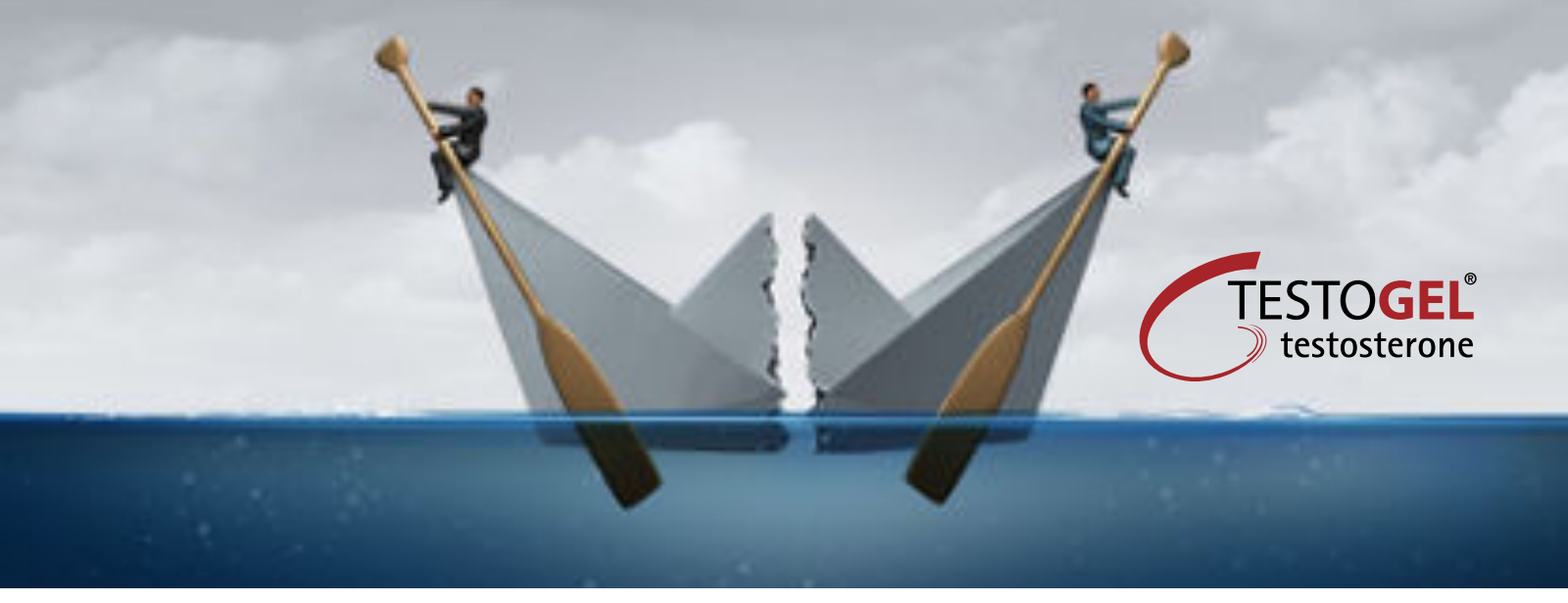
THERE ARE TWO SIDES TO THE TESTOSTERONE STORY. BUT JUST HOW LOW SHOULD WE LET MEN GO?



Not too much, not too little. Just enough. How much testosterone does the body need at each stage of life? It sounds like a simple question, and the answer is simple – enough to keep testosterone's important functions going. But over the years the importance of a normal, physiological level of testosterone has been overshadowed by noise around potential risks and harm of testosterone going too high. What's been ignored are the consequences of not having enough testosterone. New evidence is now emerging that makes it clear – it's no longer reasonable not to take a look under the hood. Because even if you think testosterone is not that important, surely cardiometabolic health and the risk of diabetes is.

How common is low testosterone anyway?

It's true, testosterone levels decrease gradually as men age, at a rate of around 1-2% each year.[1,2] The bulk of Testosterone Deficiency (TD) occurs in men who are overweight or have comorbidities like diabetes.[3,4] The challenge is that the signs of TD mirror the everyday features of advancing age, such as frailty, obesity, osteopenia, cognitive decline, and erectile dysfunction.[5] Therefore, guidelines advocate for a diagnosis of TD to be based on both biochemical confirmation of low testosterone levels as well as clinical signs and symptoms of hypogonadism (HG; Box 1).[6]

Box 1. Clinical Signs and Symptoms Associated with Hypogonadism in Ageing Men. [Adapted from McBride JA, et al. 2016].[6]

SEXUAL SYMPTOMS	NONSEXUAL SYMPTOMS	CLINICAL SIGNS
• Decreased libido • Decreased frequency of sexual thoughts • Decreased frequency or rigidity of nocturnal erections • Erectile dysfunction	• Fatigue • Decreased energy • Poor concentration • Decreased sense of wellbeing • Depressed mood • Decreased vitality • Depression	• Obesity • Decreased muscle mass and strength • Decreased bone mineral density and osteoporosis • Hot flashes • Mild anaemia • Testicular atrophy or asymmetry • Varicoceles • Penile plaques or other abnormalities • Decreased pubic hair • Gynaecomastia • Diminished prostate volume

Why bother correcting low testosterone for nonsexual symptoms?

Put simply, there's more to normal physiologic testosterone than sexual function. Some of the best evidence for testosterone replacement in older men comes from the Testosterone Trials.[5] In addition to improved sexual function, they showed that testosterone therapy improved physical function (measured by walking distance), improved mood and depressive symptoms, corrected mild to moderate anaemia, and increased bone mineral density and bone strength; however, testosterone therapy did not significantly improve energy levels or cognitive function.[5]

But it doesn't stop there. Mounting evidence suggests an elevated cardiovascular risk and all-cause mortality associated with low testosterone levels.[7] When testosterone levels are normalised markers of coronary artery disease are improved and cardiovascular risk diminished.[7] This evidence in not just from one or two studies. Now over 100 studies show cardiovascular benefits of higher endogenous testosterone levels or improved cardiovascular risk factors with testosterone therapy.[7]

Evidence linking obesity and metabolic dysfunction to low testosterone levels is also accumulating, demonstrating a bidirectional relationship between T2DM and HG.[8] TD can drive metabolic dysfunction – seen in men with prostate cancer undergoing androgen deprivation therapy who have very low testosterone levels and go on to develop osteosarcopenic obesity and insulin resistance.[3] On the flip side, body weight can impact testosterone levels – where an increase in body mass index of 4 to 5 kg/m2 or the presence of T2DM is associated with an acceleration of age-related testosterone decline.[3] While lifestyle interventions are the first-line treatment approach, compliance is difficult to achieve and they may be insufficient on their own to normalise testosterone levels and relieve symptoms of testosterone deficiency.[3] A recent review of testosterone levels in patients with T2DM captures the current international sentiment about the role of testosterone therapy in men with low testosterone levels associated with cardiometabolic dysfunction, concluding:[8]

> **"Restricting therapy to men with classical HG is not supported by evidence. The results of lifestyle intervention as sole therapy for HG in T2DM are disappointing. The balance of evidence suggests that men with T2DM, metabolic syndrome and HG are likely to benefit from testosterone therapy combined with lifestyle intervention. Meta-analyses of RCTs, rather than providing clarification, have further confused the issue by including under-powered studies of inadequate duration, non-homogenous cohorts, multiple regimes, discontinued medication, and inbuilt bias in terms of studies included or excluded from analysis."**

Notably, lifestyle interventions alone appear to be failing to prevent an increased prevalence of T2DM,[8] and clinical studies are now evaluating whether testosterone therapy can help prevent T2DM and associated comorbidities. In a long-term, real-life observational study in 316 men with prediabetes (defined as HbA1c of 5.7 to 6.4%) and total testosterone levels <12 .1 nmol/L combined with symptoms of HG, not a single man treated with testosterone progressed to overt T2DM over the 8-year follow-up, while 40.2% of untreated men developed overt T2DM.[9] These results certainly warrant further investigation. The T4DM study, a randomised controlled trial conducted in Australia and the largest study of testosterone treatment to date worldwide (N=1007), showed that testosterone treatment over two years in addition to lifestyle modification, in men with low testosterone, reduced the risk of men with type 2 diabetes beyond the effects of lifestyle modification alone (relative risk 0.59).[10] The men included in the T4DM study were aged 50-74 years, with a waist circumference of ≥95cm, serum testosterone levels of ≤14.0 nmol/L (without pathological hypogonadism) plus an impaired glucose tolerance or newly diagnosed type 2 diabetes.[10] The benefits on glucose metabolism were seen regardless of baseline testosterone levels. These findings support the notion that testosterone therapy in addition to lifestyle modifications can prevent or revert type 2 diabetes in overweight men with low testosterone even without pathological hypogonadism.[10]

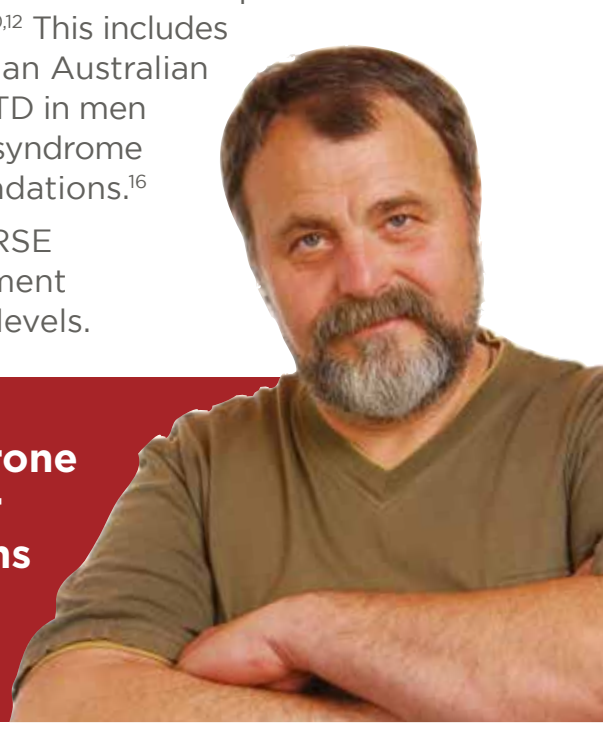
Why wouldn't you correct TD for nonsexual symptoms?

Hesitation around the treatment of TD for nonsexual symptoms comes largely from the lack of high-quality evidence from well-designed, long-term, sufficiently powered clinical studies.[4] While the Testosterone Trials demonstrated statistically significant improvements in erectile function, sex drive, anaemia, bone mineral density, lean body mass, and depressive symptoms,[11] these studies were limited to 1 year of testosterone therapy, which has drawn criticism from critics as to the long-term value.[12]

In terms of safety, cardiovascular events and prostate cancer have been highly visible discussion points. While a link between low testosterone levels and adverse cardiovascular events is recognised, studies assessing the cardiovascular safety of testosterone replacement therapy has yielded inconsistent and controversial results. Data in support of increased cardiovascular risk with testosterone treatment were subsequently found to be flawed.[1,13] A large randomised controlled trial (named TRAVERSE) is ongoing to examine the effect of transdermal testosterone gel on the incidence of major adverse cardiovascular events. Results should be available by the end of 2022. When it comes to prostate cancer, testosterone therapy is still contraindicated in patients with a history of or active diagnosis of prostate cancer, although available data suggests that there is no increased risk of prostate cancer in men who are treated with testosterone.[12]

Given the gaps in the evidence, current Australian guidelines remain conservative in their recommendations for managing sexual and non-sexual symptoms associated with low testosterone, and do not recommend testosterone treatment for older men in the absence of organic HG.[14,15] However, other international guidelines now open the door for treating this population based on careful patient selection.[10,12] This includes recognition of a broader range of signs and symptoms than Australian guidelines. International guidelines endorse screening for TD in men presenting with unexplained anaemia, diabetes, metabolic syndrome and obesity, to name but a few of their broader recommendations.[16]

For now, we await the results from the US-based TRAVERSE study for further high quality evidence to guide management recommendations for ageing men with low testosterone levels.



How long we wait to screen for low testosterone in men depends largely on what we consider more important to prevent – sexual symptoms and energy or cardiometabolic risk. How long should we make patients wait?

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