Effect of Testosterone Treatment on Type 2 Diabetes Incidence in High Risk Men Enrolled in a Lifestyle Program: A Two-year Randomized Placebo-Controlled Study. The T4DM Study.

What was the T4DM study about?

The aim of the T4DM study was to find out whether treatment with testosterone injections can prevent or reverse Type 2 diabetes in men who are at the most risk of diabetes because they have lower testosterone levels and pre-diabetes or newly diagnosed diabetes.

We appreciate the part played by our volunteer participants. Without these men, this trial would not have been possible.

How was the study conducted?

A total of 1007 Australian men aged between 50 and 74 years old enrolled into our study. Based on an oral glucose tolerance test, 200 of these men had newly diagnosed diabetes and the remainder had pre-diabetes.

Men were randomly allocated to receive three monthly injections with either testosterone or placebo.A total of 503 were allocated to receive placebo and 504 were allocated to receive testosterone. All men were given access to the WW (formerly known as Weight Watchers) lifestyle program.

The study was double-blind, meaning that men, their doctors and nurses, and the people managing the study did not know which treatment each man was receiving. The placebo injection was identical to the testosterone injection but had no active ingredient in it.

After two years, 413 men in the placebo group and 443 men in the testosterone group returned for blood tests.

On average, about 30% of men in each treatment group participated regularly in the WW program and about 70% were doing at least the recommended amount of physical activity.

What was the effect of the testosterone treatment on diabetes?

After two years of treatment:

21.1% (87/413 men)

of men in the **placebo group** had diabetes

12.4% (55/443 men)

of men in the **testosterone group** had diabetes

The proportion of men with diabetes at two years in the testosterone group was significantly lower than in the placebo group. Importantly, the effect of the testosterone did not depend on the blood concentration of testosterone measured when they first entered the study – that is, it did not depend on having a low or normal testosterone concentration.

What else did we find?

Fasting blood sugar

At two years, fasting blood sugar was, on average, lower than it was at the start of the study in both the placebo and testosterone groups. However, the decrease was larger in the testosterone group (a 0.07mmol/L decrease in the placebo versus 0.24 mmol/L decrease in the testosterone group).

Men who had lost more body fat tended to have the biggest decreases in fasting blood sugar, no matter whether they received the testosterone or the placebo.

Normal glucose tolerance on the oral glucose tolerance test

The men who joined the T4DM study had either pre-diabetes or newly diagnosed diabetes – none had normal glucose tolerance. At the end of two years, approximately half of the men in each group had normal glucose tolerance: 43.3% of men in the placebo group and 51.9% of men in the testosterone group.

These results show the importance of weight loss (achieved by healthy eating and exercise) for preventing diabetes or even reversing newly diagnosed Type 2 diabetes. Treatment with testosterone had only a small but significant additional benefit.

Body weight, fat and muscle mass, and strength

Generally, the men who were most engaged in the WW program lost the most body weight. On average, men in the testosterone group lost about the same amount of body weight as those in the placebo group. This is because on average men in the testosterone group lost fat and gained muscle whereas men in the placebo group lost both fat and muscle mass.

The specific changes were on average:

- Body weight decreased by 3.5kg with placebo and decreased by 4.5kg with testosterone treatment.
- Waist circumference decreased by 4.9cm with placebo and decreased by 7cm with testosterone treatment.
- Body fat decreased by 1.9kg with placebo and decreased by 4.6kg with testosterone treatment.
- Body muscle decreased by 1.3kg with placebo and increased by 0.3kg with testosterone treatment.
- Hand grip strength decreased by 0.5kg with placebo and increased by 1.7kg with testosterone treatment.

Sexual function

On average, there were small improvements in sexual function (including erections, orgasms, sexual desire, and satisfaction) over the two years for the men in the testosterone group. We do not know whether such small changes over two years would be noticeable to most men. We have yet to determine whether there were some men who benefited more and whether we can identify who may benefit most.

Was the treatment safe?

Very few men on the study reported serious side effects (adverse health events) and there were equal numbers of reports in each treatment group. Because the numbers were small, it is difficult to be certain about how important the reported events were. As the study was over two years, safety over a longer-term remains unknown.

The most reassuring findings are that treatment with testosterone did not increase the risk of:

- Cardiovascular or cerebrovascular disorders (heart disorders of strokes)
- Prostate cancer
- Problems passing urine.

The most common adverse event was an increase in haematocrit (the proportion of red blood cells as compared to plasma in blood). This affected 106 (22%) of men being treated with testosterone. It led to the withdrawal from the study of 25 men and was the most common reason for needing to stop treatment with testosterone. The men with higher haematocrit at the outset were most at risk of having an increase of their haematocrit in response to testosterone. A high haematocrit may increase the risk of blockages to small blood vessels in some people.

One condition that increases the risk of a high haematocrit is obstructive sleep apnoea. This is a condition where breathing stops during sleep and it may occur in up to 80% of men over the age of 50, who are overweight and are at risk of having, or have diabetes. Because breathing stops, the oxygen level in the blood decreases and that stimulates the bone-marrow to make more red blood cells. Another reason for increased haematocrit is lung damage due to smoking.

What does this mean for your health?

- Diabetes can be preventable and reversable.
- The best and safest way to prevent or reverse diabetes is through healthy eating along with regular strength training and aerobic activity.
- Talk to your GP about sleep apnoea and get tested and treated if necessary.
- Alcohol increases the risk of having diabetes and makes sleep apnoea worse. There is no safe threshold for alcohol consumption.
- If you are a smoker, you should stop smoking. For current and past smokers, it is important to check for underlying lung disease.
- Treatment with testosterone for up to 2 years might be an option for some men. However, this treatment should be combined with a thorough physical and mental health assessment and support to adopt a healthy lifestyle and very careful monitoring. However, we are not recommending the use of testosterone for prevention or treatment of type 2 diabetes based on the results of this study.

How can I find out more about the study?

We are preparing a webinar with a question and answer session.

The results of the study are being presented at the American Diabetes Association Conference on June 12, 2020. A manuscript has also been submitted for publication.

The trial was registered in Australia: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=362125

Who provided funding for this study?

NH&MRC (Grant #1030123), Bayer AG, WW, Eli Lilly, Freemasons Foundation Centre for Men's Health, University of Adelaide

Summary of the T4DM study results

- It is possible to lose weight and maintain weight loss with a structured weight loss program.
- Development of Type 2 diabetes among men at high risk can be preventable, and newly diagnosed diabetes can be reversible.
- Two years of testosterone treatment together with the lifestyle program decreased the risk of type 2 diabetes more than the lifestyle program alone did. The impact of testosterone treatment without a lifestyle program in not known.
- Testosterone treatment led to positive changes to body composition i.e. less fat, more muscle and greater hand-grip strength.
- Testosterone treatment resulted in small increases in sexual function and activity.
- The short-term safety data (over 2 years) for testosterone treatment on cardiovascular disease and prostate cancer were reassuring.
- We do not know either the durability of effect or long-term safety of testosterone for preventing type 2 diabetes.
- Testosterone treatment resulted in high haematocrit for almost one quarter of men. Risks of increased haematocrit must be considered before men are prescribed testosterone, and regularly monitored in men if they are treated.

Where was the study conducted?

The study was conducted in Adelaide (University of Adelaide and The Queen Elizabeth Hospital), Melbourne, (Melbourne University and the Austin Repatriation Hospital); Sydney (University of Sydney and Concord Hospital); Perth (University of Western Australia, Fremantle and Fiona Stanley Hospitals and the Keogh Institute), Brisbane (University of Queensland and the Princess Alexandra Hospital).