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Could a nonfunctional adrenal incidentaloma be a risk factor for increased carotid intima-media thickness and 10-year cardiovascular mortality based on the SCORE algorithm? A study from a single centre in Poland

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Abstract

Introduction: Adrenal incidentaloma (AI) secreting small amounts of glucocorticoids may cause morphological and functional changes in the blood vessels. Early stages of cardiovascular remodeling may be observed among asymptomatic patients with AI. But it is unclear whether the nonfunctional adrenal incidentalomas (NFAI) may also be a risk factor for cardiovascular diseases. The aim of this study was to determine the relationship between NFAI, carotid intima-media thickness (CIMT), and cardiovascular risk (CVR) based on Systematic Coronary Risk Evaluation (SCORE) prediction models for Europe.

Material and methods: This study from a single centre in Poland included 48 NFAI patients and 44 individuals in the control group matched for age, sex, and body mass index (BMI). All participants underwent adrenal imaging, biochemical evaluation, measurement of CIMT, and assessment of the 10-year risk of cardiovascular mortality based on the SCORE algorithm. Hormonal evaluation was conducted in AI patients.

Results: The NFAI group showed significantly higher sodium ($p = 0.02$) and glucose levels in the 2-h oral glucose tolerance test (OGTT) ($p = 0.04$), a higher CIMT ($p < 0.01$), and a higher CVR calculated according to the SCORE algorithm ($p = 0.03$). The estimated glomerular filtration rate (eGFR) was higher in the NFAI group ($p = 0.015$). Hypertension ($p < 0.01$) and IGT ($p = 0.026$) were more common in the NFAI group. Statistically significant positive correlations were found between CIMT and age ($r = 0.373$, $p = 0.003$), waist circumference ($r = 0.316$, $p = 0.029$), diastolic blood pressure ($r = 0.338$, $p = 0.019$), and CVR based on the SCORE algorithm ($r = 0.43$, $p = 0.004$). There was a statistically significant positive correlation between CIMT and serum cortisol levels after 1 mg dexamethasone suppression test ($r = 0.33$, $p = 0.02$).

Conclusion: Non-functional adrenal adenomas are associated with increased CIMT and CVR. Early stages of cardiovascular remodelling can be observed in asymptomatic NFAI patients. **(Endokrynol Pol 2023; 74 (6): 623–630)**

Key words: *nonfunctional adrenal incidentaloma; intima-media thickness; cardiovascular risk*

Introduction

Adrenal incidentalomas (AI) are asymptomatic adrenal lesions larger than 1 cm in diameter, which are detected in imaging studies performed for reasons other than adrenal pathologies. With an estimated prevalence of 3–10%, they have become a major problem in everyday clinical practice [1–6]. The pathogenetic mechanisms behind the development of AIs are still largely unknown. It has been suggested that there is a correlation of AI occurrence with hyperinsulinaemia and the insulin-like growth factor (IGF) system. Through activation of insulin and IGF-1 receptors, insulin resistance and compensatory hyperinsulinaemia may play a role in adrenal tumour growth [7, 8]. Almost 80% of adrenal lesions are benign, hormonally inactive adenomas, called non-functional adrenal incidentalomas (NFAI). The most common endocrine disorder in patients with AI is excessive cortisol secretion, the prevalence of which ranges from 1% to 29% [9]. The recommended diagnostic test for hypercortisolism is 1 mg overnight dexamethasone suppression test: serum cortisol < 1.8 μg/dL excludes hypercortisolism, 1.9–5 μg/dL suggests possible autonomic cortisol secretion, and > 5 μg/dL suggests autonomous cortisol secretion (ACS) [4, 5]. It is suggested that cortisol secretion is a continuum between normal serum cortisol concentration and overt hypercortisolism, and it shows significant

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variability in one patient [10]. The median prevalence of primary aldosteronism is 2.5%, while that of pheochromocytoma is 7%, as reported by the authors. Adrenalectomy as the standard of care is recommended only for adrenal tumours with clinically significant hormone excess [3–5].

An important aspect of diagnosing AIs is their association with an increased prevalence of cardiovascular disease (CVD) risk factors. AI patients most often suffer from obesity, hypertension (HT), diabetes mellitus (DM), impaired carbohydrate metabolism, and hyperlipidaemia [7, 10–12]. It has been remarked that such complications appear with increased frequency in AI patients due to hypercortisolaemia, including its subclinical form [13–16]. Because cardiovascular diseases are so prevalent in the general population and a leading cause of death in developed countries, studies of the cardiovascular risk (CVR) in patients with AI in comparison with the background population are of special interest. Therefore, over the past few years, attempts have been made to determine CVR in AI patients. Considering the increasing number of patients affected by AI, it seems important to perform accurate subtyping of the patients, in light of tailored treatment.

Guidelines of the European Society of Cardiology (ESC) recommend using Systematic Coronary Risk Evaluation (SCORE) models to estimate 10-year risk of CVD. The guidelines state that it is essential for clinicians to be able to assess CVR with appropriate accuracy. This led to recommending the SCORE system as a tool of choice for the European population over 40 years of age, unless they are automatically categorised as being at high risk or very high risk based on documented CVD, DM, and kidney disease [17, 18].

Carotid intima-media thickness (CIMT) measured with ultrasonography is a marker of the advancement of generalized atherosclerosis widely used to assess the risk of a cardiovascular event in both healthy people and patients with various risk factors [19–21]. CIMT and carotid plaque reflect atherosclerotic burden in the whole arterial tree. CIMT values can be affected by age, abdominal obesity, elevated blood pressure, hyperlipidaemia, and insulin resistance [22–24]. Mean values of CIMT in adults range from around 0.65 to 0.9 mm and increase on average at a rate of 0.04 mm/year [20, 25]. CIMT progression of 0.1 mm correlates with a 10%–15% increase of myocardial infarction risk and 13–18% increase of ischaemic stroke risk [20, 26] and is directly associated with increased arterial stiffness [27].

The aim of this study from a single centre in Poland was to determine the relationship between NFAI, carotid intima-media thickness (CIMT), and CVR based on SCORE prediction models for Europe.

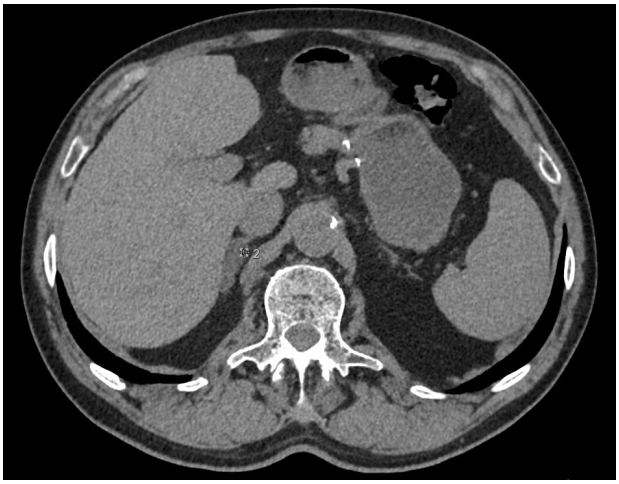

Figure 1. *Adrenal adenoma*

Material and methods

The analysed population

From total of patients with AI hospitalized in our department between January 2020 and December 2020, patients with non-secreting AI, aged 18 to 69 years were selected. The study encompassed a total of 48 patients aged 58.6 ± 9 years; 16 men (33%) and 32 women (67%). Radiological, biochemical, and hormonal diagnostics were performed as part of the standard procedure in accordance with the guidelines of the European Society of Endocrinology (ESE) to confirm hormonal inactivity and benign nature [3–6]. AI was confirmed as a gold standard by computed tomography (CT). On CT scans, adrenal tumours in their largest dimension did not exceed 4 cm, they were regularly shaped with well-defined margins, homogeneous density, < 10 HU in unenhanced CT, and ≤ 30 HU after contrast (Fig. 1). If adenomas could not be diagnosed with CT, MRI was performed [3–6].

The control group consisted of 44 asymptomatic volunteers aged 57 ± 7 years; 15 men (34%) and 29 women (66%). Both groups were age-, gender-, and body mass index (BMI)-matched. In the control group the presence of adrenal lesions was excluded by abdominal ultrasound with a Samsung SAR7-EXP-CW. This imaging method was chosen because it has no ionising radiation and relatively low cost. In a large sample study the sensitivity, specificity, and accuracy of ultrasound-based diagnosis were 89%, 99%, and 93.9%, respectively [28].

The exclusion criteria were age below 18 years or over 69 years, hormonally active adrenal adenoma, diabetes mellitus, chronic kidney disease (stage 3a renal failure with estimated glomerular filtration rate [eGFR] < 60 mL/min), ischaemic heart disease, cardiac insufficiency, uncompensated hypertension, cerebrovascular disease, peripheral arterial disease, acute and chronic inflammatory diseases, malignant neoplasm, suspected or diagnosed mental disorder, use of medications that may affect the hypothalamic-pituitary-adrenal axis, and pregnancy.

Study protocol

Medical interview and physical examination

In both groups, an interview concerning the data necessary to calculate the SCORE (age, sex, smoking) and a physical examination with anthropometric measurements (weight, height, waist circumference) were performed. In both groups, an interview and a physical examination with anthropometric measurements (weight, height, waist circumference) were performed, and the BMI was calculated as the weight in kilograms divided by square of the height in metres.

Blood pressure (BP) was measured twice from the upper right arm using an automatic device (Omron M2) after 5 minutes of rest in a seated position, and the mean of these 2 measurements was taken as the BP value. Hypertension was diagnosed on the basis of 2 criteria: systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg or, in the case of treatment with antihypertensive drugs, according to the guidelines of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) [29].

Biochemical evaluation

In both groups blood samples for baseline laboratory tests were collected from the ulnar vein in the supine position, in the morning, after 12 hours of overnight fasting. Laboratory tests included measurements of sodium, potassium, creatinine, uric acid, fasting glucose and insulin, lipid profile, and 75 g oral glucose tolerance test (OGTT). The insulin resistance index was calculated according to the Homeostasis Model Assessment — Insulin Resistance (HOMA-IR) formula from the following equation:

$$HOMA\text{-}IR = (\text{fasting plasma glucose concentration} \times \text{fasting plasma insulin concentration})/22.5$$

HOMA-IR < 2.5 was taken as the normal result [30]. Non-high-density lipoprotein (non-HDL) concentration was calculated using the following formula:

$$Non\text{-}HDL\text{-}C = TC - HDL\text{-}C \text{ [18].}$$

Dyslipidaemia was diagnosed on the basis of low-density lipoprotein (LDL) cholesterol level (LDL-C) > 115 mg/dL, and/or total cholesterol (TC) > 150 mg/dL, and/or high-density lipoprotein (HDL) cholesterol (HDL-C) < 40 mg/dL (men) and 50 mg/dL (women), or the use of lipid-lowering drugs according to the ESC and ESH guidelines [18, 19].
Diabetes, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were diagnosed according to American Diabetes Association guidelines [31].

Hormonal evaluation

Normal hormonal activity of adrenal tumours in the study group was confirmed on the basis of normal diurnal cortisol rhythm (8 a.m., 10 p.m.), adrenocorticotropic hormone (ACTH) levels in the morning > 5 pg/mL, cortisol levels below 1.8 ug/dL in a 1 mg, low-dose dexamethasone suppression test (LDDST), and normal adrenal androgen levels (dehydroepiandrosterone sulphate (DHEA-S), androstenedione). After withdrawal of diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor type 1 antagonists, aldosterone levels and plasma renin activity (PRA) were measured. Aldosterone-renin ratio below 30 ng/dL/mL/h excluded hyperaldosteronism. Pheochromocytoma was excluded by normal limits of urinary fractionated metanephrines or normal plasma catecholamine levels [3–6]. Due to no changes in the adrenal glands, hormonal evaluation of the control group was not performed.

Carotid-intima media thickness

A diagnostic imaging specialist measured the carotid intima-media thickness (CIMT) index of both groups in the supine position with the head tilted posteriorly using a Samsung SAR7-EXP-CW ultrasound scanner. Ultrasonography images were obtained of the right and the left common carotid artery of each patient at the lower 1/3 cervical region proximally and 1 cm above the carotid bulb distally in the longitudinal plane. CIMT values were calculated with the use of the arithmetic mean formula of the measured values (Fig. 2) [32].

Systematic coronary risk evaluation

The 10-year risk of fatal CVD was estimated using the coronary risk assessment algorithm (SCORE and SCORE2) in accordance with the ESC guidelines on CVD prevention. SCORE takes into account the following: gender, age, systolic blood pressure, lipid levels, and smoking.
The risk was evaluated with the SCORE calculator in the following ranges: ≥ 10%, 5–9%, 3–4%, 2%, 1%, and ≤ 1%; ≥ 10% — very high risk; 5–9% — high risk; 1–4% – moderate risk; ≤ 1% — low risk. Due to changes introduced in the 2021 edition, published after our research was completed, we assessed CVR in both the SCORE and SCORE2 algorithms. The main difference between the SCORE and SCORE2 models is that SCORE estimates the 10-year risk of death from cardiovascular causes while SCORE2 estimates the risk of fatal and non-fatal CVD [17–18].

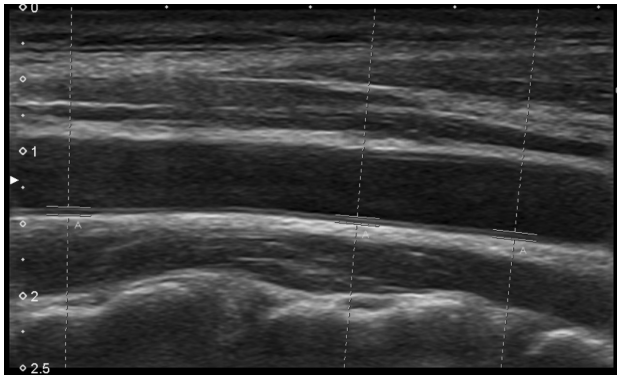

Figure 2. *Intima-media thickness*

Statistical analysis

Statistica 13.0 PL software for Windows was employed for the statistical purposes. The mean and standard deviation (mean ± SD) were calculated for all the analysed parameters. Qualitative data were presented as indices of structure (%). The normality of distribution of the obtained results was calculated with the Shapiro-Wilk test. Student's t-test was used to assess the statistical significance of differences between the analysed groups. If the variables did not meet the normality criteria, the Mann-Whitney U test was performed. The Chi-square test was used to determine differences for categorical variables. Spearman's rank correlation coefficient was applied to assess correlations between parameters. The significance level of all the performed statistical analyses was set at $p = 0.05$.

Results

As shown in Table 1, the NFAI group showed a statistically significantly higher waist circumference, as well as systolic and diastolic blood pressure. The NFAI group and the control group showed no significant differences in terms of fasting glucose level, HOMA-IR index, TC, LDL-C, HDL-C, non-HDL-C, TG, and creatinine levels. The NFAI group showed statistically significantly higher concentrations of sodium ($p = 0.02$) and glucose in 2-h OGTT ($p = 0.04$), and higher eGFR ($p = 0.015$), CIMT ($p < 0.01$), and CVR calculated according to the SCORE index ($p = 0.03$). eGFR was higher in the NFAI group ($p = 0.015$). In the NFAI group the mean CIMT value was 0.694 ± 0.158 for men and 0.619 ± 0.176 for women. In the control group the mean CIMT value was 0.516 ± 0.099 for men and 0.452 ± 0.117 for women. The differences in CIMT thickness by gender in both

Table 1. *Characteristics of the analysed groups*

Parameters	NFAI group (n = 48)	Control group (n = 44)	p-value
Women/Men (n)	32/16	29/15	
Age (years)	58,6 ± 9	57 ± 7	0.34
BMI [kg/m^2]	28.7 ± 4.6	26.8 ± 4.3	0.69
Waist circumference [cm]	97.6 ± 14	89.1 ± 9.5	< 0.01*
Systolic blood pressure [mmHg]	131.7 ± 15.1	123.6 ± 10.8	< 0.01*
Diastolic blood pressure [mmHg]	82.5 ± 9.9	75.7 ± 9.2	< 0.01*
Heart rate [per minute]	77.2 ± 11	72.5 ± 8.9	0.176
Smoker (n)	9 (19 %)	9 (20.5%)	0.8
Fasting blood glucose [mg/dL]	96.1 ± 12	100.4 ± 11	0.7
Blood glucose in 2h OGTT [mg/dL]	127.7 ± 38.2	105.1 ± 27.9	0.04
Fasting insulin [uUI/mL]	11.4 ± 4.9	8.9 ± 5.8	0.03
HOMA-IR Index	2.72 ± 1.23	2.26 ± 1.64	0.13
TC [mg/dL]	208.7 ± 43.1	207.4 ± 31.8	0.94*
LDL-C [mg/dL]	139.6 ± 44.8	139.68 ± 31.01	0.94*
HDL-C [mg/dL]	63.18 ± 15.12	63.61 ± 17.76	0.82*
Non-HDL-C [mg/dL]	144.8 ± 44.41	143.75 ± 29.63	0.91*
Triglycerides [mg/dL]	101.72 ±45.2	109.63 ± 48.7	0.62
Creatinine [mg/dL]	0.81 ± 0.14	0.85 ± 0.15	0.79
eGFR [mL/min]	82.87 ± 18.65	79.84 ± 12.86	0.015
Sodium [mmol/L]	138.54 ±18.01	139.93 ± 1.99	0.02*
Potassium [mmol/L]	4.29 ± 0.34	4.38 ± 0.34	0.2*
CIMT [mm]	0.64 ± 0.17	0.47 ± 0.11	< 0.01*
SCORE (%)	7.1 ± 6.7	4.3 ± 4.8	0.03
SCORE2 (%)	7.3 ± 5.95	5.61 ± 4.24	0.13

BMI — body mass index; CIMT — carotid intima-media thickness; eGFR — estimated glomerular filtration rate; HDL-C — high-density lipoprotein cholesterol; HOMA-IR — Homeostasis Model Assessment — Insulin Resistance; LDL-C — low-density lipoprotein cholesterol; NFAI — nonfunctional adrenal incidentalomas; Non-HDL-C — non-high-density lipoprotein cholesterol; OGTT — oral glucose tolerance test; SCORE — Systematic Coronary Risk Evaluation; TC — total cholesterol; *Mann-Whitney U test

Table 2. *Prevalence of conditions that have an effect on vascular remodelling*

Parameters	NFAI group (n = 48)	Control group (n = 44)	p-value
Hypertension	27 (56%)	12 (27%)	< 0.01
IFG	10 (20.8%)	21 (47.7%)	< 0.01
IGT	13 (27%)	4 (0.9%)	0.026
Dyslipidaemia	42 (85.7%)	42 (87.5%)	0.11
Smoker	9 (19 %)	9 (20.5%)	0.83

NFAI — nonfunctional adrenal incidentalomas; IFG — impaired fasting glucose; IGT — impaired glucose tolerance

groups were not statistically significant. Hypertension (χ^2 = 7.89, p < 0.01) and IGT (χ^2 = 4.93, p = 0.026) were more common in the NFAI group than in the control group (Tab. 2).

In the NFAI group statistically significant positive correlations were found between CIMT and age (r = 0.373, p < 0.01), waist circumference (r = 0.316, p = 0.0286), diastolic blood pressure (r = 0.3382, p = 0.0187), and CVR calculated based on SCORE (r = 0.43, p = 0.004). No correlation was found between CIMT and systolic blood pressure, fasting blood glucose, and glucose in 2-h OGTT, lipid levels, smoking, or SCORE2 index (Tab. 3).

Hormonal assessment of the hypophysis-adrenal axis in the AI group showed mean 8 a.m. cortisol 13.4 ± 3.41 μg/dL, 10 p.m. cortisol 3.6 ± 1.66 μg/dL,

Table 3. *Correlation between clinical, biochemical, and hormonal parameters and carotid intima-media thickness (CIMT) in patients with nonfunctional adrenal incidentalomas (NFAI)*

Parameters	CIMT	
	r	p
Age	0.373	< 0.01
BMI	0.201	0.171
Waist circumference	0.316	0.029
Systolic blood pressure	0.271	0.063
Diastolic blood pressure	0.338	0.019
Fasting glucose	0.035	0.815
Fasting insulin	0.122	0.409
HOMA	0.091	0.538
Glucose in 2-h OGTT	-0.005	0.976
TC	0.039	0.793
LDL-C	0.022	0.88
HDL-C	0.273	0.060
Non-HDL-C	–0.839	0.575
TG	–0.051	0.733
Sodium	0.218	0.138
Potassium	0.237	0.105
SCORE	0.430	0.004
SCORE2	0.058	0.707
Cortisol 8:00 a.m.	0.1607	0.2753
Cortisol 10:00 p.m.	0.2238	0.1262
ACTH 8:00 a.m.	0.1691	0.2504
Cortisol after LDDST	0.3334	0.0205
DHEA-S	–0.1587	0.2813

ACTH — adrenocorticotropic hormone; CIMT — carotid intima-media thickness; DHEA-S — dehydroepiandrosterone; HDL-C — high-density lipoprotein cholesterol; HOMA-IR — Homeostasis Model Assessment — Insulin Resistance; LDDST — low-dose dexamethasone suppression test; LDL-C — low-density lipoprotein cholesterol; Non-HDL-C — non-high-density lipoprotein cholesterol; OGTT — oral glucose tolerance test; SCORE — Systematic Coronary Risk Evaluation; TC — total cholesterol

cortisol in LDDST 1.23 ± 0.41 ug/dL, morning ACTH 10.32 ± 7.36 pg/mL, and DHEA-S level 115.83 ± 92.13 μg/dL. The analysis of associations between CIMT and values of steroidogenesis hormones showed a statistically significant positive correlation between CIMT and serum cortisol levels after suppression with 1 mg dexamethasone ($r = 0.33$, $p = 0.02$). There was no correlation between CIMT and morning cortisol and ACTH levels, cortisol levels at 10 p.m., or DHEA-S levels.

Discussion

In the present study, NFAI patients with no history of vascular disease presented early stages of atherosclerosis in carotid arteries and had evidence of increased CV risk assessed by SCORE algorithm. We showed positive correlation between CIMT and cortisol levels in LDDST.

The literature on the subject does not provide many data as regards assessing CVR in NFAI patients. Apart from a few papers, the studies performed so far have assessed cardiovascular complications also in patients with classical CVR factors. High prevalence of overweight and obesity, hypertension, and carbohydrate and lipid metabolic disorders in AI patients make it difficult to collect a group of patients unaffected by traditional CVR factors. In this study, the undertaken analysis encompassed only patients with well-controlled hypertension and no history of myocardial infarction, stroke, or diabetes mellitus type 2. Furthermore, additional assessment of patients for CVR according to the SCORE and SCORE2 algorithm distinguishes the study presented here from other projects.

Carotid intima-media thickness

As summarized in our review, in the groups of AI patients an increased CIMT was observed, illustrating morphological changes in carotid arteries expressed by intimal hyperplasia and endothelial atherosclerosis [33]. The association between CIMT and severity of hypercortisolism has been investigated in a meta-analysis of 14 studies of CVR in patients with ACS. CIMT and atherosclerotic carotid plaques were independently associated with severity and duration of cortisol excess, as shown in patients with active disease. This may suggest the need for a strict monitoring of early signs of subclinical cardiovascular remodelling in ACS patients. Moreover, improvement of CIMT was correlated with the median time of disease remission in cured patients, providing indirect evidence on the role of duration of cortisol excess as an important determinant of the development of subclinical atherosclerosis [34]. A 2002 study by Tauchmanov et al. involving 28 patients with subclinical Cushing's syndrome (SCS) for the first time showed an increased CIMT value compared to the control group, with no statistically significant correlation between hormonal and biochemical test results [35]. With regard to the above results, it was hypothesised that NFAI may also lead to an increase in CIMT.

In the study presented herein, the NFAI group showed significantly higher CIMT values compared to the control group. Endothelial damage in NFAI group can be also explained by dyslipidaemia. However, there were no statistical differences in lipid profile in both groups. A positive correlation between CIMT and LDDST cortisol levels was described, which suggests that AIs may in fact produce small amounts of glucocorticoids that can cause morphological and functional changes in the myocardium and blood vessels. Some studies have also revealed changes in CIMT in AI

patients. I. Androulakis et al. included patients without a diagnosis of HT, diabetes mellitus type 2 (T2DM), and hyperlipidaemia in their research (it is worth pointing out that HDL-C > 40 mg/dL, LDL-C < 160 mg/dL, and TC < 240 mg/dL were regarded as normal lipid levels). The group of 60 AI patients showed significantly higher CIMT values in cortisol-secreting AIs (CSAIs) compared with the NFAI group and the control group. Moreover, patients with NFAI presented higher CIMT values compared to the control group. The study also indicated a positive correlation between CIMT values and cortisol levels in LDDST. The authors suggested that the increased prevalence of CV risk factors described in NFAI patients could result from either a mild cortisol excess that cannot be detected with available diagnostic methods or its periodic secretion [36]. Results of studies conducted by Tuna et al., Imga et al., Evran et al., and Emral et al. were consistent and confirmed higher CIMT values in AI patients compared to the control group [37–40]. Similar conclusions were proposed by Cansu et al. based on a study that included 35 patients with NFAI without traditional CVD risk factors, namely T2DM, HT, or hyperlipidaemia. Based on a positive correlation of CIMT with cortisol levels after LDDST ($r = 0.346$, $p < 0.005$), the authors speculated that increased levels of CIMT may be attributable to subtle and undetectable cortisol autonomy in NFAI patients [41].

Systematic coronary risk evaluation

Cortisol levels seem to play a role in determining cardiovascular events in patients with AI. However, the cortisol-related mechanisms (direct effects of cortisol on cardiovascular system *vs*. indirect actions through the associated co-morbidities) leading to cardiovascular damage are still not completely understood [42]. It is still debated whether NFAIs increase the CVD risk. However, due to a multitude of metabolic disorders detected in NFAI patients, this hypothesis requires further investigation.

In the study presented herein, the NFAI group showed a higher CVR calculated according to the SCORE algorithm, defined as a high risk compared to the control group (7.1% *vs*. 4.3%, respectively). Due to the lack of statistically significant differences in age, sex, nicotinism, and concentration of lipids between groups, it seems that the difference in SCORE results mainly from the value of systolic blood pressure. The NFAI group showed a statistically significantly higher systolic and diastolic blood pressure. It may be suggested that in this group of patients there is an additional, non-traditional factor that leads to such a significant increase in the risk of developing CVD in the future. Statistically significant differences between groups were not shown for SCORE2 due to the higher value in the controls. To our knowledge, the present study is the first to determine SCORE and SCORE2 in patients with NFAIs. No correlation was found between the CVR calculated according to the SCORE algorithm and the analysed hormonal parameters. AIs might raise CVR indirectly through an increased prevalence of abdominal obesity, hypertension, or disorders of carbohydrate and lipid metabolism.

Elevated CIMT values and a high CVR in the NFAI group may suggest that subtle autonomic cortisol secretion may have an impact on endothelial damage, while NFAI may constitute an independent factor in the CVR. Several experimental studies have shown that an excess of glucocorticoids causes direct cardiovascular effects, such as increased renin-angiotensin system and sympathetic nervous system as well as decreased nitric oxide (NO) synthesis and kallikrein/kinin system [43]. NFAI is diagnosed based on hormonal tests (normal diurnal cortisol rhythm, ACTH and DHEA-S levels, cortisol levels in LDDST below 1.8 ug/dL), which seem to be contradicted by the results of biochemical tests and numerous metabolic disorders in this group of patients. This raises suspicion that LDDST as a recommended tool for diagnosis of subtle autonomic cortisol secretion is not perfect. Moreover, there are reports confirming that the effect of classical CVR factors might decrease after adrenalectomy in patients with NFAIs. In this group, this surgical procedure led to a reduction in body weight, blood pressure, as well as lipid and fasting glucose levels [44–48]. This supports our hypothesis suggesting that subtle, hard to detect, but still possible hypercortisolaemia, with normal cortisol level in LDDST may result in an increased CVR.

Limitations

It is a limitation of the present study that the groups that underwent analysis were relatively small. Additionally, no hormonal tests were performed in the control group. However, exposing patients without known adrenal lesions to additional hormonal tests was assumed to be unreasonable, especially if such tests were to be associated with taking a suppressive dose of GCs.

Conclusions

NFAIs are associated with increased CIMT and CVR assessed using SCORE algorithm. Asymptomatic NFAI patients can be observed to be undergoing early stages of cardiovascular remodelling. Based on the results obtained in the present study, it can be suggested that the standard assessment of AI patients should include both endocrine activity and the presence of

subclinical CVD. It seems that the assessment of morphological and functional changes in the cardiovascular system could facilitate distinguishing a group of patients with a high CVR. Patients with AI presenting with hypertension, impaired carbohydrate metabolism, and dyslipidaemia should be considered for primary and secondary prevention of CVD. CIMT could work as an initial indicator of a potential cardiovascular event, thus enabling doctors to implement specific therapy in a selected group of patients.

Conflict of interest

None declared.

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