

# Left Ventricular Hypertrophy in Metabolic Syndrome Patients without Hypertension

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**Abstract:** Metabolic syndrome (MetS) is association of group of cardiovascular risk factors that includes insulin resistance, impaired glucose metabolism, obesity, dyslipidemia with high triglycerides and low level of high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure. Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular events. Although left ventricular overload is the main factor responsible for LVH, other factors have been suggested to induce LVH in hypertensive patients like genetic, environmental, and metabolic factors. Previous studies have shown the strong association between MetS and LVH in hypertensive patients. However, the relation between LVH and MetS in the absence of hypertension has not been studied. Aim of the work was to compare between left ventricular mass in metabolic syndrome patients without hypertension and in healthy control subjects. **Subjects and Methods:** One hundred subjects (49 males and 51 females) were included in the study, among them 50 healthy control subjects (26 males and 24 females) and 50 metabolic syndrome patients without hypertension (23 males and 27 females). We excluded patients with hypertension, coronary artery disease, significant valvular or congenital heart disease, or congestive heart failure from the study. All patients were submitted to full history taking and clinical examination with measuring of weight, height, and waist circumference; complete 12-leads electrocardiography (ECG); laboratory testing with measuring of fasting serum lipids, fasting blood glucose, and hemoglobin A1c; and echocardiographic with assessment of left ventricular diastolic (LVEDD) and systolic dimensions (LVESD), fraction of shortening (FS), ejection fraction (EF), Doppler derived mitral valve flow velocity waves (E-wave, A-wave, E/A ratio), left ventricular mass and mass index. **Results:** Regarding clinical and laboratory data there was no significant difference between the study groups concerning age, sex, or smoking, heart rate, systolic and diastolic blood pressure. Mean weight, waist circumference, body mass index, fasting blood glucose level, hemoglobin A1c level, and triglyceride level were significantly higher while mean HDL-c level was significantly lower in patients with MetS than in control subjects. Regarding echocardiographic data (table 3), there was no significant difference between the two groups regarding LVEDD, LVESD, FS, EF, E-wave velocity, A-wave velocity, or E/A ratio. Mean posterior wall thickness, inter-ventricular septal thickness, left ventricular mass, left ventricular mass index, and incidence of LVH were significantly higher in MetS patients. There was a significant positive correlation between LVMI and all of the following: blood glucose level ( $r = 0.528$ ,  $p < 0.00001$ ), hemoglobin A1c ( $r = 0.416$ ,  $p < 0.0001$ ), and triglycerides level ( $r = 0.535$ ,  $p < 0.00001$ ). There was a significant negative correlation between LVMI and HDL-c level ( $r = -0.377$ ,  $p < 0.0001$ ). **Conclusion:** Even in the absence of hypertension, MetS patients had significantly more, LV wall thickness, more LV mass and mass index, and more incidence of LVH than control subjects.

**Keywords:** Metabolic syndrome, Diabetes mellitus, Dyslipidemia, Left ventricular hypertrophy, Left ventricular mass, Echocardiography.

## 1. Introduction

Metabolic syndrome (MetS) is association of group of cardiovascular risk factors. This group includes insulin resistance, impaired glucose metabolism, obesity, dyslipidemia with high triglycerides and low level of high-density lipoprotein cholesterol (HDL-C), and elevated blood pressure (1).

Hypertrophy of the left ventricle is an important and independent risk factor for cardiovascular events (2). So, it is an important therapeutic endpoint in hypertensive patients to prevent and/or to reduce left ventricular hypertrophy (LVH) (3). Although left ventricular overload is the main factor responsible for LVH in hypertensive patients, however LVH does not occur in all hypertensive patients (4).

Other factors have been suggested to increase LV mass in hypertensive patients like genetic factors (5), environmental factors (6), and metabolic factors (7).

It was established that the presence of metabolic syndrome is strongly associated with an increased risk of cardiovascular events, and this risk has been attributed partly to the effect of metabolic syndrome items on the developing of LVH (8).

Previous studies have shown the strong association between metabolic syndrome and increased LV mass in hypertensive patients (3, 9, 10). However, the relation between LVH and metabolic syndrome in the absence of hypertension has not been studied.

AIM OF THE WORK was to compare between left ventricular mass in metabolic syndrome patients without hypertension and in healthy control subjects.

## 2. Subjects and Methods

This study had been carried out in the Internal Medicine and Cardiology Departments, Zagazig University Hospitals, during the period between March 2014 and March 2015.

One hundred subjects, 49 males and 51 females, had been included in our study. The study group included 50 healthy control subjects (26 males and 24 females) and 50 metabolic syndrome patients without hypertension (23 males and 27 females).

Metabolic syndrome was diagnosed if the patient had 3 of the 4 items of metabolic syndrome other than hypertension according to the harmonized definition of MetS provided by the World Heart Federation and the International Association for the Study of Obesity (11), table 1.

**Table 1:** Criteria for diagnosis of MetS

Measure	Cut-Point
Waist circumference	Population and country specific definitions
Triglycerides (*)	≥ 150 mg/dl
High Density Lipo-protein cholesterol (HDL-c) (*)	Men < 40 mg/dl Women < 50 mg/dl
Blood Pressure (*)	≥ 130/ ≥ 85 mmHg
Fasting Blood Glucose (*)	≥ 100 mg/dl

\* **Drug treatment for elevated triglycerides, HDL-c, elevated blood pressure or elevated glucose are alternative indicators (11).**

Central obesity was defined if the waist circumference was ≥ 93.5 cm men and ≥ 92 cm for women (12).

Patients were excluded from the study if they had one or more of the following:

- Hypertension: defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg, or receiving antihypertensive drugs (11).
- Known coronary artery disease.
- Significant valvular or congenital heart disease.
- Congestive heart failure (CHF).

After giving an informed written consent, all subjects were subjected to the following:

- 1) Full history taking.
- 2) Thorough clinical examination, with emphasis on:
  - Body weight and height.
  - Waist circumference: it was measured using an inelastic tape, was taken after expiration at the level of mid-distance between the bottom of the rib cage and the top of the iliac crest (12).
- 3) Complete 12-leads electrocardiography:
- 4) Echocardiography: Echocardiographic and Doppler studies were performed for all subjects using GE VIVID E9 machine with 2.5 MHz transducers. The echocardiograms were obtained at rest with the subjects in the left lateral decubitus position.

The following measures were taken:

- Two-dimensional guided M-mode measurements of left ventricular end-systolic dimension (LVEDD), left ventricular end-diastolic dimension (LVESD), fraction of shortening (FS) and ejection fraction (EF).
- Doppler derived mitral valve flow velocity waves; E-wave, A-wave, and E/A ratio.
- Left ventricular (LV) mass and mass index: LV mass was calculated according to the Cube formula as following (13):

$$0.8 * 1.04 [(IVST+LVID+PWT)^3 - LVID^3] + 0.6 \text{ gm.}$$

Where IVST is the interventricular septal thickness, LVID is the left ventricular internal dimension at end of diastole, and PWT is the thickness of the posterior LV wall. All measures were taken at the end of diastole (13).

Left ventricular mass index was obtained by dividing LV mass by the body surface area in square meters.

Left ventricular hypertrophy was defined as left ventricular mass index ≥ 95 g/m<sup>2</sup> in women and 115 g/m<sup>2</sup> in men (13).

5) Laboratory tests: the following laboratory test were done to all subjects:

- Fasting serum lipids, with measuring of cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-c), and high density lipoprotein cholesterol (HDL-c).
- Fasting and two hours postprandial blood glucose level.

**Statistical analysis:** All data were analyzed using the SPSS 19 package program. Differences between patients' group and control group were analyzed using  $\chi^2$  test and student's t-test. Correlations between different variables were investigated by Pearson correlation analysis. A p value < 0.05 was regarded as being statistically significant.

### 3. Results

We enrolled 100 subjects in our study, 50 metabolic syndrome patients without hypertension and 50 healthy control subjects. Regarding clinical and laboratory data (table 2), there was no significant difference between the study groups concerning age, sex, or smoking, heart rate, systolic and diastolic blood pressure.

Mean weight was significantly higher in patients with metabolic syndrome than in control subjects (95.6±12.34 kg versus 73.5±9.63 kg, p < 0.00001).

Mean waist circumference was significantly higher in patients with metabolic syndrome than in control subjects (99.6±7.11 cm versus 81.3±9.54 cm, p < 0.00001).

Mean body mass index was significantly higher in patients with metabolic syndrome than in control subjects (33±5.12 kg/m<sup>2</sup> versus 24.3±3.31 kg/m<sup>2</sup>, p < 0.00001).

Mean fasting blood glucose was significantly higher in patients with metabolic syndrome than in control subjects (155±25.6 mg/dl versus 88±8.3 mg/dl, p < 0.00001).

Mean hemoglobin A1c was significantly higher in patients with metabolic syndrome than in control subjects (7.96±2.55 % versus 5.11±1.32 %, p < 0.00001).

Mean HDL-c was significantly lower in patients with metabolic syndrome than in control subjects (42.8±7.61 mg/dl versus 55.5±6.43 mg/dl, p < 0.00001).

Mean triglycerides was significantly higher in patients with metabolic syndrome than in control subjects (179±21.3 mg/dl versus 121±16.3 mg/dl, p < 0.00001).

Regarding echocardiographic data (table 3), there was no significant difference between the two groups regarding LVEDD, LVESD, FS, EF, E-wave velocity, A-wave velocity, or E/A ratio.

Mean posterior wall thickness was significantly higher in patients with metabolic syndrome than in control subjects (10.81±1.62 mm versus 8.91±1.65 mm, p < 0.00001).

Mean inter-ventricular septal thickness was significantly higher in patients with metabolic syndrome than in control subjects (10.52±1.86 mm versus 8.83±1.77 mm,  $p < 0.00001$ ).

Mean left ventricular mass was significantly higher in patients with metabolic syndrome than in control subjects (192.8±33.5 gm versus 141.5±15.3 gm,  $p < 0.00001$ ).

**Table 2:** Clinical and laboratory data

	Metabolic syndrome Patients (n = 50)	Control subjects (n = 50)	p
Age (ys)	52.6±6.81	50.4±8.32	> 0.05
Sex Male	23 (46 %)	26 (52 %)	> 0.05
Female	27 (54 %)	24 (48 %)	
Smoking	15 (30 %)	17 (34 %)	> 0.05
Weight (kg)	95.6±12.34	73.5±9.63	< 0.00001
Height (cm)	170.1±13.6	174±12.5	> 0.05
Waist circumference (cm)	99.6±7.11	81.3±9.54	< 0.00001
Body mass index (kg/m <sup>2</sup> )	33±5.12	24.3±3.31	< 0.00001
Heart Rate (beat/minute)	78.1±12.3	73.9±14.4	> 0.05
Systolic blood pressure (mmHg)	122±11.3	118±12.6	> 0.05
Diastolic blood pressure (mmHg)	77±7.3	74±8.6	> 0.05
Fasting blood glucose (mg/dl)	155±25.6	88±8.3	< 0.00001
Hemoglobin A1c (%)	7.96±2.55	5.11±1.32	< 0.00001
HDL-c (mg/dl)	42.8±7.61	55.5±6.43	< 0.00001
Triglycerides (mg/dl)	179±21.3	121±16.3	< 0.00001

**Table 3:** Echocardiographic data

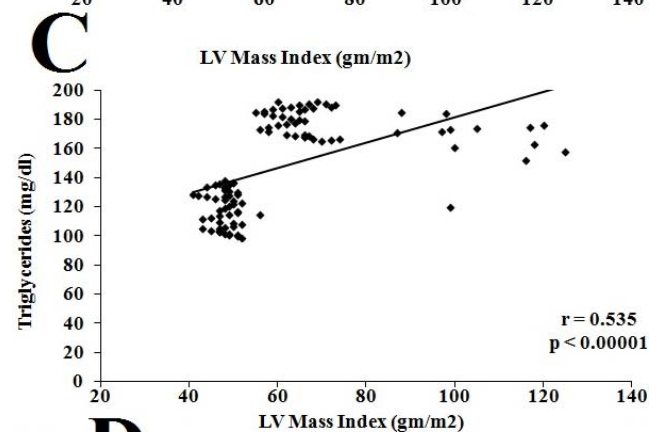
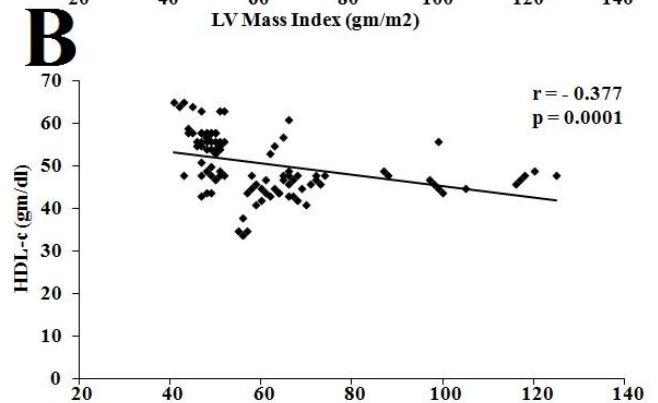
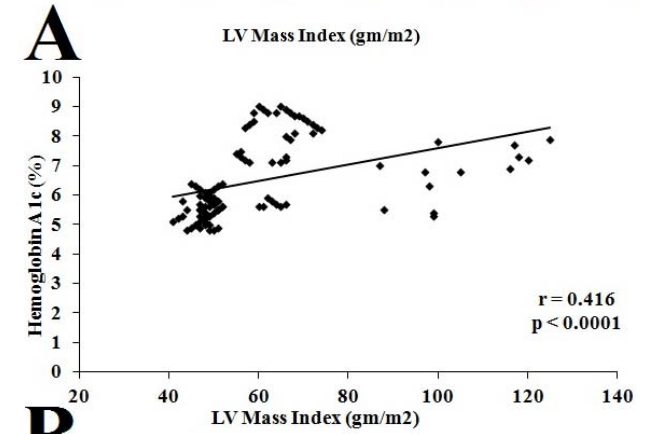
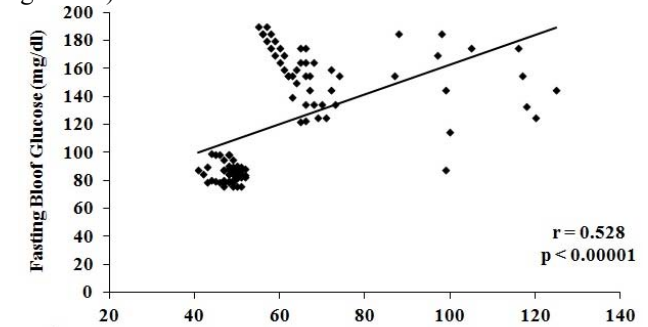
	Metabolic Syndrome Patients (n = 50)	Control Subjects (n = 50)	p
LVEDD (mm)	49.1±5.88	47.3±6.51	> 0.05
LVESD (mm)	32.2±5.31	30.1±5.83	> 0.05
FS (%)	34.4±6.33	36.4±6.18	> 0.05
EF (%)	64.6±8.35	66.8±7.23	> 0.05
PWT (mm)	10.81±1.62	8.91±1.65	< 0.00001
IVST (mm)	10.52±1.86	8.83±1.77	< 0.00001
LV mass (gm)	192.8±33.5	141.5±15.3	< 0.00001
LV mass index (gm/m <sup>2</sup> )	66.6±18.7	46.7±11.6	< 0.00001
Patients with LVH	11 (22 %)	0 (0 %)	0.004
E-wave velocity (cm/s)	87.3±15.6	92.1±13.7	> 0.05
A-wave velocity (cm/s)	90.6±18.4	89.8±17.5	> 0.05
E/A ratio	0.964±0.203	1.026±0.198	> 0.05

Mean left ventricular mass index was significantly higher in patients with metabolic syndrome than in control subjects (66.6±18.7 gm/m<sup>2</sup> versus 46.7±11.6 gm/m<sup>2</sup>,  $p < 0.00001$ ).

Incidence of left ventricular hypertrophy was significantly higher in patients with metabolic syndrome than in control subjects (11 versus 0,  $p < 0.00001$ ).

As shown in figure 1, there was a significant positive correlation between LVMI and fasting blood glucose level ( $r = 0.528$ ,  $p < 0.00001$ , figure 1A).

There was a significant positive correlation between LVMI and hemoglobin A1c concentration ( $r = 0.416$ ,  $p < 0.0001$ , figure 1B).



**Figure 1:** correlation between LVMI and blood glucose level (A), hemoglobin A1C (B), HDL-c (C), and triglycerides (D).

There was a significant negative correlation between LVMI and HDL-c level ( $r = -0.377$ ,  $p < 0.0001$ , figure 1C). There was a significant positive correlation between LVMI and triglycerides level ( $r = 0.535$ ,  $p < 0.00001$ , figure 1D).

#### 4. Discussion

Metabolic syndrome is a cluster of conditions including elevated blood pressure, elevated blood glucose level, central obesity, and abnormal blood lipoproteins levels. This syndrome is associated with an increased risk of cardiovascular disease and stroke (14).

Echocardiographically determined LVH was found to be an important and independent risk factor for developing cardiovascular events in patients with or without coronary artery disease (2).

Krumholz et al (15) have found that hypertensive patients with concentric LVH have a higher risk of cardiovascular events than those with normal LV geometry and this difference widened progressively over a 10-year follow-up, despite use of conventional antihypertensive therapy.

So, it seems beneficial to search for factors responsible for the development of LVH and to treat them, if possible. Incidence of LVH was found to be more in hypertensive patients with MetS than in hypertensive patients without MetS (3, 9, 10).

The effect of MetS on LV geometry is not limited to the developing of concentric LVH. Ratto and his colleagues (16) have found a three times higher risk of developing LV chamber dilatation in hypertensive patients with MetS even after adjusting for other factors.

Our study was carried out to compare between LV dimensions and mass in MetS patients without hypertension and in healthy control subjects.

We have found that MetS patients had significantly more left ventricular wall thickness, more LV mass, and more LV mass index than control subjects. Also there were significantly more patients with LVH among MetS patients.

We also have found a significant positive correlation between LVMI and fasting blood glucose, between LV mass index and hemoglobin A1c, and between LV mass index and triglycerides level. We also have found a significant negative correlation between LV mass index and HDL-c level.

It has been shown that metabolic factors that are present in MetS patients, together with the mechanical factor of hypertension, add an adverse effect on the developing of LVH in hypertensive patients (7).

Many factors may contribute to the development of MetS, however, insulin resistance is thought to be the maestro role in connecting different components of MetS together (17).

Verdecchia and his colleagues (18) have found a strong relation between the level of circulating insulin and left ventricular mass in hypertensive patients even in the presence of normal glucose tolerance. After regression analysis, they found that the 2-hour postload insulin was the most powerful predictor of increased LV mass.

Data from clinical and experimental studies have suggested that insulin have an effect on concentric and eccentric patterns of LV mass growth. This action occurs due to the effect of insulin on stimulation of myocardial cell growth (19-21) and activation of the sympathetic nervous system (22, 23) which may lead to concentric LVH through a direct trophic effect. This effect was found to be, at least partially, mediated through insulin growth factor-1 receptors (19, 20).

In epidemiological studies, high fasting insulin levels were found to be associated with an adverse cardiovascular outcome, independent of other risk factors (24) and this could be explained in part by the effect of insulin on left ventricular structure. In 2008, Salem and Al-Daydamony (25) had studied the relation between LV dimensions and metabolic parameters of insulin resistance in hypertensive non-diabetic patients. They have found that homeostasis model assessment (HOMA) index and fasting blood insulin levels had a significant positive correlation with LV wall thickness, LVM, LVMI.

In addition, it has been demonstrated that insulin stimulates the proliferation of vascular smooth cells and induces the hypertrophy of cardiomyocytes. These effects were found to be mediated by increasing levels of mRNA for muscle-specific genes (myosin light chain, O-actin, and troponin I) and in turn stimulating protein synthesis (20).

However, all the studies that were designed to study the effects of metabolic factors in MetS patients on LV mass and geometry were done on hypertensive patients.

To the best of our knowledge, ours is the first study to compare between LV mass in MetS without hypertension and control subjects.

Our results have shown that the effects of metabolic factors in MetS, like insulin resistance, on LV mass may be working even in the absence of elevated blood pressure and its mechanical effect on LV.

#### 5. Conclusion

Even in the absence of hypertension, MetS patients had significantly more LV wall thickness, more LV mass, and more LV mass index than control subjects. Also there were significantly more patients with LVH among MetS patients. Left ventricular mass index had a significant positive correlation with fasting glucose, hemoglobin A1c, triglycerides, and a significant negative correlation with HDL-c levels. Further researches are recommended to study the prognostic effect of LVH in MetS patients without hypertension.

#### 6. Study Limitations

- Relatively small number of patients.
- We did not follow-up our patients to find out the prognostic effect of increased LV mass in them.



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