The change of Testosterone after weight intervention in obese men

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Obesity is reaching epidemic proportions worldwide with profound impact on health resulting in reduced quality of life, early death. Deposition of excess fatty acids (FAs) into fat cells in the form of triglycerides (TGs) is the biochemical basis of obesity, thus any imbalance in food intake and energy utilization may result in obesity. This homeostasis is complex and is regulated by a host of metabolic and endocrine factors which are poorly understood. Obesity contributes to pathologies, such as the metabolic syndrome (MetS), cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), hypertension, endothelial dysfunction [ED] and testosterone deficiency (hypogonadism).

An increases in the prevalence of overweight (body mass index (BMI) 25–29.9 kg m−2) and obesity (BMI ≥ 30 kg m−2) in adult men by more than 25% in the last 8 years according to WHO estimates.

Overweight and moderate obesity is predominantly associated with reductions in total testosterone; whereas, free testosterone levels remain within the reference range, especially in younger men. Reductions in total testosterone levels are largely a consequence of reductions in sex hormone binding globulin (SHBG) due to obesity-associated hyperinsulinemia.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) are used for weight loss and insulin dose reduction in obese insulin-using type 2 diabetic patients.

A plausible mechanism by which GLP-1 RA may induce weight loss is by suppressing appetite signalling in the brain and increasing satiety, leading to a reduced food intake [9, 10]. GLP-1 receptors are present in the central nervous system suggesting direct actions of GLP-1 in the brain [11]. GLP-1 infusions can enhance satiety and reduce energy intake in type 2 diabetes patients [12]. Furthermore, GLP-1 RA attenuates binge eating in obese patients [13], suggesting a role of GLP-1 RA in certain eating types.

A recent systematic review and meta-analysis including 2.8 million people and 270 000 deaths reported increased overall mortality only in those with extreme obesity (BMI > 35 kg m−2, hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.18–1.41), but not in grade 1 obesity (BMI

30–34.9 kg m−2, HR 0.95, 95% CI 0.88–1.01) compared to their non-obese counterparts. Unfortunately, obesity is a chronic condition that is difficult to treat. Public health measures, lifestyle interventions and pharmacotherapy adopted thus far have neither registered a marked impact on the prevalence of obesity, nor markedly reduced body weight.

Hypersecretion of LH and an increased LH/FSH ratio unfavorable for folliculogenesis are frequently found in obese infertility patients (15). An association between acute energy depletion or food intake and LH secretory dynamics is reported in normal women, athletes, and men (16–19). Clinical data on the effects of weight reduction on longer term gonadotropin function in overweight women are limited. The fact that obese men have lower testosterone compared to lean men has been recognized for more than 30 years.14 Since then, multiple cross-sectional and prospective studies have consistently found negative linear correlations between both total and free testosterone levels and adiposity in men.15 In a cohort of 3219 men from the European Male Aging Study (EMAS), obesity was associated with an 8.7-fold and overweight with a 3.3-fold increased relative risk (RR) of secondary hypogonadism (defined as total testosterone of <10.5 nmol l−1 and normal luteinizing hormone (LH)), relative to normal weight3. Both total testosterone (5.9 nmol l−1) and free testosterone (54 pmol l−1) levels were lower in obese compared to lean men, with lesser but still significant reduction in overweight men (total T 2.3 nmol).

Obesity is associated with an unequivocal reduction of free testosterone levels, where LH and follicle stimulating hormone (FSH) levels are usually low or inappropriately normal, suggesting that the dominant suppression occurs at the hypothalamic-pituitary level.

Multiple observational studies in community-dwelling men suggest that obesity leads to decreased testosterone. In the prospective Massachusetts Male Aging Study (MMAS), moving from a non-obese to an obese state resulted in a decline of testosterone levels comparable to that of advancing 10 years in age.31 Similar findings have been reported in cohort studies of men from Europe and Australia. Finally, discussed in more detail, weight loss, whether by diet or surgery, increases testosterone levels proportional to the amount of weight lost.

Because of its association with sarcopenia, low testosterone may compound the effect of increasing fat mass by making it more difficult for obese men to lose weight via exercise.

Conversely, obesity in itself contributes to loss of muscle mass and function, thus escalating the effects of sarcopenia on mobility disability and functional impairment, a concept known as 'sarcopenic obesity'.

Observational evidence that weight changes are inversely associated with testosterone levels in community dwelling men have recently been reported in a longitudinal analysis of the EMAS cohort. 34 Minor weight loss (<15%) over 4.4 years was associated with modest increases (+2 nmol l−1) in total testosterone, probably as a consequence of increases in SHBG; whereas, free testosterone did not change. However, a more substantial weight loss of >15% led not only to a more marked increase (+5.75 nmol l−1) of total testosterone, but was also associated with significant increase in free testosterone (+51.78 pmol l−1), likely because of HPT activation, evidenced by a significant rise in LH (+2 U-1).

In a study of 181 men with a low testosterone (<10.4 nmol l−1), less than half of men (n = 70) reported symptoms consistent with androgen deficiency and these men had higher BMIs than asymptomatic men. A cross-sectional study of older overweight men found that loss of libido occurred at a testosterone level <15 nmol l−1, poor concentration at <10 nmol l−1 and erectile dysfunction at <8 nmol l−1. However, these thresholds confer neither sensitivity nor specificity for these symptoms, and a high specificity (> 90%) was achieved only when testosterone levels declined to <3.7–6.3 nmol l−1.106 In EMAS, while certain end-organ deficits compatible with androgen deficiency, such as reductions in muscle mass, hemoglobin and bone density; occurred more commonly in symptomatic men with a total testosterone of <12 nmol l−1, increased insulin resistance and the metabolic syndrome could only be demonstrated in men with testosterone <8 nmoll−1.29 Low testosterone either directly or via its metabolite E2 is a risk factor for osteoporotic fractures. While this may be counterbalanced by the protective effects of obesity on the skeleton, recent evidence suggests that increased VAT may have adverse consequences for skeletal health.

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