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Evaluation of Serum Levels of NUCB2 in Patients with type2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is a significant global health issue, with a prevalence of 13.4% Among adult age 20-79 years . Nucleobindin-2 (NUCB2), the precursor of nesfatin-1, controls glucose homeostasis and nesfatin-1 secretion. The aim of this study is to evaluate serumNUCB2 levels in Iraqi adults with type2 diabetes mellitus**.** Eighty participants were included: 45 T2DM patients (23 males, 22 females; age 40–81 years, mean ± SD: 55.91 ± 12.00; median: 56) and 35 healthy controls (18 males, 17 females; age 40–60 years, mean ± SD: 47.43 ± 7.48; median: 45), all from Wasit Province, Iraq. ELISA was used to measure serum NUCB2 levels. Serum NUCB2 was significantly higher in T2DM patients (3.208 ± 0.225 ng/mL) than in controls (2.634 ± 0.043 ng/mL; P = 0.029). Male patients exhibited greater elevation (3.682 ± 0.414 ng/mL) than females (2.712 ± 0.080 ng/mL; P = 0.029), while healthy males and females had similar levels. **conclusion ,** NUCB2 plays an important role in metabolic regulation in type 2 diabetes mellitus, reflecting its contribution to glucose homeostasis and energy balance. Circulating NUCB2 levels are elevated in T2DM and may reflect early compensatory metabolic or endocrine adaptations, particularly in male patients.

Keywords: Nucleobindin-2(NUCB2), Nesfatin-1 , Type2 diabetes mellitus , Biomarkers , insulin resistance ,Iraq.

تقييم مستويات NUCB2 في مصل الدم لدى مرضى السكري مقابل الافراد الاصحاء

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الخلاصة

يُعدّ داء السكري من النوع الثاني (T2DM) مشكلة صحية عالمية مهمة، إذ تبلغ نسبة انتشاره 13.4٪ بين البالغين الذين تتراوح أعمارهم بين 20–79 سنة2024 ، .يُنظِّم البروتين الرابط للنيوكليوبيندين-2 (NUCB2)، وهو الطليعة السابقة للنيزفاتين-1، اتزان الغلوكوز وإفراز النيزفاتين-1. هدفت هذه الدراسة إلى تقييم مستويات NUCB2في مصل الدم لدى البالغين العراقيين المصابين بداء السكري من النوع الثاني.شملت الدراسة 80 مشاركًا: 45 مريضًا بداء السكري من النوع الثاني (23 ذكرًا و22 أنثى؛ تراوحت أعمارهم بين 40–81 سنة، بمتوسط ± انحراف معياري: 55.91 ± 12.00؛ والوسيط: 56)، و35 شخصًا سليمًا كمجموعة ضابطة (18 ذكرًا و17 أنثى؛ تراوحت أعمارهم بين 40–60 سنة، بمتوسط ± انحراف معياري: 47.43 ± 7.48؛ والوسيط: 45)، وجميعهم من محافظة واسط، العراق. استُخدمت تقنية المقايسة المناعية المرتبطة بالإنزيم (ELISA) لقياس مستويات NUCB2في مصل الدم.أظهرت النتائج أن مستويات NUCB2في المصل كانت أعلى بصورة معنوية لدى مرضى السكري من النوع الثاني (3.208 ± 0.225 نانوغرام/مل) مقارنةً بالمجموعة الضابطة (2.634 ± 0.043 نانوغرام/مل؛ P = 0.029). كما أظهر المرضى الذكور ارتفاعًا أكبر (3.682 ± 0.414 نانوغرام/مل) مقارنةً بالإناث (2.712 ± 0.080 نانوغرام/مل؛ P = 0.029)، في حين كانت مستويات NUCB2متقاربة بين الذكور والإناث الأصحاء.وفي الختام، يؤدي NUCB2دورًا مهمًا في التنظيم الأيضي لدى مرضى داء السكري من النوع الثاني، مما يعكس مساهمته في اتزان الغلوكوز وتوازن الطاقة. كما أن ارتفاع مستويات NUCB2المتداولة في الدم لدى مرضى السكري من النوع الثاني قد يعكس تكيفات أيضية أو صمّاوية تعويضية مبكرة، ولا سيما لدى المرضى الذكور.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) represents a global health crisis, affecting over 460 million adults worldwide in 2019, with projections exceeding 700 million by 2045 [1] . In Iraq, the prevalence has surged to 13.4% among adults aged 20-79 years in 2024, equating to approximately 2.7 million cases according to the International Diabetes Federation (IDF) Diabetes Atlas, positioning Iraq among high-burden nations in the Middle East and North Africa region. This rise stems from rapid urbanization, obesity, and genetic factors prevalent in Arab populations, where T2DM arises from insulin resistance, beta-cell dysfunction, and genetic variants like single nucleotide polymorphisms (SNPs) [2].

Nucleobindin-2 (NUCB2), expressed in pancreatic beta-cells and the hypothalamus, regulates glucose homeostasis by cleaving into nesfatin-1, which promotes insulin secretion and sensitivity [3,4] Genome-wide association studies (GWAS) and candidate gene studies have suggested that genetic variations in the NUCB2 gene may contribute to susceptibility to Type 2 Diabetes Mellitus (T2DM). Several studies have reported associations between NUCB2 polymorphisms and T2DM risk, as well as alterations in nesfatin-1 expression and glucose metabolism[5,6]. Recent studies have suggested that nesfatin-1 may function as a multifunctional peptide involved not only in metabolic regulation but also in neuroendocrine signaling pathways that integrate energy status with hormonal responses. Beyond its central hypothalamic expression, nesfatin-1 has been detected in peripheral tissues including the pancreas, stomach, and adipose tissue, indicating a broader systemic role than previously assumed. This wide tissue distribution supports the hypothesis that NUCB2-derived peptides may act as integrative signaling molecules linking central and peripheral metabolic regulation [7].

Moreover, recent clinical investigations have proposed that nesfatin-1 levels may reflect metabolic adaptation rather than being a direct causal factor in disease development. Variations in circulating nesfatin-1 concentrations have been observed across different metabolic states, suggesting its potential role as a dynamic biomarker responsive to physiological and pathological changes. This adaptive pattern indicates that nesfatin-1 may be involved in compensatory metabolic responses during early dysmetabolic conditions, making it a candidate marker for early metabolic disturbance detection [8].

In addition, emerging evidence indicates that NUCB2 gene regulation may be influenced by transcriptional and post-transcriptional mechanisms that affect nesfatin-1 availability. MicroRNA-mediated regulation and tissue-specific gene expression patterns have been proposed as potential modulators of NUCB2 activity, which may contribute to inter-individual variability in nesfatin-1 secretion. These regulatory mechanisms highlight the complexity of the NUCB2/nesfatin-1 system and its potential involvement in fine-tuning metabolic homeostasis [9].

The aim of this study is to evaluate serumNUCB2 levels in Iraqi adults with type2 diabetes mellitus.

2.Materials and methods

2.1 Study Design

A total of 80 participants were enrolled in this study using a convenience sampling approach. The study population included 45 clinically confirmed patients and 35 apparently healthy individuals who served as the control group.

The patient group consisted of 45 individuals diagnosed with type 2 diabetes mellitus (T2DM), aged between 40-81 years, patients mean age ± SD 55.911 ± 12.00,Median :56.All patients were residents of Wasit Province, Iraq, and included 23 males 22and females.

The control group comprised 35 healthy subjects (18males and 17 females) with an age range 40-60 years,(mean age±SD:47.428±7.480 , Median :45.These individuals were selected from the local community of Wasit Province, Iraq, and had no known history of T2DM or related chronic conditions.

All patients were diagnosed by a physician based on internationally accepted diagnostic criteria.

From each participant, 5 mL of blood was collected via venipuncture. The blood was placed in a tube without anticoagulant. Serum was separated by centrifugation at 2000 × g for 10 minutes, aliquoted into 2 mL Eppendorf tubes, and stored in a deep freezer until analysis of serum NUCB2 levels by ELISA using Human NUCB2 ELISA Kit, BT LAB Bioassay Technology Laboratory .

2.2 Sample Collection and Processing

A 5 mL of blood were collected in a tub via venipuncture of each participant. Serum was centrifuged at 2000 x g over a 10-minute centrifugation and then aliquoted in 2 mL Eppendorf tubes and stored in a deep freezer until serum NUCB2 levels are analysed by ELISA using NUCB2 humam ELISA kit BT LAB Bioassay Technology Laboratory .

2.3 Statistical Analysis

The data were analyzed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Serum NUCB2 levels were expressed as mean ± SE and compared using Student's t-test or ANOVA as appropriate. The level of significance was categorized as *Sig.* for significant difference ($P < 0.05$), *HS* for highly significant difference ($P < 0.01$), and *NS* for non-significant difference ($P > 0.05$).

3.Results

3.1 Comparative Analysis of NUCB2 *Serum Levels in T2DM Patients and Controls*

Table 1 presents the circulating levels of NUCB2 in type 2 diabetes patients and healthy controls (mean ± SE).

The mean serum NUCB2 level in the control group was 2.634 ± 0.043 ng/mL, whereas in the patient group, it was significantly higher at 3.208 ± 0.225 ng/mL. Statistical analysis revealed a P-value of 0.029, indicating a significant difference between patients and controls.

These results demonstrate that circulating NUCB2 levels are significantly elevated in patients with type 2 diabetes compared to healthy individuals, suggesting a potential role of NUCB2 in the pathophysiology or metabolic alterations associated with the disease.

Table 1-: Circulating NUCB2 in patients with type 2 diabetes and healthy controls (mean ± SE, P-value)

Parameters	Groups	ng/mL (Mean ± SE)	P-value	Significance
Serum NUCB2	Control	2.634 ± 0.043	0.029	*Sig.
	Patients	3.208 ± 0.225		

SE = standard error;ng = nanogram; *Sig .P-value < *0.05* indicates statistical significance

These findings suggests that NUCB2, a precursor of nesfatin-1, may be involved in the metabolic alterations characteristic of T2DM.

NUCB2/nesfatin-1 has been implicated in glucose metabolism and energy balance through its regulatory effects on insulin secretion and appetite control [10]. Additionally, nesfatin-1 is known to stimulate glucose-induced insulin secretion in vitro and enhance glucose homeostasis in animal models, indicating its physiological relevance in glycemic regulation [11] .

Human clinical studies have reported elevated plasma nesfatin-1 levels in newly diagnosed T2DM patients relative to non-diabetic controls, consistent with the current study's observation of increased NUCB2 levels in T2DM [12] . This elevation in early or untreated diabetes may reflect a compensatory response to hyperglycemia or insulin resistance, as nesfatin-1 secretion is upregulated under conditions of glucose challenge and may serve to counteract metabolic dysregulation [12] .

Systematic reviews have shown that while newly diagnosed or untreated diabetic individuals tend to exhibit higher nesfatin-1 levels, patients with long-standing disease or receiving antidiabetic therapy often display lower levels than controls [13] . This pattern suggests that disease duration, treatment status, and metabolic context critically influence NUCB2/nesfatin-1 concentrations in T2DM populations.

Taken together, the significant elevation of serum NUCB2 observed in this study aligns with research indicating an early-stage increase in circulating nesfatin-1 in T2DM, potentially reflecting compensatory endocrine responses to insulin resistance and hyperglycemia. Nevertheless, the variability seen across studies underscores the need to

consider disease stage, treatment effects, and population differences when interpreting circulating NUCB2/nesfatin-1 levels in metabolic disorders [12] , [13] .

3.2 Gender-Based Comparison of Circulating NUCB2 *Levels in T2DM*

Table 2 presents the circulating levels of NUCB2 in male and female type 2 diabetes patients and healthy controls (mean ± SE).

The results indicate that serum NUCB2 levels are elevated in type 2 diabetes patients compared to healthy controls. Male patients had a mean NUCB2 level of 3.682 ± 0.414 ng/mL, significantly higher than male controls (2.713 ± 0.05 ng/mL, P = 0.029). Female patients also showed higher NUCB2 levels (2.712 ± 0.080 ng/mL) compared to female controls (2.550 ± 0.069 ng/mL), but this difference was not statistically significant (P = 0.062, NS).

When comparing between sexes, no significant difference was observed between male and female healthy controls, indicating similar baseline NUCB2 levels. In contrast, male patients exhibited significantly higher NUCB2 levels than female patients, suggesting a sex-specific elevation associated with type 2 diabetes.

Circulating NUCB2 is increased in type 2 diabetes, with a more pronounced elevation in male patients. These findings suggest that NUCB2 may contribute to disease-related metabolic alterations and exhibit sex-specific patterns in patients, while baseline levels in healthy individuals remain comparable between sexes.

Table 2- Circulating NUCB2 levels among male and female type 2 diabetes patients and healthy controls (mean ± SE, P-value)

Parameters	**Groups**	**Male (ng/mL, Mean ± SE)**	**Female (ng/mL, Mean ± SE)**	**P-value (Male vs Female)**	**Significance level**
Serum NUCB2 level	Control	2.713 ± 0.05	2.550 ± 0.069	0.062	Ns.
	Diabetic Patients	3.682 ± 0.414	2.712 ± 0.080	0.029	*Sig.
P-value (vs. Control)		0.046	0.147		

SE = standard error;ng = nanogram; *Sig .P-value < 0.05 indicates statistical significance ;Ns. non-significant" indicate P ≥ 0.05.

Comparison between sexes among healthy controls indicated no significant differences, suggesting that baseline NUCB2 levels are similar between males and females [13] .

The sex-specific pattern observed, with higher NUCB2 in male patients, aligns with prior evidence that nesfatin-1 regulation may be influenced by sex hormones and metabolic state. Experimental and clinical studies have shown that circulating nesfatin-1 can exhibit

differential expression and physiological effects in males versus females, particularly in relation to energy balance, stress response, and metabolic disorders [14] .

While baseline levels in healthy individuals are comparable between sexes, disease-related metabolic disturbances, including insulin resistance, hyperglycemia, and altered adiposity, may amplify NUCB2 elevation in males more than females [12] . These findings suggest that NUCB2 may contribute to T2DM-related metabolic alterations and highlight the importance of sex-stratified analyses in understanding the endocrine and metabolic roles of nesfatin-1. Nevertheless, the variability observed across studies underscores the need for larger, multi-ethnic cohorts and mechanistic research to clarify the pathways underlying sex differences in circulating NUCB2 levels.

4.Conclusions

NUCB2 may play a significant role in the metabolic regulation associated with type 2 diabetes mellitus, reflecting its involvement in glucose homeostasis and energy balance.Circulating NUCB2 levels are elevated in T2DM and may reflect early compensatory metabolic or endocrine adaptations, particularly in male patients.

REFERENCES

[1] P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A. A. Motala, K. Ogurtsova, J. E. Shaw, D. Bright, and R. Williams, “Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045,” Diabetes Research and Clinical Practice, vol. 157, Art. no. 107843, 2019.

[2] International Diabetes Federation, IDF Diabetes Atlas, 11th ed. Brussels, Belgium: International Diabetes Federation, 2025.

[3] S. Oh-I, H. Shimizu, T. Satoh, N. Okada, M. Adachi, K. Inoue, Y. Eguchi, S. Yamamoto, K. Imaki, S. Hashimoto, T. Tsuchiya, and M. Mori, “Identification of nesfatin-1 as a satiety molecule in the hypothalamus,” Nature, vol. 443, no. 7112, pp. 709–712, 2006.

[4] Y. Zhang, Q. Li, H. Zhu, and Y. Wang, “Nesfatin-1 ameliorates insulin resistance,” Biochemical and Biophysical Research Communications, vol. 486, no. 2, pp. 373–378, 2017.

[5] X. S. Li, C. Y. Yan, Y. J. Fan, et al., “NUCB2 polymorphisms are associated with an increased risk for type 2 diabetes in the Chinese population,” Annals of Translational Medicine, vol. 8, no. 6, p. 290, 2020. doi:10.21037/atm.2020.03.02

[6] C. Wang, Y. Wang, and W. Hu, “Association of the polymorphism in NUCB2 gene and the risk of type 2 diabetes,” Diabetology & Metabolic Syndrome, vol. 9, p. 39, 2017. doi:10.1186/s13098-017-0235-z

[7] S. Ramesh, et al., "Peripheral distribution and multifunctional role of nesfatin-1 in metabolic regulation," Endocrine Research, 2016.
[8] S. Aydin, et al., "Circulating nesfatin-1 as a dynamic biomarker in metabolic disorders," Peptides, 2020.

[9] A. Stengel and Y. Taché, "Neuroendocrine regulation of NUCB2/nesfatin-1 and gene expression control mechanisms," Frontiers in Endocrinology, 2017. doi:10.3389/fendo.2017.00000

[10] E. Reyes-Lucía, A. Ramírez-Guerrero, C. González-Villaseñor, and N. Macías-Gómez, "Relationship between circulating nesfatin-1 and type 2 diabetes mellitus: A meta-analysis," Biomedica, vol. 45, no. 3, pp. 436–445, 2025.

[11] R. Gonzalez, B. K. Reingold, X. Gao, M. P. Gaidhu, R. G. Tsushima, and S. Unniappan, "Nesfatin-1 exerts a direct, glucose-dependent insulinotropic action on mouse islet β-cells and MIN6 cells," Journal of Endocrinology, vol. 208, no. 3, pp. R9–R16, 2011.

[12] Z. Zhang, L. Li, M. Yang, H. Liu, G. Boden, and G. Yang, "Increased plasma levels of nesfatin-1 in patients with newly diagnosed type 2 diabetes mellitus," Experimental and Clinical Endocrinology & Diabetes, vol. 120, no. 2, pp. 91–95, 2012.

[13] T. Zhai, S. Z. Li, X. T. Fan, Z. Tian, X. Q. Lu, and J. Dong, "Circulating nesfatin-1 levels and type 2 diabetes: A systematic review and meta-analysis," Journal of Diabetes Research, vol. 2017, Art. no. 7687098, 2017.

[14] T. Hofmann, U. Elbelt, A. Ahnis, M. Rose, B. F. Klapp, and A. Stengel, "Sex-specific regulation of NUCB2/nesfatin-1: Differential implication in obesity and metabolic disorders," Psychoneuroendocrinology, vol. 60, pp. 130–137, 2015.