



Inflammation, Left Ventricular Mass Index and Chronic Renal Failure in Diabetic Patients

Diyabetik Hastalarda Enflamasyon, Sol Ventrikül Kitle İndeksi ve Kronik Böbrek Yetmezliği

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Abstract

Aim: The aim of this study was to determine the relationship between left ventricular hypertrophy (LVH) and inflammatory markers in patients with type 2 Diabetes Mellitus (T2DM) with diabetic nephropathy at different stages.

Methods: Our study was a cross-sectional study involving patients with various stage of T2DM. Patients with LVH were identified by 2D echocardiography. Plasma human tumor necrosis factor alpha (TNF- α), interleukin (IL)-1, IL-6, vaspin, vispatin and midkine were measured.

Results: A total of 59 T2DM patients (56% women) with a mean age of 56.1 \pm 8.8 years were included in the study. The mean left ventricular mass index was 129 \pm 30. LVH was detected in 62.7% of the patients. Patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m² had a higher incidence of LVH than patients with an eGFR \geq 60 mL/min/1.73 m² (p=0.03). The TNF- α levels in patients with LVH with low eGFR was found to be statistically significantly higher than in patients without LVH (p=0.047). The level of vaspin was statistically significantly higher in patients with LVH (p=0.01).

Conclusion: LVH was found to be more frequent in patients with low eGFR, and from inflammatory markers, it was found to be associated only with TNF- α and vaspin.

Keywords: Left ventricular mass index, inflammatory markers, diabetic nephropathy

Öz

Amaç: Çalışmamızın amacı farklı evrelerdeki tip 2 Diabetes Mellitus (T2DM) hastalarında sol ventrikül hipertrofisi (SVH) ve enflamatuvar biyobelirteçlerin arasındaki ilişkiyi ortaya koymaktır.

Yöntemler: Kesitsel çalışmamıza çeşitli evrelerdeki T2DM hastaları dahil edildi. SVH 2D ekokardiyografi cihazı ile değerlendirildi. Tümör necrosis factor alpha (TNF- α), interleukin (IL)-1, IL-6, vaspin, vispatin ve midkine serumda ölçüldü.

Bulgular: Ortalama yaşı 56,1 \pm 8,8 yıl olan 59 T2DM hastası (%56'sı kadın) çalışmaya dahil edildi. Sol ventrikül kitle indeksi 129 \pm 30 idi. SVH'si hastaların %62,7'sinde saptandı. Tahmini glomerüler filtrasyon hızı (tGFH) <60 mL/dk/1,73 m² olan hastalarda tGFH'ı \geq 60 mL/dk/1,73 m² olan hastalara göre SVH daha yüksek oranda saptandı (p=0.03). Düşük tGFH olan hastalarda SVH'ı olan hastalar SVH'ı olmayan hastalara göre TNF- α seviyesi istatistiksel olarak daha yüksek saptandı (p=0.047). Vaspin SVH'si olan hastalarda daha yüksekti (p=0.01).

Sonuç: SVH düşük tGFH'li hastalarda daha sıkı ve enflamatuvar biyobelirteçlerden sadece TNF- α ve vaspin ile ilişkili bulundu.

Anahtar Sözcükler: Sol ventrikül kitle indeksi, enflamatuvar belirteçler, diyabetik nefropati

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Introduction

Diabetes Mellitus (DM) affects many people around the world, and has been one of the most important health problems with its microvascular and macrovascular complications and increasing prevalence. In addition, it is a chronic disease associated with atherosclerosis and increased cardiovascular events (1). Left ventricular hypertrophy (LVH) is physiological adaptation to chronic afterload pressure, which leads to pathological changes in the structure and function of the cardiovascular system. DM is related with LVH and lower myocardial function independent of age, sex and hypertension (2). The Framingham study showed that the presence of LVH was associated with increased mortality (3).

Diabetic nephropathy (DNP) is the most common reason for end stage renal disease (ESRD) in the developed countries. LVH is a risk factor for mortality in patients with ESRD. Inflammation is one of the earliest events in cardiac stress situations such as pressure and volume overload, and it involves elevated levels of inflammatory cytokines. Inflammatory markers also affect cardiovascular functions either by paracrine effects or by directly affecting the vascular wall (4). In this study, we studied the frequency of LVH and the relationship of inflammatory markers with LVH in diabetic patients with low estimated glomerular filtration rate (eGFR).

Meanwhile, the inflammatory factors, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α , vaspin, midkine and visfatin, are studied in this paper. We aimed to determine the relationship of LVH with DNP, drugs, inflammatory markers and laboratory markers in a population of patients with type 2 DM (T2DM).

Methods

Our study was a cross-sectional study involving patients with DM at different stages of follow-up in the nephrology clinic of our hospital. The American Diabetes Association *criteria for the diagnosis of diabetes* were used for the diagnosis of T2DM (5). Informed consent was obtained from all patients eligible for inclusion.

Patients younger than 18 years and older than 70 years, type 1 diabetic patients, patients with acute renal dysfunction or albuminuria, non-diabetic renal disease, advanced chronic liver disease, positive hepatitis serology, high transaminase level, autoimmune disease, malignant disease, advanced cardiac or respiratory disease, history of systemic infectious or inflammatory disease or acute ischemic vascular disease within the past three months, and those without written informed consent were excluded from the study.

Age, gender, height, weight, and waist and hip circumference were recorded for all patients. Body mass

index (BMI) was calculated using the formula [BMI=weight (kg)/(height)² (m)]. Duration of DM, presence of kidney failure, and time from diagnosis of kidney failure were recorded. GFR values were estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

All the drugs the patients were using were recorded. Patients with LVH underwent 2-dimensional echocardiography (HDI 5000 Sono CT machine with a transducer 2.5 MHz). The echocardiographic technique, calculation of dimensions, and different cardiac volumes were realized according to recommendations of the American Society and European Association of Echocardiography. The echocardiographic evaluation included endocavitary dimensions of the left ventricle and other cardiac chambers. Left ventricular mass was calculated according to the Devereux formula: $(6) 0.8 \times 1.04 \times [(LVIDd + PWTd + VSTd)^3 - (LVIDd)^3] + 0.6$

LVH was determined as left ventricular mass index (LVMI) greater than 115 g/m² for men and greater than 95 g/m² for women.

Venous blood samples were taken from all patients after 12 hours of fasting and placed in gel-free dry tubes and EDTA tubes. The samples were centrifuged at 1000 G for 10 minutes and serum and plasma samples were stored at -80 °C until analysis. After the sample collection was completed, serum and plasma were melted and biochemical studies were performed. Glucose, Hemoglobin A1c (HbA1c), urea, creatinine, uric acid, sodium (Na), potassium (K), calcium (Ca), phosphorus (P), total protein, albumin, parathyroid hormone, total cholesterol, high-sensitive C-reactive protein, IL-1, IL-6 and TNF- α , LDL cholesterol, VLDL cholesterol, triglycerides, aspartate transaminase, and alanine transaminase levels were measured in all patients. Among hematological parameters, hemoglobin (Hb), total leukocyte count, mean corpuscular volume, platelet count, transferrin saturation and ferritin level were measured. The analysis of the blood samples was made in our hospital's biochemistry laboratory. Biochemical assays were performed using an Architect c16000 (Abbott Diagnostics, Chicago, Ill., USA) instrument as recommended by the manufacturer. HbA1c levels were studied by high pressure liquid chromatography (HPLC) with a TOSOH G7 (Tosoh Bioscience, South San Francisco, Calif.) analyzer. HORIBO ABX pentra dx 120 (Horiba Medical, Montpellier, France) was used for the measurement of hematological parameters.

Measurement of human TNF- α , IL-1 and IL-6 levels was performed by an enzyme-linked immunosorbent assay (ELISA) using a BIOTEK ELX50 Microplate Strip Washer and BIOTEK EL 800 Absorbance Microplate Reader (BioTec Inc., Winooski, VT, USA). ELISA

kit from Adipo Bioscience (Santa Clara, CA) was used to measure serum vaspin, visfatin, midkine with the sandwich ELISA method.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Ethics committee approval was not obtained due to the cancellation of the regulations about ethics committees by the state council while our non-experimental study had been conducted. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

The SPSS 15.0 for Windows was used for statistical analysis. Categorical variables were given in numbers and percentages and numerical variables were given in mean ± standard deviation and minimum and maximum. The Mann-Whitney U test was used when independent numerical comparisons between two groups did not satisfy the normal distribution condition. The ratios of categorical variables were tested by a chi-square test. Determinant factors were analyzed by logistic regression analysis using the forward method. A p value of less than 0.05 was considered statistically significant.

Results

A total of 59 T2DM patients (33 women and 26 men) with a mean age of 56.1±8.8 years were included in the study. The mean DM duration was 12.3±8.3 years, left ventricular mass was 240.8±60.6 cm³, and LVMI was 129±30. LVH was detected in 62.7% of the patients. 83.1% of the patients had retinopathy. The mean BMI was 30.3±4.9, average waist circumference, hip circumference and waist-to-hip ratio was 102.9±8.6 cm, 107.0±10.2 cm and 0.97±0.10, respectively. Characteristics of patients are given in Table 1. The mean systolic blood pressure (BP) and diastolic BP was 157±26 (118-240) mmHg and 81±11 (58-100) mmHg, respectively. A total of 27 (45.8%) patients were hypertensive. There was no significant difference in the number of LVH patients between hypertensive and normotensive groups [17 (63.0%) patients vs 20 (62.5%) patients, respectively, p=0.97].

Sixty-four point four percent of the patients were using insulin. Oral anti-diabetic drug (OAD) usage rate was 61%. Fifty-two point were using metformin, 20.3% - acarbose, 15.3% - sulphonylurea, 6.8% - other secretagogues (repaglinid, nateglinid), 3.4% - glitazone and 5.1% - other OAD. Antihypertensives used by the patients were as follows: ACEi (35.6%), ARB (32.2%), diltiazem (11.9%),

and other antihypertensives (42.4%). The rate of statin use was 45.8% and the rate of aspirin use was 59.3%. Insulin usage rate was significantly higher in patients with LVH (p=0.019). There was no difference in ACE inhibitors usage between patients with diabetic hypertension with and without LVH (p=0.92).

According to CKD EPI value, 59.3% of patients had an eGFR of ≥60 mL/min/1.73 m² and 40.7% of them had and eGFR of <60 mL/min/1.73 m². The incidence of LVH was statistically significantly higher in patients with an eGFR of <60 mL/min/1.73 m² than in those with an eGFR of >60 mL/min/1.73 m² (p=0.03). The TNF-α levels in patients with LVH with low eGFR was found to be statistically significantly higher than in patients without LVH (p=0.047) (Table 2).

The average values of the evaluated markers were as follows: visfatin: 3.3±3.4, midkine: 365±404, vaspin: 1.5±0.9, IL-1: 35.5±51.3, IL-6: 8.7±9.2, TNF-α: 22.3±46.5.

Among the evaluated markers, vaspin was statistically significantly higher in patients with LVH (p=0.01). There was no statistically significant difference in other markers between patients with and without LVH (Table 3). The mean values of urea, creatinine, phosphorus and leukocyte were significantly higher in patients with LVH and Hb,

Age, mean ± SD (min-max)	56.1±8.8 (29-70)
Gender, n (%)	
Women	33 (55.9)
Men	26 (44.1)
Postmenopausal, n (%)	26 (78.8)
DM duration (year), mean ± SD (min-max)	12.2±8.5 (0-30)
LV mass (cm³), mean ± SD (min-max)	240.8±60.6 (116-402)
Left ventricular mass index, mean ± SD (min-max)	129.3±30.3 (65.2-213.3)
Left ventricular hypertrophy, n (%)	
No	22 (37.3)
Yes	37 (62.7)
Diabetic retinopathy, n (%)	49 (83.1)
Weight, mean ± SD (min-max)	80.6±12.8 (55-118)
Height, mean ± SD (min-max)	163.4±8.0 (150-180)
Body mass index, mean ± SD (min-max)	30.3±4.9 (22.0-42.6)
Waist circumference, mean ± SD (min-max)	102.9±8.6 (85-126)
Hip circumference, mean ± SD (min-max)	1070±10.2 (56-127)
Waist hip ratio, mean ± SD (min-max)	0.97±0.10 (0.85-1.64)
DM: Diabetes Mellitus, LV: Left ventricle, SD: Standard deviation, min: Minimum, max: Maximum, n: Number	

hematocrit, and mean CKD EPI values were statistically significantly lower than in those without LVH (Table 4).

Discussion

Increased left ventricular mass has been associated with cardiovascular morbidity and mortality (7). Diabetic patients have an additional cardiovascular risk. The association between LVH and cardiac morbidity is well established, especially in the presence of myocardial ischemia, fibrosis and scar tissue, and atrial fibrillation. Inflammation, fibrosis and oxidative stress, as well as ischemia play a significant role and are the leading pathways. And so, we studied some inflammatory markers associated with LVH (8). Vaspin is a visceral adipose tissue-derived serine protease inhibitor. It was first studied in visceral white adipose tissues of Otsuka Long-Evans Tokushima fatty (OLETF) rats with abdominal obesity, T2DM, insulin resistance, hypertension, and dyslipidemia. (9). There is a possibility that vaspin has an effect in insulin resistance. Our study showed that there was a potential correlation between vaspin and chronic inflammation in diabetic patients. With these hypotheses, vaspin may have a role in LVH in diabetic patients. We showed that vaspin was statistically significantly higher in diabetic patients with LVH.

Table 2. Markers in the patients with low eGFR

eGFR (<60 mL/min/1.73 m ²)	Left ventricular hypertrophy		
	No	Yes	p
Visfatin	3.2±1.3	2.7±1.1	0.499
Midkine	303±160	467±447	0.644
Vaspin	1.0±0.5	1.7±0.9	0.081
IL-1	41.1±26.2	38.8±72.4	0.110
IL-6	8.6±4.8	11.0±12.7	0.803
TNF alfa	8.9±9.7	15.6±9.3	0.047

eGFR: Estimated glomerular filtration rate, TNF: Tumor necrosis factor, IL: Interleukin

Table 3. Markers in patients with and without left ventricular hypertrophy

	Left ventricular hypertrophy		
	No	Yes	p
Visfatin	2.7±1.2	3.6±4.1	0.419
Midkine	278±202	416±481	0.605
Vaspin	1.2±1.0	1.6±0.8	0.01
IL-1	34.6±45.9	36.1±54.9	0.894
IL-6	6.7±5.2	9.7±10.7	0.268
TNF alfa	29.4±74.8	18.2±13.0	0.188

TNF: Tumor necrosis factor, IL: Interleukin

Table 4. Laboratory values in patients with and without left ventricular hypertrophy

	Left ventricular hypertrophy		
	No	Yes	p
Glucose	213.4±83.7	205.7±68.4	0.531
Urea	41.5±25.2	64.2±41.1	0.014
Creatinine	1.0±0.6	1.5±1.1	0.022
Uric acid	5.2±1.5	5.8±1.6	0.246
Sodium	138.3±2.2	139.2±3.2	0.083
Potassium	4.6±0.4	4.8±0.4	0.080
Calcium	9.8±0.5	9.7±0.6	0.295
Phosphorus	3.5±0.5	4.2±0.9	0.002
Total protein	7.5±0.4	7.4±0.5	0.642
Albumin	4.2±0.5	4.1±0.4	0.070
Parathyroid hormone	73.1±38.2	77.3±67.1	0.666
Total cholesterol	217.5±75.0	236.7±68.4	0.132
High density lipoprotein	44.0±9.7	44.2±9.3	0.718
Low density lipoprotein	131.8±52.4	150.4±56.0	0.079
Very low density lipoprotein	50.0±58.4	43.5±21.1	0.605
Triglyceride	252.2±291.6	217.6±105.4	0.684
Aspartate aminotransferase	19.3±6.2	21.3±8.9	0.551
Alanine aminotransferase	24.6±11.3	22.0±11.5	0.286
HbA1C	9.0±2.4	8.7±1.5	0.969
Hemoglobin	13.4±1.5	12.1±2.0	0.005
Hematocrit	41.2±4.3	36.7±5.6	0.004
Leukocyte	7.3±1.4	8.3±1.9	0.046
Mean corpuscular volume	85.8±4.7	87.0±3.8	0.252
Platelets	279.6±64.0	269.7±68.0	0.466
Ferrous	63.6±21.2	66.7±28.5	0.919
Total Iron Binding Capacity	350.3±65.5	313.8±63.0	0.042
Transferrin saturate	0.19±0.07	0.22±0.09	0.347
C-reactive protein	0.6±0.5	0.7±0.7	0.753
Vitamin D	21.7±10.9	36.0±34.1	0.095
Insulin	12.4±9.8	13.5±9.0	0.512
C peptid	2.8±1.5	3.5±2.3	0.426
Ferritin	65.5±45.7	111.5±128.9	0.513
Proteinuria	1415.3±1773.0	2848.3±2552.6	0.057
Microalbuminuria	66.1±93.7	287.0±436.1	0.081
eGlomerular filtration rate	85.8±30.6	60.0±31.3	0.004

HbA1C: Hemoglobin A1c

Midkine has protective effects against ischaemia, reperfusion injury, cardioprotection, angiogenesis, vascular stenosis, and cardiac remodeling. Midkine protects the heart and brain from acute ischemia, reperfusion injury and infarction via its anti-apoptotic effect (10). Based on this information, we looked at the midkine values in diabetic LVH patients. No statistically significant difference was found between diabetic patients with and without LVH.

Visfatin, an adipocytokine, is produced by visceral adipose tissue and has insulin-mimetic action. Visfatin acts as an insulin analog on the insulin receptor (11). Adipocytokines participate in different stages of atherosclerosis, from endothelial dysfunction to plaque destabilization. Visfatin is a proinflammatory cytokine and is secreted in response to inflammation and upregulates cytokines such as IL-1, TNF- α , and IL-6, and probably has a potential role in the pathogenesis of inflammatory disorders (12). In their study, Dahl et al. (13) claimed that visfatin was an inflammatory mediator, synthesized by foam cell macrophages within unstable atherosclerotic lesions and played a role in plaque destabilization. And so according to this knowledge, we studied visfatin, IL-1, TNF- α , and IL-6 levels in diabetic patients who have LVH. There was no statistically significant difference between diabetic patients with and without LVH.

Among the markers, only vaspin was statistically significantly higher in patients with LVH.

There was no correlation between LVH and waist circumference, BMI, duration of DM and duration of chronic kidney disease, but there was a significant relationship between GFR and LVH. Patients with LVH were more likely to have low GFR. It is known that LVH correlates with DNP (14).

The rate of insulin use was significantly higher in patients with LVH ($p=0.019$). Hyperglycemia is associated with LVH. In their study including 16 insulin-dependent patients, Weinrauch et al. (15), noted that left ventricular mass improved with glycemic control over time and they have also described improvement in autonomic function by metabolic control. In this study, they showed that left ventricular remodeling and parasympathetic improvement could both be attained by aggressive treatment of hyperglycemia.

Patients with an eGFR of <60 mL/min/1.73 m² had a statistically significantly higher incidence of LVH than patients with an eGFR of ≥ 60 mL/min/1.73 m² ($p=0.03$). Also, the laboratory parameters of urea, creatinine and phosphorus were significantly higher ($p=0.014$, $p=0.022$ and $p=0.002$, respectively); Hb, Htc, and GFR mean were statistically significantly low ($p=0.005$, $p=0.004$ and

$p=0.004$, respectively) in patients with LVH. It means that there is a significant relationship between DNP and LVH. In diabetic patients with renal insufficiency, coronary artery disease, overload, uremia, and hypertension are the most common explanations for cardiac dysfunction.

Additionally, hyperglycemia, increases catecholamine levels and downregulates cardiac adrenoreceptors, leading to ventricular diastolic dysfunction and ventricular hypertrophy (16). Mechanisms for cardiac dysfunction in uncontrolled DM have been studied in animal models. The ventricular dimension grows with collagen accumulation due to advanced glycosylated end products, a pathological process that can be prevented by blood sugar regulation. In addition, ACE inhibitors prevent accumulation of advanced glycosylated end products in the ventricular tissue (17). However, in our study, there was no difference in patients with diabetic hypertension using ACE inhibitors with or without LVH ($p=0.92$).

In a study, Weinrauch et al. (15) declared that diabetic patients with nephropathy and severe cardiac autonomic dysfunction may have parallel improvement in left ventricular mass by restoring glycemic control through intensive therapy.

When we looked at the relationship between LVH and inflammatory markers in patients with low GFR, the TNF- α levels in patients with LVH with low GFR was found to be statistically significantly higher than in patients without LVH ($p=0.047$). TNF- α contributes to the development and progression of DNP and is correlated with increased levels of albuminuria and nephropathy (18). It is well established that TNF- α plays an important role in cardiac contractile dysfunction and cardiac hypertrophy (19). Takei et al. (20) have shown that increased TNF- α receptors might be responsible for increased left ventricular mass.

Conclusion

LVH was found to be more frequent in patients with low eGFR and TNF- α levels in patients with LVH with low GFR was found to be statistically significantly higher than in patients without LVH and, from inflammatory markers, LVH was found to be associated only with vaspin. It was also found that the rate of insulin use was significantly higher in patients with LVH; there was no difference in patients with diabetic hypertension using ACE inhibitors with or without LVH.

Authorship Contributions

Concept: E.C., M.V., S.Ö. Design: E.C., M.V., S.Ö. Data Collection or Processing: N.Ş.S. Analysis or Interpretation: E.C., M.G. Literature Search: S.U., S.K., T.E.Ş.Ö. Writing: E.C., S.Ö.

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