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Original Article

E -Selectin is associated with stable angina and myocardial infarction in a sample of Kurdish population

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Abstract

Endothelial dysfunction is the main factor that causes the onset of CAD. Leukocyte adhesion to the endothelium of the active blood artery wall has been demonstrated to be one of the early indicators of arteriosclerosis. This process is regulated by selectins. The purpose of this study is to ascertain the relationship between the polymorphisms in the E-selectin gene that have been linked to ischemic heart disease. We looked at the functional impact of the E-selectin gene polymorphism 7170G>C in Iraqi patients with IHD. This study was conducted on 200 participants who were admitted to the surgical specialty hospital-cardiac center in Erbil City, Iraq between October 2021 and May 2022. Based on the outcomes of the clinical examination, laboratory tests, coronary angiography (COA), acute myocardial infarction (MI) type ST-elevation myocardial infarction (STEMI), stable angina pectoris (SAP), and healthy control groups were tested. Each sample was subjected to Sanger sequencing. The polymorphism was significantly linked to stable angina and myocardial infarction Genotype CC was higher in SAP when compared with MI and control groups which was statistically significant with (p-value<0.05). A higher proportion of C allele was observed in SAP patients (15.7%) which was significantly higher than MI (14.58%) and control (10.8%). The statistical chi-square analysis for allele G frequency showed insignificant differences (p-value>0.05) between patients and the control group. Genetic variation in E-selectin such as polymorphism in nucleotide 7170 G>C at exon 4 region can significantly affect the outcome of cardiovascular diseases

Keywords: E-selectin, Polymorphism, Stable angina pectoris, Myocardial infarction, Kurdish population.

1. Introduction

E-Selectin, which has a molecular weight of roughly 116 kDa and is extensively expressed on the external membrane surface of vascular endothelial cells. It possesses a specific lectin domain, an EGF domain, and six CR consensus repeats, the 119-residue N-terminal lectin domain of the E-amino selectin's acid sequence is what binds the oligosaccharide after approximately six cysteine-rich consensus repetitions [1]. A small C-terminal cytoplasmic domain is connected to the stem of six consensus repeats by the EGF-like domain of E-selectin, and the bottom of the stem by a single transmembrane-helices. De novo transcription is required for E-selectin expression in response to stimuli. Therefore, the E-selectin is observable on the cell surface 3–4 hrs., after stimulation and drops to baseline levels after 16–24 h [2]. E-selectin expression increases quickly, peaks after four to six hours, and then decreases quickly due to the cleaving and shedding of the E-selectin ectodomain [3].

Leukocyte adherence to the vascular wall is lowered as a result of the ectodomain shedding of E-selectin, ICAM-1, and VCAM-1, which decreases the density of adhesion molecules on the membrane. The shed E-selectin ectodomains compete with uncleaved, membrane-bound E-selectin for the binding of leukocytes while still retaining affinity for their ligands [4].

Due to the interplay of conventional and hereditary risk factors, coronary artery disease has a complex history. The most significant contributor to the development of CAD is endothelial dysfunction. One of the early signs of arteriosclerosis has been shown to be leukocyte adherence to the wall of the active blood artery endothelium [5]. Selectins, integrins, immunoglobulins, chemokines and proinflammatory adhesion molecules, regulate this process [6]. From the bloodstream, leukocytes are drawn in and rolled across the surface of the endothelial cell. E-selectin is a key rolling mediating factor in monocyte migration and is expressed on activated endothelium. Endothelial monocyte and leukocyte adhesion and transmigration begin here. The 1q22–q25 region of the chromosome is home to the E-selectin gene. Genetic variations in the E-selectin locus may control the amounts of gene expression and impact how the protein functions biologically [7].

Numerous single nucleotide variants in the E-selectin gene were discovered, and various polymorphisms in the E-selectin gene have been linked to CAD, hypertension, and ischemic heart disease [8]. By exchanging amino acids and controlling cell-cell interactions, these functio-

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nal variations appear to be crucial in altering the secondary structure of E-selectin [9]. Atherosclerosis or hypertension may also be linked to other E-selectin variants. Additionally, it has been proven that illnesses with underlying inflammatory disorders can be impacted by the E-selectin gene polymorphism, which predisposes to chronic inflammation development/progression [10].

2. Materials and Methods

2.1. Study sample

This prospective case-control study was conducted on 200 participants who were admitted to the surgical specialty hospital-cardiac center in Erbil City, Iraq between October 2021 and May 2022. The attendees were all residents of Erbil Governorate. Based on the outcomes of the clinical examination, laboratory tests, coronary angiography (COA), acute myocardial infarction (MI) type ST-elevation myocardial infarction (STEMI), stable angina pectoris (SAP), and healthy control groups, the participants were split into three groups. The study excluded patients with severe valvular, congenital, post-MI, stroke, heart failure, cardiomyopathy, myocarditis, and pericarditis conditions. Also, people having a history of recent surgery or trauma, cancer, active inflammatory or autoimmune disorders, abnormal bleeding, or bleeding and clotting problems were not included in the study. Having received formal approval from the Erbil Directorate of Health and the heart center-surgical specialty hospital in Erbil city, the study protocol was submitted to the ethical committee at Hawler Medical University, College of Medicine. Also, each participant had the option of taking part in the study or not. In order to conduct biochemical analyses and molecular studies, five milliliters (mL) of venous blood were collected in (EDTA) and gel tubes and kept in the refrigerator. All individuals underwent coronary angiography through the right femoral artery.

2.2. Biochemical tests

Using the automated analyzer Cobas C311 to determine lipid profiles according to the enzymatic colorimetric test principle. A Swelab Alpha Coulter automated analyzer was used to calculate the whole blood count. Turbidimetric immunoassay to calculate HbA1C% utilizing an automated analyzer, Cobas C311.

2.3. Molecular analysis

2.3.1. DNA extraction from whole blood of all patients and controls

Genomic DNA was extracted from the acquired whole blood samples using a DNA extraction kit (Promega, USA) in accordance with the manufacturer's instructions using EDTA anticoagulant tubes.

2.3.2. Estimation of extracted genomic DNA

Prior to the PCR process, the quantity and quality of the isolated DNA were evaluated using two techniques: agarose gel electrophoresis and Nanodrop spectrophotometry. For DNA, pure nucleic acids typically provide a 260/280 ratio of about (1.8).

2.3.3. Primer's selection, and design

Exon-4 of the human E-selectin gene was targeted for amplification using a pair of forward GCTGCCTGTACCAATACATCC and reverse primers: TTGCTCACACTTGAGTCCAC. The E-selectin Exon-4 sequence was added to the software interface while designing the primers with Primer3Plus (V 3.2.6) [11], and the best-matching criteria were used to select the primers. The primers were tested for uniqueness to a selected target region of 107 base pairs on NCBI (National Center for Biotechnology Information). The PCR reactions were made as 25µL mix of 3µL DNA, 1.5µL forward and 1.5µL reverse primers, 15µL of Master Mix (Promega, USA) and 9 µL of nuclease-free water. T100 Thermal Cycler (Bio-Rad, USA) was used to amplify 107bp of the E-selectin gene at exon 4 region with PCR setting as 5 minutes' initial denaturation at 95°C followed by 40 cycles of 95°C for 30 seconds, 60°C for 30s, and 72°C for 60 seconds. The final extension was set at 72°C for 10 minutes.

2.3.4. DNA purification and cycle sequencing

After PCR, the reaction mixtures must be cleaned up so that unincorporated primers and dNTPs won't affect the outcomes. Only DNA was purified using magnetic beads. Bright Dye Direct Cycle Sequencing Kit (Thermo Fischer, USA) was used for cycle sequencing, and the manufacturer's instructions were followed. 1 µL of DNA, 1.5 µL of PCR primer mix (0.8 M for each primer), 5.0 µL Bright Dye direct PCR master mix, 2.5 µL, and deionized water were used for each 10 µL forward or reverse reaction. A further cycle sequencing step was completed. Agar gel electrophoresis proved that the minimum amount of PCR product required for sequencing was 20 ng. 2 µL of the Bright Dye direct sequencing master mix and 1 µL of the Bright Dye with forward or reverse primer were used for each 3 µL total reaction volume. Three liters of the sequencing reaction mix were added to the appropriate well in the corresponding forward or reverse reaction plate after the reaction mixture was produced on ice. The reaction plate was briefly spun after being covered in adhesive film or caps. A thermal cycler was used to run the reactions. Following the manufacturer's recommendations, the Brilliant Dye purification kit was used to clean the final sequencing product. The 96-well standard sequencer on the Applied Biosystems SeqStudioTM Genetic Analyzer System sequencing machine was loaded with the final response plate (Applied Biosystems). The acquired sequences were put through a BLAST search to find related genes in GenBank.

2.3.5. Sequencing of E-selectin gene

The purified E-selectin amplicons were subjected to sequence analysis using the Sanger sequencing method. Thus, SeqStudio™ Genetic Analyzer System (Applied Biosystems, CA-USA) was used according to the manufacturer's guidelines.

2.4. Bioinformatics and statistical analysis

The BioEdit program examined the sequences from the text files for each group. The exon 4 region, which contains the SNP sequence, was aligned using various sequences using the supplementary ClustalW utility in the BioEdit program. The graph files were also examined to determine whether the SNP sequence was heterozygous or homozygous. The APE program was used to perform the multiple sequence alignment of the entire E-selectin gene since it can display translated codons and deduced amino acids. Statistical analysis was performed using the

SPSS 26 program. At a significance level of 0.05, the tests employed were one-way analysis of variance (ANOVA), chi-square, and logistic regression. Chi-square was also used to compute the means, standard deviations (SDs), and Hardy-Weinberg equilibrium (HWE).

3. Results

3.1. Clinical features and baseline investigations of study groups

The hsCRP level in MI and SAP patients was significantly higher than in the control group (p-value<0.05); as revealed in Table 1. Age, systolic and diastolic blood pressure, body mass index, hemoglobin A1c, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lipid ratios, total cholesterol and triglycerides, all showed statistically significant differences (p-value<0.05) between the MI, SAP and the control group.

3.2. Analysis of genotypes and alleles distribution among study groups

Although GC showed higher genotype distribution in the patient groups compared to the control group, the difference was statistically insignificant (p-value >0.05). However, Genotype CC was higher in SAP when compared with MI and control groups which was statistically significant with (p-value<0.05). A higher proportion of C allele was observed in SAP patients (15.7%) which was significantly higher than MI (14.58%) and control (10.8%). The statistical chi-square analysis for allele G frequency showed insignificant differences (p-value>0.05) between patients and the control group (Table 2).

4. Discussion

The pathology of MI is multifactorial and one of the critical factors involved in the disease pathogenesis is rela-

Table 1. Comparison among SAP and MI with control groups in some factors.

Variables	SAP No.	MI No.	Control No.	*p*-value
		Mean± SE		
Age (years)	59.14±1.037[a]	56.32±1.19[a]	51.55±1.235[b]	0.002**
SBP (mmHg)	134.9±2.198[b]	142.4±2.614[a]		0.0205*
DBP (mmHg)	90.49±1.993[b]	97.88±2.384[a]		0.0182**
BMI (kg/m²)	29.66±0.747[a]	28.33±0.712[a]	25.76±0.486[b]	0.007**
HbA1c	6.062±0.171[a]	7.028±0.261[a]	5.221±0.087[b]	0.001**
		Inflammatory Biomarker		
hsCRP (mg/L)	10.469±0.161[a]	10.479±0.219[a]	6.24±0.145[b]	0.001**
		Lipid profile and lipid ratios		
TC (mg/dL)	204.8±8.014[a]	200.1±7.438[a]	167.8±5.684[b]	0.0054**
TG (mg/dL)	227.1±10.48[a]	239.9±11.65[a]	133.0±6.734[b]	0.001**
HDL-C (mg/dL)	33.39±0.724[a]	35.24±0.778[a]	42.34±1.645[b]	0.005**
LDL-C (mg/dL)	139.9±5.587[a]	144.9±5.827[a]	127.8±4.454[b]	0.0278*
Non-HDL (mg/dL)				
TC/HDL	6.39±0.334[a]	5.831±0.253[ab]	4.106±0.198[b]	0.0074**
LDL/HDL	4.369±0.223[a]	4.243±0.203[a]	3.146±0.156[b]	0.003**

Statistical analysis was done by using ANOVA (continuous variables), *p-value<0.05: Significant, **p-value<0.01: Highly significant. p>0.05: non-significant. Different letters mean significant differences between the groups. MI: Myocardial infarction, SAP: Stable angina pectoris, DM: Diabetes mellitus, HTN: Hypertension, FH: Family history, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, HbA1C: Hemoglobin A1C, hsCRP: High sensitivity C reactive protein, TC, Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein- cholesterol, LDL-C: Low-density lipoprotein- cholesterol.

Table 2. Distribution of genotypes and alleles of E-selectin 7170 G/C gene polymorphism among SAP, MI and control groups.

E-Sel 7170 G/C	SAP 35	MI 24	Control 15	x^2	*p*-value
	No. (%)	No. (%)	No. (%)		
	Genotypes				
GG	17 (48.57)	18 (95.83)	13 (86.66)		
GC	14 (40)	5 (20.83)	2 (13.33)	[a]1.072 [b] 6.58	[a]0.585[ns] [b]0.0371*
CC	4 (11.42)	1 (4.16)	0 (0.0)		
GC+CC	18	6	2	[a]0.771 [b]6.349	[a]0.380[ns] [b]0.0117 *
	Alleles				
G	48 (38.57)	41 (85.41)	28 (76)	[a]1.134	[a]0.287[ns]
C	22 (15.7)	7 (14.58)	2 (10.8)	[b]7.059	[b]0.0079 *

MI: Myocardial infarction, SAP: Stable angina pectoris. [a] MI vs control, [b] SAP vs control. Chi-square (x^2) and Fisher exact test were used for significant difference estimation at p-value level <0.05, p>0.05: non-significant. Allele frequencies are calculated based on Hardy-Weinberg equilibrium (HWE).

ted to the dysfunction of lipid metabolism. In the present study, the age group of both MI and SAP were at the end of their fifties. The mean age of both SAP and MI groups was significantly higher than control which is similar to the study done by Rodger and coworkers [12]. Due to the increased possibility that other risk factors, such as obesity, would develop, age is a significant risk factor for cardiovascular disease. Obesity and diabetes have both been linked to oxidative stress and chronic inflammation [13]. Older persons have a higher risk of cardiovascular disease (CVD) due to the decline of cardiovascular function brought on by aging [14]. Both cases had a higher body mass index than the control group. Similar results were observed in other studies [15, 16]. It is widely acknowledged that having a high BMI increases the chance of developing thrombotic conditions such as thrombosis in the veins, stroke, and cardiovascular disease. Obesity is a recognized risk factor for myocardial infarction [17]. There were significant differences between MI and SAP regarding SBP and DBP this was in agreement with previous studies [18].

The current study revealed a significantly higher HbA1c mean value in both MI (7.02) and SAP (6.06) compared to the control (5.22), which seems to be in line with prior reported data [19]. Given the clear relationship between persistent insulin resistance and metabolic disturbances like hyperglycemia, hypercoagulability, dyslipidemia, and inflammation, an increased HbA1c level in CAD patients is likely caused by persistent insulin resistance. This could be viewed as a key pathological mechanism for the negative effects of an elevated HbA1C level [20].

In the current study, although the majority of the patients (MI and SAP) were on particular routine medication according to case severity and physician advice, they still demonstrated dyslipidemia as higher levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and a lower level of high-density lipoprotein-cholesterol (HDL-C) were observed in patients with MI and SAP compared to controls. The results of the present study seem to be supported by those reported previously [21]. Interestingly, the most significant results observed throughout the study were related to HDL-C, LDL-C, TC/HDL and LDL/ HDL parameters.

A previous study [22] revealed significantly higher levels of TG, TC, LDL and low levels of HDL in MI patients. Additionally, it has been found that patients with low levels of HDL had rates of acute MI and CAD mortality similar to those of the entire group study including hyperlipidemia [23]. Our present study showed a significant elevation of hsCRP in both MI and SAP, the result seems to agree with previous studies [24]. The strong correlation between genetic variations and many environmental risk factors has been well documented, thus the information on the gene involvement and mechanism in CAD is very helpful for the innovation of new approaches for disease treatment and prevention [25]. One of the genes that are currently under intensive researches is the E-selectin gene, which has been reported to be involved in many human diseases.

In this study, we examined the relationship between C7170G E-selectin gene SNPs with SAP and MI risk. The early phases of atherosclerosis processes include local inflammation and endothelial dysfunction. The recruitment, rolling, and diapedesis of lymphocytes and monocytes in the blood artery wall are all critical functions of E-selectin, which is viewed in this context as a key endothelium product in the chain of events leading to plaque development and atherosclerosis [26]. In this regard, after directing an extensive search of the available literature, it turns out that this is the first study that describes the association of E-selectin gene polymorphism at C7170G and the risk of developing MI and SAP. Interestingly, we found that the C allele of the SEL-E C7170>G SNP was associated with an increased risk of developing SAP in the Kurdish population which showed a significant difference when compared with the control, however, there was no significant difference with the MI group.

At the molecular level, the nucleotide substitution of G with C at 7170 position is of missense type leading to the replacement of glycine with arginine. When the search was conducted in various interrelated resources including The Human Transmembrane Proteome (HTP) database, it was noted that this change can profoundly influence the condition in affected individuals [27]. Hence, a number of studies have demonstrated that mutations resulted in glycine to arginine in the transmembrane molecules, of which E-selectin is a member, is associated with the majority of relevant diseases [28, 29]. Indeed, there is a solid evidence that such highly charged mutations can lead to misfolding of transmembrane proteins and subsequently cause protein dysfunction [30, 31]. In a very similar study Zhao et al., studied SNPs in the same region namely exon 4 of E-selectin. They investigated the impact of C alleles of the serine to arginine polymorphism on increased risk of ischemic heart disease [32]. Additionally, in a comprehensive meta-analysis report, the association between CC genotype and increased risk of coronary artery disease in the Asian population [29]. On the other hand, despite all these findings, it was revealed that Glycine to Arginine shift is less prominent in a variety of studied risk factors. Thus, except for a family history of cardiovascular disease in SAP and a history of hypertension with statistically significant association (Figure 1 h and i), other risk factors were found to be not significantly associated with the Glycine<Arginine genotype. The link between CC genotypes in MI and hypertension is supported by the findings in other studies including the report by Wang et al that asserts the fact that carriers of the CC genotype presented a higher risk for developing hypertension [33]. However,

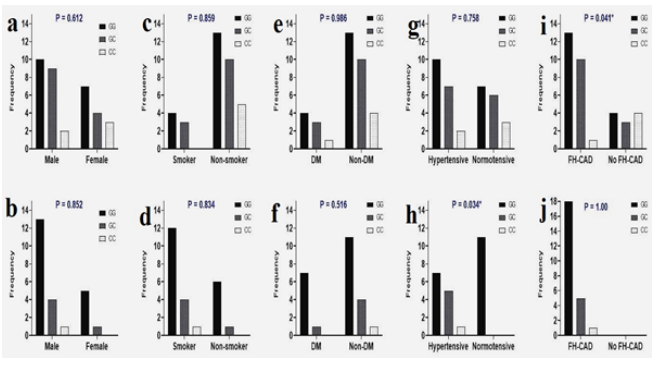

Fig. 1. Distribution of genotypes in SAP and MI according to various factors. Gender in SAP (a) and MI (b). History of smoking in SAP (c) and MI (d). Diabetes in SAP (e) and MI (f). Hypertension in SAP (g) and MI (h), and family history of CAD in SAP (i) and MI (j). Chi-square test was performed with $P < 0.05$ as statistically significant.

as mentioned above the Kurdish population is relatively closer to Caucasians than Asians which can justify the lack of significant association in studied patients as noted by other researchers that report the link between CC genotype and high CAD in Asian ethnic groups but not in Caucasians [34]. Nevertheless, the lack of significant association between a history of diabetes and CC genotype is contradictory to the findings of Alzubadiy in a group of Iraqi patients with diabetic foot lesions [35].

5. Conclusion

Finally, it can be suggested that studying the genetic variation, especially in critical proteins with transmembrane localization such as E-selectin and others can be a key indicator in determining the outcome of cardiovascular diseases.

Conflict of interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

Having received formal approval from the Erbil Directorate of Health and the heart center-surgical specialty hospital in Erbil city, the study protocol was submitted to the ethical committee at Hawler Medical University, College of Medicine.

Availability of data and material

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authors' contributions

All authors contributed equally to this research study.

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