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Association of Serum Neudesin Levels with Insulin Resistance, Metabolic Dysregulation, and Inflammatory Status in Adult Males with Type 2 Diabetes Mellitus

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ABSTRACT

There is emerging evidence that T2DM can be categorized as a systemic metabolic-inflammation condition with features of insulin resistance-induced stress, obesity, and deterioration of neuro-metabolic homeostasis. Neudesin, a neurotrophic factor involved in regulation of energy metabolism and metabolic signals, was considered as an important modulator of metabolic adaptation processes recently. To evaluating the connection between serum Neudesin concentration and metabolic-inflammatory status of T2DM in adults men. This case control study involved 90 adult male participants including 45 cases of T2DM and 45 healthy controls. Measurement of serum Neudesin level was carried out using ELISA method. Glycemic parameters, HOMA-IR index, lipid panel, body measurements and serum hs-CRP were analyzed in this study. Correlation analysis, multivariate linear regression, logistic regression and ROC analysis were performed for statistical analysis. T2DM patients had significantly lower serum Neudesin concentration than healthy controls (2.36±0.66 vs. 4.43±0.97 ng/mL, P<0.001). Correlations between Neudesin serum level and variables like HOMA-IR (r=-0.556), HbA1c (r=-0.531), fasting glucose (r=-0.482), high-sensitivity C-reactive protein (hs-CRP) (r=-0.441), triglycerides (r=-0.392), and BMI (r=-0.351) were found inversely, whereas HDL-cholesterol was correlated positively (r=+0.317). The significant independent factor predicting lower levels of serum Neudesin was HOMA-IR (β=-0.376, p<0.001). A ROC curve yielded satisfactory discriminatory ability for T2DM (area under the curve AUC=0.846). Low levels of circulating Neudesin may indicate neuro-metabolic signaling problems due to insulin resistance, adiposity-related dysfunctions, inflammation burden, and metabolic decline in patients with established T2DM.

INTRODUCTION

The occurrence of Type 2 Diabetes Mellitus (T2DM) has been found to be one of the most complicated and rapidly growing metabolic diseases that have created huge implications for the healthcare system, as well as economy and public health sector. Apart from having risen significantly, what is particularly important about this metabolic problem is the progressive nature of metabolic imbalance and the strong link to cardiovascular disease, chronic renal failure, liver disease, and early death associated with T2DM.The current understanding of T2DM is not only

about the chronic condition of hyperglycemia and rather represents a complex disease that is defined by insulin resistance, abnormal adipose tissue metabolism, inflammation, oxidative stress, and inter-organ metabolic signaling defects (GBD 2021 Diabetes Collaborators, 2023; Davies et al., 2022).

Metabolic impairment of insulin resistance is the metabolic aspect of T2DM aside from glucose itself.The failure to react properly to insulin's actions leads to the development of metabolic inflexibility, fatty acid deposition in non-fat tissue, the increase in gluconeogenesis, and uncoupling of energy metabolism. With further deterioration of metabolic homeostasis despite insulin level correction, the severity of glucotoxicity and lipotoxicity grows, contributing to other complications related to beta cell dysfunction and metabolic progression (Professional Practice Committee, American Diabetes Association, 2026).

The problem of insulin resistance is to be considered broader than simply a failure of glucose metabolism but rather an issue of malfunctioning cellular nutrient sensing, mitochondria, and metabolic pathway adaptations controlled by hormones (Tsatsoulis et al., 2013; Gonzalez-Franquesa & Patti, 2017). Evidence exists on how adipose tissue expansion in obese conditions results in a sustained state of inflammation involving polarization of macrophages, inflammasomes, cytokine release, and progressive deterioration of insulin-mediated metabolic functions (Rohm et al., 2022; Garg et al., 2023).

Indeed, in case of constant overload with nutrients, adipocytes become progressively less responsible for metabolic processes and more engaged in immunometabolism to promote inflammatory signaling in the organism (Rohm et al., 2022; Garg et al., 2023). Thus, it is essential to understand how inflammation in T2DM is involved not only in metabolic processes but also in insulin resistance.
With this in mind, it has been determined that the adipose tissue is a unique immunometabolic organ that is responsible for regulation of metabolic sensing, lipid trafficking, inflammation signaling, and overall insulin sensitivity. Dysfunctions associated with visceral fat are manifested by adipocyte hypertrophy, adipose hypoxia, increased macrophage infiltration, altered production of adipokines, and greater amounts of free fatty acid transport to the liver and muscles. Dysfunctioning of the physiological process described above serves as an important contributor to disorders such as insulin resistance, mitochondrial dysfunction, endothelial cell damage, and cardiomyocyte metabolism disorders (Alexaki, 2024; Rabiee et al., 2025). Consequently, it can be stated that the role of adipose dysfunction as a result of obesity in the development of type 2 diabetes has been successfully recognized within existing descriptions of the pathophysiology of the disease.

Another aspect of metabolism dysfunction seen in the patients with T2DM is dyslipidemia. In this context, classic manifestations of T2DM-related dyslipidemia refer to increased triglycerides, increased concentration of atherogenic lipoproteins, and lower HDL-C concentration. Recent research has found that in T2DM patients, HDL lipoproteins dysfunction results from more than just their decreased concentration; oxidative susceptibility, dysfunctional reverse cholesterol transport pathway, inflammatory modification of lipoproteins, and decreased ability to protect endothelium are also involved (Bonilha et al., 2021; Xepapadaki et al., 2021). These findings have redirected attention toward signaling molecules regulating neurobiological processes in connection with metabolism, inflammation, and adaptive hormonal responses. Neuro-metabolic signaling molecules have emerged as key mediators linking CNS functioning with metabolic homeostasis, adipocyte biology, insulin sensitivity, and metabolic resilience. Among such molecules, Neudesin or neuron-derived neurotrophic factor has been attracting increasing

attention due to the possible roles that this molecule can play in energy expenditure, adiposity, glucose metabolism, and adaptive neuro-endocrine metabolic responses.

Neudesin is a heme-binding neurotrophic factor and a member of the membrane-associated progesterone receptor family. Apart from its initial functions as a neurotrophic factor, it has also been found out that Neudesin is involved in the sympathetic nervous system regulation, adipose tissue metabolism, food intake and energy metabolism. There is some evidence indicating that Neudesin can participate in neuro-metabolic adaptation in response to nutrient overabundance by affecting sympathetic tone, adipose tissue signaling, and metabolism regulation systemically. Thus, Neudesin is no longer regarded just as a neuronal protein but rather a mediator within the metabolic-inflammation complex (Çelikkol et al., 2022; Vergani et al., 2022).

With more research done in the field, the metabolic properties of Neudesin in an already developed form of T2DM remain understudied and somewhat controversial. At present, there is conflicting information on the involvement of Neudesin in the pathology of T2DM. For instance, in a particular study, it was noted that there were variations in the amount of Neudesin in T2DM patients. In contrast, in the cases of obesity and children suffering from metabolic disorders, different amounts of expression of Neudesin were observed depending on the degree of obesity, insulin resistance, age, and metabolism (Çelikkol et al., 2022; Vergani et al., 2022). This implies that Neudesin is metabolized at varying rates depending on its stage of development.

An underlying explanation for this is that Neudesin increases during early metabolic excess as part of an adaptation to ensure energy balance. Yet when progressing towards chronic stress, glucotoxicity, adipose inflammation, mitochondrial dysfunction, and metabolic depletion, Neudesin signals may gradually decrease. This would explain the current understanding of the failure of adaptive metabolic buffering in established T2DM cases. In addition to this, there has yet to be an examination of the physiological role of circulating Neudesin in relation to insulin resistance stress, inflammatory load, adiposity dysfunction, and atherogenic metabolic remodeling within a unified clinical model. The current literature has been limited in terms of varied populations, metabolic phenotype, incomplete inflammatory profiling, and simultaneous metabolic variables analysis. Even more limited is the number of studies on adult male subjects with established T2DM. The elucidation of the biological importance of Neudesin may, therefore, offer new knowledge beyond that of conventional measures of diabetes based on glucose. Biomarkers that can incorporate features such as insulin resistance, adiposity problems, inflammation, and dyslipidemia may provide better insight into the development of metabolic disorders, thereby enabling future models for metabolic risk stratification.

Aim of Study

To evaluate the association of Neudesin in blood circulation with the metabolic-inflammatory profile of T2DM in adult males by evaluating features such as insulin resistance, adiposity, glycemic load, dyslipidemia, and inflammation. Moreover, to determine whether serum Neudesin had any discriminatory importance among other metabolic disorders of T2DM.

METHODS

Study Design

The present study was designed as a case control study to evaluate the association between serum Neudesin concentrations and insulin resistance, metabolic dysregulation, and inflammatory status in adult males with Type 2 Diabetes Mellitus (T2DM). The study was conducted at Al-Najaf Center for Diabetes and Endocrinology in cooperation with the Clinical Biochemistry Laboratory

in Al- Sadr Medical City in AL-Najaf, Iraq, during the period extending from September 2025 to April 2026.

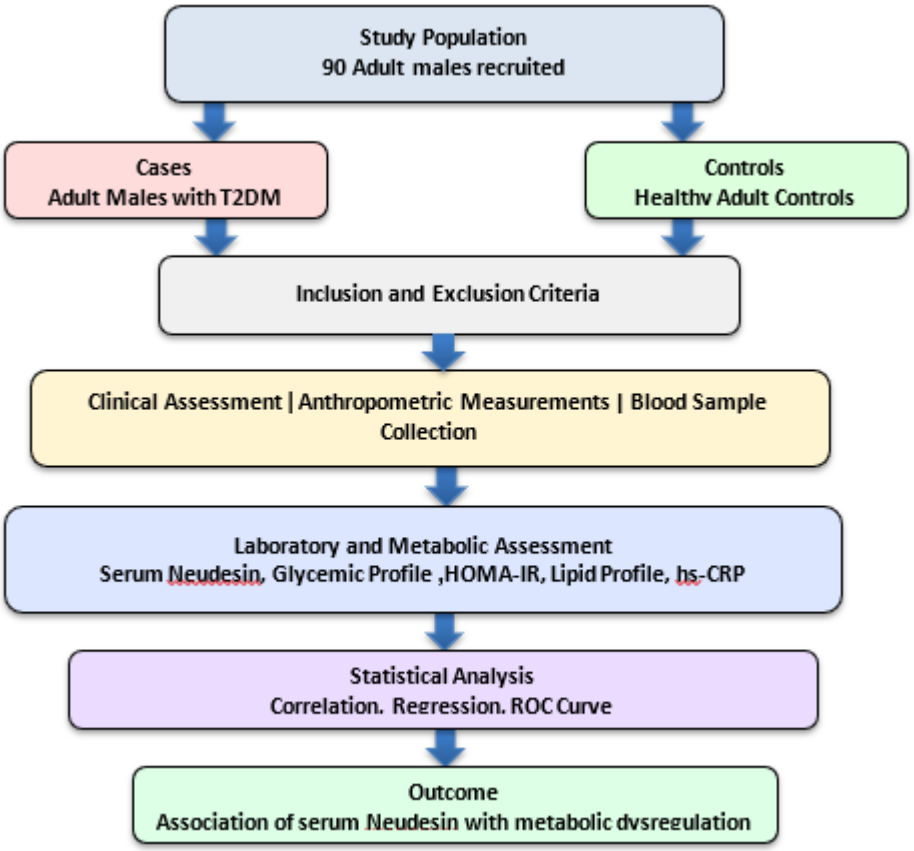

Figure 1. Case Control Study Design

Study Participants

Ninety of adult males were recruited in the current study and classified into two categories, T2DM category that comprised 45 adult males with documented T2DM and control category that comprised 45 healthy adult males who have never been affected by diabetes mellitus or any other systemic illness. The selection of the study participants from males only was deliberately made to reduce the effects of sex hormones and gender differences on body fat distribution, insulin resistance, inflammatory markers, and serum Neudesin concentrations.

Type 2 Diabetes Mellitus Diagnostic Criteria

The patients were diagnosed with T2DM based on ADA's T2DM diagnostic criteria. The participants were identified as having T2DM based on meeting at least one of the following criteria: (1) Plasma glucose level ≥126 mg/dL upon fasting; (2) Glycated hemoglobin level ≥ 6.5%; (3) Plasma glucose (random) ≥200 mg/dL in patients showing symptoms; (4) or being a previously confirmed case of T2DM by physicians with treatment for diabetes mellitus.

Inclusion & Exclusion Criteria

Inclusion Criteria

Diabetic individuals were selected based on the following selection criteria: (1) Adult males between 40 and 65 years of age; (2) Confirms a diagnosis of T2DM at least a year ago; (2) Had a

stable clinical presentation free from acute complications of DM; (3) Not on insulin treatment upon enrollment .

Exclusion Criteria

Individual who had the following criteria were excluded: (1) Type 1 diabetes mellitus; (2) Active infections; (3) Autoimmune disorders and chronic inflammation; (4) Liver impairment; (5) Kidney failure; (6) Active cancer; (7) Cardiovascular incidents in the last 6 months; (8) Endocrine disease; (9) Tobacco use; (10) Consume alcohol regularly; (11) Corticosteroid or other medications, such as immunomodulators, cholesterol reducers, or antihistamines.

Clinical and Anthropometric Evaluation

Demographic and clinical information was collected from all subjects by interviewing and reviewing their medical history records. Anthropometric evaluation was conducted under uniform protocols by qualified staff members. The body weight was measured up to 0.1 kg using an accurate electronic weighing scale, whereas height was measured up to 0.5 cm by a wall-mounted stadiometer with participants standing straight without shoes.

Body mass index (BMI) was determined using the following formula:

$$\mathbf{BMI}=\frac{\mathbf{Weight\ (kg)}}{\mathbf{Height\ (m)2}}$$

Waist circumference was determined by placing a stretch-free tape around the waist line midway between the inferior margin of the lowest rib and the top of the iliac crest during normal expiration.

Collection of Blood Samples and Processing

After an overnight fast lasting 10-12 hours, about 5 ml of venous blood was aseptically collected from each subject from 8.00 am to 10.00 am. The blood samples were categorized as blood in EDTA tube for estimating HbA1C, and blood in gel tubes for separating serum. The serum was allowed to clot for about 15-20 minutes at room temperature, followed by centrifugation at 3000 rpm for 10 minutes. The serum was then transferred to sterile Eppendorf tubes and frozen at −20°C till biochemical and immunological analyses were done.

Biochemical Assays

Fasting blood glucose (FBG), total cholesterol, triglycerides, and HDL-cholesterol levels were measured by an automated colorimetric procedure according to manufacturer's guidelines. Levels of LDL-cholesterol were calculated using the Friedewald equation when triglyceride levels were less than 400 mg/dL. The HbA1c level was also determined by standardized laboratory techniques. The concentrations of serum insulin were quantified by commercially available ELISA kits. The level of insulin resistance was calculated based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) by using the following equation:

$$\mathbf{HOMA\text{-}IR}=\frac{\boldsymbol{Fasting\ Insulin\ (\mu IU/mL)\times Fasting\ Glucose\ (mg/dL)}}{\mathbf{405}}$$

High sensitivity C-Reactive Protein (hs-CRP) levels were determined as markers of chronic low-grade inflammation by immunoassay kits (commercially available) depending on the instructions of manufacturing.

Assessment of Serum Neudesin Concentrations

Neudesin concentrations in serum samples were determined using an Elisa kit for Human Neudesin Neurotrophic Factor (NENF) provided by MyBioSource . The basic principle of the assay was the application of a quantitative double-antibody sandwich ELISA method. As per the

specifications provided by the manufacturer, the kit exhibited high sensitivity and specificity without considerable cross-reactivity with proteins having similar structures. The detection limit for the assay ranged from 0.156 to 10 ng/mL, while the minimal detection level was 0.057 ng/mL. The intra-assay coefficient of variation was <10%, and the inter-assay coefficient of variation was <12%. All samples were run in duplicate following the manufacturer's guidelines to ensure reliable results. The optical density readings were taken using a microplate ELISA reader at the specified wavelength. Biomarker concentrations were calculated based on the standard calibration curve.

Statistical Analysis

The statistical analyses in this study were conducted using IBM SPSS Statistics version-26. Values are presented as mean ± SD or median (interquartile range [IQR]) depending on the data distribution. Comparison between groups was made using independent samples t-test, Mann Whitney-U test, and chi-square test .

Correlation between Neudesin level in the serum and metabolic risk factors was assessed using Pearson correlation analysis. Independent predictors were determined using multiple linear and binary logistic regression analysis. The predictive ability of serum Neudesin was assessed using ROC analysis.

Ethical Considerations

The study received ethical approval from Al-Furat Al-Wsat Technical University and Al-Sader Medical City. Written informed consent was obtained from all participants before their inclusion in the study, in accordance with the ethical principles of medical research conducted on humans.

RESULTS AND DISCUSSION

Table (1) provides details about the demographic and anthropometric characteristics of the study participants. Patients with T2DM had a mean age of 52.8 ± 8.1 years, while healthy controls had an average age of 51.6 ± 7.5 years, with no statistical difference noted between the two groups (mean difference: 1.2 years; 95% CI: -2.1 to 4.5; p=0.462). On the other hand, there was a notable difference between T2DM patients and the control group regarding body mass index, where T2DM patients had significantly higher BMI values (30.4 ± 4.0 kg/m2) than healthy controls (26.5 ± 3.4 kg/m2) with a mean difference of 3.9 kg/m2 (95% CI: 2.4–5.4; p<0.001). Similarly, T2DM patients also had a significantly higher waist circumference (106.2 ± 8.8 cm) than healthy individuals (94.6 ± 8.1 cm) with a mean difference of 11.6 cm (95% CI: 8.1—15.1, P-value < 0.001).

Table 1. Baseline Demographic and Anthropometric Characteristics of the Study Population

Variables	**T2DM Patients *mean* ± *SD.* (n=45)**	**Healthy Controls *mean* ± *SD.* (n=45)**	**Mean Difference (95% CI)**	**P-value**
Age (years)	52.8 ± 8.1	51.6 ± 7.5	1.2 (−2.1 to 4.5)	0.462
Body Mass Index (kg/m²)	30.4 ± 4.0	26.5 ± 3.4	3.9 (2.4 to 5.4)	<0.001
Waist Circumference (cm)	106.2 ± 8.8	94.6 ± 8.1	11.6 (8.1 to 15.1)	<0.001

The results in Table (2) present that the patients with T2DM showed a significantly increased level of fasting plasma glucose compared to that in healthy controls. Their glucose levels were (184.7

± 37.9 mg/dL), while those of the controls were (92.4 ± 11.2 mg/dL) with a statistically significant difference between the two groups (P<0.001). Likewise, the percentage of HbA1c in the T2DM patients was significantly higher (8.0 ± 1.3%), compared to that in healthy controls (5.3 ± 0.5%) with a significant difference between the two groups (P<0.001). Moreover, the level of serum insulin in the T2DM group was significantly high compared to its level in the control group. The median value for the former was (16.1 µIU/mL; IQR: 12.9–21.2), while that of the latter was (9.8 µIU/mL; IQR: 7.7–12.3), which was associated with a significant difference between the two groups (P<0.001).

Table 2. Glycemic Profile and Insulin Resistance Markers Among Study Groups

Variables	T2DM Patients (n=45)	Healthy Controls (n=45)	P-value
Fasting Blood Glucose (mg/dL)	184.7 ± 37.9	92.4 ± 11.2	<0.001
HbA1c (%)	8.0 ± 1.3	5.3 ± 0.5	<0.001
Serum Insulin (µIU/mL)	16.1 (12.9–21.2)	9.8 (7.7–12.3)	<0.001
HOMA-IR	7.2 (5.8–9.8)	2.4 (1.9–3.1)	<0.001
Data are presented as mean ± SD or median (IQR) according to data distribution.			

Table (3) demonstrates the lipid profile and hs-CRP levels among the studied groups. Patients with T2DM showed significantly higher total cholesterol levels (216.9 ± 33.8 mg/dL) compared with healthy controls (174.6 ± 28.1 mg/dL, P<0.001). Likewise, triglyceride concentrations were markedly elevated in the diabetic group (221.8 ± 54.6 mg/dL) relative to controls (133.4 ± 35.8 mg/dL, P<0.001). LDL-cholesterol levels also revealed a significant increase among T2DM patients (136.7 ± 28.9 mg/dL) compared with healthy subjects (99.2 ± 24.1 mg/dL, P<0.001). In contrast, HDL-cholesterol levels were significantly reduced in the diabetic group (39.1 ± 6.4 mg/dL) in comparison with controls (48.3 ± 7.0 mg/dL, P<0.001). Furthermore, hs-CRP concentrations were significantly higher among T2DM patients (5.4 ± 1.9 mg/L) than in healthy controls (2.2 ± 0.8 mg/L), with a highly significant difference between the two groups (P<0.001).

Table 3. Lipid Profile and hs-CRP Levels Among Study Groups

Variables	T2DM Patients (n=45)	Healthy Controls (n=45)	P-value
Total Cholesterol (mg/dL)	216.9 ± 33.8	174.6 ± 28.1	<0.001
Triglycerides (mg/dL)	221.8 ± 54.6	133.4 ± 35.8	<0.001
LDL-Cholesterol (mg/dL)	136.7 ± 28.9	99.2 ± 24.1	<0.001
HDL-Cholesterol (mg/dL)	39.1 ± 6.4	48.3 ± 7.0	<0.001
hs-CRP (mg/L)	5.4 ± 1.9	2.2 ± 0.8	<0.001
Data are presented as mean ± SD.			

Table (4) and Figure (1), demonstrated that serum Neudesin levels were significantly reduced in T2DM patients (2.36 ± 0.66 ng/mL) as compared to controls (4.43 ± 0.97 ng/mL). The mean difference between the two populations was found to be −2.07 ng/mL (95% CI: −2.42 to −1.72), which suggests a highly significant reduction in serum Neudesin levels in T2DM patients (P<0.001). Moreover, the observed effect size suggested a large effect of the difference between the two populations (Cohen's d = 2.10).

Table 4. Serum Neudesin Levels in T2DM Patients and Healthy Controls

Biomarker	T2DM Patients (n=45)	Healthy Controls (n=45)	Mean Difference (95% CI)	P-value	Cohen's d
Serum Neudesin (ng/mL)	2.36 ± 0.66	4.43 ± 0.97	−2.07 (−2.42 to −1.72)	<0.001	2.10
Data are presented as mean ± SD.					

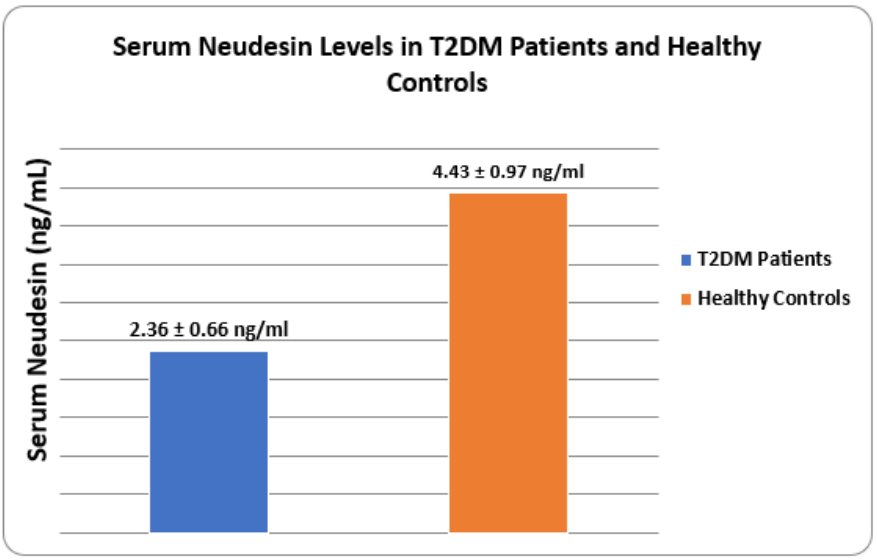

Figure 1. Comparison of Serum Neudesin Levels Between T2DM Patients and Healthy Controls

Correlation analysis between serum Neudesin levels and some selected metabolic parameters among T2DM patients was illustrated in Table (5) and Figure (2). There was a statistically significant negative correlation between serum Neudesin levels and body mass index (r = -0.351, P = 0.018), fasting blood glucose (r = -0.482, P = 0.001), HbA1c (r = -0.531, P < 0.001), HOMA-IR (r = -0.556, P < 0.001), triglycerides (r = -0.392, P = 0.008), and high sensitivity CRP (r = -0.441, P = 0.003).

Table 5. Correlation Between Serum Neudesin Levels and Metabolic Parameters in T2DM Patients

Variables	Correlation Coefficient (r)	P-value
Body Mass Index	−0.351	0.018
Fasting Blood Glucose	−0.482	0.001
HbA1c	−0.531	<0.001
HOMA-IR	−0.556	<0.001
Triglycerides	−0.392	0.008
hs-CRP	−0.441	0.003
HDL-Cholesterol	+0.317	0.038

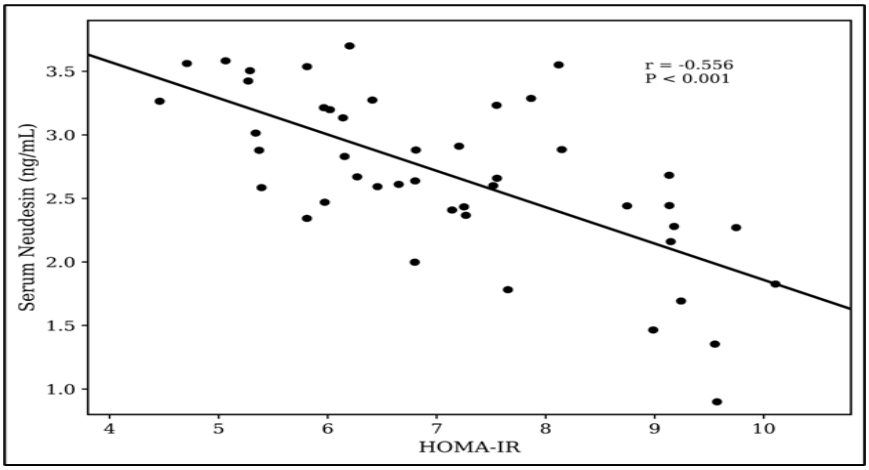

Figure 2. Correlation Between Serum Neudesin Levels and HOMA-IR in Patients with Type 2 Diabetes Mellitus

Table (6), shows the multiple linear regression analysis for the independent predictors for serum Neudesin level in T2DM patients. HOMA-IR was found to be the most significant independent predictor for serum Neudesin level (β=-0.376, t=-3.88, P<0.001), followed by HbA1c (β=-0.294, t=-3.21, P=0.002). Moreover, there was a significant independent inverse correlation between serum Neudesin level and hs-CRP (β=-0.248, t=-2.74, P=0.009). Body mass index also had a statistically significant inverse correlation with serum Neudesin level (β=-0.183, t=-2.11, P=0.041). The regression model accounted for 58% of the variability in serum Neudesin level (R^2=0.58) with an adjusted R^2 of 0.54. In addition, the entire regression model was statistically significant (F=14.6, P<0.001).

Table 6. Multiple Linear Regression Analysis of Independent Predictors of Serum Neudesin Levels

Variables	**Standardized β**	**t-value**	**P-value**
HOMA-IR	−0.376	−3.88	<0.001
HbA1c	−0.294	−3.21	0.002
hs-CRP	−0.248	−2.74	0.009
Body Mass Index	−0.183	−2.11	0.041
Model Statistics			
R^2	0.58		
Adjusted R^2	0.54		
F-statistic	14.6		
Overall P-value	<0.001		

Table (7) displays the results of the binary logistic regression analysis on the independent variables that are associated with T2DM. Serum Neudesin levels had a significant inverse association with the likelihood of T2DM (adjusted OR=0.49, 95% CI: 0.29–0.81, P=0.006). Conversely, HOMA-IR exhibited a significant positive association with the risk of T2DM (adjusted OR=1.38, 95% CI: 1.14–1.68, P=0.001). Likewise, body mass index emerged as a significant predictor of T2DM (adjusted OR=1.13, 95% CI: 1.02–1.27, P=0.021). Moreover, hs-CRP levels displayed a significant positive correlation with T2DM (adjusted OR=1.31, 95% CI: 1.07–1.62, P=0.012). The binary logistic regression model was able to show satisfactory explanation ability with Nagelkerke's R^2 value of 0.49. Additionally, the Hosmer-Lemeshow test showed a satisfactory fit of the model, with P=0.64.

Table 7. Binary Logistic Regression Analysis of Independent Predictors of T2DM

Variables	Adjusted OR	95% CI	P-value
Serum Neudesin	0.49	0.29–0.81	0.006
HOMA-IR	1.38	1.14–1.68	0.001
Body Mass Index	1.13	1.02–1.27	0.021
hs-CRP	1.31	1.07–1.62	0.012
Model Performance			
Nagelkerke R^2	0.49		
Hosmer–Lemeshow P-value	0.64		

In Table (8) and Figure (3), the diagnostic utility of serum Neudesin for discriminating between T2DM patients and controls has been shown based on ROC curve analysis. The area under curve (AUC) was found to be 0.846, which is considered very accurate. The 95% confidence interval was 0.759 to 0.933, and the results were statistically highly significant (P<0.001). The cut-off level for serum Neudesin for discriminating between controls and T2DM patients was identified as ≤3.15 ng/mL, and it exhibited a sensitivity of 80.0% and specificity of 77.8%.

Table 8. Diagnostic Performance of Serum Neudesin for Discrimination of T2DM Patients

Parameter	Value
Area Under Curve (AUC)	0.846
95% Confidence Interval	0.759–0.933
Optimal Cut-off Value	≤3.15 ng/mL
Sensitivity (%)	80.0
Specificity (%)	77.8
P-value	<0.001

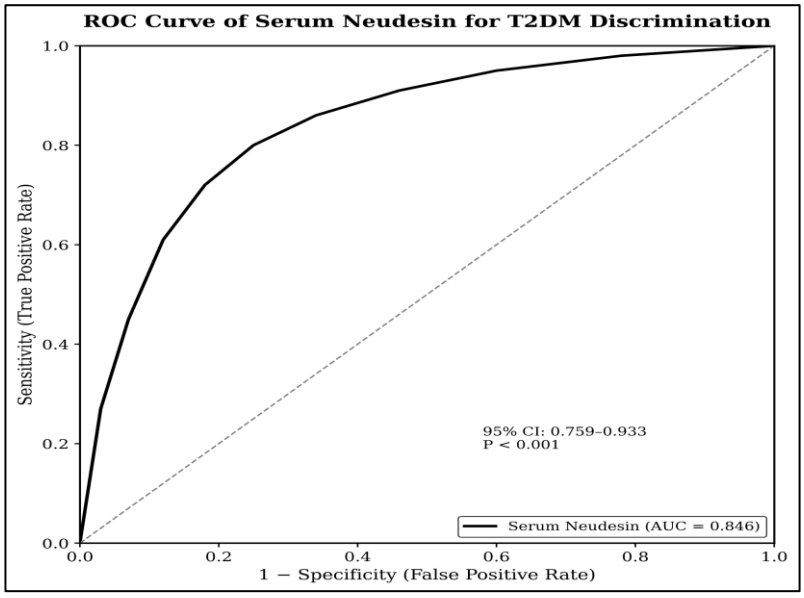

Figure 3. ROC Curve Analysis of Serum Neudesin for Discrimination of T2DM Patients

DISCUSSION

The present study indicates the involvement of Neudesin in the metabolic-inflammatory milieu associated with established cases of T2DM, in contrast to the consideration of the molecule solely as a neurotrophic marker. The patients suffering from T2DM showed a distinct metabolic profile

with increased adiposity indicators, poor glycometabolic status, insulin resistance, disordered lipoprotein profile, high levels of inflammation, as well as lower levels of Neudesin. It could be concluded that the changes observed in the levels of Neudesin in patients' serum might indicate the connection between disrupted insulin metabolism, adipocyte disorders, persistent low-level inflammation, and impaired adaptive capacity of the neuro-metabolic system. This approach to the metabolic-inflammatory mechanisms of diabetes pathogenesis has been suggested recently (Rohm et al., 2022; Davies et al., 2022).

Among the most biologically important results of the current study was the considerable decrease in Neudesin levels in patients with diabetes mellitus relative to healthy individuals. Recent evidence supports Neudesin as a secreted neurotrophic protein playing an essential role in regulating energy homeostasis, neuronal function, and metabolism. Consequently, the observed decline in patients with diabetes mellitus could be attributed to the depletion of neuro-metabolic buffer systems under conditions of continuous glucotoxicity, adipose tissue inflammation, and insulin resistance-related stress. The suggested biological mechanism is plausible based on the knowledge that persistent metabolic pressure causes the gradual conversion of adipose tissue from an insulin-sensitive endocrine organ to an inflamed dysfunctional tissue with modified adipokine production and reduced metabolic plasticity (Garg et al., 2023). Notably, the considerable effect size reported in the current study indicates that the reduction in Neudesin levels was not only statistically significant but also biologically relevant.

It is worth noting that previous experiments assessing blood Neudesin revealed contradictory results, with Karatas et al. (2021) identifying abnormal Neudesin levels in T2DM individuals and speculating about its involvement in metabolic and vascular abnormalities while the role of Neudesin in obesity and pediatric metabolic syndrome revealed varying patterns (Çelikkol et al., 2022; Vergani et al., 2022). It would be unreasonable to attribute these contradictory results solely to the use of different methodologies. Differences in the stage of diseases, obesity severity, metabolic compensation, pharmacotherapy, patient age, and degree of insulin resistance should also be taken into account. An interesting hypothesis suggested by the results obtained in this work is that Neudesin displays a biphasic pattern of metabolic action throughout the course of metabolic disorders development. Initially, when excessive nutrients and increased insulin levels occur, a temporary rise in Neudesin can serve as a compensatory mechanism to preserve metabolic balance. In contrast, with further advancement towards T2DM, prolonged insulin resistance, adipose tissue inflammation, mitochondrial dysfunction, and chronic glucotoxicity may induce exhaustion or reduced expression of Neudesin.

The inverse correlation of serum Neudesin and HOMA-IR can be considered one of the most robust findings in the current study. Not only did HOMA-IR exhibit a significant inverse correlation with Neudesin, but also it was found to be the strongest independent factor in the regression model. These results support the notion that low levels of Neudesin are closely related to the development of insulin-resistant conditions, rather than being a consequence of isolated hyperglycemia. Insulin resistance is known to involve major dysregulations of intracellular insulin signal transduction processes via IRS-1, PI3K-Akt pathway, glucose transport, and lipid metabolism in insulin-responsive tissues. In this context, adipocytes increasingly become metabolically inflexible, show increased lipolytic activity, secretion of ectopic lipids, and pro-inflammatory factors that ultimately contribute to worsening insulin resistance (Rohm et al., 2022). Thus, reduced levels of Neudesin could point towards metabolic and neuroendocrine abnormalities during persistent insulin-resistant stress.

The inverse correlation between Neudesin and HbA1c supports the idea that Neudesin is decreased in the presence of sustained hyperglycemia, not just acute fluctuations. HbA1c indicates prolonged

exposure to high glucose levels and correlates strongly with oxidative stress, mitochondrial dysfunctions, endothelial damage, and metabolic toxicity. Glucotoxicity is associated with the generation of excessive reactive oxygen species, activation of inflammatory pathways, and the development of energetic disturbances leading to metabolic decline (Davies et al., 2022). Against this background, reduced Neudesin may point at failure of neuro-metabolic regulation mechanisms in terms of maintaining normoglycemia against the background of constant hyperglycemic load. It is noteworthy that the maintenance of HbA1c as an independent variable in multivariable analysis indicates biological significance of the connection identified above.

As for the inflammatory component of the research results, the level of serum hs-CRP was considerably higher in the study cohort of people suffering from diabetes and showed inverse independent association with Neudesin levels. In this respect, Neudesin is integrated into the inflammatory-metabolic paradigm explaining pathophysiology of T2DM development. At present, obesity-induced T2DM is regarded as a state of chronic subclinical inflammation involving adipocyte infiltration with macrophages, stimulation of the NF-κB and JNK signaling pathways, release of cytokines, and impairment of insulin signaling cascade components (Rohm et al., 2022). Thus, the negative correlation between hs-CRP and Neudesin suggests that low levels of Neudesin are related to the increase in innate inflammatory response and activation of the immune system of adipose tissue. This statement is consistent with the idea that neuro-metabolic signaling mechanisms are highly susceptible to inflammatory response and metabolic overload.

Moreover, the associations revealed between Neudesin and obesity indicators provide additional support for this interpretation. Patients with diabetes had higher values of BMI and waist circumference, which negatively correlated with the level of Neudesin in blood serum. Modern ideas about obesity move beyond excess body fat storage and involve the role of adipose tissue as a highly active endocrine and immunometabolic organ. The presence of visceral fat leads to the development of adipocyte hyperplasia, hypoxia, infiltration by macrophages, secretion of pro-inflammatory cytokines, and hypersecretion of free fatty acids, forming an environment for the formation of insulin resistance and metabolic dysfunction (Garg et al., 2023).

The lipid profile abnormalities identified in the present study contribute further to our understanding. Individuals with T2DM had an atherogenic dyslipidemic profile, featuring high levels of triglycerides and LDL-C alongside low HDL-C levels. In particular, there was a correlation between Neudesin levels and HDL-C levels. It is possible that Neudesin is associated with the maintenance of a metabolic stress-resistant lipoprotein profile, which features reverse cholesterol transport, oxidative modification resistance, and less inflammation-induced remodeling of the lipoproteins. In patients with T2DM, HDL lipoproteins experience significant changes, including modifications to their composition and function. As a result, their protective properties regarding antioxidation, inflammation, and endothelial protection are compromised (Xepapadaki et al., 2021; Denimal et al., 2023). Hence, lower Neudesin levels can be associated with general cardiometabolic lipid disorders and not simply with a decreased HDL-C concentration.

One of the key strengths of the present study is the use of regression analysis, which revealed that HOMA-IR, HbA1c, hs-CRP, and BMI were independent predictors of Neudesin levels in circulation. Thus, Neudesin is affected by more than one metabolic domain. Notably, such multidimensional relationship increases the physiological significance of Neudesin and promotes its inclusion into the metabolic-inflammatory pathogenic concept underlying T2DM. Finally, the good performance of the regression model adds weight to the biological plausibility of the associations observed.

Results of the logistic regression also reinforce the autonomous role of Neudesin in T2DM. Lower levels of serum Neudesin were found to be associated with diabetes even when insulin resistance, fatness, and inflammatory state were accounted for. It means that one cannot completely attribute the link between Neudesin and T2DM either to obesity or to inflammation. Therefore, Neudesin could serve as another neuro-metabolic factor contributing to the development of diabetes. It makes physiological sense since the modern understanding of metabolic disorders is focused on disrupted organ-to-organ communication mediated by adipose tissues, liver, muscles, gastrointestinal peptides, and neuroendocrine regulation systems.

Neudesin displayed discriminatory properties sufficient to classify diabetic individuals from healthy controls based on ROC curve analysis. Even though at this stage Neudesin can hardly be considered a good biomarker due to its inability to be used as a sole diagnostic factor, the calculated AUC demonstrates biologically significant difference between insulin resistant and insulin sensitive groups. Importantly, relative balance between the values of sensitivity and specificity suggests that Neudesin might be successfully used in metabolic risk assessment algorithms involving more than one biomarker. It was recently recommended that clinically useful metabolic biomarkers should include novel pathophysiological information besides standard parameters of carbohydrate metabolism (Cohen et al., 2016). In this context, Neudesin appears to be potentially valuable since it reflects all major features of metabolic syndrome, including metabolic disturbances, inflammation, insulin resistance, and adipocyte dysfunction. Based on the above mentioned results, it could be concluded that low Neudesin serum levels might not be considered an isolated biochemical disturbance. Instead, decreased serum Neudesin concentrations might reflect interactions between impaired insulin signaling pathways, altered functioning of adipose tissue, inflammatory processes, lipid metabolism disorders, and metabolic adaptations. The current research thus expands the existing notion about the role of neuro-metabolic regulatory proteins in the progression of disease.

Strengths and Limitations

This study had some strengths worth mentioning. Firstly, Neudesin was analyzed in the context of a comprehensive metabolic model, including insulin resistance, glycemic control, obesity parameters, lipids, and inflammation. Secondly, the exclusion of females ensured that the possible influence of sex hormones on metabolic processes would not interfere with the results. Thirdly, the use of correlation analysis, multivariable regression, and ROC analysis made the results reliable and biologically plausible. Notwithstanding the limited number of participants, the study had internal validity due to multiple statistical methods used.

Still, there are some limitations that need to be considered. For example, the cross-sectional design does not allow drawing a clear conclusion concerning the cause-and-effect relationship between reduced Neudesin levels and T2DM development. Moreover, the study was not powered enough to validate the findings in a clinical setting or to distinguish patients by the stage of the disease or treatment modalities. Also, this study only included male patients, thus making it impossible to extrapolate the findings to other patient populations. Finally, the study did not assess adipokine, oxidative stress, mitochondrial function, or inflammation biomarkers.

Perspectives for the Future

Future studies must be conducted to elucidate the role of Neudesin throughout the various stages of metabolic disease progression, employing longitudinal and multicentric approaches. In parallel to studying the role of Neudesin in relation to the metabolic-inflammatory axis of T2DM, simultaneous investigation of Neudesin in conjunction with adipokines, inflammatory cytokines, indicators of mitochondrial stress, and markers of endothelial dysfunction may shed additional

light on its underlying mechanisms of action. On the other hand, future translational research should investigate whether Neudesin signaling can exert metabolic effects directly or is merely an indication of subsequent metabolic changes.

CONCLUSION

The current study finds low levels of circulating Neudesin to be a characteristic of established Type 2 Diabetes Mellitus in adult men. Low levels of Neudesin were found to be linked with insulin resistance, glycemic instability, obesity, lipoprotein abnormalities, and chronic inflammation, thereby suggesting that Neudesin plays a role in the metabolic-inflammatory framework of T2DM. Importantly, the significant associations found through regression analyses, combined with the diagnostic capabilities of ROC analyses, indicate that the decreased Neudesin is indicative of biological metabolic dysfunction and not merely a biochemical phenomenon. Altogether, these results strongly lend credence to the idea that the decreased levels of Neudesin could be a sign of impaired neuro-metabolic adaptation due to insulin-resistant stress in patients with T2DM.

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