Turk J Endocrinol Metab. 2020;24:261-269

The Association Between Thyroid Volume and Insulin Resistance in Patients with Non-Functional Adrenal Incidentaloma

Non-Fonksiyonel Adrenal İnsidentalomalı Hastalarda İnsülin Direnci ve Tiroid Volümü Arasındaki İlişki

Murat ŞAHİN, Ayten OĞUZ, Dilek TÜZÜN, Semiha ÇALKAYA, Kamile GÜL

Department of Endocrinology and Metabolism, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, TURKEY

Abstract

Objective: This study aimed to investigate the association between insulin resistance (IR) and thyroid volume (TV) along with thyroid nodule in patients with nonfunctional adrenal incidentaloma (NFAI). **Material and Methods:** Forty-five NFAI patients with a mean age of 59.00±7.00 and 43 healthy controls of comparable age and body mass index (BMI) were included. Sociodemographic data, fasting plasma glucose (FPG), alanine aminotransferase (ALT), insulin, lipid, and hormonal parameters, TV, nodule frequency, and adrenal mass dimensions were retrospectively recorded in all the patients. **Resuls:** Triglyceride (TG), insulin, HOMA-IR, basal cortisol, and cortisol levels after dexamethasone suppression test (DST) were significantly higher in the patient group ($p<0.05$). Although the frequency of thyroid nodules was higher in the patient group than in the control group, this finding was statistically insignificant (64.4% and 53.5%, respectively, $p=0.296$). TV was significantly higher in the NFAI group (13.30±5.95 and 5.99±3.04, respectively $p<0.001$). After grouping the participants according to insulin resistance; BMI, FPG, triglyceride, and fasting insulin levels were significantly higher in the IR group ($p<0.05$). Though the frequency of thyroid nodules was higher in those with IR, it was not statistically significant (62.2% and 56.9%, $p=0.617$).TV was significantly higher in participants with IR (11.23±7.15cm) compared to those without IR (8.64±4.77) ($p=0.045$). **Conclusion:** Increased insulin resistance was observed in patients with NFAI. It may play a role in increasing the TV and nodule formation, besides subclinical cortisol secretion.

Keywords: Adrenal adenoma; insulin resistance; thyroid volume

Özet

Amaç: Non-fonksiyone adrenal insidentalomalı (NFAI) hastalarda insülin direnci (IR) ile tiroid volümü (TV) ve tiroid nodülleri arasındaki ilişkiyi değerlendirmektir. **Gereç ve Yöntemler:** Endokrinoloji ve Metabolizma Hastalıkları polikliniğine başvuran ortalama yaşları 59,00±7,00 olan 45 NFAI olan hasta ile benzer yaş ve vücut kitle indeksi (VKİ)'ye sahip 43 sağlıklı kontrolalındı. Çalışmaya alınan bireylerinsosyodemografik verileri, açlık plazma glukoz (APG), alaninaminotransferaz (ALT), açlık insülinseviyesi, lipid ve hormonal parametreleri, TV, nodül sıklığı, adrenal kitle boyutları retrospektif olarak dosyadan kaydedildi. **Bulgular:** Hasta grubu (n=45) ve kontrol grubu (n=43) karşılaştırıldığında hasta grubunda trigliserid, insülin, HOMA-IR, kortizol ve deksametazonsupresyon testi (DST) sonrası kortizol seviyesi anlamlı düzeyde daha yüksek saptandı ($p<0,05$). Tiroid nodül sıklığı, hasta grubunda kontrol grubuna göre anlamlı olmamakla birlikte daha yüksek (%64,4 ve %53,5, $p=0,296$), TV ise hasta grubunda anlamlı seviyede daha yüksekti (13,30±5,95 ve 5,99±3,04, sırasıyla, $p<0,001$). Katılımcılar IR'ye göre gruplandırıldıklarında IR olanlarda; VKİ, APG, trigliserid ve açlık insülin seviyeleri anlamlı düzeyde daha yüksek saptandı ($p<0,05$).Tiroid nodül sıklığı, IR olanlarda daha yüksek olmakla birlikte istatistiksel olarak anlamlı değildi (%62,2 ve %56,9, $p=0,617$). TV ise, IR olanlarda (11,23±7,15 cm) olmayanlara (8,64±4,77) göre anlamlı derecede daha yüksekti ($p=0,045$). **Sonuç:** NFAI'lı hastalarda IR artmıştır ve TV artışı ile nodül oluşumunda etkili olabilir. Ayrıca subklinikkortizolsekresyonu da etkili diğer faktör olarak görünmektedir.

Anahtar kelimeler: Adrenal adenom; insülin direnci; tiroid volümü

Address for Correspondence: Murat ŞAHİN, Department of Endocrinology and Metabolism, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, TURKEY
Phone: +90 344 280 34 03 **E-mail:** muratsahin@me.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 27 Jun 2020 **Received in revised form:** 03 Aug 2020 **Accepted:** 25 Aug 2020 **Available online:** 30 Sep 2020

DOI: 10.25179/tjem.2020-77502

Introduction

Adrenal incidentaloma (AI) is a mass, incidentally discoveredduring radiologic imaging for another condition. A recent study reported the prevalence of AI as approximately 7% (1). Only 12% of the adrenal incidentalomasare hormonally active;the remaining 88% incidentalomasare nonfunctioning (2). Insulin resistance (IR) refers to the insufficient biological response to normal insulin concentrations; itforms a significant metabolic syndrome component. IR is involved in the pathogenesis of diseases like polycystic ovary syndrome, dyslipidemia, and type 2 diabetes mellitus. It has been suggested that IR may cause tumor development by hyperinsulinemia-associated mitogenic effects. IR is frequently observed in patients with nonfunctional adrenal incidentaloma (NFAI), which may be a consequence of either hyperinsulinemia on the adrenal gland or slightly increased cortisol production that is clinically undetectable (3).

Insulin is a thyroid growth factor that stimulates proliferation in thyroid cell cultures. Some studies suggest that IR also exerts goitrogenic effects (4). A few research typeshave established that overexpression of insulin receptors is acrucialrevelation in thyroid carcinogenesis (5).

Thyroid disorders have been reported to remarkably increasethe frequency of thyroid nodules in NFAI patients (6). However, there is insufficient data to show thyroid volume (TV) increase.

This study aimed to assess the association between IR and thyroid nodule and TV and other associated factors in NFAI patients.

Material and Methods

This retrospective study was carried out between 2016 and 2018. Institutional review board approval was obtained from the local ethics committee (Date of Approval: 20.03.2019; Decree No:2019/05). The study was conducted in accordance with the Helsinki Declaration Principles.

Subjects and Study Protocol

All subjects referred to the author's outpatient clinic with adrenal incidentaloma between 2016 and 2018 (n=95) were recorded. At the first visit, CT or MRI was performed to confirm the diagnosis. Adrenal masses with benign features including regular margins, size measuring less than 4cm, and an attenuation value of less than 10 Hounsfield units were defined as adrenal adenoma. Basal hormone and dynamic tests were performed to determine the functionality of incidentaloma. Patients with nonfunctional incidentaloma were included in the study.

Fifty patients,including those who did not complete their examinations or had a hyperfunctioning mass [high dehydroepiandrosterone sulfate (DHEAS) levels, hyperaldosteronism, Cushing syndrome (CS), pheochromocytoma], were excluded. While 45 NFAI patients with a mean age of 59.00±7.00 were included in the study. Patients with a known history of suprarenal or pituitary surgery, those on steroid therapy, thyroid dysfunction, cancer,coronary artery disease, chronic renal failure, or liver failure were not included in the study. Also, patients with imaging findings of a size greater than 4cm, irregular sharp margins, invasion to the adjacent structures, heterogeneous density, and low-fat content that suggests malignancy were not included in the study. Patients admitted to the outpatient clinic were analyzed retrospectively, and thoseshowing the involvement of adrenal glands during imaging (abdominal ultrasound, abdominal tomography, and abdominal MRI) were identified. The study also included 43 healthy controls with similar demographic characteristics and no adrenal mass in radiological imaging.

Hormonal Evaluation

Blood samples were obtained at 8:30am for sodium, potassium, adrenocorticotropic hormone (ACTH), DHEAS, and plasma cortisol to determine hormone activity of the adrenal mass. A low dose (1 mg) dexamethasone suppression test (DST) was performed. Dexamethasone was administered at 11.00 pm, and cortisol valuesbelow 1.8 mcg/dL-were considered normal. Plasmaaldosterone concentration (PAC)/Plasma renin concentration (PRC) in blood samples drawn after 15 min of rest following at least 2 h of upright position (walking or standing) was consideredfor the exclusion of primary aldosteronism. Typical values of PRC and PAC are 5.3-34 pg/mL and 38-313 pg/mL,

respectively, and obtained values of ≤38 were considered normal (7). To rule out pheochromocytoma, metanephrine and normetanephrine were studied in a 24-hour urine sample collected in 25% hydrochloric acid container following a special diet devoid of food and drinks containing phenolic acid for five days. The typical values of urine metanephrine and normetanephrine were 52-341 ug/day and 88-444 ug/day, respectively, and patients exhibiting high values of up to 1.5 times the upper limit were excluded from the study.

Anthropometric Measures

Height (meter), weight (kg), and BMI values of all patients were recorded. Body mass index was calculated using the formula-BMI=weight/height^2 (kg/m^2). BMI values between 18.5-24.9 kg/m^2 were evaluated as normal, those between 25-29.9 kg/m^2 as overweight, and those ≥30 kg/m^2 as obese.

Biochemical Analyses

Blood samples were drawn early in the morning while the patients fasted for at least 8 hto assess fasting insulin (FI), fasting plasma glucose (FPG), hormonal, and lipid parameters.

Glucose was analyzed by the glucose hexokinase method.Total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) were spectrometrically examined by Advia 1800 (Siemens, Healthcare Diagnostic Inc, USA). Chemiluminescence enzyme immunoassay kits (ADVIA Centaur XP, Siemens, Healthcare Diagnostic Inc,Ireland) were used for DHEAS, ACTH, and cortisol measurements.

Normal values were as follows: ACTH (9-52 pg/mL), DHEAS (35-560 µg/dL), Cortisol (5-23 µg/dL), Insulin (6-27 uIU/mL), thyroid stimulating hormone (TSH) (0.4-4.2 µIU/mL), and free T4 (0.8-2.7 ng/dL).

A patient having a value of ≥2.5, obtained by the formula Homeostasis Model Assessment-IR (HOMA-IR), was believed to have insulin resistance.

Conventional Thyroid Ultrasonography

Thyroid ultrasound was performed using the same device (GE Logiq P5 PRO) by a single endocrinologist for every study participant,and thyroid nodules, parenchymal features, and thyroid volume were recorded. Each lobe volume was calculated using the formula volume (mL)= π/6 x width x depth x length (8). The total volume was estimated as the sum of both the lobes.

Statistical analysis

Data were presented as arithmetic mean and standard deviation. The distribution of the samples was evaluated with the Shapiro-Wilk test. The independent t-test was used to compare the two groups with normally distributed data. The Mann-Whitney U, a nonparametric test, was used for data without normal distribution. Multiple regression analysis was performed to determine the effects of categorical and continuous variables on TV and the frequency of thyroid nodules. Enter method was used for regression analysis. A "*p*" value of less than 0.05 was considered statistically significant. The association between the frequency distributions of categorical variables was evaluated using the Chi-Square test. Descriptive statistics were expressed as mean ±SD. Relative possibilities were expressed as odds ratio (OR) and confidence interval (CI). In patients with adrenal incidentaloma, factors associated with TV were evaluated using-Pearson's andSpearman's correlation tests. The data were analyzed using the 25th version of the IBM SPSS (Statistical Package for Social Sciences) package program.

Results

Of the 95 AI patients, 68.4% (n=65) had non-functional adenoma while 32.6% (n=30) had functional adenoma. Twenty patients with NFAI were excluded from the study due to missing data;thus, thestudy was continued with the remaining 45 patients. Besides, 43 individuals without AI who applied to the Endocrinology outpatient clinic were taken as a control group. The mean BMI and age of the patient and control groups were statistically similar (mean age, 59.00±7.00 and 59.45±17.00, respectively; *p*=0.310) (mean BMI 32.99±7.03 and 32.25±6.04, respectively; *p*=0.601). The Demographic, laboratory, and radiologic findings of both groups are summarized in Table 1. Comorbidities (hypertension, hyperlipidemia, atherosclerotic heart disease) were significantly higher in the patient group

Table 1. Demographic, laboratory, and radiological characteristics of the patient and control groups.

Parameters	Patient Group (n=45)	Control Group (n=43)	p
Age (year)*	59.00±7.00	59.45±17.00	0.310
Sex (n,%)			
Female	27 (60.0)	28 (65.1)	0.620
Male	18 (40)	15 (34.9)	
BMI (kg/m²)	32.99±7.03	32.25±6.04	0.601
Comorbidity (n,%)	21 (46.6)	3 (7.0)	0.000
HT	14 (31.1)	3 (7.0)	
HL	2 (4.4)	0	
ASCVD	5 (11.1)	0	
TSH (µIU/mL)*	0.94±0.86	1.83±1.78	0.114
fT4 (ng/dL)	1.16±0.22	1.23±0.42	0.318
fT3 (ng/L)	3.19±0.65	2.91±0.34	0.421
FPG (mg/dL)	91.44±10.42	91.93±9.31	0.819
FI (µIU/mL)*	11.80±8.92	10.00±6.60	0.031
LDL (mg/dL)	128.69±31.19	128.06±34.36	0.929
TG (mg/dL)	144.51±60.53	115.32±55.48	0.021
HDL (mg/dL)	44.17±10.85	53.92±12.41	0.465
Cortisol (µg/dL)*	14.30±5.12	10.70±2.40	0.000
ACTH (pg/mL)*	19.07±15.20	19.37±10.03	0.310
DST (µg/dL)*	1.30±2.34	0.84±0.35	0.000
DHEAS (µg/dL)	95.10±83.62	-	-
Renin (ng/mL)	5.88±7.62	-	-
Aldosterone (ng/mL/h)	35.94±42.17	-	-
Metanephrine (µg/day)	87.88±48.33	-	-
Normetanephrine (µg/day)	183.03±140.66	-	-
HOMA-IR*	2.40±1.36	1.85±2.82	0.037
Adrenal mass (cm)	23.40±10.46	-	-
Thyroid US (nodule) (n,%)	29 (64.4)	23 (53.5)	0.296
TV (mL)	13.30±5.95	5.99±3.04	0.000

Data are presented as n (%) and mean±standarddeviation (Independent samples T-test).
*Data are presented as median±interquartile range (Mann-Whitney U test).
BMI, body mass index; HT, hypertension; HL, hyperlipidemia; ASCVD, atherosclerotic cardiovascular disease; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; FPG, fasting plasma glucose; FI, fasting insulin; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; DHEAS,dehydroepiandrosterone sulfate; HOMA-IR, homeostasis model assessment-insulin resistance; US, ultrasonography; TV, thyroid volume.

(46.6% vs. 7%, $p<0.01$). On evaluating the metabolic parameters, TG, insulin, and HOMA-IR levels of the patient group were statistically higher ($p=0.021$, $p=0.031$, and $p=0.037$, respectively). The levels of basal cortisol and cortisol after DST were statistically higher in the patient group ($p=<0.001$, and $p<0.001$, respectively). The average size of the adrenal mass in the patient group was 23.40±10.46cm. The frequency of thyroid nodules was higher in the patient group, although this finding was not statistically significant (64.4 and 53.5%, respectively; $p=0.296$). Mean TV was higher in the patient group; this difference was statistically significant (13.30±5.95 and 5.99±3.04, respectively, $p<0.001$).

All patients (n=88) included in the study were divided into twogroups: those with IR (n=37, 42%) and those without

IR (n=51, 58%). Demographic, laboratory, and radiological findings of the patients with and without IR have been depicted in Table 2. BMI was statistically higher in patients with IR (34.60±5.38 kg/m^2) than in the non-IR (31.21±6.97 kg/m^2) (p=0.016) group. Thyroid nodules were more frequent in the IR group, yet, this finding was not statistically significant (62.2 vs. 56.9; p=0.617). Thyroid volume was significantly higher in the IR group (11.23±7.15 cm vs. 8.64±4.77 cm; p=0.045). Additionally, while IR was observed more frequently in AI patients than the control group, this finding was not statistically significant (59.5% vs. 40.5%, p=0.182) (Figure 1).

The factors associated with TV in AI patients have been summarized in Table 3. A positive correlation between TV and HOMA-IR was noted, but statistically significant at borderline (r=0.286, p=0.057) (Figure 2).

Multiple regression analysis was performed to evaluate the factors affecting the level of TV. It was observed that the model was well-formed and significant, and affected the TV value at 25% (ANOVA p=0.005 and Dubin Watson=2.0, R2=0.25). An analysis of all parameters in this model illustrated thatA-Iaffected TV (Table 3).

Evaluation of factors affecting thyroid nodule frequency by logistic regression analysis revealed that TV, BMI, and ACTH levels as independent risk factors (Table 4).

Table 2. Demographic, laboratory, and radiological characteristics of patients with and without insulin resistance.

Parameters	Insulin resistance n=37 (42%)	Non-Insulin resistance n=51 (58%)	p
Age (year)*	59.00±12.75	60.00±8.00	0.220
Sex (n,%)			
Female	24 (64.9)	31 (60.8)	0.696
Male	13 (35.1)	20 (39.2)	
BMI (kg/m^2)	34.60±5.38	31.21±6.97	0.016
Comorbidity (n,%)	12 (32.4)	12 (23.5)	0.301
HT	7 (18.9)	10 (19.6)	
HL	2 (5.4)	0	
ASCVD	3 (8.1)	2 (3.9)	
TSH*	1.14±1.61	0.96±0.74	0.405
fT4	1.22±0.45	1.17±0.21	0.558
fT3	3.14±0.54	3.14±0.55	0.944
FPG (mg/dL)	95.38±9.05	89.00±9.59	0.002
FI (µIU/mL)*	16.85±9.03	8.07±4.01	0.000
LDL (mg/dL)	131.13±29.02	126.39±35.10	0.504
TG (mg/dL)	147.70±63.63	117.58±53.66	0.018
HDL (mg/dL)	42.30±9.90	46.98±11.51	0.049
Cortisol*	14.40±5.70	13.10±4.48	0.002
ACTH*	22.95±11.83	16.10±12.30	0.104
DST*	1.18±0.97	1.23±1.3	0.260
HOMA-IR*	3.98±2.24	1.74±0.85	0.000
Thyroid US (nodule) (n,%)	23 (62.2)	29 (56.9)	0.617
TV (mL)	11.23±3.15	8.64±4.77	0.045

Data are presented as n (%) and mean±standarddeviation.
*Data are presented as median±interquartile range.
BMI, body mass index; HT, hypertension; HL, hyperlipidemia; ASCVD, atherosclerotic cardiovascular disease; TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; FPG, fasting plasma glucose; FI, fasting insulin; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; ACTH, adrenocorticotropic hormone; DST, dexamethasone suppression test; DHEAS,dehydroepiandrosterone sulfate; HOMA-IR, homeostasis model assessment-insulin resistance; US, ultrasonography; TV, thyroid volume.

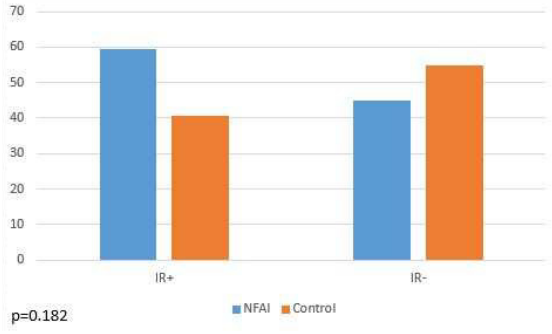

Figure 1: Insulin resistance rate in patients with nonfunctional adrenal incidentaloma.
IR: Insulin resistance; NFAI: Nonfunctional adrenal incidentaloma.

Discussion

Some studies have established that IR is more frequent in patients with AI (9,10). Accordingly, it is speculated that IR may play a role in AI pathogenesis. In humans, fetal and adult adrenal gland has been shown to express insulin-like growth factor 1/2 (IGF-1/2) and its receptors, and these play a role in the growth and function of the adrenal gland. It has also been suggested that IGF-2 overexpression may cause benign adenomas and adrenocortical carcinomas (11). Hyperinsulinemia resulting from IR is reported to increase IGF-1 and IGF-1 receptors at the same time, by increasing IGF-1 and IGF-2 levels. IGF-1 and IGF-2 levels are increased by decreasing IGF binding proteins, which leads to increased stimulation through adrenal receptors (3). Bahadir et al. reported significantly increased IGF-1 levels in NFAI patients. Additionally, the frequency of NFAI was 25% in acromegaly patients, and this value was higher than the general population (12). In a study of adrenocortical cell lines obtained from adrenocortical carcinoma, IGF-1 receptors' down regulation has been shown to inhibit adrenocortical cell line proliferation by 40% (13). Emral et al. reported that mean HOMA-IR levels were higher in NFAI patients than in controls (3.02±1.57 and 1.37±0.99, respectively) (14). In another study, the mean value of HOMA-IR was found to be 2.44±2.46 in NFAI patients, while it was 0.53±0.54 in healthy controls (15). In the present study, significantly higher FI and HOMA-IR levels were detected in AI patients compared to the control group. Besides, while IR was observed more frequently in AI patients, this finding was not statistically significant (59.5/40.5%, p=0.182). These findings propose that IR may play a causative role in the pathogenesis of NFAI.

Metabolic syndrome is a collection of cardiovascular risk factors, IR being the primary metabolic defect of this syndrome. Metabolic syndrome components, such as hypertension and dyslipidemia, are commonly seen in association with IR (16). Ribeiro et al. found that metabolic syndrome,as well as comorbidities such as hypertension and dyslipidemia, were higher in NFAI patients (metabolic syndrome: 69.2% vs. 31.0%, respectively, p<0.001) (17). In another study, NFAI patients had higher mean triglyceride levels [129.5 mg/dL (73-444) in NFAI patients, 112 mg/dL (50-271) in the control group, p=0.01] andthe mean HDL levels were lower in NFAI patients, although this finding was not statistically significant (48.3±8.8 mg/dL in NFAI patients, 50.5±9 mg/dL in the control group) (18).The present study revealed significantly higher

Table 3. Factors associated with thyroid volume.

Parameters	OR	95.0% CI	p
Age (year)	0.163	0.003–0.329	0.055
BMI (kg/m^2)	0.241	0.032–0.514	0.082
Cortisol (mcg/dL)	0.047	0.115–0.021	0.175
DST (mcg/dL)	0.486	0.558–1.587	0.642
HOMA-IR	0.818	0.526–2.162	0.230
Adrenal mass	5.925	2.278–9.571	0.002

BMI: Body mass index; DST: Dexamethasone suppression test; HOMA-IR: Homeostasis model assessment-insulin resistance.

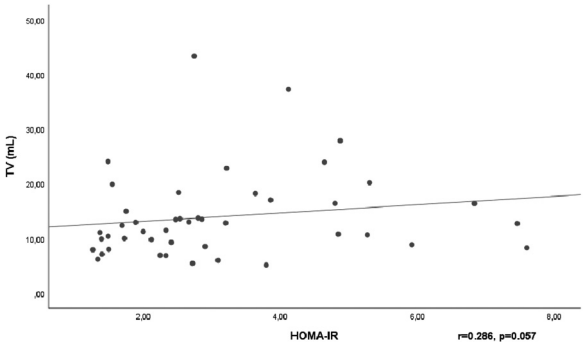

Figure 2: HOMA-IR related to thyroid volume in patients with adrenal incidentaloma (n=45).

Table 4. Factors affecting the frequency of thyroid nodules.

Parameters	OR	95.0% CI	p
TV (mL)	1.363	1.128-1647	0.001
BMI (kg/m²)	1.173	1.046-1.315	0.006
ACTH (pg/mL)	0.941	0.887-1.000	0.049

TV: Thyroid volume; BMI: Body mass index; ACTH: Adrenocorticotropic hormone.

triglyceride values in AI patients;though HDL values were lower in this study, the differencewas not statistically significant. Also, comorbidities such as hypertension, dyslipidemia, and atherosclerotic heart disease were significantly more frequent in NFAI patients in this study. These findings support the fact that the risk of metabolic syndrome and cardiovascular disease is high in patients with NFAI, which is in accordance with the results reported in the literature.

Many publications demonstrate that IR plays anessentialrole in the etiology of adrenal mass formation; yet, some studies claim that IR is caused by adrenal mass. Sanae et al. noteda decrease in post-surgical IR in 12 adrenocortical adenoma patients who had IR prior to the surgery, supporting the above view (19). It is known that in cases where there is a moderate increase in cortisol levels, the condition referred to as subclinical Cushing syndrome, obesity, IR, and type 2 DM frequency are higher in AI patients (10). Arruda et al. observed that hypertension was more frequent in NFAI patients, and that cortisol value after DST was significantly higher (thoughin the normal range) compared to the group without hypertension (20). Therefore, increased cortisol release may be seen in NFAI patients, though slightly, and may lead to some clinical results. Yener et al. revealed that both basal cortisol values and cortisol values after DST were significantly higher in NFAI patients, and the morning cortisol levels were associated with carotid intima-media thickness (21). Another study established that the cortisol AUC value was higher in NFAI patients,after the Synacthentest, compared to the healthy controls, and that urine cortisol and cortisol AUC values after the Synacthen test correlated with carotid intima-media thickness. The authors also speculated an excessive cortisol effect in response to stress in NFAI patients (22). The present study identified significantly higher basal cortisol levels and cortisol levels after DST in the NFAI group. The authors deliberated that slightly increased cortisol levels contribute to the increased frequency of IR and metabolic syndrome in NFAI patients.

The association between adrenal mass and thyroid has been evaluated in several studies. It has been found that the frequency of autoimmune thyroid disease increases (6,23), and thyroid nodules are more common (6) in AI patients, and this situation is frequently related to the underlying IR. The co-existence of adrenal and thyroid incidentaloma may be due to increased and widespread use of advanced radiologic imaging devices (24). Increased TV was reported in patients with IR (25). In the previous study by the authors involving Polycystic Ovary Syndrome patients, significantly increased TV was noted in patients with IR compared to those without IR (TV in insulin-resistant patients was 14.43±2.91, TV in patients without IR was 11.68±2.72, p=0.000) (26). The present study revealed that the frequency of thyroid nodules was higher but not statistically significant (64.4/53.5%, p=0.639), and the mean TV was significantly higher in the NFAI group (13.30±5.95 and 5.99±3.04, respectively, p<0.001). Apart from IR, TV is also affected by gender, body surface area, iodine status, height, weight, BMI, and age (27). The present study found no significant difference based on BMI and age in the patient and control group. The study's location was

the Mediterranean region, which is a mildly iodine-deficient area (28). Hence,the difference in thyroid volume difference is considerably not due to age, BMI, and iodine status. However, a positive borderline correlation between TV and HOMA-IR in patients with AI was observed (p=0.057). In addition, AI was found to be an independent risk factor for an increase in TV, although this factor does not affect HOMA-IR and thyroid nodules.

The authors also noted that an increase in TV, BMI, and ACTH affects the frequency of thyroid nodules. These findings suggest that increased TV may be detected in AI patients, and IR may be a significant contributing factor. However, HOMA-IR was not found to be effective on TV and nodularity,which may be due to the small sample size of the study. Therefore, the authors deliberate thatthe slightly increased cortisol secretion might be responsible for the increased nodularity.

In conclusion, this study proves that hyperinsulinemia increases the risk of goiter in AI. Also, a slight rise in cortisol secretion in NFAI patients may increase TV by causing IR, and these patients must be evaluated for nodular goiter.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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 Şahin; Design: Mustafa Şahin; Control/Supervision: Mustafa Şahin, Ayten Oğuz, Dilek Tüzün, Kamile Gül; Data Collection and/or Processing: Mustafa Şahin, Semiha Çalkaya, Ayten Oğuz, Dilek Tüzün; Analysis and/or Interpretation: Mustafa Şahin, Ayten Oğuz, Dilek Tüzün; Literature Review: Mustafa Şahin; Writing the Article: Mustafa Şahin; Critical Review: Mustafa Şahin, Ayten Oğuz, Dilek Tüzün; References and Fundings: Mustafa Şahin; Materials: Mustafa Şahin.

References

1. Reimondo G, Castellano E, Grosso M, Priotto R, Puglisi S, Pia A, Pellegrino M, Borretta G, Terzolo M. Adrenal incidentalomas are tied to increased risk of diabetes: findings from a prospective study. J Clin Endocrinol Metab. 2020;105:dgz284. [Crossref] [PubMed]
2. Cawood TJ, Hunt PJ, O'Shea D, Cole D, Soule S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink? Eur J Endocrinol. 2009;161:513-527. [Crossref] [PubMed]
3. Muscogiuri G, De Martino MC, Negri M, Pivonello C, Simeoli C, Orio F, Pivonello R, Colao A. Adrenal mass: insight into pathogenesis and a common link with insulin resistance. Endocrinology. 2017;158:1527-1532. [Crossref] [PubMed]
4. Rezzonico J, Rezzonico M, Pusiol E, Pitoia F, Niepomniszcze H. Introducing the thyroid gland as another victim of the insulin resistance syndrome. Thyroid. 2008;18:461-464. [Crossref] [PubMed]
5. Vella V, Sciacca L, Pandini G, Mineo R, Squatrito S, Vigneri R, Belfiore A. The IGF system in thyroid cancer: new concepts. Mol Pathol. 2001;54:121-124. [Crossref] [PubMed] [PMC]
6. Arduc A, Isik S, Ozuguz U, Tutuncu YA, Kucukler FK, Ozcan HN, Berker D, Guler S. Relationship between thyroid nodules and non-functioning adrenal incidentalomas and their association with insulin resistance. Endocr Res. 2014;39:99-104. [Crossref] [PubMed]
7. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:1889-1916. [Crossref] [PubMed]
8. Hegedüs L. Thyroid ultrasound. Endocrinol Metab Clin North Am. 2001;30:339-360. [Crossref] [PubMed]
9. Akkus G, Evran M, Sert M, Tetiker T. Adipocytokines in non-functional adrenal incidentalomas and relation with insulin resistance parameters. Endocr Metab Immune Disord Drug Targets. 2019;19:326-332. [Crossref] [PubMed]
10. Sydney GI, Ioakim KJ, Paschou SA. Insulin resistance and adrenal incidentalomas: a bidirectional relationship. Maturitas. 2019;121:1-6. [Crossref] [PubMed]
11. Angelousi A, Kyriakopoulos G, Nasiri-Ansari N, Karageorgou M, Kassi E. The role of epithelial growth factors and insulin growth factors in the adrenal neoplasms. Ann Transl Med. 2018;6:253. [Crossref] [PubMed] [PMC]

12. Bahadir CT, Ecemis GC, Atmaca H. Does IGF-1 play a role in the etiopathogenesis of non-functioning adrenocortical adenoma? J Endocrinol Invest. 2018;41:1317-1323. [Crossref] [PubMed]
13. Ribeiro TC, Jorge AA, Montenegro LR, Almeida MQ, Ferraz-de-Souza B, Nishi MY, Mendonca BB, Latronico AC. Effects of Type 1 insulin-like growth factor receptor silencing in a human adrenocortical cell line. Horm Metab Res. 2016;48:484-488. [Crossref] [PubMed]
14. Emral R, Aydoğan Bİ, Köse AD, Demir Ö, Çorapçıoğlu D. Could a nonfunctional adrenal incidentaloma be a risk factor for increased carotid intima-media thickness and metabolic syndrome. Endocrinol Diabetes Nutr. 2019;66:402-409. [Crossref] [PubMed]
15. Evran M, Akkuş G, Berk Bozdoğan İ, Gök M, Deniz A, Sert M, Tetiker T. Carotid intima-media thickness as the cardiometabolic risk indicator in patients with nonfunctional adrenal mass and metabolic syndrome screening. Med Sci Monit. 2016;22:991-997. [Crossref] [PubMed] [PMC]
16. Sasaki N, Ozono R, Higashi Y, Maeda R, Kihara Y. Association of insulin resistance, plasma glucose level, and serum insulin level with hypertension in a population with different stages of ımpaired glucose metabolism. J Am Heart Assoc. 2020;9:e015546. [Crossref] [PubMed] [PMC]
17. Ribeiro Cavalari EM, de Paula MP, Arruda M, Carraro N, Martins A, de Souza K, Coelho MC, de Oliveira E Silva de Morais NA, Moraes AB, Vieira Neto L. Nonfunctioning adrenal incidentaloma: a novel predictive factor for metabolic syndrome. Clin Endocrinol (Oxf). 2018;89:586-595. [Crossref] [PubMed]
18. Imga NN, Topcuoglu C, Berker D, Turhan T. Serum amyloid A, paraoxonase-1 activity, and apolipoprotein concentrations as biomarkers of subclinical atherosclerosis risk in adrenal incidentaloma patients. Arch Med Res. 2018;49:182-190. [Crossref] [PubMed]
19. Midorikawa S, Sanada H, Hashimoto S, Suzuki T, Watanabe T. The improvement of insulin resistance in patients with adrenal incidentaloma by surgical resection. Clin Endocrinol (Oxf). 2001;54:797-804. [Crossref] [PubMed]
20. Arruda M, Mello Ribeiro Cavalari E, Pessoa de Paula M, Fernandes Cordeiro de Morais F, Furtado Bilro G, Alves Coelho MC, de Oliveira E Silva de Morais NA, Choeri D, Moraes A, Vieira Neto L. The presence of nonfunctioning adrenal incidentalomas increases arterial hypertension frequency and severity, and is associated with cortisol levels after dexamethasone suppression test. J Hum Hypertens. 2017;32:3-11. [Crossref] [PubMed]
21. Yener S, Genc S, Akinci B, Secil M, Demir T, Comlekci A, Ertilav S, Yesil S. Carotid intima media thickness is increased and associated with morning cortisol in subjects with non-functioning adrenal incidentaloma. Endocrine. 2009;35:365-370. [Crossref] [PubMed]
22. Androulakis II, Kaltsas GA, Kollias GE, Markou AC, Gouli AK, Thomas DA, Alexandraki KI, Papamichael CM, Hadjidakis DJ, Piaditis GP. Patients with apparently nonfunctioning adrenal incidentalomas may be at increased cardiovascular risk due to excessive cortisol secretion. J Clin Endocrinol Metab. 2014;99:2754-2762. [Crossref] [PubMed]
23. Karakose M, Karbek B, Sahin M, Arslan MS, Topaloglu O, Erden G, Demirci T, Calıskan M, Delibasi T. The association of autoimmune thyroiditis and non-functional adrenal incidentalomas with insulin resistance. Arch Endocrinol Metab. 2015;59:42-46. [Crossref] [PubMed]
24. Vardanian AJ, Hines OJ, Farrell JJ, Yeh MW. Incidentally discovered tumors of the endocrine glands. Future Oncol. 2007;3:463-474. [Crossref] [PubMed]
25. Kushchayeva YS, Kushchayev SV, Startzell M, Cochran E, Auh S, Dai Y, Lightbourne M, Skarulis M, Brown RJ. Thyroid Abnormalities in Patients With Extreme Insulin Resistance Syndromes. J Clin Endocrinol Metab. 2019;104:2216-2228. [Crossref] [PubMed] [PMC]
26. Sahin M, Demircioglu D, Oguz A, Tuzun D, Sarica MA, Inanc E, Gul K. Does insulin resistance increase thyroid volume in patients with polycystic ovary syndrome? Arch Endocrinol Metab. 2017;61:145-151. [Crossref] [PubMed]
27. Suzuki S, Midorikawa S, Fukushima T, Shimura H, Ohira T, Ohtsuru A, Abe M, Shibata Y, Yamashita S, Suzuki S; Thyroid Examination Unit of the Radiation Medical Science Center for the Fukushima Health Management Survey. Systematic determination of thyroid volume by ultrasound examination from infancy to adolescence in Japan: the Fukushima Health Management Survey. Endocr J. 2015;62:261-268. [Crossref] [PubMed]
28. Erdoğan MF, Ağbaht K, Altunsu T, Ozbaş S, Yücesan F, Tezel B, Sargin C, Ilbeğ I, Artik N, Köse R, Erdoğan G. Current iodine status in Turkey. J Endocrinol Invest. 2009;32:617-622. [Crossref] [PubMed]