Testosterone replacement to prevent Type 2 diabetes? Not just yet

Naveed Sattar FMedsci[1], James G Boyle MD FRCP[2], Ebaa Al-Ozairi MD MRCP[3]

[1] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[2] Glasgow Royal Infirmary, Castle Street, Glasgow, G4 0SF, UK

[3] Clinical Research Unit, Dasman Diabetes Institute, Kuwait City, Kuwait

Correspondence:

Professor Naveed Sattar

Institute of Cardiovascular and Medical Sciences

BHF Glasgow Cardiovascular Research Centre

University of Glasgow

126 University Place

Glasgow, G12 8TA

Tel: +44 141 330 3419

Email: Naveed.Sattar@glasgow.ac.uk

ORCID: 0000-0002-1604-2593

799 words

10 references

Type 2 diabetes is linked to premature mortality and considerable morbidity. Its worldwide prevalence has risen markedly in the last four decades due to a mixture of rising obesity and life expectancies, and reductions in premature mortality in type 2 diabetes. Diabetes also appears to be a major contributor to COVID-related death.[1] Any novel mechanisms to lessen diabetes development would therefore be helpful.

In this issue of the journal, Wittert and colleagues[2] report the results of a well conducted two year placebo-controlled randomised trial of intramuscular testosterone in 1007 overweight middle-aged and older men with modestly low or low-normal (<14 nmol/l) testosterone levels and at elevated risk of type 2 diabetes. Their headline results show a 41% (95% CI 20 to 57%) reduction in risk of diabetes based on the glucose tolerance test, with an absolute placebo-corrected reduction in 2-hour glucose of 0·75mmol/l. In line with such benefits, and the known effects of testosterone, body composition improved – slightly more muscle and improved muscular strength, and slightly less fat; sexual function also improved modestly, as measured by validated questionnaires.

So far, so good and on the face of it the results align with preceding biology and emerging genetics. Low testosterone levels are associated with higher obesity and type 2 diabetes risks, and recent mendelian randomisation studies[3] suggest higher testosterone to be causally related to lower diabetes risk. In truth, this relationship is bidirectional since lifestyle interventions can lead to a rise in testosterone levels.[4] Even so, the authors are to be congratulated in conducting a large, well powered trial since randomised trials give a true sense of the net benefits and safety of novel interventions. As one of the reasons to prevent type 2 diabetes is to lessen macrovascular risks, any evidence for benefits or harms of testosterone replacement on the vascular system require particular scrutiny, as does any impact on quality of life.

With respect to patients' perceptions, whilst sexual function improved modestly, no significant improvement in health-related quality of life was noted in this trial.[2] To context these results, a recent evidence review by the American College of Physicians[5] concluded that "testosterone therapy may provide small improvements in sexual functioning and quality of life but little to no benefit for other common symptoms of aging." Testosterone therapy is therefore unlikely to be the elixir of healthy ageing.

In terms of vascular health, the present two-year trial was too short to determine net harm or benefit with only 38 cardiovascular events. In the context of frequent monitoring, haematocrit increased sufficiently to lead over a fifth of men to be withdrawn from therapy, a notable finding as higher haematocrit levels have been associated with a higher risk for coronary events.[6] There were two cases of thrombosis in the intervention arm and none in placebo, also insufficient to draw conclusions on thrombotic risks. Unfortunately, lipid levels were not measured but systolic blood pressure increased more (by 1·9mmHg, 95% CI -0·2 to 3·9mmHg) in testosterone versus placebo recipients. Whilst this change was not strictly significant, preceding mixed data on the effects of testosterone on the cardiovascular system, including a potential increase in coronary artery noncalcified plaque volume from testosterone gel,[7] suggest a need for caution. The FDA agree and have mandated that any product for age-related hypogonadism should have a cardiovascular outcome trial.[8] For this reason, TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men; NCT03518034) a 5-year trial

of testosterone gel in 6000 men is ongoing and will report in a few years. It is hoped the resulting data will at least show cardiovascular safety of testosterone treatments in men lacking a formal diagnosis of hypogonadism. If a further reminder was needed to support this latter trial, sex hormone replacement therapy in women lessens incident diabetes but increases cardiovascular and thrombotic risks.[9]

Can these new testosterone trial data influence clinical practice? The authors remind us that the testosterone-induced benefits on type 2 diabetes prevention were at least as good, if not better than metformin therapy. However, they recognise the need for careful haematocrit monitoring and the uncertainty on long-term cardiovascular risks means testosterone *cannot* currently be recommended for this purpose. We agree; one of the key goals in preventing diabetes is to slow progression to cardiovascular pathology, and given major uncertainties about testosterone's vascular effects, outcome trials are a must before any conclusions can be drawn. Concerns on prostate safety also need longer term trials. In the meantime, we should be glad that affordable, alternative type 2 diabetes preventative interventions exist, including metformin but in particular lifestyle, shown to lessen future vascular outcomes and extend life.[10] In this respect, interventions to support people make positive and sustainable lifestyle changes are improving. The challenge now is to expand implementation of these without loss of fidelity.

Author contributions

NS drafted editorial and JB and EO critically reviewed and edited it.

Conflicts of interest

NS reports personal fees and research grant from Boehringer Ingelheim, and personal fees from Amgen, AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi. JGB reports personal fees from Sanofi, and travel support from Napp and Janssen. EA reports no conflicts of interest.

Funding

There is no funding to report.

Acknowledgements

The authors thank Liz Coyle (University of Glasgow) for her assistance in the preparation of this article.

References

1 Barron E, Bakhai C, Kar P, *et al.* Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; **8**: 813–22.

2 Wittert G, Bracken K, Robledo KP, *et al.* Effect of Testosterone Treatment to Prevent or Revert Type 2 Diabetes in High-Risk Men Enrolled in a Lifestyle Program: A Two-Year Multicentre Randomised Placebo- Controlled Trial. *Lancet Diabetes Endocrinol* 2020.

3 Yuan S, Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. *Diabetologia* 2020; **63**: 2359–71.

4 Grossmann M. Low testosterone in men with type 2 diabetes: Significance and treatment. J. Clin. Endocrinol. Metab. 2011; **96**: 2341–53.

5 Diem SJ, Greer NL, MacDonald R, *et al.* Efficacy and safety of testosterone treatment in men: An evidence report for a clinical practice guideline by the American college of physicians. Ann. Intern. Med. 2020; **172**: 105–18.

6 Lowe GDO, Rumley A, Whincup PH, Danesh J. Hemostatic and rheological variables and risk of cardiovascular disease. Semin. Vasc. Med. 2002; **2**: 429–39.

7 Budoff MJ, Ellenberg SS, Lewis CE, *et al.* Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA - J Am Med Assoc* 2017; **317**: 708–16.

8 FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use | FDA. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-cautions-about-using-testosterone-products-low-testosterone-due (accessed Oct 19, 2020).

9 Gartlehner G, Patel S V, Viswanathan M, *et al.* Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women. Agency for Healthcare Research and Quality (US), 2017 http://www.ncbi.nlm.nih.gov/pubmed/29589880 (accessed Oct 19, 2020).

10 Gong Q, Zhang P, Wang J, *et al.* Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019; **7**: 452–61.