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INVITED REVIEW

Male Endocrinology

Androgen effects on skeletal muscle: implications for the development and management of frailty

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Androgens have potent anabolic effects on skeletal muscle and decline with age in parallel to losses in muscle mass and strength. This loss of muscle mass and function, known as sarcopenia, is the central event in development of frailty, the vulnerable health status that presages adverse outcomes and rapid functional decline in older adults. The potential role of falling androgen levels in the development of frailty and their utility as function promoting therapies in older men has therefore attracted considerable attention. This review summarizes current concepts and definitions in muscle ageing, sarcopenia and frailty, and evaluates recent developments in the study of androgens and frailty. Current evidence from observational and interventional studies strongly supports an effect of androgens on muscle mass in ageing men, but effects on muscle strength and particularly physical function have been less clear. Androgen treatment has been generally well–tolerated in studies of older men, but concerns remain over higher dose treatments and use in populations with high cardiovascular risk. The first trials of selective androgen receptor modulators (SARMs) suggest similar effects on muscle mass and function to traditional androgen therapies in older adults. Important future directions include the use of these agents in combination with exercise training to promote functional ability across different populations of older adults, as well as more focus on the relationships between concurrent changes in hormone levels, body composition and physical function in observational studies.

INTRODUCTION

Worldwide populations are ageing. The number of Europeans aged 65 years and over is predicted to almost double over the next 50 years, from 87 million in 2010 to 148 million in 2060.[1] Similar trends are occurring throughout the developed and developing world. In this context, understanding ageing, and particularly why some older adults progress more quickly to disability and dependency, has become a leading research priority. Sarcopenia, the loss of muscle mass and function with advancing age, is a central event in the development of frailty, the vulnerable health status that precedes overt disability in older adults.[2,3]

The etiology of sarcopenia and frailty undoubtedly involves multiple mechanisms, one of which may be the age–related decline in anabolic hormone levels.[4,5] Testosterone (T) is the primary androgenic hormone in men and has potent anabolic effects on skeletal muscle.[6–8] The majority of T in the circulation is bound to albumin or sex hormone binding globulin (SHBG), the remaining unbound fraction is referred to as free T, this fraction combined with the albumin bound fraction can be described as bioavailable T. Total T levels decline modestly with age in men, while free T levels decline more steeply due to a concomitant increase in SHBG.[9–11] These changes are influenced by health status and potentially modifiable risk factors, most notably obesity and smoking.[9,10,12]

In this context, the role of T in the development of frailty and in ameliorating this condition has attracted considerable attention.

This article reviews current understanding of the anabolic effects of androgens, sarcopenia, frailty, and the preventative and therapeutic potentials of T treatment.

ANDROGEN EFFECTS ON MUSCLE

T supplementation is associated with dose dependent increases in muscle mass and reciprocal decreases in fat mass in young and older men.[7,8] The increase in muscle mass is due to hypertrophy of type 1 (slow twitch) and type 2 (fast twitch) muscle fibers.[13,14] Correspondingly, T treatment is associated with dose–dependent improvements in muscle strength and power, the product of the force and speed of contraction.[15] Androgens, however may not affect other aspects of muscle function including fatigability and specific tension or muscle quality (the ratio of muscle strength to size).[15,16]

The anabolic effects of androgens are achieved through action on multiple cellular targets.[17] T increases satellite cell replication and activation, the number of myonuclei and effects protein metabolism.[14,18–21] *In vitro* studies suggest androgens modulate the differentiation of pluripotent mesenchymal cells preferentially towards the myogenic rather than the adipogenic lineage.[22] Multiple signaling pathways are involved in these androgen–dependent myogenic effects on cellular differentiation and proliferation and muscle protein turnover.[17] Androgen receptors, in the satellite cell as well as several

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other muscle cell types, are upregulated by androgens.[23] Androgens binding to the androgen receptor promote translocation of β–catenin to the cell nucleus of mesenchymal pluripotent cells, leading to myogenic differentiation via follistatin signaling and inhibition of transforming growth factor–β.[24] Similar mechanisms may be involved in androgen effects on satellite cell proliferation.[25] Several studies also indicate a role for notch signaling in mediating androgen effects on satellite cell activation and proliferation.[14,26,27] Other cellular mediators may include stimulation of protein synthesis via the Akt/4 mammalian target of rapamycin (mTOR) pathway and inhibition of forkhead box protein (FoxO) mediated protein breakdown, as well as upregulation of intramuscular insulin–like growth factor–1 signaling.[28–30] The relative importance of these different subcellular mechanisms and their interaction with each other are currently not well–defined.

SARCOPENIA–MUSCLE AGEING

The loss of muscle mass is one of the most striking characteristics of the ageing process. Longitudinal estimates from the Health Aging and Body Composition Study (Health ABC), a large cohort of high functioning men and women aged 70–79 years at baseline, suggest an average decline in thigh muscle cross–sectional area of 6.8% in men and 3.2% in women over 5 years.[31] The rate of decline may vary according to baseline fitness and body composition, as well as concurrent changes in body weight.[31–33] The parallel loss of muscle strength greatly exceeds this decline in lean mass.[31]

The loss in lean mass is due to a reduction in the number of muscle fibers and a decrease in size of the remaining fibers.[34] The primary mechanism of fiber loss is believed to be a progressive loss of limb motor neurons.[35] Ageing is also accompanied by further changes in muscle morphology including an accumulation of shrunken muscle fibers and a clustering of fiber types, as well as an increase in muscle fat infiltration.[36] This morphological degeneration partially explains the disproportionately greater loss in muscle strength with increasing age. However, changes in neural coordination and muscle fiber specific factors can also be relevant (for review see[37]).

The term sarcopenia has been widely accepted to capture this ageing–related decline in muscle mass and function. Early definitions of sarcopenia focused on low levels of lean muscle mass relative to threshold levels derived from young reference populations.[38,39] Definitions often focus on the lean mass of the limbs (appendicular lean mass (ALM)), reasoning that this most likely reflects functional skeletal muscle, rather than non–muscle lean tissues.[38] The amount of lean mass is normally scaled to body size (height^2), and some definitions also account for body fat.[38–41] In recent years a number of international working groups have proposed new definitions of sarcopenia based not only on the presence of low muscle mass but also low muscle function.[42–45] The European Working Group on Sarcopenia defined sarcopenia as low muscle mass combined with either slow gait speed or low grip strength.[42] Similarly, consensus statements from the International Working Group on Sarcopenia and the special interest groups on 'cachexia–anorexia in chronic wasting diseases' and 'nutrition in geriatrics' propose definitions based on low muscle mass and low gait speed.[43,45] Finally, the Society for Sarcopenia and Cachexia suggested sarcopenia with limited mobility should be considered a specific condition.[44] A summary of these different definitions is shown in **Table 1**.[38, 39, 41–49] Unsurprisingly the different definitions capture differing groups of older adults, highlighting the urgent need for a wider consensus on sarcopenia.[50,51] The recent guidelines emphasize the clinical relevance of low muscle strength and physical function. However, decreases in

muscle mass in ageing have a particular etiology and only partially explain declines in function.[36,37,52] Moreover, skeletal muscle fulfills other important physiological functions including maintenance of insulin–mediated glucose homeostasis and providing a reservoir of proteins for use throughout the body.[52,53] In this context, others have argued that 'sarcopenia' should be reserved for the decline in muscle mass, alongside terms such as 'dynapenia' and 'kratopenia' to capture the related declines in muscle function.[54,55]

FRAILTY

The age–related decline in muscle mass and function is a key process in the development and progression of frailty.[2,3] However, frailty is currently conceptualized as a more general vulnerability, presaging adverse outcomes including falls, hospitalization, disability and death in older adults.[1,4,56–58] This vulnerability arises when functional declines across multiple physiological systems lead to depleted homeostatic reserves and impaired responses to stressors.[56,58] Numerous criteria have been proposed to describe this condition.[59–62] Amongst these, the most widely accepted has been the phenotypic frailty model, proposed by Fried and colleagues, operationalized initially for the Cardiovascular Health Study (CHS).[46] This model focuses on physical frailty and comprises five criteria drawn from a hypothetical cycle of decline: shrinking or sarcopenia, muscle weakness, slow gait speed, exhaustion and low physical activity.[46] People with three or more criteria are considered frail and those with one to two are considered intermediate or prefrail. The model has been adapted for use across many ageing cohort studies.[63–67] A pared down version incorporating weight loss, exhaustion and impaired chair rising has also been proposed by the Study of Osteoporotic Fractures (SOF) group.[49,59]

The second popular model proposed by Rockwood adopts a broader approach, grading frailty according to the number of ageing related health deficits summarized as a frailty index (FI).[47,68] The health deficits may include any variable ranging from symptoms and physical signs to social isolation.[47,68] Despite this flexibility, a remarkable degree of concordance has been shown between indices generated using many different deficits across different populations.[69–71] A more recent approach, the Fatigue, Resistance, Ambulation, Illness and Loss of weight, or FRAIL Scale combines self–reported physical symptoms with the count of chronic conditions, and has utility where objective measures required for other frailty models are unavailable.[48,72] It is self–evident that relationships with potential causal factors will be specific for each model of frailty studied and therefore not generalizable across different classifications. Table 1 summarizes the key features of some current frailty models.

RELATIONSHIPS BETWEEN ANDROGENS AND FRAILTY

In recent years several studies have explored the relationships between T levels and defined frailty models. Alongside this, there has been an expansion of research on the relationships between androgens, body composition, muscle function and physical function. A summary of evidence from these studies is shown in **Table 2**.

Frailty

Several recent studies have assessed the relationships between T levels and frailty using the CHS criteria. Low bioavailable T, but not total T, was related to frailty in cross–sectional analyses in men aged ≥65 years from the Osteoporotic fractures in men study (MrOS), this relationship was marginally nonsignificant in prospective analyses.[73] Lower free and total T were associated with frailty in a sample of 552 Spanish men aged ≥65 years from the Toledo Study for Health and Aging,[74] and in a sample of 54 Taiwanese men recruited from clinical and community

Table 1: Operational definitions of sarcopenia and frailty

Authors	Components	Cut–points	Development sample
Sarcopenia			
Baumgartner et al., 1998[38]	Low appendicular lean mass/height[2]	1–2 SD below reference population aged 18–40 years	New Mexico Elder Health Survey/New Mexico Aging Process Study/Rosetta Study
Janssen et al., 2002[39]	Low skeletal lean mass/BMI×100	>2 SD below reference population aged 18–39 years	National Health and Nutrition Examination Survey
Newman et al., 2003[41]	Residuals from linear regression of appendicular lean mass with height and fat mass	Lowest 20% of residuals stratified by gender	Health Aging and Body Composition Study
Cruz–Jentoft et al., 2010[42] European Working Group	Low muscle mass with either low grip strength or low walking speed	Screening by gait speed <0.8 m s^{-1}, muscle mass and grip strength 2 SD below young reference population	Consensus from earlier published data
Fielding et al., 2011[43] International Working Group	Low whole body total or appendicular lean mass and low function	Lowest 20% from young reference population. Current suggested cut points: Gait speed <0.1 m s^{-1} ALM Ht^2<7.23 kg m^{-2} in men<5.67 kg m^{-2} in women	Consensus from earlier published data
Muscaritoli et al., 2010[45] Special interest groups	Low muscle mass with low function (gait speed)	>2 SD below reference population of young adults from the same ethnic background. Gait speed <0.8 m s^{-1} from 4 m walk	Suggest National Health and Nutrition Examination Survey for reference values
Morley et al., 2011[44] Society for sarcopenia and cachexia	Low appendicular lean mass/height[2] with poor walking ability without other specific cause of mobility difficulties	>2 SD below reference population aged 20-30 years from same ethnic group. <400 m distance in the 6 min walk or walking speed <1 m s^{-1}	Consensus from earlier published data
Frailty			
Fried et al., 2001[46] Frailty Phenotype	At least 3 from self–reported weight loss and exhaustion, low physical activity, low gait speed and low grip strength	Lowest 20% from reference population aged 65+ years stratified by gender and height/BMI	Cardiovascular Health Study
Rockwood et al., 2007[47] Frailty Index	Index of health deficits, typically including 30–40 items across a range of domains	Depends on the use of binary, ordinal or continuous items	Canadian Study of Health and Aging
Van Kan et al., 2008[48] FRAIL Scale	At least three from self–reported weight loss, exhaustion, difficult with walking, and stair climbing and more than five chronic conditions	NA	NA
Ensrud et al., 2008[49] SOF frailty phenotype	At least two from weight loss, self–reported exhaustion and poor chair rising ability	≥5% weight loss over 2 years, inability to rise from a chair five times	Study of Osteoporotic Fractures

ALM: appendicular lean mass; BMI: body mass index; SD: standard deviation; LBM: lean body mass; NA: not available

Table 2: Summary of testosterone effects on frailty

	Observational studies	Interventional studies
Frailty	Relationships seen in most studies Partially explained by adjustment for BMI and morbidities	NA
Muscle mass	Moderately related in many studies Discrepancies may reflect different LBM measures and accounting for body fat	Consistently increased by 1–2 kg Greater increases at higher doses
Muscle strength	Modestly related in many studies Prospective relationships unclear	Usually little change Improved in some studies, normally at higher doses
Physical function	Inconsistent relationships Many different tests High functioning samples	Generally little effect; improvements in specific circumstances Difficult to measure and dependent on many factors in addition to strength

settings.[75] In a report from the Concord Health and Aging in Men Project (CHAMP), lower free and total T were related to higher levels of frailty in men aged 70–97 years, greater declines in T over 2 years also predicted progression of frailty at follow up in this study.[76] Results were similar using the CHS criteria or the abbreviated SOF version.[76] Finally, reports from the Massachusetts Male Aging Study (MMAS) and the Nutrition and Health Examination Survey (NHANES) showed relationships between low free T and physical frailty, that became nonsignificant after multivariate adjustment.[77,78] No relationship with total T was seen in these studies.[77,78]

Studies using broader frailty models have also shown relationships between T levels and frailty.[79,80] Lower baseline free T was related to the FRAIL Scale in both cross–sectional and prospective analyses in men aged 70–88 years from the Health in Men Study.[79] Similarly, lower free T was related to higher levels of the FI in an analysis from the European Male Ageing Study.[80] Weaker relationships with total T were seen in these studies.[79,80]

Body composition
Studies in adult men have frequently shown moderate positive associations between T levels and lean body mass, alongside negative associations with fat mass.[81–88] Total and free T were correlated to arm and leg lean mass in men aged 24–90 years from the Baltimore Longitudinal Study on Ageing.[89] Total T and free T were related to

appendicular skeletal muscle (ASM) mass in men aged 65–97 years from the New Mexico Aging Process study.[83] Free T indices, but not total T, were associated with relative ASM (RASM) in men aged 45–85 years from the MINOS study.[86] Similarly, bioavailable T was associated with RASM in a sample of 142 men aged 64–92 years.[85] In another study SHBG/T ratio, but not total T or free T, was related to lean body mass in 403 men aged 70 years and older.[87] Free T, but not total T, was related to total and thigh lean mass in a sample of 101 men aged 60–70 years.[90] Free T and bioavailable T were related to lean body mass in a sample of 335 Malaysian and Chinese men aged ≥40 years.[84] Lastly, total and free T were related to RASM in 1489 men aged ≥65 years from the MrOS Hong Kong study.[82]

However, several recent studies did not find significant relationships between T levels and lean body mass: Vandenput *et al.*, found no association between total or leg lean body mass in 2014 men aged 69–80 years from the MrOS Sweden sample.[91] Similarly, Orwoll *et al.*, found no difference in lean body mass index (BMI) across the range of bioavailable T levels in men from the American MrOS sample,[92] while Maggio *et al.*, found no difference in calf muscle area, measured by peripheral quantitative computed tomography (pQCT) scanning, across strata of total T levels in men from the Chinati study.[93] Finally, a mild negative relationship between T levels and lean body mass was seen in men aged 20–90 years from the NHANES study,[94] with similar, but nonsignificant, trends seen in men aged 30–79 years from the Boston Area Community Health Bone Survey.[95]

This discrepancy between studies may reflect sample differences in T levels or the different lean body mass parameters and/or measurement techniques used. Another possible explanation is differential scaling to body size and/or adjustment for fat mass across studies. Higher adiposity (and therefore BMI) is positively correlated with lean body mass and associated with reduced T levels, it is possible this comparatively strong effect may obscure the more modest positive effects of T on lean mass.[81] Interestingly, a recent study in older Caribbean men suggested an inverse relationship between androgens and calf muscle fat infiltration, as well as a positive relationship with muscle density.[96] This suggests an effect of androgens on muscle composition in addition to the influence of muscle mass and further highlights the potential confounding role of body fat in the relationship between lean mass and T, particularly as most techniques, including dual–energy X–ray absorptiometry (DXA), are not sensitive to muscle composition.

In addition to these cross–sectional studies, a recent prospective study found that higher baseline total T or bioavailable T was associated with less loss of lean mass over 4.5 years follow–up in 1183 men from the MrOS cohort, with strongest effects seen in the men who lost the most weight.[97] Another study found a relationship between low baseline free T and increased likelihood of low muscle mass at 10 year follow up in Japanese men aged 40–79 years, weaker, nonsignificant trends were seen for total T.[98]

Muscle strength

Grip strength is the most widely used strength measurement in epidemiological studies, and is generally considered a good proxy for overall muscle strength and frailty.[99] Cross–sectional studies in middle–aged and older men have shown modest positive associations between T levels and grip strength in most,[82–84,87,92,93,100,101] but not all studies.[81,102] In studies using more sophisticated muscle function measurements, total T and free T Index levels were correlated to upper and lower limb muscle strength in 262 men aged 24–90 years from the Baltimore Longitudinal Study of Ageing,[89] while total and

bioavailable T levels correlated to measures of upper and lower limb muscle strength in a small sample of older African American men.[100] In a recent study, free, but not total T was weakly associated with knee extensor strength by isometric and isokinetic dynamometry in a sample of 101 men aged 60–70 years.[90] Similarly, total and free T were modestly correlated with greater knee extensor strength in a sample of 403 men aged ≥70 years,[87] while lower bioavailable T was associated with slightly lower leg power in men from the MrOs study.[92] In a prospective study, baseline T levels were not associated with 3 year change in grip or knee extensor strength in men from the Longitudinal Aging Study Amsterdam (LASA) or the Health ABC study.[103] Similarly, baseline T was not associated with 4.5 year change in grip strength or leg power in a report from the MrOs study, although there were trends towards greater losses at the lowest T levels among men who lost the most weight (≥2 kg) between waves.[97]

Physical function

Functional aspects of physical frailty are important in terms of determining clinical outcomes and quality of life. However, accurate assessment of physical function is methodologically challenging due to the large individual variability, effort dependence and practice effects. Studies on the relationships between androgens and physical function have shown equivocal results. In a small sample of black American men, total T levels were correlated with chair standing and door opening performance, but not with gait speed, timed up and go or simulated eating, while bioavailable T levels were correlated with gait speed, timed up and go and the doors task, but not with the other tasks.[100] In a cross–sectional analysis from the LASA, bioavailable and free T, but not total T levels were correlated with better physical performance.[101] A report from the MMAS found a relationship between total T and performance on the physical performance test (PPT) only below a threshold level estimated at 451 ng dl^{-1}, and no relationship with chair rising performance.[102] Similar relationships with bioavailable T were seen in this study.[102] In men from the MrOS, low bioavailable T was associated with marginally poorer performance on tests of chair rising and walking ability.[92] In men from the MrOS Hong Kong, higher total and free T were related to higher scores on a composite measure derived from several neuromuscular function tests; of the individual tests T levels were related to higher narrow walk speed and step length, but not to chair rising ability or gait speed.[82] Higher free T, but not total T levels were related to faster gait speed and improved performance on the Short Physical Performance Battery (SPPB) in middle–aged and older men from the Framingham Offspring Study.[104] In prospective analyses from this study, lower baseline free T was associated with self–reported mobility limitation at 6 year follow–up.[104] Prospective studies using objective assessments of physical performance have shown largely negative results. No relationship between baseline T levels and 3 year change in performance of a composite physical score including gait speed, chair rising and tandem stands, in men from the LASA and Health ABC studies.[103] Similarly, no overall relationship between baseline T and declines in chair standing and gait speed tests in men from the MrOS, although a mild relationship between lower T and less decline in chair stand performance was seen in men who lost the most weight between follow–up.[97]

Summary

In summary, a relationship between lower T levels (especially free T) and frailty constructs has been consistently, though not universally, found across studies. This relationship can be explained, at least partially, by confounding covariates, particularly age, BMI, morbidities

and smoking, suggesting that low T may be a marker for these risk factors underlying frailty. Nevertheless, in most studies, some relationship with T persists even after adjustment for these confounders and it is plausible that lower T may be causally linked to frailty through its effects on muscle mass. The broadly consistent relationships with lean mass, including recent prospective data, offer some support for this pathway. T has been modestly, but consistently, related to muscle strength, but less clearly related to physical function. It is likely these effects are mediated through effects on lean mass, however in one study effects on strength persisted after adjustment for ALM.[82] This may suggest additional mechanisms for androgen effects on strength that are not explained by changes in lean mass. Prospective data on progression of frailty or functional decline have shown equivocal relationships, although many studies included high functioning men.[97,103] Few studies have simultaneously measured changes in T levels and functional measures across two or more time points and this is an important area for future research.

EFFECTS OF ANDROGEN TREATMENT ON FRAILTY

This section reviews studies on the effects of T treatment on components of frailty in healthy and frail older men. Particular attention is given to body composition, muscle strength and physical function. Table 2 gives an overview of the results from these interventional studies.

Body composition

T treatment at near physiological dosages for 3–36 months has been reliably found to increase lean body mass and reduce fat mass in both healthy and frail older men with low to low normal T levels.[8,18,105–118] The magnitude of improvements in lean mass has been in the region of 1–2 kg in most trials depending on the dose and type of preparation used.[105–108,110,113,114,116,117] Larger gains of around 4 kg have been seen in trials using injected T preparations.[18,111] The minority of studies not to show an effect were limited by short treatment duration (1 month), use of the relatively insensitive bioelectrical impedance technique to assess lean mass changes, and inclusion of men with normal T levels.[119–121] An increase in lean body mass in sarcopenic older men may lead to improvements in glucose metabolism, drug tolerance and whole body protein reserves.[52] However, the important question is whether this gain in muscle mass translates to increases in strength and so functional ability.

Muscle strength

Studies in young and older men have suggested dose–dependent effects of T on muscle strength and power, without clear effects on muscle fatigability.[15,122] While power maybe more closely related to physical function in older adults,[123] it is more difficult to measure than strength,[124] and the effects of T on muscle power are probably explained by the effects on strength. Due to the wider range of strength assessments available, most studies in older men have focused on this parameter, with varying improvements seen. Grip strength, the most widely used strength assessment, has been found to increase in some trials,[62,111,125,126] but not others.[106,113–117,120] Similarly, some studies have reported improvements in lower limb strength,[18,114,127,128] while others have failed to show any effect of treatment.[107,109,111,113,117] There are several reasons why gains in lean mass may not reliably lead to improvements in muscle strength. Firstly, it is a possible that lean mass gains may not reflect increases in myofibrillar protein content. Early gains (8 weeks treatment) in lean mass may reflect water retention or accumulation of noncontractile proteins.[129] However, most studies have used longer treatment durations, and as discussed above, a variety of studies demonstrate effects of androgens on muscle protein synthesis, fiber size, myonuclear number and satellite

cell activation.[13,18,20,22] Another possibility is that gains in lean mass may be too small to lead to increases in strength: a recent study using several combinations of T and growth hormone treatments estimated that gains in lean mass of at least 1.6 kg were required to improve leg or chest press strength in a sample of healthy older men.[130] This may explain the lack of effect in some studies,[106,110] but in many others increases in lean mass were in or above this range.

Improvements in strength have most frequently been seen using 1 repetition maximum (1–RM) techniques and relatively high doses of T. A small study in healthy men ($n = 12$) showed an increase of 15 kg in leg press strength with treatment alongside a gain in lean mass of 4 kg.[18] Larger studies have also shown improvements in 1–RM leg press strength alongside smaller (<2 kg) gains in lean mass following doses of 10 mg day^{-1} transdermal T in healthy and mobility limited older men.[116,127] Improvements at lower doses (2.5–5 mg day^{-1}) have been less clear.[107,108,112] Studies using isokinetic dynamometry in healthy or frail older men have shown very limited to no improvement in lower limb strength compared to placebo, despite gains in lean mass of 1–4 kg and treatment for up to 3 years.[107,113,114,117,128] In one of these studies, improvements in knee extension strength of 6% have been shown in frail men using isometric dynamometry.[114]

1–RM protocols define maximum strength as the terminal weight lifted in a series of incrementally higher loads, while dynamometry protocols typically define strength as the highest torque generated during a muscle contraction. Isokinetic dynamometry involves a contraction at a set speed over a defined range of motioned; whereas, isometric protocols involve static contractions at a fixed joint angle. Contraction velocity in 1–RM contractions is quite slow; it has been suggested that this may be more similar to that seen during isometric contractions.[131] In older men, both the contraction velocity and rate of force development are reduced,[132,133] it is therefore likely that older men find it difficult to perform the faster contraction speeds used in many isokinetic dynamometry protocols. Consequentially, it is possible that isokinetic dynamometry may not capture improvements in strength even when there are large gains in lean mass and improvements in other muscle function measures.[111] While differences in strength assessments may partially account for small differences between studies, overall the effects of near physiological T treatments on strength can be said to be modest, with trends towards greater improvements at higher doses.

Physical function

T–induced improvements in physical function have been limited across many studies to date, with most failing to show any clear effects. Studies in healthy men have failed to show improvements in functional tasks including tests of balance, gait speed, chair rising, step height and functional reaching.[106,109,113,120,128] One study did show an improvement on a composite physical performance test including rising from a chair, a fast walk, a step height test, a door task and a stair ascent and descent over 12–36 months treatment.[111] Two studies in frailer men did not show any overall improvements in gait speed, mobility or activities of daily living tests following treatment for 6–24 months.[107,114] Although in one of these studies improvements on some scales were seen in older (≥75 years) and frailer (≥2 of Fried's criteria) men.[114] Finally, in the TOM trial, loaded stair climbing improved with treatment compared to placebo in mobility limited men ($P = 0.05$), there were also trends towards greater improvements in loaded gait speed, but not in unloaded tasks.[127]

It is possible that increases in strength were too small to lead to measureable improvements in function in some studies, particularly as relatively large improvements on functional tasks often occurred

in both groups, consistent with learning effects.[109,128] Another factor is likely to be the nonlinear relationship between muscle strength and physical function: at a certain level, dependent on the difficulty of the task used, the relationship plateaus, such that further increases in strength will not result in improvements in physical function.[134–136] It is likely that in the majority of studies participants were functioning above the most sensitive strength ranges for the assessments used. Indeed, while improvements in strength and power are dose dependent, even supraphysiological doses of T may not improve performance on functional tasks in healthy older men.[122] Finally, physical function is dependent upon a number of factors in addition to muscle function,[137] with strength making a varying contribution to the performance of different tasks.[123] T therapy might be expected to preferentially affect more strength–dependent tasks, in agreement improvements in loaded stair climbing and gait speed were correlated with increases in T and leg press strength in the TOM trial, but improvements in unloaded tasks were not.[116] It is also likely that T alone may be relatively ineffective and may need to be combined with exercise or other functional training in order to engender broad spectrum functional improvements.[138]

Summary

In summary, T treatment reliably improves body composition and may be associated with modest increases in muscle strength, especially at higher (near supraphysiological) doses. Response in physical function may preferentially improve for strength dependent tasks, but such improvements will only be detectable using tasks appropriate to the baseline ability of participants.

TIME COURSE AND DURABILITY

Improvements in lean body mass and strength in response to T treatment are reached within 6 months and can be maintained without further increment for the duration of treatment (longest study to date is 3 years).[111,113,117] Studies in healthy and frail older men suggest most of this benefit is lost within 3–6 months of discontinuing treatment, although in men experiencing the largest gains some residual benefits may remain at 3 months.[139,140]

SAFETY OF T THERAPY IN OLDER MEN

The use of T therapies in older men has been limited by concerns over adverse cardiovascular and prostatic effects. Several meta–analyses suggest T has been well–tolerated in the majority of studies in healthy older men.[141–143] The most frequent adverse effect seen is increased hematocrit, which may lead to clinically significant erthrocytosis.[141–143] T has also been shown to be well–tolerated in frailer older men, with only mild effects on hematocrit, prostate specific antigen (PSA) and blood lipids.[114] In contrast to these findings, the TOM trial of T therapy in men with limited mobility was discontinued following an imbalance in cardiovascular events in T treated men compared to placebo.[127] This discrepancy may be explained by the relatively high dose used in a comparatively high risk population: the strongest risk factor for cardiovascular events in this trial was the increase in free T.[144] This is consistent with previous findings of greater frequencies of adverse events associated with higher T doses in healthy older men.[8] Men included in the trial had a high mean BMI, as well as a very high frequency of hypertension, diabetes and hyperlipidemia.[127] This experience sounds a salutary note of caution regarding the safety of treating frail elderly men with relatively high doses of T, highlighting the importance of careful patient or trial subject selection.

The effects of T on serious prostate events are currently unclear due to the relatively small size of the studies and short duration of exposure. A 2005 meta–analysis suggested that men treated with T experienced approximately double the rate of all prostate events including biopsies, cancers, increased symptoms, increments in PSA and urinary retention.[141] However, this may be explained by monitoring bias.[141] The effects of T on prostate and cardiovascular events will only be clearly established by larger scale, longer duration, appropriately powered clinical trials.

FUTURE DIRECTIONS IN ANDROGEN THERAPIES

As described, physiological androgen therapies have shown limited improvements in muscle function and concerns remain over the safety of higher doses of T in older men. Several new approaches with the potential to address these limitations have started to emerge.

Selective androgen receptor modulators (SARMs) have been developed, aimed at maximizing anabolic effects on muscle and bone without androgenic effects on other tissues, especially the prostate and hair follicles.[145,146] The first trials of these compounds as function promoting therapies have recently been reported.[147–149] Treatment with GTx–024 (Enobosarm) has been associated with increases in lean body mass and stair climbing ability, without virilizing effects, in healthy older men and women and in patients with cancer cachexia.[147,148] In another trial, 6 months treatment with MK–0773 was well–tolerated and associated with increases in lean body mass, but not muscle strength or physical performance in older women with sarcopenia and mobility limitations.[149] Finally, in a recent dose finding study another SARM, LGD–4033, increased lean body mass without effecting PSA levels in healthy young men.[150] As demonstrated by these early studies, these agents will permit the use of androgen–based anabolic therapies in older women and raise the possibility of safely using more potent pharmacological doses to more reliably improve muscle strength not only in older adults but also in the broader context of cancer cachexia and posttraumatic and postoperative rehabilitation. In these latter indications, the shorter duration of treatment and the consistent positive effects on muscle mass (as opposed to strength and function) may well be the important primary therapeutic outcome.

Androgen therapy consistently increases lean body mass, but may not improve muscle function, while progressive resistance training may improve muscle function in older adults in the absence of gains in lean mass.[151] Two recent studies have explored the potential of combining these interventions.[152,153] The combination of 12 months progressive resistance training and T lead to greater improvements in body composition than either intervention alone in healthy older men, but did not provide additional improvements in muscle strength or physical function.[152] Similarly, in the second study the addition of T therapy for the latter 12 weeks of a 24 week resistance training program increased muscle mass, but not muscle function over men engaged in training alone.[153] Although this study may have lacked statistical power; the combined T and training group included only six men.[153] Despite the lack of evidence of synergy between the two therapies, these studies confirm their differential effects on muscle mass and function. Combining novel androgen therapies with different exercise training programs will be an essential key area for future research in combating frailty.

CONCLUSIONS

The consistent effects on lean mass in interventional studies combined with the relationships seen in observational studies and the increasingly well–characterized mechanistic pathways all suggest T is an important promoter of muscle mass gain in older men. As such, falling T levels may contribute to the development of frailty, although the decline in strength with ageing involves many more mechanisms. Correspondingly, the functional effects of T are less clear. Much of

the current research has involved high functioning older men; there is a need for more observational studies as well as interventional trials in frailer populations. The present confusion over the purported syndromes of sarcopenia and frailty presents a limitation for study design. A consensus on the most meaningful features of physical decline will assist in determining etiologies and future trial design. Focus on particular domains, such as mobility decline, may be preferable to the current syndromic definitions. More sophisticated analysis of parallel changes in hormone levels, body composition and functional outcomes over time will help to unravel the directionality of these relationships and so the true role of androgens in functional decline. The development of SARMs has the potential to limit the adverse effects of T, allow more potent functional promotion and extend the use of androgen therapies to broader populations. Deeper understanding of the molecular mechanisms underlying androgens' anabolic effects will facilitate the development of further nonsteroidal agents. The application of these agents in combination with well–designed exercise training protocols represents an exciting new direction in this field.

COMPETING INTERESTS

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