ORIGINAL ARTICLE

Serum Neudesin Levels in Obese Adolescents

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What is already known on this topic?

Neudesin is a neurotropic factor that contributes to the complex control of energy homeostasis. In addition, neudesin can influence appetite control in the hypothalamus or the anxiety-like behaviour controlled by the dentate gyrus of the hippocampus.

What this study adds?

We assessed the relationship between obesity, metabolic complications and neudesin levels in adolescents. Neudesin levels were significantly decreased in obese and morbidly obese adolescents. Neudesin may have a significant potential role in the regulatory mechanisms of obesity and other metabolic disorders.

Abstract

Objective: Advances in knowledge of neurotrophic factors are now revealing the complex control of energy homeostasis and appetite, as well as the crucial role these factors play in nervous system function. The aim of this study was to assess serum levels of neudesin in adolescents with obesity and to examine the relationship between these levels and metabolic outcomes.

Methods: Adolescents, aged 10-17 years were enrolled. Subjects were divided into normal weight, obese and morbidly obese subgroups. Serum neudesin concentrations were compared between the groups.

Results: In total, 88 adolescents were recruited, of whom 30 (34.1%) were normal weight, 15 (17.0%) were obese and 43 (48.9%) were morbidly obese. Neudesin levels were significantly lower in obese adolescents than in the control group ($p = 0.013$). A correlation analysis applied to the whole study group revealed a negative correlation between serum neudesin concentration and body mass index (BMI) z scores ($r = -0.40$, $p < 0.001$). Serum neudesin levels tended to increase in adolescents with metabolic syndrome, insulin resistance, dyslipidaemia, and hypertension but the differences were not significant ($p = 0.259$, $p = 0.246$, $p = 0.259$, and $p = 0.523$, respectively).

Conclusion: Serum neudesin levels were significantly correlated with BMI z score in obese adolescents. Generally, serum neudesin levels were low in obese and morbidly obese adolescents and tended to increase with the appearance of metabolic disorders. Both obesity and associated metabolic disorders have multifactorial causes. Therefore, we suggest that the role of the neudesin molecule in the regulatory mechanisms of obesity and metabolic disorders should be further investigated with well-designed studies enrolling larger groups.

Keywords: Obesity, neudesin, insulin resistance, metabolic syndrome

Introduction

Obesity in children and adolescents has increased worldwide in the last 30 years. The most important reasons for this increase are the decrease in physical activity in children and the negative effects of wider use of developing technology and poorer eating and drinking habits (1). The epidemic of obesity is closely associated with an increase in metabolic disorders, including diabetes, dyslipidemia and cardiovascular diseases, and this has prompted major interest in the regulation of adipose functions.

Adipose tissue can be divided into two distinct types: white and brown. White adipose tissue (WAT) is specialised for the storage of excess energy as triglycerides, whereas brown adipose tissue (BAT) dissipates energy as heat, thereby counteracting obesity. The regulation of adipose tissue function depends on the sympathetic nervous system

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(SNS), which plays a fundamental role in maintaining energy homeostasis in living organisms (2). The SNS also modulates the development of obesity because it stimulates lipolysis in WAT and enhances heat production in BAT by activating adrenergic signalling (3).

The functioning of the SNS depends on neurotrophic factors which promote the survival, differentiation and maintenance of neurons in the vertebrate nervous system (4,5,6). One newly identified neurotropic factor is neudesin, a compound that contributes to the complex control of energy homeostasis. Human neudesin is a 172 amino acid protein that shares a high sequence similarity to neudesin found in other vertebrates. Neudesin activates the mitogen-activated protein kinase and phosphoinositide 3-kinase signalling pathways and has a role in neural cell differentiation, cell proliferation and tumorigenesis (7). Neudesin is preferentially expressed in the central nervous system and the spinal cord, where it promotes neural cell differentiation. Neudesin mRNA expression has also been documented in other tissues, including adipose tissue, heart, lungs, and kidney. In addition to its neurotropic effects, neudesin can influence appetite control in the hypothalamus or the anxiety-like behaviour controlled by the dentate gyrus of the hippocampus (3).

Neudesin has been examined in only a limited number of studies to date, but the current consensus is that neudesin may have potential for the treatment of obesity and obesity-related disorders (3,7). The aim of the present study was to investigate the levels of circulating serum neudesin in a group of adolescents with obesity and to examine the relationship between these levels and metabolic outcomes that develop due to obesity.

Methods

Participants

This prospective study included adolescents aged 10 to 17 years. Of these adolescents, around two thirds were referred to the paediatric endocrinology outpatient clinic because of weight gain and were diagnosed with obesity. The other third were healthy age- and sex-matched children who served as the control group. Exclusion criteria were: chronic or hereditary diseases; endocrinological disorders including syndromes associated with obesity; and a history of drug use. Pubertal stage was assessed according to the criteria described by Marshall and Tanner (8).

A challenge in determining the prevalence of metabolic syndrome (MS) is the existence of multiple definitions and criteria used to identify this condition. In response,

the International Diabetes Federation (IDF) released the IDF Consensus Worldwide Definition of MS as a single, universally accepted tool. The IDF defines MS in children and adolescents as the presence of abdominal obesity (waist circumference ≥90th percentile by age and sex) and the presence of two or more of the following clinical features: an elevated triglyceride level (≥1.7 mmol/L), a low high-density lipoprotein cholesterol (HDL-C) level (< 1.03 mmol/L), high blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or a diagnosis of hypertension) and an elevated glucose level (≥5.6 mmol/L and/or a diagnosis of type 2 diabetes) (9). Written informed consent was obtained from the children's parents after they were informed of the aim and procedures of the study. The study was approved by the Tekirdağ Namık Kemal University University of Non-Invasive Clinical Research Ethics Committee (protocol number: 2019.137.08.09, date: 01.08.2019).

Study Design

The height of each participant was measured using a wall-mounted stadiometer sensitive to the nearest 0.1 cm (Harpenden, Holtain, Crymych, UK) and with the adolescent in a standing position, without shoes. Weight was measured using a portable calibrated scale sensitive to the nearest 0.1 kg (SECA762; Voge & Hakle, Hamburg, Germany), with the participants wearing light clothing. The body mass index (BMI) was calculated as weight (kg) divided by height (m^2). The height, weight and BMI were expressed as standard deviation scores (SDS) using the 2007 growth reference percentiles for Turkish children and adolescents (10). Children were divided into three groups - normal weight, obese, or morbidly obese (11). Blood pressure was measured using an automated sphygmomanometer. Elevated blood pressure (≥95th percentile for height) was determined using tables provided by the Task Force Report (12).

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess normality of data distribution from the control and patient groups. Parameters were evaluated according to their nonparametric and parametric distributions. Differences between different groups were assessed using the Student's t-test for parametric data, while the Mann-Whitney U test was used for data with nonparametric distribution. Relationships between parameters were investigated using Pearson correlation analysis. The correlations were modelled by linear regression analysis of different sizes and were found to be similarly significant. All statistical analyses were performed with the Statistical Package for the Social

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Sciences, version 22.0 (IBM Inc., Armonk, NY, USA). A p value of < 0.05 was considered statistically significant.

Laboratory Measurements

In both the patient and control groups, peripheral venous blood samples were collected after 12-hour overnight fasting and used for enzymatic measurements of the concentrations of glucose, insulin, free thyroxine, thyroid-stimulating hormone, low-density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides, total cholesterol (TC) and alanine aminotransferase (Roche Modular DP Automatic Biochemical Analyser; Roche Diagnostics, Indianapolis, IN, USA). We used the homeostasis model assessment of insulin resistance (HOMA-IR) to determine the presence of IR by employing the following formula: fasting glucose (mmol/L) × fasting insulin (IU/L)/22.5. The HOMA-IR cut-off values for IR were taken as 5.22 in boys and 3.82 in girls (13).

Results

In total, 58 adolescents with obesity/morbid obesity (mean age, 13.68 ± 2.01 years) and 30 healthy controls (mean age, 12.96 ± 2.5 years) were enrolled in this study. On pubertal assessment all participants were stage ≥2, based on clinical examination and palpation. No significant difference in sex distribution was observed between the two groups (p > 0.05). The characteristics and baseline laboratory values of the patients and control subjects are shown in Table 1. The BMI, BMI-SDS, waist circumference, glucose, insulin, HOMA-IR, TC, triglycerides, systolic blood pressure and diastolic blood pressure were significantly higher and the neudesin level significantly lower in the patients with obesity than in the controls (Table 1). Significant differences were noted in the presence of acanthosis and IR between the patient and control groups (p < 0.01).

The characteristics and baseline laboratory values of the patients with obesity and morbid obesity are shown in Table 2. The BMI, BMI-SDS, insulin and HOMA-IR values were significantly higher and the neudesin level significantly lower in the patients with morbid obesity than in the patients with obesity (Table 2). No statistically significant relationships were found between these groups in terms of blood pressure, glucose or lipid levels (p > 0.05).

There was a significant correlation between neudesin and BMI-SDS (Figure 1) and the systolic and diastolic blood pressures, which were all negatively correlated (r = -0.401**, r = -0.246* and r = -0.250*, respectively) (Table 3). No significant correlation was found for the other parameters assessed.

Table 1. Baseline characteristics and metabolic parameters of the obese adolescents and controls

	Obese patients (n = 58) Median (min-max)	Controls (n = 30) Median (min-max)	p value
Age (years)	14.25 (10.10-17.00)	12.78 (9.00-17.00)	0.150
Gender (female/male)	37/21	16/14	0.348
Height (cm)	161.93(138.00-180.00)	165.25 (127.0-178.20)	0.670
Height-SDS	0.66 (-2.15-2.97)	-0.07 (-1.80-2.24)	**0.001****
Weight (kg)	82.20 (55.50-130.00)	53.75 (25.00-76.00)	**< 0.001*****
Weight-SDS	3.14 (1.58-6.36)	0.09 (-1.41-1.80)	**< 0.001*****
BMI (kg/m²)	31.83 (24.96-44.70)	20.47 (15.50-24.70)	**< 0.001*****
BMI-SDS	2.73 (1.35-4.27)	0.18 (-0.91-1.40)	**< 0.001*****
SBP (mm/Hg)	120.06 (90-160)	110.20 (100-120)	**< 0.001*****
DBP (mm/Hg)	80.94 (52-105)	74.14 (70-80)	**< 0.001*****
Waist/hip ratio	0.87 (0.69-1.02)	0.83 (0.78-0.89)	**0.026***
Glucose (mg/dL)	96.33 (78-118)	90.33 (79-97)	**0.001****
Insulin (µU/mL)	27.18 (7.46-93.21)	7.53 (3.40-12.00)	**< 0.001*****
HOMA-IR	6.38 (1.46-26.01)	1.70 (0.76-2.81)	**< 0.001*****
TC (mg/dL)	146.75 (100-205)	126.40 (96-169)	**< 0.001*****
TG (mg/dL)	95.50 (33-342)	72.67 (44-122)	**0.019***
HDL (mg/dL)	44.25 (33-90)	42.40 (34-69)	0.245
LDL (mg/dL)	81.17 (37-132)	73.80 (41-101)	0.091
Neudesin (ng/mL)	2.64 (1.14-6.17)	3.12 (1.76-10.91)	**0.013***

*p < 0.05, **p < 0.01, ***p < 0.001 and significant values are indicated in bold.

The data are expressed as medians and (min-max).

BMI-SDS: body mass index-standard deviation score, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein, LDL: low-density lipoprotein, min-max: minimum-maximum

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Of the 58 patients with obesity, 31% (n = 18) were diagnosed with MS by the IDF Consensus Worldwide definition. Interestingly, neudesin levels were higher in patients with MS compared to those without MS but the differences were not significant (3.27 ± 1.54 vs 2.86 ± 1.04 ng/L, respectively). We also investigated neudesin levels in further subgroups stratified by the presence or absence of dyslipidemia, hypertension and IR but no significant relationships were observed (Table 4).
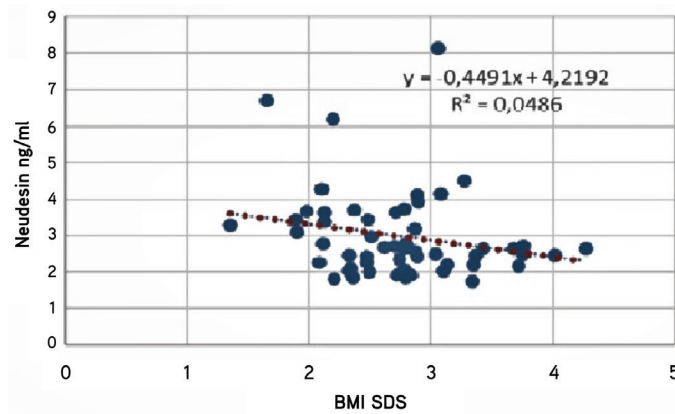

Figure 1. Correlation between neudesin and BMI-SDS

BMI-SDS: body mass index-standard deviation score

Discussion

Experimental studies suggest that neudesin may be a novel regulator of energy homeostasis and food intake, with a potential role in the development of obesity and its complications. Previously published studies reported a preferential expression of neudesin in the paraventricular nuclei and arcuate nucleus, which are important areas of the hypothalamus for regulating appetite (14,15,16). It has also been proposed that neudesin may affect melanocortin signalling, as administration of recombinant neudesin in a mouse model via an intracerebrovascular cannula increased the hypothalamic expression of proopiomelanocortin (POMC) and melanocortin 4 receptor (MC4R) mRNA and decreased food intake and body weight (14). Su et al (17) showed that neudesin (NENF) acts as a negative regulator of myogenesis in bovines and that knockdown of NENF inhibited pre-adipocyte differentiation and promoted myoblast myogenesis.

In the present study, we found significantly lower neudesin levels in adolescents with obesity, as well as a negative correlation between neudesin levels and BMI, with neudesin levels decreasing as BMI-SDS increased. The specificity of serum neudesin was 83.33%, with a likelihood ratio of 4.14 and diagnostic accuracy of 73.86% between healthy and obese adolescents. To the best of our knowledge, this

Table 2. Characteristics and metabolic parameters of the obese and morbid obese adolescents

	Obese patients (n = 15) Median (min-max)	Morbid obese (n = 43) Median (min-max)	p
Age (years)	14.70 (10.11-17.00)	14.11 (10.10-16.70)	0.192
Gender (female/male)	10/5	27/16	0.793
Height (cm)	166.10 (145.80-180.00)	161.00 (138.00-179.30)	**0.046**
Height-SDS	0.64 (-2.15-2.97)	0.72 (-0.43-2.96)	0.198
Weight (kg)	76.00 (56.80-94.50)	83.20 (55.50-130.00)	0.069
Weight-SDS	2.46 (1.58-3.84)	3.19 (1.77-6.36)	**0.005**
BMI (kg/m²)	27.87 (24.96-32.00)	33.90 (27.10-44.70)	**< 0.001**
BMI-SDS	2.10 (1.35-2.51)	2.83 (2.08-4.27)	**< 0.001**
SBP (mm/Hg)	120.00 (100-133)	120.00 (90-160)	0.201
DBP (mm/Hg)	80.00 (65-90)	81.00 (52-105)	0.631
Waist/hip ratio	0.82 (0.75-0.95)	0.88 (0.69-1.02)	0.066
Glucose (mg/dL)	92.00 (81-109)	97.00 (78-118)	0.239
Insulin (µU/mL)	21.60 (10.69-31.88)	28.00 (7.46-93.21)	**0.036**
HOMA-IR	4.58 (2.81-7.36)	6.94 (1.46-26.01)	**0.029**
TC (mg/dL)	162.00 (107-205)	144.00 (100-204)	0.482
TG (mg/dL)	81.00 (45-157)	96.00 (33-342)	0.597
HDL-C (mg/dL)	45.00 (35-90)	44.00 (33-74)	0.289
LDL-C (mg/dL)	81.00 (48-106)	81.00 (37-132)	0.791
Neudesin (ng/mL)	3.19 (1.714-6.177)	2.47 (1.144-4.502)	**0.043**

Significant values are indicated in bold.

The data are expressed as medians and (min-max).

BMI-SDS: body mass index-standard deviation score, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, min-max: minimum-maximum

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is the first description of a relationship between obesity, metabolic complications and neudesin levels in children. Very few studies have reported a similar correlation between neudesin and BMI in adults and animal models (3,18).

Bozkaya et al (19) found that circulating neudesin levels were decreased in subjects with polycystic ovary syndrome (PCOS) compared to controls. They proposed, based on their BMI data, that neudesin levels were notably lower in overweight and obese subjects than in lean subjects in both the PCOS and control groups. The work of Byerly et al (14), in their experimental study of recombinant neudesin administration showing increased hypothalamic POMC and MC4R mRNA expression and decreased food intake, suggests that neudesin acts as an anorexigenic neurotrophic factor.

Kratochvilova et al (20) also investigated serum neudesin levels and its mRNA expression in subcutaneous and visceral adipose tissue in obese subjects with or without type 2 diabetes. They found that serum neudesin concentrations in obese subjects, both with and without type 2 diabetes, did not differ from healthy lean control subjects. Similarly, Polkowska et al (21) assessed the serum levels of neudesin in children with type 1 diabetes and showed a statistically significant correlation between BMI and the levels of neudesin in the diabetic children with the longest disease duration. They found statistically higher mean neudesin concentrations in diabetic patients and proposed that IR was greater in these children with diabetes than in their healthy peers and that this difference may explain why neudesin levels were higher in patients with type 1 diabetes than non-diabetic children.

Ohta et al (3) examined the physiological role of neudesin in various tissues of wildtype mice fed a high-fat diet or normal chow food. They showed decreased food intake by

Table 3. Correlation analysis of anthropometric and metabolic parameters

		BMI-SDS	Neudesin (ng/mL)	Waist/hip ratio	Glucose (mg/dL)	Insulin (µU/mL)	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	SBP (mm/Hg)	DBP (mm/Hg)
BMI-SDS		1										
Neudesin (ng/mL)	r	-0.401**	1									
	p	**< 0.001**										
Waist/hip ratio	r	0.293**	-0.042	1								
	p	**0.006**	0.705									
Glucose (mg/dL)	r	0.284**	-0.073	0.092	1							
	p	**0.007**	0.511	0.395								
Insulin (µU/mL)	r	0.634**	-0.228*	0.258*	0.497**	1						
	p	**< 0.001**	**0.037**	**0.015**	**< 0.001**							
TC (mg/dL)	r	0.317**	-0.090	0.120	0.195	0.185	1					
	p	**0.003**	0.415	0.265	0.069	0.085						
TG (mg/dL)	r	0.283**	0.040	0.198	-0.041	0.298**	0.230*	1				
	p	**0.008**	0.720	0.064	0.703	**0.005**	**0.031**					
HDL-C (mg/dL)	r	0.032	-0.034	-0.033	-0.012	-0.168	0.333**	-0.296**	1			
	p	0.766	0.760	0.760	0.915	0.118	**0.002**	**0.005**				
LDL-C (mg/dL)	r	0.173	-0.071	-0.033	0.196	0.085	0.743**	0.185	-0.029	1		
	p	0.108	0.520	0.757	0.067	0.431	**< 0.001**	0.084	0.786			
SBP (mm/Hg)	r	0.474**	-0.246*	0.089	0.357**	0.430**	0.058	0.214*	-0.078	0.042	1	
	p	**< 0.001**	**0.024**	0.409	**0.001**	**< 0.001**	0.592	**0.045**	0.472	0.695		
DBP (mm/Hg)	r	0.461**	-0.250*	0.187	0.241*	0.442**	0.996**	0.297**	**-0.043**	**-0.028**	0.509**	1
	p	**< 0.001**	**0.022**	0.082	**0.024**	**< 0.001**	**< 0.001**	**0.005**	0.690	0.797	**< 0.001**	

Significant values are indicated in bold.
*Correlation is significant at the 0.05 level (two-tailed).
**Correlation is significant at the 0.01 level (two-tailed).
BMI-SDS: body mass index-standard deviation score, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, TG: triglycerides, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol

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Table 4. Comparison of median neudesin levels in subgroups

	Waist/hip ratio > 90 percentile (n = 29)	Waist/hip ratio < 90 percentile (n = 26)	p value
Neudesin (ng/mL)	2.63 (1.14-4.50)	2.62 (1.71-6.17)	0.745
	Hypertensive (n = 25)	Non-hypertensive (n = 33)	
Neudesin (ng/mL)	2.64 (1.14-4.50)	2.46 (1.35-6.17)	0.523
	Insulin resistance (n = 43)	Non-insulin resistance (n = 15)	
Neudesin (ng/mL)	2.64 (1.14-6.17)	2.40 (1.35-4.15)	0.246
	Impaired fasting glucose (n = 24)	Non-impaired fasting glucose (n = 34)	
Neudesin (ng/mL)	2.47 (1.14-4.50)	2.64 (1.35-6.17)	0.730
	Dyslipidemia (n = 18)	Non-dyslipidemia (n = 40)	
Neudesin (ng/mL)	2.64 (1.35-6.17)	2.43 (1.14-4.10)	0.379
	MS (n = 18)	Non-MS (n = 40)	
Neudesin (ng/mL)	2.64 (1.14-4.50)	2.52 (1.35-6.17)	0.259

The data are expressed as medians and (minimum-maximum).
MS: metabolic syndrome, min-max: minimum-maximum

neudesin knockout mice fed normal chow, suggesting that neudesin increased food intake. By contrast, the food intake was similar between wildtype and neudesin knockout mice when fed a high-fat diet, showing that resistance to diet-induced obesity in neudesin knockout mice was independent of food intake. Neudesin administration might therefore only be efficacious in lean mice, while its effects on food intake are blunted in obese mice fed a high-fat diet. Ohta et al (3) also suggested that high fat diet-induced adipocyte hypertrophy was significantly suppressed in neudesin knockout mice. The weights of the liver and BAT were significantly smaller in neudesin knockout mice fed a high-fat diet, and they proposed that these changes might be attributed to increased sympathetic nerve activity (14).

In our study group, 18 obese children were diagnosed with MS, and this prevalence of MS was similar to previous reports from our country (22,23). Neudesin levels tended to be higher in patients with MS; however, the levels were statistically comparable between obese children with or without MS. Triglyceride levels, TC levels, the HOMA-IR index and systolic and diastolic blood pressures were significantly higher in our obese group, but no statistically significant relationships were found between the neudesin levels and IR, dyslipidemia, or hypertension subgroups. In addition, neudesin levels were not different when stratified by waist/hip ratio. Waist/hip ratio was significantly greater in our obese adolescent group compared to the healthy control group, but not strikingly so. In fact, since waist/hip ratio did not show any difference between obese and morbidly obese groups, no significant difference could be found also in neudesin levels. We found no previous studies on neudesin levels in obese children with which to compare our findings.

The study performed by Ohta (18) showed that neudesin knockout mice were protected from obesityinduced metabolic dysfunction and exhibited increased energy expenditure due to increased sympathetic activity. This, in turn, resulted in increased heat production and fatty acid oxidation in BAT and enhanced lipolysis in WAT. They proposed that glucose tolerance was impaired and insulin sensitivity was aggravated by a high-fat diet, whereas neudesin knockout mice were protected from IR induced by a high-fat diet (3).

Kratochvilova et al (20) also reported a possible role of neudesin in the development of obesity-related metabolic disturbances, based on the observed effects of acute fasting and selected weight-reducing interventions, like endoscopic duodenojejunal bypass liner implantation or gastric plication. An obese diabetic group undergoing duodenojejunal bypass liner implantation showed significantly increased concentrations of circulating neudesin. Their serum neudesin levels were also positively correlated with insulin levels and inversely with BMI, while BMI and insulin levels were correlated in subjects undergoing acute fasting.

Study Limitations

There were some limitations in our study. IR was derived by calculation rather than by insulin clamp technique, the gold standard but an invasive method. In addition, we examined the relationship between neudesin levels and metabolic outcomes. However, we could not assess its possible significance in body weight and metabolic control after weight reducing interventions.

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Conclusion

In conclusion, the serum neudesin levels were low in obese and morbidly obese adolescents and tended to increase with the appearance of metabolic disorders. These findings suggest that neudesin may play a role in the regulation of adipose tissue or energy metabolism. However, the potential role of neudesin in MS-related disorders appears to be limited, based on the findings of this study. More research is needed for a better and more robust understanding of the role of the neudesin molecule in the regulatory mechanisms in obesity and related metabolic disorders.

Ethics

Ethics Committee Approval: The study was approved by the Tekirdağ Namık Kemal University University of Non-Invasive Clinical Research Ethics Committee (protocol number: 2019.137.08.09, date: 01.08.2019).

Informed Consent: Written informed consent was obtained from the children's parents after they were informed of the aim and procedures of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Çiğdem Binay, Concept: Aliye Çelikkol, Çiğdem Binay, Design: Aliye Çelikkol, Çiğdem Binay, Savaş Güzel, Data Collection or Processing: Aliye Çelikkol, Çiğdem Binay, Özge Ayçiçek, Savaş Güzel, Analysis or Interpretation: Aliye Çelikkol, Çiğdem Binay, Özge Ayçiçek, Savaş Güzel, Literature Search: Aliye Çelikkol, Çiğdem Binay, Özge Ayçiçek, Savaş Güzel, Writing: Aliye Çelikkol, Çiğdem Binay, Savaş Güzel.

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