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EDITORIAL

Hypoandrogenism in obese men: pathophysiological implications *versus* practical consequences

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Hormone concentrations vary considerably within, and between, subjects, depending on factors such as gender, age, diurnal patterns, nutritional condition, medication, and nonendocrine diseases. These factors may profoundly confound the interpretation of analytical results of hormone measurements in the evaluation of endocrine diseases. In clinical endocrinology, patients present with symptoms which are carefully evaluated by a detailed medical history and physical examination. Employing this diagnostic strategy, many potentially confounding factors are identified prior to further analysis of circulating hormone concentrations. Thus, the physician can estimate the pretest likelihood of (endocrine) disease by weighing the impact of confounding by these other factors against the evidence for true hormonal secretion defects. These considerations apply to the interpretation of the low serum testosterone concentrations frequently observed in men with obesity.

In this issue of the Journal, Hofstra *et al.* report in a careful study that the majority (58%) of a cohort of obese men had plasma testosterone concentrations well into the hypogonadal range.[1] Moreover, the degree of obesity was inversely correlated with total and (calculated) free testosterone concentrations, in accordance with previous observations, such as by Lima *et al.*[2] Because testosterone is a lipophylic hormone, its transportation in blood requires binding to plasma proteins, primarily sex hormone binding globulin (SHBG). Previous studies have shown an inverse relationship between circulating SHBG concentrations and (subcutaneous) fat mass, which can fully explain the well-known reduction of circulating *total* testosterone in obese subjects.[3] In contrast, for some unclear reason, Hofstra *et al.*[1] do not find such a relationship between body fat indices and SHBG and therefore other mechanism(s) must explain low serum total testosterone levels in their study. In keeping with previous reports, for example Giagulli *et al.*,[4] this decrease in testosterone levels occurred without a compensatory increase in gonadotrophins, suggesting enhanced negative feedback restraint of gonadotrophin release. This can be explained by irreversible conversion of testosterone to oestradiol by aromatase in adipose tissue, resulting in decreased testosterone and elevated oestrogen levels in obese men. Since oestrogens, just as testosterone, exert negative feedback regulation onto the hypothalamic-pituitary system, this, at least in part, explains the biochemical pattern of hypogonadotropic hypogonadism in many obese men. This notion is strongly supported by previous observations by de Boer *et al.*, demonstrating that aromatase inhibition by letrozole normalises serum testosterone levels in severely obese men with the biochemical pattern of hypogonadotropic hypogonadism.[5] Moreover, testosterone, free testosterone and SHBG levels tend to normalise in response to weight loss,[6] indicating that the endocrine alterations in sex hormone metabolism are a consequence of obesity.

PATHOPHYSIOLOGICAL IMPLICATIONS

What are the pathophysiological implications of hypoandrogenism in obese men? Is it an endocrine epiphenomenon, merely reflecting an adaptive process balancing regulatory pathways in the face of excess fat? Or are a majority of obese men truly hypogonadal? There are at least several issues that require careful consideration in this respect. Obesity is associated with reduced fertility both in women and in men.[7] Many obese men suffer from erectile dysfunction,[8] and weight loss improves sexual function in obese males.[9] Spermatogenesis is reduced in proportion to body mass index in males.[10] Finally, hypoandrogenaemia is associated with the metabolic syndrome in men and

some data suggest that androgen therapy beneficially modifies fat distribution and ameliorates metabolic anomalies in abdominally obese men,[11] but it is unclear whether these effects were due to physiological rather than pharmacological effects of testosterone. Nonetheless, these data suggest that inhibition of pituitary-gonadal activity by excess adipose tissue provokes reproductive and metabolic anomalies in men. However, there is at present no appropriate evidence for androgen-replacement therapy and/or gonadotrophin treatment for hypoandrogenaemic obese men. For example, it is unclear if low serum testosterone levels are the proximate cause of erectile and spermatogenic anomalies and it remains to be determined if androgen replacement facilitates erectile function, whereas it most certainly will not improve spermatogenesis. Moreover, although various small-scale studies indicate that testosterone replacement beneficially impacts on various components of the metabolic syndrome in obese insulin-resistant men, it is uncertain below which serum testosterone level obese men might benefit from testosterone replacement, which dose should be used and what serum level of testosterone should be strived for, and if long-term testosterone administration is safe in obese insulin-resistant individuals. Indeed, the general uncertainty with respect to the thresholds of normal *vs* abnormal testosterone levels, as mentioned in the recent clinical practice guideline of the Endocrine Society,[12] also applies to this condition.

PRACTICAL IMPLICATIONS

Therefore, we strongly recommend against screening of sex hormone levels in obese men in general. Instead, the assessment of sex hormone levels in obese men is only indicated if there are consistent signs and symptoms of hypogonadism. We appreciate that the clinical diagnosis of androgen deficiency in men is difficult, because symptoms and signs are nonspecific and modified by age, comorbid illness, severity and duration of androgen deficiency, variation in androgen sensitivity, and previous testosterone therapy.[12] First, medical history should be thoroughly checked for symptoms of androgen deficiency. These include muscle weakness, hot flashes, reduced sexual desire, infertility, erectile dysfunction and minor trauma to the testes. Second, careful physical examination should focus on gynaecomastia, pubic, body and facial hair, and testicular atrophy. Third, we recommend obtaining blood samples for measurement of testosterone only in the morning hours on at least two occasions. There is considerable diurnal variation in serum testosterone levels, with the highest levels in the morning.[13] Moreover, the recommendation of the analysis of at least two samples is based on the reality that there is a considerable within-subject variation in testosterone levels. In general, on repeated evaluation, 30% of the men with an initially low level will have a normal level upon repeat testing.[14] Fourth, the age of the patient should be taken into consideration in the interpretation of the test results, because there is a considerable age-dependent decline in total and free testosterone levels of 35 to 50% between the ages of 20 and 80 years, which is not taken into account by the fixed range of normal values provided by many laboratories.

In a patient with signs and/or symptoms of hypogonadism low serum total and free testosterone concentrations in the face of increased luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels indicate primary hypogonadism. Low serum total and free testosterone levels and (sub)normal LH and FSH values point to secondary (i.e. hypogonadotrophic) hypogonadism, which can either be a feature of obesity *per se* or a reflection of pituitary disease, requiring further evaluation of pituitary function.

We are very reluctant to treat obesity-associated low serum testosterone concentrations in the absence of any other clues for the presence of pituitary or testicular disease, because of the absence of consistent evidence that androgen replacement is safe and effective. In contrast, the available evidence does indicate that weight loss reinstates normal pituitary-gonadal function and ameliorates metabolic and reproductive anomalies in obese men.

REFERENCES

1. Hofstra J, Loves S, van Wageningen B, Ruinemans-Koerts J, Janssen I, de Boer H. High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment. Neth J Med 2008;66(3):103-9.
2. Lima N, Cavaliere H, Knobel M, Halpern A, Medeiros-Neto G. Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat. Int J Obes Relat Metab Disord 2000;24:1433-7.
3. Nielsen TL, Hagen C, Wraae K, et al. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. J Clin Endocrinol Metab 2007;92:2696-705.
4. Giagulli VA, Kaufman JM, Vermeulen A. Pathogenesis of the decreased androgen levels in obese men. J Clin Endocrinol Metab 1994;79:997-1000.
5. De Boer H, Verschoor L, Ruinemans-Koerts J, Jansen M. Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. Diabetes Obes Metab 2005;7:211-5.
6. Bastounis EA, Karaviannakis AJ, Syrigos K, Zbar A, Makri GG, Alexiou D. Sex hormone changes in morbidly obese subjects after vertical banded gastroplasty. Eur Surg Res 1998;30:43-7.
7. Pasquali R, Patton L, Gambineri A. Obesity and infertility. Curr Opin Endocrinol Diabetes Obes 2007;14:482-7.
8. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med 2003;139:161-8.

9. Esposito K, Giugliano F, Di Palo C, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA 2004;291:2978-84.

10. Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K. Persistent organochlorines, sedentary occupation, obesity and human male subfertility. Hum Reprod 2005;20:208-15.

11. Mårin P, Holmäng S, Jönsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord 1992;16:991-7.

12. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010.

13. Walton MJ, Anderson RA, Kicman AT, Elton RA, Ossowska K, Baird DT. A diurnal variation in testicular hormone production is maintained following gonadotrophin suppression in normal men. Clin Endocrinol 2007;66:123-9.

14. Kazi M, Geraci SA, Koch CA. Considerations for the diagnosis and treatment of testosterone deficiency in elderly men. Am J Med 2007;120:835-4.