

**Background:** In men aged 50+ years at high risk of, or with newly diagnosed type 2 diabetes (T2D) testosterone (T) treatment reduced the risk T2D at 2-years by 40% beyond lifestyle change alone (Wittert et al Lancet Diabetes and Endocrinol 2021). **Aim:** Determine whether changes in total fat mass (kg), abdominal fat mass (%), lean mass (kg), and non-dominant handgrip (kg) mediate the effect of T treatment on glycaemia. **Hypothesis:** The effect of testosterone on glycaemia is mediated by changes in fat and functional skeletal muscle mass **Methods:** A randomised placebo-controlled trial enrolled 1007 men, 50–74 years, waist circumference (WC)  $\geq$  95cm, serum total T  $\leq$  14nmol/L (chemiluminescent RIA) and either impaired glucose tolerance or newly diagnosed T2D on an oral glucose tolerance test (OGTT). Participants were enrolled in a lifestyle program (WW) and randomised 1: 1 to 3 monthly IM injections of 1gm testosterone undecanoate or placebo. The primary outcome of T2D at 2-yrs (OGTT $\geq$ 11.1mmol/L) was assessed by binomial regression with a log-link function. Mediators of interest were fat mass % abdominal fat, lean mass (dual x-ray absorptiometry) and non-dominant hand-grip strength (hand-grip dynamometry). Mediation was determined by including the baseline and change at two years for each of the 4 factors of interest in the model. Significance:  $P < 0.05$ . There was no imputation for missing data. **Results:** There were complete data for 775 men (77.5%). For the outcome of T2D at 2-yrs, the unadjusted RR for treatment was 0.59 (95% CI: 0.43–0.80), which became 0.66 (95% CI: 0.51–0.87) after adjustment for baseline values of the proposed treatment mediators and OGTT. After inclusion of changes in body composition (total fat mass, abdominal fat percentage, lean mass) and grip strength, the effect of treatment was attenuated, RR 0.85 (95% CI: 0.61–1.19). The individual effects for changes in fat mass, abdominal fat, lean mass, and grip strength were 0.88 (0.64–1.19), 0.79 (0.59–1.07), 0.52 (0.38–0.71) and 0.64 (0.48–0.86) respectively. **Conclusion:** After including change in fat mass the RR increased and the effect of T was no longer significant indicating the decrease in fat mass mediates the effect of T. This did not however, entirely explain the effect of T to decrease risk for T2D. Although lean mass and hand grip strength increased, neither mediated the effect of testosterone on T2D.

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### *Prevention of Type 2 Diabetes by Testosterone in the T4DM Trial: Analysis of Effect Mediation*

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