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TITLE OF CASE <i>Do not include "a case report"</i>
Obesity related hypogonadism: A reversible condition
SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
<p>Obesity is associated with hypogonadism. Whilst this association is widely accepted, the underlying mechanisms remain unclear. Furthermore, obesity is a risk factor for hypogonadism and conversely hypogonadism may be a risk factor for obesity. We present the case of a 30-year-old morbidly obese man with hypogonadotrophic hypogonadism that underwent a Roux-en-Y gastric bypass operation. Following the surgical treatment of his obesity the testosterone level returned to normal with improvements in hypogonadal symptoms, which allowed discontinuation of exogenous testosterone therapy. This case report demonstrates reversal of hypogonadism following weight loss with restoration of gonadal function.</p>
BACKGROUND <i>Why you think this case is important – why did you write it up?</i>
<p>Obesity is highly prevalent with recent figures suggesting that 25-27% of the UK population aged 16 years or over are overweight or obese.[1,2] By 2050 obesity is predicted to be prevalent in as much as 60% of adult men, 50% of adult women and 25% of children (Foresight 2007).[3] It is well recognised that obesity is associated with an increased risk of heart disease, stroke, type 2 diabetes, obstructive sleep apnoea and certain cancers. However, less well described is the association between hypogonadism leading to sexual dysfunction and poor well being. Of interest, the prevalence of obesity in hypogonadal patients with sexual dysfunction is increasing.[4]</p> <p>The most recent National institute of Clinical Excellence (NICE) guidelines for Obesity management, published in August 2016, recommend that adults with a body mass index (BMI) above 50 kg/m² are offered a referral for a bariatric surgical assessment. The rationale is to improve quality of life, reduce obesity-associated morbidity and to reduce the risk of premature mortality.[5]</p> <p>Bariatric surgery is by far the most effective way in improving the testosterone levels in obese hypogonadal patients as it results in higher weight reduction than other interventions such as low-fat diet and exercise. In fact bariatric surgery can have similar effect on testosterone levels with replacement therapy including testosterone gels and patches.[6]</p>
CASE PRESENTATION <i>Presenting features, medical/social/family history</i>
<p>A 30-year-old man was referred to the Endocrinology clinic with long-standing history of tiredness and a weight gain of 25 kg over a six-year period. He had a BMI of 47 kg/m² with no obvious underlying endocrine cause. There was a maternal history of type 2 diabetes mellitus and hypothyroidism. He had co-existing depression and obstructive sleep apnoea and was not receiving any medication. He volunteered to have poor sexual function. Examination showed a weight of 139 kg, normal cardiovascular and respiratory system findings. He was clinically euthyroid, eupituitary with no signs of Cushing's disease. The confrontation visual test was normal. Thyroid function tests on two separate occasions within the last three years had showed low free thyroxine (FT₄) levels and normal thyroid-stimulating hormone (TSH) levels.</p>

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There was evidence of hypogonadotrophic hypogonadism with a low testosterone level, inappropriately normal Luteinizing hormone (LH) and Follicle Stimulating hormone (FSH) levels. A short synacthen test (SST) was performed which was normal. Because of the excess weight and the patient had claustrophobia an MRI scan of the pituitary gland could not be undertaken so a computed tomography (CT) scan of his pituitary gland was performed that was reported as being unremarkable. He was commenced on testosterone 50 milligrams once daily by transdermal application. Despite this and being treated with continuous positive airway pressure (CPAP) the patient complained of tiredness and lethargy, and gained a further 12 kg over the next 12 months resulting in a weight of 151kg with a BMI of 51 kg/m². He was started on replacement with levothyroxine at a dose of 50 micrograms per day in view of his symptoms and weight gain and discharged from the endocrine clinic. A referral was made to the local Tier 3 bariatric clinic.

When seen in Tier 3 weight assessment and management clinic he was commenced on treatment with orlistat and referred to dietetics services and to Tier 4 services for consideration of bariatric surgery. Sixteen months later he had sleeve gastrectomy resulting in excess weight loss of 58% one year after surgery but at 30 months his BMI was 41.7 kg/m² and weighed 124.8 kg with 36.5% excess weight loss due to poor diet. The patient was adamant that had an insufficient portion of his stomach removed and insisted to go on bypass. Last year, 45 months after his first operation, he had a Roux-en-Y gastric bypass that resulted in an extra 41 kg loss and now weighs 71 kg with a BMI of 24 kg/m². His testosterone level significantly increased after the weight loss and currently is off the testosterone replacement therapy with improvement of his sexual function and quality of life.

INVESTIGATIONS *If relevant*

Full blood count, renal and liver and profiles were normal.
His random cortisol level was 266 nmol/L, prolactin was 248 mU/L
FSH was 3.9U/L, LH was 1.8 U/L, TSH at 4.2 mU/L with an FT4 of 11.9 pmol/L.
His testosterone level prior replacement was 4.6nmol/L.
His SST showed basal cortisol level of 370 nmol/L and 950 nmol/L at thirty minutes.
CT scan of his pituitary gland, as there was an element of claustrophobia, was normal.

DIFFERENTIAL DIAGNOSIS *If relevant*

The main differential diagnosis at the initial consultation with the Endocrinology team was a pituitary lesion causing secondary hypothyroidism or hyperprolactinemia. However CT pituitary scan did not reveal any pituitary tumour and prolactin levels were normal. There were no clinical or biochemical findings suggestive of Cushing's syndrome. The patient was not on opiates and did not abuse alcohol. There was no history of anabolic steroids use or any severe/chronic illness. This established the diagnosis of obesity associated with hypogonadotrophic hypogonadism.

TREATMENT *If relevant*

For the impaired sexual function and the low testosterone levels, the patient was started on testosterone gel. This had no significant effect on his symptoms and was subsequently discontinued following the bariatric surgery. As he had abnormal thyroid function tests with symptoms possibly related to hypothyroidism associated with weight gain, he also had treatment with levothyroxine.

After confirmation with sleep studies he was given continuous positive airway pressure treatment with some good effect.

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He underwent two bariatric surgery procedures the first was a sleeve gastrectomy followed by a Roux-en-Y Gastric Bypass operation. The result was a 53% reduction of his body weight to 71 kg and a BMI of 24 kg/m² with normalization of his testosterone levels to the highest ever level of 15.8 nmol/L, not on replacement therapy (table1).

Table 1 - Biochemical characteristics of patient and changes after bariatric surgery

	Before surgery	1 M after surgery	8 M after surgery
Body mass index (kg/m ²)	51	39	24
Body Weight (kg)	152	112	71
Total testosterone (nmol/L)	4.6	7.5	15.8
LH (IU/L)	1.8	3.6	2.0
FSH (IU/L)	3.9	3.9	6.3

OUTCOME AND FOLLOW-UP

This patient after the bariatric surgical procedure lost a significant amount of excess body weight and his quality of life improved. This led to normalisation of the testosterone levels and improvement of his sexual life. It reduced as well the symptoms related to his OSA. To our knowledge he has not gained back any of the lost weight. He is now on supplements with vitamins and minerals after the operation.

DISCUSSION *Include a very brief review of similar published cases*

Obesity and male hypogonadism are often associated, as evidenced by many cross-sectional studies.[7] Data from prospective studies show that hypogonadal patients are at increased risk of becoming obese. Amongst obese patients the incidence of hypogonadism is high.[4,7] So there is a two-way relationship between the two conditions.[8] The results of a meta-analysis show that obesity treatment is very effective for the associated hypogonadism as well.[9]

It is not entirely clear how obesity causes hypogonadism and several mechanisms have been proposed such as dietary-induced hypothalamic inflammation, along with a decreased gonadotropin-releasing hormone (GnRH) secretion.[10] The proportion of obese patients that seek medical treatment for sexual dysfunction is increasing. Good quality studies suggest that treatment with testosterone results in an increase in lean mass and a decrease in fat mass. So the combined effect on the body weight is negligible.[11] As previously mentioned the mechanism by which obesity causes hypogonadism is under debate and so far several theories are proposed such as the impairment of the hypothalamo-pituitary-gonadal axis and the disruption of the pulsatile manner of GnRH secretion.[12] Other proposed mechanisms include the increased levels of oestrogens, involvement of hormones like ghrelin, possible leptin resistance and increased levels of tumor necrosis factor alpha, that is known to cause apoptosis.[13] Finally impaired expression of several receptors like the glucose transporter-4 and the kisspeptin has been investigated.[14]

In a meta analysis, examining the available data from clinical intervention studies, greater weight loss resulted in a greater rise in testosterone levels. Additionally, there was an

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increase in sex hormone binding globulin (SHBG), calculated free testosterone, LH, FSH and reduction of oestradiol levels.[9] The intervention that had the best results in increasing testosterone levels was bariatric surgery by achieving more weight loss than others like lifestyle changes. More specifically, the mean % body weight loss with bariatric surgery was 32% as opposed to only 9% with diets that aimed to reduce calorie intake. The mean increase in testosterone levels was 9 nmol/L in the former and 3 nmol/L in the latter. □The same increase in testosterone levels after bariatric surgery was observed with replacement therapy with gels/patches of testosterone.[8] So we can safely conclude that before proceeding to replacement therapy with testosterone, every effort should be made to lose weight, with bariatric surgery being by far the most successful.

There is evidence that male hypogonadism may have a causal relationship to obesity. We know that androgens have an important role in male metabolism by influencing energy balance and lipolysis.[15] When the androgen receptor is activated this leads to a negative effect on visceral adiposity and a good example is androgen-deprivation therapies that often induce obesity.[16] Again, the molecular mechanism by which male gonadal dysfunction leads to obesity remain unclear. Evidence from studies show that is associated with impairments in hepatic gluconeogenesis, excessive fat accumulation in white adipose tissue and hyperlipidemia, independent of adipocyte lipid metabolism. So, impaired hepatic gluconeogenesis is proposed as a major pathway of obesity caused by male hypogonadism.[17] Further studies are needed to better analyze the molecular mechanisms underlying obesity caused by male gonadal dysfunction.

As opposed to primary hypogonadism, obesity-associated hypogonadism is due to the increased conversion of androgen precursors to oestrogen in the large adipose tissue volume resulting in hyperestrogenemia. A recent study that looked into the response to testosterone therapy in hypogonadal men showed variation according to their BMI and more specifically demonstrate that severely obese hypogonadal men do not benefit from testosterone therapy as much as men with lower BMI.[18] So, testosterone treatment is not the answer in this case and every effort should be made to treat underlying obesity with the best way being bariatric surgery. The management of obesity is complex because it has an underlying genetic basis that can be exacerbated by lifestyle and eating habits.[19]

It is evident that an integrated approach on obesity is necessary. Patients with severe obesity who have not responded to previous Tier interventions should have access to Tier 3 services. A Tier 3 service is comprised of a multi-disciplinary team (MDT) of specialists, led by a clinician and typically including a physician, a specialist nurse, a specialist dietitian, a psychologist and a physiotherapist. Engagement in Tier 3 services might lead to bariatric surgery which is a part of Tier 4 service and is supported by an MDT in the preoperative period and the postoperative period as well.

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

- There is a reactive association between obesity and male hypogonadism through complex pathogenetic mechanisms.
- There is higher prevalence of symptomatic hypogonadism in obese patients.
- An approach within a multidisciplinary team is the ideal one for having the best results in male obesity-related hypogonadism.
- Bariatric surgery is by far the most effective way in improving the levels of testosterone in severely obese hypogonadal patients as it leads to the highest body

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weight reduction.

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