Endocrine testing in obesity

John P H Wilding

Obesity and Endocrinology Research, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK

Correspondence
should be addressed
to J P H Wilding
Email
J.P.H.Wilding@liverpool.ac.uk

Abstract

Endocrine disorders such as Cushing's syndrome and hypothyroidism may cause weight gain and exacerbate metabolic dysfunction in obesity. Other forms of endocrine dysfunction, particularly gonadal dysfunction (predominantly testosterone deficiency in men and polycystic ovarian syndrome in women), and abnormalities of the hypothalamic-pituitary-adrenal axis, the growth hormone-IGF-1 system and vitamin D deficiency are common in obesity. As a result, endocrinologists may be referred people with obesity for endocrine testing and asked to consider treatment with various hormones. A recent systematic review and associated guidance from the European Society of Endocrinology provide a useful evidence summary and clear guidelines on endocrine testing and treatment in people with obesity. With the exception of screening for hypothyroidism, most endocrine testing is not recommended in the absence of clinical features of endocrine syndromes in obesity, and likewise hormone treatment is rarely needed. These guidelines should help reduce unnecessary endocrine testing in those referred for assessment of obesity and encourage clinicians to support patients with their attempts at weight loss, which if successful has a good chance of correcting any endocrine dysfunction.

*European Journal of
Endocrinology*
(2020) **182**, C13–C15

Obesity is a common and important disease with many adverse health consequences (1). Endocrinologists see many people with obesity, either because of clinical suspicion of an underlying endocrine cause for weight gain or because of concern that obesity may have caused endocrine dysfunction. This bidirectional relationship between obesity and endocrine dysfunction is complex, and the ESE has provided both a systematic review looking at the associations between obesity and common endocrine disorders (2) and practical guidance about appropriate investigations and treatment (3).

Key areas investigated in the systematic review were the prevalence of thyroid disorders (overt hypothyroidism, subclinical hypothyroidism and hyperthyroidism) in obesity, hypercortisolism and gonadal dysfunction – low testosterone in men and PCOS in women. It is important to highlight that most of the studies were not population-based, but clinical samples of people seeking treatment for obesity, including several studies of people considering or undergoing bariatric surgery, and did not include comparator populations of people without obesity

investigated using similar methodology. Although the researchers have followed guidance for such systematic reviews and assessed risk of bias, the wide range of prevalence reported for all of the conditions studied clearly highlights the uncertainty around these estimates and highlights some important areas for future clinical research.

Thyroid disease

For hypothyroidism the reported prevalence (combining diagnosed and undiagnosed hypothyroidism) varied from 1.7 to 47% with a mean of 14% across studies. Subclinical hypothyroidism was equally common. These results seem higher than the reported prevalence of these conditions in unselected populations in Europe (4, 5). This may reflect the age and gender of the studied populations (older with a greater proportion of females), rather than a genuinely higher rate in obesity. Nevertheless, the recommendation to screen for thyroid dysfunction in obesity seems pragmatic, given the high prevalence

and relatively straightforward treatment. However, the authors are correct to recognise that thyroid dysfunction is rarely a cause for obesity and highlight that, in most people, the increase in weight with hypothyroidism is modest (a few kg) and usually reversible with thyroxine treatment. For those with subclinical hypothyroidism (elevated TSH with normal free T4), thyroxine treatment is not recommended as a means to encourage weight loss.

Glucocorticoid excess

Compared with thyroid disease, glucocorticoid excess is rare and other clinical features are often present. It is important to note that some of the studies included in the systematic review only included patients with additional features such as hypertension, diabetes or other symptoms and signs of glucocorticoid excess, so it is likely that these studies are of populations somewhat enriched for the likelihood of Cushing's syndrome. Most used simple screening tests (either an overnight dexamethasone suppression test, salivary or urinary cortisol) followed by further investigation if these were suggestive of glucocorticoid excess. All the studies were small and only identified a few cases of Cushing's syndrome. Overall, the prevalence was 0.9%, which seems high compared to the general population (6), and again may reflect that these were clinical populations, none were population-based studies and some found no cases of glucocorticoid excess. The interpretation of screening tests for glucocorticoid excess in obesity is difficult because obesity and associated conditions such as depression may result in subtle abnormalities in the hypothalamic-pituitary-adrenal axis. Nevertheless, secondary screening investigations such as with a high dose dexamethasone suppression test would usually identify such patients, and it was done in most of the reported studies; it thus seems likely that most of the reported cases reflect true glucocorticoid excess, although in some the workup seemed inconclusive. The conclusion to offer screening tests in the presence of clinical features seems reasonable given the relatively low prevalence in largely unselected populations.

Hypogonadism in males

There is no question that male hypogonadism is associated with an increase in body fat that may contribute to metabolic abnormalities, such as dyslipidaemia and dysglycaemia. Obesity may itself result in dysfunction of the hypothalamic-pituitary-gonadal axis and thus

contribute to hypogonadism in men. In the meta-analysis, the prevalence of male hypogonadism in obesity was 37% and was higher in those with more severe obesity, such as in patients seeking bariatric surgery, which is consistent with the known biology. Most men with obesity-associated hypogonadism will be asymptomatic, although non-specific features such as fatigue are common. Those with specific symptoms such as erectile dysfunction, infertility and other clinical features are more likely to have significant hypogonadism, and in these people, investigation is deemed appropriate. Assessment of gonadal function is not always straightforward, and full clinical evaluation is recommended in those with symptoms, including examination of testicular size as well as appropriate biochemical testing either of free testosterone or total testosterone (in fasted early morning samples) plus SHBG along with measurement of gonadotrophins.

Weight loss may restore gonadal function and is recommended as the first line of treatment unless other pathology is present; however, a trial of testosterone replacement can be considered in the presence of symptoms and confirmed biochemical hypogonadism, with the usual caveats about avoiding use in those with prostate cancer, with PSA screening, prior and during treatment. Monitoring full blood count is also recommended to check for an increased haematocrit.

Gonadal dysfunction in females - polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is common, affecting between 9 and 25% of women with obesity, according to the systematic review, but it is also similarly prevalent in the absence of obesity (7). Screening for PCOS is not advised in obesity, unless women have symptoms such as menstrual disturbance, infertility or hirsutism.

The guidelines advise that weight loss should be the first line approach for women with obesity and PCOS. Metformin is recommended in the guidelines for those with metabolic syndrome, although the evidence supporting its use is relatively weak, and it is not currently licensed for use in women with PCOS. There is some evidence of benefit in women with PCOS who also have glucose intolerance, and this is the only group in whom it is recommended by NICE in the United Kingdom. The risks and benefits of metformin should be made clear to patients and potential adverse effects, including gastrointestinal symptoms and vitamin B12 deficiency discussed if it is to be prescribed. Metformin is also not recommended during pregnancy,

which is an important consideration, as many women with PCOS will present with infertility.

Growth hormone and IGF1

Growth hormone (GH) deficiency contributes to an increase in body fat and a decrease in muscle mass. It is also associated with metabolic abnormalities, including an atherogenic lipid profile and glucose intolerance. Growth hormone secretion may be impaired in severe obesity; however, there is little evidence that this results in lower IGF-1 concentrations or contributes to the metabolic abnormalities. The guidelines correctly conclude that GH and IGF-1 testing is not necessary in people with severe obesity and that GH treatment is not indicated unless there is clear evidence of GH deficiency.

Vitamin D and parathyroid hormone

Vitamin D deficiency is common in Northern European populations and low vitamin D concentrations are prevalent in obesity. The guidelines do not support routine testing for vitamin D or PTH testing, except in those undergoing bariatric surgery, as there is little evidence to support the idea that vitamin D replacement will favourably alter metabolic status or body weight, even in those who are clinically deficient.

Measurement of other hormones: leptin and ghrelin

Circulating concentrations of the adipose tissue hormone leptin are usually increased in obesity; the exception being rare cases of leptin deficiency that would be expected to present at a very young age with severe obesity. Routine testing of leptin is therefore unnecessary. The gut hormone ghrelin is a powerful stimulus to appetite, but there is no evidence that excess ghrelin is a cause of obesity, although raised ghrelin may contribute to increased appetite in Prader–Willi syndrome. Measurement of ghrelin or other gut hormones that influence appetite such as GLP-1 is not helpful in the management of people with obesity.

In conclusion, people with obesity and many referring clinicians often seek reassurance from endocrinologists

that an underlying hormonal imbalance is the cause of their weight gain and associated symptoms. In most people, simple reassurance is all that is required, but some (encouraged by inaccurate information available online and elsewhere) can request repeated and complex investigations to exclude endocrine disease or the use of hormones in the mistaken belief that these will help them lose weight. These new guidelines from the ESE should be welcomed, as they provide clear recommendations about screening for endocrine conditions in people with obesity and a rational approach to further investigation and treatment when endocrine conditions are suspected or diagnosed.

Declaration of interest

The author has acted as a consultant for and received lecture fees from Novo Nordisk, Rhythm pharmaceuticals and Orexigen who produce treatments for obesity. None of these treatments are discussed in this article.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- 1 Bray GA, Kim KK, Wilding JPH & World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obesity Reviews* 2017 **18** 715–723. (<https://doi.org/10.1111/obr.12551>)
- 2 van Hulsteijn LT, Pasquali R, Casanueva F, Haluzik M, Ledoux S, Monteiro MP, Salvador J, Santini F, Toplak H & Dekkers OM. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. *European Journal of Endocrinology* 2020 **182** 11–21. (<https://doi.org/10.1530/EJE-19-0666>)
- 3 Pasquali R, Casanueva F, Haluzik M, van Hulsteijn L, Ledoux S, Monteiro MP, Salvador J, Santini F, Toplak H & Dekkers OM. European Society of Endocrinology Clinical Practice Guideline: endocrine work-up in obesity. *European Journal of Endocrinology* 2020 **182** G1–G32. (<https://doi.org/10.1530/EJE-19-0893>)
- 4 Mendes D, Alves C, Silverio N & Marques FB. Prevalence of undiagnosed hypothyroidism in Europe: a systematic review and meta-analysis. *European Thyroid Journal* 2019 **8** 130–143. (<https://doi.org/10.1159/000499751>)
- 5 Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F & Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 923–931. (<https://doi.org/10.1210/jc.2013-2409>)
- 6 Sharma ST, Nieman LK & Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. *Clinical Epidemiology* 2015 **7** 281–293. (<https://doi.org/10.2147/CLEP.S44336>)
- 7 Sirmans SM & Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology* 2013 **6** 1–13. (<https://doi.org/10.2147/CLEP.S37559>)

Received 5 February 2020

Revised version received 12 February 2020

Accepted 18 February 2020