OBES SURG (2011) 21:54–60
DOI 10.1007/s11695-010-0297-6

CLINICAL RESEARCH

Prevalence of Endocrine Diseases in Morbidly Obese Patients Scheduled for Bariatric Surgery: Beyond Diabetes

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Published online: 15 October 2010
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Abstract
Background Bariatric surgery allows stable body weight reduction in morbidly obese patients. In presurgical evaluation, obesity-related co-morbidities must be considered, and a multidisciplinary approach is recommended. Precise guidelines concerning the endocrinological evaluation to be performed before surgery are not available. The aim of this study was to evaluate the prevalence of common endocrine diseases in a series of obese patients scheduled for bariatric surgery.
Methods We examined 783 consecutive obese subjects (174 males and 609 females) aged 18–65 years, who turned to the obesity centre of our department from January 2004 to December 2007 for evaluation before bariatric surgery. Thyroid, parathyroid, adrenal and pituitary function was evaluated by measurement of serum hormones. Specific imaging or supplementary diagnostic tests were performed when indicated.
Results The overall prevalence of endocrine diseases, not including type 2 diabetes mellitus, was 47.4%. The prevalence of primary hypothyroidism was 18.1%; pituitary disease was observed in 1.9%, Cushing syndrome in 0.8%, while other diseases were found in less than 1% of subjects. Remarkably, the prevalence of newly diagnosed endocrine disorders was 16.3%.
Conclusions A careful endocrinological evaluation of obese subjects scheduled for bariatric surgery may reveal undiagnosed dysfunctions that require specific therapy and/or contraindicate the surgical treatment in a substantial proportion of patients. These results may help to define the extent of the endocrinological screening to be performed in obese patients undergoing bariatric surgery.

Keywords Bariatric surgery · Obese patients · Endocrinological evaluation

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Introduction

Conservative treatments, such as low-calorie diets, behavioural modifications and physical exercise, are the mainstay of therapy for obesity, the pharmacological treatment being considered as further approach. Unfortunately, the results of these measures are often disappointing, with many patients either losing an inadequate amount of weight or, more frequently, experiencing total weight regain within a short period. Because of the failures of these conservative methods, several surgical procedures have been developed which have proven to be effective in achieving a stable weight loss, reducing the mortality rate and ameliorating co-morbidity [1–6]. As convened by international conference on the guidelines for gastrointestinal surgery in severe obesity, the selection of the patients requires a multidisciplinary approach that includes medical, surgical, nutritional and psychological assessment [7–9]. Currently, obesity surgery is considered appropriate for adult patients with either a body mass index (BMI) of 40 kg/m^2 or more, or a BMI between 35 and 40 kg/m^2 with obesity-related co-morbidity. In the preoperative evaluation, obesity-related co-morbidities must be carefully considered before referral for bariatric surgery. These disorders not only serve to make

the patient a stronger candidate for surgery, but specific therapies must also be evaluated and optimized to reduce perioperative morbidity and mortality. Contraindications to bariatric surgery should be considered. In particular, endocrinological disorders that may cause obesity should be identified since patients may experience substantial weight loss with specific treatment of their disease, and in any case, they should not undergo bariatric surgery until the disease is properly managed [10–12]. However, precise guidelines concerning the endocrinological evaluation of patients scheduled for bariatric surgery are currently not available.

The aim of this study was to evaluate the prevalence of common endocrine diseases in a series of obese patients scheduled for bariatric surgery, to reveal undiagnosed dysfunctions that may require specific therapy and/or contraindicate the surgical treatment.

Materials and Methods

Patients

We examined 783 consecutive obese subjects (174 males and 609 females) aged 18–65 years (mean age±SD, 44±12 years) who turned to the obesity centre of our department from January 2004 to December 2007 for evaluation before bariatric surgery. Clinical, haematological and instrumental examinations of each patient were performed following international guidelines for the treatment of obesity [8, 9, 13], and each patient was treated according to appropriate protocols for his/her condition. The main phenotype characteristics of the study group are shown in Table 1.

Methods

BMI was calculated as the weight in kilogrammes divided by the square of the height in metres. Standing height without shoes was measured (to the nearest 1 cm) with the use of a stadiometer. Body weight in light clothing was measured (to the nearest 0.1 kg) with the use of a digital electronic scale. Waist circumference (to the nearest 1 cm) was measured, in the standing position, midway between the iliac crest and the lower costal margin. Hip circumference (to the nearest 1 cm) was measured, in the standing position, at the maximum circumference over the buttocks.

Table 1 Main phenotype characteristics of 174 males and 609 females scheduled for bariatric surgery

	Males	Females
Age (years)	43±11	44±12
BMI (kg/m^2)	46.8±8.5	45.2±7.7
Weight (kg)	141.7±25.1	116.7±21.6
Height (m)	1.74±0.08	1.61±0.07
WC (cm)	137.5±14.9	123.1±15.6
HC (cm)	130.8±15.7	130.5±14.5

Values are reported as mean±SD

WC waist circumference, *HC* hip circumference

In all subjects, blood samples were drawn after an overnight fasting for measurement of various serum hormones and serum glucose. Standard diagnostic criteria were used to classify people without diagnosed diabetes, with administration of 75 g oral glucose tolerance test when needed [14]. FT4 and FT3 were measured by an automated analyser with a chemiluminescent method (Vitros, Ortho-Clinical Diagnostics, Johnson and Johnson, Amersham, UK); the normal range was 7.0–17.0 pg/ml for FT4 and 2.7–5.7 pg/ml for FT3. Thyroid Stimulating Hormone (TSH) was measured by a solid phase, two-site chemiluminescent immunometric assay (third-generation TSH Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, USA); the normal range was 0.4–3.4 μU/ml.

Antithyroglobulin and antithyroperoxidase autoantibodies (TPOAb) were determined by automated analyser enzyme immunoassay system (AIA-1800, Tosoh Corporation, Tokyo, Japan). Values greater than 30 and 10 U/ml, respectively, were considered positive. Calcitonin was measured by an immunoradiometric assay (IRMA-hCT, CIS Bio International, Gif-Sur Yvette Cedex, France). A value greater than 10 pg/ml was considered positive. Intact Parathyroid Hormone (PTH) was measured by a chemiluminescent immunoassay (Liason, DiaSorin, Stillwater, MN, USA) and ionized calcium by calcium ion selective electrode method (Nova Biomedical, Maltham, MS, USA); normal values in our laboratory were as follows: PTH 10–65 pg/ml, ionized calcium 1.13–1.30 mmol/L, respectively. 25OH vitamin D (25-OHD) was measured by a radioimmunoassay (DiaSorin, Stillwater, MN, USA); values greater than 30 ng/ml were considered sufficient [15]. Cortisol was measured by a solid-phase competitive chemiluminescent enzyme immunoassay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, USA). The normal range for basal cortisol at 8:00 AM was 85–260 ng/ml. Adrenocorticotropic Hormone (ACTH) was measured by an immunoradiometric assay (ELISA-ACTH, CISbio International, Gif-Sur Yvette Cedex, France); the normal range was 9–52 pg/ml. Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), estradiol, progesterone, testosterone and prolactin (PRL) were measured by automated immunoassay analysers (Unicell, Beckman Coulter, Fullerton, CA). Macroprolactin was excluded by measuring serum PRL after polyethilenglycole precipitation [16]. Serum GH and IGF 1 were determined by advantage chemiluminescent commercial kits (Nichols Institute Diagnostics, San Juan, Capistrano, CA, USA).

Thyroid ultrasound examination was performed in all patients using a real-time instrument (Technos, Esaote

Biomedica, Genova, Italy), with a 7.5-MHz linear transducer. The thyroid volume was calculated according to the formula of the ellipsoid model: width × length × thickness × 0.52 [17]. Upper normal limit for thyroid volume was 18 ml in males and 13 ml in females [18]. Fine-needle aspiration of nodular lesions greater than 1 cm was also performed for cytological examination. Thyroid diseases were diagnosed according to guidelines for diagnosis of thyroid diseases [19].

Hypercortisolism was diagnosed by administering 1 mg dexamethasone orally at 11:00 PM and by measuring serum cortisol the following morning between 8:00 and 9:00 AM. Suppression of serum cortisol to 30 ng/ml was chosen as the cut-off point for normal suppression in obese subjects [20]. In patients with serum cortisol levels>30 ng/ml, hypercortisolism was suspected. False-positive results were detected by a normal suppression of cortisol on a standard Liddle 48 h 2 mg/day low dexamethasone suppression test. When hypercortisolism was confirmed, further evaluations were performed to differentiate between ACTH-dependent and independent forms including an overnight 8 mg dexamethasone test, CT or magnetic resonance imaging (MRI) when indicated. Abdominal ultrasound evaluation was performed in all patients. Measurement of serum catecholamines, aldosterone and renin was performed in cases of incidentally discovered adrenal masses. The diagnosis of primary hyperparathyroidism was based on the finding of increased ionized calcium and serum PTH concentrations in the absence of 25-OHD deficiency; specific imaging was performed to locate parathyroid adenomas. Low serum 25-OHD, IGF-I and testosterone (in men) are common findings in morbidly obese subjects, secondary to obesity and reversible after weight loss. We did not include them among endocrine diseases or perform specific diagnostic procedures for these disorders.

Results

One hundred and ninety-four subjects had type 2 diabetes mellitus (24.8%). Among them, 52 were firstly diagnosed at the time of evaluation, and adequate treatment was started and optimized before surgery.

The overall prevalence of other endocrine diseases was 47.4% (371/783 patients). Among them, 16 patients had two or more coexisting endocrine diseases.

Thyroid disease was by far the most frequent. Among 206 patients with nodular disease, 75 patients were firstly diagnosed during our evaluation. Fine-needle aspiration showed a suspicious of malignancy in four patients with thyroid nodules, who underwent thyroidectomy; the pathological examination revealed a papillary thyroid cancer in all of them. One medullary thyroid cancer was found on histology in one subject with a thyroid nodule associated with elevated serum calcitonin.

One hundred and thirty-four subjects had autoimmune thyroiditis; thirty-eight were euthyroid; 96 subjects were hypothyroid. Nine hypothyroid subjects were firstly diagnosed at the time of evaluation with serum TSH values ranging from 3.84 to 14.8 μU/ml, and levothyroxine (LT4) replacement therapy was started. Thirty-five subjects had acquired hypothyroidism after thyroidectomy for nodular goitre, Graves' disease or thyroid carcinoma. Nine subjects were hypothyroid after radioiodine treatment for Graves' diseases or toxic adenoma. One subject was under LT4 treatment for amiodarone-induced hypothyroidism; a second one was diagnosed at the time of our evaluation, and LT4 was then administered. The overall prevalence of acquired hypothyroidism was 142/783 (18.1%). Among patients already under LT4 therapy, the daily dose had to be increased in 33 subjects and decreased in 22 to restore euthyroidism before surgery. Graves' disease was newly diagnosed in two subjects, and specific therapy was then administered.

Cushing's syndrome was diagnosed in six patients. Further evaluation allowed us to diagnose five patients with ACTH-dependent hypercortisolism due to pituitary adenomas and one with ACTH-independent hypercortisolism due to adrenal adenoma. In all cases, bariatric surgery was not performed, and patients were treated appropriately as to their disease. Interestingly enough, none of these patients had clinical features evocative of Cushing's syndrome (Fig. 1). One additional patient had been previously operated on for an ACTH-secreting pituitary adenoma and had a normal pituitary function at the time of evaluation. One patient had previously undergone monolateral surrenectomy for a cortisol-secreting adenoma. No additional functioning adrenal nodules were detected in our cohort of obese subjects. One case of primary aldosteronism due to bilateral idiopathic adrenal hyperplasia with low serum potassium and hypertension was diagnosed, and appropriate treatment was then started.

In four subjects, asymptomatic hypercalcaemia with increased serum PTH concentrations and normal serum 25OH-D was found. Further evaluation by conventional means allowed us to diagnose primary hyperparathyroidism. Three of these patients were then submitted to parathyroid surgery according to the guidelines fixed by the NIH consensus development conference statement on primary hyperparathyroidism [21], and a parathyroid adenoma was histologically confirmed. The fourth one did not meet the criteria for surgery and was placed on follow-up. Three subjects had acquired hypoparathyroidism post-thyroidectomy and were receiving calcium and calcitriol replacement therapy; in all of them, the dose regimen had to be optimized before surgery.

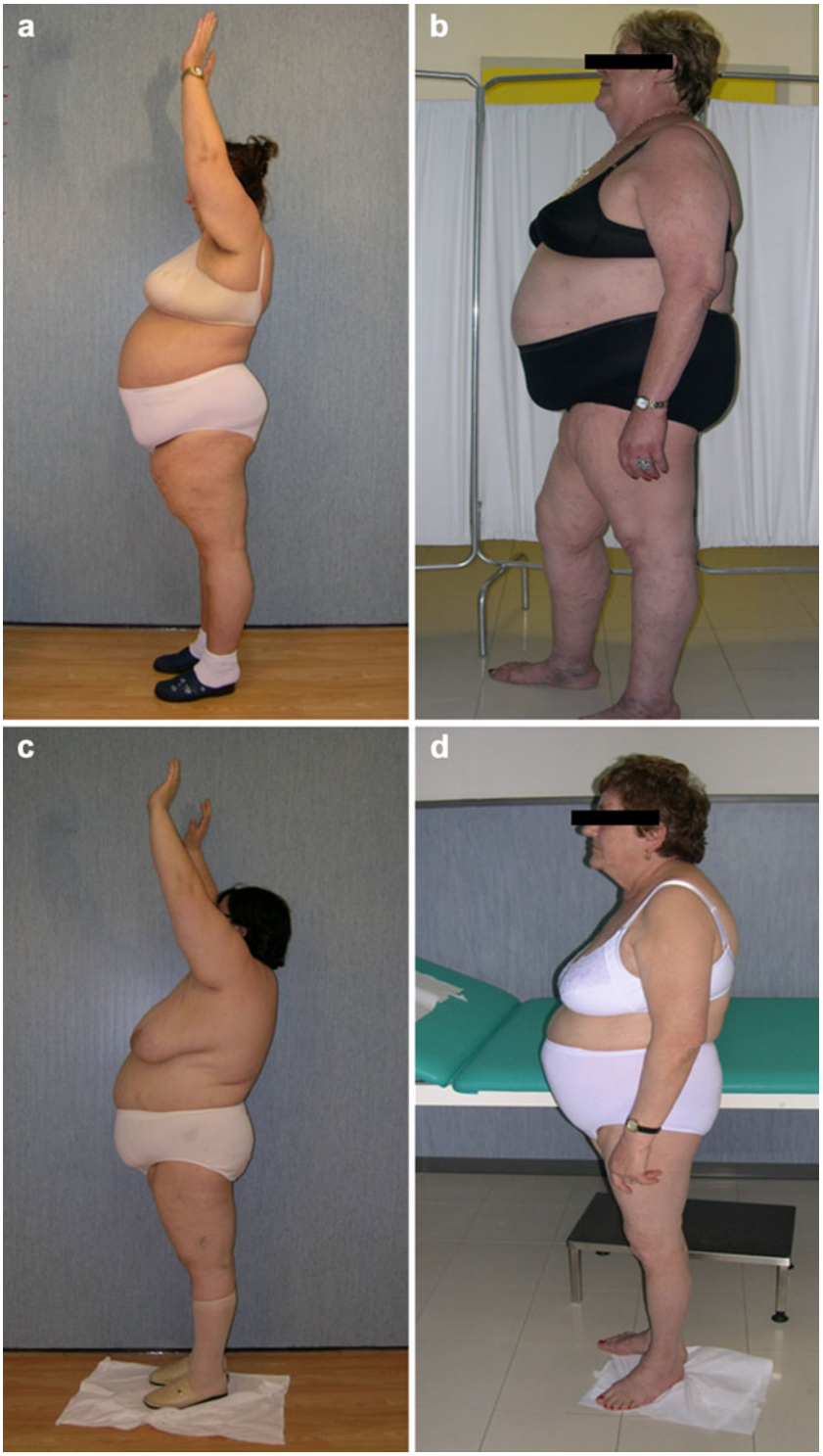

Fig. 1 The obese phenotype of two representative patients with Cushing's syndrome (**a**) and (**b**) as compared with two patients with central obesity and normal adrenal function (**c**) and (**d**). The four patients belonged to the study group

The basal assessment of pituitary function revealed low serum concentrations of FSH and LH in two postmenopausal women and asymptomatic hyperprolactinemia in one premenopausal woman; an MRI of the pituitary region showed an empty sella in all three subjects. No additional hormonal abnormalities were discovered, and no specific treatment was required in these three women. One man was found with hyperprolactinemia; the MRI revealed a pituitary macroadenoma that required surgical excision. The histological examination and immunohistochemical

staining showed a non-functioning pituitary adenoma. Four subjects had previously diagnosed asymptomatic empty sella with normal pituitary function, and one had a previously diagnosed prolactinoma under dopaminergic treatment.

Overall, beyond diabetes, in our cohort of obese subjects who were candidates for bariatric surgery, the prevalence of newly diagnosed endocrine disorders was 128/783 (16.3%; Table 2); among these, 30 patients needed a specific therapy.

Discussion

The number of surgical procedures for the treatment of obesity has been steadily increasing worldwide during the past decades. Several factors contribute to this trend including the increase in the prevalence of extreme class III obesity, the limited effectiveness of medical therapies and a growing body of literature supporting the positive effects of durable and substantial weight loss after bariatric surgery on weight-related co-morbidities and, in general, on the relative risk of death [1–6]. To increase the success rate and in order to diminish the complication rate of surgery, a multidisciplinary approach is recommended. The medical evaluation includes assessment for the conditions that commonly accompany severe obesity such as diabetes, hypertension, hyperlipidemia, coronary artery disease, sleep apnoea, pulmonary hypertension and musculoskeletal disease [7, 22–24]. Careful selective investigation of these conditions in subjects with high surgical risk serves several purposes. It facilitates optimal medical management before surgery, identifies problems that may influence the perioperative and postoperative course and provides a baseline set of clinical data for evaluating the benefit of surgery. In addition, the multidisciplinary approach should include a supervised training to improve the motivation to life style change and increase patients' strength.

Table 2 Prevalence of newly diagnosed endocrine diseases in 783 obese subjects scheduled for bariatric surgery

	Number of patients
Nodular goitre	70
Thyroid carcinoma	5
Autoimmune thyroiditis (hypothyroid)	35 (9)
Amiodarone induced hypothyroidism	1
Graves' disease	2
Cushing's syndrome	6
Primary hyperparathyroidism	4
Pituitary adenoma	1
Empty sella	3
Primary aldosteronism	1
Total	128

With regard to endocrine diseases, it could be argued that the clinical examination of the patient should be sufficient to guide the diagnostic process. However, the complications that are frequently associated with obesity could mask a concomitant endocrine dysfunction. Additionally, there are several common endocrine disorders that, if not properly identified and treated, may represent a limit for the success rate of the bariatric surgery or may increase the perioperative risk.

The prevalence of type 2 diabetes mellitus in our cohort was 24.8%, similar to that reported in a comparable population of obese subjects [4]. It should be underlined that the development of type 2 diabetes and its severity depends on many variables, and duration of obesity before effective treatment has a major impact. Among other endocrinopathies, the prevalence of newly diagnosed diseases was 16.3% while the overall prevalence of endocrine diseases was 47.4%. Like in the general population, thyroid diseases were the most frequent endocrine disorders. The prevalences of nodular disease (26.3%) and autoimmune thyroiditis (17.1%) were higher than that reported in an iodine deficiency Italian community (17% and 3.5%, respectively) [18]. This apparent discrepancy is due to the high proportion, among our obese subjects, of adult females (77.8%) who represent the subgroup of population with the greatest prevalence of thyroid disease. The prevalence of hypothyroidism for any causes was 18.4%, similar to the prevalence reported in previous studies on obese subjects scheduled for bariatric surgery [25–28]. It should be highlighted that, in ten patients, hypothyroidism was undiagnosed at the initial observation, and they had to start an adequate replacement therapy before surgery.

The five newly diagnosed thyroid cancer patients (four with papillary and one with medullary cancers) are also remarkable because their diagnosis changed the clinical approach and delayed the bariatric surgery that was performed when the remission of neoplasia was documented. Yet, the sample size of our cohort is too small to ascertain whether obesity represents a risk factor for thyroid cancer.

In our study group, we found a prevalence of Cushing's diseases of 0.8%, greater than that reported in the general population [29]. Previous studies [20, 30–32] showed a prevalence of Cushing's diseases in diabetic and non-diabetic obese subjects ranging from 1 to 5.7%. Recently, among 369 overweight or obese subjects, none was found to have Cushing's syndrome [33]. Overall, these results indicate that, among obese subjects, patients with Cushing's disease correspond to a small proportion, and monitoring for worsening symptoms over time may be more useful

than routine screening. However, in view of bariatric surgery, also considering the possible lack of distinguishable features of hypercortisolism in severely obese subjects, we believe that a simple overnight 1 mg dexamethasone test may be performed to avoid an improper treatment of patients with Cushing's syndrome. With regard to primary hyperparathyroidism, we found a prevalence of 0.5%, similar to that reported in the general population [34, 35]. The prevalence of pituitary dysfunction was also low.

It should be emphasized that the results of this study, whilst representative of a population of severely obese subjects who were candidates for bariatric surgery, cannot be extended to the entire obese population. Indeed, the prevalence of various disorders may be overestimated since it was derived from a selected group of subjects who sought treatment for their condition, and their perceived well-being could have been affected by an underlying disease associated with obesity. In addition, it will be interesting to reconsider the course of the various endocrine diseases after effective weight loss due to bariatric surgery.

The endocrinological evaluation performed in these subjects was far more extensive that would ever be justified for such patients outside of the study aim. We believe that the results of the study do not warrant sweeping recommendations to screen all bariatric patients for all potential endocrine disorders, also considering the costs and resource use that this recommendation would carry. Yet, the prevalence of unrecognized hypothyroidism, hyperthyroidism and Cushing's syndrome in our study group was noteworthy, and, in our view, it is sufficiently high to suggest pre-operative screening of these conditions.

In conclusion, a careful endocrinological evaluation of obese subjects scheduled for bariatric surgery may reveal undiagnosed dysfunctions that require specific therapy and/or contraindicate the surgical treatment in a substantial proportion of patients. Furthermore, in patients with already diagnosed endocrine disorders, it allows adjustment of the hormonal therapy to improve the perioperative course. Our data may be helpful to define the extent of the endocrinological screening to be performed in the preoperative management of obese patients undergoing bariatric surgery. We suggest that routine screening for thyroid dysfunction and hypercortisolism should be performed to facilitate success of the treatment, decrease the perioperative risk and exclude conditions that contraindicate the surgical procedure.

Funding This work was supported by Ministero dell'Università e della Ricerca, Programmi di Ricerca Scientifica 2007 "Pathogenic mechanisms determining the obese phenotype and influencing the response to treatment", Ministero dellla Salute, Programmi di Ricerca Finalizzata 2006 "Integrate protocols for the prevention and the treatment of obesity".

Conflict of interest PF, AP, SM, GS, GS, MG, AP, GG, IR, TR, CD, MA, PV and FS declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of research reported.

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