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ORIGINAL RESEARCH

Association Between Genotype and Plasma Levels of EPCR in Type 2 Diabetes Mellitus in Jazan Region, Saudi Arabia: A Case-Control Study

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Background: Type 2 diabetes mellitus (T2DM) is a major health burden in Saudi Arabia. Its prevalence is estimated at 16.4% to 28% among adults. It is characterized by chronic hyperglycemia inducing low-grade inflammation, which drives various physiological changes, including endothelial dysfunction. The endothelial protein C receptor (EPCR) is a membrane-bound receptor expressed on normal endothelial cells and is released upon endothelial dysfunction into the blood as soluble EPCR (sEPCR). Increased cleavage and release of EPCR is associated with the EPCR rs867186 polymorphism. Therefore, the current study aimed to investigate the pattern and frequency of EPCR rs867186 polymorphism and plasma levels of sEPCR in patients with T2DM and healthy controls.

Materials and Methods: The current case-control study was performed in Jazan region, Saudi Arabia. Two hundred and thirty-four blood samples were collected from the 136 patients with T2DM and 98 healthy controls for DNA analysis and hematological and biochemical assessments.

Results: The plasma levels of sEPCR were significantly elevated in T2DM patients compared to controls, despite no association being found between sEPCR levels and the genotype in either cohort. The pattern of EPCR rs867186 polymorphism revealed AA in 83.8% (n=196) and AG in 16.2% (n=38) of total cohorts (n=234), with comparable genotype distribution between patients and controls.

Conclusion: This study highlights a significant elevation in plasma levels of sEPCR in patients with T2DM, indicating increased shedding of membrane EPCR and suggesting endothelial dysfunction. Importantly, the levels of sEPCR were not associated with rs867186 polymorphism. These findings suggest that sEPCR could be a useful biomarker for predicting early inflammation and endothelial dysfunction in T2DM.

Keywords: EPCR, polymorphism, soluble EPCR, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent condition worldwide and represents a significant burden on both public health and the economy, given its impact on mortality, morbidity, and healthcare costs.[1] In Saudi Arabia, T2DM has reached alarming levels, with a prevalence estimated from 16.4% to 28% among adults, ranking the country 2nd in the Middle East and 7th globally, with around 7 million adults affected by the disease and over 3 million considered pre-diabetic.[2] T2DM complications are significantly associated with high mortality and morbidity rates, accounting for up to 11.3% of the world's mortality rate.[3]

Hyperglycemia is recognized as a primary driver of complications in T2DM, leading to thrombotic complications and low-grade inflammation that contribute to endothelial dysfunction.[4] This endothelial dysfunction impairs blood vessel function and contributes to cardiovascular disease development, a common complication in T2DM.[5] The endothelium is crucial in maintaining hemostasis, which is the balance between clot formation and the prevention of excessive clotting

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(anticoagulation). Normal endothelium produces and expresses activated mediators such as prostacyclin and nitric oxide to regulate platelets and anticoagulant mediators such as heparin, antithrombin, and protein C (PC).[6] The PC pathway depends on the endothelial protein C receptor (EPCR), which is the major factor in the PC pathway by regulating the coagulation cascade and preventing excessive clot formation.[7] EPCR is a glycoprotein expressed on the surface of endothelial cells that activates PC. It can be cleaved and released into circulation as soluble EPCR (sEPCR), with elevated levels indicating endothelial dysfunction.[8] Elevated sEPCR levels have been found to influence the regulatory mechanism of coagulation, thus inhibiting the activation of activated protein C.[9] Therefore, it has been suggested that elevated sEPCR levels enhance plasma procoagulant activity and increase the risk of prothrombotic tendency, thereby increasing the risk of thrombosis.[9] In addition, elevated levels of sEPCR have been reported in T2DM, which have been associated with disease outcomes.[10,11] Elevated sEPCR levels have been suggested as a biomarker for endothelial dysfunction in T2DM and other related conditions.[10,11] The plasma levels of sEPCR have been strongly associated with genotype, mainly with the Ser219Gly variant polymorphism (rs867186). The rs867186 polymorphism accounts for 50–80% of the variation in plasma sEPCR levels, making it a strong candidate for genetic association studies.[12–15] Individuals with the Ser219Gly variant have significantly higher levels of sEPCR compared to other variants.[16] Therefore, the current study aimed to (i) investigate the frequency of the EPCR rs867186 polymorphism in healthy individuals and patients with T2DM in Jazan region, Saudi Arabia, (ii) assess the plasma levels of sEPCR in both cohorts and (iii) correlate the pattern of rs867186 polymorphism and plasma sEPCR levels with demographic data, as well as biochemical and hematological parameters in T2DM.

Materials and Methods

Study Setting and Design

The current study is a case-control study comprising patients with confirmed T2DM and healthy individuals from Jazan City, Saudi Arabia. One hundred and thirty-six patients with T2DM (patient group) and 98 healthy blood donors (control group) were included in the current study. The full cohort demographic and health characteristics, hematological and biochemical, have been previously published.[17]

Sample Size Calculation

The sample size of 136 patients and 98 controls was determined based on feasibility and availability of participants in the region. A post-hoc power calculation revealed 98% power to detect a medium effect size (d=0.5) in sEPCR levels between groups at alpha =0.05.

Ethical Considerations

This study was approved by the Jazan Health Ethics Committee, Ministry of Health, Jazan (Reference number 2038). The study participants were informed about the study's details and procedures, and their consent was obtained. The study was carried out according to the Declaration of Helsinki.

Sample Collection

Venous whole blood was collected from the patient group and the control group. Blood collection was performed specifically for this study during participant visits. The blood was drawn into ethylenediaminetetraacetic acid (EDTA) and sodium citrate tubes using a 21-gauge vacutainer. The collection was performed by a trained phlebotomist following laboratory guidelines. The EDTA tubes were used for complete blood count (CBC), hemoglobin A1C (HbA1C) estimation, and DNA extraction. Sodium citrate tubes were used to obtain plasma for EPCR analysis.

Demographic and Clinical Variables

The following data were collected from all participants: age, gender, body mass index (BMI), comorbidity, HbA1c levels, and complete blood count parameters including white blood cells (WBC), red blood cells (RBC), RBC indices, hemoglobin (Hb), hematocrit (HCT), platelet count and platelet indices.

Complete Blood Count

The Sysmex XN-550 Hematology Analyzer (Sysmex, Kobe, Japan) was used for the measurement of CBC parameters.

Measurement of Hemoglobin A1C

A DxC 7000 AU chemistry analyzer (Beckman Coulter, USA) was used for HbA1C measurement using HbA1C advanced method and reagent (lot number 1069D) provided by the manufacturer.

Plasma Preparation

The sodium citrate tube was centrifuged at room temperature for 30 min at 3000 rpm to obtain platelet-free plasma. The plasma was stored at −80°C for the measurement of soluble EPCR.

DNA Extraction

The genomic DNA was extracted from peripheral blood (EDTA tubes) immediately after collection according to the manufacturer's protocol for the Thermo Scientific Gene JET Genomic DNA Purification Kit (Thermo Scientific Fisher, Paisley, UK). The DNA concentrations were measured by Nano-Drop 2000 spectrophotometer (Thermo Scientific, USA). The DNA purity was evaluated by the absorbance ratios of A260/A280 and then stored at −80°C.

PCR Assay and Sequencing

The primer sequences utilized in this study were adopted from previously published studies.[18] The mixture of the PCR assay to amplify the desired region included DryTech TEMPase 5x master mix (Ampliqon, Denmark), nuclease-free water (Sigma, UK), forward primer, reverse primer (Macrogen, South Korea), and DNA template at a fixed concentration of 50 ng/µL. The PCR Thermal Cycle (MultiGene^{TM}Mini, China) was programmed in 3 stages. The first stage was the initial denaturation step at 95°C for 15 minutes, followed by stage two, which has 35 cycles of heating at 95°C for 30 seconds, followed by cooling to 60°C for 40 seconds and incubating at 72°C for 1 minute. The final stage was a single extension step at 72°C for 10 minutes.

The PCR amplification was evaluated by agarose gel electrophoresis conducted by dissolving 2% (w/v) agarose gel in 1xTAE buffer. Each PCR product was loaded onto the gel with a DNA ladder (100 base pairs). The gel was run at 125V for around 1 hour. The size of the PCR product to the DNA ladder was assessed using the Molecular Imager Gel Doc XR system (Bio-Rad). The expected size was 668 bp. A representative result of the gel and band is shown in Figure 1A. All PCR products were sent for purification and DNA sequencing (Macrogen, South Korea). A representative chart of the sequencing is presented in Figure 1B.

Soluble EPCR Assay

The plasma levels of sEPCR were measured in a subset of participants (n = 96 T2DM patients and n = 47 controls) using a commercially available human soluble sEPCR enzyme-linked immunosorbent assay (ELISA) (MyBioSource, USA). The measurements were conducted according to the manufacturer's instructions.

Statistical Analysis

The statistical analysis was performed using GraphPad Prism version 8.0 (GraphPad Software Inc., San Diego, CA, USA). The data were presented as mean ± standard deviation (SD). A normality test was conducted on all the data. The independent t-test was applied for normally distributed data. The Mann–Whitney *U*-test was used for non-normally distributed data. The correlation between the study variables was applied using the chi-square test. The allelic frequency of *EPCR* gene polymorphisms was calculated using Hardy-Weinberg equilibrium. $P<0.05$ was considered statistically significant.

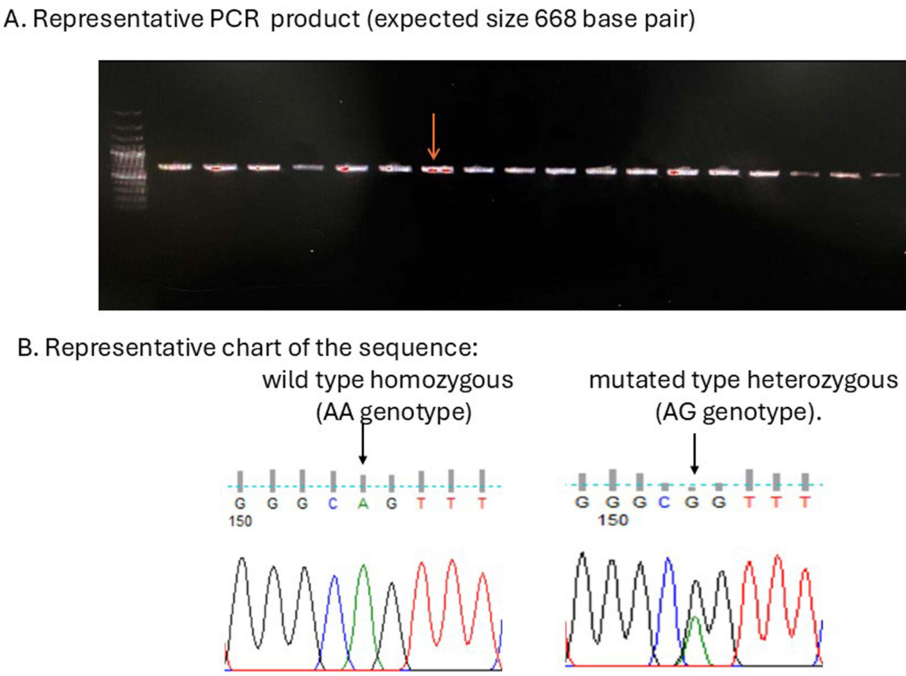


Figure 1 Representative photo of the gel (**A**- upper photo – PCR product) and sequencing (**B** - lower photo). Top photo (**A**) is a representative result of gel with the PCR product. Lower photo (**B**) is a representative chart of the DNA sequence of the wild type homozygous (AA indicated by the arrow) and heterozygous (AG indicated by the arrow).

Results

Genotyping of rs867186

The total genotyping of EPCR in the study cohorts (T2DM patients and controls) showed 196 individuals had the wild type (AA genotype), while 38 exhibited heterogeneity (AG genotype), representing 83.8% and 16.2%, respectively (Table 1). Among patients with T2DM, 78.7% (n = 107) had the wild type, and 21.3% (n = 29) had the heterozygous genotype. In the control group, 92.7% (n = 89) had the wild type, and 9.2% (n = 9) had the heterogenous genotype. Overall, the pattern of the genotypes in both the patient and control cohorts was consistent with the expected genotypes for the population according to the Hardy-Weinberg equilibrium (χ^2 = 1.018, p=0.6011).

Levels of sEPCR in Plasma

The results revealed that the levels of sEPCR were significantly higher in patients with T2DM compared to the controls (p<0.0001) (Figure 2).

Categorization of Plasma sEPCR Levels Based on Genotype

The plasma levels of sEPCR based on genotyping were comparable between individuals with the wild type (AA genotype) and those with heterogeneous genotypes (AG genotype) in both groups (p>0.05 for both comparisons) (Table 2).

Table 1 Genotyping of *rs867186* Among T2DM Patients and Healthy Controls

Group	Number of Participants	EPCR Genotypes			Chi-Square Value	*P*-Value
		AA	AG	GG		
T2DM	136	107 (78.7%)	29 (21.3%)	0%	2.072	0.3548
Control	98	89 (90.8%)	9 (9.2%)	0%	1.006	0.6048
Total	234	196 (83.8%)	38 (16.2%)	0%	1.230	0.5406

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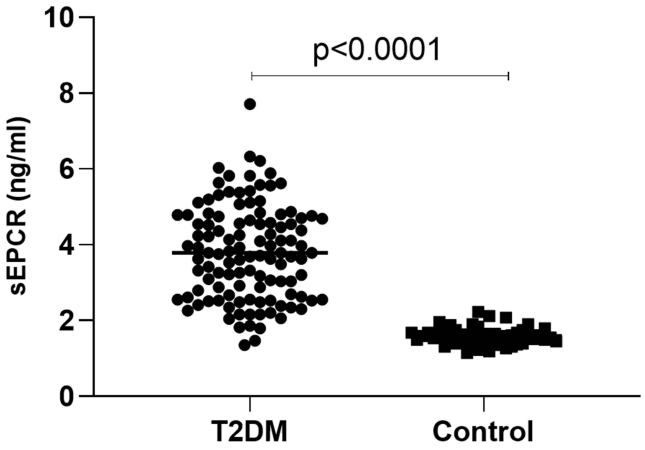


Figure 2 Plasma level of sEPCR in the study cohort. The levels of sEPCR in T2DM (n=96) as compared to healthy controls (n=47). Unpaired *t*-test was used for statistical analysis.

Correlation Study

The analysis of sEPCR plasma levels in the patient group showed significant correlations with several hematological parameters, including neutrophils, MCH, MCHC, RDW-CV, HCT, platelet count, and platelet indices, including platelet distribution width (PDW), mean platelet volume (MPV), and platelet-large cell ratio ($p<0.05$; Table 3). However, no significant correlations were observed with other parameters such as BMI, age, HbA1C, RBC count, Hb, and RDW-SD. In the control group, sEPCR plasma levels were significantly correlated with neutrophils, lymphocytes, and basophils ($p<0.05$; Supplementary Table 1), but no significant correlation was found with other parameters. Across the overall cohort, sEPCR plasma levels showed a significant correlation with age, neutrophils, basophils, RBC count, Hb, HCT, MCV, RDW-CV, RDW-SD, platelet count, and platelet indices, including PDW, MPV, and P-LCR ($p<0.05$; Supplementary Table 2). No significant correlations were observed between sEPCR plasma levels, HbA1C, and BMI.

Discussion

The current study reported a significant elevation in the plasma levels of sEPCR in patients with T2DM compared to healthy controls. This finding aligns with previous research conducted in Saudi Arabia[10] and other regions.[11] Elevated levels of sEPCR have been observed in T2DM with complications such as diabetic nephropathy compared to T2DM without complications.[11] The diabetic complications in our patient cohort had not been reported, so a comparison between T2DM with and without complications cannot be performed. This represents a study limitation that should be addressed in future research.

EPCR is physiologically expressed by normal endothelial cells in the vascular system, and its cleavage and release into circulation as sEPCR indicates endothelial dysfunction and vascular injury, which occurs in DM.[10,11,19] The potential mechanism linking EPCR *rs867186* cleavage to T2DM pathophysiology involves enhanced endothelial activation under hyperglycemic conditions, leading to increased protease activity (such as metalloproteinases) that cleave membrane-bound EPCR. This results in elevated sEPCR levels confers a pro-thrombotic and pro-inflammatory phenotype through impaired generation and efficacy of the cytoprotective Activated Protein C pathway.[11,12,20]

Table 2 sEPCR Levels with Genotyping in Both T2DM and Control Groups (n=96 for T2DM and n =47 Controls). Unpaired *t*-Test was used for Statistical Analysis

	T2DM			Control		
Genotype	**Wild Type AA**	**Heterogeneity AG**	**P Value**	**Wild Type AA**	**Heterogeneity AG**	***P* Value**
Plasma sEPCR levels (ng/mL)	3.7 ± 1.2	3.9 ± 1.5	>0.05	1.6 ± 0.3	1.5 ± 0.1	>0.05

Table 3 Correlation of Plasma sEPCR Levels with Demographic and CBC Parameters in T2DM Group

EPCR Correlation (T2DM)				
	R	**95% Confidence Interval**	**R Squared**	***P*-Value**
BMI	−0.06245	−0.2485 to 0.1280	0.003900	0.5208
Age	0.05406	−0.1328 to 0.2372	0.002922	0.5713
HBA1C	0.05632	−0.1298 to 0.2386	0.003172	0.5535
WBC	0.1589	−0.02838 to 0.3353	0.02524	0.0959
ANC (10^3/ µL)	0.2233	0.01456 to 0.4134	0.04987	0.0365
ALC (10^3/ µL)	0.1595	−0.02767 to 0.3360	0.02546	0.0944
AMC (10^3/ µL)	0.1519	−0.05945 to 0.3502	0.02307	0.1578
RBC	0.1619	−0.02529 to 0.3381	0.02620	0.0896
Hb (g/dL)	−0.02708	−0.2124 to 0.1601	0.0007333	0.7778
HCT (%)	0.4005	0.2314 to 0.5462	0.1604	<0.0001
MCV (fL)	0.1135	−0.1075 to 0.3238	0.01288	0.3130
MCH (pg)	−0.1986	−0.3712 to −0.01264	0.03943	0.0367
MCHC (g/dL)	−0.5385	−0.6588 to −0.3914	0.2900	<0.0001
RDW-SD (fL)	0.1244	−0.06345 to 0.3038	0.01548	0.1932
RDW-CV (%)	−0.4818	−0.6131 to −0.3246	0.2322	<0.0001
Platelet (10^3/ µL)	−0.2976	−0.4585 to −0.1177	0.08854	0.0015
PCT (%)	−0.04170	−0.2263 to 0.1458	0.001739	0.6639
PDW (fL)	0.4253	0.2595 to 0.5668	0.1809	<0.0001
MPV (fL)	0.4835	0.3266 to 0.6145	0.2338	<0.0001
P-LCR (%)	0.4573	0.2962 to 0.5932	0.2092	<0.0001

Abbreviations: BMI, body mass index; HbA1C, hemoglobin A1C; WBC, white blood cells; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; RBC, red blood cells; Hb, hemoglobin; HCT, hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; RDW, red blood cell distribution width; PCT, plateletcrit; PDW, platelet distribution width; MPV, mean platelet volume; P-LCR, Platelet large cell ratio.

The *rs867186* mutation, which involves the substitution of serine with glycine (Ser219Gly) in EPCR, significantly accounts for 50% to 80% of the variation observed in sEPCR levels in plasma.[12–15] Therefore, the current study is the first to report the *rs867186* polymorphism in T2DM in Jazan region, Saudi Arabia. The genotype frequency of the *rs867186* polymorphism in T2DM and control groups was not statistically significant following the Hardy-Weinberg equilibrium equation, and the homozygous mutant (GG) genotype, observed in another study,[18] was not observed in our findings. Currently, there are no studies in Saudi Arabia to directly compare the findings of this research. However, the observed frequency of the *rs867186* polymorphism aligns with the frequencies reported in other populations.[21] The current study further investigated the relationship between sEPCR levels and the *rs867186* polymorphism among participants. While the findings revealed that patients with T2DM exhibited significantly higher levels of sEPCR compared to the control group, no association was found between this elevation and the *rs867186* polymorphism. This finding is consistent with previous research that also demonstrated no association between elevated plasma sEPCR levels and specific genotypic patterns,[22] contrasting with other reports that revealed different outcomes.[12–15,22] Indeed, genetic

polymorphisms have been associated with sEPCR levels, which is estimated that 56% to 87% of the observed variations in plasma sEPCR levels can be attributed to genetic factors.[12–15,23] Multiple mutations in the EPCR gene have been reported, including a polymorphism in exon 4 (A6936G). The A6936G, also known as the *rs867186* SNP.[20,21] This genetic variation leads to substituting the amino acid serine with glycine at codon 219 in the membrane-spanning domain of the EPCR protein. The "A" allele of the *rs867186* SNP is associated with haplotypes H1, H2, or H4, while the "G" allele is exclusively linked to the H3 haplotype of EPCR.[24] This means that individuals with the H3 haplotype will have the G allele in the *rs867186* position. The substitution of serine with glycine at codon 219 due to the *rs867186* SNP results in elevated levels of sEPCR. This indicates that there is an enhanced release of EPCR from the endothelial membrane into the bloodstream. The G allele in the *rs867186* SNP is associated with higher levels of sEPCR,[25] and is considered a risk factor for thrombosis.[20] The rs867186 SNP has also been implicated in regulating protein C levels and is associated with a higher risk of thrombosis, especially venous thromboembolism.[12,14] While various disorders, including thrombosis, have been the subject of numerous studies examining EPCR polymorphisms[10,14,18,22,25–29] the impact of these polymorphisms on T2DM is not fully known. Importantly, polymorphisms can vary significantly among different ethnicities, which may impact the interpretation of these findings.[16,30] In addition, the current study did not report the homozygous mutant (GG genotype) in both cohorts. Although the heterozygous mutation (AG genotype) of the EPCR has not influenced the plasma levels of sEPCR, the effect of GG on the levels of sEPCR cannot be excluded.

The impact of hyperglycemia on various hematological parameters, including RBCs, WBCs, and platelets, in patients with T2DM, as well as the induction of endothelial dysfunction through RBCs interacting with endothelial cells is well known.[17,31] The presence of low RBCs, low Hb, and development of anemia have been reported among T2DM.[17,32,33] Moreover, the reduction in RBC count has been associated with the development of microvascular complications in patients with T2DM.[34] In addition, the adhesion of RBCs to the endothelial cells has been correlated with the severity of vascular complications.[35] The present study identified a significant negative correlation of plasma levels of sEPCR with RBC indices MCH, MCHC, and RDW-CV, potentially attributed to anemia.[17,32]

Low-grade inflammation is a major factor in T2DM pathophysiology, which can impact various WBC, including neutrophils, lymphocytes, and monocytes.[36] The current study reported that T2DM patients exhibited a positive correlation between neutrophil counts and sEPCR levels but not with WBC count. Neutrophil counts significantly increased in T2DM patients and have been associated with an increased risk of DM.[37] In addition, inflammation is vital in the cleavage and release of EPCR in T2DM.[38] There is a link between sEPCR and neutrophils, mainly activated neutrophils.[39] Notably, neutrophils in diabetic patients release significantly higher levels of pro-inflammatory cytokines such as IL-8, IL-1b, and TNF-a, disrupting normal signaling pathways and contributing to increased infection susceptibility, chronic inflammation, and impaired wound healing.[40] Indeed, sEPCR is linked to an increase in inflammatory response.[41]

Platelet indices, including MPV, PCT, PDW, and P-LCR, predict the severity of many diseases and were suggested as predictors of microvascular complications in T2DM.[42] The current study reported a significant negative correlation between sEPCR levels and platelet count, alongside a significant positive correlation with MPV, PDW, and P-LCR ($p<0.01$). MPV has been linked to microvascular complications and stroke in T2DM patients.[43] MPV was significantly lower in patients with T2DM compared to controls, consistent with other platelet indices, though contrasting with previous reports.[42,44] These correlations need further exploration to elucidate their clinical implications.[44]

Moreover, significant risk factors for developing T2DM, including aging, being overweight, having poor glucose tolerance, and having a family history, have all been identified. The prevalence of diabetes is higher among the elderly population, which is consistent with our data.[38]

Despite the valuable insights gained from this study, several limitations should be addressed. The relatively small sample size, in comparison to the high incidence of T2DM in Saudi Arabia, can limit the generalizability of the findings. Additionally, the study was conducted exclusively with male patients. Further studies should include other endothelial, inflammatory, and hemostatic markers to fully assess the role of endothelial cells and hemostasis in T2DM. Furthermore, the study duration was limited, which might affect the ability to draw definitive conclusions. The lack of data on diabetic complications and the potential influence of treatment, which represent additional limitations. Furthermore, other genetic polymorphisms beyond rs867186 may influence sEPCR levels and should be considered in future studies. Therefore, conducting further multi-center, prospective studies with a larger sample size would be beneficial to determine the precise

role of EPCR in T2DM complications and management. Additionally, elucidating the association between EPCR and full clinical characteristics and follow-up with disease outcomes in the same cohort will answer the long-term effect of EPCR in patients with T2DM.

Conclusion

This study reports a significant elevation in plasma sEPCR levels in patients with T2DM compared to healthy controls, suggesting enhanced cleavage of membrane-bound EPCR and indicating underlying endothelial dysfunction. Importantly, however, this elevation was not associated with the EPCR rs867186 polymorphism in our cohort, nor was the homozygous mutant (GG) genotype detected. These findings should be interpreted in light of several study limitations, including the modest sample size, the absence of data on diabetic complications, and the exclusive inclusion of male participants—all of which may affect generalizability.

Furthermore, while rs867186 is a major known genetic determinant of sEPCR levels, other SNPs within the EPCR gene or in related pathways may also influence sEPCR expression and endothelial function in T2DM. Future multi-center studies with larger, more diverse populations, longitudinal design, and expanded genetic profiling are needed to clarify the role of EPCR in T2DM pathophysiology and its complications. Despite these limitations, our data support the potential utility of sEPCR as a biomarker for early inflammation and endothelial dysfunction in T2DM.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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NA

Disclosure

The authors declare no conflicts of interest in this work.

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