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Insulin resistance and metabolic syndrome in patients with nonfunctioning adrenal incidentalomas: a cause-effect relationship?

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Abstract

The objective of the study was to assess insulin resistance (IR) and metabolic syndrome (MS) in patients with nonfunctioning adrenal incidentalomas (NFAIs). Among a total cohort of 46 patients with adrenal incidentalomas, we studied 29 patients with NFAIs (mean age, 54 ± 9 years; body mass index, 29 ± 3 kg/m^2) and 37 age-, sex-, and body mass index–matched healthy controls. Besides the endocrine workup, IR was evaluated using fasting glucose and insulin concentrations, homeostasis model assessment of IR, and quantitative insulin sensitivity check index. In a subgroup of patients undergoing an oral glucose tolerance test, Matsuda index and total area under the curve for glucose and insulin were also evaluated. Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and other biochemical parameters were measured with standard techniques. Body composition was determined with dual-energy x-ray absorptiometry. Patients with NFAIs exhibited higher fasting glucose, insulin, and homeostasis model assessment of IR values; decreased quantitative insulin sensitivity check index and Matsuda index; and an increased—although not statistically significant—area under the curve for glucose and insulin compared with controls ($P < .05$). In addition, they exhibited higher systolic and diastolic blood pressure, triglycerides, and γ-glutamyltransferase and lower high-density lipoprotein cholesterol levels compared with controls ($P < .05$). Patients with NFAIs were all obese with a central type of fat accumulation and increased appendicular lean mass. Indices of IR showed a positive correlation with indices of MS ($P < .05$), but no correlation with markers of hormonal activity. Nonfunctioning adrenal incidentalomas are characterized by IR, hypertension, dyslipidemia, and fatty liver disease, all of them being components of MS. Thus, patients with NFAIs should be screened for MS during their initial workup to identify those at cardiometabolic risk and implement the appropriate interventions.
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1. Introduction

Adrenal incidentalomas (AIs) are defined as incidentally discovered adrenal masses in the process of performing an abdominal imaging procedure for unrelated extraadrenal complaints [1,2]. Adrenal incidentalomas exhibit a steadily increasing prevalence, in parallel with the widespread application of sophisticated imaging modalities, ranging from 1 to 8.7% or 0.1 to 1.9% according to autopsy or radiological series, respectively [3-6].

The vast majority of AIs comprise benign and nonfunctioning adrenocortical adenomas (NFAIs) with a presumably persistent functional inactivity and an extremely low potential of evolving to malignancy [1,2,7]. The rest of them may represent functional hormone-producing adenomas and primary or metastatic malignancies [1,2,7].

The relationship of NFAIs with metabolic disorders, components of metabolic syndrome (MS), and adverse cardiovascular outcomes remains quite underestimated. An apparently paradoxical and thought-provoking association of NFAIs with insulin resistance (IR) and MS has been reported in a limited number of studies, using relatively small numbers of patients [8-13]. It has been proposed that

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NFAIs might be an underestimated causative factor for MS phenotype [10] or an unrecognized manifestation of IR [9], possibly accounting for a higher global cardiometabolic risk compared with the general population [14]. However, the real nature of this cause-effect relationship and the underlying pathogenetic mechanisms have not been conclusively delineated and remain to be further elucidated.

The principal aim of the present study was to assess in a comprehensive way IR or, conversely, insulin sensitivity, as well as other parameters of MS, in a number of patients with AIs, focusing on the NFAIs, in comparison with age-, sex- and body mass index (BMI)–matched healthy controls. We secondarily aimed to investigate different patterns of body fat and lean mass distribution using absorptiometrically derived data in patients with NFAIs compared with healthy controls.

2. Subjects and methods

2.1. Study population

From a total of 46 patients diagnosed with AIs by abdominal computed tomography (CT) or magnetic resonance imaging (MRI), we evaluated 29 patients with NFAIs. The mean age of our study population was 54 ± 9 years. Mean BMI was 29 ± 3 kg/m^2, and the mean waist circumference was 100 ± 13 cm (overweight and abdominally obese patients). All studied patients did not suffer from any known disease and did not receive any medication at the time of diagnosis or had stopped treatment at least 2 weeks before evaluation. In addition, 37 subjects without adrenal disease, strictly matched with patients in terms of age, sex, BMI, waist circumference, smoking habits, and menopausal status for women, were also enrolled in the study and served as controls. The study protocol was approved by the Medical Research Ethics Committee of our Institution. A written informed consent was obtained from all participants.

2.2. Study protocol

All patients and healthy controls gave a detailed personal and family medical history and underwent a thorough physical and hemodynamic evaluation including weight, height, BMI (weight in kilograms divided by height in meters squared), waist and hip circumferences, waist to hip ratio, and blood pressure.

2.2.1. Metabolic evaluation

On day 1 of the study protocol, at 8:30 AM and after an overnight fasting, blood was drawn from all subjects for a routine biochemical evaluation including total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, urea, creatinine, electrolytes, uric acid, and liver enzymes, which were all measured with standard techniques.

At the same day, in 12 patients with NFAIs and 20 controls, a 2-hour oral glucose tolerance test (OGTT) was performed, after a prior 3-day dietary instruction for increased carbohydrate consumption. Patients received an oral glucose load of 75 g; and blood samples were collected at 0, 30, 60, 90, and 120 minutes for the measurement of plasma glucose and insulin concentrations. Diagnosis of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes mellitus (DM) was made according to the revised criteria of the Expert Committee for Diagnosis and Classification of Glucose Metabolism Disorders [15]. Based on fasting plasma glucose and insulin concentrations, we estimated homeostasis model assessment of insulin resistance index (HOMA) and quantitative insulin sensitivity check index (QUICKI) for an evaluation of IR and insulin sensitivity, respectively [16,17]. The whole-body insulin sensitivity index, obtained from OGTT, was calculated in patients and controls according to the formula developed by Matsuda and DeFronzo [18]. The response of glucose and insulin to 75-g glucose load was assessed from the total areas under the curve (AUCs) for glucose and insulin, respectively, which were calculated according to the trapezoidal rule based on Tai's mathematical model [19].

2.2.2. Endocrine evaluation

Patients were screened for hormonal activity through a detailed endocrine workup, based on blood and 24-hour urinary hormones evaluation, according to the recommendations of the National Italian Study Group on Adrenal Tumors [7].

On day 4, blood was drawn for determination of basal levels of pituitary and adrenal hormones (cortisol, corticotropin, aldosterone, plasma renin activity, adrenal androgens). At the same day, patients performed a 24-hour urine collection, after 3 days on appropriate diet; and vanillylmandelic acid, catecholamines, metanephrines, and free cortisol were determined. A second blood sample was drawn at 23:00 h for cortisol measurement and evaluation of cortisol circadian rhythm.

Days 5 and 6 were dedicated to the short-duration dexamethasone suppression test consisting of administration of dexamethasone (2 mg/d for 2 consecutive days). On day 7, early in the morning, blood was drawn for postdexamethasone cortisol measurement.

The average time needed for completion of the procedures for every participant ranged between 5 and 7 days. Throughout this period and at least 2 weeks before the enrollment of subjects in the study protocol, all drugs that could potentially interfere with the hormonal assays were discontinued; and they were replaced if necessary by other more appropriate regimens.

Diagnosis of NFAIs, which constitute the vast majority of cases examined, was made after exclusion of hormone secretion from the affected adrenal glands.

2.2.3. Imaging evaluation

Computed tomography and/or MRI scans were carefully inspected from experienced radiologists of our department

for evaluation of the benign or malignant nature of the adrenal tumors according to the existing criteria (tumor size, shape, density, margins, enhancement after intravenous contrast medium administration, attenuation values on unenhanced CT, duration of washout period, etc) [2].

2.2.4. Body composition analysis

Ten patients with NFAIs and 25 controls were scanned with dual-energy x-ray absorptiometry (DXA) for a whole-body composition analysis (Hologic QDR Discovery series, Bedford, MA). The automatically derived DXA parameters that were compared between patients with NFAIs and controls were as follows: total fat mass, percentage of fat mass, total lean mass, and trunk fat. Manually defined subregions for thoracic, abdominal, and gluteofemoral fat were additionally used to evaluate central and peripheral type of fat distribution in the studied subjects. Appendicular lean mass (lean mass of upper and lower extremities) was used to assess the adequacy of peripheral muscle tissue in patients with incidentalomas. The abdominal to gluteofemoral fat ratio was used as an absorptiometrically determined surrogate of waist to hip ratio, reflecting preferential central fat deposition.

2.3. Statistical analysis

All data are given as mean ± standard deviation (SD). Differences in means between subgroups of patients were analyzed using the Mann-Whitney *U* unpaired test. Correlation analyses were performed using Spearman correlation coefficient. A stepwise multiple regression analysis was performed to assess variables independently associated with selected dependent variables. Differences were considered statistically significant at a P level < .05. Data analysis was performed using the SPSS statistical program (SPSS 10.0 for Windows; SPSS, Chicago, IL).

3. Results

From the total number of 46 patients with AIs, 29 patients (63%) carried the diagnosis of NFAIs, the rest of them being functioning adenomas, whereas in 2 patients, adrenocortical carcinoma was diagnosed.

Our analysis is mainly focused on the subgroup of NFAIs, as this group represented the vast majority of the studied cases. The demographic and anthropometric characteristics of the study group are depicted in Table 1. The radiologically determined size of the masses ranged from 1 to 11 cm in diameter; 12 were right-sided, 9 were left-sided, and 8 were bilaterally localized (6 bilateral adenomas, 2 bilateral hyperplasia). Three subjects from the group of NFAIs reported to have been previously diagnosed with diabetes under treatment, so they were excluded from the further analysis. Regarding the clinical follow-up of studied patients, 3 patients with large NFAIs (>6 cm) underwent surgical excision of their tumors; and the histology report revealed benign adenomas.

Table 1
Clinical characteristics of patients with NFAIs and healthy controls

Parameters	NFAIs	Controls	*P* value
n	29	37	
Sex (male/female)	10/19	12/25	.980
Age (y)	54 ± 9	52 ± 9	.132
BMI (kg/m^2)	29 ± 3	30 ± 5	.422
Waist circumference (cm)	100 ± 13	104 ± 23	.626
Hip circumference (cm)	108 ± 6	113 ± 15	.256
Waist to hip ratio	0.92 ± 0.1	0.94 ± 0.1	.920
Systolic blood pressure (mm Hg)	127 ± 15	118 ± 17	.011[a]
Diastolic blood pressure (mm Hg)	82.2 ± 9.4	76 ± 9	.033[a]
Mean blood pressure (mm Hg)	97 ± 10	90 ± 11	.036[a]
Smoking status[b] (Y/N)	13/16	10/27	.185
Family history[b] (Y/N)	13/16	12/25	.570
Menopausal status[b] (Y/N/P)	15/2/2	14/8/4	.210

Data are expressed as mean values ± SD.

[a] Significant differences between patients with NFAIs and controls.

[b] For smoking status and family history: Y = yes, N= no. For menopausal status: M = menopause, R = reproductive age, P = perimenopausal period.

Patients with NFAIs did not differ from the control group in terms of age, male to female ratio, BMI, waist circumference, and waist to hip ratio, as depicted in Table 1. In addition, there were no differences between NFAIs and controls regarding smoking status and the family history for cardiometabolic disease, whereas the studied women were fully comparable with control women in terms of menopausal status (Table 1).

Based on fasting plasma glucose levels, 3 patients with NFAIs had diabetes (10.3%), 4 had IFG (13.8%), and 22 were normal (75.9%), percentages that were not significantly different from the age-, sex-, and BMI-matched control group. However, fasting plasma glucose and insulin levels—and therefore HOMA and QUICKI proved to be significantly different between patients and controls (Table 2).

Based on OGTT, the ratio of IGT and normal glucose metabolism was almost comparable between patients with NFAIs and controls. However, AUC for glucose and insulin tended to be higher—although not statistically significant—in patients with NFAIs. Moreover, Matsuda index, reflecting postabsorptive and generalized IR, differed significantly between the compared groups, being lower and thus worse in the group of NFAIs (Table 2).

As far as other components of MS are concerned, systolic, diastolic, and mean blood pressures were significantly higher in patients with NFAIs compared with controls (Table 1). In addition, patients with NFAIs exhibited increased levels of triglycerides and decreased levels of HDL cholesterol (Table 3), whereas there were no significant differences in terms of total and LDL cholesterol levels. Higher levels of γ-glutamyltransferase were also observed in patients with NFAIs in comparison with controls (Table 3).

In terms of body composition, patients with NFAIs had a tendency for increased fat accumulation in the chest, trunk,

Table 2
Indices of IR or sensitivity in patients with NFAIs and healthy controls

Parameters	NFAIs (n = 29)[b]	Controls (n = 37)[b]	*P* value
Fasting glucose (mg/dL)	92 ± 16	85 ± 13	.05[a]
Fasting insulin (μU/mL)	15 ± 7	11 ± 5	.034[a]
HOMA-IR	3.6 ± 1.7	2.4 ± 1.5	.009[a]
QUICKI	0.32 ± 0.02	0.35 ± 0.03	.022[a]
Mean glucose OGTT values (mg/dL)	132 ± 23	129 ± 36	.414
Mean insulin OGTT values (μU/mL)	70 ± 30	67 ± 43	.586
Matsuda Index (10^{-4} min^{-1} [μU/mL]$^{-1}$)	3.1 ± 0.95	5.2 ± 2.8	.05[a]
Total AUC for glucose (mg/[dL h])[c]	8477 ± 1449	7695 ± 1448	.215
Total AUC for insulin (μU/[mL h])[c]	4884 ± 2261	4413 ± 2649	.378

Data are expressed as mean values ± SD.

[a] Statistically significant differences between patients with NFAIs and controls.

[b] These numbers are for fasting glucose, fasting insulin, HOMA-IR, and QUICKI. For OGTT data, n = 12 for NFAIs and n = 20 for controls.

[c] The calculation of the AUC for glucose and insulin was based on 5 values during OGTT (0, 30, 60, 90, and 120 minutes).

and abdominal regions, which did not however reach statistical significance (Table 4). Furthermore, patients with NFAIs exhibited increased appendicular lean mass, namely, increased peripheral lean mass, compared with controls (Table 4).

It is noteworthy that AUC for glucose and insulin was higher in patients with large unilateral adenomas (>4 cm) and bilateral adenomas compared with smaller (<4 cm) and unilateral adenomas, respectively (data not shown). Although bilateral hyperplasia was observed in only 2 patients, there was no significant difference in the studied metabolic parameters between hyperplasia and adenomas. No direct correlation between size of the adenomas and metabolic parameters was found.

Table 3
Laboratory data in patients with NFAIs and controls

Biochemical parameters	NFAIs (n = 29)	Controls (n = 37)	*P* value
Urea (mg/dL)	32 ± 13	32.5 ± 10	.608
Creatinine (mg/dL)	0.94 ± 0.2	0.9 ± 0.2	.583
Total cholesterol (mg/dL)	213 ± 48	220 ± 31	.508
Triglycerides (mg/dL)	145 ± 70	109 ± 62	.02[a]
HDL cholesterol (mg/dL)	48 ± 17	59 ± 16	.012[a]
LDL cholesterol (mg/dL)	133 ± 44	139 ± 34	.294
Uric acid (mg/dL)	4.9 ± 1.3	5 ± 1.5	.844
Aspartate aminotransferase (mg/dL)	23 ± 16	21.2 ± 5.4	.267
Alanine aminotransferase (mg/dL)	25 ± 12	23.2 ± 8.6	.756
γ-glutamyltransferase (mg/dL)	33 ± 21	20 ± 12.3	.048[a]
Alkaline phosphatase (mg/dL)	91 ± 41	77 ± 33	.106
Basal serum cortisol (μg/dL)	16 ± 9	12 ± 4	.161
Basal plasma corticotropin (pg/mL)	17 ± 8	12 ± 4	.572
Midnight serum cortisol (μg/dL)	4.9 ± 2	4.2 ± 1.5	.593
Postdexamethasone serum cortisol (μg/dL)	1.5 ± 0.2	0.6 ± 0.3	<.001[a]

Data are expressed as mean values ± SD.

[a] Statistically significant differences between patients with NFAIs and controls.

Table 4
DXA-derived parameters of body composition (lean and fat mass distribution) in patients with NFAIs and controls

Parameters of body composition analysis	NFAIs (n = 10)	Controls (n = 25)	*P* value
Total lean mass (g)	53418 ± 9138	52987 ± 17383	.359
Appendicular lean mass (g) (lean mass of arms and legs = peripheral lean mass)	22882 ± 4791	19120 ± 4350	.05[a]
Trunk fat (g)	15619 ± 3307	11687 ± 4558	.09
Abdominal fat (g)	3256 ± 1050	2454 ± 1161	.161
Chest fat (g)	7130 ± 1412	5141 ± 2392	.122
Gluteofemoral fat (g)	12211 ± 2345	11292 ± 2854	.606
Total fat mass (g)	30562 ± 5984	33454 ± 14818	.872
Fat mass (%)	35.4 ± 5.7	36.6 ± 6.5	.767

[a] Statistically significant differences between patients with NFAIs and controls.

In the group of patients with NFAIs, HOMA showed a positive correlation with BMI (r = 0.486, P = .026), triglycerides (r = 0.520, P = .019), and uric acid levels (r = 0.546, P = .035) and a negative correlation with HDL cholesterol values (r = −0.565, P = .009) and with QUICKI and Matsuda index (r = −0.99, P < .001 and r = −0.497, P = .05, respectively). In addition, HOMA showed a positive correlation with indices of body fat distribution, namely trunk fat (r = 0.9, P = .037), abdominal fat (r = 0.902, P = .036), and percentage of fat (r = 0.9, P = .037). The QUICKI Index showed a positive correlation with HDL cholesterol levels (r = 0.466, P = .05) and a negative correlation with triglycerides (r = −0.527, P = .025) and uric acid levels (r = −0.546, P = .035), abdominal fat (r = −0.9, P = .037), and percentage of fat (r = −0.9, P = .037). The multiple stepwise regression analysis revealed that abdominal fat was the only variable that was independently associated with HOMA and QUICKI values (β = 0.7, R^2 = 0.959, P = .01 and β = −0.651, R^2 = 0.963, P = .009, respectively).

4. Discussion

The present study shows that patients with NFAIs are obese with a tendency for central fat deposition and exhibit various hemodynamic and metabolic abnormalities, such as hypertension, IR, dyslipidemia, and increased liver enzymes, to a greater extent than age- and sex-matched obese controls. The above abnormalities cannot be explained by differences in anthropometric parameters, smoking habits, family history for cardiometabolic disease, or menopausal status in women because the studied groups were appropriately and strictly matched for all these characteristics. This is translated to an obese phenotype of patients with NFAIs, with an increased prevalence of MS, which is an interesting and thus provocative finding.

More specifically, patients with NFAIs proved to be obese and insulin resistant, exhibiting increased fasting glucose and insulin levels and consequently higher HOMA and lower QUICKI, compared with the obese control group. Based on these observations, NFAIs are characterized by an IFG state, suggesting an underlying hepatic IR. In accordance with our data, Reincke et al [9], in a study of 13 patients with NFAIs, showed that they were all insulin resistant at fasting state and also obese with an increased total fat mass centrally distributed. The importance of fasting hyperinsulinemia is highlighted by the recent findings from the RISC Study (Relationship between Insulin Sensitivity and Cardiovascular Disease) supporting that fasting insulin represents a strong and independent contributor to cardiometabolic risk and atherosclerosis [20].

Regarding the postabsorptive state, patients with NFAIs exhibited higher—although not statistically significant—AUC for glucose and insulin as well as significantly decreased Matsuda index compared with the obese controls, suggesting that NFAIs are associated with a generalized IR. In support of this, Terzolo et al [10] showed that the 2-hour postchallenge glucose was significantly higher in patients with NFAIs than in controls. Furthermore, Midorikawa et al [11] demonstrated that the 12 studied subjects with NFAIs were all insulin resistant based on the steady state of plasma glucose. Moreover, Ivovic et al [12] found lower insulin sensitivity in 22 patients with NFAIs studied with a short-duration insulin tolerance test. Based on the existing knowledge that either fasting or postabsorptive IR constitutes the major pathogenetic mechanism for the development of MS and diabetes, our data strongly suggest that patients with NFAIs are confronted with such an increased risk.

In addition, patients with NFAIs were hypertensive and dyslipidemic, showing increased levels of systolic, diastolic, and mean blood pressure; increased levels of γ-glutamyltransferase and triglycerides; and decreased levels of HDL cholesterol compared with controls. In other words, patients with NFAIs seem to have a higher prevalence of MS. In support of this observation, Midorikawa et al [11] found that 58% of patients with NFAIs exhibited hypertension, whereas 75% were diagnosed with disturbed glucose tolerance. In accordance, Zhang et al [13] reported high prevalence rates of MS in 24 patients with NFAIs. In addition, Bernini et al found an increased prevalence of diabetes and hypertension in 9 patients with NFAIs, who were perfectly restored to normal after surgical adrenalectomy [14]. Moreover, Ermetici et al [21] reported increased levels of proinflammatory markers, such as interleukin-6, resistin, tumor necrosis factor–α, and monocyte chemoattractant protein–1, in patients with NFAIs, supporting the pathogenetic role of subclinical inflammation as the missing link between NFAIs, IR, MS, and cardiometabolic risk.

Based on DXA-derived data of body composition, it seems that patients with NFAIs are obese and display a tendency for a central type of fat distribution, namely, increased accumulation of fat in the abdominal, chest, and trunk subregions. Despite the lack of statistical significance, these differences are of considerable magnitude, as shown in Table 4, and should be taken into consideration because they seem to reflect a clinically meaningful pattern of fat distribution, which might prove to be a significant finding when studying larger groups of patients with NFAIs. A rather unexpected and apparently inexplicable finding was the increased appendicular lean mass that was observed in patients with NFAIs compared with controls. Although muscle tissue is traditionally considered to be metabolically active and protective, an increased lean muscle mass has been paradoxically reported in women with polycystic ovary syndrome and obese postmenopausal women at increased cardiovascular risk [22,23]. These findings render the role of lean tissue rather ambiguous and warrant further research to be definitely confirmed or rejected. In our study, the expanded peripheral lean tissue of patients with NFAIs cannot be characterized as protective because it is likely to be insulin resistant and therefore qualitatively defective and dysfunctional.

Regarding the putative mechanisms underlying the association of NFAIs with IR and MS, they remain at present mainly speculative. According to 2 in vivo studies, an increased expression of functional corticotropin receptors or enzymes involved in endogenous cortisol production as well as increased cytochrome P450 activities have been associated with a clinically and biochemically undetectable adrenal steroid overproduction, with a possible impact in promoting metabolic disorders [24,25]. In our study, although no correlation between indices of IR and markers of hormonal activity could be observed, the above-mentioned mechanisms cannot be excluded.

It has been proposed that NFAIs might have a causative role for various adverse clinical and biochemical manifestations related to MS, which are basically determined by the composite interplay between the endogenous steroidogenic potential of adrenocortical cells and other in vivo factors that remain at present largely unknown. The most convincing proof for the existing relationship between NFAIs and MS is the complete reversal of metabolic disorders after the surgical resection of the tumors [11,14,26]. However, an alternative theory suggests that NFAIs might be an effect of MS, in a similar way that polycystic ovary syndrome is regarded as the result of insulin-mediated stimulation of ovary growth [9,27].

In agreement with large systematic reviews examining AIs, our data showed that NFAIs were found in the right adrenal gland in 41.3%, in the left adrenal gland in 31%, and bilaterally in 21% [5]. It has to be noted that there was no difference in IR and other metabolic parameters depending on the unilateral or bilateral location of the adenoma, the size, or the distinction between adenoma and hyperplasia, although hyperplasia was found in only 2 cases. However, a trend toward higher AUC for glucose and insulin in patients with bilateral and large adenomas

(>4 cm) vs unilateral and smaller ones was observed, as previously reported.

A number of long-term follow-up studies have tried to shed light on potential risk factors for developing hormonal hyperactivity during the natural course of NFAIs. These studies evaluated the long-term morphologic and functional evolution of initially inactive incidentalomas and registered all cases of transition to hyperfunctional states [28-31]. Libé et al [28] evaluated prospectively 64 patients for a median period of 26 months and reported that 18 patients developed subtle endocrine alterations during the follow-up. Subclinical autonomous cortisol hypersecretion is the most frequent hormonal abnormality that might emerge intermittently in patients with NFAIs sometime during the course of their disease [28-31]. In the same study, the cumulative risk of developing endocrine abnormalities was 17% at 1 year, 29% at 2 years, and 47% at 5 years. The risk was higher in the first 2 years of follow-up if the initial tumor diameter was at least 3 cm [28]. In a further large-scale study by Barzon et al [31] the estimated cumulative risks to develop adrenal hyperfunction were 4% after 1 year, 9.5% after 5 years, and 9.5% after 10 years. These findings indicate that AIs constitute a continuum between functioning and nonfunctioning tumors; and thus, there is need for periodic hormonal and morphologic evaluation for several years.

To the best of our knowledge, this is the first clinical study that evaluates in such a comprehensive way patients with NFAIs using a great variety of indices for IR, parameters known as components of MS, and data on body composition. The major limitation of the study is the relatively small number of patients with NFAIs, which is however quite similar to the existing studies [10-14]. Given the scarcity and heterogeneity of data regarding the relationship between NFAIs and cardiometabolic syndrome, our data appear to be rather provocative.

In conclusion, NFAIs constitute an emerging clinical entity, which seems to carry an adverse cardiometabolic prognosis. An increased proinflammatory status, aggravated by the “silent” hormonal dysfunction that is commonly observed in NFAIs, might explain the development of IR and/or MS. On the other hand, the possibility of the development of NFAIs as the clinical result of sustained hyperinsulinemia cannot be excluded. In practical terms, our data suggest that the detailed endocrine workup of all AIs, including NFAIs, should include the evaluation of MS components to identify patients at a high cardiometabolic risk and implement the appropriate lifestyle and possibly therapeutic interventions.

5. Declaration of interest and funding

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Furthermore, this research did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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