Serum Nesfatin-1 and Ghrelin Levels in Relation to Glucose and Lipid Metabolism and Type 2 Diabetes Mellitus Progression: A Postprint

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Abstract

Background: Food intake and energy expenditure are dually regulated by hypothalamic and peripheral neural signals. The hypothalamic neurofactor Nesfatin-1 plays an important role in inhibiting food intake, while Ghrelin secreted by the gastrointestinal mucosa promotes food intake. However, their roles in the progression of obesity and diabetes remain unclear.

Objective: To investigate the correlations of Nesfatin-1 and Ghrelin with blood glucose, insulin resistance, and blood lipids, analyze their potential involvement in glucose and lipid metabolism, and provide new insights for the prevention and treatment of metabolic diseases such as diabetes and obesity.

Methods: One hundred seventy patients with type 2 diabetes mellitus (T2DM) hospitalized in the Department of Endocrinology, First Affiliated Hospital of Baotou Medical College from January 2020 to February 2021 were selected as the experimental group, and 85 healthy individuals undergoing physical examination during the same period served as the control group. General information and clinical parameters of both groups were collected. Serum levels of Nesfatin-1 and Ghrelin were measured by enzyme-linked immunosorbent assay (ELISA). Pearson correlation analysis and Spearman rank correlation analysis were used to explore the correlations of Nesfatin-1 and Ghrelin with glucose and lipid metabolism, diabetic chronic complications, and diabetes duration. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of Nesfatin-1 and Ghrelin for diabetes diagnosis.

Results: Nesfatin-1 was negatively correlated with glycated hemoglobin (HbA1c), fasting blood glucose, BMI, high-density lipoprotein cholesterol (HDL-C), homeostasis model assessment of insulin resistance (HOMA-IR), visceral fat area (VFA), and subcutaneous fat area (SFA) [r(rs) = -0.58, -0.59, -0.51, -0.26, -0.23, -0.37, -0.27, $P<0.05$], whereas Ghrelin was positively

correlated with the above indicators [r(rs) = 0.41, 0.41, 0.43, 0.15, 0.24, 0.50, 0.30, P<0.05]. Serum Nesfatin-1 level in the T2DM group was lower than that in the control group, while Ghrelin level was higher, with statistically significant differences (P<0.001). The area under the ROC curve (AUC) of Ghrelin for predicting T2DM was 0.861 (95%CI = 0.816~0.906), with an optimal cutoff value of 30.328 g/L. The AUC value of Nesfatin-1 for predicting T2DM was 0.764 (95%CI = 0.704~0.824), with an optimal cutoff value of 78.579 g/L.

Conclusion: Nesfatin-1 and Ghrelin regulate glucose and lipid metabolism by influencing multiple aspects such as blood glucose levels and insulin resistance, and possess predictive value for diabetes diagnosis.

Full Text

Correlation Analysis of Serum Nesfatin-1 and Ghrelin Levels with Glucose and Lipid Metabolism and the Progression of Type 2 Diabetes Mellitus

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Abstract

Background
Food intake and energy expenditure are regulated by both hypothalamic and peripheral neural signals. The hypothalamic neuropeptide Nesfatin-1 plays an important role in inhibiting food intake, while Ghrelin secreted by the gastrointestinal mucosa promotes feeding. However, the roles of these two factors in the progression of obesity and diabetes remain unclear.

Objective
To investigate the correlation between Nesfatin-1, Ghrelin and blood glucose, insulin resistance, and blood lipids, and to analyze their potential involvement in glucose and lipid metabolism, providing new insights for the prevention and treatment of metabolic diseases such as diabetes and obesity.

Methods
A total of 170 patients with type 2 diabetes mellitus (T2DM) hospitalized in the Department of Endocrinology at the First Affiliated Hospital of Baotou Medical College between January 2020 and February 2021 were selected as

the experimental group, along with 85 healthy individuals undergoing physical examinations during the same period as the control group. General clinical data and laboratory parameters were collected from both groups. Serum Nesfatin-1 and Ghrelin levels were measured by enzyme-linked immunosorbent assay. Pearson correlation analysis and Spearman rank correlation analysis were used to explore the relationships between Nesfatin-1, Ghrelin and glucose/lipid metabolism, chronic diabetic complications, and disease duration. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of Nesfatin-1 and Ghrelin in diabetes diagnosis.

Results

Nesfatin-1 levels were negatively correlated with glycated hemoglobin (HbA1c), fasting plasma glucose, BMI, high-density lipoprotein cholesterol (HDL-C), homeostatic model assessment of insulin resistance (HOMA-IR), visceral fat area (VFA), and subcutaneous fat area (SFA) [r(rs) = -0.58, -0.59, -0.51, -0.26, -0.23, -0.37, -0.27, respectively; $P < 0.05$]. Ghrelin levels showed positive correlations with these same indicators [r(rs) = 0.41, 0.41, 0.43, 0.15, 0.24, 0.50, 0.30, respectively; $P < 0.05$]. Serum Nesfatin-1 levels were significantly lower in the T2DM group compared to the control group, while Ghrelin levels were significantly higher ($P < 0.001$). The area under the ROC curve (AUC) for Ghrelin in predicting T2DM was 0.861 (95% CI = 0.816–0.906) with an optimal cutoff value of 30.328 g/L. For Nesfatin-1, the AUC was 0.764 (95% CI = 0.704–0.824) with an optimal cutoff value of 78.579 g/L.

Conclusion

Nesfatin-1 and Ghrelin regulate glucose and lipid metabolism by influencing blood glucose levels, insulin resistance, and other metabolic parameters, demonstrating predictive value for diabetes diagnosis.

Keywords

Metabolic diseases; Nesfatin-1; Ghrelin; Glucose and lipid metabolism; Type 2 diabetes mellitus; Obesity

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Introduction

Glucose and lipid metabolism are essential for health, and unhealthy lifestyle factors such as overeating, nutritional imbalance, and physical inactivity can easily disrupt metabolic homeostasis. Diabetes mellitus is a metabolic disease, with type 2 diabetes mellitus (T2DM) characterized by insulin resistance as the main pathological feature, accounting for the majority of diabetes cases. The dual epidemic of obesity and T2DM worldwide represents a major public health concern. The global incidence of diabetes is rising, with projections indicating a 25% increase by 2030 and a 51% increase by 2045. Obesity is primarily caused by an imbalance between food intake and energy expenditure. As glucose and lipids are the main sources of energy, a deeper understanding of their homeostatic regulatory mechanisms is crucial for the prevention and

control of metabolic diseases.

Food intake and energy expenditure are mainly regulated by the hypothalamus, which is closely related to the development and progression of obesity. The arcuate nucleus (ARC) in the basal hypothalamus contains various neurons that regulate appetite signals, including orexigenic neuropeptide Y (NPY), agouti-related protein (AGRP), opioid peptides, and γ-aminobutyric acid (GABA), as well as anorexigenic pro-opiomelanocortin (POMC) and its derivatives. These neurons can specifically activate POMC, AGRP, and melanocortin-3/4 receptor neurons in hypothalamic nuclei, and can regulate insulin secretion and fat metabolism. Research on the mechanisms of feeding-related factors can provide new biomarkers and therapeutic targets for the clinical diagnosis, prevention, and treatment of obesity and diabetes.

In recent years, Nesfatin-1 and Ghrelin have attracted widespread attention as two novel biomarkers. Nesfatin-1 is a negative regulator of glucose levels that plays a role in glucose homeostasis and participates in adipocyte differentiation, regulating both glucose and lipid metabolism. Ghrelin, known as the "hunger hormone," is primarily produced by gastric mucosal cells, with small amounts also released by the small intestine, pancreas, and brain. It can stimulate appetite, increase food intake, promote fat storage, and plays an important role in regulating systemic glucose and energy homeostasis. Nesfatin-1 and Ghrelin are closely related to glucose and lipid metabolism and the development of T2DM, and have potential associations with diabetes duration, disease control, and chronic complications, though their mechanisms of action remain unclear. Through correlation analysis of serum Nesfatin-1 and Ghrelin levels with glucose, lipid metabolism, and obesity, this study explores the in vivo mechanisms of Nesfatin-1 and Ghrelin to deepen understanding of energy balance and appetite regulation, and to provide a reference basis for developing new drugs or treatment regimens.

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1. Subjects and Methods

1.1 Study Subjects A total of 170 patients with T2DM hospitalized in the Department of Endocrinology at the First Affiliated Hospital of Baotou Medical College between January 2020 and February 2021 were selected as the experimental group, and 85 healthy individuals served as the control group. This study was approved by the Human Research and Ethics Committee of the First Affiliated Hospital of Baotou Medical College [Ethics Approval No. (2024) 016] and conducted in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent.

Inclusion criteria for the experimental group: Diagnosis of T2DM was based on the *Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition)*, defined as: (1) typical diabetes symptoms

plus random plasma glucose $\geq$ 11.1 mmol/L; or (2) fasting plasma glucose $\geq$ 7.0 mmol/L; or (3) 2-hour plasma glucose $\geq$ 11.1 mmol/L during oral glucose tolerance test; or (4) HbA1c $\geq$ 6.5%.

Inclusion criteria for the control group: (1) Fasting plasma glucose between 3.9–6.1 mmol/L and 2-hour postprandial glucose $<$ 7.8 mmol/L; (2) HbA1c $<$ 6.5%; (3) Total cholesterol (TC), low-density lipoprotein (LDL), and triacylglycerol (TG) levels within normal ranges, and high-density lipoprotein (HDL) within normal range; (4) Blood pressure: systolic 90–140 mmHg, diastolic 60–90 mmHg (1 mmHg = 0.133 kPa); (5) BMI between 18.5–23.9 kg/m^2; (6) Normal urinalysis without proteinuria.

Exclusion criteria: (1) Other genetic metabolic diseases, endocrine disorders, or central nervous system diseases; (2) Type 1 diabetes or special types of diabetes; (3) Acute diabetic complications; (4) Hepatic or renal insufficiency; (5) Severe cardiovascular or cerebrovascular diseases; (6) Malignant tumors; (7) Pregnant or lactating women; (8) Eye diseases such as cataracts or glaucoma that interfere with fundus photography.

1.2 Data Collection 1.2.1 General Information

Subjects avoided strenuous exercise within 24 hours before blood collection and fasted overnight. Height and weight were measured the next morning without shoes or hats and wearing light clothing. Basic patient information was collected through the electronic medical record system, including gender, age, diabetes duration, medication use, abdominal ultrasound results, waist circumference, hip circumference, waist-to-hip ratio, systolic blood pressure, diastolic blood pressure, hypertension, hyperlipidemia, coronary heart disease, and cerebral infarction.

1.2.2 Laboratory Examinations

Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured non-invasively using bioelectrical impedance analysis. Diabetic retinopathy (DR) was assessed through funduscopic examination of retinal microvascular lesions, observing the extent and severity of lesions. Diabetic nephropathy (DN) was evaluated using the urinary microalbumin-to-creatinine ratio. Diabetic peripheral neuropathy (DPN) was assessed through nerve conduction studies and electromyography to examine motor nerve damage and muscle atrophy. Diabetic peripheral vascular disease (DPVD) was evaluated using the ankle-brachial index (ABI) to detect lower extremity circulation.

Fasting venous blood samples were collected from subjects, and serum was separated. Serum glucose, low-density lipoprotein cholesterol (LDL-C), HbA1c, high-density lipoprotein cholesterol (HDL-C), TC, and TG levels were measured using a cobas c8000 automatic biochemical immunoanalyzer. Fasting insulin (FI) and fasting plasma glucose (FPG) were measured, and insulin resistance index (HOMA-IR) was calculated using the formula: HOMA-IR = (FI $\times$ FPG) / 22.5. Serum Ghrelin and Nesfatin-1 levels were measured by enzyme-linked

immunosorbent assay. All tests were performed in the laboratory of the First Affiliated Hospital of Baotou Medical College.

1.3 Statistical Methods Statistical analysis was performed using SPSS 21.0 software. Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using independent samples t-test. Non-normally distributed continuous data were expressed as median (P25, P75) and compared using one-way ANOVA. Correlations between Nesfatin-1, Ghrelin and various parameters were analyzed using Pearson correlation analysis for normally distributed data and Spearman rank correlation analysis for non-normally distributed data. Receiver operating characteristic (ROC) curves were used to evaluate the performance of Nesfatin-1 and Ghrelin in predicting T2DM diagnosis, and the area under the ROC curve (AUC) was calculated for comparison. $P < 0.05$ was considered statistically significant.

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2. Results

2.1 Comparison of General Data A total of 255 subjects completed the assessment, including 170 in the T2DM group (92 males [54%], 78 females [46%]; mean age 56.0 ± 11.8 years) and 85 in the control group (41 males [48%], 44 females [52%]; mean age 42.6 ± 12.0 years). There were no significant differences between the two groups in gender distribution, diastolic blood pressure, or fatty liver ($P > 0.05$). However, significant differences were observed in age, waist circumference, hip circumference, waist-to-hip ratio, systolic blood pressure, VFA, SFA, hypertension, hyperlipidemia, coronary heart disease, cerebral infarction, and BMI ($P < 0.05$) .

2.2 Comparison of Clinical Blood Indicators Between Groups The T2DM group had significantly higher levels of HbA1c, FPG, HOMA-IR, TG, TC, and Ghrelin compared to the control group ($P < 0.05$). In contrast, the T2DM group had significantly lower levels of fasting C-peptide, HDL-C, serum creatinine, and Nesfatin-1 ($P < 0.05$). There were no significant differences in serum uric acid or LDL-C between the two groups ($P > 0.05$) .

2.3 Correlation Analysis of Serum Nesfatin-1 and Ghrelin Levels with Glucose and Lipid Metabolism Correlation analysis revealed that Nesfatin-1 levels were negatively correlated with HbA1c, FPG, HOMA-IR, BMI, VFA, SFA, and HDL-C ($P < 0.05$), and positively correlated with serum uric acid ($P < 0.01$). No significant correlations were found between Nesfatin-1 and fasting C-peptide, age, TC, TG, LDL-C, blood pressure, serum creatinine, waist circumference, hip circumference, waist-to-hip ratio, hypertension, hyperlipidemia, coronary heart disease, or cerebral infarction ($P > 0.05$) .

Ghrelin levels were positively correlated with fasting C-peptide, HbA1c, FPG, HOMA-IR, BMI, VFA, SFA, and HDL-C ($P < 0.05$), and negatively correlated

with serum uric acid ($P < 0.01$). No significant correlations were observed between Ghrelin and age, LDL-C, TC, TG, hypertension, serum creatinine, waist circumference, hip circumference, waist-to-hip ratio, hyperlipidemia, coronary heart disease, or cerebral infarction ($P > 0.05$) .

2.4 Relationship Between HbA1c, Diabetes Duration, Chronic Complications and Serum Nesfatin-1, Ghrelin Levels Based on the *Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus (2020 Edition)*, T2DM patients were divided into three subgroups according to HbA1c levels: HbA1c $< 7\%$, $7\% \leq$ HbA1c $\leq 9\%$, and HbA1c $> 9\%$. No significant differences in serum Nesfatin-1 or Ghrelin levels were found among these three subgroups ($P > 0.05$) .

Based on the interquartile range (IQR) of diabetes duration in the T2DM group, patients were divided into four subgroups: duration ≤ 2 years, $2 <$ duration ≤ 5 years, $5 <$ duration ≤ 11 years, and duration > 11 years. No significant differences in serum Nesfatin-1 or Ghrelin levels were observed among these four subgroups ($P > 0.05$) .

T-test analysis showed no significant differences in Nesfatin-1 or Ghrelin levels between patients with and without diabetic nephropathy (DN vs. NDN) , diabetic retinopathy (DR vs. NDR) , diabetic peripheral neuropathy (DPN vs. NDPN) , or diabetic peripheral vascular disease (DPVD vs. NDPV) ($P > 0.05$) .

2.5 Diagnostic Value of Serum Nesfatin-1 and Ghrelin Levels for T2DM ROC curve analysis showed that the AUC values for Nesfatin-1 and Ghrelin in diagnosing T2DM were 0.764 (95% CI = 0.704–0.824, $P < 0.001$) and 0.861 (95% CI = 0.816–0.906, $P < 0.001$), respectively. The optimal cutoff values were 78.579 g/L for Nesfatin-1 and 30.328 g/L for Ghrelin, with sensitivities of 0.453 and 0.941 and specificities of 0.953 and 0.649, respectively [Figure 1: see original paper].

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3. Discussion

Nesfatin-1 and Ghrelin are two hormones that have attracted considerable attention in the biomedical field in recent years. Nesfatin-1 is an 82-amino acid neuropeptide that reduces food intake, regulates energy balance, and decreases body weight. Studies have shown that Nesfatin-1 is closely associated with metabolic diseases such as obesity and diabetes, and its abnormal expression may lead to insulin resistance and lipid metabolism disorders. Ghrelin is an appetite-stimulating hormone containing 28 amino acid residues, primarily secreted by P/D1 cells in the gastric fundus, which promotes food intake, reduces energy expenditure, and increases body weight. It is closely associated with various growth and developmental disorders.

The present study found that serum Nesfatin-1 levels in diabetic patients were significantly lower than those in healthy individuals and were negatively correlated with HbA1c, fasting plasma glucose, and BMI. These findings indicate that as Nesfatin-1 levels decrease, patients' blood glucose levels and BMI gradually increase, thereby elevating the risk of developing diabetes. Similar results have been reported by Li et al. and KHALIL et al., who confirmed that fasting plasma Nesfatin-1 levels in T2DM patients were significantly lower than in healthy subjects. Nesfatin-1 can regulate insulin sensitivity in the brain and promote insulin secretion, thereby maintaining glucose homeostasis. However, some studies have reported no significant correlation between Nesfatin-1 levels and fasting glucose, or even elevated Nesfatin-1 levels in overweight and obese individuals, which may be related to pathophysiological processes such as chronic low-grade inflammation and oxidative stress.

Regarding lipid metabolism, few studies have directly examined the relationship between Nesfatin-1 and specific lipid indicators. Nesfatin-1' s role in regulating energy balance and body weight indirectly affects lipid metabolism. Since Nesfatin-1 can inhibit food intake and reduce body weight, it helps decrease fat accumulation. In overweight and obese individuals, elevated Nesfatin-1 levels may represent a compensatory response to counteract obesity-related pathophysiological processes.

Ghrelin is a potent stimulator of caloric intake, promoting carbohydrate metabolism and fat accumulation. It is secreted by the gastric mucosa during negative energy balance and in anticipation of regular meals. This study demonstrated that Ghrelin levels were positively correlated with HbA1c, fasting plasma glucose, BMI, insulin resistance index, and visceral fat area (VFA). As Ghrelin levels increased, both HOMA-IR and VFA showed upward trends, suggesting that Ghrelin may influence insulin resistance and fat distribution. Ghrelin binds to its receptor GHSR-1a, releasing neuropeptide Y and affecting agouti-related protein in hypothalamic arcuate nucleus neurons, thereby triggering hunger and feeding behavior. This mechanism further illustrates that Ghrelin can promote food intake and weight gain. Additionally, Ghrelin can regulate glucose and lipid metabolism by affecting the expression of the intracellular nutrient-energy sensor AMPK and the GHSR-ERK1/2-PI3K-PKB pathway, further promoting fat accumulation. Therefore, elevated Ghrelin levels may contribute to the development and progression of obesity and diabetes by enhancing food intake, promoting fat accumulation, and exacerbating insulin resistance. NGUYEN et al. similarly confirmed the correlation between Ghrelin levels and visceral fat.

The specific mechanisms through which Ghrelin affects insulin resistance remain controversial. ZANG et al. found a strong negative correlation between acylated Ghrelin levels and excessive body fat mass and insulin resistance, while TAM et al. discovered that unacylated Ghrelin could restore impaired insulin signaling and autophagy in skeletal muscle of diabetic mice. These findings suggest that Ghrelin' s effects on insulin resistance are complex, involving interactions among

multiple signaling pathways that require further investigation.

This study found no significant association between Nesfatin-1 and Ghrelin with diabetes duration and its complications. This may be because diabetes pathogenesis is complex, involving interactions among multiple factors, with Nesfatin-1 and Ghrelin representing only one part of the picture. Additionally, the limited sample size may not have been sufficient to fully reflect the overall situation. Future studies should expand the sample size and consider more factors that may influence diabetes duration and complications to more comprehensively explore the roles of Nesfatin-1 and Ghrelin in diabetes.

The limitations of this study include its relatively small sample size, which requires further expansion to validate the relationships between Nesfatin-1, Ghrelin levels and glucose/lipid metabolism and obesity to make the conclusions more convincing. Regarding baseline age characteristics, the T2DM group was older, which, although consistent with the trend of increasing diabetes prevalence with age, makes it difficult to exclude the confounding effect of age on the expression levels of these two factors. Therefore, larger sample sizes are needed to explore the relationship between T2DM and Nesfatin-1/Ghrelin under more standardized age-matched conditions. Furthermore, this study used HbA1c as the primary single indicator to evaluate diabetes status, which is representative and scientific for objectively reflecting disease control. However, the specific medication regimens were not analyzed in detail as subgroup variables, which may introduce some bias. In clinical practice, the case group had numerous treatment regimens involving hypoglycemic, antihypertensive, and lipid-lowering agents, with various formulations (oral and injectable) and combinations (monotherapy, polytherapy, combination therapy) with individualized dosing. Attempting to perform subgroup analysis by medication regimen resulted in too many groups with small sample sizes, making it difficult to draw representative conclusions. Therefore, further comprehensive and in-depth studies to reveal the effects of different medications on Nesfatin-1 and Ghrelin levels will be a direction for future research.

In summary, Nesfatin-1 and Ghrelin play important roles in glucose and lipid metabolism and body weight regulation. This study confirms their close correlation with metabolic risk factors and their diagnostic and predictive value for T2DM, which has important clinical significance for the prevention and treatment of metabolic diseases such as obesity and diabetes. Future research should focus on the trends of Nesfatin-1 and Ghrelin in newly diagnosed T2DM patients, individuals with impaired fasting glucose regulation, and prediabetic populations with abnormal glucose tolerance.

Author Contributions

Zhang Yunuò: Data collection and organization, statistical analysis, figure and table preparation, drafting of the manuscript.

Li Ruìbīn: Quality control and review of the article, revision of the manuscript. Wang Wěi: Conceptualization and design of the study, overall responsibility for the article.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.