

Lectin-like oxidized low density lipoprotein receptor 1(LOX-1) levels and endothelial dysfunction in patients with primary essential hyperhidrosis

Primer esansiyel hiperhidroz hastalarında lektin benzeri okside düşük dansiteli lipoprotein reseptör 1(LOX-1) düzeyleri ve endotel disfonksiyonu

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ABSTRACT

Objective: Primary essential hyperhidrosis (PEH) is a disorder characterized by excessive sweating of palms, soles and axilla. Although its etiology was not fully understood, increased activity of the autonomic nervous system may play a role in the pathogenesis of PEH. In the study we aimed to investigate flow mediated dilatation and lectin like oxide LDL receptor 1 (LOX-1) levels as an indicator of endothelial dysfunction in patient with PEH.

Methods: Thirty-three PEH patients diagnosed with starch-iodine test and age- and sex-matched 19 healthy controls were included in the study. Flow-mediated dilatation was performed by ultrasonographical measurement of brachial artery. Serum LOX-1 levels were analyzed with Enzyme-Linked Immuno-Sorbent Assay (ELISA) kit.

Results: Brachial artery FMD diameters and post-nitrate dilatation diameters were not different between patients and the controls. There was no difference between patient and control groups when compared for LOX-1 levels.

Conclusion: Larger studies are needed to understand, indeed, whether excessive hyperhidrosis in PEH is only a peripheral excessive response to normal sympathetic activity or a systemic sympathetic hyperactivity with cardiovascular effects, which is disguised by compensatory mechanisms, such as nitric oxide (NO).

Key words: endothelial dysfunction, flow mediated dilatation, lectin like oxidized low density lipoprotein receptor 1, primary essential hyperhidrosis

ÖZET

Amaç: Primer esansiyel hiperhidroz avuç içi ayak tabanı ve aksiler bölgenin aşırı terlemesi ile karakterize bir hastalıktır. Etyolojisi henüz açıklığa kavuşmamış olmakla beraber otonom sinir sisteminin artmış aktivitesinin rolü tartışılmaktadır. Biz bu çalışmada primer esansiyel hiperhidroz hastalarında akım aracılı dilatasyon ve lektin benzeri okside düşük dansiteli lipoprotein reseptör 1 düzeylerini inceleyerek endotel disfonksiyonunun varlığını araştırmayı amaçladık.

Yöntemler: Tanısı nişasta iyot testi ile konmuş otuzüç primer esansiyel hiperhidroz hastası ile 19 yaş ve cinsiyet uyumlu kontrol bu çalışmaya dahil edildi. Akım aracılı dilatasyon ultrasonografik olarak brakial arterden ölçüldü. Serum LOX-1 seviyeleri Enzim-Bağlı İmmun Sorbent Testi (ELISA) ile ölçüldü.

Bulgular: Brakial arter akım aracılı dilatasyon çapları ve post nitrat dilatasyon çapları hasta ve kontrol grubu için istatistiksel olarak farklı değildi. LOX-1 değerleri açısından karşılaştırıldığında da hasta ve kontrol grubu arasında istatistiksel olarak fark yoktu.

Sonuç: Primer esansiyel hiperhidrozda aşırı terleme erkin bezlerin normal sempatik aktiviteye verdiği aşırı bir periferik yanıt mı yoksa kardiyovasküler etkileri nitrik oksit ile maskelenmiş sistemik sempatik bir hiperaktivite mi olduğunu anlamak için daha geniş çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Endotel disfonksiyon, akım aracılı dilatasyon, lektin benzeri okside düşük dansiteli lipoprotein reseptör 1, primer esansiyel hiperhidroz

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INTRODUCTION

Primary essential hyperhidrosis (PEH) is a common disease characterized by excessive sweating that negatively affects the quality of life of the patients and complicates adaptation to social media [1]. Sympathetic cholinergic nerves activate in both thermoregulatory perspiration and emotional perspiration. The stimulus may stimulate many areas in the body and is controlled by numerous neurons in the central nervous system [2]. If there is a dysfunction in vascular autonomic control, the vascular structure, function of which is regulated by innervation by sympathetic cholinergic fibers may be affected by such dysfunction [3]. Endothelium is the monolayer of endothelial cells lining the lumen of blood vessels. It maintains a balance between vasoactive and vasodilator substances and the loss of this function leads to endothelial dysfunction. Insight into the function of endothelium has led to the development of tests for its assessment. All of these tests are based on the vasomotor response of endothelium to vasoactive stimuli [4]. Recently, flow-mediated dilatation (FMD), a non-invasive measurement method of vascular dysfunction was defined. The FMD is mediated by nitric oxide (NO) and is used as an index of endothelial function of large arteries. The level of oxidized low-density lipoprotein (OxLDL) increases in patients with coronary artery disease or diabetes and serves as an independent predictor for future cardiac events in these patients. In 1997, a lectin-like oxidized low-density lipoprotein receptor (LOX-1) was identified in endothelial cells. Since then, LOX-1 has been shown to mediate many biological effects of OxLDL in endothelial cells [5]. (LOX-1) level, a molecular marker of vascular dysfunction and an oxidized LDL receptor, are used to measure endothelial dysfunction [6]. The aim of the present study was to investigate vascular dysfunction in EH patients by examining flow-mediated dilatation and LOX-1 level.

METHODS

Thirty-three EH patients diagnosed with starch-iodine test and age- and sex-matched 19 healthy controls were included in the study. Informed consent was obtained from the patients and the control group and the study was approved by Local ethical committee.

Patients with coexisting coronary heart disease, type 2 diabetes mellitus, history of smoking, familial hyperlipidemia, using medication such as aspirin, anti-hypertensive agent, were excluded.

Fibrinogen and C-reactive protein (CRP) were analyzed with turbidimetric method and fasting blood glucose and total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride with spectrophotometric method. Serum LOX-1 levels were analyzed with USCN Life Science Enzyme-Linked Immuno-Sorbent Assay (ELISA) kit.

Systolic and diastolic blood pressure was measured from brachial artery. Flow-mediated dilatation was performed by ultrasonographical measurement of brachial artery. Mean of three different measurements of post-flow brachial artery lumen diameter (endothelial-dependent vasodilator response [EDVR]) was recorded. Flow-mediated dilatation was defined as increase in percentage (%) compared to baseline vessel diameter (BD). Flow-mediated dilatation was calculated via the equation, "FMD=[(EDVR)- BD]/BD)x100". For measurement of endothelial-independent vasodilator response (EIVD), basal conditions were reconstituted, and the patients were given 5 mg isosorbide-dinitrate sublingually, known as exogenous resource of nitric oxide (NO). Five minutes later, brachial artery lumen diameter was measured at three different sites, mean of the measurements was obtained, and percentage of EIVP was calculated. Endothelial-independent vasodilatation was calculated using the equation, "EIVD=[(EIVP)- BD]/BD)x100".

Statistical analysis

The data were assessed with Statistical Package for the Social Sciences (SPSS) version 16. The analyses were performed using Mann Whitney U, Student's T, and Chi-square tests.

RESULTS

There was no difference between the mean ages of 15 male and 18 female, totally 33 patients (mean age, 26.7±1.5 years) and six male and 13 female, totally 19 healthy controls (mean age, 30.2±2.0 years) included in the study. Twenty-one, 26, and 27 patients described axillary, palmar, and plantar hyperhidrosis, respectively. Mean duration of hyperhidrosis was 12.8 years, and mean age of on-

set of hyperhidrosis was 13.9 years. There was no statistical difference between the EH group and the control group when body mass index, systolic blood pressure, diastolic blood pressure, and blood glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, LDL-cholesterol, and triglyceride levels were compared (Table 1). Brachial artery

FMD diameters and post-nitrate dilatation diameters were not different for patient and control groups ($p>0.05$). There was no difference between patient and control groups when compared for LOX-1 levels ($p>0.05$). There was no correlation between duration of hyperhidrosis and LOX-1 level and FMD and post-nitrate dilatation diameters.

Table 1. Demographic characteristics and laboratory values

Gender (F/M)	Hyperhidrosis group (n=33) (mean)	Control group (n=19) (mean)	P values
Age	18/15	13/6	0.326
BMI (kg/m ²)	26.7	30.21	0.165
SBP (mmHg)	23.13	24.53	0.723
DBP (mmHg)	114.70	118.42	0.343
Total cholesterol (mg/dl)	73.79	77.11	0.151
LDL-cholesterol (mg/dl)	184.978	211.158	0.190
HDL-cholesterol (mg/dl)	118.33	135.22	0.104
Triglycerides (mg/dl)	52,48	52,53	0.146
Glucose (mg/dl)	125.35	115.57	0.704
LOX-1 (ng/ml)	91.63	90.56	0.966
FMD (%)	0.5900	0.6756	0.13
EIVD (%)	6	8	0.28

BMI: Body mass index, F/M: Female/Male, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, LOX-1: Lectin-like oxidized low-density lipoprotein receptor 1, FMD: Flow mediated dilatation, EIVD: Endothelial independent vasodilator response

DISCUSSION

PEH commonly affects armpit (axillary hyperhidrosis), palm (palmar hyperhidrosis), sole (plantar hyperhidrosis), and face (craniofacial hyperhidrosis). Heat, emotional state, and spicy food (gustatory hyperhidrosis) may increase sweating [1]. The underlying mechanism in PEH is yet unclear. It is considered to be characterized by excessive stimulation of sympathetic cholinergic sudomotor fibers. Decrease in palmar hyperhidrosis after thoracic sympathectomy supports the consideration. It is known that hyperactive sympathetic cholinergic fibers leave the superior dorsal ganglion at T2-T3 level, and cause abnormal innervation of eccrine glands, thus, vasoconstriction and decrease in skin temperature. T2-T4 ganglions are also on the direct sympathetic innervation pathway of the heart [2]. Therefore, it is suggested that PEH is not only a local disorder, but also general dysfunction of autonomic nervous

system affecting cardiac and vascular autonomic control [3].

There are various studies investigating cardiac autonomic control in patients of hyperhidrosis. Those studies investigated cardiac autonomic tests, changes in heart rate and blood pressure, and endothelial dysfunction. De Marinis and colleagues assessed cardiac functions with sympathetic and parasympathetic tests, and showed that both sympathetic and parasympathetic autonomic tests impaired [7]. On the contrary, the studies by Kaya and colleagues which assessed heart rate alterations in patients with EH, and by Senard and colleagues which assessed blood pressure and heart rate alterations and catecholamine levels showed no differences between PEH patients and control groups [8,9]. Sağlam and colleagues found that left ventricular filling function in PEH patients was decreased compared to the control group, and suggested that it might be

an early finding of left ventricular failure in PEH patients [10]. In one study that assessed endothelial dysfunction with FMD method, Esen and colleagues found no difference between PEH patients and control group [3]. Also in the present study, to support the study by Esen and colleagues, there was no difference between PEH patients and control group in terms of endothelial dysfunction assessed with FMD method. Additionally, in our study no difference was found in LOX-1 levels between EH and control groups.

Lectin-like oxidized LDL receptor 1 is a type 2 membrane protein for oxidized LDL and plays a role in host-defense system, inflammatory response, and pathogenesis of various diseases, such as hypertension, atherosclerosis, and cardiovascular diseases. Recent studies showed that LOX-1 was a multiligand receptor induced by reactive oxygen metabolites and oxidative stress, and increased the oxidative stress more by its expression. Therefore, LOX-1 has an important role in oxidative stress that induces cellular damage [11]. Nitric oxide has an important role in regulation of vasomotor response and adjustment of blood pressure due to sympathetic stimulation. It is reported that the role of NO in such regulation impaired [12]. In another study, plasma NO levels in PEH patients were found significantly higher than control group [13]. May NO levels be increased in PEH patients as a compensatory mechanism to prevent development of vascular endothelial dysfunction against the stress occurring as a result of excessive sympathetic stimulation? If so, that may account for indifference between PEH and control groups in terms of LOX-1 and FMD levels, since; various investigators previously demonstrated that LOX-1 and NO might affect levels of each other inversely in endothelial cells [14].

In conclusion, there are contradictory results in numerous publications on the effects of sympathetic hyperactivity on cardiovascular system in EH. Larger studies are needed to understand, indeed, whether sympathetic hyperactivity in EH is only a peripheral excessive response or a multisystem dis-

order, cardiovascular effects of which is disguised by compensatory mechanisms, such as NO.

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