Testosterone, incretins and improving cardiometabolic health

An endocrinologist's perspective

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Testosterone, an anabolic hormone, can prevent or revert type 2 diabetes in men at high risk. Incretin-based weight-loss therapy is effective in both men and women, but reduces lean mass, as well as fat mass. Exercise may be the vital ingredient for preserving muscle and improving cardiometabolic health.

Treating obesity and preventing type 2 diabetes and cardiovascular disease are major contemporary health priorities. Testosterone treatment, which increases lean mass and reduces fat mass, may prevent or revert type 2 diabetes in high-risk men when used in conjunction with lifestyle intervention. However, other considerations preclude the widespread use of testosterone for this purpose. First- and next-generation incretin-based antiobesity pharmacotherapies are commanding increasing interest, and their advantages and disadvantages are reviewed in this article. The importance of considering changes in lean mass as well as fat mass is highlighted. This article also advises on the benefits of exercise in preference to testosterone treatment in overweight or obese men, and as an adjunct to incretin-based antiobesity pharmacotherapy in women and men.

MedicineToday 2024; 25(6 Suppl): 21-23

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KEY POINTS

- Obesity is a gateway condition for type 2 diabetes and cardiovascular disease, and is associated with low testosterone concentrations in men.
- On a background of lifestyle intervention, testosterone treatment, which increases lean mass and reduces fat, can prevent or revert type 2 diabetes in men at high risk.
- Exercise training is more beneficial for overweight or obese men, promptly increasing fitness and muscle mass, and reducing fat, compared with testosterone treatment.
- Incretin-based antiobesity pharmacotherapy results in marked weight loss, primarily reducing fat but also reducing lean mass.
- Optimising body composition (enhancing muscle mass while reducing fat) may be the key to improving cardiometabolic health during ageing.

Testosterone and diabetes prevention

Men with lower testosterone concentrations are more likely to have or develop the metabolic syndrome or diabetes.[1,2] A large Australian multicentre, randomised controlled trial (RCT), Testosterone for the Prevention of Type 2 Diabetes Mellitus in men at high risk (T4DM), has proven this relation is causal.[3] In the T4DM trial, 1007 men aged 50 to 74 years with a waist circumference of 95 cm or above and impaired glucose tolerance or newly diagnosed type 2 diabetes were randomly allocated to two years of treatment with testosterone versus placebo, on a background of lifestyle intervention. At the end of the trial, men on testosterone were 40% less likely to have type 2 diabetes than placebo recipients.[3] A post-hoc mediation analysis concluded that changes in fat mass were the predominant contributor to the testosterone treatment effect.[4] However, a striking finding reported in the primary outcomes paper was the change in body composition: men on testosterone gained on average 0.39 kg of muscle mass and lost 4.6 kg of fat, whereas men in the placebo group lost 1.3 kg of muscle and 1.9 kg of fat.[3] A haematocrit level

greater than 54% occurred in 22% of men in the testosterone group compared with 1% in the placebo group, leading to cessation of treatment in 26 men (25 in the testosterone group or 5% of men in the initial enrolment into that arm of the trial).[3] Prudence is needed when translating the results of the T4DM trial given the requirement for a concomitant lifestyle intervention, uncertainty over the optimal duration of treatment, the need to monitor haematocrit levels and prostate risks (such as abnormal examination findings or elevation of prostate-specific antigen levels).[3,5] Testosterone treatment in this context is only applicable to men and, following cessation of treatment, endogenous hypothalamic–pituitary–testicular axis function typically recovers over six to 12 months (but may take longer), whereas metabolic gains diminish with extended follow up.[6,7]

Testosterone, central adiposity and cardiovascular risk

Excess weight and central adiposity are associated with lower testosterone concentrations, partly from reduced activity of the hypothalamic–pituitary–testicular axis, and from reduced sex hormone-binding globulin concentrations.[8,9] Reducing excess weight results in increased testosterone concentrations.[10] An analysis from the UK Biobank, and a meta-analysis of 11 prospective cohort studies that measured testosterone levels using mass spectrometry, showed no association of endogenous testosterone concentration with incidence of major adverse cardiovascular events in men.[11,12] This is consistent with the recent Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) RCT, which was designed as a cardiovascular safety trial. The TRAVERSE trial included 5204 men with cardiovascular disease or cardiac risk factors (mostly overweight, obesity or type 2 diabetes) who received testosterone therapy for a mean duration of 22 months. The trial showed no effect of testosterone treatment on the risk of major adverse cardiovascular events over 33 months of follow up.[13] Of note, in the TRAVERSE trial, men receiving testosterone had a higher incidence of atrial fibrillation,[13] a finding reflected in an observational analysis of healthy older men in which higher endogenous testosterone concentrations were associated with higher incidence of atrial fibrillation.[14] In the TRAVERSE trial, men in the testosterone arm also had a higher incidence of clinical fractures.[15] In the T4DM trial, testosterone treatment increased cortical and total volumetric bone mineral density, and cortical thickness at tibial and radial sites, and increased areal bone mineral density at the lumbar spine.[16] Therefore, the excess of clinical fractures in the TRAVERSE trial is surprising, and warrants further investigation.

To summarise, endogenous testosterone is related to diabetes risk, and exogenous testosterone treatment modulates this risk. However, there appears to be no independent association of testosterone treatment with risk of major adverse cardiovascular events in men.

Testosterone versus exercise in men with overweight or obesity

If the effects of testosterone to reduce the risk of type 2 diabetes in the presence of a concomitant lifestyle intervention are mediated via changes in body composition, a key question is how testosterone compares with exercise to induce metabolically favourable changes in lean and fat mass. A single-centre RCT investigated the effects of testosterone and exercise, alone and in combination, in overweight and obese men aged 50 to 70 years.[17] This testosterone and exercise study showed that a centre-based supervised exercise training program incorporating both aerobic and resistance components, individualised and monitored by an exercise physiologist over 12 weeks, increased cardiorespiratory fitness, increased lean mass and reduced fat, outperforming testosterone.[17] There may be an additive effect of testosterone and exercise on lean mass and strength. Over the 12-week intervention, exercise improved endothelial function and ambulatory blood pressure whereas testosterone treatment did not.[18,19] Therefore, exercise training, provided it is correctly implemented and achieved, should be considered as an initial intervention in the setting of overweight or obesity. In a more general context, exercise is open to, and largely beneficial for, both men and women.

Incretin-based antiobesity pharmacotherapy

Glucagon-like peptide-1 (GLP-1) receptor agonists are a well-established therapy for people with type 2 diabetes, with their use now extended into the setting of obesity. In middle-aged adults with overweight or obesity, treatment with the GLP-1 receptor agonist semaglutide over 68 weeks reduced body weight by 14.9% (–15.3 kg) compared with 2.4% (–2.6 kg) for placebo.[20] A cardiovascular outcomes trial demonstrated a 20% reduction in the risk of major adverse cardiovascular events with semaglutide in people with overweight or obesity over a 40-month duration.[21] Next-generation incretin-based antiobesity pharmacotherapies are now available. In middle-aged adults with overweight or obesity, treatment with tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, resulted in 20.9% (–22.1 kg) weight loss after a 72-week intervention compared with 3.1% (–3.2 kg) for placebo.[22] The corresponding RCT of tirzepatide in people with obesity and type 2 diabetes showed a slightly attenuated result, with 15.7% weight loss over 72 weeks.[23] In middle-aged adults with overweight or obesity, treatment with retatrutide, a triple GLP-1, GIP and glucagon receptor agonist, at the highest dose resulted in 24.2% (–26.4 kg) weight loss over 48 weeks (–2.1% for placebo).[24] In these RCTs, although the headline results illustrated average changes in the groups, some individual participants lost substantially more weight. For example, in the retatrutide study, effects were dose-dependent and, at the highest dose, 48% of participants lost 25% or more of their body weight and 26% of participants

lost 30% or more.[24] Retatrutide is currently not available in Australia.

All three agents, semaglutide, tirzepatide and retatrutide, are administered as a weekly subcutaneous injection, demonstrate clear cardiometabolic benefit and provide for the first time effective medical alternatives to bariatric surgery. There are recognised side effects: patients should be warned about risks of nausea, vomiting, diarrhoea and constipation, and advised on how to mitigate or pre-empt these. For example, take small regular meals if nausea occurs, and maintain hydration and fibre intake to ward against constipation. Another increasingly recognised phenomenon is that although large amounts of weight are lost, and most of this is fat, some is lean or muscle mass. In the semaglutide RCT cited earlier, in the subgroup where body composition was analysed using dual energy x-ray absorptiometry, fat mass was reduced by 24.7% (–10.4 kg) and lean mass was reduced on an average by 13.9% (–6.9 kg).[20] In the tirzepatide RCT, in the subgroup studied using dual energy x-ray absorptiometry, 33.9% (about 17 kg) of total fat mass was lost, but also 10.9% (about 6 kg) of lean mass.[22]

Importance of preserving lean mass while losing fat

Muscle, which comprises a large portion of lean mass, is metabolically active and a major contributor to basal metabolic rate.[25] Loss of muscle mass reduces basal metabolic rate, predisposing to weight gain and fat accumulation. On cessation of semaglutide or tirzepatide therapy, more than half of the weight lost was regained after 12 months.[26,27] It is an open question whether or not loss of lean mass contributes to ease of weight regain.[28] Reduced muscle mass also predisposes older adults to sarcopenia and frailty, which carry adverse consequences for health. Thus, it would be prudent to counsel patients receiving incretin therapy to maintain protein intake, but the loss of lean mass remains a potential concern.

In a study of men with obesity who received 10 weeks of a very-low-calorie diet, testosterone therapy until 56 weeks enhanced fat loss and led to regain of lean mass.[29] In another study, following eight weeks of calorie restriction, adults with obesity were randomised to one of four strategies: liraglutide plus exercise group, liraglutide group, exercise group or placebo.[30] The exercise group aimed to achieve aerobic physical activity targets. Liraglutide with or without exercise led to more weight loss, whereas exercise alone increased lean mass and blunted overall weight regain.[30] These studies were designed to examine maintenance of achieved weight loss, and both pre-date the emergence of the newer incretins. Studies of adjunctive interventions applied concomitantly with incretin-based antiobesity pharmacotherapies are awaited. Nevertheless, the scope for interventions that build lean mass is clear. In the testosterone and exercise study discussed earlier, the exercise training regimen comprised a mixture of aerobic and resistance exercise stations.[17] Compared with aerobic exercise, resistance or weight-based exercise training has a greater effect to increase muscle mass and strength.[31] Therefore, pending further studies there is a strong argument to apply resistance exercise training as an adjunct to incretin-based weight loss interventions, to preserve lean mass and enhance fat loss, and possibly reduce weight regain on cessation of pharmacotherapy.[28]

Broader perspectives and conclusion

In men who are hypogonadal because of hypothalamic, pituitary or testicular disease, testosterone treatment is indicated to ameliorate the symptoms and signs of androgen deficiency.[32] Testosterone is not approved for the prevention or treatment of type 2 diabetes, and men who are found to have a low testosterone concentration may be referred to an endocrinologist for assessment. Testosterone treatment should be considered in hypogonadal men in whom no reversible causes or contraindications are present, and where fertility is not an issue, and they should be appropriately supervised and monitored.[33] The T4DM and TRAVERSE trials provide added reassurance with regards to cardiovascular (as well as prostate) safety of testosterone therapy.[3,13] Testosterone is an anabolic hormone, diabetes is a risk factor for dementia, and men with lower testosterone concentrations are at higher risk of dementia.[34] Therefore, the results of the T4DM and TRAVERSE trials provide a foundation for future studies in the general population of men, particularly those aged 70 years and above in whom Leydig cell impairment appears.[9] One such future RCT should be a large multicentre (possibly or necessarily multinational) RCT of testosterone treatment to prevent frailty and dementia in ageing men.

The newer incretin-based antiobesity pharmacotherapies are attracting increasing attention because of their demonstrated efficacy in the setting of cardiometabolic disease.[20-24] Although the potential benefits are substantial, side effects including loss of lean mass and the issue of weight regain on cessation of therapy merit close consideration. Every opportunity to encourage healthy lifestyle behaviours should be taken. In this and other health settings, exercise training should be considered to enhance outcomes and mitigate side effects.[28] Resistance exercise may be an important, nonpharmacological intervention to protect or even enhance muscle mass, thus optimising body composition and longer-term outcomes. A contemporary approach might involve general practitioners working with practice nurses, dieticians, psychologists and exercise physiologists, facilitating exercise and resistance exercise to improve cardiometabolic health in different health settings. MT

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Professor Yeap has received speaker honoraria and conference support from Bayer, Lilly and Besins Healthcare, research support from Bayer, Lilly and Lawley Pharmaceuticals, and participated in advisory roles for Lilly, Besins Healthcare, Ferring and Lawley Pharmaceuticals.

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