



Frequency of Nodular Goiter in Patients with Non-Functional Adrenal Incidentaloma

Non-Fonksiyonel Adrenal Insidentalomalı Hastalarda Nodüler Guatr Sıklığı

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Abstract

Objective: Thyroid nodules and metabolic disorders such as obesity, insulin resistance (IR), and dyslipidemia are frequently reported in patients with non-functional adrenal incidentaloma (NFAI). This study aimed to evaluate the structural and functional properties of the thyroid gland and to elucidate whether there is any relationship between these and metabolic parameters in patients with NFAI. **Material and Methods:** Fifty-four patients diagnosed with NFAI and 54 age, gender, and body mass index (BMI) matched healthy controls were included in the study. Free thyroxine (fT4), thyroid-stimulating hormone (TSH), anti-thyroperoxidase antibody (anti-TPO), fasting blood glucose (FBG), fasting insulin level, lipid profiles, C-reactive protein (CRP) levels were estimated in the patients and controls. Furthermore, patients and controls were evaluated by ultrasonography to determine thyroid structure, thyroid volume, and thyroid nodules. **Results:** The mean total thyroid volume of the NFAI group (13.48±6.3 mL) was significantly higher as compared to that of the control group (13.13±10 mL) ($p<0.001$). Thyroid nodules were detected in 18 (33.3%) of 54 subjects in the NFAI group and 16 (29.6%) of 54 subjects in the control group, resulting in an insignificant difference ($p = 0.836$). However, the average number of thyroid nodules was significantly higher in the NFAI group (1.72) compared to the control group (1.06) ($p<0.001$). The thyroid nodule size of the NFAI group (17.83±9.01 mm) was also significantly larger than the control group (11.68±4.68 mm) ($p=0.017$). Moreover, a significant association between the thyroid nodule and TSH ($p=0.026$) and between thyroid nodule size and adenoma size ($p=0.046$) in the NFAI group was pronounced. **Conclusion:** In our study, we found that certain parameters related to the thyroid gland, such as thyroid volumes, average number of thyroid nodules, and thyroid nodule sizes, were significantly higher in NFAI patients than in healthy controls. There was no significant difference in terms of thyroid functions and thyroid nodule frequency. In this regard, studies with larger sample size, encompassing all factors that may affect thyroid structure and functions, are essential.

Keywords: Adrenal incidentaloma; thyroid nodule; goiter

Özet

Amaç: Nonfonksiyonel adrenal insidentalomalı (NFAİ) hastalarda; tiroid nodülleri ve obezite, insülin direnci ve dislipidemi gibi metabolik bozukluklar yaygın olarak görülür. Bu çalışmanın amacı, NFAİ olan hastalarda tiroid bezinin yapısal ve fonksiyonel özelliklerini ve bu özelliklerle metabolik parametreler arasında bir ilişki olup olmadığını belirlemektir. **Gereç ve Yöntemler:** NFAİ tanısı alan 54 hasta ile yaş, cinsiyet ve vücut kitle indeksi (VKİ) uyumlu 54 sağlıklı kontrol çalışmaya dâhil edildi. Hasta ve kontrol gruplarının serbest tiroksin (sT4), tiroid stimulan hormon (TSH), anti-tiroperoksidaz antikorunu (anti-TPO), açlık kan şekeri (AKŞ), açlık insülin seviyesi, lipid profilleri, C-reaktif protein (CRP) düzeyleri ölçüldü. Ayrıca, hasta ve kontrol grupları tiroid yapısı, tiroid hacmi ve tiroid nodüllerinin belirlenmesi için ultrasonografi ile değerlendirildi. **Bulgular:** Ortalama toplam tiroid hacmi NFAİ grubunda (13,48±6,3 ml) kontrol grubuna göre (13,13±10 ml) anlamlı olarak yüksekti ($p<0,001$). NFAİ grubundaki 54 hastanın 18'inde (%33,3), kontrol grubundaki 54 hastanın 16'sında (%29,6) tiroid nodülleri tespit edildi ve anlamlı fark saptanmadı ($p=0,836$). Ortalama tiroid nodül sayısı NFAİ grubunda (1,72) kontrol grubuna göre (1,06) anlamlı olarak yüksekti ($p<0,001$). Tiroid nodülü boyutu NFAİ grubunda (17,83±9,01 mm) kontrol grubuna göre (11,68±4,68 mm) anlamlı olarak yüksekti ($p=0,017$). Ayrıca, NFAİ grubunda tiroid nodülü ile TSH ($p=0,026$) düzeyi arasında ve tiroid nodülü boyutu ile adenom boyutu ($p=0,046$) arasında anlamlı bir ilişki tespit edildi. **Sonuç:** Çalışmamızın sonuçlarına göre, NFAİ hastalarında tiroid hacimleri, ortalama tiroid nodül sayıları ve tiroid nodül boyutları normal popülasyona göre daha yüksek, tiroid fonksiyonları ve tiroid nodül sıklığı normal popülasyonla benzer olarak tespit edildi. Bu konu ile ilişkili olarak, daha büyük örneklem boyutuna sahip olan, tiroid bezinin yapısını ve fonksiyonlarını etkileyebilecek tüm parametreleri içeren çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Adrenal insidentaloma; tiroid nodülü; guatr

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Introduction

The adrenal masses identified by chance during performed radiological imaging methods, conducted for reasons other than adrenal disease, are defined as adrenal incidentaloma. Studies have revealed the prevalence of this disease is about 3% in the 50s and increases with age, up to 10% (1). NFAI accounts for approximately 80% of AI's (2).

Thyroid nodules are commonly observed in the population. Nodule incidences are known to increase with age, and the sonographic prevalence is found to reach 50% over 50 years. In our country, the sonographic prevalence of thyroid nodules was estimated to be 23.5% between 18-65 years of age and 37.4% above 65 years of age (3). Advanced age, female gender, iodine deficiency, and radiation exposure are predisposing factors that augment the incidence of thyroid nodules (4). Recent studies have documented a high prevalence of insulin resistance, metabolic syndrome, and obesity is associated with an increase in thyroid volume and nodule frequency in iodine-sufficient regions (5).

The response of endocrine cells to growth-stimulating factors dictates the process of adrenal and thyroid nodular formation (6,7). Adrenocorticotrophic hormone (ACTH) and TSH are the main growth stimulating factors that trigger the growth of adrenal and thyroid cells. Moreover, the insulin/insulin-like growth factor system is thought to be responsible for promoting the growth of adrenal and thyroid cells (8,9).

Metabolic disorders, including obesity, insulin resistance, dyslipidemia, are also common in patients with NFAI (10). Compared to the normal population, insulin resistance is more frequent in NFAI patients. The hyperinsulinemia accompanying insulin resistance induces activation of insulin/IGF receptors and causes a mitogenic effect on the adrenal cortex. Insulin resistance is also found to be correlated with adenoma size (11).

The presence of common growth factors stimulating the growth of adrenal and thyroid cells, coupled with the increased frequency of thyroid nodules in patients with metabolic disorders such as obesity, insulin resistance, and dyslipidemia (common in

NFAI patients), indicate that there may be a relationship between NFAI and thyroid nodules.

In our study, we tried to evaluate the structural and functional status of the thyroid gland in NFAI patients and to determine if there is a relationship between them and the metabolic parameters.

Material and Methods

This study was conducted between 01.01.2020 and 31.03.2020 at Meram Faculty of Medicine, Department of Endocrinology, and Metabolism. The study protocol was approved by the Ethics Committee of Meram Medical Faculty on 21/02/2020 with the decision numbered 2020/2325 and was carried out following the Helsinki Declaration Principles. Informed consent was obtained from all participants. The study comprised of 54 patients diagnosed with NFAI. The diagnosis of adenoma was achieved by an unenhanced CT scan. The adrenal lesion was accepted as an adenoma if attenuation was ≤ 10 HU on an unenhanced CT scan. Patients with adrenal lesion attenuation >10 HU on an unenhanced CT scan were excluded from the study. No specific hormone excess signs and/or symptoms were detected in patients with NFAI. There were no signs and/or symptoms of active endocrine or non-endocrine disease that could affect screening test results. All NFAI patients were diagnosed with Cushing's syndrome, subclinical Cushing's syndrome, and pheochromocytoma, and NFAI patients with hypertension and/or hypokalemia were also screened for primary hyperaldosteronism. NFAI patients were subjected to a 1 mg overnight dexamethasone suppression test to rule out a diagnosis of Cushing's syndrome. The test was performed by administration of 1 mg dexamethasone at 11pm, and determination of fasting plasma cortisol at 8am the following day. Patients without serum cortisol levels <1.8 $\mu\text{g/mL}$ were excluded from the study. In terms of pheochromocytoma, patients with 24-hour urinary metanephrine or normetanephrine levels equal to or higher than two times the upper limit of normal were excluded from the study. In terms of primary hyperaldosteronism, patients having a plasma aldosterone concentration >15 ng/dL or plasma

aldosterone/plasma renin activity ratio >20 were excluded from the study. Based on these tests, patients whose AI was determined to be non-functional were included in the study.

The control group incorporated 54 healthy volunteers. Control subjects were selected from healthy volunteers with normal adrenal imaging (abdomen and/or adrenal CT) who matched with the patients in terms of age, gender, and BMI. Patients and healthy controls under 18 and over 65 years of age, with known thyroid disease, diabetes mellitus, hyperlipidemia, chronic liver and kidney diseases, atherosclerotic cardiovascular disease, were excluded from the study.

The height (m), weight (kg), hip circumference (HC), waist circumference (WC) of patients and controls were assessed, and WHR (Waist-Hip Ratio) was calculated. After a 10-minute rest period, blood pressure was measured from both arms and was recorded as systolic (SBP) diastolic (DBP).

Biochemical and hormonal laboratory data of the patients were collected from patient files. IR was computed according to the formula below.

HOMA-IR (Homeostatic Model Assessment of Insulin Resistance): $(\text{FBG (mg/dL)} \times \text{fasting insulin (mU/l)})/405$.

The lower and upper limits were as follows: TSH: 0.28-4.5 mU/L; fT4: 0.94-1.77 ng/dL; anti-TPO Ab: 0-35 U/mL. Anti-TPO concentrations exceeding 35 IU/mL were considered positive.

The patients and controls underwent ultrasonography at our clinic under the supervision of an experienced endocrinologist using a 12MHz linear probe on a LOGIQ 3 ultrasonography (US) device. Lesions larger than 3 mm detected in the US were regarded as nodules. Thyroid volumes were estimated separately for each lobe using the elliptical shape volume formula ($\times \text{width} \times \text{length} \times \text{height} \times 0.479$). Adding up both the thyroid lobe volumes, the total thyroid volume was obtained.

Statistical analysis was computed using the SPSS 22.0 (Statistical Package for Social Sciences) program. Continuous variables were represented as mean \pm standard deviation for normal distribution and as median (minimum-maximum) if the distribution was not normal. In the comparison of independ-

ent group differences, the significance test of the difference between the two means (Independent samples t-test) was used when the parametric test assumptions are provided; The Mann-Whitney U test was applied to compare the independent group differences when the parametric test assumptions were not provided. Pearson's and Spearman's tests were adopted for correlation analysis between numerical variables showing normal distribution. For differences, $p < 0.05$ value was considered statistically significant.

Results

The study involved 108 cases, including 54 NFAI patients and 54 healthy control. Of the 54 patients, 36 (66.6%) were female, 18 (33.4%) were male. The mean age of the NFAI patients was 48.89 ± 10.7 years. The control group (54 subjects) comprised of 35 (64.8%) female and 19 (35.2%) male.

The mean age of the control group was 48.57 ± 10.5 years (Table 1). Adenoma was located on the right in 17 patients (31.5%), on the left in 28 patients (51.9%), and bilaterally in nine patients (16.7%). The mean adenoma size was 20.7 ± 7.5 mm.

Hypertension (HT) was detected in 22 (40.7%) of 54 NFAI patients and 10 (18.5%) of 54 controls. Statistical analysis revealed the frequency of HT was significantly higher in the NFAI group ($p=0.020$). BMI, WHR, SBP, DBP, FBG, plasma insulin, HOMA-IR, total cholesterol, and LDL-C (Low-Density Lipoprotein-Cholesterol) levels were higher in the NFAI group than the control group, though the difference was statistically insignificant. HDL-C (High-Density Lipoprotein-Cholesterol), TG (Triglyceride), CRP (C-Reactive Protein), TSH, fT4, anti-TPO levels were lower in the NFAI group compared to the control group, but there was no significant difference (Table 1).

Total thyroid volume was 13.48 ± 6.3 mL for the NFAI group and 13.13 ± 10 mL of the control group. The total thyroid volume of the NFAI group was significantly higher than the control group ($p < 0.001$). Thyroid nodules were observed in 18 (33.3%) of 54 NFAI patients and 16 (29.6%) of 54 controls. No significant difference was obtained between the NFAI and control groups in terms of the presence of thyroid nodules

Table 1. Demographic and clinical characteristics of NFAI and control groups.

	NFAI (n=54)	Control (n=54)	p
Age (years)	48.89±10.7	48,57±10.5	0.831
Gender (female/male)	36-18	35-19	0,840
Hypertension n (%)	22 (40.7)	10 (18.5)	0.020
BMI (kg/m ²)	30.80±6.11	29.65±6.46	0.323
WHR	0.88±0.06	0.84±0.06	0.728
SBP (mmHg)	122±16	116±17	0.092
DBP (mmHg)	78±11	77±10	0.995
Glucose (mg/dL)	95.57±8.97	95.17±9,26	0.390
Insulin (μU/mL)	13.88±7.32	13.78±10.17	0.282
HOMA-IR	3.26±1.69	3.23±2.35	0.296
Total-cholesterol (mg/dL)	193.71±43.62	193.48±36.76	0.961
HDL-cholesterol (mg/dL)	48.91±14.94	50.36±15.09	0.433
LDL-cholesterol (mg/dL)	114.97±38.11	108.97±35.56	0.559
TG (mg/dL)	150.32±78.81	159.67±101.87	0.988
CRP (mg/dL)	3.63±2.98	4.61±5.09	0.672
TSH (μU/mL)	1.89±1.12	2.11±1.13	0.257
ft4 (ng/dL)	1.25±0.19	1.25±0.22	0.614
anti-TPO (U/mL)	21.54±24.03	27.58±43.30	0.775
anti-TPO positive n (%)	6 (11.1)	5 (9.3)	0.751
Thyroid volume (mL)	13.48±6.3	13.13±10	<0.001
Thyroid nodule n (%)	18 (33.3)	16 (29.6)	0.836
Number of thyroid nodule	1.72±0.22	1.06±0.14	<0.001
Thyroid nodule size (mm)	17.83±9.01	11.68±4.68	0.017

BMI, body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; HOMA- IR, homeostasis model assessment insulin resistance index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; C-reactive protein; TSH, thyroid-stimulating hormone; anti-TPO, anti-thyroperoxidase antibody (anti-TPO), Values are shown as mean ±SD.

(p=0.836). The average numbers of thyroid nodules were 1.72 and 1.06 in the NFAI group and the control group, respectively. In comparison to the control group, the average number of thyroid nodules was significantly higher in the NFAI group (p<0.001). The mean nodule size of the NFAI and control groups were 17.83±9.01 mm and 11.68±4.68 mm, respectively, which was found to be significantly higher in the NFAI group than in the control group (p=0.017) (Table 1). In terms of nodule structure, 66.7% of the nodules in the NFAI group were solid, 5.6% cystic, 27.7% mix (solid + cystic). On the other hand, 68.8% of the nodules in the control group were solid, 6.3% cystic, and 24.9% mix. It was quite evident that there was no difference between the two groups in terms of nodule structure (p=0.877).

Correlation analysis revealed a positive association between a thyroid nodule and TSH (p=0.026) and a positive correlation between thyroid nodule size and adenoma size (p=0.046). However, no significant relationship was found between the other parameters.

Discussion

Predisposing factors, including advanced age, female gender, presence of metabolic syndrome, white race origin, improvement, and frequent use of imaging techniques, are attributed to the increasing incidence of adrenal incidentaloma. NFAI accounts for approximately 80% of AI's (2). The mitogenic effects of compensatory hyperinsulinemia are predicted to be responsible for the onset of IR and metabolic syndrome, which in turn, are thought to enhance the incidences

of both adrenal incidentaloma and thyroid nodule in the iodine-sufficient regions, recently (12).

Some previous studies have reported that IR and other metabolic disorders that are components of metabolic syndrome are often seen in NFAI patients (13,14). It is presumed that the undetectable amount of cortisol secreted from AI, leads to the development of these metabolic disorders (15,16). Furthermore, complete recovery of metabolic disorders following surgical resection of adenoma in patients with NFAI has also been shown as important evidence to substantiate the relationship between NFAI and metabolic disorders (17-19). On the other hand, with the growth factor-like effect of insulin, compensatory hyperinsulinemia observed in IR may lead to the onset of adrenal incidentaloma (5).

Terzolo et al. reported that SBP, DBP, OGTT (Oral Glucose Tolerance Test) 2nd-hour glucose level, insulin sensitivity index (ISI) level were significantly higher in patients with NFAI than controls. Terzolo et al. also highlighted enhanced levels of FBG, fasting insulin, LDL-cholesterol, HDL-C, TG in NFAI patients; however, this result failed to portray any statistical significance (20). Peppia et al. showed that in the NFAI group, SBP, DBP, TG, HOMA-IR, and FBG levels were higher than the control group and HDL-C were lower than the control group (10). On the contrary, in our study, no difference between NFAI and control groups was witnessed in terms of SBP, DBP, WHR, HOMA-IR, FBG, fasting insulin, total cholesterol, and LDL-C levels.

There are limited studies investigating thyroid structure and functions in patients with NFAI. The retrospective and prospective autopsy studies, exploring the relationship between thyroid nodules and adrenal adenomas, reported no relation between them (21). In the study conducted by Arduç et al. with NFAI patients, they found the number of subjects with thyroid nodules and the number of thyroid nodules higher in the NFAI group than in the control group. However, the correlation analysis failed to demonstrate any parameter associated with the number of subjects with thyroid nodules and the number of thyroid nodules. There was no significant difference between NFAI

and control groups in terms of thyroid volume, TSH, FBG, insulin level, HOMA-IR, and lipid levels (22). In the present study, thyroid volume, the average number of thyroid nodules, and thyroid nodule size were significantly higher in the

NFAI patients. Nonetheless, there was no difference between NFAI and control groups in terms of the number of cases with thyroid nodules. No correlation was obtained between other metabolic parameters and thyroid parameters.

Another study, elucidating the relationship between thyroid functions and metabolic syndrome components, established a significant relationship between lipid levels and FT4 levels and also between FT4 levels and IR (23). In a study by Karaköse et al. with NFAI patients, they reported that FT4, anti-thyroglobulin, and anti-TPO levels were significantly higher in the NFAI group compared to the control group, whereas, thyroid volumes, TSH, and FT3 levels were comparable in both the groups. Moreover, they determined a significant relationship between HOMA-IR levels and thyroid volume and FT4 levels (24). The present study failed to obtain any difference between NFAI and control groups in terms of TSH, FT4, and anti-TPO levels.

Owing to the presence of common growth factors that stimulate the growth of both adrenal and thyroid cells, coupled with the increased frequency of thyroid nodules in metabolic disorders such as obesity, insulin resistance, and dyslipidemia, which are common in NFAI patients, it was assumed that thyroid sizes, thyroid nodule frequency, and the number of nodules would be higher in NFAI patients.

The finding from our study clearly indicated significantly higher levels of thyroid volumes, the average number of thyroid nodules, and thyroid nodule size in NFAI patients than healthy controls. However, there was no difference between the groups in terms of the frequency of thyroid nodules. We believe that the absence of any difference between the groups in terms of the frequency of thyroid nodules may be justified by the fact that factors that may affect the thyroid structure such as iodine deficiency were not estimated in our study and the sample size was small.

Conclusion

Our study thus concluded that thyroid volumes, the average number of thyroid nodules, and thyroid nodule sizes in NFAI patients were significantly higher than healthy controls. Nevertheless, there was no difference between NFAI patients and controls in terms of thyroid functions and thyroid nodule frequency. In this regard, for further in-depth knowledge, it is essential to conduct studies with a larger sample size and, including all factors that may affect thyroid structure and functions.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mustafa Can, Melia Karaköse, Feridun Karakurt; Design: Mustafa Can, Melia Karaköse, Mustafa Kulaksızoğlu; Control/Supervision: Feridun Karakurt, Mustafa Kulaksızoğlu; Data Collection and/or Processing: Mustafa Can, Muhammet Kocabaş, İlker Çordan; Analysis and/or Interpretation: Mustafa Can, Melia Karaköse; Literature Review: Muhammet Kocabaş, İlker Çordan; Writing the Article: Mustafa Can, Muhammet Kocabaş; Critical Review: Melia Karaköse, Hatice Çalışkan Burgucu; References and Fundings: Mustafa Can; Materials: Muhammet Kocabaş, Hatice Çalışkan Burgucu.

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