Understanding functional hypogonadism

Serum testosterone as a marker of chronic disease and cardiometabolic risk in men

GARY WITTERT MB BCh, MD, FRACP, FRCP

In men with obesity, a low serum testosterone concentration in the absence of pathology of the hypothalamic-pituitary-testicular axis is termed functional hypogonadism and is mostly due to obesity. Such a finding should prompt a comprehensive assessment for underlying chronic disease and cardiometabolic risk.

Key points

- **Ageing in men is not inherently associated with a significant decrease in serum testosterone concentrations until the process is very well advanced (>80 years).**
- **Obesity, where the excess fat is stored in viscerally located adipose tissue and associated with insulin resistance, dyslipidaemia and inflammation, decreases serum testosterone concentration by both central and peripheral mechanisms.**
- **The low serum testosterone concentration resulting from obesity is reversible with weight loss and is therefore best thought of as obesity-associated functional hypogonadism.**
- **Men with visceral obesity, the metabolic syndrome and low serum testosterone concentrations are at increased risk for type 2 diabetes.**
- **Other causes of functional hypogonadism include medication (opioids), smoking cessation, excess alcohol consumption, inflammatory processes and subtypes of depression.**
- **A low serum testosterone concentration caused by a definable abnormality in the hypothalamus, pituitary or testes is termed pathological hypogonadism.**
- **The finding of a low serum testosterone concentration requires a thorough clinical and endocrinological assessment to establish the reason it is low, and treatment instituted accordingly.**

This article explains the biological pathways of testosterone production, the difference between pathological and functional hypogonadism and the relationship between serum testosterone concentrations, obesity and obesity-associated chronic disease. An approach is provided to recognising functional hypogonadism as a red flag to undertake comprehensive assessment for the presence of, or risk factors for, chronic disease and the appropriate management thereof.

Physiology of the hypothalamic-pituitary-testicular (HPT) axis

Leydig cells of the testes produce and secrete testosterone under the control of luteinising hormone (LH), which provides the positive feed-forward stimulus to testosterone production. Gonadotroph cells in the anterior pituitary gland secrete LH in a pulsatile manner in response to gonadotropin releasing hormone (GnRH). Neurones in the medio basal hypothalamus produce and secrete GnRH, which reaches the anterior pituitary via the pituitary stalk. Kisspeptin in turn regulates GnRH from a separate group of kisspeptin neurons that connect the regulation of GnRH to other brain regions that

ENDOCRINOLOGY TODAY 2022; 11(2): 37-40

Professor Wittert is Senior Consultant Endocrinologist at the Royal Adelaide Hospital; Senior Principal Research Fellow at the South Australian Health Medical Research Institute; Director of Freemasons Centre for Male Health and Wellbeing, South Australian Health; and Professor of Medicine at the University of Adelaide, Adelaide, SA.

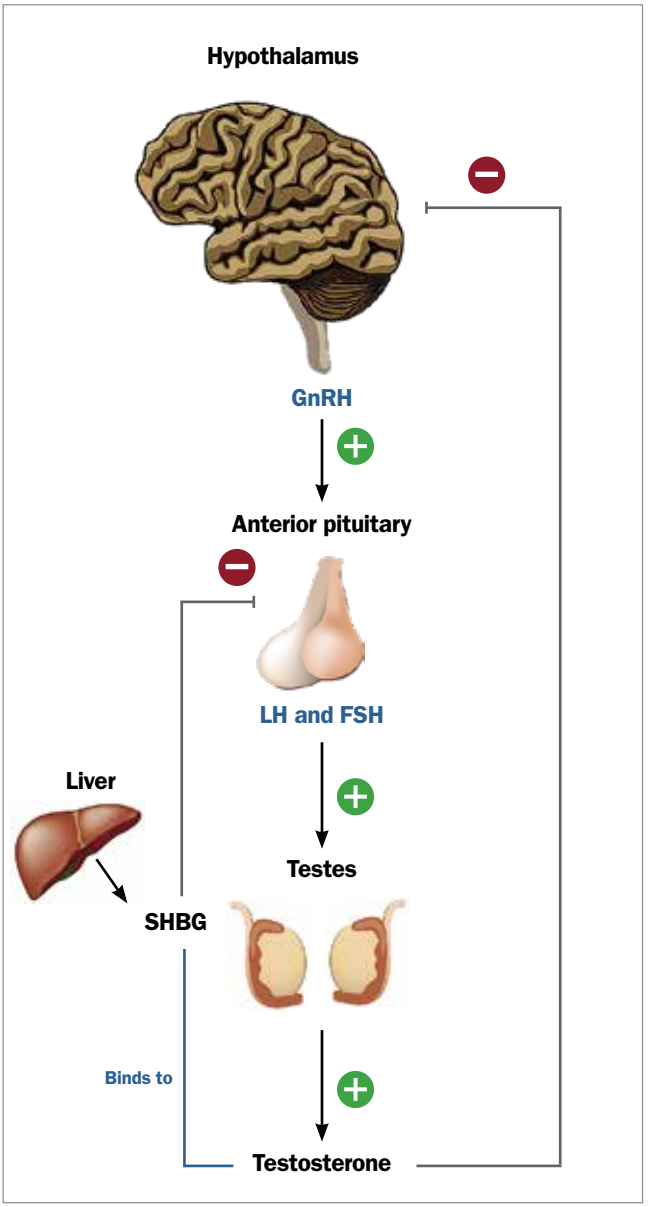

Figure. Hypothalamic-pituitary-testicular (HPT) axis. Testosterone (and its byproduct oestradiol) mediate a negative feedback loop, inhibiting production of LH and GnRH.

Abbreviations: FSH = follicle stimulating hormone; GnRH = gonadotropin releasing hormone; LH = luteinising hormone; SHBG = sex hormone binding globulin.

provide information relating to nutrition, body composition and sleep (Figure).[1,2]

Rather than being under circadian control like cortisol, testosterone production depends on sleep, and increases during slow wave sleep. After waking, there is a gradual decrease in serum testosterone concentration over the course of the day. From a practical perspective, this means that testosterone should be measured first thing after waking. There is little point in measuring testosterone at 8 am in a shift worker who did not sleep overnight.[3]

Both undernutrition and obesity are associated with impaired GnRH regulation and, consequently, LH and testosterone production and secretion. This is the consequence of failure of leptin signalling; deficiency in the case of undernutrition and leptin resistance in the case of obesity.[4]

Testosterone circulates predominantly bound to one of two carrier proteins: sex hormone binding globulin (SHBG) and albumin, both produced in the liver. Attachment to a binding protein is necessary to prevent degradation in the circulation. The entry of testosterone into cells occurs by gradient diffusion after dissociation from its binding protein.

Once testosterone reaches its cellular destination, it is biotransformed in a tissue-specific manner to either oestradiol by aromatase or dihydrotestosterone by 5-alpha reductase. These metabolites of testosterone circulate in low concentrations and standard chemiluminescent assay technology is generally not sufficiently accurate to provide useful information unless high concentrations are clinically suspected.

A negative feedback loop is mediated by both testosterone and oestradiol. LH is inhibited by oestradiol. Testosterone and oestradiol each independently inhibit GnRH.

Increased secretion of the hormone prolactin may also induce negative feedback on GnRH and LH. Prolactin, like LH is produced in the anterior pituitary gland, but by separate cells called lactotrophs. Prolactin is under inhibitory control mediated by dopamine, which is produced in the hypothalamus, reaches the lactotrophs via the pituitary stalk and binds to dopamine type 2 receptors. It is unclear what the function of prolactin is in men, but when the concentration of prolactin increases it causes central inhibition of hypothalamic-pituitary-testicular (HPT) function.

Sex hormone binding globulin (SHBG)

SHBG is a dimeric protein, synthesised in hepatocytes, that binds all sex steroids in a one-to-one ratio. SHBG synthesis and secretion are tightly linked to the regulation of hepatic lipid metabolism. Serum SHBG concentrations increase when fatty acid oxidation increases and hepatic triglyceride synthesis decreases. Thyroid hormone and pulsatile growth hormone secretion and oestradiol increase fatty acid oxidation, inhibit hepatic triglyceride synthesis and increase SHBG concentration. When fatty acid oxidation decreases and the synthesis of triglyceride from carbohydrate increases (de novo lipogenesis), then SHBG concentration decreases. This is what occurs in individuals who are insulin resistant and explains the lowering of SHBG that occurs with a high monosaccharide intake. Pro-inflammatory cytokines also down regulate SHBG concentrations.[5,6] SHBG concentrations decrease during puberty as testosterone concentrations increase; however, the decrease in serum testosterone that occurs in obesity-associated functional hypogonadism does not result in an increase in SHBG concentration. A low serum SHBG concentration is typically a feature of visceral obesity, insulin resistance, fatty liver, and raised serum triglyceride and reduced HDL-cholesterol concentrations.[7]

SHBG concentration may increase for a number of reasons, including:

- weight loss
- insulin administration in lean individuals with type 1 diabetes
- hepatic fibrosis in progressive fatty liver disease
- liver cirrhosis of any cause
- hyperthyroidism.

Measurement of serum testosterone concentration and evaluation of the HPT axis

Important steps in measuring serum testosterone levels and evaluating the HPT axis are as follow.

- Standard laboratory assays that measure total testosterone concentration, which is affected by variations in SHBG concentration. It is, therefore, important to also measure SHBG concentration and understand the causes of a high or low SHBG concentration.
- If the serum testosterone concentration is low, then LH and follicle stimulating hormone concentrations must be measured.
- An elevated LH concentration implies a failure of inhibitory feedback due to insufficient testosterone production by the testes (i.e. primary hypogonadism). The underlying cause is always pathological and advice from an endocrinologist should be sought.
- If the LH concentration is inappropriate for the concentration of testosterone (lower than or within the normal range) then it needs to be established whether a specific pathology is affecting the central components of the HPT axis (i.e. secondary hypogonadism). In the first instance, measure serum prolactin, triiodothyronine, thyroxine and thyroid stimulating hormone concentrations. Further work up and management should be undertaken by an endocrinologist.

Functional hypogonadism

Functional hypogonadism occurs when a low serum testosterone concentration with normal or low-normal LH concentration is not attributable to inherent pathology of the HPT axis, but is caused by potentially reversible external factors, including obesity, lifestyle behaviours and medication use.[8,9] Increasing age is not, in and of itself, a cause of functional hypogonadism.[8,9] If good health is maintained, serum testosterone concentration decreases only minimally until extreme old age, when a more marked decline may occur.[10]

Obesity and obesity-related chronic disorders

Obesity is a heterogeneous condition and one source of variability is the distribution of adipose tissue. Increased adipose tissue located only subcutaneously in an otherwise fit and physically active individual is generally without significant adverse health consequences. However, lipid-filled adipose tissue that accumulates viscerally around organs in the abdomen and hepatocytes of the liver and infiltrates skeletal muscle is associated with insulin resistance, inflammation and dyslipidaemia. It is in these circumstances that HPT dysfunction occurs together with a substantial increase in risk for subsequent type 2 diabetes and cardiovascular and cerebrovascular disease.[11-13]

Body mass index (BMI) is a commonly used measure of obesity. BMI is confounded by variability in skeletal muscle mass and does not provide information related to the distribution of adipose tissue. Visceral obesity is best assessed by measuring waist circumference, which has a much closer association with increased cardiometabolic risk and low serum testosterone concentrations than does BMI.[11] Serum SHBG concentration decreases as waist circumference increases above 94 cm in Caucasians men (lower cut-offs are applicable to South-East Asian and Indian populations); however, this only partially explains the reduction in serum testosterone.[14] Both the decrease in SHBG and testosterone concentrations are reversible with weight loss, with increments being proportional to the amount of weight lost.[15]

Functional hypogonadism occurs when a low serum testosterone concentration with normal or low-normal luteinising hormone concentration... is caused by potentially reversible external factors, including obesity, lifestyle behaviours and medication use

Independent of obesity, there is no effect of blood glucose concentrations on serum testosterone in people with type 2 diabetes.[16] Obstructive sleep apnoea (OSA) is highly prevalent and affects around 52% of men over the age of 40 years, and it is moderate to severe in half of these men. The prevalence of OSA increases with increasing age and obesity. OSA is bidirectionally associated with type 2 diabetes.[17] OSA does not cause a low serum testosterone concentration, and treatment with continuous positive airway pressure does not increase testosterone concentrations.[18,19] Depression and anxiety may be associated with obesity, OSA, diabetes and cardiovascular disease in men, and although a subtype of depression may cause lower serum testosterone concentrations, there is no evidence that functional hypogonadism causes depression.[20]

Lifestyle behaviours

There is some evidence that optimal intake of high-quality protein from fish, poultry and eggs and regular physical activity increase serum testosterone concentrations, independent of obesity.[21] By contrast, heavy alcohol consumption, and binge drinking in particular, decrease testosterone concentrations.[22] Smoking cessation often leads to weight gain but, independent thereof, a decrease in serum testosterone concentration.[8]

Medications

Opioids are powerful inhibitors of the HPT axis, an effect seen even with low doses and, although arguably of lesser magnitude, also with newer opioids such as tapentadol.[23,24] Antipsychotic medications that have dopamine type 2 receptor agonist effects increase prolactin and inhibit the HPT axis. Orally and parenterally administered glucocorticoids lower serum testosterone. Statins have been shown to lower serum testosterone; however, the effect is minor.[25]

Conclusion

The finding of low serum testosterone in a man with obesity and no inherent pathology of the HPT axis or elevation of serum prolactin should serve as a sentinel indicator to assess health-related behaviours, medication use and obesity phenotype, as well as look for OSA, disorders of glucose and lipid metabolism, indicators of cardiovascular disease and depression. This is particularly important in so far as depression is concerned because men tend to somatise symptoms that might incorrectly be attributed to the low serum testosterone. **ET**

References

1. Zhai L, Zhao J, Zhu Y, et al. Downregulation of leptin receptor and kisspeptin/GPR54 in the murine hypothalamus contributes to male hypogonadism caused by high-fat diet-induced obesity. Endocrine 2018; 62: 195-206.
2. Navarro VM. Metabolic regulation of kisspeptin - the link between energy balance and reproduction. Nat Rev Endocrinol 2020; 16: 407-420.
3. Wittert G. The relationship between sleep disorders and testosterone. Curr Opin Endocrinol Diabetes Obes 2014; 21: 239-243.
4. Grossmann M, Wittert GA. Dysregulation of the hypothalamic-pituitary-testicular axis due to energy deficit. J Clin Endocrinol Metab 2021; 106: e4861-e4871.
5. Simo R, Saez-Lopez C, Barbosa-Desongles A, Hernandez C, Selva DM. Novel insights in SHBG regulation and clinical implications. Trends Endocrinol Metab 2015; 26: 376-383.
6. Selva DM, Hogeveen KN, Innis SM, Hammond GL. Monosaccharide-induced lipogenesis regulates the human hepatic sex hormone-binding globulin gene. J Clin Invest 2007; 117: 3979-3987.
7. Gyawali P, Martin SA, Heilbronn LK, et al. Cross-sectional and longitudinal determinants of serum sex hormone binding globulin (SHBG) in a cohort of community-dwelling men. PLoS One 2018; 13(7): e0200078.
8. Shi Z, Araujo AB, Martin S, O'Loughlin P, Wittert GA. Longitudinal changes in testosterone over five years in community-dwelling men. J Clin Endocrinol Metab 2013; 98: 3289-3297.
9. Camacho EM, Huhtaniemi IT, O'Neill TW, et al. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur J Endocrinol 2013; 168: 445-455.
10. Sartorius G, Spasevska S, Idan A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man study. Clin Endocrinol (Oxf) 2012; 77: 755-763.
11. Ross R, Neeland IJ, Yamashita S, et al. Waist circumference as a vital sign in clinical practice: a consensus statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol 2020; 16: 177-189.
12. Zhou L, Han L, Liu M, Lu J, Pan S. Impact of metabolic syndrome on sex hormones and reproductive function: a meta-analysis of 2923 cases and 14062 controls. Aging (Albany NY) 2020; 13: 1962-1971.
13. Kim M, Kyung YS, Ahn TY. Cross-sectional association of metabolic syndrome and its components with serum testosterone levels in a korean-screened population. World J Mens Health 2020; 38: 85-94.
14. Eriksson J, Haring R, Grarup N, et al. Causal relationship between obesity and serum testosterone status in men: a bi-directional mendelian randomization analysis. PLoS One 2017; 12: e0176277.
15. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab 2011; 96: 2341-2353.
16. Giagulli VA, Castellana M, Carbone MD, et al. Weight loss more than glycemic control may improve testosterone in obese type 2 diabetes mellitus men with hypogonadism. Andrology 2020; 8: 654-662.
17. Huang T, Lin BM, Stampfer MJ, Tworoger SS, Hu FB, Redline S. A population-based study of the bidirectional association between obstructive sleep apnea and type 2 diabetes in three prospective U.S. cohorts. Diabetes Care 2018; 41: 2111-2119.
18. Clarke BM, Vincent AD, Martin S, et al. Obstructive sleep apnea is not an independent determinant of testosterone in men. Eur J Endocrinol 2020; 183: 31-39.
19. Knapp A, Myhill PC, Davis WA, et al. Effect of continuous positive airway pressure therapy on sexual function and serum testosterone in males with type 2 diabetes and obstructive sleep apnoea. Clin Endocrinol (Oxf) 2014; 81: 254-258.
20. Westley CJ, Amdur RL, Irwig MS. High rates of depression and depressive symptoms among men referred for borderline testosterone levels. J Sex Med 2015; 12: 1753-1760.
21. Yeap BB, Marriott RJ, Antonio L, et al. Sociodemographic, lifestyle and medical influences on serum testosterone and sex hormone-binding globulin in men from UK Biobank. Clin Endocrinol (Oxf) 2021; 94: 290-302.
22. Duca Y, Aversa A, Condorelli RA, Calogero AE, La Vignera S. Substance abuse and male hypogonadism. J Clin Med 2019; 8: 732.
23. Wehbeh L, Dobs AS. Opioids and the hypothalamic-pituitary-gonadal (HPG) axis. J Clin Endocrinol Metab 2020; 105: dgaa417.
24. Therapeutic Goods Association. TGA Australian public assessment report for tapentadol. Australian Government Department of Health and Ageing: Canberra; 2011. Available online at: https://www.tga.gov.au/sites/default/files/auspar-palexia.pdf (accessed April 2022).
25. Schooling CM, Au Yeung SL, Freeman G, Cowling BJ. The effect of statins on testosterone in men and women, a systematic review and meta-analysis of randomized controlled trials. BMC Med 2013; 11: 57.

COMPETING INTERESTS: Professor Wittert has received research support from Bayer; honoraria for participation in advisory boards from Bayer and Elsevier; and speaker fees from Bayer and Lawley Pharmaceuticals.