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Research Article

Investigation of Serum Endocan Levels in Diabetic Peripheral Artery Patients

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ABSTRACT

Background: Endocan, also known as specific molecule-1 in endothelial cell, plays an important role in endothelial dysfunction and inflammatory reaction [1, 2]. Serum endocan, a new biochemical marker of endothelial dysfunction, plays a role in the development of cardiovascular disease (CVD). In this study, we investigate there was a difference in serum endocan, CYP2R1, and Haptoglobin protein levels between patients with DM (+) PAH and those with DM (-) PAH.

Methods: 55 volunteer patients who were diagnosed with DM (-) PAH and 24 volunteer patients who came to the same polyclinic and were diagnosed with only DM (+) PAH as a result of the examination were included. Endocan, Haptoglobulin and 25-hydroxylase (CYP2R1) measurements were made with the quantitative Enzyme linked immunosorbent analysis kit.

Results: Serum haptoglobulin levels were 1877.01 ± 564.67 (g/L) in the group with DM (-) PAH, 1745.94 ± 612.59 (g/L) in the group with DM (+) PAH, 25-hydroxylase (CYP2R1) levels were 51.41 ($2.53-2722.18$) (ng/ml) in the group with DM (-) PAH and 25.36 ($9.43-624.57$) (ng) in the group with DM (+) PAH. /ml) was detected. Serum endocan levels are: 157.95 ($29.16-7026.64$) (pg/ml) in the group with DM (-) PAH, and 586.23 ($138.79-3876.51$) (pg/ml) in the group with DM (+) PAH was detected.

Conclusion: We compared serum endocan levels in patients with DM(+) PAH and DM(-)PAH, and we found that there was a significant difference ($p < 0.001$). We found that serum endocan levels were significantly higher in patients diagnosed with DM(+) PAH compared to the other group.

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Introduction

Peripheral artery disease (PAH) is a disease that causes atherosclerotic cardiovascular morbidity [1]. Death from PAH is mostly due to critical limb ischaemia or surgical complications [3]. PAH risk factors; advanced age, male gender, smoking, cardiovascular disease, DM, HT, hypercholesterolemia, metabolic and inflammatory (obesity, hyperhomocysteinemia, inflammation, poverty, industrialization, infection, ethnicity, genotype) [3]. Hyperglycemia, dyslipidemia, and insulin resistance are all symptoms of diabetes mellitus (DM). These

pathological abnormalities, which are similar to coronary or carotid artery disease, increase the development and progression of PAH [2, 4-6].

In research, some biomarkers have been linked to PAH. Cytokines or chemokines, endothelial dysfunction markers, angiogenesis inhibitors, lipoprotein or lipid-related proteins, oxidative stress or ischaemia indicators, and coagulation factors are examples of these. None of these indicators, however, are unique to PAH because they are also elevated in coronary artery disease (CAD) and other vascular abnormalities [7].

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Endothelial Cell-Specific Molecule-1 (Endocan) is a soluble 50 kDa proteoglycan that is found in endothelial cells. Endocan cell adhesion, tumor growth, inflammatory abnormalities, vascular disorders, the endothelial-mesenchymal transition pathway, and endothelial dysfunction are all affected by it. Numerous cytokines and growth factors influence endocan expression. It has been shown that TNF- α and interleukin 1 β increase endocan gene expression [8].

It is suspected to play a function in atherosclerosis and is secreted by endothelial cells in several organs. Endocan levels have been found to rise as a result of chronic kidney dysfunction, renal transplant rejection, hypertension, and tumor invasion [9]. Atherosclerosis underlies the pathogenesis of PAH. Endocan, thought to be associated with atherosclerosis, may be an immunoinflammatory marker associated with PAH. Endocan is a possible endothelial cell biomarker that represents endothelin immunoinflammatory activity, according to growing data [10, 11].

Haptoglobin is a glycoprotein made up of two and two-polypeptide chains that is generated in the liver. Normal serum plasma levels are 40-280 mg/dl [12]. He identified two alleles in humans, Hp1 and Hp2. Plasma haptoglobin levels vary throughout life, being less in childhood than in adulthood. However, the main change in serum levels occurs with increased synthesis in cases of stress, acute inflammation, tissue necrosis, and infection. Increased haptoglobin has anti-inflammatory properties. Owing to its antioxidant properties, it acts as a protector against oxidative stress that occurs during inflammation. It also accelerates wound healing by inducing angiogenesis [13].

Vitamin D is converted to 25 hydroxy (OH) vitamin D3 and 25OH vitamin D2 by the 25 Hydroxylase enzyme (including CYP2R1, CYP2D11, CYP2D25 enzyme systems) in the liver. The CYP2R1 enzyme is the key enzyme, and a homozygous mutation in this enzyme leads to low circulating 25 (OH) D3 levels and the classic symptoms of vitamin D deficiency [14].

A lack of vitamin D is linked to a higher prevalence of various cardiovascular risk factors [15, 16]. BMI, hypertension, diabetes mellitus, and hyperlipidemia (total cholesterol and triglyceride) are all inversely related to vitamin D insufficiency [16].

In a study, it was found that the GC rs7041-CYP2R1 rs1993116 polymorphism increased the risk of developing T2DM [17]. From a clinical perspective, low serum 25OHD levels have been associated with an increased risk of cardiovascular disease, including hypertension, coronary artery disease, ischaemic heart disease, heart failure, stroke, and type 2 DM [18-21]. The presence of vitamin D abnormalities and the pathophysiological processes underlying atherosclerosis, such as inflammation, increased arterial stiffness, abnormal vascular function, abnormal vascular endothelial reactivity, decreased coronary blood flow, and uremia, strengthened the reliance on the important association with vascular calcification [22-24]. We detected a significant difference ($p < 0.001$) between serum endocan levels in patients with DM (+) PAH and DM(-)PAH in our study. In comparison to the other group, serum endocan levels were considerably greater in patients diagnosed with DM(+) PAH.

Materials and Methods

This study was conducted with 55 volunteer patients between the ages of 18-75 who came to the cardiovascular surgery polyclinic of Kahramanmaraş Sütçü İmam University Medical Faculty Hospital and were diagnosed with DM (-) PAH as a result of routine examinations, and only DM (+) PAH as a result of the examination. Twenty-four volunteer patients between the ages of 18-75 who were diagnosed with the disease were recruited. Of these patients, those with any chronic inflammatory disease, psychiatric diseases, malignant diseases, neurogenic diseases and collagen tissue disease were excluded from the study. Sterile 5 cc venous blood from each individual participating in the study was taken into a biochemistry tube, centrifuged and serum separated. Then, it was stored at -80 °C until the endocan measurement was made with the ELISA method.

The Gaziantep University Clinical Research Ethics Committee approved our study before it began, and it was carried out in compliance with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. All participants signed a written informed consent form. The quantitative Enzyme linked immunosorbent analysis (ELISA) kit was used to test endocan, haptoglobulin, and 25-hydroxylase (CYP2R1). For continuous variables established by measurement, mean and standard deviation or median and minimum-maximum values will be given as descriptive statistics, whereas frequency and percentage values will be given for qualitative variables. In group comparisons, the test of significance of the difference between the two means was employed if the parametric test conditions were fulfilled, and the Mann-Whitney U test was used if the parametric test conditions were not met for continuous variables specified by measurement. For group comparisons of qualitative variables, the Chi-square test was used.

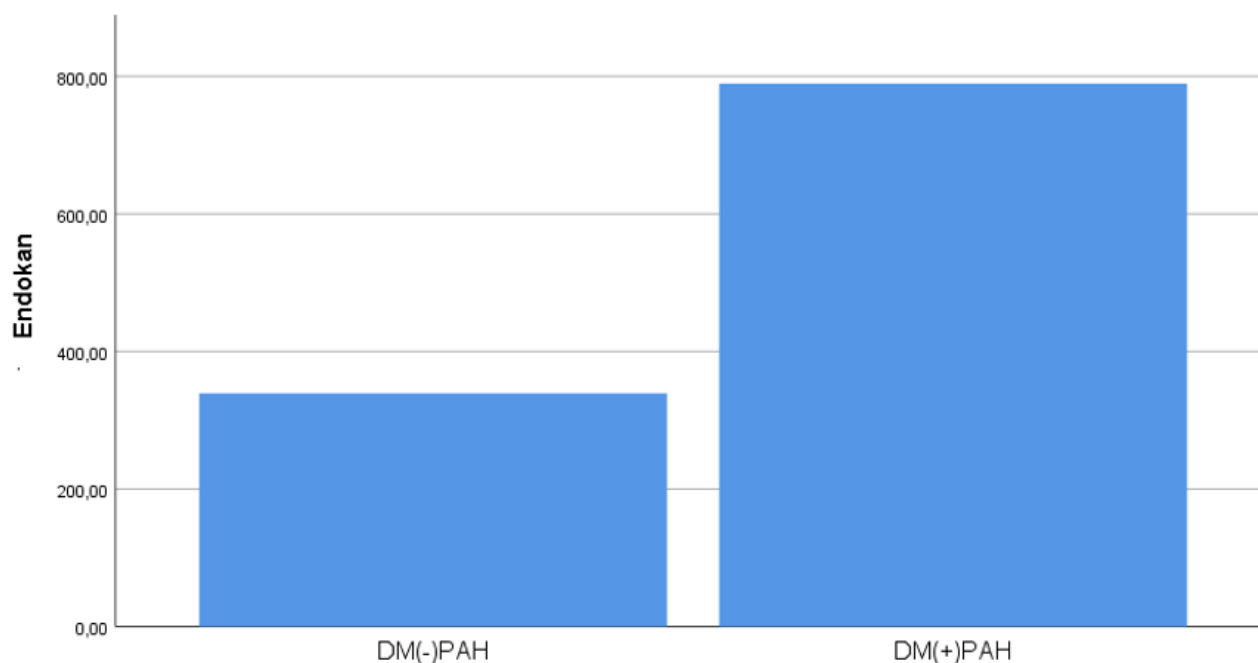
Results

The mean age of the patients in the study population consisting of 79 patients was 56.53 ± 9.3 years. They were divided into 2 groups as those diagnosed with PAH and those with and without DM. 55 patients were included in the DM (-) peripheral artery disease group and 24 patients in the DM (+) group. Of the patients in the DM (-) group, 28 (50.9%) were male and 27 (49.1%) were female. Ten (41.7%) of the patients in the DM (+) group were male and 14 (58.3%) were female. There was no difference in age between the two groups. Gender did not make a statistically significant difference between the groups ($p = 0.45$). The group with DM (-) PAH had a mean age of 58 ± 9.70 years, while the group with DM (+) PAH had a mean age of 54 ± 10.01 years ($p = 0.45$). The presence of chronic disease was 29% in the group with DM (-) PAH, while it was 71% in the group with DM (+) PAH (Table 1). Serum haptoglobulin levels were 1877.01 ± 564.67 (g/L) in the group with DM (-) PAH, 1745.94 ± 612.59 (g/L) in the group with DM (+) PAH, 25- hydroxylase (CYP2R1) levels were 51.41 (2.53 - 2722.18) (ng/ml) in the group with DM (-) PAH and 25.36 (9.43 - 624.57) in the group with DM (+) PAH. (ng/ml) was determined. Serum endocan levels are; 157.9506 (29.16 - 7026.64) (pg/ml) in the group with DM (-) PAH and 586.2365 (138.79 - 3876.51) (pg/ml) in the group with DM (+) PAH (Table 1 & Figure 1).

Table 1: Demographic, clinical and laboratory values of all patients included in the study.

	DM (-) PAH (n:55)	DM (+) PAH(n:24)	p
Age mean±standard deviation	58±9,70	54 ±10,01	0.2*
Gender	Male: 28 (%50.9) Female: 27 (%49.1)	Male:10 (% 41.7) Female:14 (%58.3)	0.45**
Chronic disease	20 (%29)	49 (%71)	0.479**
Smoking	6 (17,6%)	28 (82,4%)	0.004
Haptoglobin (g/L) mean±standard deviation	1877,01±564,67	1745,94±612,59	0.358*
25-hydroxylase (CYP2R1) (ng/ml)	51,41 (2,53- 2722,18)	25,36 (9,43- 624,57)	0.332***
Endocan (ESM1) (pg/ml)	157,9506(29,16- 7026,64)	586,23 65(138,79- 3876,51)	p<0.001***

n: number of individuals, * Student t testi, ** Ki-kare testi, ***Mann-Whitney U test.

**Figure 1:** Comparison of serum endocan levels of both groups.

Discussion

In this study, we looked to see if there was a difference in serum endocan, CYP2R1, and Haptoglobin protein levels between patients with DM (+) PAH and those with DM (-) PAH. PAH is a slowly progressive disease caused by plaque accumulation in the arterial system [1]. An average of 79 patients were included in the study. The mean age of the patients was 56.53 ± 9.3 years. PAH is more common as people get older. In the NHANES Report, the prevalence of PAH was 14.5% among patients aged 70 years and 4.3% in patients younger than 40 years [25].

Studies have found that the risk of developing PAH is twice as high in smokers compared to non-smokers [3]. Additionally, the rate of development of intermittent claudication symptoms in PAH patients who smoke is 3 times higher than that in non-smokers [26]. Quitting smoking is linked to a lower risk of peripheral artery disease. It would take more than 20 years for this risk to be the same as for someone who

has never smoked. DM has been linked to both asymptomatic and symptomatic PAH in many epidemiological studies [27, 28]. Smoking is the most significant modifiable risk factor for PAH development. In our study, 28 (82.4%) of the patients in the DM (+) PAH group had a history of smoking. It was significantly higher in individuals with both DM and PAH risk factors ($p=0.004$).

In obese mice's liver homogenates, CYP2R1 protein expression and enzyme activity were decreased by 50% compared to controls [29]. Other researchers discovered that fasting for 12 hours markedly decreased CYP2R1 mRNA, and that the effect was considerably stronger after 24 hours (50 and 80 percent, respectively) in both mouse and rat models [30]. In our study; we observed that there was no difference between serum 25-hydroxylase (CYP2R1) (ng/ml) levels in patients with DM (+) PAH and DM (-) PAH ($p=0.332$).

In some studies, the role of haptoglobin phenotype was investigated in patients with cardiovascular risk, but the results were inconsistent [31,

32]. They showed that the Hp 1 allele is a risk of cardiovascular diseases [33]. Other researchers found that the Hp 1 allele poses a risk of macroangiopathy in patients with Type 2 Diabetes [34]. In this study; we compared serum haptoglobin levels in patients with DM (+) PAH and DM (-) PAH and found no significant difference ($p=0.358$).

PAH has been associated with inflammatory cytokines or chemokines, endothelial dysfunction markers, angiogenesis or vascular regeneration mediators, lipoproteins, oxidative stress or ischaemia, reperfusion markers, metabolic modulators, and coagulation factors [35]. By causing adhesion, vascular inflammation plays a significant role in the progression of atherosclerosis. Increases in cell adhesion molecules such as VCAM-1, ICAM-1 and lymphocyte function-related antigen 1 (LFA-1) have been linked to elevated endocan levels [36]. In a study, it was observed that there was a strong correlation between serum endocan and VCAM-1 [37]. CHONG-Rong Qiu *et al.* in a study that included 216 patients diagnosed with acute myocardial infarction (AMI) and 60 volunteers without AMI diagnosis as the control group, serum endocan levels were found to be high in the AMI group [38]. In another study, when AMI patients with DM (+) were compared with non-DM (-) AMI patients, serum endocan levels were found to be significantly higher in DM (+) AMI patients [39]. In another study, PAH with distal involvement was found to be associated with the presence of DM [26].

Vitamin D insufficiency is common in type 2 diabetes patients. Jing Yuan *et al.* in his study, It was discovered that lower serum vitamin D levels in Type 2 diabetic patients were linked to an increased risk of PAH [40]. By mechanisms analogous to coronary or carotid arterial disease, DM increases the development and progression of PAH [41]. Endocan levels were discovered to be considerably greater in patients with chronic renal failure (CRF) by Yilmaz *et al.* [42]. Endocan has been demonstrated to be a possible biomarker in cancer, tumor development, and sepsis in studies. It has the potential to be employed as a serum biomarker in the early detection and prognosis of various disorders. It may also be of clinical importance in the follow-up [8]. Blum *et al.* investigated the relationship of haptoglobin genotype (type 1 and 2) with myocardial infarct sizes in their study on diabetic mice [43]. It has been shown that the dimensions of myocardial infarction are closely related to the developing ischaemia-reperfusion injury, and this damage is increased by predisposing factors such as DM, which increases oxidative stress and induce the inflammatory response. As haptoglobin is a protein that regulates this oxidative stress, it is thought that especially Hp 2 may be related to the dimensions of myocardial infarct with DM.

We detected a significant difference ($p<0.001$) between serum endocan levels in patients with DM (+) PAH and DM (-)PAH in our study. In our study; we compared serum endocan levels in patients with DM (+) PAH and DM(-)PAH and found a significant difference ($p<0.001$). When comparing patients with DM (+) PAH to the other group, serum endocan levels were found to be considerably higher.

The modest number of patients is owing to the fact that this is a single-center trial, which has its own set of constraints. In addition to these statistical data and considering these important findings, multicenter studies with larger patient numbers are needed. As a result, as an early biochemical predictor, we discovered that endocan level was statistically substantially greater in the DM (+) PAH group. In addition to these; due to the small number of patients, it does not seem possible to reach a

definite conclusion; however, considering these important results, multicenter studies with more patient numbers are needed.

Limitations

The modest number of patients is related to the fact that it is a single-center trial, which has its own set of constraints. In addition to these statistical data and considering these important findings, multicenter research including a larger number of patients are required.

Acknowledgement

Not applicable.

Ethical Approval

The Clinical Research Ethics Committee at Gaziantep University gave its approval to this study. (Protocol number 2020/103 registered), (Protocol number 2021/198 registered).

Conflicts of Interest

None.

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