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**| RESEARCH ARTICLE**

# The Association of *LEP G2548A* Polymorphism with Type 2 Diabetes Mellitus in the Iraqi Population

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**| ABSTRACT**

Background: Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder influenced by both environmental and genetic factors. Leptin, a key hormone regulating energy homeostasis and insulin sensitivity, has been linked to T2DM pathogenesis. The *LEP* gene promoter polymorphism *G2548A* (*rs7799039*) has been associated with altered leptin expression and metabolic dysregulation in various populations. Objective: This study investigated the association between the *LEP G2548A* variant and T2DM risk among Iraqi adults. Materials and Methods: A case-control study was conducted involving 150 T2DM patients and 150 healthy controls matched for age, sex, and BMI. Genotyping of the *G2548A* polymorphism was performed using allele-specific PCR. Fasting blood glucose, insulin, leptin levels, and lipid profiles were measured. Insulin resistance was assessed using the HOMA-IR index. Associations between genotypes, allelic frequencies, and biochemical parameters were evaluated under multiple genetic models. Results: The frequency of the A allele and AA genotype was significantly higher in T2DM patients compared to controls (41.7% vs. 19.0%, $p< 0.00001$; OR = 3.39). The AA genotype was associated with a 5.1-fold increased risk of T2DM, while the GA genotype conferred a 2.6-fold risk. Carriers of the A allele showed significantly elevated levels of serum leptin, insulin, and HOMA-IR. These findings suggest a strong association between the *LEP G2548A* polymorphism and both hyperleptinemia and insulin resistance in T2DM patients. Conclusion: The *LEP G2548A* polymorphism is significantly associated with increased risk of T2DM and contributes to elevated leptin levels and insulin resistance in the Iraqi population. The A allele may serve as a potential genetic marker for early identification of individuals at higher risk for T2DM.

**| KEYWORDS**

Type 2 diabetes mellitus, leptin, *LEPG2548A* polymorphism, insulin resistance, Iraqi population.

**| ARTICLE INFORMATION**

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## 1. Introduction

Diabetes is a multifaceted, endogenous metabolic illness (Tibaldi, 2013). Insulin resistance with an insulin secretary malfunction or relative insulin deficit are two of its etiology (Algenabi et al., 2021). Globally, T2DM represents one of the most significant public health challenges, with increasing prevalence across all age groups and populations (Chen et al., 2012). According to the International Diabetes Federation (2021), Iraq has seen a considerable rise in T2DM cases, now affecting approximately 9.4% of the adult population, equivalent to over two million individuals. The economic and healthcare burden of T2DM underscores the need for identifying at-risk individuals and implementing early preventive strategies.

T2DM is multifactorial in origin, with both environmental and genetic determinants contributing to disease susceptibility (Tremblay & Hamet, 2019). Lifestyle factors such as poor diet, physical inactivity, and obesity are well-established contributors (Wang et al., 2020). However, accumulating evidence points to the pivotal role of genetic predisposition in the development of T2DM, especially in individuals with a strong family history or those who present with early-onset disease (Franks, 2012).

Genetic studies have increasingly focused on polymorphisms in genes involved in glucose metabolism, insulin signaling, and adipokine regulation. Leptin, a hormone secreted primarily by adipose tissue, plays a vital role in energy balance, food intake regulation, and glucose homeostasis. It exerts its effects via binding to leptin receptors in the hypothalamus and peripheral tissues, thereby modulating appetite and insulin sensitivity (Picó et al., 2022). Elevated leptin levels are frequently observed in obese individuals and are associated with leptin resistance, a condition that diminishes leptin's regulatory effects, leading to further weight gain and insulin resistance (key features in T2DM pathophysiology) (Ramos-Lobo & Donato, 2017; Obradovic et al., 2021).

The human *LEP* gene, which encodes leptin, is located on chromosome 7q32.1 and contains several single nucleotide polymorphisms (SNPs) that influence leptin expression and function (Jarrar et al., 2024). Among these, the *G2548A* polymorphism (*rs7799039*) in the promoter region of the *LEP* gene has garnered considerable attention. This SNP involves a substitution of guanine (G) with adenine (A) and is believed to alter gene transcription, leading to changes in leptin secretion (Franek et al., 2010 & Aboelros et al., 2017). Several studies across different populations have demonstrated an association between the *A* allele and increased leptin levels, obesity, insulin resistance, and T2DM (Boumaiza et al., 2012 & Bains et al., 2020). However, findings have been inconsistent across ethnic groups, suggesting that the impact of this polymorphism may be modulated by population-specific genetic backgrounds and environmental interactions. The present study aims to explore the association between this polymorphism and T2DM risk, as well as its impact on leptin levels, insulin resistance, and related metabolic parameters.

## 2. Materials and Methods Summary

### *2.1 Study Design*

This case-control study was conducted in the Department of Biochemistry at the College of Medicine, University of Kufa, Iraq, between October and December 2024. A total of 300 participants were enrolled, comprising 150 patients with type 2 diabetes mellitus (T2DM) and 150 age-, sex-, and BMI-matched apparently healthy controls. The study was approved by the Al-Kufa Medical College Ethical Committee.

### *2.2 Inclusion and Exclusion Criteria*

Participants in the diabetic group were aged 30–65 years and diagnosed with T2DM based on fasting blood glucose levels >126 mg/dl, consistent with ADA diagnostic criteria (Genuth et al., 2018). Exclusion criteria included type 1 diabetes, use of insulin therapy, pregnancy or lactation, and comorbidities such as cardiovascular disease, hepatitis, nephropathy, hypertension, and cancer. The control group consisted of individuals aged 30–65 years with no history of diabetes, selected from relatives, friends, and medical staff. Participants with any suspected or diagnosed chronic illness were excluded from the control group.

### *2.3 Biochemical Measurements*

After overnight fasting (12 hours), 6 ml of venous blood was collected and separated into three portions: A 2 ml for HbA1c analysis (EDTA tube), 2ml for biochemical and hormonal assays (serum), and 2 ml for DNA extraction (EDTA tube). Anthropometric data, including weight and height, were collected to calculate BMI using the Asian-specific criteria for obesity classification (Dhawan & Sharma, 2020).

Biochemical assessments included fasting plasma glucose (glucose oxidase-peroxidase method), triglycerides, total cholesterol, and HDL-C measured via enzymatic colorimetric methods. LDL-C and VLDL-C levels were calculated using the Friedewald formula (Friedewald et al., 1972; Hong et al., 2023). Insulin and leptin concentrations were determined using commercial ELISA kits, following the manufacturers' instructions. Insulin resistance was assessed

using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index: HOMA-IR = [glucose (mg/dL) × insulin (μU/mL)] / 405 (Matthews et al., 1985; Matsuda & DeFronzo, 1999).

### *2.4 DNA Extraction*

Genomic DNA was extracted from whole blood samples using the Add Prep Genomic DNA Mini Kit (Geneaid, Korea), which relies on the binding of DNA to a silica column matrix under high salt conditions, followed by ethanol washing and elution in TE buffer. DNA concentration and purity were measured using spectrophotometry (BioDrop, UK), with acceptable A260/A280 ratios ranging from 1.7 to 2.0 (Tataurov et al., 2008). DNA integrity was confirmed by 1.5% agarose gel electrophoresis and UV visualization (Robinson & Lafleche, 2000; Harisha, 2008).

### *2.5 Genotyping of LEP G2548A (rs7799039) Polymorphism*

Genotyping was conducted using allele-specific polymerase chain reaction (AS-PCR). The PCR reactions utilized allele-specific forward primers, the sequences of primers of *LEP G2548A* (Allele G: GTTTTGCGACAGGGTTGCG, Allele A: GTTTTGCGACAGGGTTGCA) and reverse primer CCTATTCTGGTCCCCACTGC, a GoTaq® G2 Green Master Mix (Promega, USA), which contains Taq polymerase, dNTPs, $MgCl_2$, and tracking dyes (Denhart & Doraiswamy, 2001).

The PCR reactions were executed in 25 μl volumes comprising of 12.5 μl master mix 2X (GoTaq®Green Master Mix, Promega, USA), 2 μl of each primer (Allele *G*, Allele *A*, and reverse primer), template DNA 6 μl, nuclease-free water up to 25 μl. PCR conditions were optimized by testing various primer concentrations, DNA template volumes, and annealing temperatures (55–65°C). Thermal cycling was performed on a Biometra thermocycler with the following conditions for *rs7799039*: initial denaturation at 95°C for 5 minutes, followed by 35 cycles of denaturation (95°C, 30s), annealing (60.5°C, 30s), extension (72°C, 1 min), and a final extension at 72°C for 5 minutes. PCR products were analyzed by 1.5% agarose gel electrophoresis and visualized using UV documentation systems.

### *2.6 Statistical Analysis*

Statistical analysis was performed using SPSS version 26.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± standard deviation (SD). The Student's t-test and ANOVA were used to compare biochemical and anthropometric data between groups. Chi-square ($\chi^2$) tests were used to compare genotype and allele frequencies between T2DM patients and controls. Associations between genotypes and T2DM were examined under codominant, dominant, recessive, additive, and allelic models using logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported, both unadjusted and adjusted for age, sex, and BMI (Camey et al., 2014).

The study's genetic power was calculated using the OSSE online sample size estimator, ensuring >95% power for detecting genotype associations (Purcell et al., 2003; Evans & Purcell, 2012). The genotype distribution in controls was tested for Hardy-Weinberg equilibrium (HWE) using chi-square analysis to validate random mating assumptions and genotyping accuracy.

## 3. Results

### *3.1 Clinical and biochemical parameters of the study groups*

The demographic analysis showed no significant differences in age, sex, or body mass index (BMI), ensuring comparability between groups. However, significant differences were observed in various biochemical parameters, as illustrated in Table 3.1.

**Table 3.1** *Demographic and biochemical features of study participants*

| Parameters | Control (n= 150) | T2DM (n= 150) | P-Value |
|---|---|---|---|
| No (M/F) | 150 (77/73) | 150 (83/67) | |
| Age (y) | 52.12 ± 6.71 | 53.36 ± 6.74 | 0.111 |
| BMI (Kg/m2) | 27.51 ± 2.46 | 28.02 ± 2.32 | 0.071 |
| TG (mg/dl) | 138.16 ± 16.69 | 241.61 ± 22.02 | <0.001 |
| TC (mg/dl) | 159.16 ± 16.01 | 230.83 ± 17.36 | <0.001 |
| VLDL-C (mg/dl) | 27.63 ± 3.34 | 48.26 ± 4.41 | <0.001 |
| LDL-C (mg/dl) | 85.33 ± 13.51 | 142.19 ± 15.97 | <0.001 |
| HDL-C (mg/dl) | 46.19 ± 4.53 | 40.35 ± 3.01 | <0.001 |
| FBG (mg/dl) | 92.37 ± 7.66 | 222.15 ± 29.23 | <0.001 |
| HbA1C % | 5.10 ± 0.394 | 9.53 ± 1.46 | <0.001 |
| Insulin (µU/L) | 5.40 ± 2.92 | 10.10 ± 5.33 | <0.001 |
| HOMA-IR | 1.24 ± 0.69 | 5.50 ± 2.88 | <0.001 |
| Leptin (ng/ml) | 2.02 ± 0.869 | 4.49 ± 2.45 | <0.001 |

NO., Number of participants; BMI, Body mass index; TG, triglyceride; TC, total cholesterol; VLDL-C, very low density lipoprotein; HDL-C, high density lipoprotein; FBG, fasting blood glucose; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; P<0.05, significant**.**

Genotyping for *LEP G2548A* (*rs7799039*) polymorphism achieved via Allele-Specific PCR (AS-PCR). After amplification of PCR products on a 1.5% agarose gel electrophoresis, three genotyping for *LEP G2548A* SNP were detected, which are wild homozygous (*GG*), mutant homozygous (*AA*), and heterozygous (*GA*) with 1586 bp for each one as shown in Figure 1.

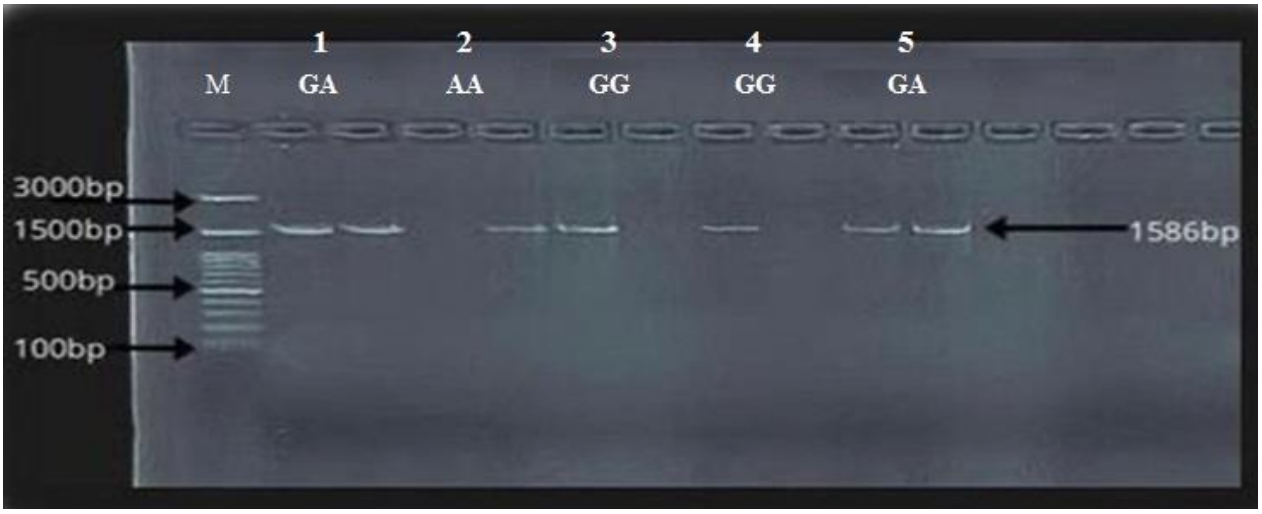


**Figure 1**. *AS-PCR-Technique genotype of LEP gene rs7799039G>A on 1.5% agarose gel electrophoresis. M; DNA ladder. Lanes 1 and 5 indicate the (GA) genotype. Lane 2 indicates the (AA) genotype. Lanes 3 and 4 indicates (GG) genotype.*

### *3.2 Genotype and allele frequencies distribution of rs7799039*

Genotype frequencies revealed significant associations between this SNP and T2DM risk, as shown in Table 3.2. For *LEP G2548A*, the homozygous *AA* genotype conferred a 5.18-fold increased risk of T2DM compared to the *GG* genotype ($p < 0.0001$), and the *GA* genotype showed a 2.62-fold increased risk ($p < 0.0001$); under the dominant model (*GA+AA* vs. *GG*), the risk increased by 3.24-fold. The minor *A* allele was significantly more frequent in T2DM patients (41.7%) than in controls (19.0%), conferring a 3.39-fold increased risk ($p = 0.00001$).

**Table 3.2** *Genotype and allele frequency of rs7799039 SNP of LEP gene in T2DM patients and controls*

| Model | Genotype/Allele | T2DM (n=150) No. (%) | Control (n=150) No. (%) | Adjusted OR (95% CI) | P-value |
|---|---|---|---|---|---|
| **Codominant** | *GG* | 60 (40%) | 104 (69.34%) | Ref. | |
| | *GA* | 55 (36.66%) | 35 (23.33%) | 2.62 (1.52-4.49) | <0.0001 |
| | *AA* | 35 (23.34%) | 11 (7.33%) | 5.18 (2.43 -11.05) | <0.0001 |
| **Dominant** | *GA + AA* | 90 (60%) | 46 (30.6%) | 3.24 (1.99-5.27) | <0.0001 |
| **Over Dominant** | *GG + AA* | 95 (63.34%) | 115 (76.66%) | 1.84 (1.10-3.07) | 0.02 |
| | *GA* | 55 (36.66%) | 35 (23.34) | | |
| **Recessive** | *GG + GA* | 115 (76.66%) | 139 (92.67%) | 3.66 (1.76-7.58) | 0.0002 |
| | *AA* | 35 (23.34%) | 11 (7.33%) | | |
| **Allele** | *G* | 175 (58.34%) | 243 (81%) | 3.39 (2.01-5.72) | 0.0001 |
| | *A* | 125 (41.66%) | 57 (19%) | | |

### *3.3 Association of LEP rs7799039 polymorphism with anthropometric parameters in T2DM patients*

Further genotype-phenotype correlation analyses demonstrated that carriers of the *LEP A* allele (*GA* and *AA* genotypes) had significantly elevated serum insulin, HOMA-IR, and leptin levels under both codominant and dominant models, with no significant differences observed for BMI, FBG, HbA1c, or lipid parameters as observed in Table 3.3.

**Table 3.3** *Biochemical characteristics of T2DM patients in revelence to the genotypes of rs7799039 polymorphism under codominant model*

| Parameters | *GG*=60 (Mean ± SD) | *GA*=55 (Mean ± SD) | *AA*=35 (Mean ± SD) | P value |
|---|---|---|---|---|
| BM(Kg/m2) | 27.73 ± 2.46 | 28.20 ± 2.28 | 28.23 ± 2.14 | 0.475 |
| TG (mg/dl) | 239.22 ± 24.16 | 243.36 ± 21.96 | 242.94 ± 18.14 | 0.581 |
| TC (mg/dl) | 230.41 ± 16.96 | 232.05 ± 17.09 | 229.62 ± 18.81 | 0.796 |
| VLDL (mg/dl) | 47.80 ± 4.83 | 48.68 ± 4.40 | 48.42 ± 3.65 | 0.585 |
| LDL-C (mg/dl) | 141.72 ± 15.06 | 143.32 ± 15.78 | 141.21 ± 18.02 | 0.803 |
| HDL-C (mg/dl) | 40.90 ± 3.12 | 39.98 ± 2.94 | 40.00 ± 2.88 | 0.207 |
| Leptin (ng/ml) | 3.68 ± 1.82 | 3.97 ± 2.19 | 6.69 ± 2.52 | <0.001 |
| FBG (mg/dl) | 220.95 ± 32.18 | 223.13 ± 26.55 | 222.69 ± 28.71 | 0.921 |
| HbA1C % | 9.45 ± 1.52 | 9.57 ± 1.32 | 9.61 ± 1.59 | 0.861 |
| Insulin (µU/L) | 8.51 ± 4.72 | 9.74 ± 4.76 | 13.37 ± 5.87 | <0.001 |
| HOMA-IR | 4.59 ± 2.44 | 5.35 ± 2.62 | 7.31 ± 3.19 | <0.001 |

## 4. Discussion

The supposition on causes and effects of type 2 diabetes in humans have been extensively researched across many communities around the world in an effort to lessen its influence on the health care system, which costs a lot of budget, effort, and affects community vitality. In this study, the *rs7799039* SNP of the *LEP* gene *G>A* was investigated to determine the development of type 2 DM in the Iraqi population.

The results revealed that a significant dyslipidemia was noted in the participants with type 2 diabetes mellitus (T2DM), as shown in Table 3.1. The levels of triglycerides (TG), total cholesterol (TC), VLDL-C, and LDL-C were substantially higher in the diabetic group (all $p < 0.001$), whereas HDL-C levels were considerably reduced ($p < 0.001$). These lipid irregularities are typical of diabetic dyslipidemia, which heightens the risk of cardiovascular diseases in individuals with diabetes (Bawah et al., 2021).

Our data showed that HOMA-IR and insulin levels were markedly higher in diabetics, suggesting a marked state of insulin resistance, a key component of the pathophysiology of type 2 diabetes (Ashraf et al., 2022). The diabetic group also had greater levels of leptin. Insulin resistance and obesity are frequently linked to elevated leptin levels, leptin which is produced by adipose tissue, directly affects pancreatic β-cells by attaching to their receptors and inhibiting the generation and release of insulin (Ramos-Lobo & Donato, 2017). On the other hand, insulin induces adipose tissue to release leptin (De la Cruz Concepción et al., 2023). The pancreas and fat tissue have a reciprocal interaction that is essential for controlling metabolism as a whole. Insulin resistance and type 2 diabetes can develop as a result of abnormal insulin production caused by defective leptin signaling in pancreatic cells, such as leptin resistance (Tsai et al., 2012). Insulin resistance prevents glucose from being utilized by target tissues such as muscle, liver, and adipose, resulting in hyperglycemia (Ashcroft & Rorsman, 2012).

The data concerning the *rs7799039 G>A* SNP in the leptin gene indicated a notable correlation between the minor allele *A* and the incidence of Type 2 Diabetes Mellitus (T2DM). Individuals with the homozygous *AA* genotype exhibited five folds increased risk of developing the disease compared to those with the *GG* wild genotype. Additionally, carriers of the heterozygous *GA* genotype demonstrated a 2.6-folds increased risk of T2DM in relation to wild-type carriers. These findings remained consistent after adjusting for sex, age, and BMI. Analysis under various inheritance models corroborated the involvement of the *A* allele in the development of T2DM. Specifically, the dominant, recessive, and over dominant models indicated risk factors of 3.2, 3.6, and 1.8 folds, respectively.

Our findings are in agreement with several studies linking the *rs7799039 G>A* SNP with T2DM, for instance North Indian Punjabi population (Bains et al., 2020), the Malay population (Al Fahham et al., 2022), Egyptian population (Mohamed et al., 2023). Contrary to our findings, several studies found no difference between diabetes patients and non-diabetic participants in the genotypic and allelic frequencies of the leptin gene promoter *G2548A* variation in Egyptian and Chinese population (Motawi et al., 2015; Yang et al., 2016), Racial disparities, the research population's genetic origins, the population's sample size, and regional variance can all contribute to contradictory findings.

The leptin gene's 5' end of the promoter region has the *LEP G2548A* polymorphism, which is situated at position -2548 upstream of the ATG start site (Sabi et al., 2022). This polymorphism, which comprises a change from guanine (*G*) to adenine (*A*), has been linked to a number of metabolic disorders, such as obesity, type 2 diabetes, and insulin resistance (Aboelros et al., 2017; Sabi et al., 2022).

Table 3.3 demonstrated the analyzed biochemical characteristics of type 2 diabetes mellitus (T2DM) patients based on the genotype of *LEP rs7799039* (*G>A*) under a codominant model. Leptin levels are notable genotypic variations, with *AA* carriers exhibiting higher leptin levels than *GA* and *GG* in *rs7799039* SNP. This is consistent with research showing that the *A* allele affects leptin production because of its position in the gene promoter (Franek et al., 2010; Abdullah, 2020; Ali et al., 2022). Research suggests that the *G2548A* variation in the leptin gene may lead to leptin resistance. studies found that the *G2548A* variant in the leptin gene promoter may impact gene expression and secretion in adipose tissue (Sahin et al., 2013; Shabana & Hasnain, 2016). Insulin and HOMA-IR: *AA* genotype is associated with raised insulin levels and insulin resistance, compared to *GA* and *GG* genotypes, this indicates a role

of the *A* allele in exacerbating metabolic dysfunction, which obtained in Tunisian volunteers (Boumaiza et al., 2012) and in Egyptian population (Aboelros et al., 2017).

The limitations of our study are Population diversity is limited (The findings may not be applicable to other populations), limited control over confounding variables like dietary habits, physical activity, socioeconomic status, and smoking.

## 5. Conclusion

The current study found that among the Iraqi population, T2DM was significantly correlated with the *G2548A* (*rs7799039*) of *LEP* gene. In individuals with type 2 diabetes, elevated fasting leptin and insulin levels are substantially correlated with the *AA* genotype of the *LEP* gene SNP. These results reinforce earlier research linking these polymorphisms to diabetes-related traits by highlighting the genetic effect on leptin signaling pathways in T2DM pathogenesis.

**Declaration of Interests:** The authors declare that they have no competing interests.

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**Ethics and Consent to Participate:** This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and received institutional approval from the Ethical Committee at the Faculty of Medicine, University of Kufa. Each participant provided written informed consent, which was obtained prior to enrollment, including provisions for confidentiality, along with withdrawal at any stage without prejudice.

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