Kocatepe Tıp Dergisi
Kocatepe Medical Journal
23:339-343 / Temmuz 2022 Sayısı

ARAŞTIRMA YAZISI / RESEARCH ARTICLE

KRONİK OTOİMMÜN TİROİDİT VE NESFATİN-1 DÜZEYİ ARASINDAKİ İLİŞKİ

ASSOCIATION BETWEEN CHRONIC AUTOIMMUNE THYROIDITIS AND NESFATIN-1 LEVELS

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ÖZET

AMAÇ: Bu çalışmanın amacı kronik tiroiditli hastalarda nesfatin-1 düzeyi ile tiroid otoimmünitesi arasındaki ilişkiyi değerlendirmektir.

GEREÇ VE YÖNTEM: Hashimoto tiroiditli 49 premenopozal kadın ve yaş ve vücut kitle indeksi (VKI) uyumlu 23 sağlıklı kadın, bu kesitsel karşılaştırmalı çalışmaya dahil edildi. Plazma nesfatin-1, açlık ve tokluk glukoz, hemoglobin A1c (HbA1c), açlık insülin, kolesterol parametreleri, serbest tiroksin (ST4), serbest T3 (ST3), tirotropin (TSH), anti-tiroid peroksidaz antikor (anti-TPO) and anti-tiroglobin (anti-TG) antikor değerleri için kan örnekleri alındı. Ek olarak tüm vakalarda, insülin direnci için homeostatik model değerlendirmesi (HOMA-İR) ve vücut kitle indeksi (VKİ) hesaplandı ve bel/kalça oranı ölçüldü.

BULGULAR: Hashimoto tiroiditli hastaların ortalama yaşı 35,5±8,1, kontrol grubunun ise 33,2±7,1 idi (p=0.324). VKI ve bel/kalça oranı, gruplar arasında benzerdi (p=0.239 ve p=0.317). TSH, anti-TPO ve anti-TG düzeyleri hasta grubunda anlamlı derecede yüksekti (p=0.023, p<0.001 ve p<0.001). Hastalarda trigliserid düzeyleri istatistiksel anlamlılık sınırında daha yüksekti(p=0.05). Her iki grup arasında nesfatin düzeyleri açısından istatistiksel anlamlı farklılık yoktu [0,4 (0,39-0,43), 0,39 (0,39-0,39) ng/ml;p=0.329].

SONUÇ: Kronik otoimmün tiroiditte tiroid hormon değişiklikleri ya da otoimmünite, nesfatin-1 düzeylerinde değişikliğe yol açmayabilir. Hashimoto tiroiditli hastalardaki tokluk ve enerji tüketiminden nesfatin-1 dışındaki mekanizmalar sorumlu olabilir.

ANAHTAR KELİMELER: Hashimoto tiroiditi, Kronik otoimmün tiroidit, Nesfatin, Tiroid stimulan hormon, Tiroid otoantikor.

ABSTRACT

OBJECTIVE: The aim of this study was to evaluate relationship between nesfatin-1 levels and thyroid autoimmunity in cases with chronic thyroiditis.

MATERIAL AND METHODS: A total of 49 consecutive premenopausal women with Hashimoto's thyroiditis and, age and body mass index (BMI)-matched 23 healthy female subjects were included in this cross-sectional comparative study. Levels of nesfatin-1, fasting and postprandial blood glucose, hemoglobin A1c (HbA1c), fasting insulin, cholesterol, free thyroxine (FT4), free triiodothyronine (FT3), thyrotropin (TSH), anti-thyroid peroxidase antibody (anti-TPO) and anti-thyroglobulin antibody (anti-TG) were obtained for all cases. Additionally homeostatic model assessment for insulin resistance (HOMA-IR) and BMI was calculated and waist-to-hip ratio (WHR) was measured for each case.

RESULTS: The mean age of the group with Hashimoto's thyroiditis was 35.5±8.1 years and of the healthy controls was 33.2±7.1 years old (p=0.324). BMI and WHR were similar between the groups (p=0.239 and p=0.317). TSH, anti-TPO and anti-TG levels were significantly higher in cases with Hashimoto's thyroiditis (p=0.023, p<0.001 and p<0.001). Triglyceride levels were higher in the patients with Hashimoto's thyroiditis at the limit of statistical significance (p=0.05). Nesfatin levels were not different statistically in between two groups [0.4 (0.39-0.43) , 0.39 (0.39-0.39) ng/ml;p=0.329].

CONCLUSIONS: Alterations in thyroid hormones or autoimmunity in chronic autoimmune thyroditis may not alter nesfatin-1 levels. Different mechanisms, other than nesfatin-1, may be responsible for changes in satiety and energy expenditure in Hashimoto's thyroiditis.

KEYWORDS: Hashimoto's thyroditis, Chronic autoimmune thyroditis, Nesfatin, Thyroid stimulating hormone, Thyroid autoantibody.

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Kabul Tarihi / Accepted: 15.11.2021
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Etik Kurul / Ethical Committee: Ankara Training and Research Hospital Ethics Committee (26.01.2011/0402).

INTRODUCTION

Nesfatin-1 is a neuropeptide involved in satiety, metabolism and energy expenditure and identified in paraventricular nucleus of the hypothalamus and pancreatic tissue (1 - 3). It is associated with decreased food intake, reduced body weight and increase in arterial blood pressure (4). Its levels vary in various diseases which are also associated with alterations in metabolism (5 - 8).

Thyroid disorders have been also connected with certain changes in satiety, metabolism and energy homeostasis. Moreover nesfatin-1 affects the membran potential of thyroid releasing hormone (TRH) neurons as its neurons are located near the TRH neurons in the paraventricular nucleus (2). Previous studies have shown conflicting results on the changes in nesfatin-1 levels in cases with thyroid dysfunction (3, 9 - 16). Hashimoto thyroiditis is the most frequent autoimmun disorder of the thyroid gland. There are few studies investigating the relationship between thyroid autoimmunity and nesfatin-1 level (13). Herein our aim was to evaluate association between nesfatin-1 levels and autoimmunity in cases with chronic thyroiditis.

MATERIALS AND METHODS

The patient group was composed of 49 consecutive premenopausal women with Hashimoto's thyroiditis applying to our endocrinology outpatient clinic. Age and body mass index (BMI)-matched 23 healthy female subjects comprised the control group. Cases who had previous surgical and/or medical theraphy and/or radiotherapy for thyroid disease were excluded. Additionaly, patients with other autoimmune disorders, diabetes mellitus, acute/chronic hepatic or renal disease, cancer, acute/chronic inflammatory and infectious disease, pregnancy, lactation and less than 18 years of age were not included in the study.

Diagnosis of Hashimoto's thyroiditis (chronic autoimmune thyroiditis) was determined by presence of antibodies to thyroglobulin (anti-TG) and/or thyroid peroxidase (anti-TPO) and/or ultrasonographical features suggestive of Hashimoto's thyroiditis (enlarged gland, which is hypoechoic, with coarsened parenchyma and is often hypervascular) and/or previous pathologic verification after a fine-needle aspiration biopsy for thyroid nodule evaluation (17).

Demographic features were obtained for all cases. BMI was calculated as weight of patient divided by the square of the height (BMI=kg/m^2). Additionally waist-to-hip ratio (WHR) was evaluated for each case. Blood was obtained to determine fasting blood glucose (Normal 75-100 mg/dl), fasting insulin (Normal: 2-25 µIU/mL), C-peptide levels (Normal: 0.28-2 nmol/L), postprandial blood glucose, hemoglobin A1c (HbA1c) (Normal:4.8-6%), low-density lipoprotein (LDL) (Normal: 60-130 mg/dl), triglyceride (Normal: 50-200mg/dl), high-density lipoprotein (HDL) (40-85 mg/dL) levels for each case. Insulin resistance was calculated by homeostasis model of assessment (HOMA-IR) according to formula that fasting blood glucose x fasting insulin / 405. Cases with HOMA-IR >2.5 were considered to have insulin resistance (18). Chemiluminescence immunoassay was performed to assess thyrotropin (TSH) (N: 0.35-5.5 µIU/mL), free thyroxine (FT4) (N: 0.7-1.76 ng/dL), free triiodothyronine (FT3) (N: 2.3-4.2 pg/mL), anti-TPO (N: 0-60 U/mL) and anti-TG (N : 0-60 U/mL) (Advia Centaur System,Siemens). Nesfatin-1 levels were measured by using RayBio® Nesfatin-1 Enzyme Immunoassay (EIA) Kit (Cat. no. EIA-NES-1, RayBiotech, Inc). Normal range is 0.1-1 ng/ml, inter-assay CV <15% and intra-assay CV <10% for Nesfatin-1. All of the parameters were evaluated according to the antibody titers and compared with the healthy controls.

All the subjects read and signed the informed consent forms before enrolling in the study.

Ethical Committee

Local ethics committee approved the study protocol (Ankara Training and Research Hospital, 26.01.2011/0402).

Statistical Analysis

The data was statistically analyzed with the SPSS 17.0 package program. The Chi-square test was used for categorical variables. Sample distribution was evaluated with the Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared by using the student's T test, presenting the results as mean and standart deviation. Continuous va-

riables with non-normal distributions were compared by using the Mann-Whitney U test and the results were presented as median and interquartile range [IQR]. The Pearson's correlation coefficient was used for calculation of associations between variables. p<0.05 was considered statistically significant.

RESULTS

The mean age of the group with Hashimoto's thyroiditis was 35.5±8.1 years and of the healthy controls was 33.2±7.1 years old (p=0.324). BMI of the cases with Hashimoto's thyroiditis and of the healthy controls was 27.5±5.2 and 25.8±6.7 kg/m2 (p=0.239). Waist-to-hip ratio (WHR) in cases with Hashimoto's thyroiditis was 0.8±0.06 and in healthy controls was 0.8±0.04 (p=0.317). FT4, TSH, anti-TPO and anti-TG levels were significantly higher in cases with Hashimoto's thyroiditis (p=0.014, p=0.023, p<0.001 and p<0.001). Triglyceride levels tended to be higher in the group with Hashimoto's thyroiditis (p=0.050). Nesfatin-1 levels were comparable between the two groups (p=0.329). Other laboratory values were also similar between the groups **(Table 1)**.

Table 1: Comparison of the age, antropometric and laboratory parameters between cases with Hashimoto thyroiditis and healthy controls

	Hashimoto's Thyroiditis (n=49)	Healthy Controls (n=23)	p
Age (years)	35.5±8.1	33.2±7.1	0.324
BMI (kg/m²)	27.5±5.2	25.8±6.7	0.239
WHR	0.8±0.06	0.8±0.04	0.317
Fasting glucose (mg/dl)	90 (85-95)	90 (84-96)	0.914
Fasting insulin (mIU/ml)	11.2 (7.9-14.6)	8.8. (4.9-14.1)	0.248
C-peptide (mIU/ml)	1 (0.7-1.5)	0.8 (0.6-1.3)	0.278
HOMA-IR	2.2 (1.4-3)	1.8 (0.9-2.9)	0.213
Postprandial glucose(mg/dl)	93 (81-107)	96 (84.8-110.5)	0.671
HbA1c (%)	5.5 (5.4-5.7)	5.4 (5.3-5.7)	0.363
Total cholesterol (mg/dl)	180 (154.5-195.5)	186 (157-205)	0.592
LDL (mg/dl)	109 (89.5-124)	112 (95-142)	0.423
HDL (mg/dl)	47 (40-54)	50 (44-53)	0.394
Triglyceride (mg/dl)	104 (78.5-142)	82 (62-106)	**0.050**
Free-T3 (pg/ml)	3.3 (3.1-3.5)	3.4 (3.2-3.6)	0.279
Free-T4 (ng/dL)	0.9 (0.8-1.1)	1 (0.9-1.1)	**0.014**
TSH (mIU/mL)	3.3 (1.7-7.1)	1.8 (1.3-2.7)	**0.023**
Anti-TPO (IU/ml)	596.8 (88.2-1300)	44.6 (37.5-50.9)	**<0.001**
Anti-TG (IU/ml)	118.5 (50.4-253.7)	29.8 (24.2-40.1)	**<0.001**
Nesfatin-1 (ng/ml)	0.4 (0.39-0.43)	0.39 (0.39-0.39)	0.329

Data was expressed as median (IQR: 25th -75th percentiles)

BMI: body mass index, WHR: waist-to-hip ratio HOMA-IR: homeostasis model of assessment for insulin resistance, HbA1c: hemoglobin A1c, LDL: low-density lipoprotein (LDL), HDL: high-density lipoprotein, Free-T3: free triiodothyronine, Free-T4: free thyroxine, TSH: thyroid stimulating hormone, Anti-TPO: anti-thyroid peroxidase antibody, Anti-TG: anti-thyroglobulin antibody

In the entire cohort and also in only cases with Hashimoto's thyroiditis nesfatin-1 levels were positively correlated with HbA1c and triglyceride levels (For HbA1c in entire cohort: r=0.3,p=0.009 and in Hashimoto's cases: r=0.4, p=0.004. For triglyceride in entire cohort: r=0.3, p=0.021 and in Hashimoto cases: r=0.4, p=0.012) **(Figure 1 and 2)**. Neither in the entire cohort nor in cases with Hashimoto's thyroiditis nesfatin-1 levels were correlated with FT3, FT4, TSH, anti-TPO or anti-TG levels.

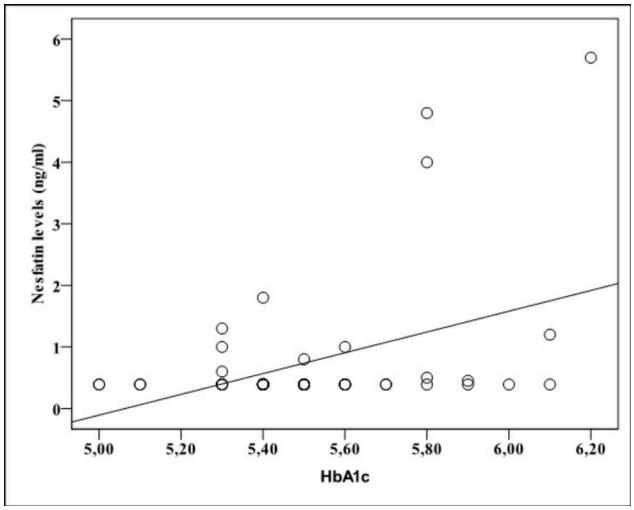

Figure 1: Nesfatin levels and HbA1c in cases with Hashimoto's thyroiditis were positively correlated

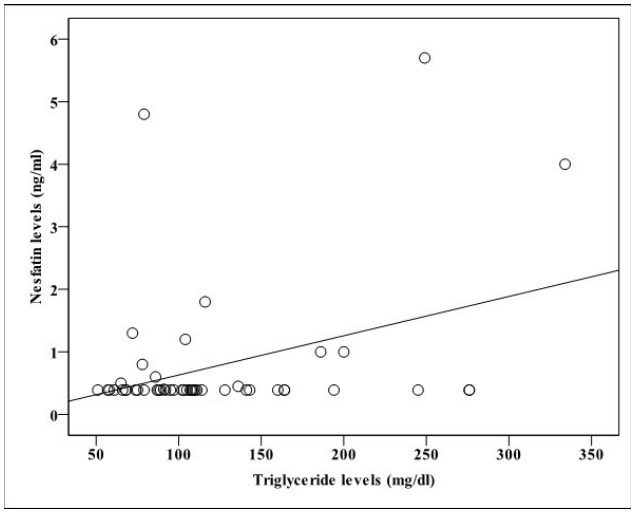

Figure 2: Nesfatin levels and triglyceride levels in cases with Hashimoto's thyroiditis were positively correlated

DISCUSSION

In the current study, Hashimoto's thyroiditis and control group had similar levels of nesfatin-1. Nesfatin-1 levels were correlated with HbA1c and triglyceride levels both in the entire cohort and the group with Hashimoto's thyroiditis. However there was not any correlation between nesfatin-1 levels and thyroid hormones or antibody levels. This means although nesfatin-1 may have certain impacts on metabolic control, these effects are not dependent on the thyroid hormone status or thyroid autoimmunity.

Nesfatin-1 is an anorexic peptide responsible for apetite supression and control of glucose homeostasis (1 - 2, 4, 8). Thyroid hormones also

have effect of satiety and metabolism. They share certain common points in their mechanism of effects (2, 19 - 21). Therefore it is of concern whether there could be a change in the levels of nesfatin-1 with changing thyroid hormone status or altered autoimmunity in thyroid disorders. Certain studies have shown changes in nesfatin-1 levels in cases with thyroid disorders, while others have not shown any change.

In the present study, despite the difference in the levels of FT4, TSH, anti-TPO and anti-TG, none of these parameters were correlated with nesfatin-1 levels both cases with Hashimoto's thyroiditis and healthy controls. Sawicka et al. (3) have shown decreased nesfatin-1 levels in children with Hashimoto's thyroiditis having subclinical hypothyroidism. However the same study has not proven a relationship between nesfatin-1 and thyroid hormones. Therefore the decrease in nesfatin-1 levels could not be attributed to change in hormone levels (3). Similarly, another study determined that nesfatin-1 levels were not correlated with FT3, FT4, TSH, anti-TG and anti-TPO levels (13). In a more recent study consisted of patients with Hashimoto's thyroiditis, serum nesfatin-1 concentrations were comparable when patients were divided into three different TSH range groups (< 4.5, 4.5-6.5, and > 6.5 m IU/L) (12). Thyroid function was negatively correlated with nesfatin-1 levels and recovered after the restoration of the thyroid function in rats (14). In a recent study conducted with rats exposed to mobile phone radiation, plasma nesfatin-1 level was correlated negatively with oxidative stress, apoptosis, and thyroid dysfunction (11). Xu et al. have shown that nesfatin-1 were positively correlated with TSH in depressed patients with subclinical hypothyroidism. This may be indicate that the mechanism underlying the comorbidity of depression and subclinical hypothyroidism might be related to the dysfunction of the hypothalamus–pituitary–thyroid axis (16). Another study on cases with subclinical and overt hyperthyroidism have not shown a significant change in nesfatin-1 levels (10), but Tohma et al. (15) have determined nesfatin-1 levels are remarkably affected by hyperthyroidism. It was correlated with TSH negatively and with FT3 and FT4 positively. They pointed that nesfatin-1 levels decreased after restoration of euthyroidism (15). In disagreement with this study, we did not find any correlation between nesfatin-1 and FT3, FT4 in our study. We also would like to point that all metabolic parameters were comparable between groups and our results showed neither the change in thyroid hormones nor the antibody levels cause change in nesfatin-1 levels. Metabolic parameters were also similar between the groups, thereby we could exclude confounding factors which could have impact certain effects on nesfatin-1 levels.

In the entire cohort and also in only cases with Hashimoto's thyroiditis nesfatin-1 levels were positively correlated with HbA1c and triglyceride levels revealing effect on glucose and lipid metabolism in our study. Sahin et al. (13) also found no significant correlation between nesfatin-1 levels and BMI, waist circumference, fasting and postprandial plasma glucose, fasting insulin and HOMA-IR while a significant negative correlation with triglyceride levels. In another study, similar results was achieved related to correlation between nesfatin-1 and anthropometric and biochemical parameters, except for triglyceride levels which was not correlated with nesfatin-1 levels (12). In a systematic review and meta-analysis, it was determined that nesfatin-1 levels and type 2 diabetes were related. Type 2 diabetes mellitus was characterized higher nesfatin-1 levels in early stages of disease, whereas its lower levels in late stages of the disease or in patients recieving antidiabetic treatment (8). The mechanism of these alterations is presently not well understood.

In conclusion; we did not find any alteration in serum levels of nesfatin-1 in patients with Hashimoto's thyroiditis. Different mechanisms other than nesfatin-1 may be responsible for changes in satiety and energy expenditure in Hashimoto's thyroiditis. Further studies are needed with larger sample sizes examining the relationship between Nesfatin-1 and thyroid autoimmunity.

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