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Impact of Adiponectin on Left Ventricular Mass Index in Non-complicated Obese Subjects

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Abstract. To evaluate the relationship between the adiponectin levels and left ventricular mass index (LVMI) in uncomplicated obese subjects. Fifty-nine subjects were assigned to the obese (BMI≥30 kg/m^2) and 58 to the lean (BMI<30 kg/m^2) group. Plasma glucose, insulin, serum total cholesterol and high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and adiponectin were measured. Insulin resistance was determined by the Homeostasis Assessment Model (HOMA-IR). The left ventricular functions of all subjects were determined by 2D and pulse wave Doppler echocardiography. LVMI was calculated as left ventricular mass (LVM) normalized for height in m$^{2.7}$. The obese group displayed significantly higher LVMI and late mitral inflow velocity. Thirty-three obese subjects met the criteria for left ventricular hypertrophy (LVH) and had lower serum adiponectin levels compared with obese subjects without LVH and lean subjects ($p<0.05$). Adiponectin was negatively correlated with LVMI (R: –0.277, p: 0.002). Furthermore, during the partial correlation analysis where HOMA-IR was controlled, the negative correlation between adiponectin and LVMI progressed (r: –0.283, p: 0.002). The linear regression analysis showed an independent relationship between LVMI and adiponectin. (β: –0.214, p: 0.01) Obesity is associated with LVH. This study showed direct influence of adiponectin on LVMI.

Key words: Adiponectin, Left ventricular mass index, Obesity, Echocardiography

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OBESITY leads to serious changes in cardiac structure and functions [1]. These changes are characterized by an increase in left ventricular mass index (LVMI), diastolic dysfunction, and in advanced stages of the condition, systolic dysfunction [2]. It is currently believed that hemodynamic factors alone do not account for obesity-related cardiac structure abnormality. An investigation of possible metabolic inflammatory causes of left ventricular hypertrophy (LVH) in obesity may help the prevention and treatment of these changes [3].

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Recent studies have shown that adipose tissue acts like an endocrine organ and synthesizes various hormones. One of these hormones is adiponectin, which is believed to possess anti-atherogenic and anti-diabetic qualities [4]. Obesity or other obesity related complications are associated with decreased adiponectin levels [4], and thus is believed to play a role in the etiology of a number of diseases such as obesity, insulin resistance, hypertension, dyslipidemia, and atherosclerotic heart disease. Therefore, hypoadiponectinemia may be a factor in obesity-related LVH [5], which may be an independent effect or result of complications, such as obesity or obesity-related insulin resistance and hypertension [5]. Thus, an improvement in adiponectin levels can be expected to lower obesity-related morbidity and mortality [6]. However, there are few studies in

the literature concerning this issue.

The aim of the present study is to evaluate the relationship between adiponectin levels and LVMI in uncomplicated obese subjects.

Materials and Methods

The study was conducted at the Internal Medicine and Cardiology Clinics of Kırıkkale University Medical School in Turkey. All subjects resided in Kırıkkale and had applied to the internal diseases clinic for a check-up and weight loss program. Individuals were included in the study if they were free of diabetes mellitus, hypertension, cardiovascular disease (*e.g.* arrhythmia, valve disease, systolic dysfunction, coronary artery disease etc.) and were not taking any regular medication. The subjects were divided into two groups based on their body mass index (BMI) values: obese (BMI≥30 kg/m^2) and lean (BMI<30 kg/m^2). Fifty-nine subjects were assigned to the obese group and 58 to the lean control group. In addition, all subjects included in the total study group had normal oral glucose tolerance test, fasting glucose (<5.5 mmol/L), normal resting arterial blood pressure (systolic<140 mmHg; diastolic <90 mmHg for at least three measurements). All patients were informed of the study and their informed consent was obtained prior to participation. All measurements were made in accordance with the standard protocol. Therefore, weight, height and waist circumference measurements were made with light clothing and no shoes; body mass index (BMI) values were calculated by dividing body mass into height square; and blood pressure was averaged by 3 different measurements following 15-minute rests.

From the blood samples drawn after 12 hours of fasting, plasma glucose, serum total, HDL cholesterol and triglyceride values were measured using the spectrophotometric method; plasma insulin levels were measured using electrochemiluminescence immunoassay (ECLIA) method; and serum adiponectin levels were measured using the ELISA method. LDL cholesterol was calculated using the Friedewald equation formula. The insulin resistance homeostasis model assessment (HOMA), calculated as fasting plasma glucose concentration (mmol/L) multiplied by fasting plasma insulin concentration (pmol/L) and divided by 22.5, was used as an index of insulin resistance.

Echocardiographic evaluation

The left ventricular functions of all subjects were determined via transthoracic echocardiography using 2D, M-Mode, pulse wave Doppler. The echocardiographic examinations of all subjects were made during rest in left lateral decubitus position, using GE Vivid 7 pro and standard techniques. Echocardiograms were recorded with Echopac PC software for later evaluation. 2D long-axis views were used to obtain linear measurements of left ventricular cavity (Left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD)) and walls (interventricular septum (IVST) and posterior wall (LPWT)), according to the recommendations of the American Society of Echocardiography [7]. Left ventricular mass (LVM) was estimated by using the anatomically validated formula of Devereux *et al*. [7]. $LVM = 0.8\ [1.04\ (IVST + LVEDD + LPWT)^3\text{-}LVEDD^3] + 0.6$. LVM was normalized for height in $m^{2.7}$ to obtain LVMI [8].

Mitral inflow velocities were obtained by pulse wave Doppler in the apical 4-chamber view with the sample volume placed at the tips of the mitral valve leaflets. The peak early (E) and late (A) diastolic mitral inflow velocities and deceleration time were measured and averaged over 5 cardiac cycles during normal respiration. The ratio of early to late peak diastolic mitral inflow velocities was calculated.

Statistical analysis

All variables are expressed as mean ± standard deviation, unless otherwise stated. Pearson's correlation was used to evaluate the association of study variables with adiponectin and HOMA-IR. Partial correlation was used to correct for the effect of HOMA-IR. Comparisons between groups were performed by Student's t test, chi-square test or one-way analysis of variance (ANOVA) as appropriate. Multiple linear stepwise regression analysis was also used to assess the independent relationship between the LVMI and study variables. P value of <0.05 was considered significant. Analyses were performed with the SPSS 11.5 package for Windows.

Table 1. Comparison of selected characteristics between obese and lean subjects (n = 117).

Characteristics	Lean (n = 58)	Obese (n = 59)	*P*
Female/Male	17/41	16/43	.47
Age (years)	43.1 ± 7.3	43.5 ± 7.3	.76
BMI (kg/m^2)	25.90 ± 2.52†	33.03 ± 2.72†	.0003
Waist circumference (cm)	91.88 ± 9.07†	103.79 ± 9.55†	.0002
Systolic blood pressure (mmHg)	118.53 ± 17.60	123.94 ± 18.49	.10
Diastolic blood pressure (mmHg)	77.84 ± 9.42	80.00 ± 10.94	.25
Serum triglycerides (mmol/L)	1.63 ± 0.63*	1.95 ± 0.80*	.01
Cholesterol (mmol/L)	5.62 ± 0.96	5.72 ± 1.00	.56
HDL cholesterol (mmol/L)	1.18 ± 0.21*	1.10 ± 0.23*	.04
LDL cholesterol (mmol/L)	2.86 ± 0.70	2.88 ± 0.79	.84
Fasting plasma insulin (mmol/L)	50.11 ± 31.95*	66.70 ± 30.08*	.002
Fasting blood glucose (mmol/L)	4.22 ± 0.64	4.38 ± 0.76	.17
HOMA-IR	1.81 ± 1.40*	2.41 ± 1.21*	.009
Adiponectin (μg/mL)	6.50 ± 0.65†	5.69 ± 0.97†	.0006

BMI: Body mass index, HOMA-IR: Homeostasis model assessment insulin resistance, HDL: High density lipoprotein, LDL: Low density lipoprotein. Means were compared by Student's test *: p<0.05, †: p<0.001

Table 2. Comparisons of echocardiographic data between obese and lean subjects (n = 117).

Echocardiographic Parameters	Obese (n = 59)	Lean (n = 58)	*P*
Ejection fraction (%)	66.90 ± 6.27	66.63 ± 6.01	0.80
E (m/s)	0.83 ± 0.16	0.80 ± 0.16	0.21
A (m/s)	0.77 ± 0.17*	0.70 ± 0.22*	0.04
E/A	1.11 ± 0.26	1.20 ± 0.28	0.07
E Deceleration time (ms)	255.18 ± 66.49	257.67 ± 81.66	0.84
LVM (g)	190.03 ± 54.49	172.48 ± 47.31	0.06
LVMI (g/m$^{2.7}$)	52.26 ± 13.15†	43.15 ± 11.78†	0.0001

E: Early mitral inflow velocity, A: Late mitral inflow velocity, LVMI: Left ventricular mass index. Means were compared by Student's test.
*: p<0.05, †:p<0.001

Results

Fifty-nine obese subjects and 58 lean control subjects were included in the study between January and June 2005. The demographic, anthropometric and metabolic parameters of obese and lean groups are shown in Table 1, and echocardiographic parameters are given in Table 2. No significant age and sex difference was found between the groups. The obese group displayed significantly higher LVMI and late mitral inflow velocity (A) (Table 2). Thirty-three of the 59 obese subjects had LVH. When compared, there was no significant difference for age, HOMA-IR, BMI, systolic and diastolic blood pressure levels between obese subjects with and without LVH. Adiponectin level was significantly lower in both obese subjects with LVH (5.44 ± 1.13 μg/mL) and without LVH

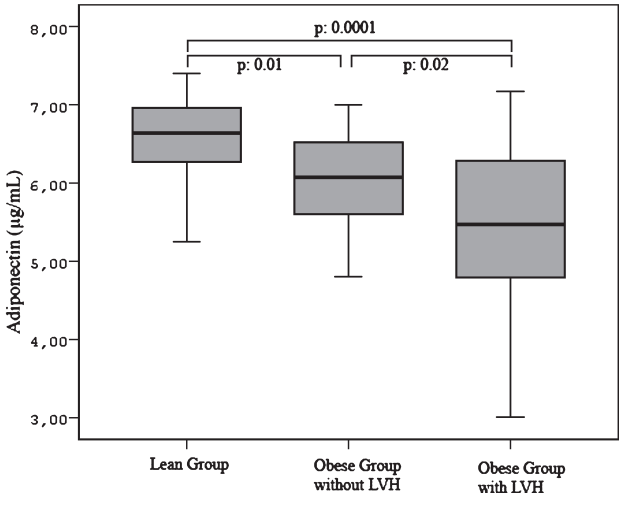

Fig. 1. Comparisons of adiponectin levels between lean subjects and obese subjects with LVH or without LVH.

Table 3. Simple correlation coefficients between study variables and adiponectin.

Variables	R	p
LVMI (g/m$^{2.7}$)	–.277*	.002
HOMA-IR	–.252*	.006
BMI (kg/m^2)	–.461†	.0001
Fasting plasma insulin (mmol/L)	–.270*	.001
Triglyceride (mmol/L)	–.193*	.04
Age (years)	.037	.69
Waist circumference (cm)	–.385†	.0001
Cholesterol (mmol/L)	–.084	.37
HDL cholesterol (mmol/L)	.030	.75
LDL cholesterol (mmol/L)	–.056	.55
Systolic blood pressure (mmHg)	–.018	.84
Diastolic blood pressure (mmHg)	–.053	.56

LVMI: Left ventricular mass index, BMI: Body mass index, HOMA-IR: Homeostasis model assessment insulin resistance, HDL: High density lipoprotein, LDL: Low density lipoprotein.
*: p<0.05, †: p<0.001

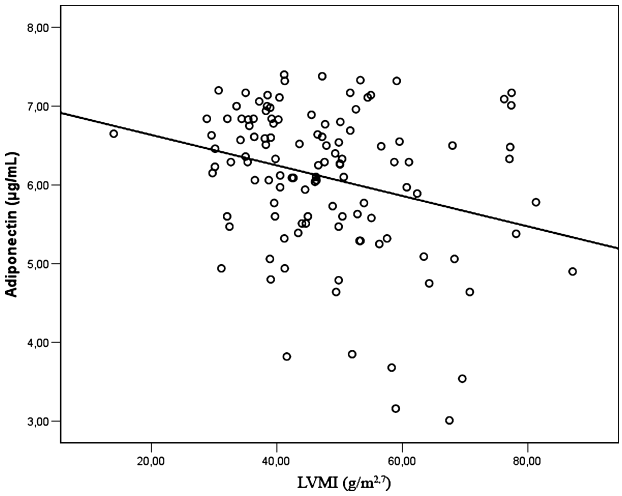

Fig. 2. Correlation between adiponectin and left ventricular mass index (LVMI).

(6.01 ± 0.61 µg/mL) than lean group (6.51 ± 0.66 µg/mL, p: 0.0001 p: 0.01, respectively) (Fig. 1). However, Adiponectin levels of obese subjects with LVH were still lower than those without LVH (adiponectin: 5.44 ± 1.13 µg/mL and 6.01 ± 0.61 µg/mL respectively, p: 0.02) (Fig. 1).

Adiponectin levels correlated negatively with HOMA-IR (R: –0.252, p: 0.006), BMI (R: –0.461, p: 0.0001), fasting insulin (R: –0.270, p: 0.001), waist circumference (R: –0.385, p: 0.0001), triglycerides (R: –0.193, p: 0.04) level and LVMI (R: –0.277, p: 0.002) (Table 3) (Fig. 2) in the Pearson's correlation analysis. Furthermore, during the partial correlation analysis where HOMA-IR was controlled, the negative correlation between adiponectin and LVMI progressed (R: –0.283, p: 0.002). There was no significant correlation between adiponectin and E, A, E/A ratio and Deceleration time (p>0.05). A multivariate analysis was performed using the linear regression with LVMI as the dependent variable and with BMI, HOMA-IR, adiponectin and age as independent variables. LVMI was negatively associated with adiponectin (β: –0.214, p: 0.01), HOMA-IR (β: –0.212, p: 0.03) and positively associated with BMI (β: 3.679, p: 0.002) and age (β: 2.93, p: 0.004).

Discussion

This study showed that obese subjects with LVH had lower serum adiponectin levels than both obese subjects without LVH and lean subjects. Furthermore, the present study revealed a significant inverse relationship between LVMI and serum adiponectin levels in uncomplicated obese subjects. The association was independent of BMI, age and HOMA-IR.

LVH is not infrequent in obese individuals [2]. Although changes to the heart caused by obesity are well-known, the effective mechanisms are not. Despite largely emphasized hemodynamic effects, other metabolic and inflammatory factors may also exist [9].

The increased metabolic need accompanying obesity causes hyperdynamic circulation as the blood volume increases. Additionally, peripheral vascular resistance and increased vascular stiffness is developed, leading to hemodynamic overload. Consequently, an increase in LVMI and disturbance in diastolic functions may be expected [1]. However, the common belief is that the influential mechanisms are not limited to hemodynamic changes [9]. The negative relation between adiponectin and LVMI may also contribute to this mechanism. In other words, a lack of protective effects of adiponectin may cause LVH in obese individuals.

The decrease in adiponectin plasma levels plays an important part in the etiopathogenesis of many comorbid situations, and mainly insulin resistance [4, 10–14]. The effects of adiponectin on the heart, which are thought to be anti-atherogenic, may not be limited to

this. It has been experimentally shown that decreased plasma adiponectin levels may lead to LVH by directly affecting LVMI, and that an increase in adiponectin levels may be effective in correcting the pathologic changes in the cardiac structure [15]. However, the effects of adiponectin on LVMI are not yet known. Very few clinical studies exist in this field [13, 16].

In one of these few studies, hypertensive patients were studied by Hong *et al*., who reported an inverse association between LVMI and adiponectin levels [13]. However, hypertensive states may have confounded the association because hypertension could cause both LVH and a reduction in adiponectin levels [13]. In addition, some antihypertensive agents are known to increase adiponectin levels. Therefore, an examination of this association in non-complicated obese subjects not taking any medication may be valuable. A second study was performed with a non-obese healthy Japanese population [16]. Mitsuhashi *et al*. showed in this study an association between adiponectin and LVH, which was defined by electrocardiography. However, electrocardiography is not a sufficient tool to define LVH, which necessitates additional studies supported with echocardiography. Despite the limited number of participants, our findings support the hypothesis that decreased adiponectin levels may be influential in LVMI increase.

Several mechanisms have been suggested to explain the hypothesis that hypoadiponectinemia may cause LVH. A possible effect of adiponectin on LVMI may be to directly inhibit hypertrophic signaling in the myocardium by activating adenosine monophosphate-activated kinase, which activates eukaryotic elongation factor-2 kinase and the inhibitor of cardiac myocyte protein synthesis [15, 16].

Another possible mechanism may be the suppression of angiotensin II-stimulated myocyte hypertrophy with adiponectin [13]. Our study is not sufficient to explain these mechanisms because of its cross-sectional design. However, a lack of disease like hypertension which causes angiotensin (or another mediator) stimulation in our study group suggests that decreased myocardial protein synthesis via the inhibition of hypertrophic signaling may play a more important role in explaining adiponectin-associated myocardial protection.

In sum, even if not complicated, obesity increases LVMI. Increased hemodynamic load may be the main reason for the development of this change. The present study showed the direct influence of adiponectin on LVMI. Clinical long-term follow-ups with large numbers of participants are needed to validate the effects of adiponectin on LVH.

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