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Original article

Emerging Roles of Asprosin and Nesfatin-1 in Uncontrolled Type 2 Diabetes

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Abstract
The global surge in diabetes and obesity underscores the role of adipokines. Asprosin disrupts glucose homeostasis, while nesfatin-1 may offer protective effects. This study investigated their serum levels in poorly controlled T2DM and associations with hyperglycemia and obesity. The study included 110 type 2 diabetes patients and 70 healthy controls, aged 40–70 years. Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) were measured using the Roche Cobas Integra 400 Plus. Serum asprosin and nesfatin-1 levels were quantified by ELISA, and body mass index (BMI) was calculated as weight/height². T2DM patients exhibited significantly higher serum levels of asprosin and nesfatin-1 compared to controls ($p < 0.001$). A significant positive correlation was observed between asprosin and nesfatin-1, as well as between nesfatin-1 and disease duration ($p = 0.01$). Serum asprosin was strongly associated with glucose levels, whereas neither biomarker showed a significant correlation with BMI. Elevated asprosin and nesfatin-1 levels in poorly controlled T2DM patients contribute to disease mechanisms. Increased nesfatin-1 represents a compensatory mechanism to mitigate insulin deficiency, highlighting its potential as a predictive biomarker.
Keywords: *Asprosin, Nesfatin-1, T2DM, Obesity, Glucose.*

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Introduction

Diabetes mellitus is a metabolic disease characterized by high blood glucose levels, caused by various factors [1,2]. It affects protein, fat, and carbohydrate metabolism due to insulin deficiencies [3]. Type 2 diabetes mellitus is the most common, accounting for 90% of global cases [4,5]. Environmental factors, including excessive calorie intake and sedentary lifestyles, result in obesity and insulin resistance, which is the primary defect in T2DM patients, causing hyperinsulinemia and compensatory increases in insulin production [6-8]. The protein profibrillin-1, which contains asprosin, is encoded by the *FBN1* gene and secreted in response to hunger. There are 140 amino acids in the protein [9], and the latter's C-terminus undergoes specific proteolysis to release it. It has also been demonstrated to promote appetite and fat accumulation by stimulating the hypothalamic feeding center [10]. Asprosin levels were discovered to be pathologically high in patients with obesity [11,12], insulin resistance [13,14], type 1 diabetes mellitus (T1DM) [15], and T2DM [16]. Furthermore, in T2DM, elevated asprosin levels have been associated with the atherosclerotic risk factor for cardiovascular disease as well as insulin resistance [16]. Because asprosin has a prediabetogenic action [3], it is important to remember that asprosin release can also be caused by hyperlipidaemia [17].

Nesfatin-1 is a peptide hormone that was identified in 2006 [18] and is composed of 82 amino acids. Originating from precursors of nucleobindin 2 (NUCB2), nesfatin-1 is a calcium and DNA-binding peptide. It is expressed by peripheral tissues such as the digestive system and adipose tissue, as well as the central and peripheral neurological systems [19–21]. It is secreted by endocrine cells such as mucosal cells and beta cells of the stomach, intestines, and pancreas [19]. Nesfatin-1 is marketed as a possible catabolic agent that might regulate body weight and potentially balance energy levels. It contains a lot of chemical messengers that reduce hunger. After a meal, the circulatory system's level of nesfatin-1/NUCB2 rises, and during a fast, it falls. Through melanocortin signals, it has an impact on food intake that is not dependent on the leptin pathway [21]. It is believed to be a G-protein coupled receptor (GPCR) even though its receptor has not yet been identified [22]. Asprosin and nesfatin-1 are important in the Iraqi population because they are biomarkers for metabolic diseases like type 2 diabetes, obesity, and cardiovascular disease, which are prevalent in the region [23]. The purpose of this study is to determine the levels of nesfatin-1 and asprosin in the serum of patients with T2DM by comparing them to controls who appear to be in good health and to determine whether there is a relationship between the study's parameters and obesity.

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Methods

Study Population

This study included 110 patients with type 2 diabetes mellitus (T2DM), aged between 40 and 70 years with a mean age of 55.18 ± 8.44 years. Among them, 38 were men and 72 were women. The control group consisted of 70 apparently healthy individuals matched for age (mean 54.90 ± 8.98 years), including 24 men and 46 women. Recruitment of patients and controls took place between February 2023 and July 2024 at the Internal Medicine Unit of Baquba Teaching Hospital, Diyala, Iraq.

Diagnostic and Classification Criteria

Diagnosis of T2DM was based on the standards of the American Diabetes Association (ADA), while patients were categorized according to body mass index (BMI) using World Health Organization (WHO) criteria. The mean duration of diabetes in the patient group was 8.8 ± 4.1 years.

Sample Collection

Blood samples were collected intravenously using disposable 5 mL syringes after an overnight fast of 8–10 hours. The first milliliter of blood was placed into EDTA tubes for HbA1c determination, while the remaining 4 mL was transferred into gel tubes for serum separation. Serum was used immediately for fasting plasma glucose determination, while the remainder was stored at −20°C until further analysis of asprosin and nesfatin-1.

Laboratory Analyses

The concentrations of asprosin and nesfatin-1 were measured using the enzyme-linked immunosorbent assay (ELISA) method (MyBioSource, USA). Fasting plasma glucose and HbA1c were determined with the Roche Diagnostics Cobas Integra 400 Plus auto-analyzer. Additional demographic and clinical data were also collected, including sex, age, marital status, disease duration, age at onset, treatment received, family history, and previous medical or surgical history.

Exclusion criteria

Patients with T1DM, those with neurological illnesses, those with liver or kidney disease, and those with other autoimmune diseases such as Hashimoto's thyroiditis are excluded. those receiving cortisol medication, pregnant women, those with a history of acute or chronic infections, and those with any other chronic illnesses.

Ethical Clearance

Each subject group received a separate explanation of the purpose and methods of the study. In order to participate in the study, they granted their consent. The Diyala Health Department-Training and Human Development Centre Research Committee (No.30887). gave its approval for the project.

Results

Patients with Type 2 diabetes mellitus (T2DM) had significantly higher mean concentrations of Asprosin and Nesfatin-1 ($p < 0.001$) than those who appeared to be in good condition. When comparing patients to control subjects, the mean difference in HbA1c and fasting plasma glucose (FPG) was substantially greater ($p < 0.001$). The patient's mean BMI concentration was greater (29.41±4.36) than that of the control group, but there was not a significant difference ($p = 0.064$) (Table 1) and (Figure 1).

Table 1: Comparison of the mean values of the study's parameters between patients and controls.

Variables	Groups	Mean± SD	P value
Asprosin (ng/ml)	Control	3.91± 0.55	< 0.001
	Patients	8.84± 2.11	
Nesfatin-1 (pg/ml)	Control	158.57± 12.60	< 0.001
	Patients	286.80± 64.02	

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Glucose (mg/dl)	Control	101.71± 9.26	< 0.001
	Patients	275.58± 75.19	
HbA1c (%)	Control	5.41± 0.51	< 0.001
	Patients	10.47± 2.00	
BMI kg/m2	Control	28.13± 4.66	0.064
	Patients	29.41± 4.36	

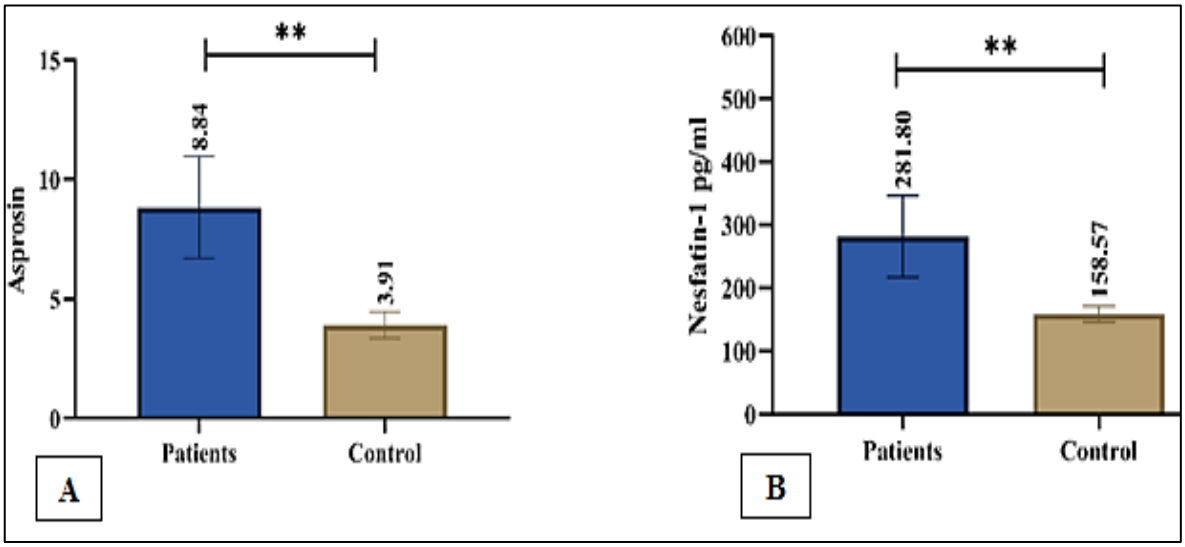

Figure 1: Mean differences in (A) asprosin and (B) nesfatin-1 levels between T2DM patients and healthy controls.

Correlation Analysis of Variables Among T2DM Patients

Asprosin and nesfatin showed a significant positive correlation in T2DM patients (r = 0.44 and p = 0.001) (Figure 2). Serum nesfatin-1 showed a significant positive correlation with the duration of T2DM (r = 0.24 and p = 0.01), as was the case with asprosin and the fasting plasma glucose (FPG) level in the patient's serum (r = 0.21 and p = 0.02). HbAIc and BMI did not significantly correlate. Nesfatin-1 did not significantly correlate with glucose, HbA1c, or BMI (Table 2).

Table 2: Correlation coefficients between the studied parameters and glucose, HbA1c, BMI, and disease duration in patients with diabetes mellitus.

Variables		Nesfatin-1	FPG	HbA1c	BMI	Disease Duration
Asprosin ng/ml	r	0.44	0.21	0.09	0.26	0.15
	p	0.001 *	0.02*	0.35	0.92	0.11
Nesfatin-1 pg/ml	r		0.02	0.12	-0.18	0.24
	p		0.80	0.22	0.08	0.01*
*Correlation is significant at 0.05						

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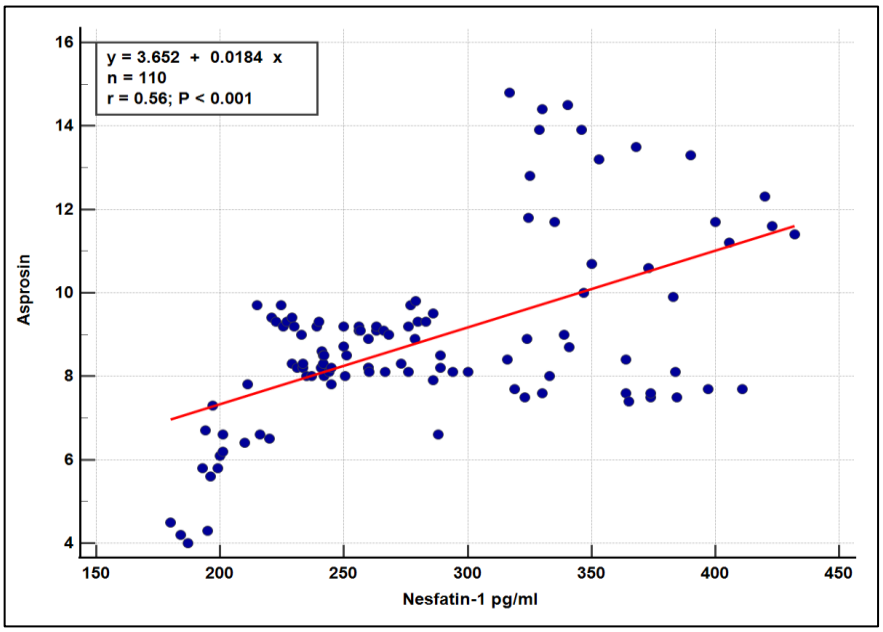

Figure 2: Scatterplots of asprosin and nesfatin-1 with fitted correlation lines.

ROC Curve Analysis of Asprosin and Nesfatin-1

ROC curve analysis demonstrated that asprosin had an area under the curve (AUC) of 0.990 ± 0.0052 ($p < 0.0001$), indicating excellent discriminatory ability between T2DM patients and healthy controls. At a cut-off value of >4.86, asprosin achieved a projected sensitivity of 96.36% and specificity of 98.57% (Figure 3A). Similarly, nesfatin-1 showed an AUC of 0.998 ± 0.0142 ($p < 0.0001$), with a cut-off value >190.8 providing a projected sensitivity of 97.27% and specificity of 100% (Figure 3B). These findings suggest that both biomarkers, particularly nesfatin-1, are highly effective in distinguishing T2DM patients from healthy individuals.

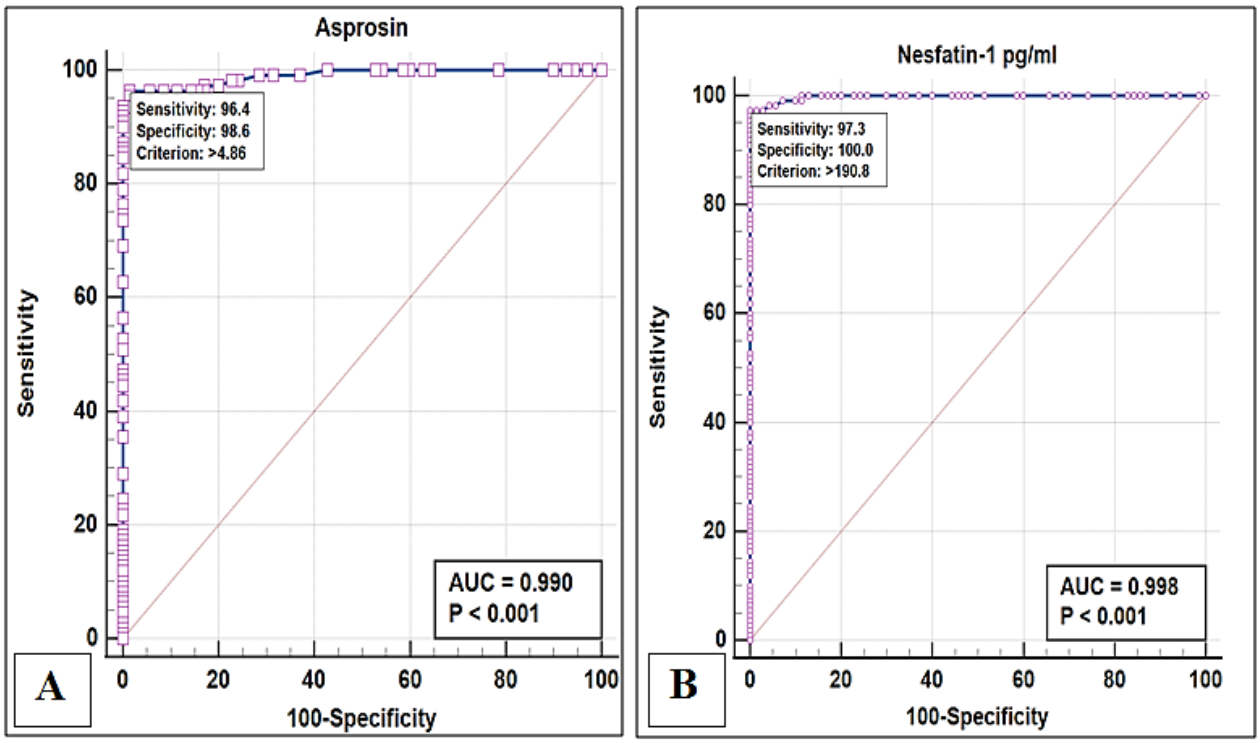

Figure 3 (A & B): Illustrates the ROC curves for nesfatin-1 and Asprosin, highlighting their ability to differentiate between patients and controls.

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Discussion

In this experiment, we assessed the blood asprosin and nesfatin-1 levels in a group of individuals with Type 2 diabetes mellitus (T2DM) and their correlation with plasma glucose concentration, HbA1c, and BMI. Glucose levels and asprosin levels are closely associated. While high glucose levels, as in the feeding state, limit asprosin synthesis, low glucose levels during the fasting state maintain it. Asprosin levels vary according to the circadian rhythm; they rise sharply after an overnight fast and then fall after eating [24]. Recombinant asprosin enhances the inflammatory response in a dose-dependent manner [25]. Due to this, myocytes' insulin sensitivity is impaired by asprosin due to the promotion of inflammation and endoplasmic reticulum stress, resulting in IR in skeletal muscle [26]. Apart from its association with T2DM, researchers have investigated the various roles of asprosin in different diseases. The proposed mechanism by which nesfatin-1 affects glucose metabolism is by improving insulin sensitivity and reducing IR. The production of nesfatin-1 and NUCB2 in the β-cells of the pancreas has a potential effect on the regulation of insulin secretion [27]. Where the effect of nesfatin-1 on insulin is affected by the concentration of glucose in the blood and the NUCB2/nesfatin-1 is released, the pancreas can increase the response to glucose and thus increase the secretion of insulin caused by glucose [28]. The results in the present study are in agreement with other studies have shown there is a significant correlation between serum concentration of asprosin and concentration of FPG [29,30]. Asprosin is considered as a highly sensitive biomarker of T2DM and obesity [31]. As reported by Zhang [32], high asprosin levels are a risk factor for type 2 diabetes; moreover, individuals with type 2 diabetes exhibit aberrant asprosin release in reaction to glucose fluctuations [33]. Nesfatin-1 and FPG, HbA1c, and BMI did not significantly correlate in the group of patients and controls with type 2 diabetes, according to these results, which were in agreement with findings from another study [34]. IR can occur in adipose tissue; it is an important aspect of the development of metabolic disorders, including obesity and T2DM and humans with IR have elevated asprosinemia [35]. Since there is a close relationship between nesfatin-1 and medical variables that occur with IR, such as high blood sugar, insulin, obesity, and blood pressure, this may explain the significant correlation between asprosin and nesfatin-1 [36]. While there is no direct correlation between nesfatin-1 and asprosin, both hormones are involved in the regulation of appetite and energy balance. Nesfatin-1 reduces food intake, while asprosin can increase it. Therefore, it is possible that these two hormones may interact in the complex network of signals that regulate food intake and energy balance. However, further research is needed to fully understand the relationship between nesfatin-1 and asprosin. The accuracy of asprosin and nesfatin-1 as biomarkers for pathogenesis and hyperglycemia was assessed using the area under the curve (AUC). The ROC curve was used to evaluate the diagnostic utility of serum asprosin and nesfatin-1 for the pathophysiology of type 2 diabetes mellitus. The ROC for blood asprosin and nesfatin-1 levels is important for separating cases from controls and is very accurate in separating T2DM patients from controls. The AUC values for distinguishing between the two research groups showed that blood asprosin and nesfatin-1 levels are sensitive and trustworthy biomarkers for the complications in type 2 diabetes, with over 96% projected sensitivity and over 97% projected specificity at various cutoff values.

Conclusion

As T2DM progresses, serum levels of asprosin and nesfatin-1 rise. Asprosin may serve as a marker to distinguish T2DM patients from healthy individuals, while elevated nesfatin-1 likely represents a compensatory response to insulin deficiency. Both biomarkers hold potential as predictive indicators of disease progression and insulin resistance in T2DM.

Conflict of interest. Nil

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