ORIGINAL ARTICLE

High prevalence of obesity in patients with non-functioning adrenal incidentalomas

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Abstract

OBJECTIVE: The influence of obesity on cancer development has been proven for numerous tumours. In contrast, the association between obesity and non-secreting adrenal incidentaloma has never been proven. Therefore, the aim of this study was to investigate this relationship in a large sample of patients.
METHODS: 143 patients with benign non-secreting adrenal incidentalomas treated in the Department of Endocrinology at the Poznan University of Medical Sciences between the years 2000–2007 were examined. To rule out subclinical hyperfunctioning lesions, serum dehydroepiandrosterone sulphate, cortisol (8 am, 6 pm, and after 1 mg dexamethasone suppression), sodium and potassium, along with concentrations of sodium, potassium, vanillylmandelic acid, metanephrine and normetanephrine in 24-hour urine collection were determined. Radiological evaluation included computed tomography and/or magnetic resonance imaging. Only non-secreting lesions and those of benign radiologic appearance were considered. The patients body mass index was compared to that of the general population of Poland and the Western Poland Region of Wielkopolska.
RESULTS: The average body mass index of our patients was 28.77 kg/m^2 (SD=4.71), with a 40% prevalence of obesity in the study group. One-proportion z-test showed a statistically significantly higher prevalence of obesity as compared to the general population of Poland and Wielkopolska (40% vs 12.5%, $p<0.005$); the results were similar for the whole cohort, and for each gender separately.
CONCLUSIONS: This clinical research study demonstrates a strong association between obesity and incidentally discovered non-functioning adrenal tumours.

INTRODUCTION

Obesity and cancer both represent a severe health problem of a worldwide range, and importantly, they both co-exist because obese individuals are at a higher risk of cancer. In addition, a steady increase in the prevalence of overweight and obesity has been noted: the prevalence of obesity in Europe in 1995 was estimated to be 10–20% for men and 15–25% for women, whereas more recent studies show an increase in those values being approximately 22% for children, 26% for men and 31% for women (Willborn *et al.* 2005). In the US, obesity has reached epidemic proportions: 35% of adult Americans are overweight (BMI ≥ 25 kg/m^2), 30% obese (BMI ≥ 30 kg/m^2), and 4.7% extremely obese (BMI>40 kg/m^2) (Rubenstein 2005). Obesity influences tumour development,

Abbreviations:
BMI - body mass index
CT - computed tomography
DHEA-S - dehydroepiandrosterone sulphate
MRI - magnetic resonance imaging
rr - reference range
VMA - vanillylmandelic acid
yrs - years

which has been proven for colorectal, breast, endometrial, renal, oesophageal, pancreas, liver and gallbladder cancers, and for leukaemia, multiple myeloma and non-Hodgkin's lymphoma (Lane 2008; Pischon *et al.* 2008; Renehan *et al.* 2008; Rubenstein, 2005). Another group of tumours that may be linked to obesity are hormone-producing adrenal masses. For example, patients with cortisol secreting adrenal tumours are commonly obese. However, associations between obesity and non-functioning adrenal tumours, or non-functioning incidentalomas, are less clear.

Adrenal incidentalomas are adrenal masses discovered unexpectedly in a patient undergoing non-adrenal related investigation (Bhargav *et al.* 2008). The incidence of incidentalomas in computed tomography (CT) scans ranges from 0.43% to 10% and is increasing due to the progress in sensitivity and availability of radiologic imaging techniques, such as ultrasonography, CT or magnetic resonance imaging (MRI) (Babinska *et al.* 2006; Bertherat *et al.* 2002; Bovio *et al.* 2006; Graham and McHenry 1998; Thompson and Young 2003). Tumours are mostly found in patients aged from 40 to 70, with a slightly higher prevalence among women than men. The vast majority of adrenal masses are benign, although adrenocortical carcinoma or metastases can also occur (Mysliwiec *et al.* 2007). Those lesions can be either non-secreting or hormone-producing. The first group includes adenomas, cysts, myelolipomas, adrenocortical carcinomas, metastases and infectious infiltrations. Secreting tumours are less common and may produce a variety of hormones: glucocorticoids, androgens, aldosterone, or catecholamines (Angeli *et al.* 1997; Arnaldi *et al.* 2000; Bhargav *et al.* 2008; Kebebew *et al.* 2006; Mysliwiec *et al.* 2007; Tsvetov *et al.* 2007; Tutuncu and Gedik 1999).

Since obesity increases the risk of development of numerous tumours cited above, hypothetically it may also increase the prevalence of non-functioning adrenal incidentalomas. Consequently, patients with non-functioning adrenal lesions might have a higher prevalence of obesity. Therefore, the aim of this study was to investigate the prevalence of obesity in a large number of patients with non-functioning adrenal lesions.

MATERIALS AND METHODS:

This retrospective investigation was performed at the Department of Endocrinology of Poznan University of Medical Sciences in the years 2000–2007. After initial selection, out of 207 files examined, the cases of 143 patients with non-functioning adrenal incidentalomas were analysed in this research.

In all patients, and prior to endocrine evaluation, adrenal lesions were found incidentally during ultrasound examination of the abdomen. The indications for this procedure included cholelithiasis, gastrointestinal upset or routine screening by general family practitioners. Subsequently, patients with diagnosed incidentalomas were admitted to our Department for further clinical evaluation which included interview, physical examination, blood and urine laboratory tests and computed tomography and/or magnetic resonance imaging of the adrenal glands. In order to differentiate secreting from non-secreting lesions, the following laboratory tests were performed: serum cortisol levels at 8.00 am (reference range: 220–660 nmol/L), 6.00 pm (rr. 50% of the morning value) and in the overnight 1 mg dexamethasone suppression test (cut-off value: 100 nmo/L), and serum dehydroepiandrosterone sulphate [(DHEA-S), rr men: 100–300 μg/dL, women: 70–300 μg/dL], sodi um and potassium levels. In addition, concentrations of sodium (rr: 40–220 mmol/24h), potassium (rr 25–125 mmol/24h), vanillylmandelic acid (VMA), metanephrine and normetanephrine were determined in 24-hour urine collection. The reference ranges for urine VMA, metanephrine and normetanephrine were less than: 8 mg/24 h, 350 μg/24h, and 600 μg/24h, respectively. All the medications that might have possibly influenced results were withdrawn in advance. The imaging techniques revealed the size and character of lesions; benign lesions characteristics included size of 4.5 cm or less, unenhanced CT attenuation lower than 10 Hounsfield units and CT contrast-medium washout higher than 50% in 10 min. Only benign non-secreting tumours were included into the study. Secreting adrenal tumours have been excluded from the study due to the possibility of obesity resulting from the hormonal activity of those lesions.

Body mass index (BMI) was calculated by dividing body mass in kg by height squared in meters. According to WHO, BMI lower than 18.5 kg/m^2 corresponded to underweight, 18.5–24.9 kg/m^2 to normal body weight, 25.0–29.9 kg/m^2 to overweight and values of 30 kg/m^2 or more to obesity. The percentage of patients representing each BMI group was calculated to show the distribution of BMI. Then, a one-proportion z-test was used to compare the prevalence of obesity in the group examined to that of the general Polish population. Since the average age of the subjects was 60.6 yrs, data on the 12.5% prevalence of obesity at the age of 60 yrs. in the population of Western Poland Wielkopolska Region were taken into consideration (the data obtained from Central Statistical Office of Poland, investigation done in 2004). As cited above, the incidence of incidentalomas in CT scans ranges from 0.43% to 10%, and it is about 6–8% in the sixth and seventh decades of life (Babinska *et al.* 2006; Bertherat *et al.* 2002; Bovio *et al.* 2006; Graham and McHenry 1998; Thompson and

Young 2003). For the purpose of statistical analysis, a 7% prevalence of adrenal incidentaloma in the general Polish population at their seventh decade of life was assumed. This assumption was based on the values reported by numerous authors, and under the circumstances of a lack of precise statistical data for Poland and for the majority of other European countries.

In order to investigate the influence of gender on the results, calculations were done for the whole sample of patients, and for each sex separately.

RESULTS

After an initial search of 207 cases, only 143 patients were included into the study: 43 men and 100 women. The excluded patients had a history of subclinically functioning tumours, or of taking medications that influenced laboratory results. The mean age of the patients in the sample was 60.57 ± 11.62 yrs, ranging from 19 to 85. Men were 27–85 yrs old (mean 58.81 ± 11.14), women were aged between 19 and 80 (mean 61.32 ± 11.80).

The sizes of tumours at the moment of their discovery varied from 7 to 47 mm, with the mean size of 24.26 ± 9.02 mm. In men, the average tumour size was 24.91 ± 9.28 mm, with a minimal value of 10 mm and maximal of 42 mm; in women, respectively: 23.98 ± 8.96 mm, 7 mm, and 47 mm.

Neither interview, nor physical examination showed features of any hormonal hypersecretion in any of those patients. Namely, no buffalo hump, trunkal obesity, cutaneous striae, or bruises and skin lesions indicative of hypercortisolemia were found, no paroxysmal hypertension with tachycardia and tremor indicative of phaeochromocytoma were demonstrated, and no signs or symptoms of hyperandrogenism in women were disclosed. These clinical findings were subsequently confirmed with laboratory tests, and the final decision whether or not to include a patient into the study was based upon the results of these tests. Since this was not a cross-sectional study, it was impossible to have a control group. Nevertheless, to rule out or to confirm subclinical adrenal hypersecretion we used the cut-off values established by endocrine care professionals and presented in generally accepted English-language professional handbooks (Aron *et al.* 2007; Don and Lo 2007; Fitzgerald 2007). They were in agreement with the reference range and cut-off values presented in the Material and Methods Section of this article.

In the whole cohort, the mean serum cortisol at 8.00 am was 496 ± 174 nmol/L, at 6.00 pm 197 ± 102 nmol/L and after suppression with 1 mg dexamethasone 49 ± 24 nmol/L. Those results were respectively for men: 456 ± 141 nmol/L, 199 ± 83 nmol/L and 49 ± 22 nmol/L, for women: 508 ± 180 nmol/L, 194 ± 107 nmol/L, and 49 ± 24 nmol/L. In the whole cohort, the mean DHEA-S serum concentration was 77.2 ± 63.4 μg/dL, in men 109.7 ± 71.2 μg/dL and in women 26.3 ± 54.5 μg/dL. The mean serum sodium and potassium levels were 139 ± 11 mmol/L and 4.38 ± 0.40 mmol/L in the whole group, whereas in men 140 ± 2 mmol/L and 4.49 ± 0.33 mmol/L, and in women 139 ± 13 mmol/L and 4.33 ± 0.41 mmol/L, respectively. In the whole group, results of the 24-hour urine collection were as follows: sodium of 138 ± 65 mmol/24h, potassium of 45.5 ± 18.9 mmol/24h, VMA <8 mg/24h, metanephrine of 95.2 ± 35.7 μg/24h and normetanephrine of 361 ± 121 μg/24h. In men: sodium 185 ± 68 mmol/24h, potassium 51.0 ± 16.0 mmol/24h, VMA <8 mg/24h, metanephrine 100.0 ± 34.8 μg/24h, normetanephrine 365 ± 94 μg/24h. In women: sodium 117 ± 52 mmol/24h, potassium 42.8 ± 19.7 mmol/24h, VMA <8 mg/24h, metanephrine 92.0 ± 37.6 μg/24h and normetanephrine 359 ± 139 μg/24h.

BMI (kg/m^2) ranged from 16.51 to 45.25, with the mean of 28.77 ± 4.71. Consequently, in the whole group: two patients (1.40%) were underweight, 28 (19.58%) of normal body weight, 56 (39.16%) overweight and 57 (39.86%) were obese (distribution of BMI see Figure 1). Out of the male subjects, one patient (2.33%) was underweight, 6 (13.95%) were of normal body weight, 21 (48.84%) were overweight and 15 (34.88%) obese,

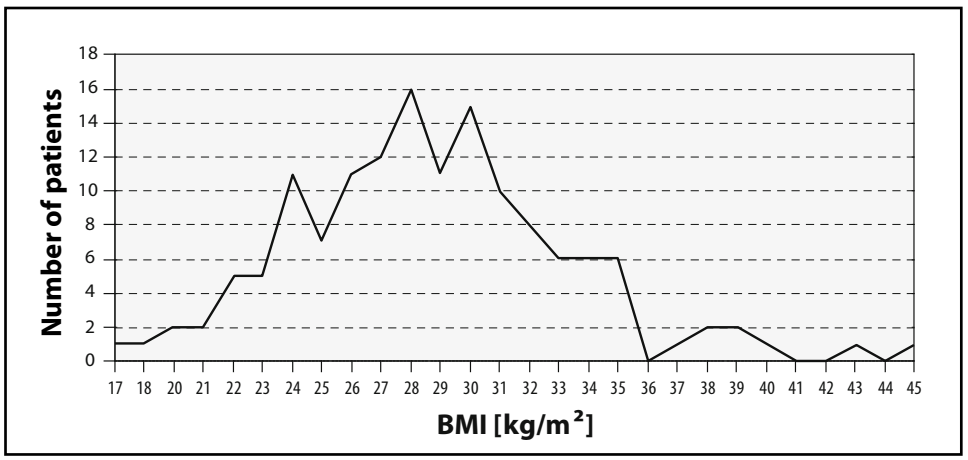

Fig.1. Distribution of BMI in the subjects examined.

Tab. 1. Results of the one-proportion z-test comparing all subjects examined to the data for the population of Poland and Wielkopolska Region.

	Poland	Patients with incidentaloma	Wielkopolska	Patients with incidentaloma
Size of the population	38 157 000	143	3 372 400	143
Percentage of obesity	12.55%	39.86%	13.01%	39.86%
Percentage of normal body weight	59.12%	19.58%	56.87%	19.58%
Statistical significance	**0.00000**		**0.00000**	

Tab. 2. Results of the one-proportion z-test comparing men examined to the data for male population of Poland and Wielkopolska Region.

	Men in Poland	Men in the group of patients with incidentaloma	Men in Wielkopolska	Men in the group of patients with incidentaloma
Size of the population	18 454 000	43	1 635 610	43
Percentage of obesity	12.60%	34.88%	12.80%	34.88%
Percentage of normal body weight	61.70%	13.95%	59.50%	13.95%
Statistical significance	**0.00366**		**0.00400**	

Tab. 3. Results of the one-proportion z-test comparing women examined to the data for female population of Poland and Wielkopolska Region.

	Women in Poland	Women in the group of patients with incidentaloma	Women in Wielkopolska	Women in the group of patients with incidentaloma
Size of the population	19 703 000	100	1 736 790	100
Percentage of obesity	13.00%	42.00%	13.00%	42.00%
Percentage of normal body weight	57.00%	22.00%	54.00%	22.00%
Statistical significance	**0.00000**		**0.00000**	

whereas those distribution values for women were, respectively: 1 (1.00%), 22 (22.00%), 35 (35.00%) and 42 (42.00%). The results of a one-proportion z-test used to investigate whether any associations between the prevalence of obesity and adrenal incidentalomas exist are shown in Table 1 for the whole cohort, and in Tables 2 and 3 for men and women, respectively.

DISCUSSION

To the best of our knowledge, this is the first study investigating associations between obesity and the existence of adrenal incidentalomas. In this large-sample analysis we demonstrate a high prevalence of obesity in patients with incidentally discovered, non-functioning adrenal masses. Here we show for the first time that this prevalence is higher in the group examined than in the similarly aged general population.

To date, very scanty information on the associations between non-functioning adrenal tumours and obesity exist. For example, in a study of 33 patients with adrenal masses carried out at the Medical University of Silesia (Poland), a higher incidence of overweight and obesity has been noticed only among female patients with adrenal lesions (Legierska *et al.* 2006). However, no strong statistical association was shown, possibly due to a low number of patients examined. Moreover, contradictory data on the possible associations between subclinical hormonal function of those tumours and their influence on obesity exist: Mantero *et al.* demonstrated that obesity is less common in patients with non-functioning adrenal incidentalomas than in individuals with subclinical Cushing syndrome (Mantero *et al.* 2000), whereas Rossi *et al.* demonstrated similar values of BMI in subclinical Cushing syndrome patients and in patients with non-functioning incidentalomas (Rossi *et al.* 2000). In line with the latter, an increased prevalence of metabolic syndrome in patients with non functioning adrenal masses has been recently reported in a small group of 35 patients (Erbil *et al.* 2009). Results of neither of those studies, however, demonstrated any significant difference between the prevalence of obesity in the overall population and in incidentaloma subjects that we show here in a large cohort. Based on our find-

ings and on the papers cited above, one could put forward a tempting hypothesis that BMI is not influenced by hormonal activity of clinically silent adrenal lesions but obesity *per se* might stimulate the growth of adrenal tumours. This hypothesis stands in contrast to the concept of the majority of authors that obesity in patients suffering from adrenal incidentalomas is explained by the existence of subclinical Cushing syndrome. Indeed, in our study a thorough verification of hormonal activity was carried out to eliminate that possibility. Despite the non-existence of hormonal activity, a 40% prevalence of obesity was observed in the patients examined. This value was much higher than the 12.5% prevalence of obesity in the general Polish population.

In contrast to numerous papers on cancerogenesis in obesity that have already been published, the influence of obesity on adrenal tumours has not been widely investigated yet, although some earlier reports suggested that hyperinsulinemia stimulated adrenocortical tumor formation (Reincke *et al.* 1996). Here we demonstrate a clear relationship between obesity and adrenal tumours, and we suggest that this relationship may be based on unknown mechanisms similar to those involved in other cases of cancerogenesis in obese patients. A higher incidence of these lesions and a stronger correlation between obesity and incidentaloma observed in women are in favour of this hypothesis, presumably because of the permissive oestrogen influence on other hormone action. Obviously, further research investigating these mechanisms will be needed.

Our results may have some impact on practical endocrine care. In the face of an increased prevalence of obesity in patients with adrenal lesions, we advocate a modified approach to the obese patient. In our opinion, as the obese population seems to be a group with a higher risk of adrenal tumours, many of these patients should have their adrenal glands visualized; in this way the diagnosis of adrenal tumours would be earlier and surgical removal of suspicious lesions would be easier, thus improving the overall prognosis.

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