Indications for testosterone therapy in men

Mathis Grossmann[a,b]

Purpose of review
Testosterone replacement therapy for men with organic hypogonadism due to medical disease of the hypothalamic-pituitary-testicular (HPT) axis is uncontroversial. In these men, testosterone replacement replaces the deficient hormone and relieves the signs and symptoms of androgen deficiency. In contrast, the role of testosterone treatment in middle-aged or older men who have clinical features consistent with androgen deficiency accompanied by reductions in serum testosterone but lack identifiable HPT axis disease, a scenario sometimes referred to as 'functional' or 'late onset' hypogonadism, has been uncertain.

Recent findings
Three large randomized controlled clinical trials, discussed in this review, have reported new data regarding short-term to medium-term benefits and risks of testosterone therapy in such middle-aged and older men, including effects on sexual function, vitality, cognition and mood, glucose metabolism, physical function, hematologic parameters, as well as bone, cardiovascular and prostate health.

Summary
The findings of these trials allow for a more nuanced, personalized approach to testosterone therapy in such men. However, long-term benefits and risk of testosterone therapy (beyond 3–4 years) remain unknown.

Keywords
androgen deficiency, hypogonadism, testosterone, testosterone therapy

INTRODUCTION

Testosterone replacement in men with classical hypogonadism due to identifiable hypothalamic-pituitary-testicular (HPT) disease is uncontroversial. By contrast, the role of testosterone therapy in older men with low serum testosterone and with symptoms (e.g. low libido or energy), signs (e.g. reduced muscle bulk, adiposity) or end-organ deficits (e.g. anaemia, osteoporosis) consistent with hypogonadism in the absence of identifiable HPT axis disease, a scenario referred to as 'functional' or 'late onset hypogonadism', has been less certain. This was primarily due to the absence of large randomised controlled trials that firstly, identify clinical characteristics of men who might benefit from testosterone therapy, secondly define specific benefits of testosterone treatment, and thirdly clarify potential risks. In this narrative review, I will first summarize the evidence for testosterone replacement in men with classical hypogonadism. Next, I will discuss the results of three recent pivotal large clinical trials of testosterone therapy in older men with age-related reductions in testosterone and their clinical implications. I will end this review with applying the effects of testosterone therapy reported in these RCTs to clinical practise and highlight knowledge gaps for future research.

While the focus of this review is on testosterone therapy, it should be noted that in older men without classical hypogonadism, many of the clinical features of androgen deficiency are nonspecific and might potentially modified by comorbidities (e.g. depression, obesity, obstructive sleep apnoea). Indeed, there is evidence discussed elsewhere [1,2▪] that treatment of such comorbidities might improve androgen deficiency-like symptoms and lead to increases in serum testosterone. Hence, testosterone therapy, if considered, should only be provided in the context of an individualized holistic approach geared towards optimizing the overall health of such men.

[a]Department of Medicine (Austin Health), The University of Melbourne, Melbourne and [b]Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia

Correspondence to Dr Mathis Grossmann, Austin Health, Studley Road, Heidelberg, VIC 3084, Australia. Tel +613 9496 5489; fax +613 9496 2980;. e-mail: mathisg@unimelb.edu.au

Curr Opin Endocrinol Diabetes Obes 2024, 31:000–000
DOI:10.1097/MED.0000000000000890

KEY POINTS

- Testosterone replacement therapy for men with classical hypogonadism due to organic hypothalamic-pituitary-testicular (HPT) axis disease aims to restores physiologic concentrations of serum testosterone and relieves the symptoms and signs of androgen deficiency. Evidence for benefit stems from sound physiologic principles, open label clinical trials of testosterone replacement, and from experimental clinical studies supressing endogenous serum testosterone concentrations with graded exogenous testosterone add-back.
- In older men with hypogonadal symptoms and lowered serum testosterone, but who lack identifiable HPT axis therapy, recent clinical trials have provided important information regarding short to medium-term benefits and risks of testosterone therapy, allowing personalized discussion about testosterone treatment in such men.
- Before testosterone treatment can be routinely recommended to such older men, longer term testosterone trials to inform about long-term benefits and risks of testosterone therapy are still required.
- A lowered serum testosterone can be a marker of ill health, and a holistic approach, including implementation of healthy lifestyle measures and assiduous care of comorbidities should be part and parcel of the clinical approach, irrespective of whether testosterone treatment is considered or not.

BENEFITS AND RISKS OF TESTOSTERONE REPLACEMENT IN MEN WITH CLASSICAL HYPOGONADISM

There is general consensus that men with classical hypogonadism due to identifiable HPT axis disease (e.g. anorchia, pituitary mass lesion) require testosterone replacement to relieve the clinical features of androgen deficiency. In these men, testosterone treatment is considered replacement therapy, that is, the deficient hormone is replaced in order to restore physiologic concentrations of serum testosterone. This concept is based firstly on sound physiologic principles (i.e. restoring physiology akin to hormone replacement in other endocrine deficiency syndromes, e.g., thyroxine replacement in hypothyroidism or glucocorticoid replacement in adrenal insufficiency), secondly on decades of clinical experience, and thirdly on results of clinical studies. Due to ethical constraints, men with classical hypogonadism have not been subjected to placebo-controlled, randomized clinical trials. Instead, the published evidence for benefit for testosterone replacement stems primarily from uncontrolled open-label clinical trials and from short to medium-term experimental studies combining induced hypogonadism with testosterone add-back.

In uncontrolled open-label trials of men with classical hypogonadism, testosterone replacement has been reported to increase self-reported sense of energy [3], sexual function [3,4] and mood [4], to increase lean mass [3–6], muscle size and strength [4,6], to reduce fat mass [3–5], to increase haematocrit [3,4], to reduce bone turnover markers [5,7], to increase bone density [5,7,8] trabecular architecture [5,9] and cortical bone density [10] and to increase prostate volume [3] and PSA [4]. Key studies are summarized in Table 1. Adverse effects of testosterone replacement include polycythaemia, increase in PSA (expected as prostate is an androgen-dependent organ and untreated frankly hypogonadal men may have a lower than normal PSA), oily skin, acne, and importantly impaired fertility. This is because exogenous testosterone reduces follicle-stimulating hormone, which is important for spermatogenesis. In addition, exogenous testosterone does not achieve sufficiently high intratesticular testosterone necessary for spermatogenesis. Less common adverse effects of testosterone replacement include reduced testicular volume (due to reduced spermatogenesis), gynaecomastia and male pattern baldness.

In addition to evidence from open-label trials of testosterone replacement, evidence for benefit for testosterone replacement also stems from experimental studies combining gonadotrophin-releasing hormone (GnRH) agonists to suppress endogenous serum testosterone with graded testosterone add-back. These studies have shown clear dose-response relationships between serum testosterone and clinical features of androgen deficiency in younger and older men. For example, in a study of 198 healthy young men aged 20–50 years given a GnRH agonist to supress endogenous gonadal steroids for 16 weeks, in those receiving sub-physiologic testosterone add-back, sexual desire declined, body fat increased, lean muscle, thigh-muscle area and leg-press strength decreased, bone density decreased, and bone turnover markers increased [11]. Likewise, in a similarly designed study of 177 older men aged 60–80 years receiving a GnRH agonist for 16 weeks, those receiving sub-physiologic testosterone add-back experienced reduced sexual desire and erectile dysfunction, increases in body fat, and increases in bone turnover markers [12]. These experimental studies illustrate the importance of maintaining physiologic serum testosterone concentrations to prevent clinical features of androgen deficiency and indirectly support the concept using testosterone replacement to restore physiology and to prevent clinical features of androgen deficiency. Of note, these studies [11] have also shown that some of the clinical features of male hypogonadism are not directly due to testosterone deficiency but rather

Table 1. Effects of testosterone replacement in men with classical hypogonadism due to organic pathology of the hypothalamic-pituitary-testicular axis

Domain	Testosterone effects	Remarks
Sexual function	Large improvements in self-reported sexual function with increases from 24 to 66% (using a scale from 0 to 100%) with significant increases in all aspects of sexual function (including desire/motivation, performance, enjoyment, erection satisfaction, % erection).	These effects occur principally within the first 1–3 months of treatment.
Vitality and mood	Marked improvements in self-reported sense of energy with increases from 49 to 66% (using a scale from 0 to 100%) with significant increases in positive moods and significant decreases in negative moods.	These effects occur principally within the first 3 months of treatment.
Fat mass	Decreases in fat mass (by 0.9 kg) and decreases in percentage body fat (by 14%).	These effects are evident within the first 3 months of treatment.
Muscle strength and function	Increases in lean mass (by 2.7–3.1 kg); increases in triceps arm and quadriceps leg muscle; increases in muscle strength (11–13 kg in leg press and 1.5–3.0 kg in arm/chest press strength); increases in muscle strength as assessed by repetition maximum weightlifting exercises.	Increases in lean mass occurred principally within the first 6 months of treatment.
Bone health	Increases in lumbar spine bone mineral density of 2.2–7.7% and of femoral bone density of 1.1–4.0%; increases in spine trabecular bone mineral density and of cortical bone density of ~5.0%. Improvements in bone microarchitecture assessed by MRI. Decreases in bone resorption markets (urine deoxypyridinoline and urine N-telopeptide/creatinine ratio) and increases in bone formation markers (osteocalcin, procollagen and bone-specific alkaline phosphatase.	Increases in bone mineral density reached maximum at 24 months of treatment.
Haematologic parameters	Marked increase in haematocrit from 0.38 (mildly anaemic) to 0.43	Increase occurred within 3 months of treatment with haematocrit stable thereafter.
Prostate health	Prostate volume increased markedly from subnormal (12 ml) to normal (22 ml), and significant increases in PSA by ~30%	These effects occur principally within the first 3–6 months of treatment. PSA concentrations above the upper limit of the normal range were infrequent (<3%).

The data are from References [3–10]; effects on glucose metabolism and cardiovascular health were not reported in these studies recruiting otherwise healthy young to middle-aged men presumed to be at a low risk of dysglycaemia and cardiovascular disease.

due to the concomitant oestradiol deficiency. These findings support the use of testosterone replacement as the treatment of choice in classical hypogonadism as testosterone is aromatised to estradiol and hence not only normalizes serum testosterone but also estradiol. Finally, testosterone also provides dihydrotestosterone (DHT), which has important androgenic actions in the prostate and the hair follicle. Therefore, testosterone is also sometimes referred to as 'three hormones in one' [13].

BENEFITS AND RISKS OF TESTOSTERONE THERAPY IN OLDER MEN WITH AGE-RELATED REDUCTIONS IN SERUM TESTOSTERONE

In this section, I will review the clinical evidence regarding benefits and risk of testosterone therapy in older men with age-related declines in their serum testosterone. I will focus on three recent pivotal trials, the T-Trials, T4DM and TRAVERSE. Men with classical hypogonadism due to recognizable organic HPT axis disease were generally excluded from these trials.

Sexual function

Sexual dysfunction is one of the most common reasons why men seek medical advice about testosterone therapy. Moreover, among hypogonadal symptoms, sexual symptoms (poor morning erection, low sexual desire, erectile dysfunction) were most closely associated with low serum testosterone in observational studies [14]. In the T-Trials, testosterone therapy increased sexual activity especially during the first 9 months of the study [15]. Testosterone therapy also modestly improved 10 of 12 measures of sexual activity (including sexual desire and overall sexual satisfaction) [16]. Men in the testosterone group were more likely than those in

the placebo group to report that their sexual desire had improved, which suggests that this effect was of clinical relevance. With respect to erectile function, testosterone treatment was associated with an increase of 2.64 in the erectile function domain of the International Index of Erectile Function [IIEF] score. This was below the clinically significant threshold of 4.0 derived from studies of phosphodiesterase inhibitors for erectile dysfunction, although in men with mild erectile function, an increase in the IIEF of more than 2 may be clinically relevant [17]. Likewise in T4DM, testosterone therapy improved sexual desire (assessed by the IIEF sexual desire subscore) by more than 2 points, an effect size considered to be clinically meaningful [18]. Erectile function improved by 2.1 (using the IIEF score) in T4DM [18], similarly to the improvement seen in the T-Trials [15]. In TRAVERSE which recruited men at high risk of or with preexisting cardiovascular disease, testosterone therapy modestly improved sexual desire, but had no significant effect on erectile function [19▪]. In summary, testosterone appears to have a clinically meaningful effects on sexual desire and modestly improves most aspects of sexual function. Effects on erectile function are more moderate and clinically relevant mostly for men with mild erectile dysfunction. Men with significant cardiovascular disease might have erectile dysfunction refractory to testosterone.

Vitality, mood and cognitive function

In the T-Trials, testosterone therapy had no significant effects on vitality or mood in the primary outcome analysis. However, men with baseline low vitality and mood had a significantly improved SF-36 vitality score, and improved mood scores in the PANAS affect and PHQ9 depression questionnaires [15]. In secondary analyses which included all T-Trials participants, men randomized to testosterone had small benefits in vitality and mood; they also were more likely to report an increase in energy *vs* placebo [15]. In T4DM, testosterone therapy had no effect on measures of health-related quality of life (using SF-36), nor on a variety of psychosocial health parameters, including self-reported sense of mastery, sense of coherence or sleep quality; there was no effect on depressive symptoms [18]. In TRAVERSE, in men with modest depressive symptoms ($n = 2643$) and in all randomized participants ($n = 5204$), testosterone therapy was associated with modest but significant improvements in mood and energy, but not in sleep quality; testosterone did not improve mood in the subgroup of men with more severe depression [20▪]. One of the potential reasons for the discrepant findings in T-Trials/TRAVERSE reporting small benefits on mood/vitality vs. T4DM reporting no benefits might be that T4DM had a higher serum testosterone cut-off as an entry criterion. With respect to cognition, there was no effect of testosterone treatment in the T-Trials Cognitive Function sub-study [21], nor in TRAVERSE [20▪]. Overall, in men with serum testosterone concentrations ($\leq$10.4 nmol/l), testosterone treatment is associated with small but significant effects on vitality, and modest improvements in mood in men with mild depressive symptoms but has no effect on cognitive function.

Glucose metabolism

In a secondary analysis of the T-Trials, 37% of whom had baseline T2D, testosterone modestly but significantly decreased fasting insulin and homeostatic model assessment–insulin resistance [22]. In T4DM, testosterone therapy on the background on a lifestyle programme reduced the absolute incidence of T2D by 40%, based on an oral glucose tolerance test, but had no effect on HbA1c [18]. Given testosterone affects haematocrit (see below) HbA1c may not be a valid indicator to assess glycaemic effects of testosterone therapy. In T4DM, the glycaemic benefit of testosterone therapy was predominantly mediated by reductions in fat mass [23]. In contrast to T4DM, in the TRAVERSE Diabetes sub-study, testosterone treatment did not affect glycaemic outcomes (fasting glucose, HbA1c) [24▪]; differences in testosterone formulation, in glycaemic outcome measures and/or use of a lifestyle programme in T4DM but not in TRAVERSE might explain these differences. In summary, testosterone therapy might have modest benefits on glycaemic parameters, and may prevent T2D in high-risk men, at least in the context of a lifestyle programme, but not all of the data are consistent.

Muscle and physical function

In the primary analysis of the T-Trials [15], testosterone therapy did not improve walking distance or gait speed in men who were frail (defined as self-reported difficulty with walking or climbing stairs and distance walked $<$ 445 m in a 6-min walking test). In secondary analyses including all men enrolled in the T-Trials, self-reported walking and the 6-min walk test improved. However, testosterone therapy had no effect on incident falls [25]. In T4DM, testosterone therapy significantly increased grip strength [18]. To date, no data on muscle strength, power or physical function have been published from TRAVERSE. Overall, testosterone therapy might improve muscle strength and some aspects of physical function.

Bone health

In the T-Trials Bone Study ($n = 211$), testosterone therapy for 12 months increased volumetric BMD at the trabecular spine and increased estimated spine trabecular bone strength [26]. In the T4DM bone sub-study (T4Bone; $n = 600$), testosterone therapy increased areal BMD of the lumbar spine, total hip and femoral neck. In a subset of 177 men significantly increased total and cortical volumetric BMD measured by high-resolution peripheral quantitative CT, an independent determinant of fracture risk. Surprisingly however, a recent analysis of the TRAVERSE cohort reported that testosterone therapy was associated with an increased risk of clinical fractures [27▪▪]. Excess fractures occurred early, suggesting that the increased risk might be due to behavioural effects of testosterone therapy, a hypothesis supported by the fact that fractures typically associated with trauma (ankle and rib) accounted for the majority of the excess fractures [28]. Of note, men in all these studies were not selected based on low bone density or osteoporosis. The effects of testosterone therapy on bone architecture, bone strength or incident fracture have not been systematically evaluated in men with low serum testosterone concentrations who are at high fracture risk.

Haematologic parameters

In the T-Trials, among men with baseline anaemia (16% of participants), anaemia resolved in 58% of testosterone-treated men, compared to 22% placebo-treated men [29]. In TRAVERSE, 15.6% of participants had baseline anaemia, and anaemia resolved in a greater proportion of testosterone-treated than placebo-treated men, 41.0 vs. 27.5% after 6 months of treatment; increased haemoglobin was associated with increased energy [30].

Conversely, erythrocytosis is one of the most common adverse effects of testosterone therapy. In the T-Trials, testosterone therapy resulted in erythrocytosis in 1.5% of participants without baseline anaemia [29]. In TRAVERSE, only 0.15% men in the testosterone group discontinued the study because of persistent erythrocytosis [30]. In T4DM, 22% the testosterone developed a haematocrit more than 0.54, although only 0.5% discontinued treatment because of a persistent a haematocrit more than 0.54 [18]. The higher incidence of erythrocytosis in T4DM vs. the T-Trials and TRAVERSE is likely because T4DM used intramuscular testosterone therapy, while the T-Trials and TRAVERSE used topical testosterone gel. Overall, while testosterone might resolve unexplained anaemia, erythrocytosis can be an adverse effect, with however few men having to stop treatment.

Cardiovascular health

In the T-Trials atheroma sub-study ($n = 73$ testosterone and 65 placebo-treated men), testosterone therapy was associated with greater increases in noncalcified and total coronary atheroma plaque volume. However, there was a baseline difference in plaque volumes between the groups which might confound the results [31]. In the T-Trials [15], and in T4DM [18], rates of major adverse cardiovascular events (MACE) were low and similar between men randomized to testosterone or placebo therapy. However, both trials were underpowered to detect a difference.

TRAVERSE was, to date, the only study designed and powered assess the effects of testosterone therapy on MACE [32▪▪]. There was no difference between testosterone and placebo-treated men in the incidence of the primary outcome of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke (7.0 and 7.3% in the testosterone and placebo groups, respectively, mean treatment duration = 22 months; $P < 0.001$ for noninferiority). Moreover, there was no difference in overall mortality (5.5 vs. 5.7% in the testosterone and placebo group). However, there was an excess of nonfatal arrhythmia (primarily atrial fibrillation) warranting intervention in the testosterone group (5.2 vs. 3.3% in placebo; $P = 0.001$) [32▪▪].

With respect to venous thromboembolism (VTE), VTE rates were low, 0.5 and 0.8% in the testosterone and placebo groups, in the T-Trials [32▪▪], and 2 vs. 0 in T4DM [18]. In TRAVERSE, there was also a similar incidence of VTE in both groups, 1.7 vs. 1.2% in the testosterone and placebo groups; hazard ratio 1.46; confidence interval (CI) 0.92–2.32 [32▪▪]. There was an apparent excess of pulmonary embolism, 24 events in testosterone-treated men vs. 12 in placebo-treated men, but the numbers were too small for a formal statistical analysis. Overall, except for a possible increase in atrial fibrillation and pulmonary embolism, the trials suggest that, in carefully selected men, testosterone therapy at least in the short to medium term is unlikely to confer significant cardiovascular risks (or benefits).

Prostate health

Given that the prostate is an androgen-dependent organ, it is not surprising that in the T-Trials [33], more men in the testosterone group than in the placebo group (1.9 vs. 0.3%) had serum PSA at least 4.0 ng/ml [15]. In T4DM [18], 23% of testosterone and 19% of placebo-treated men had an increase of more than 0.75 ng/ml in PSA. In TRAVERSE, the increase in PSA from baseline was greater in testosterone, compared to placebo-treated men (0.20 ± 0.61 vs. 0.08 ± 0.90 ng/ml, $P < 0.001$) [32▪▪]. None

of the trials was powered for prostate cancer, and men at high risk of prostate cancer (baseline PSA >4 ng/ml, history of prostate cancer abnormal digital rectal exam) were excluded in all trials.

Lower urinary tract symptoms (LUTS) did not differ significantly between testosterone and placebo groups all three trials, but men with severe benign prostatic hyperplasia (BPH) (baseline International Prostate Symptom Score [IPSS] >19) were excluded. In the T-Trials, IPSS scores did not differ between the groups. In T4DM, incident BPH with LUTS was reported in eight testosterone-treated vs. three placebo-treated men. There was no difference in incident BPH with LUTS in in TRAVERSE (45 vs. 46; $P = 0.92$, but there was a trend toward increased incident urinary retention (50 vs. 34 testosterone and placebo-treated men, respectively ($P = 0.08$)). In TRAVERSE, acute kidney injury was more common in the testosterone group (60 vs. 40 men, $P = 0.04$), an unexpected finding that might have been due to chance [18]. Overall, in low-risk men receiving short to medium-term therapy, testosterone therapy does not appear to increase the risk of de-novo prostate cancer or to promote BPH with LUTS.

CONCLUSION: CLINICAL SYNTHESIS AND OUTLOOK

In men with classical hypogonadism due to organic HPT axis disease, testosterone replacement intended to restore physiologic concentrations of testosterone (and its downstream products estradiol and

Table 2. Testosterone treatment effects in men with age-related reductions in serum testosterone

Domain	Testosterone effects	Remarks
Sexual function	Clinically relevant effects on sexual desire, modest improvements in most aspects in sexual function; effects on erectile function might be clinically meaningful only in men with mild erectile function; erectile function in men with significant cardiovascular disease might not respond to testosterone.	Men with severe erectile dysfunction and/or significant cardiovascular disease should receive a phosphodiesterase-5 inhibitor (PDE-5i); whether testosterone and PDE-5i have synergistic effects requires further study.
Vitality and mood	Small improvements vitality and depressive symptoms.	Men with severe depressive symptoms do not respond to testosterone and need effective targeted therapy (e.g. an antidepressant).
Glucose metabolism	Modest improvements in insulin sensitivity. In combination with a lifestyle programme, testosterone reduces T2D risk, although not all data are consistent.	Comparisons to metformin or newer antidiabetic agents with proven cardiorenal benefits, e.g., Glucagon-like peptide-1 receptor agonists (GLP1-RA) or sodium-glucose cotransporter-2 (SGLT2) inhibitors are lacking
Muscle strength and function	Modest improvements in some aspects of physical function without effect on falls risk.	Few studies have assessed whether effects of testosterone treatment can be augmented by targeted exercise programmes.
Bone Health	Improvements in improves bone structure, bone density and volumetry, and bone strength. Surprisingly testosterone may be associated with an increase in (traumatic) fractures, although confirmation of these findings is needed.	Men at high risk of fracture should receive osteoporotic drug therapy with proven antifracture benefits irrespective of whether they are being considered for testosterone treatment or not.
Haematologic parameters	On the one hand, improvements in anaemia, and on the other hand increased risk of erythrocytosis (although few men have to stop treatment due to erythrocytosis, especially with topical testosterone gel).	While improvements in anaemia have been associated with improvements in self-reported energy, further study is needed whether improvements in anaemia lead to improved health outcomes.
Cardiovascular health	Testosterone treatment, in the short to medium term does not increase the risk of major adverse cardiovascular vents, but might increase the risk of arrythmias (e.g. atrial fibrillation) and venous thromboembolism (e.g. pulmonary embolism), although this requires further study.	Cardiovascular effects of long-term testosterone treatment (beyond 3–4 years) remain unknown.
Prostate health	Testosterone treatment increases PSA, but there is no evidence that, in low-risk men and with short to medium-term treatment, testosterone treatment increases risk of prostate cancer, or that, in low-risk men, it worsens benign prostate hypertrophy and or lower urinary tract symptoms.	Prostate effects of longer-term testosterone treatment (beyond 3–4 years) remain unknown, and there has been no testosterone trial with prostate cancer as primary endpoint.

The data are from the T-Trials, T4DM and TRAVERSE.

DHT) relieves the clinical features of androgen deficiency, although it can impair fertility. Although evidence from placebo-controlled, randomized clinical trials is (due to ethical reasons) lacking, testosterone replacement is generally accepted as the treatment of choice for men with classical hypogonadism. This notion is supported by physiologic principles, by parallels to other endocrine deficiency states, by experimental clinical trials combining suppression of endogenous gonadal steroid production with testosterone add-back, and by the marked benefits of testosterone replacement reported in open-label clinical trials. The benefits of testosterone replacement in men with classical hypogonadism are summarized in Table 1.

Consistent with the widespread expression of the androgen receptor, the T-Trials, T4DM and TRAVERSE recruiting men with age-related reductions in serum testosterone have shown that testosterone treatment has pleiotropic actions in many tissues and organ systems. These effects are summarized in Table 2. It is evident that for some deficits in isolated domains, there is better evidence for targeted therapies (e.g. phosphodiesterase 5-inhibitor treatment for severe erectile dysfunction due to neurovascular disease, osteoporotic drug therapy with proven antifracture benefit for men at high risk of fracture). Moreover, in the absence of longer-term, larger studies that inform about long term benefits and risks of testosterone therapy, it is difficult to formulate precise indications for testosterone therapy. Decisions about testosterone therapy not only require balancing the benefits and potential risks, but also involve cost and potential inconvenience of testosterone therapy (e.g. daily gel application or regular injections, periodic blood test to measure serum testosterone, haematocrit and in some men, PSA). It also has been postulated that prolonged testosterone treatment might create androgen dependence in some men [34], although this is less of a problem with shorter (6–12 month) courses of therapy [2▪].

Nevertheless, the data from the T-Trials, T4DM and TRAVERSE allow first steps towards applying 'precision medicine' to testosterone therapy for middle-aged and older men with clinical and biochemical features of possible hypogonadism but no identifiable HPT axis therapy. The results from these RCTs enable a more nuanced approach to counselling such men about the short to medium term benefits (up to 3–4 years), and risks of testosterone treatment. It is intuitive that the more testosterone-responsive domains a patient has disease burden in (Table 2), the more attractive testosterone treatment would be for this individual. Thus, an older man with confirmed low serum testosterone measured by a reliable assay who has low libido, mildly reduced erectile dysfunction, mildly reduced mood and energy and otherwise unexplained anaemia and who is at high risk of diabetes could be counselled that testosterone treatment might improve his symptoms, increase his haemoglobin and, in conjunction with a lifestyle programme, could reduce his risk of developing type 2 diabetes. Risks of cardiovascular disease and adverse effects on prostate health in the short to medium term would be expected to be low, provided he is not at high risk for prostate cancer and does not have significant BPH. However, there might be small excess risk of arrythmias (especially atrial fibrillation) and of VTE (especially pulmonary embolism). The patient should also be advised about the lack of data on long term (>3–4 years) effects of testosterone treatment, and of the possible risk of HPT axis suppression with prolonged treatment. Overall, before testosterone treatment can routinely be recommended to older men with clinical and biochemical features consistent with hypogonadism, but who do not have identifiable HPT disease, larger longer term trials of testosterone therapy to better define health benefits and risks are still required. In the interim, the clinical consultation with a patient concerned about his low testosterone offers an opportunity to provide holistic patient centred care, with the emphasis on implementing healthy lifestyle measures and assiduous care of comorbidities.

Acknowledgements

None.

Financial support and sponsorship

M.G. has received research funding from Bayer, Otsuka and speaker's honoraria from Besins Healthcare and Novartis.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. J Clin Endocrinol Metab 2017; 102:1067–1075.
2. ▪ Grossmann M, Jayasena CN, Anawalt BD. Approach to the patient: the evaluation and management of Men ≥ 50 years with low serum testosterone concentration. J Clin Endocrinol Metab 2023; 108:e871–e884.

A practical, clinical case-based approach to clinical assessment and treatment of older men with presenting with a low serum testosterone.

3. Snyder PJ, Peachey H, Berlin JA, *et al.* Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000; 85:2670–2677.

4. Wang C, Swerdloff RS, Iranmanesh A, *et al.* Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 2000; 85:2839–2853.
5. Katznelson L, Finkelstein JS, Schoenfeld DA, *et al.* Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 1996; 81:4358–4365.
6. Bhasin S, Storer TW, Berman N, *et al.* Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 1997; 82:407–413.
7. Wang C, Swerdloff RS, Iranmanesh A, *et al.* Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. Clin Endocrinol (Oxf) 2001; 54:739–750.
8. Aminorroaya A, Kelleher S, Conway AJ, *et al.* Adequacy of androgen replacement influences bone density response to testosterone in androgen-deficient men. Eur J Endocrinol 2005; 152:881–886.
9. Benito M, Vasilic B, Wehrli FW, *et al.* Effect of testosterone replacement on trabecular architecture in hypogonadal men. J Bone Miner Res 2005; 20:1785–1791.
10. Finkelstein JS, Klibanski A, Neer RM, *et al.* Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab 1989; 69:776–783.
11. Finkelstein JS, Lee H, Burnett-Bowie SA, *et al.* Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013; 369:1011–1022.
12. Finkelstein JS, Lee H, Burnett-Bowie SM, *et al.* Dose-response relationships between gonadal steroids and bone, body composition, and sexual function in aging men. J Clin Endocrinol Metab 2020; 105:2779–2788.
13. Yeap BB, Grossmann M, McLachlan RI, *et al.* Endocrine Society of Australia position statement on male hypogonadism (part 2): treatment and therapeutic considerations. Med J Aust 2016; 205:228–231.
14. Wu FC, Tajar A, Beynon JM, *et al.* Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010; 363:123–135.
15. Snyder PJ, Bhasin S, Cunningham GR, *et al.* Effects of testosterone treatment in older men. N Engl J Med 2016; 374:611–624.
16. Cunningham GR, Stephens-Shields AJ, Rosen RC, *et al.* Testosterone treatment and sexual function in older men with low testosterone levels. J Clin Endocrinol Metab 2016; 101:3096–3104.
17. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 2011; 60:1010–1016.
18. Wittert G, Bracken K, Robledo KP, *et al.* Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol 2021; 9:32–45.
19. ▪ Pencina KM, Travison TG, Cunningham GR, *et al.* Effect of testosterone replacement therapy on sexual function and hypogonadal symptoms in men with hypogonadism. J Clin Endocrinol Metab 2024; 109:569–580.

Informative secondary analysis of TRAVERSE, the largest testosterone trial to date, reporting that testosterone treatment, compared to placebo improved hypogonadal symptoms and sexual desire, but not erectile function.

20. ▪ Bhasin S, Seidman S, Travison TG, *et al.* Depressive syndromes in men with hypogonadism in the TRAVERSE trial: response to testosterone replacement therapy. J Clin Endocrinol Metab 2024; 109:1814–1826.

Secondary analysis from TRAVERSE, reporting that testosterone modestly but significantly improved in mood and energy but not cognition or sleep quality, compared to placebo.

21. Resnick SM, Matsumoto AM, Stephens-Shields AJ, *et al.* Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017; 317:717–727.
22. Mohler ER 3rd, Ellenberg SS, Lewis CE, *et al.* The effect of testosterone on cardiovascular biomarkers in the testosterone trials. J Clin Endocrinol Metab 2018; 103:681–688.
23. Robledo KP, Marschner IC, Handelsman DJ, *et al.* Mediation analysis of the testosterone treatment effect to prevent type 2 diabetes in the Testosterone for Prevention of Type 2 Diabetes Mellitus trial. Eur J Endocrinol 2023; 188:613–620.
24. ▪ Bhasin S, Lincoff AM, Nissen SE, *et al.* Effect of testosterone on progression from prediabetes to diabetes in men with hypogonadism: a substudy of the TRAVERSE Randomized Clinical Trial. JAMA Intern Med 2024; 184:353–362.

Secondary analysis from TRAVERSE reporting no benefit of testosterone therapy on diabetes incidence or remission.

25. Bhasin S, Ellenberg SS, Storer TW, *et al.* Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the Testosterone Trials. Lancet Diabetes Endocrinol 2018; 6:879–890.
26. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, *et al.* Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. JAMA Intern Med 2017; 177:471–479.
27. ▪▪ Snyder PJ, Bauer DC, Ellenberg SS, *et al.* Testosterone treatment and fractures in men with hypogonadism. N Engl J Med 2024; 390:203–211.

Secondary analysis from TRAVERSE reporting that testosterone treatment compared to placebo unexpectedly increased fracture risk.

28. Grossmann M, Anawalt BD. Breaking news - testosterone treatment and fractures in older men. N Engl J Med 2024; 390:267–268.
29. Roy CN, Snyder PJ, Stephens-Shields AJ, *et al.* Association of testosterone levels with anemia in older men: a controlled clinical trial. JAMA Intern Med 2017; 177:480–490.
30. Pencina KM, Travison TG, Artz AS, *et al.* Efficacy of testosterone replacement therapy in correcting anemia in men with hypogonadism: a randomized clinical trial. JAMA Netw Open 2023; 6:e2340030.
31. Budoff MJ, Ellenberg SS, Lewis CE, *et al.* Testosterone treatment and coronary artery plaque volume in older men with low testosterone. JAMA 2017; 317:708–716.
32. ▪▪ Lincoff AM, Bhasin S, Flevaris P, *et al.* Cardiovascular safety of testosterone-replacement therapy. N Engl J Med 2023; 389:107–117.

Largest testosterone trial to date reporting cardiovascular safety of short to medium-term testosterone treatment.

33. Cunningham GR, Ellenberg SS, Bhasin S, *et al.* Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: data from a controlled trial. J Clin Endocrinol Metab 2019; 104:6238–6246.
34. Handelsman DJ, Grossmann M, Yeap BB, *et al.* Long-term outcomes of testosterone treatment in men: a T4DM postrandomization observational follow-up study. J Clin Endocrinol Metab 2023; 109:e25–e31.