EDITORIAL OPEN ACCESS

Hypogonadism in men with diabetes: Should testosterone replacement therapy be based on evidence based testosterone levels and lifetime risk reduction?

Sudarshan Ramachandran, Geoffrey I. Hackett, Richard C. Strange

While data from numerous randomized controlled trials have allowed the establishing of evidence based guidelines for statin use in the prevention of cardiovascular disease (CVD)[1], there remains considerable debate as to which patients should be treated. Indeed, as far back as 2000, we questioned whether lipid lowering treatment guidelines should be based on absolute risk reduction (ARR) or relative risk reduction (RRR) [2]. Until recently, treatment strategies have focused on high absolute risk thresholds in order to obtain maximal ARR as opposed to RRR. However, evidence for considering lifetime risk reduction as opposed to ARR is mounting and this has been highlighted in the latest Joint British Societies 3 recommendations for prevention of CVD [1].

We recently showed that hypogonadism (HG), defined as sexual symptoms and total testosterone < 12.0 nmol/l (346.1 ng/dl), in men with type 2 diabetes (T2DM) is associated with higher all-cause mortality [3].

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Importantly, testosterone replacement therapy (TRT) in such men abolishes this increased risk, independently of improvements in metabolic parameters and, statin and phosphodiesterase 5-inhibitor treatments. We further characterized this benefit by showing that TRT alters the association between age and mortality [4].

Figure 1 demonstrates the discrepancy between ARR and lifetime risk reduction following a mean TRT of 3.7 years duration [3, 4]. This figure shows the ARR, RRR and lifetime risk reduction that could be expected by treating these men at 55 and 65 years of age. Whilst the ARR is greater in the treated 65-year-old (8.1%) than in the 55-year-old (3.6%) man, lifetime risk reduction is significantly greater when TRT is initiated at 55 years of age. Similar to lipid lowering, the RRR associated with TRT is similar at both ages selected. Based on these results we make a case for earlier treatment and also for not using absolute risk thresholds in men with diabetes and HG. We acknowledge that we have not taken cost effectiveness into account as the underlying risk of mortality in men with HG and T2DM is very high, as evident in Figure 1.

Laboratory testosterone measurement is recommended in men with HG (including T2DM) and

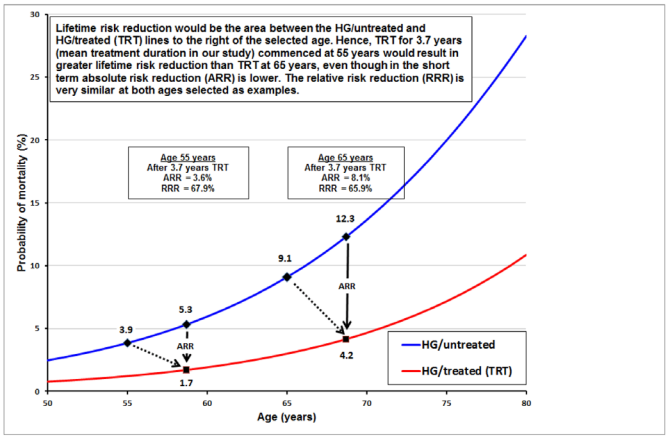

Figure 1: A comparison of absolute risk reduction, relative risk reduction and lifetime risk reduction in men with hypogonadism (sexual symptoms and total testosterone < 12 nmol/l (346.1 ng/dl) and type 2 diabetes, treated and untreated with testosterone.

obesity [5, 6]. The threshold testosterone level requiring TRT should also be addressed. Quoted laboratory reference ranges (Mayo Medical Laboratories: total testosterone reference range 240–950 ng/ml (8.3–33.0 nmol/l); http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83686 in adult men) are often inconsistent with the clinical presentation [7]. Thus, evidence exists indicating that treatment thresholds should be 8.7 nmol/l (250.9 ng/dl) in non-diabetic [8] and 10.4 nmol/l (300.0 ng/dl) in diabetic men [9], unless contraindicated. It is important that laboratories keep up with research developments and move away from reference ranges based on the population distribution of the analyte to levels more likely to be clinically useful. Hence, interaction between clinicians and laboratory personnel is essential. To further illustrate this point we turn again to cholesterol concentrations and statin treatment, a field mature in evidence based medicine. Statin treatment is tailored to the underlying risk of the individual and not a laboratory reference range. The low density lipoprotein cholesterol reference range has been replaced by a target value of 1.8 mmol/l (70 mg/dl) in secondary prevention based on evidence [10]. We conclude that it is also important that we observe developments in parallel clinical conditions and apply them when appropriate to our own field.

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Keywords: Hypogonadism, Mortality risk reduction, Testosterone, Testosterone replacement therapy, Type 2 diabetes

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Author Contributions

Sudarshan Ramachandran – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Geoffrey I. Hackett – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Richard C. Strange – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Professor Geoffrey I Hackett has received honoraria for serving as a speaker for Bayer plc who provided the study grant. Professor Sudarshan Ramachandran has received honoraria for serving as a speaker for Besins Health Care Ltd. Professor Geoffrey I Hackett has spoken at various national and international meetings on testosterone and PDE5I treatments in men and sits on the committee of the European Society for Sexual Medicine.

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