

The inverse relationship between obesity and testicular function

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Reduced testicular function among obese men, as documented in several papers, suggests that increasing adiposity and impaired testicular function are associated. Whether this is cause or effect remains to be determined.

It is well recognised that obesity is a risk factor for female infertility. However, the effects of obesity on male reproductive function, in particular spermatogenesis, are less clear. Here we will briefly review the relationship

between obesity and sex hormone-binding globulin (SHBG); hypogonadotrophic hypogonadism with severe obesity; the effects of bariatric surgery; and recent studies on the inverse association between obesity and sperm output. While the association is generally thought to be causal, we conclude with a discussion about the alternative possibility that impaired testicular function may predispose to or aggravate obesity.

The relationship between obesity and SHBG/testosterone

The evaluation of male hypogonadism always includes measurement of serum testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Measurement of total testosterone will usually be sufficient in identifying patients with androgen deficiency. However, in obese patients, knowledge of the SHBG and testosterone relationship is important for interpreting the result of tests on men with possible hypogonadism presenting with erectile dysfunction, infertility or osteoporosis. It is well established that serum concentrations of SHBG and testosterone decrease with increasing adiposity.^{1,2} There is evidence which suggests that insulin resistance, which accompanies obesity, especially visceral obesity, contributes to the decreased concentrations of these hormones.^{3,4}

Insulin has been shown to inhibit the synthesis of SHBG by a human hepatoma cell line in vitro.⁵ Since testosterone is bound to SHBG in plasma, changes in SHBG concentrations will lead to changes in total testosterone concentrations. A pronounced reduction in SHBG levels is thus frequently observed in obese men and this is the main cause of the decrease in total testosterone. Therefore, in clinical practice, the measurement of total testosterone may be misleading, as a patient with gross obesity may have low SHBG concentrations caused by increased adiposity rather than other factors, which are known to inhibit SHBG production such as androgen therapy, acromegaly, hypothyroidism, nephrotic syndrome or binding protein defects. To differentiate between obesity-associated low SHBG and low SHBG levels caused by other factors (such as those listed above), it is recommended to measure free testosterone, as it is not affected by changes in SHBG.

Hypogonadotrophic hypogonadism with morbid obesity

Morbid obesity may cause secondary hypogonadotrophic hypogonadism in men. It has been shown that both total and free testosterone and gonadotrophin levels decrease, while estradiol levels increase, in obese men in proportion to the degree of their obesity.^{6,7,8,9} It is thought that the increase in adipose tissue, increases aromatase activity and estradiol levels. The elevated estradiol levels in turn inhibit pituitary gonadotrophin secretion, thereby reducing stimulation of the Leydig cells in the testis, resulting in a reduction in testosterone synthesis.^{7,9,10}

The implication that elevated estradiol levels are largely responsible for the endocrine abnormalities observed in obese men is supported by data which demonstrates the therapeutic effects of aromatase inhibitors on hypogonadal obese men.^{11,12,13} Aromatase inhibitors inhibit estrogen biosynthesis by decreasing peripheral conversion of testosterone to estradiol, which limits estrogen production and preserves testosterone levels.¹¹ Aromatase inhibitors have been successfully used for the treatment of estrogen-dependent breast cancers in postmenopausal women.¹⁴ The aromatase inhibitors anastrozole, letrozole and testolactone have been shown to be effective in not only reversing hypogonadism in obese men, but in some cases, also improving semen quality.^{11,12,15,16} While these inhibitors have been shown to be equally effective, testolactone is, however, a steroidal inhibitor, which affects not only the aromatase enzyme, but also several steroidogenic enzymes, thus there is the potential risk of adrenal steroid inhibition.¹¹

In a study of 140 subfertile obese men (BMI over 35) with low testosterone-to-estradiol ratios, who were treated with either 100 to 200 mg testolactone or 1 mg anastrozole daily for a mean of 6 and 4.7 months respectively, normalisation of testosterone and estradiol levels and testosterone-estradiol ratios were observed. There were significant improvements in the semen quality of oligozoospermic but not azoospermic men. Anastrozole and testolactone had similar effects on the endocrine and semen profiles.¹¹ A study of six severely obese men (BMI 38 to 73 kg/m²), who were treated with testolactone 1 g daily for six weeks, all showed increased testosterone and decreased estradiol levels and an increase of LH pulse amplitude, particularly at night, post-treatment.¹² More recently, a six-month study with letrozole 2.5 mg once a week was found to normalise serum total testosterone and estradiol levels in 12 severely obese (BMI over 35) hypogonadal men within the first six weeks of treatment. However, free testosterone rose to supraphysiological levels, leading the authors to recommend a starting dose of less than 2.5 mg.¹⁵

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In a case report, a 29-year-old male who presented with oligozoospermia, morbid central obesity (BMI 54.5 kg/m²) and infertility (his partner was a healthy 32-year-old), was treated for obesity-related hypogonadism with anastrozole. Six months post-treatment, the patient showed normalised testosterone, estradiol and gonadotrophin levels and enhanced spermatogenesis. The couple subsequently conceived.¹⁶ While the short-term benefits of aromatase inhibitors for treating obesity-related hypogonadism have been demonstrated, long-term efficacy and safety data from placebo-controlled studies are lacking.

Effects of substantial weight loss after bariatric surgery on obesity-related hypogonadism

Massive weight loss after bariatric surgery has been shown to improve obesity-related hypogonadism in morbidly obese men. In a study of 19 morbidly obese men, serum sex hormone levels were measured preoperatively and 12 months postoperatively, after vertical banded gastroplasty. The mean weight loss and BMI (pre and postoperative) were 70 kg and 57 kg/m² and 34.7 kg/m² respectively. Postoperative follow-up showed a significant increase in serum FSH, total testosterone and SHBG levels and a decrease in estradiol levels.¹⁷ Similarly, in another study, silastic ring vertical gastroplasty of 17 morbidly obese men caused a significant weight loss (mean 40 kg, BMI decreased from 44.3 kg/m² to 31.6 kg/m² postoperatively) and after 12 months, all low serum testosterone (total and free) and inhibin B levels normalised.¹⁸

More recently, biliopancreatic diversion performed on 20 morbidly obese men caused a significant reduction in mean weight and BMI with respective pre and postoperative values of: 132.1 kg and 93.5 kg and 47.3 kg/m² and 33.5 kg/m². The 12-month postoperative follow-up test results showed significant increases in gonadotrophin and total testosterone levels and a decrease in estradiol levels. Unfortunately, free testosterone and SHBG levels were not measured in this study.¹⁹ While the available literature suggests that substantial weight loss attained by bariatric procedures in morbidly obese men improves obesity related hypogonadism, with improved or even normalised testosterone, SHBG and estradiol levels, it remains to be determined whether weight reduction improves semen quality.

Obesity and semen quality

Several studies have shown negative relationships between obesity and semen quality. Hammoud and colleagues (2008) retrospectively

examined 526 infertile patients and found that oligozoospermia and a low progressively motile sperm count (defined as less than 10×10⁶ progressively motile sperm) were more frequent with increasing BMI.²⁰ Aggerholm and colleagues (2008) used data derived from five separate occupational and environmental population-based semen studies to create one database (n=2139). Men who were overweight were found to have a lower age and abstinence adjusted sperm concentration and total sperm count than men with a normal BMI.²¹ Young Danish military conscripts (n=1558) with either low or high BMI less than 20 kg/m² or greater than 25 kg/m² had lower sperm numbers and percentage normal morphology than those with BMI in the normal range.²² In a study of 520 men from infertile couples, a BMI greater than 25 kg/m² was associated with lower numbers of normal chromatin-intact-motile sperm cells per ejaculate.²³ Other smaller studies have also shown a negative relationship between obesity and semen quality^{24, 25, 26}, although one study failed to find any association.²⁷

A few studies have also shown that male obesity is associated with an increased risk of infertility.^{28, 29, 30} The risk of infertility may be particularly high if the female partner is also overweight or obese.³⁰ We have similar data on the relationship between adiposity and testicular function in fertile men who participated in a surveillance study of testicular function. Men underwent physical examination, semen and hormone (FSH, LH, SHBG, testosterone and inhibin B) analyses (in preparation).

The association between obesity and reduced sperm output – cause or effect?

The mechanism of the obesity-reduced semen quality association is not known, however, it may be that obesity impairs testicular function, or that defective spermatogenesis predisposes to obesity in ways that are not fully understood at present. Most authors assume that the obesity must be impairing testicular function and do not consider the alternative possibility that defective spermatogenesis predisposes to obesity. None of the subjects in our study showed features of gonadotrophin deficiency and FSH levels are not low in the obese group. The FSH/inhibin B ratio was significantly higher in the obese group, which together with the inverse relationship between FSH and total sperm count, is consistent with a primary testicular defect. Thus, we suggest reduced testicular function may predispose to or aggravate obesity. It has been known from traditional animal husbandry that castration increases body fat.³¹ Studies of men having testosterone reduction therapies for prostatic cancer indicate increased fat mass and reduced muscle mass.^{32, 33, 34}

The relationship between obesity and polycystic ovary syndrome (PCOS) may have a similar association. Whether obesity is a cause of PCOS or obesity is a result of PCOS is unclear, but given that not all women with PCOS are obese, it is unlikely that obesity is central to its cause. Obesity could, however, exacerbate or aggravate PCOS in a similar way that we suggest obesity could interact with reduced testicular function.

Conclusion

Low serum SHBG and testosterone levels, together with low gonadotrophins, are frequently observed in men with severe obesity. This needs to be considered when interpreting test results on obese men in whom hypogonadism is clinically suspected. However, the association between obesity and sperm output needs more study, for example, therapeutic trials in the obese to determine whether this is cause or effect in terms of adiposity impairing spermatogenesis or reduced testicular function promoting fat deposition.

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References

1. Vermeulen A, Kaufman JM and Giagulli VA. Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. *J Clin Endocrinol Metab.* 1996; 81: 1821-6.
2. Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, *et al.* Contribution of body fatness and adipose tissue distribution to the age variation in plasma steroid hormone concentrations in men: The heritage family study. *J Clin Endocrinol Metab.* 2000; 85: 1026-31.
3. Seidell JC, Bjorntorp P, Sjostrom L, Kvist H and Sannerstedt R. Visceral fat accumulation in men is positively associated with insulin, glucose, and c-peptide levels, but negatively with testosterone levels. *Metabolism* 1990; 39: 897-901.
4. Pasquali R, Casimirri F, De lasio R, Mesini P, Boschi S, Chierici R, *et al.* Insulin regulates testosterone and sex hormone-binding globulin concentrations in adult normal weight and obese men. *J Clin Endocrinol Metab.* 1995; 80: 654-8.
5. Plymate SR, Matej LA, Jones RE and Friedl KE. Inhibition of sex hormone-binding globulin production in the human hepatoma (hep g2) cell line by insulin and prolactin. *J Clin Endocrinol Metab.* 1988; 67: 460-4.
6. Glass AR, Swerdloff RS, Bray GA, Dahms WT and Atkinson RL. Low serum testosterone and sex-hormone-binding-globulin in massively obese men. *J Clin Endocrinol Metab.* 1977; 45: 1211-9.
7. Schneider G, Kirschner MA, Berkowitz R and Ertel NH. Increased estrogen production in obese men. *J Clin Endocrinol Metab.* 1979; 48: 633-8.
8. Zumoff B, Strain GW, Miller LK, Rosner W, Senie R, Seres DS, *et al.* Plasma free and non-sex-hormone-binding-globulin-bound testosterone are decreased in obese men in proportion to their degree of obesity. *J Clin Endocrinol Metab.* 1990; 71: 929-931.
9. Vermeulen A, Kaufman JM, Deslypere JP and Thomas G. Attenuated luteinizing hormone (lh) pulse amplitude but normal lh pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. *J Clin Endocrinol Metab.* 1993; 76: 1140-6.
10. Strain GW, Zumoff B, Kream J, Strain JJ, Deucher R, Rosenfeld RS, *et al.* Mild hypogonadotropic hypogonadism in obese men. *Metabolism* 1982; 31: 871-5.
11. Raman, JD and Schlegel PN. Aromatase inhibitors for male infertility. *J Urol.* 2002; 167: 624-9.
12. Zumoff B, Miller LK and Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. *Metabolism* 2003; 52: 1126-8.
13. Cohen PG. Obesity in men: The hypogonadal-estrogen receptor relationship and its effect on glucose homeostasis. *Med. Hypotheses* 2008; 70: 358-60.
14. Miller WR, Bartlett J, Brodie AM, Brueggemeier RW, di Salle E, Lonning PE, *et al.* Aromatase inhibitors: Are there differences between steroidal and nonsteroidal aromatase inhibitors and do they matter? *Oncologist* 2008; 13: 829-37.
15. Loves S, Ruinemans-Koerts J and de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. *Eur. J Endocrinol* 2008; 158: 741-7.
16. Roth MY, Amory JK and Page ST. Treatment of male infertility secondary to morbid obesity. *Nat Clin Pract Endocrinol Metab.* 2008; 4: 415-9.
17. Bastounis EA, Karayiannakis AJ, Syrigos K, Zbar A, Makri GG and Alexiou D. Sex hormone changes in morbidly obese patients after vertical banded gastroplasty. *Eur Surg Res.* 1998; 30: 43-7.
18. Globerman H, Shen-Orr Z, Karnieli E, Aloni Y and Charuzi I. Inhibin b in men with severe obesity and after weight reduction following gastroplasty. *Endocr Res.* 2005; 31: 17-26.
19. Alagna S, Cossu ML, Gallo P, Tilocca PL, Pileri P, Alagna G, *et al.* Biliopancreatic diversion: Long-term effects on gonadal function in severely obese men. *Surg Obes Relat Dis.* 2006; 2: 82-6.
20. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT and Meikle AW. Male obesity and alteration in sperm parameters. *Fertil Steril* electronically published ahead of print: pubmed 2008; 18178190.
21. Aggerholm AS, Thulstrup A, Toft G, Ramlau-Hansen CH and Bonde JP. Is overweight a risk factor for reduced semen quality and altered serum sex hormone profile? *Fertil Steril* electronically published ahead of print: pubmed 2008; 18068160.

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