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Neudesin Levels in Patients with Thyroidism

Hadeel Abdul Latif Jouad , Shatha Abdul Wadood AL- Shammaree
Department of Chemistry, College of Science, University of Baghdad, Iraq
***Corresponding author:** Hadeel Abdul Latif, Mobile: 07708994614, **Email:** hadeel.abdullateef1205m@sc.uobaghdad.ed

ABSTRACT

Background: Neudesin is a peptide secreted in brain and adipose tissues that has neural and metabolic functions. Its role as regulator of energy expenditure leads to assumption that its level may be regulated depending on thyroid gland pathology.

Objective: This study aimed to investigate serum neudesin levels in patients with thyroidism and to evaluate$_1$ any possible relationship between plasma neudesin levels and thyroid hormone levels.

Methods: The study included 100 women with newly diagnosed thyroidisim were subdivided into two groups: hyperthyroidism group (50 female patients with$_1$ age ranged from 18 to 60 years) and hypothyroidism group (50 female patients with age ranged from 18 to 75 years). A control group (30 healthy females with age ranged from 18 to 70 years) was also included for comparison. Body mass index (BMI) was evaluated. Plasma glucose, lipid profile, triiodothyronine (T3), thyroxin (T4), free T3, free T4, thyroid stimulating hormone (TSH), and neudesin levels were evaluated in all participants using ELISA kit.

Results: The hyperthyroidism group had significantly (p=0.001) higher serum neudesin concentrations (4.47 ± 2.28 ng/mL) than in hypothyroidism (1.15 ± 0.43 ng/mL) and control groups (1.06 ± 0.36 ng/mL). A correlation analysis$_1$ applied to the whole study group revealed a positive correlation between serum neudesin concentration and T4 in patients with hypothyroidism.

Conclusions: Due to the relation of increased$_1$ levels of neudesin in hyperthyroidism, neudesin may$_1$ be related with one of pathophysiologic pathways of thyroidism. Still, it is not certain that higher neudesin level is involved in the pathogenesis$_1$ of thyroidism or as a result of the disorder.

Keywords: Neudesin, Hyperthyroidism, Hypothyroidism.

INTRODUCTION

The thyroid gland is essential for the balance and control of metabolism and growth in the human body [(1)]. Through the continual release of thyroid hormones into the bloodstream in response to physiological demands, it helps to control a variety of altering body activities [(2)]. Thyroid disorders are the most endocrine diseases that doctors need to be familiar with in order to practice [(3)]. The thyroid hormones regulate appetite and caloric intake. T3 affects body weight, thermogenesis, and lipid metabolism by regulating metabolic and energy homeostasis [(4)].

Preadipocytes have receptors for thyroid stimulating hormone (TSH), which causes them to differentiate into adipocytes, increasing adipose tissue [(5)]. The two most prevalent thyroid conditions are hypothyroidism and hyperthyroidism [(6)]

Neudesin is membrane-associated progesterone receptor, also referred to as neuron-derived neurotrophic secreted protein (NENF), and is involved in energy metabolism and tumorigenesis. It has a steroid-binding domain that binds to cytochrome 5-like heme [(7)]. The expression pattern of the progesterone receptor and neudesin genes in the rat forebrain is largely similar. It has been suggested that neudesin may regulate neuroendocrine function by binding to progesterone receptors as a result [(8)].

A protein with 172 amino acids, human neudesin has a high degree of sequence similarity to neudesin from other vertebrates. The signaling pathways of phosphoinositide 3-kinase and mitogen-activated protein kinase (MAPK) are both stimulated by neudesin [(7)] Neudesin being found in the spinal cord and central nervous system, it prompts neural cell differentiation.

Additionally, adipose tissue, the heart, the lungs, and the kidney all display neudesin mRNA expression.

In addition to its neurotropic effects, neudesin can affect how the hypothalamus regulates appetite or how the dentate gyrus of the hippocampus regulates anxiety-like behavior [(9)] Neudesin$_1$ has only been studied in a small number of studies, but current consensus suggests that it may have potential for treating obesity and disorders related to obesity because of its ability to reduce appetite and promote weight loss. [(7, 9)] In the current study, serum neudesin levels in$_1$ a group of thyroidism patients were to be measured.

METHODS

Subjects: In this study, 100 women with previously untreated thyroidisim, aged 18 to 75, participated in a case-control study. In the control group, there were thirty healthy females (aged 18–70 years). Patients were chosen from Al-Imameen Al-kazimin Medical Hospital, Baghdad. The study was conducted through the period from October 2021 to the end of January 2022.

Exclusion criteria: Pregnant women, smokers, people with acute or chronic inflammatory$_1$ diseases, diabetes mellitus (T2DM or T1DM), chronic or hereditary diseases, and family history of thyroidism.

Ethical consent:

This study was accepted$_1$ by the Ethics Committee of the Deanship of Baghdad University Collage of Science. Informed$_1$ consent was obtained

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from each patient. This work was conducted in accordance with the Code of Good Practice and the guidelines of Declaration of Helsinki.

Anthropometric measurement:

/Body mass index (BMI) was calculated after measurement the standing height by stadiometer, and weight using precision scales by the following equation: weight in (kg)/ (height in meter)².

Collection of blood samples:

After an overnight fasting, 5 ml of venous blood from each participant was taken, allowed to clot at room temperature for 10 minutes, and centrifuged at 2400 rpm for 10 minutes before being used for analysis, the separated serum was kept in Eppendorf tubes at -20 ◦C.

Laboratory assessments:

Atellica IM300 (Siemens, Germany) device was used to measure the TSH, T3, and T4 levels, while Cobas Roche was used to measure the levels of free T3 (fT3) and free T4 (fT4) (Hitachi, Germany).

A Cobas Roche was used to measure the levels of glucose, calcium, vitamin D, triglycerides, total cholesterol, and high density lipoprotein cholesterol (HDL-c) using enzymatic methods (Hitachi, Germany).

The Friedewald's equation, which states that low density lipoprotein cholesterol (LDL-C) is equal to total cholesterol minus (HDL-C plus triglycerides/5), was used to calculate LDL-C. Serum neudesin levels were measured using sandwich enzyme-linked immunosorbent assay (ELISA) kit from Al-shkairate establishment according to the manufacturer's instructions (Cat. No: RDEEH4312; Germany).

Statistical analysis

Results are expressed as means ± SD for the comparison of non-parametric variables in both groups. The patients and control groups were compared by using ANOVA test (unpaired student t-test). Correlation between serum neudesin levels and other parameters were assessed by Pearson's correlation analysis. Statistical analysis was performed with SPSS 26 statistical software. A P value for significance was set at 0.05.

RESULTS

Clinical characteristics of the patients and control groups are described in table (1), which revealed non-significant difference in age, height and BMI, when compared with control group, while significant higher levels in weight of hyperthyroidism group than those of hypothyroidism and control groups were observed.

Table (1): Demographic data of test groups (age, weight, height and BMI)

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	p- value
Age (years)	34.32±12.56 (18-70)	39.1±14.01 (18-75)	34.93±12.76 (18-60)	0.320
Weight (kg)	63.96±3.78 (53-72)	77.66±11.08a (63-110)	*68.0±9.11[a] (61-85)	**0.000**
Height (M)	162.85±7.72 (145-174)	160.26±7.86 (145-178)	163.83±7.47 (145-179)	0.186
BMI (kg/m²)	23.58±1.38 (22.3-26.63)	30.37±3.69 (24.5-31.5)	31.44±3.25 (20.5-33.2)	0.284

*P value <0.05. The small letters refer to presence of significance; a: significant when compared with control.

The properties and baseline laboratory values of the patients with thyroidism in comparison with control are shown in table (2). Lipid profile showed different significant levels in the two patient groups when compared to the control group. A significant (P<0.05) increase of TC, LDL-C, and TG levels was found in hypo- and hyperthyroidism when compared to control group.

Table (2): Lipid profile in hyperthyroidism, hypothyroidism, and control groups

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	p- value
TC (mg/dl)	146.86±17.0	*231.93±26.1[a]	204.20±21.4 a,b	**0.00**
TG mg/dl	92.66±16.55	*123.06±6.77[a]	*120.05±4.43[a]	**0.006**
HDL-C mg/dl	53.59±9.10	52.36±10.78	52.82±11.14	0.903
LDL-C mg/dl	102.41±14.57	171.27±8.54a	*143.78±8.96[a]	**0.018**
VLDL mg/dl	24.35±4.49	25.68±5.16	26.86±5.62	0.484

*P value <0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

With statistical significance (P 0.05), the hormonal levels of T3, T4, and FT3 in the hyperthyroidism group were higher than those in the hypothyroidism and control groups, as expected, while the TSH level was significantly lower in the hyperthyroidism group. TSH levels in the hypothyroidism group were significantly higher than those in the hyper and control groups, whereas T3, T4, and FT3 levels were significantly lower than those of the control group (Table 3).

Table (3): Thyroid hormones levels in hyperthyroidism, hypothyroidism, and control groups

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	p- value
TSH µlU/ml	2.43±0.56	*8.45±2.76[a]	*0.50±0.06[a,b]	**0.001**
T3 nmol/L	1.25±0.30	*0.37±0.01 [a]	*2.34±0.10[a,b]	**0.001**
T4 (µg/dl)	9.6±1.08	*3.16±0.99 [a]	*13.37±2.57[a,b]	**0.001**
FT3 pmol/L	3.48±0.28	*3.01±0.17 [a]	3.96±0.55	**0.001**
FT4 (ng/dl)	1.24±0.19	1.21±0.2	1.52±0.15	0.285

*P value <0.05. The small liters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

Neither calcium, nor vitamin D differed significantly between the three groups. However, although glucose level was in the normal range, patients in hypothyroidism group showed significantly lower level (86.96±10.03 mg/dl) than controls (96.96±10.51 mg/dl), as shown in table (4).

Table (4): Ca, Glucose and Vit. D of hyperthyroidism, hypothyroidism, and control groups

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	p- value
Calcium (mg/dl)	8.66±0.699	8.76±0.68	8.66±0.57	0.808
Glucose (mg/dl)	96.96±10.51	86.96±10.03 [a]	91.08±17.33	**0.018**
Vitamin D (ng/ml)	28.66±5.99	25.24±5.05	26.29±4.26	0.211

*P value <0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

Serum neudesin level was significantly higher in hyperthyroidism group (4.47 ± 2.28 ng/mL) with respect to hypothyroidism group (1.15±0.43 ng/mL) and controls (1.06 ± 0.36 ng/mL) (p = 0.001) , while non-significant difference was found between hypothyroidism and control groups, as shown in table (5) and figure (1).

Table (5): Neudesin in hyperthyroidism, hypothyroidism, and control groups

Variables	Controls (n=30)	Hypothyroidism (n=50)	Hyperthyroidism (n=50)	P- value
Neudesin, ng/ml	1.06±0.26	1.15±0.03	4.47±1.28[a ,b]	**0.001**

*P value <0.05. The small letters refer to presence of significance; a: significant when compared with control, b: significant when compared between hypo and hyper.

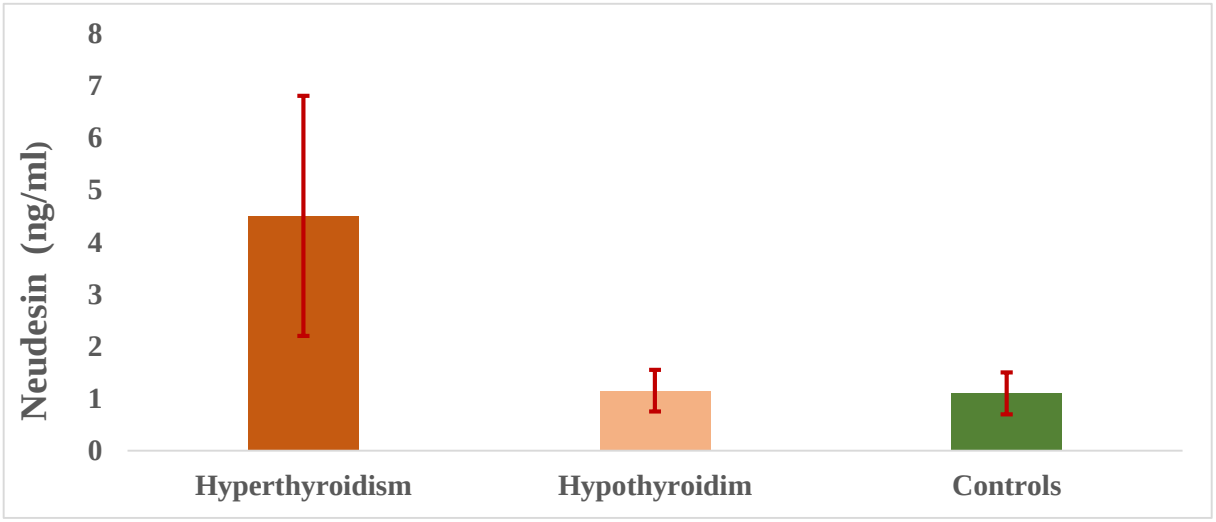
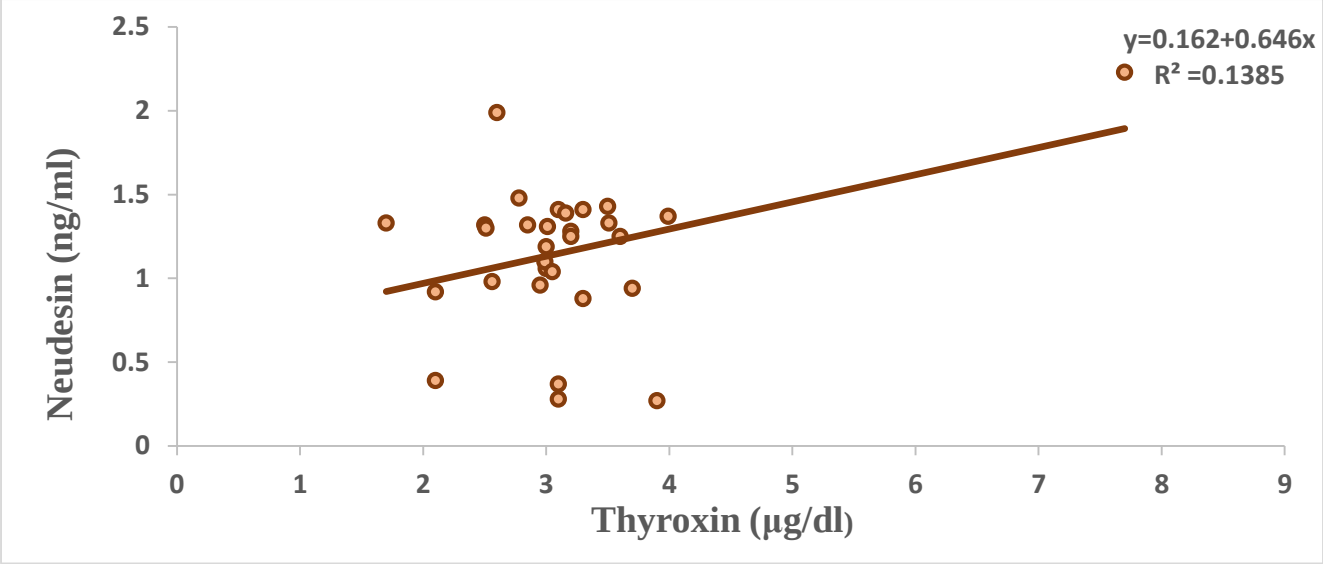


Figure (1): Mean serum level of neudesin in the three groups



There was non-significant correlation between neudesin with other variables in patients with hyperthyroidism and control group. A significant positive correlation was found for thyroxin with neudesin in patients with hypothyroidism (r= 0.373; p= 0.042), which is presented in table (6) and fig (2).

Table (6): Pearson's correlation of neudesin with other variables in patients with hypothyroidism

Variables	Neudesin	
	R	P-value
Age	-0.132	0.487
Weight	-0.033	0.861
Height	-0.212	0.261
BMI	0.128	0.502
TSH	-0.175	0.355
T3	-0.053	0.780
T4	**0.373**	**0.042**
FT3	0.232	0.217
FT4	-0.040	0.835
TC	-0.027	0.888
TG	-0.128	0.501
HDL-C	-0.080	0.674
LDL-C	0.034	0.885
VLDL	-0.167	0.335
Calcium	0.313	0.092

Figure (2): Scatter plot and regression line between thyroxin and neudesin in patients with hypothyroidism.

DISCUSSION

Neudesin may be a novel regulator of food intake and energy homeostasis, according to experimental studies, and it may play a part in the onset of obesity and its complications. An important region of the hypothalamus for controlling appetite, the paraventricular$_1$ nuclei and arcuate nucleus, were found to preferentially express neudesin in earlier studies [10, 11, 12]. Neudesin administration in a mouse model increased the hypothalamic expression of pro-opiomelanocortin (POMC) and melanocortin 4 receptor (MC4R), decreased food intake, and reduced body weight leading to the suggestion that neudesin may affect melanocortin signaling [10]. Neudesin is a negative regulator of myogenesis in cattle, as demonstrated by **SU *et al.*** [11]. Neudesin knockdown inhibited pre-adipocyte differentiation and facilitated myoblast myogenesis. In patients with newly diagnosed type 2 diabetes, serum neudesin levels were discovered to be elevated and to be correlated with HOMA-IR values. Therefore, it was determined that elevated neudesin levels could possibly be linked to insulin resistance. Neudesin may regulate insulin sensitivity and glucose metabolism, according to a study done on adults and children with T2DM and T1DM, respectively [12].

To the best of our knowledge, circulating neudesin concentrations have never been assessed in thyroidism and this is the first assessment of neudesin in thyroidism. According to this study, hyperthyroidism has significantly higher neudesin levels than

hypothyroidism and the control groups. Serum neudesin in human blood has only been examined in a small number of studies, with mixed results. A study that compared patients with functional hypoglycemia, healthy controls, and obese adults (81% with T2MD) undergoing endoscopic bariatric procedures found no differences in the serum neudesin levels of any of these groups. As a result, the authors proposed that neudesin behaves differently under chronic versus acute energy restriction [(13)].

On the other hand, compared to controls of the same age and BMI, adult patients with newly diagnosed T2DM had higher serum levels of neudesin [(14)]. However, the detected serum concentrations of neudesin are roughly 30 times greater than those in our paper in the majority of the earlier papers [(14 15, 16)] It was noted that obese adolescents' plasma levels of neudesin were significantly lower than those of normal-weight adolescents [(17)]. The release of neudesin into the blood was thought to be a defence mechanism against IR and being overweight [(18)].

Thyroid hormones$_1$are important determinants$_1$of cellular metabolism and regulate a number of pathways involved in the metabolism of carbohydrates, lipids, and proteins in a variety of target tissues. Notably hyperthyroidism causes a hypermetabolic state characterized by increased resting energy expenditure, lower cholesterol levels, increased lipolysis and gluconeogenesis, and weight loss, whereas hypothyroidism causes a hypometabolic state characterized by increased resting energy expenditure, higher cholesterol levels, lower lipolysis and gluconeogenesis, and weight gain[(18)].

CONCLUSION

Neudesin, because of the role it plays in metabolism, plays an essential role in thyroidism. To verify these findings, we need to conduct additional research. Because of these properties, neudesin has the potential to be the focus of additional research regarding the treatment and prevention of thyroidism.

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