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The Investigation of Lectin-Like Oxidized LDL Receptor 1 (LOX-1) K167N Polymorphism, Inflammation, and Lipid Status in Patients with Coronary Artery Bypass Grafting

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ABSTRACT

Objective: Coronary artery disease (CAD) is a pathological condition resulting from atherosclerosis in the coronary arteries. Besides traditional risk factors, genetic factors such as single nucleotide polymorphs (SNPs) can be involve in disease process. Inflammation plays a role in pathological changes throughout atherosclerosis, from initiation to progress. In this study, we aimed to evaluate the effects of lectin-like oxidized LDL receptor 1 (LOX-1) K167N polymorphism, inflammation, and lipid status in patients with coronary artery bypass grafting (CABG).

Material and Methods: The study population consisted of 129 CAD patients who had undergone CABG, and 71 healthy controls. The LOX-1 K167N polymorphism was genotyped using PCR-RFLP technique. Plasma interleukin-1 β (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-33 (IL-33) levels were determined by enzyme-linked immunosorbent assay (ELISA) kits.

Results: The distribution of the LOX-1 K167N genotypes and alleles did not differ significantly between CAD patients with CABG and controls. There were no significant differences in plasma IL-1 β , TNF- α , IL-33, HDL-C, and LDL-C levels between the patients and controls. IL-1 β and systolic blood pressure values were significantly higher in KK genotype patients compared to the same genotype controls(P<0.05). Similarly, systolic blood pressures were higher in NK genotype patients compared with NK genotype controls (P<0.01).

Conclusions: IL-1 β and systolic blood pressure values were found to be higher in post CABG CAD patients with the KK genotype compared to healthy controls with the same genotype while inflammatory markers and lipid profiles selected according to LOX-1 K167N polymorphism genotype and allele distributions did not differ between groups. Although we couldn't find an assocation between LOX-1 K167N polymorphism and CAD other than high BP in our study, studies with larger sample sizes might reveal such a relation.

Keywords: Coronary artery bypass grafting, LOX-1 gene, K167N polymorphism, inflammation, lipid level.

INTRODUCTION

Coronary artery disease (CAD) is a pathological condition in which obstructive or nonobstructive atherosclerotic plaques accumulate in the epicardial arteries (1). In addition to modifiable factors such as smoking, physical inactivity, overweight, uncontrolled stress, and unhealthy diet, there are non-modifiable factors such as advanced age, male gender, race, and family history of CAD (2). Genetic factors are also effective in the development of CAD, and associations between the risk of CAD and ~60 genetic loci has been found (3).

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The most important step in the development of atherosclerosis is endothelial damage and accumulation of low-density lipoprotein-cholesterol (LDL-C) in the inner arterial wall (4). As a result of endothelial damage, the activities of cell adhesion molecules increase, so that monocytes adhere to endothelial cells. Modification of lipoproteins in arteries leads to a lipid peroxidation chain reaction, which forms toxic aldehyde metabolites. This reaction triggers inflammation in vascular cells. Moreover, inflammatory cells accelerate the cellular uptake of lipoprotein-derived lipids. Acetylated and oxidized LDLs (oxLDLs), which are modified lipoproteins, can not be recognized by native LDL receptors whilst macrophages recognize altered LDLs express families of scavenger receptors that through scavenger receptors that recognize altered LDLs. The lectin-like oxidized LDL receptor-1 (LOX-1) is one of these scavenger receptors that recognize oxLDLs. Macrophages that take up oxLDLs induce lipid accumulation and foam cell formation (4-6). Foam cells proliferate to form early lesions of atherosclerosis called fatty streaks. These lesions trigger signals that attract vascular smooth muscle cells (VSMCs) to the fatty streak region. The development of atherosclerotic plaque and the extracellular matrix produced by VSMCs lead to the progression of the lesion to fibrous plaque. Small blood vessels are formed that can calcify the fibrous plaque lining the lumen of the coronary vessel. This lesion has a complex structure that contains a lipid-rich core, a fibrous cap, and highly thrombogenic, and necrotic material (7).

Case-control association studies have been conducted to determine the genetic causes of CAD. It has been reported that genes associated with this disease process can be divided into three categories: disease-causing genes, susceptibility genes, and disease-linked genes (8, 9). In addition, SNPs or genetic variants of many candidate genes have been identified and have been reported to be associated with increased or decreased risk of CAD (7, 10, 11).

A single nucleotide polymorphism G501C in exon 4 of the LOX-1 gene is a missense mutation (p.K167N) involving a G to C transition at nucleotide 501, resulting in the conversion of lysine (K) at position 167 to an asparagine (N) (12). The amino acid residue 167 is located in the lectin domain of LOX-1, which is the ligand-binding domain. Basic residues in the lectin domain are important for enhancing ligand binding, and substitution of these residues results in decreased binding and internalization of oxLDL (12, 13).

Despite evidence for the functional role of this polymorphism, results from epidemiological studies are controversial. Previous studies have examined the relationship between the K167N polymorphism in the LOX-1 gene and vascular diseases, but conflicting findings have been reported (13-22). In addition, in our literature search, a study investigating LOX-1 K167N polymorphism and circulating inflammatory status in patients with the coronary artery bypass graft (CABG) did not draw attention. In this study, we aimed to investigate possible association of LOX-1 K167N gene polymorphism and inflammatory markers as well as serum lipid levels in CAD patients who underwent CABG.

MATERIAL and METHODs

Subjects: This case-control study included 129 patients (30 women, and 99 men) with CAD and who had CABG surgery and 71 healthy controls (29 women, and 42 men). The median age of patients and controls were 62 and 49 years, respectively. Healthy persons without any history of cardiovascular events and without any symptoms of CAD were selected for the control group. The exclusion criteria included cancer, autoimmune, kidney, or hepatic disease. All study subjects were of Turkish origin and provided signed informed consent before the sample and data collection. This study was approved by the Local Hospital Ethics Committee (Approval Number: 2022/162). All procedures followed the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all participants for being included in the study.

Blood collection: Blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes after an overnight fast. After centrifugation at 400 x g for 10 min at 4°C, plasma samples were separated in Eppendorf tubes and frozen at -80 °C until analysis.

Measurement of plasma inflammatory and lipid parameters: Plasma interleukin-1 β (IL-1 β), tumor necrosis factor-alpha (TNF- α), and interleukin-33 (IL-33) levels were enzyme-linked immunoassay measured by using commercially available kits (Diaclone, Besancon, France). The coefficients of intra- and inter-assay variations were 6.0 % and 5.7 %, 5.6 %, and 6.7 %, 6.3 %, and 6.9 %; respectively. In addition, plasma high-density lipoproteincholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) levels were measured by automated colorimetric methods with commercially available kits (Cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany).

DNA isolation and genotyping: Blood was drawn into EDTA-containing tubes for DNA isolation The Roche DNA purification kit (Roche Diagnostics GmbH, Mannheim, Germany) was used to extract DNA from peripheral blood leukocytes in accordance with the manufacturer's instructions. Isolated DNA samples were kept frozen at -80° C. The LOX-1 K167N polymorphism was genotyped using standard PCR procedures and restriction enzyme digestion, as explained by Trabetti et al. (20). Forward primers were used in PCR to provide a MboII (Chimerx, Milwaukee, WI, USA) restriction site for K167N detection. There were two primer pairs used: 167F: 5'- GGGCTCATTTAACTGGGAAA-3' and 167R: 5'-CAAGAATTCCTCCAGTGACAG-3'. 25 ng of gDNA, 10 pmol/ µl of each primer, 2 x PCR master mix solution (intron Biotechnology, Korea), which involves 2.5 mM of each dNTP, 2.5 U of i-TaqTM DNA polymerase, 1x of PCR buffer, and 1x of gel loading buffer, were the components of the PCR mixture (20 µl total volume). A Techne Thermal Cycler (Applied Biosystems Gene Amp PCR System 9700, Singapore) was used to perform the PCR. PCR conditions were as follows: initial denaturation at 94 °C for 2 min, followed by 40 cycles of denaturation at 94 °C for 20 s, annealing at 52 °C for 10 s, and elongation at 72 °C for 30 s. The final amplicon extension was performed at 72 °C for 5 min.

PCR amplicons were separated by electrophoresis in 2 % agarose gel, and ethidium bromide staining was used to identify them. The K167N PCR product was 171 bp. The amplified PCR products were directly digested with the MboII restriction enzyme (10 U/ μ l) at 37 °C for overnight. After MboII restriction, two fragments were obtained: 139 and 31 bp for the K allele and a single fragment of 171 bp for the N allele. The digested DNAs were separated on 3 % agarose gel in 1 x Tris borate EDTA buffer followed by staining with ethidium bromide solution. The K167N genotypes were detected using a Polaroid camera and viewed under ultraviolet light.

Statistical analysis: The SPSS Statistic 21.0 program was used for the analyses of the patients and control values. Hardy–Weinberg equilibrium was tested by Chi-square analysis. Genotype and allele frequencies were compared between cases and controls by Chi-square analysis. The odds ratio (OR) and respective 95 % confidence intervals (CIs) evaluated the effects of any difference between the allelic and genotype distributions. The unpaired Student's test (normally distributed variables) or Mann–Whitney U test (not normally distributed variables) were used for the comparison of other parameters. A value of p<0.05 was considered the minimum statistical significance.

RESULTS

The characteristics of patients undergoing CABG and the control groups are summarized in Table 1. There was no significant difference in terms of sex, body mass index (BMI), and alcohol consumption between the patient and control groups (p>0.05). There were significant differences in cigarette smoking behavior, hypertension, the presence of diabetes mellitus disease, and systolic and diastolic blood pressure values between patients and controls (p=0.004, p=0.001, p=0.001, p=0.016, and p=0.013, respectively). No statistically significant difference was observed in the plasma IL-1 β , TNF- α , IL-33, HDL-C, and LDL-C values between the CABG and the control groups (p>0.05, for all) (**Table 1**).

We investigated the LOX-1 K167N gene polymorphism, the frequencies of the genotypes in CABG patients and control groups were shown in Table 2. The distribution of KK, NK, and NN genotypes was 70%, 13%, and 17%, respectively in the cases and 47, 34, and 19%, respectively in the controls. All healthy controls in the study were in Hardy-Weinberg equilibrium. No statistically significant difference was observed in the LOX-1 K167N gene polymorphism between the two groups (p > 0.05). Also, the distribution of K and N alleles was 76% and 24%, respectively in the cases, and 78% and 22%, respectively in the controls (p > 0.05).

We compared these parameters among the genotype groups in patients and controls to assess whether LOX-1 K167N polymorphism had any effect on inflammatory and lipid parameters, and blood pressure (Table 3). The IL-1 β levels were higher in patients with the KK genotype than in controls with the KK genotype (9.15±1.12 pg/mL, and 8.42±0.79 pg/mL respectively; p<0.05). The systolic blood pressure levels were higher in patients with the KK genotype than in the control with the KK genotype (137.48±14.97 mmHg, and 126.72±14.92 mmHg, respectively; p<0.05). Also, the systolic blood pressure levels were higher in patients with the NK genotype than in the control with the NK genotype (141.25±8.77 mmHg, and 121.57±7.34 mmHg, respectively; p<0.01). No significant difference was detected in the comparison of the same genotypes of other parameters between the patient and control groups.

Table 1. Clinical characteristics of patients undergoing coronary artery bypass grafting and healthy controls were included in the study.

	Controls (n=71)	Patients (n=129)	p value
Sex, n, (M/F)	42/29	99/30	NS
BMI (kg/m ²)	27.46±3.72	26.67±3.02	NS
Alcohol consumption, n, (+/-)	8/63	30/99	NS
Cigarette Smoking, n , (+/-)	25/46	90/39	0.004
Hypertension, n, (+/ -)	0/71	69/60	0.001
Diabetes mellitus, n, (+/ -)	0/71	39/90	0.001
Systolic Blood Pressure (mm Hg)	126.81±6.54	136.14±18.50	0.009
Diastolic Blood Pressure (mm Hg)	81.30±12.34	74.81±10.56	0.013
IL-1 β (pg/mL)	8.83±2.26	9.56±1.69	NS
TNF- α (pg/mL)	12.15 ± 2.64	12.57±2.96	NS
IL-33 (pg/mL)	18.24 ± 6.05	17.78 ± 4.98	NS
HDL- C (mg/dL)	43.18±6.06	41.74±11.26	NS
LDL- C (mg/dL)	128.73±38.39	133.17±11.63	NS

Data were presented as mean \pm SD, Body mass index (BMI), Interleukin-1 β (IL-1 β), Tumor necrosis factor alpha (TNF- α), Interleukin-33 (IL-33), High-density lipoprotein-cholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C) NS: No significant.

Table 2. Distribution of genotypes and allele frequencies of K167N polymorphism in patients undergoing coronary artery bypass grafting and control groups.

Gene	Controls n (%)	Patients n (%)	р	OR (CI 95%)
LOX-1 K167N polymorphism	71	129		
Genotypes				
KK	50 (47)	90 (70)		1
NK	11 (34)	17 (13)	0.886	1.165 (0.506-2.680)
NN	10 (19)	22 (17)	0.785	0.818 (0.359-1.864)
Alleles				
K	111 (78)	197 (76)		1
Ν	31 (22)	61 (24)	0.680	0.902 (0.552-1.474)

Genotypes and allele frequencies were shown as n (%), OR: Odds Ratio, CI: Confidence Interval.

Table 3. The levels of IL-1 β , TNF- α , IL-33, HDL-Cholesterol, LDL-Cholesterol, systolic blood pressure, and diastolic blood pressure in patients undergoing coronary artery bypass grafting and controls according to LOX-1 K167N polymorphism.

	Control Group LOX-1 K167N polymorphism			Patient Group LOX-1 K167N polymorphism		
Parameters	KK	NK	NN	KK	NK	NN
IL-1β (pg/mL)	8.42±0.79	10.33±4.94	9.35±0.78	9.15±1.12*	10.87±1.71	8.82±0.60
TNF-α (pg/mL)	12.34±3.02	11.34±1.53	11.28±1.24	12.88±4.02	12.18±0.73	12.34±1.54
IL-33 (pg/mL)	17.90±6.57	19.62±5.96	18.01±1.98	17.48±4.83	16.68±2.10	15.94±3.24
HDL-C (mg/dL)	44.67±6.98	43.00±9.81	41.00±9.56	38.85±8.33	43.75±10.21	41.50±10.34
LDL-C (mg/dL)	139.17±49.18	119.00±18.09	124.00±36.07	118.85±34.17	119.50±31.27	138.75±44.11
Systolic Blood Pressure (mm Hg)	126.72±14.92	121.57±7.34	145.00±21.21	137.48±14.97*	141.25±8.77**	140.75±18.99
Diastolic Blood Pressure (mm Hg)	80.12±11.84	79.00±11.15	90.00±15.98	78.29±10.18	75.75±8.09	85.50±11.12

Data were presented as mean \pm SD, Interleukin-1 β (IL-1 β), Tumor necrosis factor alpha (TNF- α), Interleukin-33 (IL-33), High-density lipoproteincholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C). Bold values indicate statistical significance (P<0.05), *KK genotypes in patient group vs. KK genotypes in controls (P<0.05)**NK genotypes in patient group vs. NK genotypes in controls (P<0.01), (Student's t-test or Mann-Whitney U test).

DISCUSSION

The LOX-1, which is the main receptor for ox-LDL in endothelial cells, may play a role in atherogenesis and atherothrombosis through various mechanisms (5, 23) Some single nucleotide polymorphs (SNPs) in the LOX-1 gene may explain a functional change caused by an amino acid change. Concerning this, the rs11053646 SNP (c.501 G>C) results in an amino acid change at position 167 (p.K167N), which is linked to lower ox-LDL binding and uptake (24). In this study, the LOX-1 K67N polymorphism was investigated in patients who underwent CABG, and circulating markers of inflammation and lipid levels were also evaluated.

In the literature, studies investigating the LOX-1 K67N polymorphism in vascular diseases have reported conflicting findings (13-17, 20). Mango et al. examined the gene variants of the K167N polymorphism in patients with myocardial infarction, and they stated that the frequency of the N variant was lower in patients than in controls, and that the N allele could have a protective effect (14). Similarly, Kurnaz et al. found that the frequency of 501G/C+ 501C/C in CAD patients was significantly lower (p<0.01) than in healthy people (15). Ohmori et al. reported that the frequency of LOX-1 501C/C or 501C/G gene variants decreased as the severity of CAD increased. The lowest frequency was observed in patients with three-vessel disease (19).

However, there are also studies reporting increased LOX-1 K167N polymorphism in vascular diseases. Tatsuguchi et al. found that the frequency of 501G/C+ 501C/C was significantly higher in patients with myocardial infarction than in healthy people, and that G501C caused a missense mutation in the LOX-1 protein (16). Similarly, Zhang et al. reported that the presence of the CC genotype and the carrier of the C allele were significantly higher in ischemic stroke patients than in controls (p =0.001, for both) (17).

However, Trabetti et al. did not find an association between the K167N polymorphism and acute myocardial infarction in the Italian population (20). In the Japanese population, Hattori et al. did not find an association between the K167N polymorphism and ischemic cerebrovascular disease (13). According to Knowles and colleagues, there was no association between cardiovascular risk and the LOX-1 K167N SNP (22). Morgan et al. did not find an association between acute coronary syndrome and G501C SNP (21). In Poles under 45 years old who had a myocardial infarction, the K167N SNP showed no significant difference from the control group (18). Our findings were consistent with those of Hattori et al.(13), Sakowicz et al.(18), Trabetti et al. (20), Morgan et al. (21), and Knowles et al.(22)s' results. There was no significant change in the LOX-1 K167N genotype and allele distributions of CABG patients and healthy volunteers. Increased or decreased K167N polymorphism findings in the literature may be due to different genetic backgrounds in studied populations.

In addition to genetic factors, modifiable risk factors are also important in the development of atherosclerotic vascular disease. Epidemiological studies have reported that risk factors such as smoking, high cholesterol level, hypertension, and diabetes mellitus play a role in the development of atherosclerosis (2). In the early stages of atherosclerosis, high plasma LDL-C causes the deposition of LDL in the aortic wall, and subsequent oxidation of LDL to oxLDLs (25). Proinflammatory risk factors such as oxLDL activate interleukin-1 (IL-1) and TNF-a proinflammatory cytokines. Increased proinflammatory cytokine levels accelerate atherosclerosis progression. TNF- α is a proinflammatory cytokine involved in cell homeostasis and immune response regulation. TNF- α is also plays an important role in the development of atherosclerosis. The progression of atherosclerosis and local increase in TNF- α production in atherosclerotic plaques are directly related to blood TNF-a levels (25, 26). IL-1 β , a member of the IL-1 family, is a proinflammatory cytokine produced by myeloid cells. In a mouse experimental model, the proatherogenic properties of IL-1 β , such as involvement in macrophage activation and upregulation of the expression of adhesion molecules by endothelial cells, were confirmed (26, 27). In our study, we assessed another molecule, interleukin-33 (IL-33), which is a member of the IL-1 family. It has potent immunomodulatory properties and is a potent inhibitor of oxLDL uptake and foam cell formation (28). It was reported that the administration of soluble IL-33 receptor (ST2L) reduced atherosclerosis in a mouse model (29).

While proinflammatory cytokines accelerate the progression of atherosclerosis, anti-inflammatory cytokines are involved in the recovery of the disease. In the research of Gu et al., patients undergoing minimally invasive CABG showed a significant decrease in postoperative morbidity and hospital stay due to a reduced systemic inflammatory response (30). In our study, plasma TNF- α , IL-1 β , IL-33, and LDL-C levels were not significantly different in the CABG group compared with the control. The lack of an increase in inflammation in CABG patients may explain the decrease in morbidity.

We also investigated the effect of the same genotype on modifiable risk factors in the patient and control groups. Patients with the KK genotype had higher levels of IL- 1 β than controls with the same genotype. Also, the systolic blood pressure levels were higher in patients with the KK and NK genotypes than the controls with KK and NK genotypes (p<0.05, and p<0.01, respectively) (**Table 3**). Zhang et al. reported that K167N polymorphism and N allele carriage represent a higher risk for ischemic stroke, and other independent risk factors are high serum LDL-C level, hypertension, and smoking (17).

CONCLUSION

Our findings show that there is no significant change in LOX-1 K167N polymorphism, and circulating markers of inflammation and lipid profile in CABG patients. These results may be a result of the population's different genetic backgrounds and further studies seems to be needed for better understanding of such a complex, multifactorial disease process like atherosclerosis.

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Ethical approval: This study was approved by the Local Hospital Ethics Committee (Approval Number: 2022/162). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for being included in the study.

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