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Original Article

RAGE gene polymorphism (rs1800625) and type 1 diabetes mellitus: A potential new model for early diagnosis and risk prediction

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Abstract

Studies have associated advanced glycation end-products (AGEs) and the polymorphism of the AGEs receptor (*RAGE*) gene with clinical disorders, such as diabetes, in certain ethnic groups. However, its association with type 1 diabetes mellitus (T1DM) in Egyptians has not yet been explored. The aim of this study was to investigate the association between the *RAGE* gene polymorphism rs1800625 and T1DM susceptibility in Egyptians. A case-control study was conducted with 177 T1DM patients and 177 age- and sex-matched healthy controls. Variables included glycemic markers (fasting blood glucose (FBG), postprandial blood glucose (PBG), hemoglobin A1c (HbA1c)), anthropometric measurements (waist circumference, body mass index (BMI)), lipid profile (total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL)), renal function (albumin-to-creatinine ratio (A/C ratio), serum creatinine), and history of hypertension and smoking. Genotype distribution and allele frequency of the *RAGE* rs1800625 polymorphism (TT, TC, CC genotypes; T and C alleles) were assessed. This study identified the *RAGE* rs1800625 polymorphism as a significant genetic factor associated with T1DM susceptibility. The CC genotype was significantly more prevalent in patients compared to controls (29.9% vs 11.9%; OR: 3.62; 95%CI: 1.87–6.97; $p<0.001$). Similarly, the C allele was more common in patients (54.5% vs 41.0%, OR: 1.73; 95%CI: 1.28–2.33; $p<0.001$). Multivariate analysis revealed that HbA1c (adjusted OR (aOR): 12.97; 95%CI: 4.00–42.05; $p<0.001$), FBG (aOR: 8.96; 95%CI: 1.59–50.47; $p=0.010$), and the rs1800625 polymorphism (aOR: 1.82; 95%CI: 1.146–2.876; $p=0.010$) were significant predictors of T1DM. In conclusion, a genetic association was found between the *RAGE* gene polymorphism rs1800625 and T1DM susceptibility, with the CC genotype and C allele being more common in T1DM patients. FBG, HbA1c, and rs1800625 were identified as key predictors for T1DM, with HbA1c being the strongest. These findings highlight the importance of integrating genetic and metabolic factors in managing T1DM.

Keywords: Type 1 diabetes mellitus, autoimmune, receptor for advanced glycation end-products gene, *RAGE*, polymorphism

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Introduction

American Diabetes Association classifies diabetes into several categories, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes, and other specific forms, such as drug-induced diabetes, exocrine pancreas disorders, and monogenic diabetes syndromes [1]. T1DM has emerged as a significant global health concern, affecting 8.4 million people worldwide in 2021, with 500,000 new cases annually. Additionally, it is associated with a substantial mortality rate, with an estimated 35,000 deaths occurring within the first 12 months of symptom onset [2]. The global burden of diabetes has risen sharply, particularly in low- and middle-income countries [3]. In Egypt, over 7.8 million individuals were diagnosed with diabetes in 2015, with this number expected to rise substantially [4]. Epidemiological data on childhood T1DM in Egypt remain limited; however, studies in urban areas, including Heliopolis and Cairo, have reported prevalence rates of 109 and 112 per 100,000, respectively. These numbers underscore the growing burden of T1DM in the region [5,6].

Managing T1DM poses significant challenges due to the risk of acute complications, such as hypoglycemia and hyperglycemia, which are often triggered by stress, illness, or physical activity [7,8]. Over time, individuals with T1DM are prone to chronic complications, including neuropathy, nephropathy, retinopathy, and cardiovascular disease, all of which significantly impair quality of life [9]. T1DM is an autoimmune disorder characterized by the destruction of pancreatic β-cells, mediated by immune cells, including CD4+ and CD8+ T cells, and the production of autoantibodies [10]. Autoantibodies such as insulin autoantibody (IAA), anti-glutamic acid decarboxylase (GAD), and anti-protein tyrosine phosphatase (anti-IA-2) impair insulin regulation, resulting in chronic hyperglycemia [11]. Persistent hyperglycemia contributes to complications, including neuropathy, nephropathy, and retinopathy [12-14].

T1DM progression is influenced by both genetic and environmental factors [15]. Genetic predisposition, particularly HLA alleles, accounts for 40–50% of familial clustering; despite identical genetic makeup, 70% of monozygotic twins do not develop T1DM [16,17]. Environmental triggers, including viral infections (e.g., enteroviruses) and advanced glycation end-products (AGEs), exacerbate β-cell destruction by activating the immune system [18,19]. Dietary habits, such as consumption of processed foods and high-temperature cooking techniques, increase AGEs exposure, inducing oxidative stress, inflammation, and β-cell damage [20,21]. These mechanisms contribute to complications, including retinopathy and neuropathy.

A key mechanism in T1DM involves the interaction between AGEs and AGEs receptor (*RAGE)*, a polymorphic receptor expressed on endothelial, immune, and pancreatic β-cells [21,22]. Elevated AGE levels in T1DM upregulate *RAGE* expression, activating intracellular pathways such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) [23]. These pathways drive inflammation and oxidative stress, impair circulation and β-cell integrity, and exacerbate disease complications [24-26]. Genetic polymorphisms in *RAGE*, such as rs1800625, may affect receptor expression and function, thereby modulating T1DM progression through altered interactions between AGEs and *RAGE* [27,28]. Investigating these polymorphisms offers insights into disease mechanisms and potential for personalized therapeutic strategies [29,30].

Egyptian population, due to its unique genetic diversity at the crossroads of Africa, the Middle East, and Europe, presents an ideal setting for studying genetic variations such as *RAGE* polymorphisms [20]. While most genetic research has focused on European populations, examining *RAGE* polymorphisms in Egyptians helps address this gap and promotes global health equity [31,32]. Environmental factors, such as diets rich in AGEs, may interact with genetic predispositions to influence disease outcomes [33]. A previous study emphasized that Western diets are particularly rich in AGEs, primarily due to the high consumption of processed foods and the prevalent use of high-temperature cooking techniques, including frying, grilling, and roasting [33]. However, research on the association between *RAGE* polymorphisms and T1DM in Egypt is limited, with only one study addressing genetic factors related to diabetic nephropathy in this population [34]. The aim of this study was to investigate the association between the *RAGE* gene polymorphism rs1800625 and T1DM susceptibility in Egyptians, focusing on the prevalence of CC and C alleles. It also identified predictive factors for T1DM by assessing metabolic markers

and examining the combined effects of genetic predisposition and metabolic dysregulation. By including Egyptians in genetic research, this study contributes to global health equity and personalized medicine for underrepresented populations.

Methods

Study design and setting

A case-control study was conducted at the outpatient clinic of the National Institute of Diabetes and Endocrinology, Cairo, Egypt, involving 354 participants. The study population comprised 177 patients diagnosed with T1DM and 177 age- and sex-matched healthy controls. Recruitment occurred between March 2023 and March 2024, including clinic attendees and their accompanying relatives who met the inclusion and exclusion criteria. Genotyping of the rs1800625 single nucleotide polymorphism (SNP) (-429T/C) in the *RAGE* gene was performed. Dependent variables included glycemic markers such as fasting blood glucose (FBG), postprandial blood glucose (PBG), and HbA1c. Anthropometric measurements included waist circumference and body mass index (BMI). Lipid profile parameters comprised total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Renal function indicators included the albumin-to-creatinine ratio (A/C ratio) and serum creatinine levels. History of hypertension and smoking status were recorded. The genotype distribution and allele frequency of the *RAGE* rs1800625 polymorphism (TT, TC, and CC genotypes; T and C alleles) were assessed.

Eligibility criteria

The case group included T1DM patients meeting the American Diabetes Association (ADA) [35] and World Health Organization (WHO) criteria [36], with fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL, or HbA1c ≥6.5%, along with autoantibodies such as glutamic acid decarboxylase (GAD), islet cell cytoplasmic autoantibodies (ICA), and insulin autoantibodies (IAA) [37]. Healthy controls were participants with no clinical history of diabetes (T1DM, T2DM, or gestational), FBG levels between 70–99 mg/dL, HbA1c <5.7%, and normal biochemical markers, including renal markers such as serum creatinine (100–129 mg/dL) and albumin-to-creatinine ratio (men: <17 mg/g; women: <25 mg/g), as well as a lipid profile with total cholesterol <200 mg/dL, triglycerides between 150–200 mg/dL, HDL (men ≥40 mg/dL; women ≥50 mg/dL), and LDL between 100–129 mg/dL. Exclusion criteria included participants with T2DM or other forms of diabetes, significant comorbidities (cardiovascular diseases, chronic inflammatory conditions, thyroid dysfunction, cancer), hepatic diseases (hepatitis B/C, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH)), recent major illness or surgery within the last three months, alcohol or drug abuse, morbid obesity (BMI ≥40 kg/m²), and pregnancy or lactation. Dropout criteria included withdrawal of consent, incomplete data, non-compliance, or adverse events. Dropout patients were excluded, and eligible participants were recruited to replace dropouts, ensuring sample size and statistical power.

Sample size and sampling method

Sample size was determined based on the 11.94% minor allele frequency (MAF) of the rs1800625 SNP, as reported in the SNPedia database [38], and the expected effect size, quantified by the odds ratio (OR). Sample size calculation aimed for an expected OR of 2.0, with 80% power (1-β) and a significance level of 0.05 (α) [38]. Subsequently, a total of 354 participants (177 per group) was sufficient to detect an association while minimizing type I and II errors. Participants were recruited via convenience sampling from clinic attendees and accompanying relatives, with inclusion based on willingness to provide informed consent and biological samples.

Data collection

Epidemiological data were collected via in-person interviews, covering demographics (age and sex), lifestyle factors (smoking, drug use, and family history), and anthropometric measures (weight, height, BMI, and waist circumference). Clinical data included medical histories of hypertension, smoking, and other conditions. Physical examinations and abdominal ultrasounds were conducted, with ultrasound findings aiding in the diagnosis of NAFLD and NASH. Blood

samples were collected after an 8-hour fast for glycemic markers (FBG, PPG, and HbA1c), renal function markers (serum creatinine and ACR), and lipid profile (total cholesterol, triglycerides, HDL, and LDL).

Anthropometric measurements

Anthropometric measurements, including weight, height, and waist circumference, were taken to assess nutritional status, following the standards outlined in the Anthropometric Standardization Reference Manual [39]. Height was measured to the nearest 0.1 cm using a Holtain portable anthropometer. Weight was recorded to the nearest 0.01 kg with a "Seca Scale Balance" while the subject was dressed in minimal clothing and without shoes. BMI was calculated using the formula weight (kg) divided by height (m^2). All measurements were interpreted using the World Health Organization (WHO) growth standards, with the results analyzed via the Anthro Program (WHO, Geneva, Switzerland) [40]. Waist circumference was measured with a flexible, non-stretchable tape, rounded to the nearest 0.1 cm.

Blood sample collection

Blood sampling involved the collection of 7 mL of venous blood from each participant following an 8-hour fasting period. The blood was subsequently divided into two vacutainers: one containing EDTA for DNA extraction and HbA1c analysis, while the other additive-free for serum analysis. A 3 mL portion of blood was placed in a dry, sterile vacutainer, allowed to clot at room temperature for 15 minutes, and then centrifuged at 3000 rpm for 10 minutes at 24°C. Biochemical parameters, including serum creatinine, lipid profiles (triglycerides, HDL, LDL), HbA1c, and blood glucose levels, were measured using the Beckman Coulter AU5800 Automated Chemistry Analyzer (Beckman Coulter, Brea, CA, USA). HbA1c analysis was conducted using a glycohemoglobin kit compatible with the Beckman Coulter AU5800 Automated Chemistry Analyzer (Beckman Coulter, CA, USA).

DNA extraction

Genomic DNA was extracted from venous blood using the QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA), a silica membrane-based system designed for high-purity DNA isolation. Blood samples were collected in EDTA vacutainers to prevent coagulation and preserve sample integrity. The extraction process began with cell lysis by combining 200 µL of blood with 20 µL of proteinase K and 200 µL of AL buffer, which was vortexed and incubated at 56°C for 10 minutes. Ethanol (96–100%) was added to the lysate to precipitate DNA, which was then transferred to a QIAamp Mini spin column. DNA was bound to the silica membrane during centrifugation at 6000 × g for one minute. Contaminants were removed through two sequential washes with Buffer AW1 and AW2, followed by high-speed centrifugation (20,000 × g) to eliminate residual buffer. DNA was eluted with 200 µL of Buffer AE, incubated at room temperature for five minutes, and collected by centrifugation. DNA quality and concentration were assessed using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA), with a 260/280 absorbance ratio of 1.8–2.0 indicating purity. DNA integrity was confirmed via 1% agarose gel electrophoresis.

RAGE gene polymorphism genotyping

Genotyping of the rs1800625 SNP (-429T/C) in the *RAGE* gene was conducted using the TaqMan Allelic Discrimination Assay on the Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific, Waltham, MA, USA). DNA templates (10 ng/µL) were prepared, and the reaction mix included TaqMan Genotyping Master Mix along with a pre-designed SNP-specific primer and probe set (Assay ID: C_8848033_1). The PCR cycling conditions comprised initial denaturation at 95°C for 10 minutes, followed by 40 amplification cycles at 95°C for 15 seconds and 60°C for 1 minute. Fluorescently labeled probes (VIC and FAM) were used to differentiate the T and C alleles based on fluorescence emission. Following amplification, allelic discrimination plots were analyzed using Applied Biosystems software, enabling accurate and specific determination of genotypes. This method offers high sensitivity for the detection of genetic variants associated with T1DM [41,42]. The rs1800625 SNP (-429T/C) of the *RAGE* gene, located on chromosome 6p21.3, was chosen due to its global minor allele frequency (MAF) exceeding 10%

and its potential association with T1DM, a relationship that has been minimally explored. According to the SNPedia database (retrieved January 7, 2023), rs1800625 has a global MAF of 11.94%, with considerable variability across different populations [43].

Statistical analysis

Data analysis was performed using SPSS version 24.0 (IBM, New York, USA). The Kolmogorov-Smirnov test was used to assess data normality. Categorical data were summarized as frequencies and percentages, and comparisons were made using Pearson's Chi-squared or Fisher's Exact test. Continuous data were presented as mean ± SD for normally distributed variables and median with IQR for non-normally distributed variables. The independent t-test was used to compare normally distributed data between two groups, while the Mann-Whitney U test was used for non-normally distributed data. For comparisons involving more than two groups, One-way ANOVA with post hoc Duncan's test was applied for normally distributed data, and the Kruskal-Wallis test was used for non-normally distributed data. Associations between groups and the *RAGE* gene polymorphism rs1800625 were assessed using OR and 95%CI. Multivariate logistic regression with backward selection identified significant predictors of T1DM. Effect sizes were reported as adjusted odds ratios (aOR) with 95%CIs, with significance set at $p<0.05$ and high significance at $p<0.01$. Hardy-Weinberg equilibrium was tested for the control group using the Chi-squared test, and results were interpreted by comparing observed and expected genotype frequencies.

Results

Characteristics of the included T1DM patients and healthy controls

This study included 354 participants, consisting of 177 T1DM patients and 177 age- and sex-matched healthy controls. No significant differences were found in age ($p=0.440$) or sex distribution ($p=0.920$), ensuring demographic comparability between the groups. However, significant anthropometric differences were observed. Although the case group exhibited a higher mean BMI (31.81±5.76 kg/m²) compared to the control (30.70±5.32 kg/m²), the difference was not statistically significant ($p=0.060$). In contrast, waist circumference, a measure of central obesity, was significantly greater in the case group (109.53±13.75 cm) than in the control group (92.60±9.51 cm, $p<0.001$). This finding suggests that central obesity may have a more significant role in the metabolic dysregulation associated with T1DM than overall obesity as indicated by BMI. Hypertension was significantly more prevalent in the case group, affecting 21.5% of patients compared to none in the control group ($p<0.001$). Smoking was also significantly higher in the case group (19.8%) than in the control group (1.7%; $p<0.001$), underscoring its potential role in exacerbating disease progression and contributing to complications, including cardiovascular and renal conditions (**Table 1**).

T1DM patients exhibited significantly elevated glycemic markers compared to controls. The median FBG level was 179 mg/dL in case group versus 90 mg/dL in control group, and the median post-prandial blood sugar levels were 250 mg/dL and 110 mg/dL, respectively (both $p<0.001$). Additionally, HbA1c levels were significantly higher in patients (9.21±2.09%) compared to controls (3.75±0.58%; $p<0.001$), reflecting poor long-term glycemic control in the case group (**Table 1**).

Dyslipidemia was prevalent in T1DM patients, with median serum cholesterol levels of 190.0 mg/dL in case group versus 150.0 mg/dL in control group ($p<0.001$). Triglyceride levels were also elevated in case group (189.0 mg/dL) compared to controls (155.0 mg/dL; $p<0.001$). The case group had lower HDL levels (33.90±8.13 mg/dL) than the control group (43.03±8.13 mg/dL; $p<0.001$), while LDL levels were higher in the case group (117.92±16.82 mg/dL) than the control group (105.56±12.27 mg/dL; $p<0.001$). These findings indicated that atherogenic dyslipidemia contributes significantly to the increased cardiovascular risk in T1DM (**Table 1**).

Markers of renal function showed significant impairment in T1DM patients. The median A/C ratio was significantly higher in the case group (202.6 mg/g) compared to the control group (20.0 mg/g, $p<0.001$), suggesting early-stage nephropathy. Serum creatinine levels were also elevated in patients (1.20 mg/dL) compared to controls (1.0 mg/dL, $p<0.001$) (**Table 1**).

Table 1. Comparison of demographic, anthropometric, glycemic, lipid, and renal parameters between T1DM patients and healthy controls

Variables	Case group (n=177) n (%)	Control group (n=177) n (%)	*p*-value
Sex			
Male	89 (50.3)	90 (50.8)	0.920[a]
Female	88 (49.7)	87 (49.2)	
Age (years), mean±SD	53.75±9.52	52.88±11.37	0.440[b]
BMI (kg/m²), mean±SD	31.81±5.76	30.70±5.32	0.060[b]
Waist (cm) mean±SD	109.53±13.75	92.60±9.51	<0.001[b**]
History of hypertension			
No	139 (78.5)	177 (100)	<0.001[c**]
Yes	38 (21.5)	0 (0)	
Smoking status			
No	142 (80.2)	174 (98.3)	<0.001[c**]
Yes	35 (19.8)	3 (1.7)	
Fasting blood glucose (mg/dL), median (IQR)	179.0 (140.0–216.0)	90.0 (80.0–97.0)	<0.001[d **]
Postprandial blood sugar (mg/dL), median (IQR)	250.0 (200.0–300.0)	110.0 (100.0–123.0)	<0.001[d**]
HbA1c (%), mean±SD	9.21±2.09	3.75±0.58	<0.001[b**]
A/C ratio, median (IQR)	202.6 (115.0–317.95)	20.0 (15.0–23.0)	<0.001[d**]
Serum creatinine (mg/dL), median (IQR)	1.20 (0.97–1.23)	1.0 (0.9–1.1)	<0.001[d**]
Cholesterol (mg/dL), median (IQR)	190.0 (170.0–200.0)	150.0 (134.0–156.0)	<0.001[d**]
Triglyceride (mg/dL), median (IQR)	189.0 (180.0–190.0)	155.0 (135.0–166.0)	<0.001[d**]
HDL (mg/dL), mean±SD	33.90±8.13	43.03±8.13	<0.001[b**]
LDL (mg/dL), mean±SD	117.92±16.82	105.56±12.27	<0.001[b**]

A/C ratio: albumin-to-creatinine ratio; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; SD: standard deviation.
[a] Analyzed using Chi-squared test
[b] Analyzed using independent Student t-test
[c] Analyzed using Fisher's Exact test
[d] Analyzed using Mann-Whitney test
[*] Statistically significant at $p<0.05$
[**] Statistically significant at $p<0.01$

Genotype distribution and allele frequency of *RAGE* gene polymorphism rs1800625 in T1DM patients and healthy controls

Hardy-Weinberg equilibrium test for the control group indicated conformance to equilibrium for rs1800625 ($\chi^2=1.261$; $p=0.537$), validating the genetic analysis. Significant differences in genotype distribution were observed between T1DM patients and healthy controls. The CC genotype was more prevalent in the case group (29.9%) compared to the control group (11.9%), while the TT genotype was more common in the control group (29.9%) than in the case group (20.9%). The TC genotype, which was the most frequent in both groups, was less common in the case group (49.2%) than in the control group (58.2%). The CC genotype was associated with a threefold increase in the likelihood of developing T1DM (OR: 3.62; 95%CI: 1.87–6.97; $p<0.001$) (**Table 2**).

The C allele was significantly more frequent in the case group (54.5%) than in the control group (41.0%), while the T allele was more prevalent in the control group (59.0%) than in the case group (45.5%). The C allele was associated with an increased likelihood of T1DM (OR: 1.73; 95%CI: 1.28–2.33; $p<0.001$), suggesting its critical role in susceptibility to T1DM (**Table 2**). When combining TC and CC genotypes, a higher prevalence was observed in the case group (79.1%) compared to the control group (70.1%). The dominant model analysis revealed more than a one-and-a-half times increased odds of T1DM in the case group compared to the control group (OR: 1.62; 95%CI: 1.0–2.63; $p=0.048$), further highlighting the genetic predisposition associated with the C allele (**Table 2**).

Association between the genotype distribution of *RAGE* gene polymorphism rs1800625 and glycemic, lipid, and renal parameters in T1DM patients and healthy controls

No significant differences were observed in glycemic parameters (FBG, PBG, HbA1c), renal markers (A/C ratio, serum creatinine), or lipid profile (cholesterol, triglycerides, HDL, LDL)

across the TT, TC, and CC genotypes (all $p>0.05$). These findings suggest that the rs1800625 polymorphism does not have a direct impact on biochemical markers in this cohort. Furthermore, all η^2 values indicated small effect sizes, supporting the absence of meaningful differences between genotypes (**Table 3**).

Table 2. Genotype distribution and allele frequency of *RAGE* gene polymorphism rs1800625 between T1DM patients and healthy controls.

RAGE gene polymorphism rs1800625	Case group (n=177) n (%)	Control group (n=177) n (%)	OR (95%CI)	*p*-value
Genotypes				
TT	37 (20.9)	53 (29.9)	1	
TC	87 (49.2)	103 (58.2)	1.21 (0.73–2.01)	0.462[a]
CC	53 (29.9)	21 (11.9)	3.62 (1.87–6.97)	<0.001[a**]
Alleles				
T	161 (45.5)	209 (59.0)	1	
C	193 (54.5)	145 (41.0)	1.73 (1.28–2.33)	<0.001[a**]
Dominant model				
TT	37 (20.9)	53 (29.9)	1	
TC+CC	140 (79.1)	124 (70.1)	1.62 (1.0–2.63)	0.048[a*]

CI: confidence interval; OR: odds ratio
[a] Analyzed using Chi-squared test
[*]Statistically significant at $p<0.05$
[**]Statistically significant at $p<0.01$

Table 3. Association between the genotype distribution of *RAGE* gene polymorphism rs1800625 and glycemic, lipid, and renal parameters in T1DM patients and healthy controls.

Variables	*RAGE* gene polymorphism rs1800625			F	η^2	*p*-value
	TT (n=37)	TC (n=87)	CC (n=53)			
Fasting blood glucose (mg/dL), median (IQR)	170.0 (131.0–214.0)[a]	178.0 (140.0–220.0)[a]	187.0 (146.5–210.0)[a]	0.1	294.4	0.530[b]
Postprandial blood sugar (mg/dL), median (IQR)	230.0 (200.0–285.0)[a]	250.0 (200.0–300.0)[a]	250.0 (200.0–300.0)[a]	0.4	4313.2	0.580[b]
HbA1c (%), mean±SD	9.73±2.52[a]	9.12±2.07[a]	9.0±1.76[a]	1.5	1464.2	0.230[b]
A/C ratio, median (IQR)	208.3 (123.0–345.0)[a]	202.6 (87.0–293.0)[a]	202.0 (122.0–331.0)[a]	0.5	8638.0	0.520[b]
Serum creatinine (mg/dL), median (IQR)	1.2 (1.0–1.37)[a]	1.1 (0.9–1.20)[a]	1.2 (1.05–1.30)[a]	2.0	0.3	0.090[b]
Cholesterol (mg/dL), median (IQR)	180.0 (170.0–200.0)[a]	190.0 (170.0–200.0)[a]	190.0 (178.0–200.0)[a]	1.7	3115.3	0.450[b]
Triglyceride (mg/dL), median (IQR)	187.0 (180.0–190.0)[a]	189.0 (170.0–190.0)[a]	190.0 (180.0–210.5)[a]	1.7	3094.4	0.230[b]
HDL (mg/dL), mean±SD	33.84±8.11[a]	33.68±8.32[a]	34.30±7.967[a]	0.1	6.5	0.910[b]
LDL (mg/dL), mean±SD	115.62±16.78[a]	117.36±17.16[a]	120.45±16.27[a]	1.0	281.6	0.370[b]

A/C ratio: albumin-to-creatinine ratio; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; IQR: interquartile range; LDL: low-density lipoprotein; SD: standard deviation.
[a] Analyzed using Duncan's post hoc test; means with different superscripts are significantly different from other experimental groups, while those with the same superscript indicate no significant difference, at $\alpha=0.05$.
[b] Analyzed using Kruskal-Wallis test
[*] Statistically significant at $p<0.05$
[**] Statistically significant at $p<0.01$

Key predictors of T1DM development: A multiple logistic regression analysis

FBG has been identified as a significant predictor of T1DM in logistic regression analyses. The β-coefficient of 2.192 ($p=0.01$) indicates a strong positive association between elevated FBG levels and the likelihood of T1DM. The aOR of 8.955 (95%CI: 1.59–50.47) suggests that individuals with higher FBG levels have nearly nine times the odds of developing T1DM. These findings

underscore the critical role of FBG as a marker of metabolic dysregulation in T1DM pathophysiology. Among the variables studied, HbA1c demonstrated the strongest predictive value for T1DM. With a β-coefficient of 2.563 (p<0.001) and an aOR of 12.971 (95%CI: 4.00–42.05), elevated HbA1c levels significantly increase the risk of T1DM, highlighting the importance of long-term glycemic control in its development (**Table 4**).

RAGE gene polymorphism rs1800625 showed a significant association with T1DM (β=0.600, p=0.01). The aOR of 1.815 (95%CI: 1.146–2.876) suggests a moderate genetic predisposition linked to this polymorphism. The model's constant (β=(–13.180), p<0.001) provides the baseline log odds for T1DM when all predictors are set to zero. This large negative value reflects the low probability of T1DM in the absence of significant predictive factors, reinforcing the contributions of FBG, HbA1c, and the *RAGE* gene polymorphism (**Table 4**).

Logistic regression analysis demonstrated that several variables commonly associated with T1DM in broader contexts were not significant predictors in this study. These included waist circumference (p=0.257), history of hypertension (p=0.983), and smoking status (p=0.457). Similarly, markers of glycemic trends and renal impairment, such as PBG (p=0.695), A/C ratio (p=0.341), and creatinine (p=0.428), were not significant. Lipid profile parameters, including cholesterol (p=0.071), triglycerides (p=0.142), HDL (p=0.345), and LDL (p=0.227), also did not show statistical significance (**Table 4**).

Table 4. Multiple logistic regression analysis to identify key predictors of T1DM development.

Variables	β-coefficient [a]	Standard error	aOR (95%CI)	p-value [a]
Waist circumference	0.615	0.543	1.850 (0.639–5.359)	0.257
History of hypertension	-0.014	0.646	0.986 (0.278–3.494)	0.983
Smoking status	0.477	0.642	1.612 (0.458–5.678)	0.457
Fasting blood glucose	2.190	0.880	8.960 (1.590–50.470)	0.010*
Postprandial blood sugar	0.540	1.379	1.715 (0.115–25.571)	0.695
Glycated hemoglobin (HBA1c)	2.560	0.600	12.970 (4.000–42.050)	<0.001**
Albumin-to-creatinine ratio	1.050	1.102	2.859 (0.330–24.799)	0.341
Creatinine	0.548	0.692	1.730 (0.446–6.719)	0.428
Cholesterol	1.184	0.656	3.267 (0.903–11.818)	0.071
Triglyceride	1.491	1.017	4.443 (0.606–32.590)	0.142
High-density lipoprotein (HDL)	-0.743	0.787	0.475 (0.102–2.225)	0.345
Low-density lipoprotein (LDL)	1.041	0.862	2.833 (0.523–15.346)	0.227
RAGE gene polymorphism rs1800625	0.600	0.240	1.820 (1.150–2.880)	0.010*
Constant	-13.180	2.460		<0.001**

aOR: adjusted odds ratio; β: regression coefficient; CI: confidence interval
[a] Analyzed using backward multivariate logistic regression
* Statistically significant at p<0.05
** Statistically significant at p<0.01

Discussion

Egyptian population provides a unique context for studying genetic polymorphisms, such as *RAGE* rs1800625, due to its genetic diversity, high prevalence of diabetes, and distinct environmental factors [44]. This study highlights the intersection of genetic susceptibility, lifestyle behaviors, and metabolic dysregulation in T1DM. This setting allows for the exploration of genetic susceptibility, lifestyle behaviors, and metabolic dysregulation in T1DM [31]. The study investigated the association between *RAGE* rs1800625 polymorphism and T1DM susceptibility in Egyptians, revealing that the CC genotype (OR: 3.62; p<0.001) and C allele (OR: 1.73; p<0.001) were significantly more prevalent in T1DM patients, with a dominant model showing increased risk (OR: 1.62; p=0.048). T1DM patients exhibited significantly higher waist circumference (p<0.001), hypertension (p<0.001), smoking prevalence (p<0.001), poor glycemic control (elevated FBG, PPBS, HbA1c; all p<0.001), dyslipidemia (higher cholesterol, triglycerides, LDL, lower HDL; all p<0.001), and renal impairment (elevated A/C ratio and serum creatinine; both p<0.001). Logistic regression identified HbA1c (aOR: 12.97; p<0.001), FBG (aOR: 8.96; p=0.010), and rs1800625 polymorphism (aOR: 1.82; p=0.010) as key predictors of T1DM, emphasizing the role of genetic predisposition and metabolic dysregulation in T1DM pathogenesis. Among these, HbA1c proved to be the strongest indicator of chronic glycemic

control. Although the impact of the *RAGE* gene polymorphism rs1800625 was less pronounced compared to glycemic markers, its genetic association emphasizes the role of hereditary factors in T1DM etiology, consistent with existing evidence on the genetic underpinnings of immune-mediated β-cell destruction [27].

Patients with T1DM exhibited significantly larger waist circumference, higher rates of hypertension, and increased smoking prevalence compared to controls. These findings emphasize the role of central obesity, vascular dysfunction, and modifiable lifestyle factors in exacerbating T1DM pathophysiology and complications. The observed associations align with existing literature that links central obesity, hypertension, and smoking as key risk factors for T1DM-related complications [45,46]. Unlike BMI, waist circumference provides a more accurate measure of visceral fat, a primary contributor to insulin resistance and inflammation [47]. This distinction is particularly important, given the limitations of BMI in assessing health risks across diverse age, sex, and ethnic groups [48-50]. These results underscore the necessity of targeted interventions that address modifiable risk factors to enhance clinical outcomes in T1DM.

The global incidence of T1DM is increasing by 3–4% annually, particularly in affluent nations, highlighting the interaction between genetic predisposition and environmental factors [17,51]. AGEs, which are prevalent in processed diets, contribute to β-cell dysfunction and insulin resistance [18]. In Egypt, where dietary patterns are characterized by high consumption of processed foods, the accumulation of AGEs may exacerbate the risk and progression of T1DM [33,52]. The significant association between *RAGE* rs1800625 and T1DM observed in this study is noteworthy, with the CC genotype conferring a threefold increased risk (OR: 3.62; 95%CI: 1.87–6.97; $p<0.001$) and the C allele being more prevalent in T1DM patients (OR: 1.73; 95%CI: 1.28–2.33; $p<0.001$). These findings support the evidence that rs1800625 enhances *RAGE* expression, promoting inflammation and oxidative stress [53]. Mechanistically, *RAGE* binds ligands such as AGEs, HMGB1, and S100 proteins, activating downstream signaling pathways (e.g., NF-κB, MAPK, janus kinase/signal transducer and activator of transcription (JAK/STAT)) that lead to cytokine production, oxidative stress, and β-cell damage [26,54]. Chronic hyperglycemia further exacerbates this cycle by promoting AGE accumulation and *RAGE* ligand synthesis, thereby amplifying inflammation and accelerating disease progression [19].

The association between rs1800625 and T1DM varies across populations. While this study identified significant associations in an Egyptian cohort, previous studies in European populations reported weaker or no associations [32,55]. Although studies on the rs1800625 polymorphism in American populations are limited, dietary habits involving high AGE intake may interact with genetic factors, influencing T1DM susceptibility and progression [19]. These discrepancies may be attributed to genetic heterogeneity, variations in allele frequency, and population-specific environmental exposures [56,57]. Egypt's distinctive dietary and lifestyle patterns may amplify the effect of this polymorphism, whereas genetic and environmental differences in European populations may attenuate its impact [56,57]. In Egypt, a diet rich in AGEs, along with higher rates of central obesity and smoking, may enhance the pro-inflammatory and oxidative effects of the rs1800625 polymorphism, thereby increasing T1DM risk [55-57].

Conflicting findings have been reported regarding the association between *RAGE* SNPs and diabetes complications. Some studies have associated rs1800625 with an increased risk of T1DM and diabetic nephropathy [58], while others have found no significant association with either type 1 or type 2 diabetes, nephropathy, or retinopathy [59]. Although this study did not identify significant associations between rs1800625 and biochemical markers, FBG and HbA1c levels, along with the rs1800625 polymorphism, were significant predictors of T1DM-related hyperglycemia. The rs1800625 polymorphism likely contributes to hyperglycemia in T1DM by upregulating *RAGE* expression, which amplifies inflammation and oxidative stress, leading to β-cell dysfunction and impaired insulin regulation [60-62]. The lack of significant associations between rs1800625 and biochemical markers such as lipids or renal function suggests that the polymorphism's primary role may be in modulating glucose metabolism rather than directly influencing lipid metabolism or renal dysfunction [63-65]. These effects may be mediated through distinct genetic or environmental pathways, underscoring the need for larger, multi-ethnic studies to further validate these findings.

Elevated RAGE plays a central role in the pathophysiology of diabetes and its complications, including autoimmune conditions such as Crohn's disease and systemic lupus erythematosus [66]. Ligand binding to RAGE activates signaling pathways, including JAK/STAT, GSK-3β, and NADPH oxidase, which drive inflammation, oxidative stress, and angiogenesis, contributing to β-cell damage and vascular complications [22,54]. Hyperglycemia further promotes *RAGE* expression and the synthesis of pro-inflammatory ligands [67]. Polymorphisms affecting *RAGE* activity may precede the clinical onset of T1DM, increasing susceptibility to the disease and its vascular complications, including nephropathy, neuropathy, and retinopathy [19,68].

AGEs-RAGE axis plays a critical role in the progression of diabetes-related complications, including T1DM [69,70]. In diabetic nephropathy, AGEs-RAGE interactions activate NF-κB signaling, impairing the filtration barrier and promoting cytokine overproduction [22,71]. Studies in RAGE-deficient diabetic mice have shown reduced cytokine production, greater resistance to kidney cell death, and slower disease progression [14,72]. Although these findings are derived from nephropathy models, mechanisms such as NF-κB activation are also implicated in T1DM pathophysiology and may be influenced by the rs1800625 polymorphism [22,70,73].

RAGE activation has been implicated in peripheral neuropathy and diabetic retinopathy. Elevated levels of RAGE and high mobility group box 1 (HMGB1) trigger neuronal inflammation in neuropathy, while HMGB1 binding to RAGE in retinopathy activates NF-κB signaling, leading to retinal inflammation and demyelination [26,74,75]. Chronic hyperglycemia and enhanced AGEs-RAGE interactions exacerbate tissue damage and inflammation, which are central to T1DM progression [65,76]. The rs1800625 polymorphism, by influencing *RAGE* expression, may amplify these pathways, contributing to T1DM susceptibility and complications [27,77]. This mechanism likely explains the poor glycemic control and renal impairment observed in T1DM patients in this study. Dietary habits rich in AGEs, commonly found in processed foods, further exacerbate these effects by increasing the availability of ligands for *RAGE*, thereby amplifying the inflammatory cascade [78]. Additionally, the rs1800625 polymorphism, located in the promoter region of the *RAGE* gene, has been associated with increased *RAGE* expression, leading to enhanced inflammatory responses and oxidative stress [79]. This combination of dietary factors and genetic predisposition contributes to poor glycemic control and renal impairment in individuals with T1DM.

Targeting RAGE presents a promising therapeutic approach, with current strategies encompassing extracellular interventions (e.g., peptides, anti-RAGE antibodies, DNA aptamers) and intracellular targets (e.g., toll/interleukin-1 receptor domain-containing adapter protein (TIRAP), diaphanous-related formin 1 (DIAPH1)) [80,81]. AGE inhibitors, such as benfotiamine and aminoguanidine, along with soluble RAGE (sRAGE) antagonists, have demonstrated potential in mitigating T1DM complications [80]. Early intervention targeting the AGEs-RAGE axis may offer benefits, particularly for T1DM patients with the rs1800625 polymorphism. The findings of this study suggest that genetic screening for the rs1800625 polymorphism could help identify high-risk individuals, enabling timely interventions, especially in those with the C allele or CC genotype and significant environmental risk factors. Proper patient selection and counseling are essential to ensure the clinical utility of rs1800625 testing while minimizing unnecessary costs. Screening for the rs1800625 polymorphism is particularly relevant for individuals at elevated risk of T1DM or related complications, such as those with a family history of T1DM, autoimmune disorders, or early diabetic complications like nephropathy or retinopathy. It is also advantageous for patients with poor glycemic control, comorbid conditions (e.g., obesity, hypertension, or smoking), or those from populations with a high prevalence of the C allele, such as Egyptians. Screening allows for the assessment of genetic risk, stratification of complication risks, and the formulation of personalized treatments targeting the AGEs-RAGE pathway while also informing family planning decisions [82]. Conversely, screening is unnecessary for low-risk individuals without a family history or significant metabolic issues. Additionally, research has linked the rs1800625 polymorphism to an increased risk of hepatocellular carcinoma in specific populations, further emphasizing the importance of considering genetic factors in disease susceptibility [82].

Therapeutic strategies targeting the AGEs-RAGE pathway, in combination with lifestyle modifications to reduce dietary AGE intake and manage central obesity, hypertension, and

smoking, could improve disease management and reduce T1DM-related complications [83]. Targeted therapies modulate the AGEs-RAGE axis through distinct mechanisms, necessitating careful patient selection. RAGE is most appropriate for managing inflammatory-driven complications [84], anti-RAGE antibodies for autoimmune processes [85], and AGE inhibitors for the early prevention and management of hyperglycemia-related damage [86]. Each therapeutic approach requires careful consideration of the patient's disease stage, comorbidities, and potential contraindications to optimize both efficacy and safety.

This study provides valuable insights into T1DM in the underrepresented Egyptian population, integrating genetic, anthropometric, clinical, and lifestyle data. It highlights the role of the *RAGE* rs1800625 polymorphism in T1DM susceptibility and hyperglycemia, offering a foundation for targeted interventions. The findings have clinical relevance for developing therapeutic strategies. The study's rigorous methodology, with well-defined criteria and advanced techniques, ensures reliable and valid results.

This study has several limitations. The small sample size may reduce the generalizability and statistical power of the findings. The cross-sectional design limits the ability to establish causal relationships, and focusing solely on the rs1800625 polymorphism restricts a broader understanding of RAGE's role in T1DM. Although dietary and lifestyle factors were considered, precise contributions were not directly assessed. The findings are specific to the Egyptian population and require validation in more diverse cohorts. Financial constraints limited the sample size and prevented the analysis of additional SNPs, potentially overlooking other significant associations. Future studies should explore the functional implications of rs1800625, particularly its diagnostic and therapeutic potential. Investigating interactions among key predictors could improve predictive models and inform targeted interventions. Expanding research to diverse populations is essential for validation, while examining the interplay between genetic, epigenetic, and environmental factors could enhance understanding of T1DM susceptibility and guide tailored treatments.

Conclusion

A significant genetic association was found between the *RAGE* gene polymorphism rs1800625 and susceptibility to T1DM, with the CC genotype and C allele more prevalent in T1DM patients. However, the polymorphism did not significantly affect key laboratory markers, as indicated by small effect sizes (η^2) in glycemic control, renal markers, and lipid profiles. Logistic regression identified FBG, HbA1c, and rs1800625 as key predictors for T1DM development, with HbA1c being the strongest, highlighting the importance of chronic glycemic control. These findings underscore the need for a multifactorial approach to T1DM, integrating genetic and metabolic factors.

Ethical approvals

Ethical approval was obtained from the Ethical Committee of General Organization of Teaching Hospitals and Institutions, Cairo, Egypt (Approval number: IDE00296), and the Ethical Committee of Beni-Suef University, Beni-Suef, Egypt (Approval No. REC-H-PhBSU-23057). This study is registered at ClinicalTrials.gov (NCT05874323; approval date: May 24, 2023).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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