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Screening for Insulin Resistance in Benign Non-Functioning Adrenal Tumors: A Metabolic Approach

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Abstract **Original Research Article**

Benign non-functioning adrenal incidentalomas (NFAI) represent the majority of adrenal masses incidentally discovered during imaging studies. Although traditionally considered hormonally inactive, several studies suggest their association with metabolic abnormalities, particularly metabolic syndrome and insulin resistance. The objective of our study is to evaluate the metabolic profile of patients with NFAI and to analyze the association between these lesions, metabolic syndrome, and insulin resistance. We conducted a descriptive cross-sectional study including 30 patients with NFAI, followed in the Department of Endocrinology, Diabetology and Nutrition at Mohammed VI University Hospital of Marrakech between October 2015 and December 2024. Out of 60 medical records concerning adrenal tumors during the study period (2015–2024), 31 cases of incidentalomas were identified, of which 30 were eligible. The mean age of patients was 56.2 years, with a female predominance (70%). The majority of lesions were unilateral non-functioning adenomas (70%). From a metabolic perspective, 30–36% of patients presented with metabolic syndrome, and 30% showed insulin resistance as evidenced by a HOMA-IR index > 2.4. Obesity (50%), hypertension (40%), and dyslipidemia (20%) were frequently associated. These findings confirm the close relationship between NFAI, metabolic syndrome, and insulin resistance, highlighting the importance of integrating metabolic approach in the management of NFAI.

Keywords: Adrenal incidentaloma, non-functioning adenoma, metabolic syndrome, insulin resistance.

INTRODUCTION

Benign non-secreting adrenal tumors are among the most frequently diagnosed neoplasms in recent years. Continuous improvements in imaging techniques have led to a significant increase in the number of incidental findings of adrenal tumors, often detected during examinations performed for other medical reasons. The non-secreting (or non-functional) subtype accounts for the majority of cases. These tumors are characterized by benign radiological features and the absence of clinical or biological signs of hormonal hypersecretion. However, patients with non-secreting adrenal tumors are frequently observed to have metabolic disorders such as high blood pressure, dyslipidemia, glucose intolerance, and obesity, all of which are closely associated with insulin resistance. It remains unclear whether these metabolic abnormalities are more common in patients with benign non-secreting adrenal tumors, or whether they result from subtle or intermittent glucocorticoid hypersecretion that is not detected by standard hormone tests. The objective of this study is to evaluate insulin resistance parameters in consecutive patients with benign non-secreting adrenal tumors.

MATERIELS AND METHODS

This is a descriptive cross-sectional study conducted in the endocrinology, diabetology, metabolic diseases and nutrition department of the Mohammed VI University Hospital in Marrakesh. Its main objective was to describe the metabolic profile of patients with benign non-secreting (non-functional) adrenal tumours and, secondarily, to analyse the association between these tumours and metabolic syndrome and insulin resistance.

Clinical, biological and imaging data were collected from the medical records of patients followed

between October 2015 and December 2024, including demographic, clinical (circumstances of discovery), metabolic (prediabetes/diabetes, hypertension, dyslipidaemia, BMI, waist circumference, insulin resistance using the HOMA index with a cutoff value of 2.4) and imaging data (discovery methods: CT scan, ultrasound, lesion characteristics, etc.).

Patients with a benign non-secreting adrenal tumour confirmed by imaging (size < 4 cm, spontaneous density < 10 HU on CT scan), with positive low-dose dexamethasone suppression test, normal urinary methoxyl derivatives, and normal serum potassium levels were included. Patients with multiple endocrine neoplasia or a genetic syndrome predisposing to adrenal tumours were excluded, as were patients receiving treatment that affects carbohydrate or lipid metabolism (e.g. corticosteroids, antipsychotics).

RESULTS

We collected 61 cases of adrenal masses, and included 30 patients with benign non-secreting adrenal tumors in our study. The age at which an adrenal mass was discovered in our patients ranged from 20 to 77 years, with an average of approximately 56.2 years. There was a predominance of females, with a female/male ratio of 2.3. The adrenal mass was discovered incidentally in 50% of our patients (Fig. 1).

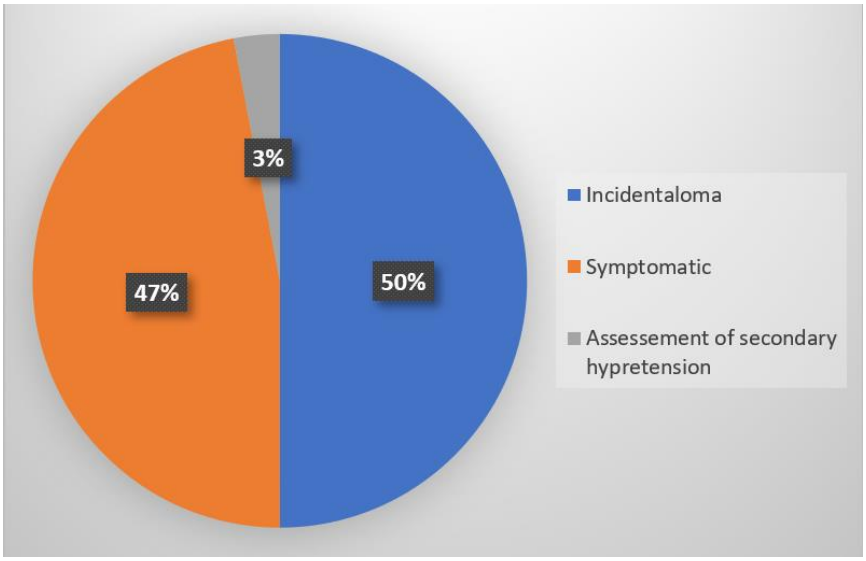

Figure 1: The circumstances of discovery

As for the main symptoms reported by our patients, pain was the predominant symptom in 14 patients (46.6%), mainly localized in the lumbar region.

The Body Mass Index (BMI) was specified for all our patients, with an average of 27.84 kg/m², and half of our patients were obese. (Fig. 2)

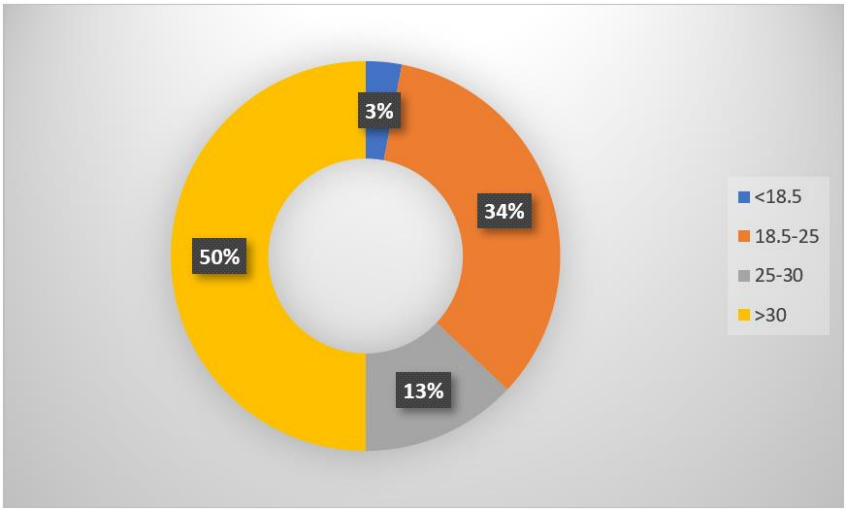

Figure 2: Distribution of patients according to their BMI (kg/m²)

Waist circumference was pathological in 14 women (with a waist circumference >80 cm) and in 4 men (with a waist circumference >94 cm) in our series.

Blood pressure was measured in all our patients and classified according to the WHO staging system (140/90 mmHg), with 40% of patients being hypertensive.

As for paraclinical investigations, biological tests were requested to rule out secreting adrenal tumors. All our patients underwent specific testing. Free urinary cortisol (FUC) was 1.2 times the normal level in 2 patients and normal in 28 patients (93.3%). The dexamethasone suppression test was positive in all our patients, with an average of 0.9 +/-0.5 ug/dl. The urinary methoxyl derivative test was negative in 30 patients. Plasma aldosterone and plasma renin activity with the aldosterone/renin ratio were measured in two cases and were normal in both patients. Tests to check for androgen hypersecretion, including testosterone and dehydroepiandrosterone sulfate levels, were performed in one case and were normal. Lipid profiles were performed in 23 patients (76%), revealing dyslipidemia in six patients (20%). (Fig. 3)

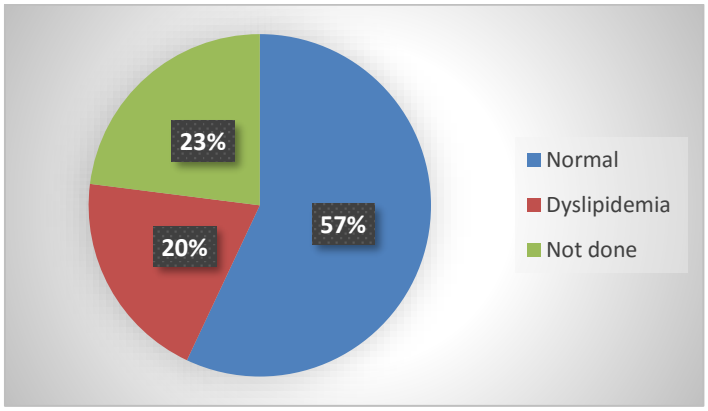

Figure 3: Percentage of lipid profile

With regard to morphological data, radiological examinations enable the size, content, location, and signs of malignancy of the tumor to be determined. These criteria are important for choosing the therapeutic and surgical method. Several methods are used in our series. The most commonly requested imaging technique was abdominal CT, which was performed in all patients. According to the morphological assessment, the tumor was unilateral in 23 patients (76.6%) and bilateral in 7 patients (23.3%). Tumor size was measured in all cases in our series. The average size was 19.8 mm, ranging from 10 mm to 30.2 mm (Fig. 4).

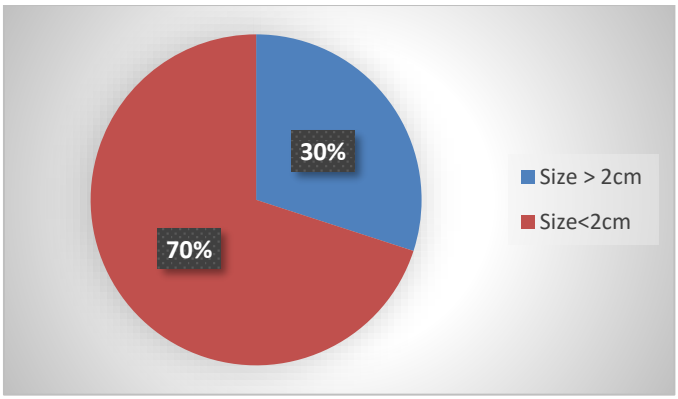

Figure 4: Distribution of cases according to tumor size

No signs of malignancy (calcifications, central necrosis, signs of locoregional extension) were observed in our series. The masses had a spontaneous density <10 HU in all 30 patients. In our series, adrenal CT scans with contrast injection were performed in 22 cases, with the following results: absolute washout >60% in 20 patients.

Insulin resistance in non-secreting adrenal tumors was assessed in all of our patients. Metabolic syndrome was found in 30% of cases in our series. The HOMA-IR index was measured in 20 patients (66.6%), revealing insulin resistance with a threshold >2.4 in 9 patients (30%), while 11 patients had a normal HOMA-IR index <2.4 (36.6%). HbA1c was measured in 16 patients, revealing diabetes in 6 patients and prediabetes in 4 patients, while HbA1c was normal in the remaining patients.

DISCUSSION

Benign non-secreting adrenal adenomas are the most common type of tumor in the adrenal gland. Their exact prevalence remains difficult to determine, but various clinical studies provide an estimate. A systematic review [1] conducted by the French Society of Endocrinology (FSE) found a prevalence of incidentalomas between 0.3 and 4.4%, of which 71% were non-secreting adenomas.

The prevalence of incidentalomas detected by computed tomography (CT) varies, depending on the series, between 0.5 and 5% [2]. They are bilateral in approximately 11 to 16% of cases [3-4]. The majority of these lesions are non-secreting adenomas, found in 55 to 94% of cases [5]. Among benign adrenal tumors, adrenal adenoma is the most frequently found etiology.

These lesions may remain non-functional, with undetectable cortisol secretion, or may present as subclinical corticosteroid-secreting adenomas (SCSAs) that may reveal clinical Cushing's syndrome. Even when cortisol secretion is very low, it is well established that these SCSAs expose patients to increased metabolic risks, including glucose intolerance, type 2 diabetes, obesity, and high blood pressure (HBP). There is also an increase in fat mass and a higher risk of cardiovascular disease [6,7].

Our study aimed to determine whether these same risks were present in patients with non-secreting adrenal masses by assessing the metabolic status of a population of individuals in whom the adenoma had been discovered incidentally, without criteria for hormone secretion or malignancy. The majority of patients with non-secreting adrenal masses had clinical and biological characteristics consistent with metabolic syndrome, particularly abdominal obesity. In our series, the prevalence of metabolic syndrome was 30%. The link between theses lesions and metabolic syndrome is thought to be related to excess glucocorticoids, which alter hepatic insulin sensitivity by decreasing glycogenesis and increasing neoglucogenesis, while reducing peripheral tissue insulin sensitivity, leading to hyperglycemia. For non-secreting adenomas, Morelli *et al.*, suggested that this phenomenon could be linked to a polymorphism of glucocorticoid receptors, leading to variable metabolic responses even with low cortisol secretion. [8]

In our population, 40% of our patients were hypertensive among the 30 included. These results are within the range reported in the literature, where the prevalence of hypertension in patients with adrenal adenomas varies from 40 to 90% according to Barzon *et al.*, In addition, Szychlińska *et al.*, showed that patients with non-secreting adrenal tumors had significantly higher systolic and diastolic blood pressure than controls, confirming that hypertension is a common metabolic abnormality in this context. [9, 10,6,11]

With regard to carbohydrate metabolism abnormalities, our results confirm that even so-called "non-functional" tumors are frequently associated with significant carbohydrate disturbances. Similarly, Krzyżewska *et al.*, found a high prevalence of diabetes (30.5%) and glucose tolerance abnormalities (39.8%) in a cohort of 131 patients with non-secreting adenomas. [6,12-14].

With regard to abdominal obesity, non-secreting adrenal tumors are associated with a significant increase in waist circumference and an increased risk of metabolic syndrome, regardless of apparent hormonal function. [9,11]

The literature also clearly shows that patients with non-secreting adrenal adenomas often present with insulin resistance syndrome with a high HOMA-IR index, associated with an increased cardiovascular risk. These patients have been shown to have decreased insulin sensitivity and pancreatic beta cell dysfunction, leading to increased insulin secretion. This phenomenon is observed whether the adenoma is non-secreting or has subclinical cortisol secretion. [15,16]

The relationship between non-secreting adrenal masses (NSAM) and insulin resistance (IR) is increasingly recognized as complex and bidirectional, characterized by mutual amplification. Initially considered clinically insignificant, NSAMs are now associated with metabolic properties and increased cardiovascular risk.

Although classified as "nonfunctional," there is evidence suggesting that NFAIs may secrete small, inappropriate amounts of glucocorticoids (cortisol) that fall below traditional clinical criteria for diagnosing hypercortisolism but increase metabolic risk over time. This subtle secretion of cortisol has direct and indirect effects on insulin sensitivity and glucose metabolism. [17,18,14]

In summary, the relationship between non-secreting adrenal adenomas and insulin-resistance IR /metabolic syndrome is a self-amplifying vicious circle. NFAIs may contribute to I through subtle cortisol secretion, and IR, in turn, may promote the growth of these adenomas through mechanisms related to hyperinsulinism and the IGF system. This complex interrelationship underscores the importance of monitoring the metabolic function of patients with NFAI, even if they are initially classified as non-functional.

CONCLUSION

Non-functioning adrenal adenomas (NFAAs) have been shown to be significantly associated with various metabolic disorders. In our series, a significant proportion of patients had metabolic syndrome, and nearly one-third had insulin resistance as measured by the HOMA-IR index. These results reinforce the idea,

supported by the literature, that NFAAs are not completely "non-functional," but may reflect an underlying metabolic imbalance. The exact pathophysiology of this link remains under debate. Subclinical hypersecretion of glucocorticoids, undetectable by routine endocrine tests, could explain the onset of insulin resistance, hypertension, and dyslipidemia observed. Whatever the explanation, the correlation observed in our study confirms that NFAAs must be considered from a broader perspective, going beyond simple morphological assessment. In practical terms, these results highlight the importance of systematic monitoring of metabolic parameters in all patients with NFAA. The analysis of insulin resistance, often neglected in routine practice, deserves special attention, as it is an early indicator of the risk of diabetes and cardiovascular complications.

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