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

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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. Results: 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

Anahtar kelimeler: Adrenal adenom; insulin direnci; tiroid volümü

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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

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Introduction

Adrenal incidentaloma (AI) is a mass, incidentally discovered during radiologic imaging for another condition. A recent study reported the prevalence of AI as approximately 7% (1). Only 12% of the adrenal incidentalomas are hormonally active; the remaining 88% incidentalomas are non-functioning (2). Insulin resistance (IR) refers to the insufficient biological response to normal insulin concentrations; it forms 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 type-shave established that overexpression of insulin receptors is a crucial revelation in thyroid carcinogenesis (5).

Thyroid disorders have been reported to remarkably increase the 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 non-functional 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, 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 those showing 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 values below 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 considered for 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 h to 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)= \(\pi/6 \times \text{width} \times \text{depth} \times \text{length}\) (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 and Spearman’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, the study 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.
(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 two groups: those with IR (n=37, 42%) and those without IR (n=51, 58%).
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/m²) than in the non-IR (31.21±6.97 kg/m²) (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 that A-I affected 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 | Non-Insulin resistance | p     |
|-------------------------------------|--------------------|------------------------|-------|
|                                     | n=37 (42%)         | n=51 (58%)             |       |
| 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)              |       |
| 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)                |       |
| BMI (kg/m²)                         | 34.60±5.38         | 31.21±6.97             | 0.016 |
| 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±standard deviation. *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.
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 compared to the control group, 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] and the 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

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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/m²)      | 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.
triglyceride values in AI patients; though HDL values were lower in this study, the difference was 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 an essential role in the etiology of adrenal mass formation; yet, some studies claim that IR is caused by adrenal mass. Sanae et al. noted a 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 Synacthen test, 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 coexistence 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 that the 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.

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