.31 ± 17.83	0.0001

IVST: interventricular septal thickness; LVID: left ventricular internal diameter at diastole; LVPWT: left ventricular posterior wall thicknesses; LVM: left ventricular mass; LVMI: left ventricular mass index.

Table 3 – The correlation of LVMI with laboratory and anthropometric parameters.

	LVMI					
	Control group		Obese group		All patients	
	r	*p* value	*r*	*p* value	*r*	*p* value
Fasting glucose	0.083	0.607	0.065	0.658	0.119	0.265
Waist circumference	0.164	0.185	0.065	0.657	0.527	<0.001
BMI	0.013	0.935	0.061	0.675	0.513	<0.001
LDL	0.12	0.457	−0.173	0.235	0.140	0.189
Triglyceride[a]	0.002	0.988	−0.009	0.95	0.311	0.003
Insulin[a]	0.058	0.717	−0.069	0.635	0.340	0.001
HOMA-IR[a]	0.149	0.340	−0.155	0.298	0.314	0.003

LVMI: left ventricular mass index; BMI: body mass index; LDL: low-density lipoprotein; HOMA-IR: homeostasis model of assessment-estimated insulin resistance.
[a] Spearman's rho correlation analysis was used.

Table 4 – Left ventricular mass with respect to HOMA-IR categories in the overall study population (below vs. above median value).

HOMA-IR	Left ventricular mass		*p* value
	Mean ± SD	Median (min–max)	
≤27.74 (*n* = 45)	134.7 ± 39.8	119.7 (75.2–250.1)	<0.001
>27.74 (*n* = 45)	187.0 ± 47.1	185.8 (119.6–344.4)	

HOMA-IR: homeostasis model of assessment-estimated insulin resistance.
Mann–Whitney *U* test.

3.6. *LVM values with respect to HOMA-IR categories of below and above median value*

HOMA-IR values of >27.74 than ≤27.74 were associated with significantly higher LVM values (187.0 + 47.1 vs. 134.7 + 39.8, $p < 0.001$) (Table 4).

4. Discussion

Our findings revealed increased levels for plasma glucose, plasma insulin, and HOMA-IR levels as well as increased levels for total cholesterol, LDL cholesterol, VLDL cholesterol, and triglyceride levels in obese than control subjects. Although obese patients had significantly higher values for all echocardiographic parameters including IVST, LVPWT, LVID, LVM, and LVMI, no significant correlation of LVMI was noted with glycemic parameters, lipid parameters, and anthropometrics in the obese group.

Numerous studies have been conducted investigating the relationship between LVM increase and obesity, and majority of them reported to have identified a correlation in-between.[13,14] In a past study on the relationship of BMI with changes in cardiac geometry and function, as evaluated by transthoracic echocardiography in 5898 patients, a significant direct association between BMI and LVM was reported.[12] Evaluation of the relationship between obesity and LVH among 2072 obese adolescents revealed a direct negative effect of obesity on cardiovascular function staging early in teenage years.[27] In a meta-analysis of 22 studies of 5486 patients on the relationship between obesity and LVH, direct correlation between BMI and LVM was concluded.[28]

Cuspidi et al. reported higher rate of eccentric than concentric hypertrophy in obese individuals,[28,29] whereas alike to our findings in obese patients, data from a study by Messerli et al. revealed higher rate of concentric hypertrophy in obese individuals.[30] Prevalence rates of eccentric and concentric LVH showed a great variability across the studies, probably due to differences in demographic/clinical characteristics of obese individuals as well as echocardiographic criteria used to define left ventricular geometric patterns.[28]

There have been studies investigating a suspected causal relationship between IR and LVH as well.[16,18,31] In vitro studies have shown that with the IR-associated hyperinsulinemia impact, an increase is observed in the sympathetic stimulation, peripheral vascular resistance, renal sodium retention, cardiac workload, and the anabolic effect on cardiac proteins. However, none of the studies have demonstrated a significant relationship between LVM and IR or hyperinsulinemia.[20]

On the other hand, in the MESA study, insulin resistance and waist-to-hip ratio were reported to be associated with concentric left ventricular (LV) remodeling independent of BMI. The results of MESA supported the emerging hypothesis that the cardiometabolic phenotype, defined by insulin resistance and central obesity, may play a critical role in LV remodeling independently of BMI.[32] Nonetheless, it should be noted that a growing literature support inflammation and IR as a potential etiology for cardiovascular damage in both "obese" and "nonobese" individuals.[32] Identification of cardiovascular damage also in nonobese individuals seems to emphasize the role of visceral fat distribution and adipositopathy.

Insulin level and HOMA-IR values, indicative of IR, were high in the obesity group patients in this study, and increased waist circumference was observed to have a significant relationship with insulin level and HOMA-IR. Additionally, observation of higher levels of total cholesterol and triglycerides and low HDL-cholesterol in the obesity group than in the control group is indicative of obesity impairing glucose and lipid metabolisms as expected. An Iranian study, conducted with 2309 participants, has also determined that central obesity has a significant relationship with lipid parameters

and severity of obesity.[33] IVST, LVID, LVPWT, LVM, and LVMI levels of the obesity group participants were significantly higher than those of the control group participants in this study. LVH incidence in the obesity group was higher compared to the control group. LVH, LVM, and LVMI were not correlated to glucose, lipid parameters, insulin, HOMA-IR, or waist circumference in this study.

In a past study conducted with 153 healthy individuals from Turkey, no association of LVH was found with either IR or fasting insulin level. Obesity is considered an independent risk factor for LVH.[3] Gubbio study, conducted in 2002 in Italy with 91 normotensive patients, failed to determine a significant association of LVM with insulin and IR.[31]

Another study reported higher levels of LVM increase among obese than nonobese hypertensive patients (52% vs. 30%). In the same study, the increase in LVM was reported to be independent of blood pressure values in obese women.[34] In another study conducted with nondiabetic hemodialysis patients with uremia, insulin resistance and hypertension were reported to be independent risk factors for LVH.[35] Although obese patients in our cohort had increased LVH, LVM, and LVMI, this increase was not correlated with insulin level or HOMA-IR.

Correlation of neither anthropometric nor glycemic parameters with LVMI among obese patients in our cohort seems contrary to common yet inconclusive literature data on determinants of LVH. Albeit relatively low sample size and female gender predominance limit drawing exact conclusions, this seems a novel finding indicating the likelihood of mechanisms other than impaired carbohydrate metabolism or IR along with the possible role of visceral fat distribution and adipositopathy to underlie the increase in LVH, LVM, and LVMI noted among obese patients.

Notably, limited data are available on the relationship of LVMI with hormones and cytokines, such as adiponectin, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6, in the literature.[36] Data from a past study from Turkey revealed the presence of a significant relationship of LVH in nonobese dialysis patients to the increased levels of adiponectin, TNF-alpha, and IL-6. On the basis of the association of increased adiponectin levels with increased proinflammatory cytokines in dialysis patients, adiponectin has been suggested to have a role in the development of LVH.[36]

The present study has a number of limitations that should be taken into account in evaluating the results. First, relatively low sample size prevented us to perform mutually adjusted multivariate analysis to evaluate combined effects of glycemic parameters, lipid parameters, and anthropometrics on LVH parameters in obese patients. Second, due to inclusion of comparatively more females, findings may not prove applicable to general normotensive nondiabetic population. Third, lack of data on proinflammatory status of patients is another limitation, which otherwise would extend the knowledge achieved in the current study.

5. Conclusion

In conclusion, our findings revealed increased IVST, LVPWT, LVID, LVM, and LVMI and poorer glycemic status and lipid profile among obese patients as compared with control subjects, whereas no correlation of LVMI with glycemic, anthropometric, and lipid parameters in obese patients. Though findings of the present study suggest increased LVH in obese subjects compared to controls, it appears that the increased LVM or LVH is not linked to BMI and insulin resistance in this study population. Future studies are needed to explain through which mechanisms obesity causes LVH.

Conflicts of interest

The authors have none to declare.

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