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REVIEW ARTICLE

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Testosterone and ageing: what have we learned since the Institute of Medicine report and what lies ahead?

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SUMMARY
A 2003 report by the Institute of Medicine (IOM) surveyed the literature on the benefits and risks of testosterone replacement therapy in older men and identified knowledge gaps and research needs. This review summarises some key studies published since the IOM report. The possible relationship of testosterone to risk of prostate cancer remains a concern; however, no new evidence has emerged to suggest that testosterone replacement therapy increases the risk. Recent studies have demonstrated that hypogonadism in men may be more prevalent than previously thought, is strongly associated with metabolic syndrome, and may be a risk factor for type 2 diabetes and cardiovascular disease. Clinical studies have shown that testosterone replacement therapy in hypogonadal men improves metabolic syndrome indicators and cardiovascular risk factors. Maintaining testosterone concentrations in the normal range has been shown to contribute to bone health, lean muscle mass, and physical and sexual function, suggesting that testosterone replacement therapy may help to prevent frailty in older men. Based on current knowledge, testosterone replacement therapy is unlikely to pose major health risks in patients without prostate cancer and may offer substantial health benefits. Larger, longer-term randomised studies are needed to fully establish the effects of testosterone replacement therapy.

Review Criteria
Articles were identified by searching PubMed (January 2003 to April 2006) using the following terms: hypogonadism, androgen deficiency, prostate cancer, metabolic syndrome, cardiovascular disease and sexual function. Current treatment concepts were also reviewed regarding diagnosis and treatment options for hypogonadism.

Message for the Clinic
Hypogonadism is not just a quality-of-life condition, but a condition associated with long-term negative outcomes, especially metabolic syndrome and perhaps a predictor for type 2 diabetes mellitus. Diagnosis and treatment of hypogonadism in primary care is necessary to improve frailty in ageing men and perhaps improve long-term outcomes.

Introduction

In 2002, the National Institute on Aging and the US National Cancer Institute asked the Institute of Medicine (IOM) to assess existing evidence regarding testosterone replacement in older men (1). The resulting IOM report, published in 2003, considered the following: (i) epidemiological data on normal testosterone concentrations during the lifespan; (ii) associations between testosterone concentration and morbidity/mortality; (iii) risks and benefits of testosterone replacement therapy; (iv) the potential public impact of testosterone replacement therapy in the USA and (v) ethical issues related to the conduct of clinical trials of testosterone replacement therapy (1). On the basis of its findings, the IOM panel also recommended future research directions for testosterone therapy in older men (1).

The IOM report identified critical gaps in knowledge. A clear decline was found in testosterone concentrations as men aged, but it was unclear if lower testosterone concentrations affected health outcomes in older men (1). The panel concluded that available evidence suggested potential benefits of testosterone replacement for older men, including improved body composition, strength, bone density, frailty, cognitive function, mood, sexual function and quality of life, but evidence of benefit for these health outcomes was generally mixed and inconclusive (Table 1; 1). With the exception of increased haematocrit, no definitive evidence of risk was identified, and the report called for more research into the relationship between testosterone replacement therapy and prostate health in older men (1). In the summary of its findings, the panel recommended longer-duration placebo-controlled trials with larger sample sizes to evaluate the efficacy and safety of testosterone therapy in older men (1).

This review summarises key findings that have emerged since the publication of the IOM report. This analysis focuses on the following areas in which new evidence has been used to address questions raised by the IOM report: the prevalence of hypogonadism in ageing men; prostate health; metabolic syndrome/body composition; cardiovascular health; physical function and sexual health. It is beyond the scope of this review to consider differences between available testosterone replacement therapy products,

Table 1 Summary of key findings of the Institute of Medicine Report

Topic
Changes in testosterone levels in ageing men
• Testosterone levels decrease as men age
• Hypogonadism may be underdiagnosed
• Testosterone levels alone are not diagnostic of hypogonadism in asymptomatic elderly men
Bone
• Major reductions in testosterone and oestradiol result in bone loss in men
• The associations between fracture risk and endogenous or exogenous testosterone have been inconsistent in clinical studies
Body composition and strength
• The relationship between changes in body composition and decreasing levels of testosterone in ageing men is not well understood
• Controlled studies of testosterone replacement therapy have generally reported increased lean body mass and decreased fat mass
• Muscle strength was unchanged in most controlled studies of testosterone replacement therapy, but increased in two studies of hypogonadal men
Physical function
• Decreased testosterone may be one of many contributors to frailty in ageing men
• Effects of testosterone replacement therapy on physical function were mixed in controlled studies
Cognitive function
• An association between testosterone and cognitive function is plausible but unproven in older men
• Cognitive function was improved or unchanged in controlled studies of testosterone replacement therapy in older men
Mood and depression
• An association between testosterone levels and mood is plausible, but results in older men are inconsistent
• Mixed results have been obtained in clinical studies of testosterone replacement therapy and mood in older men, but men who are already depressed or ill/frail may be likely to show improvement in mood
Sexual function
• A significant association has not been established between testosterone levels and sexual dysfunction in older men
• Clinical studies generally demonstrated beneficial effects of testosterone replacement therapy in hypogonadal men, and mixed results in eugonadal men
Health-related quality of life
• Some studies reported improved health-related quality of life with testosterone replacement therapy, but generalisation of the available results was difficult because of variations in clinical study design
Cardiovascular and haematological outcomes
• Low testosterone levels may be associated with risk factors for cardiovascular outcomes (e.g. hypertension, atherogenic lipid profile, prothrombotic factors and type 2 diabetes)
• A positive or negative effect of testosterone replacement therapy on blood lipids and cardiovascular morbidity/mortality had not been demonstrated conclusively
Prostate outcomes
• Testosterone is required for the development and growth of prostate cancer, but testosterone may also suppress prostate tumours
• Studies of testosterone replacement therapy have not established a significant effect on prostate-specific antigen levels
• Cases of prostate cancer during testosterone replacement therapy have been reported, but an association has not been established clearly by controlled studies

or to review the IOM topics for which limited new evidence has been published. However, clinicians should become familiar with these issues prior to initiating testosterone replacement therapy.

Prevalence of hypogonadism in ageing men

The IOM panel reported that the prevalence of hypogonadism is not known with certainty, but it is probably underdiagnosed (1). One reason for uncertainty about the true prevalence is the lack of a clearly defined standard for diagnosis (Table 2). In the Massachusetts Male Ageing Study, the prevalence of androgen deficiency was 6.0% at baseline and 12.3% at follow-up assessment 7.0–10.4 years later, when androgen deficiency was defined as a total testosterone level < 200 ng/dl (6.94 nmol/l), or at least three symptoms of hypogonadism with a total testosterone level between 200 and 400 ng/dl (13.88 nmol/l) (2). These values yielded estimates of 2.4 million men aged 40–69 years with androgen deficiency and 481,000 newly diagnosed cases in this group annually in the USA (2). A much higher prevalence estimate of 13 million American men was obtained from the Hypogonadism. In Males (HIM)

study, which used a definition for hypogonadism of total testosterone concentration < 300 ng/dl (10.41 nmol/l) to obtain a crude prevalence rate of 38.7% in men aged ≥ 45 years (3).

Assessment of the prevalence of hypogonadism is complicated further by inconsistencies in the use of total testosterone, bioactive testosterone [not bound to sex hormone-binding globulin (SHBG)] or free testosterone (not bound to SHBG or albumin) to define hypogonadism (1). As men age, SHBG levels increase and the proportion of bioavailable or free testosterone decreases, even if the total testosterone concentration is unchanged (1). For example, a recent French study reported that the prevalence of hypogonadism among men aged 50–85 years was approximately 22% with a free testosterone cutoff of 4.2 ng/dl (0.146 nmol/l), but only 9% with a total testosterone cutoff of 257 ng/dl (8.92 nmol/l) (4). An American study of patients with type 2 diabetes determined that the overall prevalence of hypogonadism was 25% with free testosterone < 5.0 ng/dl (0.174 nmol/l) and 44% with total testosterone < 300 ng/dl (5).

The IOM report acknowledged that symptoms of hypogonadism, and not just the testosterone level (1), should be considered in the diagnosis of hypogonadism. However, many hypogonadal symptoms are nonspecific, and clinicians may not agree on which symptoms are diagnostic of hypogonadism (Table 3). The nonspecific nature of symptoms was demonstrated by a Swedish survey of men aged 55–75 years, in which most subjects reported some symptoms of hypogonadism, regardless of their testosterone levels (6). Individual susceptibility to the effects of testosterone may also contribute to variable symptoms and responses to testosterone replacement therapy (7). In one recent study, the testosterone concentration that elicited symptoms in a given patient was highly reproducible, but the exact concentration varied between patients (8). Thus, although newer studies have contributed to our understanding, they have not answered questions raised by the IOM report about the definition and prevalence of hypogonadism in ageing men. These two areas are unresolved and remain crucial gaps in knowledge. Additional studies on disease prevalence

Table 2 Prevalence of hypogonadism in recent studies

Study	No.	Population	Definition of hypogonadism	Prevalence estimate
MMAS (2)	1691	40–70 years	TT < 200 ng/dl (6.94 nmol/l) or TT, 200–400 ng/dl (6.94–13.88 nmol/l) with ≥ 3 symptoms	6.0% at baseline; 12.3% after 7.0–10.4 years of follow-up (n = 1087)
HIM (3)	2162	≥ 45 years	TT < 300 ng/dl (10.41 nmol/l)	38.7%
Szulc et al. (4)	792	50–85 years	FT < 4.2 ng/dl (0.146 nmol/l)	22.3% per FT cutoff
			TT < 257 ng/dl (8.92 nmol/l)	8.6% per TT cutoff
Dhindsa et al. (5)	103	28–80 years, type 2 diabetes	FT < 5.0 ng/dl (0.174 nmol/l)	24.6% per FT cutoff
			TT < 300 ng/dl (10.41 nmol/l)	43.7% per TT cutoff

FT, free testosterone; HIM, Hypogonadism In Males study; MMAS, Massachusetts Male Ageing Study; TT, total testosterone.

Table 3 Symptoms of Androgen Deficiency in Ageing Males

Androgen Deficiency in Ageing Males (ADAM) Questionnaire* (80)	Massachusetts Male Ageing Study (MMAS) Questionnaire†(2)
1 Do you have a decrease in libido (sex drive)?	Libido – 'How frequently do you feel sexual desire' (1–8)
2 Do you have a lack of energy?	Erectile dysfunction – 13-item composite (1–4)
3 Do you have a decrease in strength and/or endurance?	Depression – antidepressant use (yes/no)
4 Have you lost height?	Lethargy – past week (1–4)
5 Have you noticed a decreased 'enjoyment of life'?	Inability to concentrate – past week (1–4)
6 Are you sad and/or grumpy?	Sleep disturbance – past week (1–4)
7 Are your erections less strong?	Irritability – past week (1–4)
8 Have you noted a recent deterioration in your ability to play sports?	Depressed mood – past week (1–4)
9 Are you falling asleep after dinner?	
10 Has there been a recent deterioration in your work performance?	

*A positive ADAM questionnaire was defined as a 'yes' answer to question 1, question 7 or any three other questions. †A positive MMAS questionnaire was defined as three or more positive symptoms (1–2 for libido, 'yes' for antidepressant use and 2–4 for all other items).

and a consistent definition of hypogonadism are clearly needed.

Prostate health

The IOM report concluded that there was no clear evidence of a link between testosterone levels and benign prostatic hypertrophy (BPH) (1). However, a major safety concern raised by the IOM report was the potential risk of prostate cancer during testosterone replacement therapy. Based on available evidence at that time, the panel concluded that 'the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined, but could greatly influence the risk-benefit ratio for supplementation in both young and elderly populations' (1). The primary source of concern about prostate cancer arose from animal studies and anecdotal case reports, which cannot be extrapolated to determine whether testosterone replacement therapy increases risk relative to the high background incidence of prostate cancer in ageing men. For example, a recent review of the files of six urologists revealed 20 cases of clinically significant prostate cancer during testosterone therapy (9), but the total number of patients receiving testosterone replacement therapy and the incidence of prostate cancer in the absence of testosterone replacement therapy were not provided for comparison.

The IOM panel also reported that higher endogenous testosterone concentrations may be associated with less aggressive forms of prostate cancer (1), and recent clinical studies have supported this conclusion. Examination of total testosterone concentrations in men with localised prostate cancer showed that pretreatment concentrations were lower among men with non–organ confined cancer than among those with organ-confined cancer (10). Similarly, evaluation of total testosterone before radical prostatectomy for clinically localised cancer revealed that lower preoperative testosterone concentrations were associated with advanced pathological stage (11). Finally, a retrospective study determined that poorly differentiated prostate cancer was associated with significantly lower testosterone concentrations (12). Thus, it seems that low serum testosterone may portend a more aggressive degree of prostate cancer.

Comparative trials have revealed no consistent effect on prostate outcomes. A recent meta-analysis of 19 randomised, double-blinded, controlled clinical studies evaluated the safety of > 3 months of testosterone therapy in 651 men ≥ 45 years of age (13). Testosterone-treated men were 1.78-fold more likely than men in the placebo groups to have any prostate event. However, the 'prostate event' was largely attributable to the increase in prostate biopsy rates during testosterone replacement therapy (odds ratio, 1.87) caused by a rise in serum prostate-specific antigen (PSA) (odds ratio, 1.19). In this meta-analysis, the risks of individual events and the risk of prostate cancer (odds ratio, 1.09) did not increase significantly during testosterone replacement therapy.

Because of concerns about prostate health, randomised trials of testosterone replacement therapy have not been performed in men with a history of prostate cancer. A retrospective analysis of hypogonadal men who underwent prostate biopsy prior to testosterone replacement therapy revealed no increase in the risk of prostate cancer in men with vs. those without prostatic intraepithelial neoplasia at baseline (14). Two recent reports in a limited number of hypogonadal men with a history of organ-confined or locally advanced prostate cancer provided no evidence of cancer recurrence with long-term testosterone replacement therapy (15,16).

Nor have recent clinical studies demonstrated an abnormal effect of testosterone replacement therapy on PSA levels (17–20). A non-comparative analysis of hypogonadal men who received open-label testosterone replacement therapy for 36 months, after initially participating in a 6-month controlled trial, found no effect of long-term testosterone replacement therapy on PSA levels (17). Similarly, a study of 187 men with erectile dysfunction reported that testosterone replacement therapy for 1 year did not increase PSA (18). A retrospective study of men receiving testosterone replacement therapy reported that changes in PSA were not influenced by the mode of testosterone replacement therapy, patient age, or baseline levels of PSA or testosterone (19). In a recent randomised clinical trial, use of a testosterone gel or a testosterone patch for 24 weeks in 162 hypogonadal men did not result in significant changes from baseline in either PSA or prostate volume (20). Increases in PSA of < 0.5 ng/ml/year are expected in hypogonadal men during testosterone replacement therapy, particularly elderly men receiving testosterone replacement therapy (21). Hypogonadal men have depressed PSA levels compared with eugonadal age-matched men – androgen suppression with finasteride has been shown to reduce serum PSA 2.2-fold (22) – so regression to the mean is expected for PSA levels during testosterone replacement therapy. Prostate health should be monitored closely before and during testosterone replacement therapy, including assessment of PSA level, documentation of voiding history and digital rectal examination (DRE) to rule out nodules, asymmetry or areas of increased firmness (23). The value of performing both DRE and PSA testing during

testosterone replacement therapy was supported by 20 case reports of prostate cancer; 25% of patients presented with elevated PSA alone, 35% with abnormal DRE alone and 40% with both abnormalities (9).

The rate of change in total PSA, or PSA velocity, is more predictive of prostate outcomes than is a single PSA measurement; indeed, prostate cancer can develop in men with PSA values < 4 ng/ml (23). Although specific recommendations vary, most experts agree that clinicians should perform baseline DRE and PSA before starting a patient on testosterone replacement therapy, and PSA should be checked again within 3–6 months, regardless of the route of administration of testosterone (21,23–25). PSA should then be monitored semi-annually as long as the patient remains on testosterone replacement therapy, in addition to annual or semi-annual DRE (23,26). Typically, a PSA velocity > 0.75 ng/ml/year (regardless of the baseline PSA) or a nodule on DRE during testosterone replacement therapy should prompt further evaluation by a urologist and possible prostate biopsy (23). However, the optimal frequency of monitoring and cutoff points, both for referral to urology and prostate biopsy, remain somewhat controversial. This ambiguity is reflected in the various PSA cutoff points that have been suggested, ranging from > 0.4 to > 1.5 ng/ml/year, depending on how many years of observation are considered (Table 4; 21,23).

In summary, evidence for an association between testosterone replacement therapy and prostate cancer is still inconclusive. That said, no new prostate safety issues have been reported in studies published since the IOM report, including studies of men at highest risk for prostate cancer. These data continue to provide reassurance that at present, there is no conclusive evidence to link hypogonadism and testosterone replacement to worsening of BPH symptoms or to the development of prostate cancer.

Table 4 Recommendations for monitoring prostate health before and during testosterone replacement therapy (21,23)

- Before initiating therapy
  - Normal DRE
  - PSA < 4.0 ng/ml
  - Evaluate individual risk of prostate cancer (21)
- During therapy
  - Measure PSA:
    - At 3–6 months
    - Semi-annually as long as treatment continues
  - Perform DRE
    - Semi annually as long as treatment continues
  - Refer for urological evaluation and possible prostate biopsy if
    - Prostate is abnormal on DRE or
    - PSA > 4 ng/ml or
    - PSA increase > 1 ng/ml after 3–4 months on testosterone treatment or
    - PSA velocity > 1.5 ng/ml/year or > 0.75 ng/ml/year over 2 years (23,24) or
    - PSA velocity > 0.4 ng/ml/year over an observation period of < 3 years (using PSA after 6 months on testosterone therapy as a reference point) (21)

Adapted (21,23). DRE, digital rectal examination; PSA, prostate-specific antigen.

Metabolic syndrome/body composition

The IOM report also cited evidence for a possible association of low endogenous testosterone with components of metabolic syndrome (1), which has been defined in various ways but generally includes insulin resistance, obesity, abnormal lipid profiles and borderline or overt hypertension (27). Recent studies have confirmed that hypogonadism predisposes men to insulin resistance, obesity, abnormal lipid profiles and borderline or overt hypertension (27). In 2005, a systematic review concluded that the evidence linking hypogonadism and metabolic syndrome is strong enough that the definition of metabolic syndrome in men may be expanded in the future to include hypogonadism as a diagnostic parameter (27).

Among men with diabetes, the prevalence of hypogonadism has been reported to range from 20% to 64% (3,5,28). A systematic review and meta-analysis of 43 prospective and cross-sectional studies concluded that men with type 2 diabetes had significantly lower concentrations of testosterone than men with normal fasting glucose (29). An analysis of > 1200 men with erectile dysfunction reported prevalences of hypogonadism of 24.5% among diabetic men and 12.6% among non-diabetic men (30). In addition, the HIM study reported a greater prevalence of diabetes among hypogonadal men (30.9%) than eugonadal men (17.9%) (3).

Table 5 summarises the findings of recent studies evaluating the relationship between testosterone concentrations and components of metabolic syndrome. In several of these studies, testosterone was positively associated with insulin sensitivity (or inversely associated with insulin resistance) (31–34), but other studies were not able to demonstrate a significant correlation (28). This is the only study to date to show no correlation of insulin sensitivity with endogenous testosterone levels. Recent clinical studies have also confirmed that total testosterone is inversely associated with body mass index, waist-hip ratio and

Table 5 Testosterone and the metabolic syndrome: studies published since the 2003 IOM report

Author/year	Study design	Key findings
Fukui et al. 2003 (35)	Cross-sectional study of 253 men with type 2 diabetes (mean ± SD age, 62.0 ± 9.9 years)	Correlations with total testosterone: ↓Patient age ↓Age of diabetes onset ↓Duration of type 2 diabetes ↑Total cholesterol ↓Intima-media thickness ↔Cardiovascular disease ↔Cerebral infarction ↔Coronary artery disease
Corrales et al. 2004 (28)	Cross-sectional study of 55 diabetic men aged > 50 years, eight ageing controls and 32 young controls	Correlations with total testosterone: ↔Fasting glucose ↔Fructosamine ↔Insulin ↔C-peptide ↑HbA_{1c} Prevalence of hypogonadism 20–55% among diabetic men, depending on the criteria used
Pitteloud et al. 2005 (32)	Cross-sectional study of 60 men with normal glucose tolerance (n = 27), impaired glucose tolerance (n = 12) or type 2 diabetes (n = 21)	Correlations with total testosterone: ↓Insulin resistance ↓Body mass index ↓Waist-hip ratio ↓Body fat, % Hypogonadal men (total testosterone < 9.7 nmol/l) were twice as insulin resistant 90% of hypogonadal men met the criteria for metabolic syndrome
Kalme et al. 2005 (34)	Cross-sectional study of 335 men aged 70–89 years	Correlations with total testosterone: ↓Glucose ↓Insulin ↓Age ↓Body mass index ↓Triglycerides ↑HDL cholesterol
Basaria et al. 2006 (31)	Cross-sectional study of 18 hypogonadal, androgen-deprived men with prostate cancer; 17 eugonadal men with prostate cancer and 17 eugonadal healthy men	Correlations with total testosterone: ↓Glucose ↓Insulin ↓Insulin resistance ↓Leptin
Smith et al. 2006 (33)	Single-arm treatment study of leuprolide depot and bicalutamide in 25 non-diabetic men with locally advanced or recurrent prostate cancer	Androgen blockade increased HbA_{1c}, insulin level, insulin resistance, total cholesterol, HDL cholesterol and triglycerides

HbA_{1c}, glycosylated haemoglobin; HDL, high-density lipoprotein; SD, standard deviation; TT, total testosterone; ↑positive correlation; ↓negative correlation; ↔no correlation.

percentage body fat (32–35). Insulin resistance among hypogonadal men may be an indirect effect of changes in body composition, inhibition of lipoprotein lipase or decreased circulating free fatty acids (36,37).

A series of data analyses from the Kuopio Ischemic Heart Disease Risk Factor Study, conducted in Finland, reported that non-diabetic men were nearly fourfold more likely to develop metabolic syndrome if they were hypogonadal (38), twice as likely to develop diabetes or metabolic syndrome within an 11-year period if they were in the lowest quartile for testosterone levels (39), and up to 2.9 times as likely to develop hypogonadism during the 11-year follow-up period if they had metabolic syndrome at baseline (40). These results were based on a cross-sectional database of approximately 1900 men, of whom approximately 700 provided follow-up data after

11 years. Therefore, it is highly evident that low testosterone is positively correlated with onset of metabolic syndrome, and perhaps type 2 diabetes. This correlation may have both clinical and economic significance because of the high prevalences and substantial costs of diabetes and metabolic syndrome in the USA (41–43).

The potential reversibility of the link between metabolic syndrome and hypogonadism was suggested by a recent observational study and a recent interventional study. In the observational study, new-onset hypogonadism was 5.7–7.4 times more common among men with metabolic syndrome at baseline and final visit, and approximately three times greater among men who also had new-onset metabolic syndrome; however, no increased risk of hypogonadism was observed among men who had metabolic syndrome at baseline that had resolved by the final visit (40). In the interventional study of 58 obese men with metabolic syndrome, the prevalence of hypogonadism [total testosterone < 317 ng/dl (11.0 nmol/l)] was 48% at baseline, 9% after the men lost an average of 16.3 kg on a very low-calorie diet and 21% when men regained approximately 2 kg on average during a 12-month weight-maintenance programme (44). Significant improvements in insulin sensitivity, fasting glucose, high-density lipoprotein (HDL) levels, and triglycerides were observed at the end of each treatment phase (44).

Emerging evidence suggests that testosterone replacement therapy may ameliorate some of the elements of metabolic syndrome, but results of these studies have been mixed. Several studies reported that testosterone replacement therapy in hypogonadal men decreased body weight, decreased waist-hip ratio, decreased body fat, improved glycaemic control, improved insulin resistance and/or improved lipid profile (45–50). However, some of these studies reported that one or more of the parameters of metabolic syndrome were not significantly improved by testosterone replacement therapy. Additional long-term studies are still needed to elucidate the role of testosterone replacement therapy in improving body composition and clinical outcomes associated with metabolic syndrome.

Cardiovascular health

Historically, testosterone was widely assumed to increase risk of heart disease, based on the relative incidence of heart disease among men vs. women. However, the IOM report found that no clear link – either positive or negative – had been established between testosterone and cardiovascular outcomes (1). No long-term studies of testosterone replacement therapy and cardiovascular morbidity/mortality (e.g. stroke, deep-vein thrombosis and myocardial infarction) had been performed, but testosterone had been shown to have a positive association with HDL cholesterol and inverse associations with hypertension, hyperlipidaemia and prothrombotic factors.

Epidemiological evidence published since the IOM report has confirmed and extended these findings. A systemic review of 35 cross-sectional studies found no evidence that testosterone is positively associated with coronary heart disease; in fact, the majority of studies reported an inverse association (51); low testosterone is associated with prevalence of coronary artery disease.

Testosterone replacement may be associated with clinical improvement of symptoms of coronary artery disease. Recent clinical studies reported that testosterone concentrations were inversely associated with intima media thickness and artery plaque score (35,52); inversely associated with the proinflammatory cytokine tumour-necrosis factor α (TNF-α) and positively associated with the anti-inflammatory cytokine interleukin-10 (IL-10) (48) and with systemic arterial compliance (53); and did not negatively influence markers of coagulation (54). In fact, in one study, testosterone concentrations were independently associated with degree of coronary artery disease, despite the finding that traditional risk factors for myocardial infarction were not (55). A placebo-controlled crossover study in men with ischaemic heart disease and hypogonadism reported that the time to 1-mm electrocardiographic ST segment depression was increased, total cholesterol decreased, exercise time increased, symptoms of hypogonadism decreased and mood improved with testosterone replacement therapy (56). A recent clinical study reported that testosterone therapy reduces myocardial ischaemia in men with cardiovascular disease, with beneficial modulation of coronary vascular tone by testosterone as a hypothesis (57). A placebo-controlled study found that 12 weeks of testosterone replacement therapy improved brachial artery vasoreactivity in men with coronary artery disease (58). Combined, these small studies provide preliminary evidence of possible clinical benefits of testosterone replacement therapy in men with coronary artery disease.

Testosterone replacement therapy may also be beneficial in men with chronic heart failure, as suggested by the findings of several small trials that reported increased cardiac index and decreased systemic vascular resistance (59), increased exercise capacity and symptomatic improvement by at least one NYHA class (60) and no significant change in TNF-α (61). The risk/benefit profile of testosterone replacement therapy in hypogonadal men with heart

failure remains to be established by controlled clinical studies.

Physical function

The IOM report evaluated the cross-sectional and placebo-controlled studies available in 2003 and noted that there was inconclusive evidence of associations between testosterone and body composition, strength and bone mineral density (1). The IOM reported that it was not clear what concentration of testosterone was associated with positive effects on bone, but that testosterone replacement therapy appeared to increase lean mass and decrease fat mass (1).

A recent study of 58 healthy men found that deprivation of testosterone, oestradiol or both led to excess bone resorption (62). In a cross-sectional study of middle-aged men with coronary artery disease, the men with low bone mineral density had significantly lower testosterone concentrations and testosterone/oestradiol ratios than did men with normal bone mineral density (63). Men with prostate cancer and osteoporosis who were treated with maximal androgen blockade for 1 year demonstrated marked bone loss in another study (64).

A survey of 1356 men aged 55–75 years in Sweden reported a significant age-related increase in abdominal circumference and decreases in muscle strength and/or endurance, libido, erection strength and energy levels; however, the authors noted that a causal relationship could not be established between these parameters and testosterone levels (6). A potential link between testosterone levels and physical function was reported in a case–control study, in which 6 months of androgen-deprivation therapy for prostate cancer decreased skeletal muscle (65). Similarly, a cross-sectional study of men aged 50–85 years reported that total testosterone concentrations were positively associated with muscle mass and inversely associated with bone mineral density and risk of falling (4).

Several placebo-controlled clinical trials published after the IOM report evaluated the effects of testosterone replacement therapy on bone mineral density and muscle strength. In one study, men given long-term systemic glucocorticoid treatment were randomly assigned to receive concomitant therapy with testosterone, the testosterone analogue nandrolone or placebo (66). Six months of testosterone replacement therapy increased muscle mass, muscle strength and bone mineral density of the lumbar spine (66). Another study enrolled hypogonadal men aged ≥ 65 years, regardless of bone mineral density and allocated them to 36 months of double-blind treatment with testosterone alone, testosterone plus finasteride or placebo (67). By the end of the study, bone mineral density had improved at both the spine and the hip with testosterone replacement therapy, with or without concomitant finasteride (67). In a separate analysis from the same study, testosterone replacement therapy (with or without finasteride) increased lean body mass, decreased fat and leptin levels, increased handgrip strength and improved overall physical performance (68).

These studies provide support for the role of low testosterone in the decreased physical function associated with ageing, and they suggest a potential role for testosterone replacement therapy in maintaining physical function and preventing frailty in the ageing male. Additional clinical studies are clearly needed to confirm these conclusions.

Sexual function

Recent studies have confirmed the long-held belief that adequate testosterone concentrations are important for sexual function and decreased testosterone concentrations are associated with impaired sexual health (7,69,70). Testosterone replacement monotherapy has been shown to improve sexual desire and function in hypogonadal men (7,46,69,71), with effects persisting for up to 3 years (72).

Testosterone replacement therapy given in combination with phosphodiesterase inhibitors is an evolving concept: Testosterone replacement therapy given in combination with phosphodiesterase inhibitors has been shown in early studies to improve sexual function in androgen-deficient men with suboptimal response to phosphodiesterase inhibitors alone, yielding greater potency, erectile function, orgasmic function and overall satisfaction (73,74). This effect may be related to the effects of testosterone replacement therapy on endothelial function, as described in the preceding section on cardiovascular health. Erectile dysfunction has been shown to be associated with biochemical markers of endothelial function and atherosclerosis (75,76). In men with erectile dysfunction who take testosterone replacement therapy with sildenafil, testosterone levels have been shown to correlate with penile arterial inflow (77). Different degrees of testosterone deficiency may reflect a sequence of molecular penile events leading to reduced capacity for penile smooth muscle relaxation and a decrease in endothelial cells (78). Therefore, improvement in hypogonadism might be expected to improve endothelial dysfunction, thereby improving erectile function.

What lies ahead

The IOM report concluded that as men live longer, more and larger clinical trials are needed to confirm

the safety of testosterone therapy, particularly with regard to prostate diseases and disorders. Clinical trials are also needed to confirm the relationship between testosterone replacement therapy and health outcomes associated with hypogonadism, especially with regard to metabolic syndrome, type 2 diabetes, cardiovascular disease, and the various components of frailty, all of which are important health concerns in an ageing population.

It is generally agreed that the scope of definitive safety and efficacy trials of testosterone replacement therapy should be vast, but the specific size and duration of such trials remain undetermined. It has been estimated that a prospective study in older hypogonadal men would require thousands of patients to demonstrate prostate safety within a 1- to 6-year time frame (13,79). However, definitive studies of the potential benefits of testosterone therapy may require substantially fewer participants, particularly for outcomes such as cardiovascular disease, diabetes and frailty, which are more prevalent than prostate cancer in ageing men.

Clinical research published since the 2003 IOM report on testosterone and ageing has begun to clarify the relationship between testosterone and numerous key health outcomes in ageing men. Increasing evidence supports the associations between hypogonadism and metabolic syndrome, cardiovascular disease and frailty in ageing men; hypogonadism clearly is not just a quality-of-life issue. The IOM report concluded that the risks and benefits of testosterone replacement in older men with hypogonadism remain to be fully defined by large, long-term clinical trials. The justification for these trials has increased as results of smaller controlled studies have expanded our understanding of the importance of testosterone in the health of ageing men.

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