

Study of the Association of *EDN1* rs5370 Polymorphism to Type 2 Diabetes Complications

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Introduction: Type 2 diabetes mellitus (T2DM) is common in the Arab population. Endothelin-1 (ET-1) is an vasoconstrictor agent produced by the endothelin-1 gene (*EDN1*). Circulating ET-1 has been shown to be increased in T2DM. The current examined the association between the *EDN1* rs5370 polymorphism and T2DM.

Methods: The investigation was a case-control study and included 190 T2DM patients and 120 healthy subjects. Polymerase chain reaction was employed to determine rs5370 genotypes among the study participants.

Results: The frequency of the G allele was 78.3% among the control group and 74.7% in T2DM ($P=0.306$). Plasma ET-1 protein levels were higher in T2DM than in controls ($p<0.01$). However, no association was found between rs5370 and T2DM. The frequencies of GG, GT, and TT genotypes were 60.8%, 35%, and 4.2% in the control group and 53.7%, 42.1%, and 4.2% in the patient group, respectively ($P=0.447$). With respect to T2DM complications, a significantly higher incidence of nephropathy was observed among patients with TT/GT genotypes compared to patients with the GG genotype ($P<0.05$). Furthermore, a marginal statistical significance was found between rs5370 and cardiovascular diseases in T2DM ($P=0.06$).

Conclusion: Circulatory ET-1 levels were elevated in T2DM. The *EDN1* rs5370 polymorphism might impact the development of nephropathy in T2DM.

Keywords: endothelin-1, *EDN1*, ET-1, rs5370 polymorphism, Saudi Arabia, diabetes

Introduction

Diabetes is a set of metabolic disorders characterized by persistently high blood glucose levels, which can cause damage to various parts of the body and lead to dysfunction.¹

Diabetes mellitus type 2 (T2DM) is common in the Arab population and around the world. In Saudi Arabia, T2DM ranks second in the Middle East and seventh globally. The number of cases worldwide is expected to rise to more than 500 million by 2030.² Elevated blood glucose and insulin resistance are the main features of the disease. In addition, as the disease progresses, several comorbidities develop, including retinopathy, nephropathy, hypertension, cardiovascular disease, neuropathy, and others. The disease can be avoided by improving lifestyle choices such as balanced diet, physical activity, and quitting smoking.^{3,4}

A complex interaction between genetic and environmental factors is thought to be the cause of T2DM.⁵ Endothelin is a group of endogenous peptides synthesized in various tissues and acting as regulators of growth, vascular tone, and hormone synthesis. Endothelin is released mainly from endothelial cells. Endothelin has many isoforms, the most common of which is ET-1.^{6,7} ET-1 acts by interacting with both type A and type B receptors, leading to cell growth and vasoconstriction.^{8,9} ET-1 plays a role in the pathophysiology of cardiovascular diseases and renal diseases. For example, endothelial dysfunction leads to increased in ET-1 production, resulting in atherogenesis, vascular hypertrophy, and glomerulosclerosis.^{10–12} Patients with

T2DM have been found to have increased levels of ET-1 in their plasma.^{13,14} Treatment of cultured human cells with glucose has been shown to increase the expression of ET-1 via epigenetic mechanisms.¹⁵ In addition, variations in the *EDN1* gene have been shown to modulate the development of some morbidities associated with T2DM.^{8,16} The rs5370G>T polymorphism of the *EDN1* gene is a mis-sense mutation that causes the replacement of lysine by asparagine in ET-1. This polymorphism has been shown to impact ET-1 in the circulation.^{17,18} In addition, the rs5370 polymorphism has been associated with some T2DM complications.¹⁹ In the present study, the associations between ET-1 and *EDN1* rs5370 polymorphism with susceptibility to T2DM and its associated complications were examined among patients from Saudi Arabia.

Materials and Methods

Study Subjects

The study was case-control in design and included 190 subjects with T2DM (case group) and 120 healthy subjects (control group). Patients were recruited from various hospitals in Madinah, SA during the period since 07 January 2024 to 05 January 2025. Patients were diagnosed with T2DM based on World Health Organization (WHO) diagnostic criteria, which include HbA1C $\geq$ 6.5%, and fasting blood glucose (FBG) $\geq$ 7.0 mmol/L. Patients with acute illnesses, cancer, pregnant women, and liver diseases were excluded from cases and controls. Nephropathy diagnosis based on glomerular filtration rate (GFR) less than 60 mL/min, and urine albumin-to-creatinine ratio (UACR) $\geq$ 30 mg/g,²⁰ any borderline or type 1 diabetes were excluded. Retinopathy diagnosed by fundus findings (microaneurysms, hemorrhages, neovascularization) with retinal imaging.²¹ Cardiovascular disease diagnosed based to ADA outlines includes clinical and lab markers.²² Neuropathy diagnosed based to American academy of neurology includes clinical signs and nerve conduction study.²³

The study protocol was permitted by the “Research Ethics Committee” of Taibah University (Approval No. CLS 202097). The committee operates in accordance with the “1964 Declaration of Helsinki and its amendments”. Written informed consent was obtained from study participants prior to participation.

Biochemical Parameters

Blood samples were collected from participants in oxalate tubes for blood glucose testing and in EDTA tubes for other measurements. ET-1 levels were measured using an ELISA assay developed by Thermo-Fisher company (USA).²⁴ Glucose, lipids, urea, creatinine, and albumin levels were measured enzymatically with Dimension[®] EXL[™] 200 Integrated Chemistry analyzer (Siemens, Erlangen, Germany). Albumin to creatinine ratio was measured as previously described.²⁵ HbA1c was determined using a D-10[™] Hemoglobin Analyzer from Bio-Rad (Nyocard, USA).

DNA Extraction

Blood DNA was extracted using a kit obtained from Fermentas company (USA). The quality/quantity of extracted DNA were verified using spectrophotometric methods by measuring absorbance at a wavelength 260/280 nm. DNA was kept at -30°C until further applications.

Genotyping of EDN1 rs5370 Polymorphism

The “polymerase chain reaction amplification-refractory mutation system (PCR-ARMS)” was used to genotype *EDN1* rs5370 polymorphism as previously described.²⁶ PCR amplification was performed using a thermocycler obtained from BioRad (model MT100tm, USA). The used primers were: Reverse common primer 5′AGTCAGGAACCAGCAGAGGA3′, and forward allele specific primers: G allele- 5′ATCCGAAGCTGAAAGGCAAG3′, and T allele-5′ATCCGAAGC TGAAAGGCAAT3′. PCR reaction was performed in 0.5mL PCR tube in a total reaction volume of 25 μ L (2X master mix obtained from ThermoFisher Scientific, 100ng of genomic DNA and 50 pmol of each primer. Two reactions for each sample were performed to distinguish amplification from the two forward primers. Amplification conditions were denaturation (5min/95°C), 35 cycles (95°C/60s, 58°C/45s and 72°C/45s), and a final extension (72°C/5min). Gel electrophoresis was performed on 2.5% agarose gel, and DNA fragments were visualized under UV light and EtBr. The amplified PCR fragment from each forward primer was 179bp. Amplification from both allele specific primers indicates the heterozygous genotype (GT).

Amplification from a single allele specific primer indicates the homozygous genotype (GG or TT depending on the forward primer used).

Statistical Analysis

Data were analyzed using SPSS version 23. For comparison, the unpaired Student's *t*-test, ANOVA, Fisher exact test, or Chi-square test were used as appropriate. A $P < 0.05$ indicates a statistically significant difference.

Results

Baseline Characteristics of Participants

Table 1 shows the demographic and clinical data of T2DM patients and the control group. No statistical differences were observed in gender, age, and smoking status between the two groups ($P > 0.05$). On the other hand, there were differences between patients and controls in fasting blood glucose, HbA1c, lipid profile, urea albumin to creatinine ratio, creatinine, nephropathy, retinopathy, neuropathy, cardiovascular disease, and hypertension ($P < 0.05$). Plasma ET-1 levels in the studied groups. ET-1 was significantly higher in patients than controls ($p < 0.01$).

Distribution of *END1* Gene rs5370 Polymorphism

Table 2 shows the distribution of genotypes and alleles of the rs5370 *EDNI* polymorphism among T2DM and controls. The rs5370 *EDNI* polymorphism is in Hardy-Weinberg equilibrium in the study sample ($P = 0.113$). The frequency of the G allele was 78.3% in the control group and 74.7% in the T2DM group ($P = 0.306$). The frequencies of the GG, GT, and TT genotypes were 60.8%, 35%, and 4.2% in the control group and 53.7%, 42.1%, and 4.2% in the T2DM group,

Table 1 Demographic and Clinical Characteristics of Participants

Parameters	Cases (n=190)	Controls (n=120)	P-value
Gender (males, females)	112, 78	70, 50	0.914
Age (year)	53.3±5.47	53±6.53	0.687
BMI	25.17 ±2.04	23.52±1.88	<0.001*
Blood pressure			
SBP (mm/Hg)	121 ±6.58	119.1±1.75	0.002*
DBP (mm/Hg)	81.3±4.34	80.2±1.43	0.009*
Hypertensive patients	15 (7.9%)	—	
Smoking	61 (32.1%)	29 (24.2%)	0.084
ET-1 (pg/mL)	1.26±0.1	1.05±0.06	<0.001*
FPG (mmol/l)	7.4±0.92	5.1±0.31	<0.001*
HbA1c %	7.3±0.62	4.9±0.30	<0.001*
Lipids			
TC (mmol/l)	4.14±0.35	3.41±0.18	<0.001*
TG (mmol/l)	1.61±0.1	1.32±0.1	<0.001*
LDL (mmol/l)	2.63±0.21	2.31±0.11	<0.001*
HDL (mmol/l)	1.18±0.05	1.26±0.04	<0.001 [#]
U-albumin/creatinine ratio [g/mol]	26.9 ± 3.8	1.81 ± 0.74	<0.001*
Creatinine mol/L	79±11.3	70.2±12.4	<0.001*
Nephropathy	19 (10%)	—	—
Retinopathy	13 (6.8%)	—	—
Cardiovascular diseases	19 (10%)	—	—
Neuropathy	9 (4.7%)	—	—

Notes: *significant higher in cases compared to controls ($p < 0.01$). [#]significant lower in cases compared to controls ($p < 0.01$).

Abbreviations: BMI, body mass index; NW, normal weight; OW, overweight; OB, obese; SBP, systolic blood pressure; DBP, diastolic blood pressure; ET-1, Endothelin-1; FPG, fasting plasma glucose; TC, Total cholesterol; TG, triglyceride; LDL, low density lipoprotein cholesterol; HDL, High density lipoprotein cholesterol; U-albumin, urinary albumin.

Table 2 Distribution of ET-I (EDN1) Gene rs5370 Polymorphisms Genotypes and Alleles in Patients with T2DM Diabetic and Controls

Genotype	Cases (n=190)	Controls (n=120)	P-value
TT	8 (4.2%)	5 (4.2%)	0.447
GT	80 (42.1%)	42 (35%)	
GG	102 (53.7%)	73 (60.8%)	
Allele percent (%)			0.306
T	96 (25.3%)	52 (21.7%)	
G	284 (74.7%)	188 (78.3%)	

respectively ($P=0.447$). Thus, the rs5370 polymorphism was not associated with susceptibility to T2DM in the studied population ($P>0.05$).

Distribution of EDN1 Gene rs5370 Polymorphism with Different Aspects

To further examine the contribution of the *EDN1* gene rs5370 polymorphism to T2DM pathology, Table 3 shows the different clinical measures across rs5370 genotypes in T2DM group. The results showed a significantly high frequency of nephropathy among patients with TT genotype compared to patients with the GG genotype ($P=0.033$, OR [95% CI]: 8.14 [1.60–41.32]). In addition, BMI, total cholesterol, fasting glucose, and ET-1 were significantly higher in patients with TT genotype compared to other genotypes ($P<0.05$). With respect to the relationship between cardiovascular disease and the rs5370 polymorphism, a marginal association was observed ($P=0.060$; OR [95% CI]: 1.75 [0.80–3.81]). However, no association was observed between rs5370 and T2DM complications including neuropathy OR [95% CI]: 0.82 [0.25–2.73]), hypertension (OR [95% CI]: 1.64 [0.69–3.89]), and retinopathy (OR [95% CI]: 1.75 [0.70–4.39]). Moreover, rs5370 did not affect biochemical parameters including HbA1c, LDL, and HDL among T2DM ($P>0.05$). Thus, the TT genotype seems to impact several clinical parameters in T2DM.

Table 3 Distribution of ET-I (EDN1) Gene rs5370 Polymorphisms Genotypes and Alleles in Patients with T2DM with Different Clinical and Anthropometric Aspects

Item	Sub-Item	GG (102)	GT (80)	TT (8)	P-value
Nephropathy n (%)	Yes	7(6.9)	9(11.2)	3(37.5)	0.033*
	No	95(93.1)	71(88.8)	5(62.5)	
Retinopathy	Yes	6(5.8)	5(6.3)	2(25)	0.114
	No	96(94.2)	75(93.7)	6(75)	
Cardiovascular diseases	Yes	9(8.8)	7(8.7)	3(37.5)	0.060
	No	93(91.2)	74(91.3)	5(62.5)	
Neuropathy	Yes	6(5.8)	2(2.4)	1(12.5)	0.232
	No	96(94.2)	79(97.6)	6(87.5)	
Hypertension	Yes	7(6.9)	6(7.5)	2(25)	0.234
	No	95(93.1)	74(92.5)	6(75)	
BMI		25.2±1.86	24.8±1.87	28.3±3.1	<0.001**
Total cholesterol		158.7±12.8	160.2±8.5	180.1±38.0	<0.001**
LDL		102.3±8.21	100.9±7.0	105.6±16.3	0.228
HDL		45.8±1.9	45.4±1.9	44.5±3.18	0.118
Triglycerides		158.6±12.8	160.2±8.5	153.0±25.1	0.002**
HbA1c		7.31(0.6)	7.28±0.5	7.61±1.5	0.357
Fasting glucose		131.2±12.1	133±15.1	152±47.8	0.002**
ET-I		1.22±0.42	1.17±0.37	2.63±1.08	<0.001**

Notes: Significant higher in cases compared to controls *($p<0.05$) **($p<0.01$).

Abbreviation: n, number.

Discussion

T2DM predisposes individuals to numerous complications, including hypertension, neuropathy, cardiovascular disease, nephropathy, and retinopathy. T2DM is caused by both genetic and environmental factors. Hundreds of genetic variations have been shown to modulate the risk of developing T2DM.²⁷

The rs5370 variant of the *EDN1* gene causes a Lys/Asn amino acid substitution, which may impact ET-1 maturation in endothelial cells.²⁸ The clinical significance of rs5370 is well documented.^{29–31} In the current study, we investigated the possible association between the rs5370 and T2DM complications.

The study showed no association between rs5370 *EDN1* gene polymorphism and T2DM. This finding is consistent with previous studies conducted in Caucasian, Chinese and Jordanian populations.^{19,25,32} Thus, it appears that the rs5370 polymorphism does not affect the risk of T2DM.

The study also examined the relationship between T2DM complications and the rs5370 polymorphism. The rs5370 was found to be associated with nephropathy and marginally associated with cardiovascular disease in T2DM. The rs5370 TT genotype was found to increase the risk of these complications in T2DM. A meta-analysis reported that the rs5370 increased the risk of ischemic stroke.²⁹ In a study conducted in Iran, rs5370 was found to be associated with coronary atherosclerosis.³³ In addition, rs5370 was found to be associated with the severity of coronary artery disease in the Russian population.³⁴ In contrast, no association between rs5370 and nephropathy was observed among Caucasians with T2DM.^{25,35} The current study showed no association between the rs5370 and blood pressure, neuropathy, and retinopathies in T2DM patients. Similar findings have been reported in studies from Iran, Jordan, and China.^{32,33,36} However, a previous study reported an association between rs5370 and retinopathy in T2DM patients.¹⁹ Moreover, the rs5370 polymorphism has been shown to impact blood pressure in individuals with obesity.^{28,37–39} Thus, the association between rs5370 and complications of T2DM seems to be complex and modulated by the genetic background of the population.

In the present study, ET-1 levels were found to be elevated in T2DM, consistent with previous studies.^{40–42} Moreover, in a recent in vitro study in Saudi Arabia, there was a markedly elevated in *EDN1* gene expression as a result of exposure to high glucose in cell culture.⁴³ ET-1 is a vasoconstrictor agent and involved in fibrosis and inflammation responses. ET-1 has been found to impact renal function through modulation of vascular/mesangial tone; ions excretion; and cell division and matrix remodeling.^{8,44}

Among the limitations of the study is the low sample size, specially number of individuals with T2DM complications, which might lower the study power analysis. In addition, data regarding covariates that might impact observed associations like duration of diabetes, medication use, or family history were not collected. Therefore, we recommend a larger study to confirm the study findings.

Conclusions

Circulatory ET-1 levels are elevated in patients with T2DM. The *EDN1* rs5370 polymorphism might impact the risk of nephropathy in T2DM. Further studies with a larger sample are needed to confirm the present findings.

Ethics

Ethical clearance for this research was obtained from the Research Ethics Committee at the College of Applied Medical Sciences, Taibah University, Madinah, Saudi Arabia (Approval No. CLS 202097), following the ethical guidelines established in the 1964 Declaration of Helsinki and its later revisions.

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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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Disclosure

The authors report no conflicts of interest in this work.

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