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ISA, ISSAM and EAU recommendations for the investigation, treatment and monitoring of late-onset hypogonadism in males: Scientific background and rationale

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Abstract
Prescription sales for testosterone products have substantially increased over the last several years reflecting the growing awareness of physicians for the potential benefits of testosterone replacement therapy in men with hypogonadism. Indiscriminate administration of testosterone poses a risk and has to be deprecated. Testosterone supplementation to treat late-onset hypogonadism (LOH), a term for androgen deficiency in elderly men, is still controversially discussed mainly due to a lack of large, controlled clinical trials on efficacy and safety. To provide guidance for physicians primarily dealing with aging men, ISSAM is periodically updating and publishing its recommendations as new data become available [Morales A, Lunenfeld B. International Society for the Study of the Aging Male. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. Aging Male 2002;5:74–86 and Morales A, Lunenfeld B. Androgen replacement therapy in aging men with secondary hypogonadism. Draft recommendations for endorsement by ISSAM. Aging Male 2001;4:1]. Following a panel discussion at the 4th ISSAM Congress in Prague in February 2004, the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM) and the European Association of Urology (EAU) revised existing recommendations on the definition, diagnosis and management of LOH. The recommendations are based on the currently available scientific data on androgen supplementation therapy and should be regarded as provisional until larger-scale, long-term studies are available. While certainly not intending to be exhaustive, this review will highlight some relevant background information and provide the underlying scientific rationale for the ISA, ISSAM and EAU recommendations on LOH published in this issue.

Keywords: *Late-onset hypogonadism, androgen deficiency, testosterone, aging*

Introduction

The change of endocrine profiles over lifespan and the decline of peripheral testosterone affecting a significant percentage of the aging male population is undoubtedly a recognized reality [1–6]. Age-related androgen deficiency in men, also termed late-onset hypogonadism (LOH), has been found to be associated with a variety of pathological conditions in the elderly population. According to estimates 4 to 5 million American men may be afflicted by LOH [7]. However, the condition is largely underdiagnosed and undertreated. Testosterone supplementation has the potential to counteract the signs, symptoms, and health risks of LOH thereby promoting successful male aging. Indiscriminate and uniformed use of testosterone entails risks and can only be considered malpractice. Its rational application by well-informed physicians, conversely, entails the chance to maintain and improve the health status of elderly men. This may not only result in a significant reduction of health and social costs, but allow the elderly to keep an active and productive lifestyle for the enrichment of society and for their own personal fulfillment. While the biochemical evidence on age-related decrease in androgen production is irrefutable, there is an ongoing misunderstanding and confusion on the definition of LOH, its clinical implications, clinical assessment, and management in daily practice.

Definition, prevalence and clinical picture of LOH

According to *Recommendation 1*, LOH is defined as a ''clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and deficiency in serum testosterone levels''. Cross-sectional and longitudinal studies confirm a progressive decrease of the serum testosterone concentration with age [3–6]. The population-based Massachusetts Male Aging Study investigated the age-related alteration of peripheral hormone concentrations in men (age range: 39–70 years). Cross-sectional analysis ($N = 1709$) showed a continuous decrease of both, free testosterone (1.2% per year) and albumin-bound testosterone (1.0% per year) [3].

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Compared to the cross-sectional trend, the longitudinal decline within subjects between baseline and follow-up after 7–10 years was found to be even steeper with 1.6% per year for total testosterone and 2–3% per year for bioavailable testosterone [4]. Analysis of samples from 890 men participating in the Baltimore Longitudinal Study on Aging corroborates this finding revealing an average change of − 0.124 nmol/L testosterone per year [5]. The incidence of hypogonadal testosterone levels was about 20% in men over 60 and increased steadily to 50% in men over 80 years of age [6]. To further characterize the epidemiology of androgen deficiency, the crude and age-specific prevalence and incidence rates were calculated based on data available from the Massachusetts Male Aging Study ($N = 1{,}691$ at baseline, $N = 1{,}087$ at follow-up). Crude prevalence was found to be 6.0% at baseline and 12.3% at follow-up after 7–10 years. A projection for the US male population led to an estimate of 2.4 million 40–69 year old US males with androgen deficiency. The rate increased significantly ($p < 0.0001$) with age. Based on this analysis, 481,000 new cases of androgen deficiency per year are anticipated in the United States [8].

Recommendation 1 clearly states the potentially detrimental impact of testosterone deficiency on the function of various organ systems and on quality of life. LOH may encompass numerous, sometimes vague and non-specific symptoms. Clinical features of LOH summarized in *Recommendation 2* include negative effects on body composition, bone mineral density (BMD), sexuality, the skin, and the central nervous system. Initially, patients putatively having LOH may be assessed using a validated questionnaire [9–11] and clinical examination. However, the physician is strongly advised to start testosterone therapy only when both, biochemical evidence of testosterone deficiency and the clinical picture, indicate the presence of LOH (*Recommendation 5*) [12]. An algorithm for the diagnosis and management of hypo-gonadism in the aging male is presented in Figure 1.

LOH and the beneficiary effects of testosterone supplementation

Sexuality – Recommendation 2(1)

Diminished sexual function is commonly considered as a natural part of the aging process. Many biological facets of sexuality, such as erectile function, desire, orgasm, and overall ability, show a sharp decline when age-related alterations begin to occur in the male hormonal system. A range of studies suggest an interrelation of declining serum testosterone levels and reduced libido and a positive influence of testosterone supplementation on sexual desire [13–16]. While many mediators of erectile capacity have been identified lately, a gap of knowledge is evident regarding the impact of testosterone deficiency on psychogenic and reflexogenic erectile function. Systemically collected data from the Massachusetts Male Aging Study stress the growing incidence of erectile dysfunction (ED) with age. The annual incidence rate was found to rise from 12.4 cases per 1000 man-years (95% CI 9.0–16.9) for men aged 40–49 years to 46.4 cases (95% CI 36.9–58.4) in men between 60 and 69 years of age [17]. The largest US study of prevalence and risk factors for ED to date with 31,742 participants enrolled documented a 10-fold difference in relative risk for ED associated with older age, regardless of health status or previous erectile function [18]. Although extensive research has been

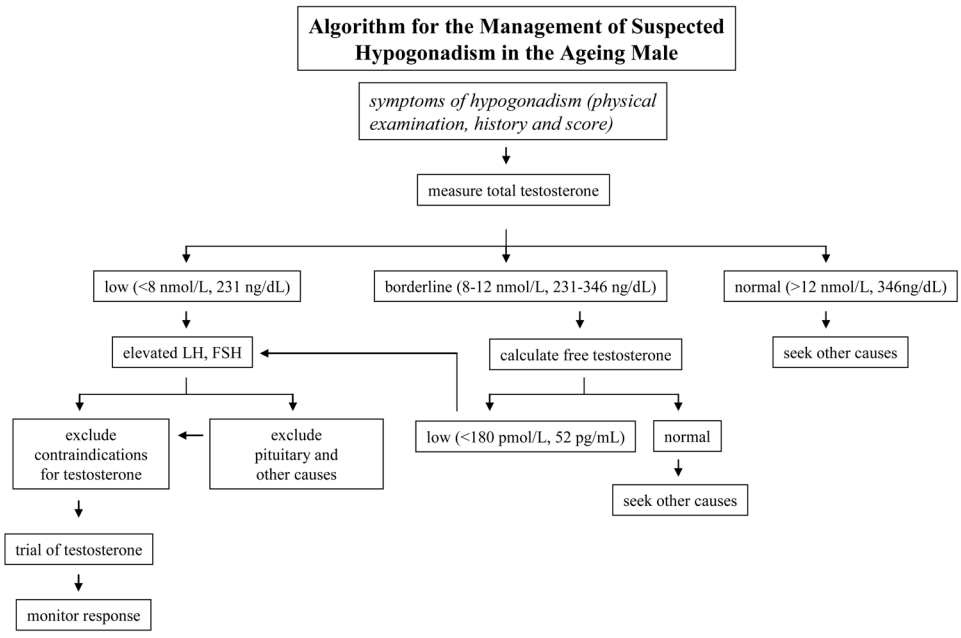

Figure 1. Algorithm for the diagnosis and management of hypogonadism in the aging male.

performed in recent years, up to now, a correlation between low serum testosterone levels in elderly men and ED has still to be conclusively demonstrated. According to the Massachusetts Male Aging Study, ED does not interrelate with low serum testosterone levels in elderly men [19]. Similarly, another study examining the relation of various hormonal factors to impotence in older men found that LOH and impotence are common, but independently distributed conditions. It was observed that even severely hypogonadal men may maintain erectile capacity [20]. Estimates for hypogonadism as the major underlying reason for ED vary widely [21–23]. In a retrospective review of data obtained from patients presenting for initial evaluation and therapy of erectile dysfunction ($N = 2{,}823$), serum testosterone was less than 280 ng/dL in 528 (18.7%) and less than 220 ng/dL in 210 (9.2%) patients [24]. In a study with men ($N = 521$), who were diagnosed with ED based on self-assessment, 37% of the participants were found to be hypogonadal [25]. Corona et al. reported a prevalence rate of 22.3% for hypogonadism in men with ED and normal fasting glucose. The rate was substantially increased in diabetic patients with ED (34%) [26]. Animal studies clearly support the role of testosterone in erectile function [27–29]. A number of studies in humans pinpoint to a significant association between ED and low bioavailable testosterone or free testosterone, respectively. Free testosterone levels were examined in 52 impotent patients without confounding risk factors for ED and the results point towards an age-independent correlation between low free testosterone and impaired function of cavernous endothelial and corporal smooth muscle cells in men with ED [30]. A Japanese investigation on 130 patients presenting because of sexual function problems showed a significant positive correlation of bioavailable testosterone levels with the International Index of Erectile Function-5 score for erectile function [31]. In a Korean study with participants suffering from LUTS (age range: 31–78 years), regression analysis corrected for age indicated a significant correlation of the five domain scores of the IIEF (International Index of Erectile Function) with free testosterone levels. Decrease in free testosterone was linked to impairment of erectile function ($r = 0.2136$, $p = 0.005$) and orgasmic function ($r = 0.179$, $p = 0.020$), whereas total testosterone levels showed no significant relation to any of the five domains of the IIEF. Similarly, Pearson coefficients of IIEF-5 score and total testosterone did not reveal any significant correlation ($r = 0.0163$, $p = 0.612$) in a study on 1,071 men performed in the course of a free screening program for prostate cancer [32]. In a recent study with 162 elderly men (age $\geqslant 60$ years), hypogonadism (< 3 μg/L total testosterone) was significantly associated with failure of sildenafil (odds ratio 1.89, 95% CI 1.12–3.16) and testosterone supplementation was suggested for enhancement of sildenafil efficacy in this patient population [33]. In a prospective, randomized, placebo-controlled pilot study ($N = 20$), transdermal testosterone (5 mg/day) was administered to patients characterized by sildenafil-refractory, arteriogenic ED, normal sexual desire and testosterone and free testosterone in the lower quartile of normal range. A significant improvement in erectile function domain score at IIEF was observed in the androgen but not in the placebo-treated patients (21.8 ± 2.1 vs. 14.4 ± 1.4, $p < 0.05$) [34]. In a placebo controlled, double-blind, parallel group, multicenter study, 75 hypogonadal men (age range: 18–80 years, morning serum total testosterone 400 ng/dL or less) having a confirmed lack of response to sildenafil monotherapy were randomized to a daily dose of 1% testosterone gel (1%) or placebo gel as adjunctive therapy to 100 mg sildenafil for 12 weeks. Testosterone treated subjects showed significantly enhanced erectile function compared to the placebo group (at week 4: 4.4 vs. 2.1, $p = 0.029$, 95% CI 0.3–4.7). Furthermore, the investigators observed improvements in orgasmic function, overall satisfaction, total IIEF score and percentage of IIEF responders [35]. These results are corroborated by another small study with 35 tadalafil-refractory patients receiving a combination therapy of testosterone gel/tadalafil [36]. Sildenafil non-responders with diabetes mellitus type II ($N = 120$) showed improvement in erections, a significant increase in IIEF scale and increased sexual contacts when treated with a combination therapy of oral testosterone undecanoate and sildenafil [37]. In a study with 20 patients having arteriogenic ED and low-normal androgen levels, transdermal testosterone induced a significant increase in arterial inflow to cavernous arteries as compared with placebo (32 ± 3.6 vs. 25.2 ± 4 cm/s, $p < 0.05$), accompanied by significant improvement in erectile function domain score at IIEF (21.8 ± 2.1 vs. 14.4 ± 1.4, $p < 0.05$) and significant changes in the GAQ score (80% vs. 10%, $p < 0.01$) [38]. These findings underline that in some men with ED, who are not responding to phosphodiesterase 5 inhibitors, testosterone supplementation seems to be of help. Conversely, treatment with phosphodiesterase-5-inhibitors may be warranted in patients with inadequate response to testosterone alone (*Recommendation 14*) [39]. The finding that erectile response to visual erotic stimuli in hypogonadal men is androgen-independent emphasizes the multifactorial complexity of ED [40]. Estimates imply that testosterone supplementation may restore erectile response in a proportion of 40–60% of hypogonadal patients [39,41–45]. Common comorbidities associated with ED include diabetes, psychogenic disorders, and lower urinary tract syndrome (LUTS) [46–51]. Erectile dysfunction is frequently a manifestation of underlying cardiovascular problems [52] and *Recommendation 4(3)* addresses the need to monitor cardiovascular status and lipids in aging patients with ED.

Central nervous system and behavior – Recommendation 2 (2 and 3)

Testosterone plays an important role in the modulation of mood and cognitive function [53]. Anxiety, irritability, insomnia, memory impairment, and a decrease in mental acuity and intellectual activity have been postulated to be associated with reduced endogenous testosterone levels in aging men. A curvilinear relationship between spatial performance and serum testosterone concentrations has been observed in male right-handers with intermediate levels of testosterone being associated with better spatial functioning [54]. In the Rancho Bernardo Study, a U-shaped association between testosterone and several tests of cognitive function and memory was seen with both subnormal and supraphysiological serum testosterone levels causing cognitive impairment [55]. In a longitudinal study carried out in the Baltimore area, higher free testosterone index (FTI) was positively correlated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning, and a reduced rate of longitudinal decline in visual memory [56]. When measuring cognitive function in 310 elderly men (mean age: 73.0 $\pm$ 7.1) using the Mini-Mental State Examination (MMSE), Trails B, and Digit Symbol, researchers found no consistent association between total testosterone level and cognitive test scores. However, elderly men with high bioavailable testosterone showed better cognitive test scores on all three tests ($p \leqslant 0.001$) [57]. A positive effect of supplemental testosterone on cognition remains uncertain and, obviously, a differential impact has to be assumed [58,59]. A 12-month supplementation with oral testosterone undecanoate (80 mg twice daily) did not improve scores in visuospatial tests or mood and quality of life scales in older men with mild hypogonadal status ($N = 76$, age $\geqslant$ 60 years, FTI = 0.3–0.3) [60]. In a second study, similar findings were described [61]. Other studies state that testosterone administration significantly enhanced spatial cognition [62], spatial and verbal memory [58], and working memory [63]. Animal studies, a case report and a follow-up study in castrated men indicate a potential role of testosterone in the prevention of Alzheimer's disease, although these findings have to be regarded as preliminary [64–67]. Accordingly, the Baltimore Longitudinal Study of Aging found lower free testosterone concentrations in men who developed Alzheimer disease prior to diagnosis [68]. A recently published review addressed the neuroprotective role of testosterone and evaluated the future prospects of testosterone therapy in mild cognitive impairment and Alzheimer's disease [69]. Studies examining the relationship between testosterone and depression led to conflicting results [70]. While an integral role of reduced testosterone levels in major depressive disorder is not conclusively demonstrated and appears rather doubtful [71–74], several studies highlight the etiological importance of androgen deficiency in mild depressive conditions, such as dysthymia [75–78]. Certainly, in this context, it should be kept in mind that a myriad of factors contribute to depression and a predisposition for suicide. A historical cohort study ($N = 78$, age $\geqslant$ 45 years, mean age: 65 years) showed that the 2-year incidence of diagnosed depressive illness was 21.7% in hypogonadal men (free testosterone $\leqslant$ 0.9 ng/dL) versus 7.1% in others [$chi^2(1) = 6.0$, $p = 0.01$]. According to Kaplan-Meier survival analysis, time to diagnosed depression differed significantly between hypogonadal and eugonadal men (log-rank test $chi^2(1) = 6.9$, $p = 0.008$) [79]. These results were confirmed by a second study involving 748 men (age $\geqslant$ 50 years) without prior ICD-9-diagnosed depression. A hazard ratio of 2.1 (95% CI 1.3 to 3.2, $p = 0.002$) was found for depressive illness in men with low testosterone levels [75]. Linear regression and quartile analysis of the Rancho Bernardo Study ($N = 856$, age range: 50–89 years) revealed a significant inverse correlation between the Beck Depression Inventory (BDI) score and bioavailable testosterone ($p = 0.007$) [76]. A relation between depression and the androgen receptor CAG repeat lengths has been seen when investigating 1000 men aged 48–79 years (mean age: 62.6 years) [80]. Several underlying reasons for this finding were proposed including the faster age-related decline in testosterone levels observed in men with shorter CAG repeat lengths [81]. Testosterone replacement studies have demonstrated that exogenous testosterone decreases anger, irritability, sadness, tiredness, and nervousness in hypogonadal men [82]. It has been reported that testosterone therapy may be more beneficiary in men with late-onset depression than in early-onset patients [83]. Two studies indicate that exogenous testosterone may be an effective augmentation treatment for SSRI-refractory major depression in hypogonadal men. These studies also implied a high rate of hypogonadism in men with treatment-refractory depression [84,85].

Muscle strength and metabolic syndrome – Recommendation 2 (4 and 5)

Aging generally entails progressive muscle loss and muscle weakness accompanied by impaired physical ability, reduced functional performance, and a higher incidence of falls and fall-related injuries [86–90]. Among various factors involved, decreasing serum free-testosterone was found to be linked to a decline in muscle mass and strength when analyzing a cross-sectional sample of elderly men from the New Mexico Aging Process Study [91]. Evaluation of the data from 845 men aged 45–85 years participating in the MINOS study showed that sarcopenic men defined as the lowest quartile of relative appendicular skeletal muscle mass index in the studied cohort

(< 6.32 kg/m$^{2.3}$) had concomitantly lower values for apparent free testosterone concentration (AFTC) and free testosterone index (FTI) [92]. A study among African-American males (age range: 70–102 years) with bioavailable testosterone levels below the normal range of young males demonstrated a positive relation between bioavailable testosterone and upper- and lower-limb strength and functional tests [93]. Furthermore, testosterone levels were found to have a significant positive impact on functional parameters of both, the upper and lower extremities [94]. A cross-sectional study of 370 nursing home residents revealed an inverse trend between testosterone levels and dependency in activities of daily living [95]. Similarly, a positive correlation of non-SHBG-bound testosterone (bio-available testosterone) with muscle strength and increase in fat mass was found in a cross-sectional study in healthy elderly men ($N = 403$ men, age range: 73–94 years) [96]. Several studies prove a positive influence of testosterone supplementation on muscle status, strength, and body composition in hypogonadal patients. Testosterone enanthate (100 mg/week, im injections) was administered to 7 hypogonadal men (age range: 19–47 years) for 10 weeks. A significant increase of fat-free mass (change: $+5.0 \pm 0.7$ kg; $p = 0.0004$), of the cross-sectional area of the triceps arm muscle (from 2421 ± 317 to 2721 ± 239 mm^2; $p = 0.045$) and the quadriceps leg muscle (from 7173 ± 464 to 7720 ± 454 mm^2; $p = 0.0427$), and of muscle was observed following testosterone treatment [97]. A small, randomized trial with older hypogonadal men ($N = 17$, mean age 65 ± 7 years) demonstrated that testosterone therapy (injections of 200 mg testosterone cypionate biweekly for 12 months) leads to improved bilateral grip strength ($p < 0.05$ by ANOVA) [98]. In a small controlled study, older hypogonadal males (bioavailable testosterone < 70 ng/dL) given testosterone enanthate (200 mg/mL, im, every 2 weeks for 3 months) experienced a significant increase in right hand muscle strength [99]. A decrease of lean body mass and an increase in adipose tissue mostly in intra-abdominal deposits occurs over the lifespan in both genders [86]. The examination of 36 adult men with acquired hypogonadism (age range: 22–69 years; median: 58 years) inferred that testosterone enanthate administration (100 mg/week for 18 months) leads to a decrease in body fat ($14 \pm 4\%$, $p < 0.001$) and subcutaneous fat ($13 \pm 4\%$, $p < 0.01$) and an increase in lean muscle mass ($7 \pm 2\%$, $p = 0.01$) [100]. Accordingly, investigators of a double blind study (duration: 36 months) with 108 men (age > 65 years) randomly assigned either to a testosterone patch or a placebo patch concluded that elevating the serum testosterone concentrations to the mid-normal range for young men decreases fat mass, primarily in the arms and legs, and increases lean mass, mainly in the trunk [101]. In a randomized, double-blind, placebo-controlled clinical trial (duration: 9 months) with healthy, obese men (age range: 40–60 years) having serum testosterone levels in the low-normal range (2–5 ng/mL), testosterone enanthate supplementation led to a continuous decrease of subcutaneous fat, whereas visceral fat was observed to slightly grow from month 3 to 9 [102]. Following a 3 month testosterone enanthate treatment (100 mg weekly, im), a significant increase in lean body mass was seen in healthy men (age range: 57–76 years) with a low or borderline low serum testosterone level ($\geqslant 13.9$ nmol/L) [103]. Compared with placebo, oral administration of testosterone undecanoate (80 mg, twice daily) for 1 year to 76 healthy men (age $\geqslant 60$ years) with a free testosterone index of 0.3–0.5 improved lean body mass ($p = 0.0001$) and decreased fat mass ($p = 0.02$) [104]. Most recently, a placebo-controlled study with 70 men (testosterone < 350 ng/dL, age $\geqslant 65$ years) evaluated the effect of testosterone enanthate (200 mg, every 2 weeks) in combination with finasteride (5 mg, daily). Following 36 months of treatment, a significant improvement in performance assessed by a timed functional test ([$4.3 \pm 1.6\%$ (mean $\pm$ SEM, T-only) and $3.8 \pm 1.0\%$ (T + F) vs. $-5.6 \pm 1.9\%$ for placebo; $p < 0.002$ for both T and T + F vs. placebo)], increased handgrip strength ($p < 0.05$), and lean body mass 3.77 ± 0.55 kg (T-only) and 3.64 ± 0.56 kg (T + F) vs. -0.21 ± 0.55 kg for placebo ($p < 0.0001$)] have been seen. The addition of finasteride to the testosterone regimen resulted in the prevention of a PSA increase and the attenuation of an increase in prostate size. Of note, differences in the incidence of prostate cancer have not been observed among the groups [105]. In a study with 61 eugonodal men (18–35 years). Bhasin et al. established a dose-response relationship between testosterone and body composition, muscle size, strength, power, and various other body systems. Randomized to one of five groups study participants received monthly injections of a long-acting gonadotropin-releasing hormone agonist to suppress endogenous testosterone secretion, and weekly injections of testosterone enanthate (25, 50, 125, 300, or 600 mg for 20 weeks). Fat-free mass increased dose dependently (change: 125mg: + 3.4 kg; 300 mg: + 5.2 kg, and 600 mg: + 7.9 kg, respectively). The changes in fat-free mass were found to be highly dependent on testosterone dose ($p = 0.0001$) and correlated with log testosterone concentrations ($r = 0.73$, $p = 0.0001$). Increase in leg press strength, leg power, thigh, and quadriceps muscle volumes were positively correlated with testosterone concentrations, while changes in fat mass and plasma high-density lipoprotein (HDL) cholesterol were negatively correlated [106]. Subsequently, the investigators performed a randomized, double-blind trial with analogous design to compare responsiveness of androgen-dependent outcomes to graded testosterone doses in older men ($N = 60$, age range: 60–75

years) with the data previously obtained in young men. 52 of the 60 older men completed the study. Changes in serum total testosterone and hemoglobin levels were dose-related in older men and significantly greater in older men than in young men (each $p < 0.0001$). The changes in fat free mass (25 mg: -0.3 kg, 50 mg: $+1.7$ kg, 125 mg: $+4.2$ kg, 300 mg: $+5.6$ kg, and 600 mg: $+7.3$ kg in the five ascending dose groups) and muscle strength in older men were correlated with testosterone dose and concentrations and did not significantly differ from those found in young men. An inverse correlation was observed for fat mass and testosterone dose ($r = -0.54$; $p < 0.001$) with a significant difference in young vs. older men ($p < 0.0001$). With low frequency of adverse events and significant gains in fat-free mass and muscle strength, a testosterone dose of 125 mg was found to be best in older men [107]. The reader is referred to an excellent review written by Bhasin for detailed information on the impact of testosterone on the skeletal muscle [108].

Testosterone levels have been found to negatively correlate with plasma triglycerides. A decline in total cholesterol and low density lipoprotein cholesterol caused by testosterone supplementation has been observed in a number of studies [99,104]. Testosterone was demonstrated to be the most important independent hormonal determinant of high density lipoprotein in healthy middle-aged men [109]. An impairment of insulin metabolism and a reduction of insulin sensitivity have been seen in men with low plasma testosterone levels [110]. *Recommendation 4(2)* stresses that ''diabetes should be evaluated and treated before or simultaneously with testosterone substitution'' in LOH patients. Low total testosterone has been suggested to predict development of the metabolic syndrome and diabetes based on a longitudinal study with 702 middle-aged Finnish men participating in a population-based cohort study. Men with total testosterone, calculated free testosterone, and SHBG levels in the lower fourth had a several fold higher risk of acquiring the metabolic syndrome (odds ratio 2.3, 95% CI 1.5–3.4; 1.7, 1.2–2.5; and 2.8, 1.9–4.1, respectively) and diabetes (2.3, 1.3–4.1; 1.7, 0.9–3.0; and 4.3, 2.4–7.7, respectively) after adjustment for age and other confounders including cardiovascular disease, smoking, alcohol intake, and socioeconomic status [111]. The Rancho Bernardo Study found an odds for newly diagnosed diabetes of 2.7 (95% CI 1.1–6.6) for men in the lowest quartile of total testosterone and significant association with insulin resistance in unadjusted and multiple adjusted analyses ($p < 0.05$). However, reports on testosterone as an independent predictive factor for insulin resistance remain conflicting. The inverse association of testosterone with insulin resistance was observed to be confounded by SHBG and mediated through increased body fat [112,113]. Another report stated that low plasma levels of bioavailable testosterone do not independently predict excessive insulin resistance [114]. In a series of studies with a range of different formulations and treatment durations, including injection of a single dose of testosterone enanthate (500 mg), administration of oral testosterone undecanoate or transdermal testosterone and dihydrotestosterone, a decrease in glucose tolerance was found in obese men with the most pronounced effect in men with relative hypogonadism from the outset [115]. Oral testosterone undecanoate (120 mg daily, for 3 months) improved glucose homeostasis in middle-aged men with type 2 diabetes and mild androgen deficiency [116]. While these studies are encouraging, larger trials are warranted to irrefutably prove positive effects of testosterone on features of the metabolic syndrome including insulin resistance.

Body hair and skin – Recommendation 2(6)

Alterations in androgen homeostasis are known to exhibit a profound effect on body hair and skin. Several functions of the skin including sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis and wound healing are regulated by the action of androgens on certain nuclear androgen receptors [117–120]. The association of locally increased androgen activity and skin disorders is obvious in acne, hirsuitism, and androgenetic alopecia in males [121–123]. A small study investigating the hormonal pattern of 37 men with premature alopecia found that the frequency of subnormal values in testosterone and epitestosterone (but not in free androgen index) was significant in balding men [124]. Recently, it was demonstrated that the skin is an endocrine organ capable to independently carry out the total biosynthesis of testosterone [125,126]. A decline in tissue androgen concentrations in most tissues with age has been reported for both sexes [118,127]. LOH is known to be accompanied by body hair and skin alterations [128,129]. A study with men older than age 50 having low serum testosterone (mean: 2.68 ± 0.51 ng/ml, range: 1.21–4.13 ng/ml) documented a loss of pubic hair in 70% and loss of axillary hair in 55% of the participant [130]. At present, research does not provide detailed information how exogenous testosterone affects the skin of aging men.

Bone mineral density – Recommendation 2(7)

Although osteoporosis, the most predominant metabolic bone disease, particularly affects postmenopausal women and guidelines for diagnosis and management are primarily geared toward female patients, it is increasingly recognized that also in men prevention of osteoporosis is strongly warranted, since it is a common cause of morbidity, mortality and health care expenditure. One in eight men older than 50 years will experience an osteoporotic fracture. The mortality rate caused by hip

fractures has been found to be almost doubled in men (31%) as compared to women (17%) one year after fracture [131]. Major risk factors for male osteoporosis include prolonged glucocorticoid therapy, hypercalciuria, androgen ablation therapy in prostate cancer patients, gastrointestinal disease, and high alcohol consumption [132,133]. Up to now, the biphosphonate aledronate and the recombinant parathyroid hormone teriparatide are the only preventive measures against male osteoporosis approved by the regulatory authorities. Over the last decade, numerous studies have been aimed to establish a link between age-associated hormonal endocrine deficiencies and lowered bone mineral density (BMD), which predisposes elderly men for osteoporosis and bone fractures [134]. Among the sex steroids investigated, bioavailable estradiol was found to be one of the strongest determinants for age-related bone loss [96,135,136]. Although generally weaker in aging men, the association between low bioavailable testosterone and low BMD is now widely considered as established [96,137–139]. In men with idiopathic osteoporosis, lower levels of estradiol (91.3 ± 5.8 vs. 114.6 ± 7.8 pmol/L; $p = 0.044$), higher levels of sex hormone binding globulin (31.5 ± 3.1 vs. 24.2 ± 1.4 nmol/L; $p = 0.034$) and a decreased free androgen index (42.6 ± 5.2 vs. 56.4 ± 5.9; $p = 0.016$) have been observed [140]. A cross-sectional study with 83 men (age > 65 years) having low bioavailable testosterone levels ($\leqslant 4.44$ nmol/l) showed that bioavailable testosterone, body mass index (BMI), and physical activities (assessed by the PASE questionnaire) are significant predictors of femoral neck BMD. Testosterone accounted for 20.7%, physical activity score for 9.0%, and BMI for 6.5% of femoral neck BMD [141]. The MINOS study with 1040 elderly men demonstrated that low apparent free testosterone concentration (AFTC) appears to have the best discriminative power for densitometric, biochemical, and functional parameters of bone resorption, followed by free testosterone index (FTI) and total testosterone. Hypogonadal elderly men were found to have increased bone resorption, an impaired static and dynamic balance, a higher risk of falls, and a slightly lower BMD [142]. Analysis of data from a geographically defined cohort in Rancho Bernardo gave a positive correlation between higher bioavailable testosterone levels and BMD of the ultradistal radius, spine, and hip in older men ($N = 534$, mean age: 68.6 years) [143]. A longitudinal 4-years study with 200 elderly men (age range: 55–85 years) found that the ratio between serum estradiol and serum testosterone as an indirect measure for aromatase activity was decreased in osteoporotic subjects indicating that the ability to aromatize testosterone to estradiol is an important factor contributing to a healthy bone metabolism in the elderly [144]. Several trials were performed to clarify whether testosterone therapy can normalize and sustain BMD to prevent bone fragility in hypogonadal men. Testosterone in a range of different formulations was proven to exhibit beneficiary effects on BMD suggesting that testosterone supplementation helps to avoid bone frailty and heightened fracture risk [100,145–150]. Interestingly several studies point towards an inverse relationship between the basal serum concentration of testosterone and the increase in BMD attained during testosterone treatment [151]. A randomized, placebo-controlled, double blind study over 36 months ($N = 108$, age > 65 years) investigating the effect of a testosterone patch revealed that the lower the pre-treatment serum testosterone concentration, the greater the outcome of testosterone therapy on lumbar spine bone density ($p = 0.02$). An increase of $5.9 \pm 2.2\%$ in lumbar spine BMD was calculated for a pre-treatment testosterone concentration of 200 ng/dL (6.9 nmol/L) using linear regression analysis [152]. Most recently, a controlled, randomized study in elderly men with low serum testosterone (< 12.1 nmol/L) was carried out to investigate the potential of combination therapy with testosterone enanthate (TE) (200 mg, every 2 weeks) and finasteride (F) (5 mg, daily) to increase BMD and concurrently attenuate postulated negative effects on the prostate. Finasteride administration was found to be beneficiary with a significant lower increase in prostate volume in the TE + F group compared with both the TE-only and placebo groups ($p = 0.02$). BMD in these men improved at the lumbar spine [$10.2 \pm 1.4\%$ (mean percentage increase from baseline $\pm$ SEM; TE-only)] and [$9.3 \pm 1.4\%$ (TE + F) vs. $1.3 \pm 1.4\%$ for placebo ($p < 0.001$)] and in the hip [$2.7 \pm 0.7\%$ (TE-only) and $2.2 \pm 0.7\%$ (TE + F) vs. $-0.2 \pm 0.7\%$ for placebo, ($p \leqslant 0.02$)] [153]. The mechanisms underlying the effects of testosterone on BMD remain to be elucidated. Postulated contributing factors include a potential direct action on androgen receptors and associated cytokines and growth factors and aromatization of testosterone to estrogens [12]. A small randomized, double blind study with 51 men receiving either testosterone (200 mg mixed esters), nandrolone decanoate (200 mg), or placebo (im, every fortnight for 12 months) indicated that aromatization is necessary for androgen action on bone but not on muscle [154].

Biochemical assessment of LOH

Recommendation 3 provides information on the biochemical investigations which should be performed to diagnose age-related testosterone deficiency. Testosterone in the blood is mainly bound to serum proteins with only 2% of the hormone circulating as free testosterone. Sex hormone binding globulin (SHBG) accounts for 60% of testosterone binding and 40% of the total testosterone is bound by albumin or other proteins. Bioavailable testosterone, referring to free and

albumin-bound testosterone together, is thought to reflect an individual's biologically active, circulating testosterone. Biochemical parameters commonly used to assess androgen deficiency include total testosterone, free testosterone, calculated free testosterone, bioavailable testosterone, and free androgen index [155]. The basic evaluation starts with the measurement of total serum testosterone levels, which is inexpensive, automated, and available in most clinical laboratories. However, results have been found to be misleading when SHBG is elevated. Calculation of free testosterone based on serum levels of testosterone and SHBG may be used to avoid inaccuracies in assessing the individual degree of androgenicity in a cost-effective manner and is suggested by *Recommendation 3(1)* [156]. An easy to use free automatic calculator can be found at: www.issam.ch. Alternatively, the equilibrium dialysis method can be employed to measure free testosterone more precisely [157]. A study undertaken to evaluate the currently available assays provides a valuable overview on methods for serum testosterone quantification [158]. Measurement should ideally be performed between 8 and 11 am due to the circadian rhythm of testosterone production by the testicles. According to *Recommendation 3(2)*, total serum testosterone levels below 8 nmol/L (231ng/dL) or free testosterone below 180 pmol/L (52 pg/mL) indicate hypogonadism and testosterone supplementation may be appropriate following exclusion of alternative causes. Total testosterone levels above a threshold of 12 nmol/L (346 ng/dL) or a free testosterone level above 250 pmol/L (72 pg/mL) is commonly regarded as normal [12].

Recommendation 3(4) addresses the need for repeated measurements "if testosterone levels are below or at the lower limit of the accepted normal young adult male values" considering that large intra-individual fluctuations in the level of serum testosterone over time have been observed [158]. Total testosterone levels between 8 and 12 nmol/L should be re-measured and followed up by calculation of free testosterone from total testosterone and SHBG concentrations (www.issam.ch) or by measurement of free testosterone levels by the dialysis method, or bio-available testosterone by the ammonium sulfate precipitation method. Since normal ranges vary significantly from laboratory to laboratory depending on the methods used and/or the assay kits employed [159], the assays to be used need to be under strict quality control and it is advisable to establish normal ranges in each laboratory [160,161]. The results from each patient should then be compared with the normal ranges established by each laboratory. An assessment of serum luteinizing hormone (LH) and prolactin is recommended to rule out other causes for hypogonadism [162,163]. The concentrations of several other hormones including thyroid hormones, cortisol, dehydroepiandrosterone(sulfate) (DHEA(S)), melatonin, GH and IFG-1 are known to decrease in men when growing old [164]. The levels of these hormones may be determined in certain individuals with suspected endocrine disorders according to *Recommendation 4(1)*. However, a routine evaluation of these parameters is not warranted until the clinical relevance of the observed changes is better clarified.

Formulation, dosage and alternative therapies (*Recommendation 7 and 8*)

Testosterone and its derivatives are commercially available in injectable, oral, buccal, transdermal, and subdermal preparations (Table I) [165]. Physicians treating patients with LOH should make themselves familiar with the different delivery forms currently marketed and their advantages and drawbacks (*Recommendation 7(1)*). The patient should be informed accordingly. Esterification of the testosterone molecule at the 17β-hydroxy position generates injectable testosterone esters, such as testosterone propionate, testosterone cypionate, testosterone en-

Table I. Available testosterone formulations *obsolete.

Administration route	Available formulation	Dose
injectable	testosterone in solution	10–50 mg, im, every 2 days
	testosterone cypionate (in oil suspension)	50–250 mg, im, every 2–4 weeks
	testosterone propionate (in oil suspension)	10–25 mg, im, twice a week
	testosterone enanthate (in oil suspension)	50–250 mg, im, every 2–4 weeks
	testosterone undecanoate (in oil suspension)	1000 mg, every 10–14 weeks
oral	testosterone undecanoate capsules (in oleic acid)	40–80 mg/day
	testosterone undecanoate capsules (in a mixture of castor oil and propylene glycol laurate)	initially: 120–160mg/day for 2–3 weeks, then: 40–120 mg/day
	fluoxymesterone*	2.5–20 mg/day
	methyltestosterone*	10–20 mg/day
	mesterolone	75–150 mg/day
buccal	testosterone buccal system	30 mg/twice a day
transdermal	testosterone patch	5 mg/day
	testosterone gel	5 g of 1% testosterone gel
subcutanous	pellets of crystalline testosterone	600 mg every 4–6 months

anthate, and testosterone undecanoate, which all can be administered intramuscularly to avoid the hepatic first pass effect. Hydrolysed to testosterone at the injection site, the ester derivatives are prone to produce swings in serum levels with peak testosterone levels rising rapidly to the supraphysiological range. This, however, is not the case with the new long-acting preparation of testosterone undecanoate [166]. To be able to rapidly react and stop treatment, when side effects and contraindications emerge, the advice is given not to use the long-acting injectable and testosterone implants in LOH, and favor the short-acting transdermal, oral and buccal delivery modes (*Recommendation 7(2)*). Unanimous agreement could not be reached on *recommendation 7(2)*. Three members of the panel (A.M, B.L. & J.J.L.) felt that no evidenced based documentation exists to recommend one over any other testosterone preparation. There is no evidence that the use of a long acting testosterone undecanoate in men with symptomatic late-onset hypogonadism is contra-indicated. The concerns on prostate safety are addressed in *Recommendation 10* suggesting initial monitoring every 3 months and quarterly for the first 12 months. Since the use of testosterone undecanoate requires periodic injections (initially at 6 weeks and subsequently every 12 weeks), the safety concerns are addressed by recommending a DRE, PSA and Hb prior to each injection. This will ensure compliance of both the patient and treating physician. Furthermore, a total androgen blockade using antiandrogens can be applied according to an expert opinion (F. Labrie personal communication 2005), in case an excessive high level of Hb or a prostate cancer is diagnosed during testosterone treatment.

Transdermal, oral and buccal administration routes are convenient and can be carried out by the patient himself. Testosterone patches bring serum testosterone to normal levels and imitate the circadian production of testosterone [167]. However, it is of note that thus far no evidence exists for any implications of mimicking the circadian rhythm. In some individuals, the use of testosterone patches leads to skin irritation, which occasionally can be severe. Newer testosterone patches in phase III clinical trials seem not to cause skin irritation [168]. The newly introduced testosterone gels minimize these problems while providing flexibility in dosing and a low discontinuation rate [169]. Orally administrable formulations include testosterone undecanoate as capsules, fluoxymesterone, methyltestosterone, and mesterolone. As emphasized in *Recommendation 8(1)*, the 17α-alkylated testosterone derivatives are obsolete due to their reported hepatotoxicity [170,171]. Oral testosterone undecanoate is co-absorbed with the lipophilic solvent from the intestine into the lymphatic system thereby circumventing first-pass inactivation in the liver. Therefore, it is free of liver toxicity. Following release into the plasma, testosterone undecanoate is hydrolyzed to testosterone and brings serum testosterone levels within physiological range. One major drawback of the older preparation lies in its short shelf-live (3 months) causing inconvenient storage. Recently, a formulation of testosterone undecanoate in a mixture of castor oil and propylene glycol laurate has been introduced with markedly increased stability (3 years at room temperature) [172]. *Recommendation 7(3)* stresses the lack of scientific data regarding optimal serum testosterone levels for treatment of LOH. Table I summarizes the approved dose for each delivery form. The best approach appears to aim at mid to lower young adult male serum testosterone levels and to avoid temporary supraphysiological levels.

Recommendation 8(2 and 3) notes that at present alternative supplements such as dihydrotestosterone (DHT), dehydroepiandrosterone(sulphate) (DHEA(S)), androstenediol, androstenedione, and hCG, are not considered as a treatment option in LOH due to a paucity of scientific data regarding safety and efficacy in aging men (*see Recommendation 4(1)*). DHEA, androstenediol, and androstenedione are converted to testosterone and are marketed as nutritional supplements for the prevention of age-related disorders in the USA [173]. Androstenediol and androstenedione have not been sufficiently evaluated in older men. Due to a lack of well-conducted, long-term human trials the use of DHEA is still controversially discussed, although the extensive practical experience and some recent studies suggest positive effects on various body systems [174,175]. Human chorionic gonadotropin (hCG) stimulates the production of testosterone in Leydig cells and is used to initiate spermatogenesis in patients with hypogonadotropic hypogonadism [176,177]. Only a few studies have been carried out to investigate whether hCG administration may be indicated in age-related androgen deficiency yielding some positive results of hCG on muscle mass, osteoblastic collagen formation, and lipids [178–180].

Contraindications, potential risks and monitoring during therapy

Contraindications for testosterone therapy are summarized in *Recommendation 6* and include suspected or confirmed carcinoma of the prostate or breast, significant polycythemia, sleep apnea, severe heart failure, and severe symptoms of lower urinary tract obstructions (LUTOS) due to benign prostatic hyperplasia (BPH). Fluid retention, BPH, sleep apnea, erythrocytosis, gynecomastia, acne, skin irritations (high incidence with ''first-generation'' patches), and hepatotoxicity (for 17α-alkylated derivatives) have been reported as side effects [181]. When androgen deficiency has been diagnosed and testosterone supplementation has been initiated, monitoring becomes a life-time obligation to check effectiveness and safety of testosterone therapy (*see Recommendation 9*) and to assure timely detection of

newly acquired medical conditions, for which testosterone is contraindicated. The patient has to be aware of and to assume his responsibility to comply with continuous monitoring [1].

Prostate or breast malignancies

In cases of suspected or confirmed prostate or breast malignancies, it is an absolute necessity to refrain from testosterone therapy. Androgens have been found to stimulate the growth of clinically diagnosed cancer [182] and androgen-deprivation therapy remains the gold standard to treat metastatic prostate cancer [183,184]. Despite of what may appear to be obvious, the theory of causality between high testosterone and the progression of preclinical to clinical cancer does not stand on the firm ground of evidence-based medicine at present and continuous to be controversially discussed. Several reports indicate that testosterone can exacerbate prostate cancer by converting occult microscopic loci into clinically apparent lesions [185–187]. On the other hand, compilation of published prospective studies of testosterone replacement therapy ($N = 461$) gave a prevalence rate of prostate cancer (1.1%) in testosterone-treated men not differing from the general population [181]. A comparative 1-year testosterone supplementation study ($N = 75$) indicated that hypogonadal men with high grade prostatic intraepithelial neoplasia (PIN), which is believed to be a prostatic precancerous lesion, do not have a higher risk of cancer than men without PIN [188]. Kaufman and Agarwal administered testosterone in men following curative radical prostatectomy when PSA levels have remained undetectable. According to these authors, testosterone is not contraindicated in hypogonadal men after successful treatment of prostate cancer, provided that close monitoring is performed [189,190].

Recommendation 10 stresses that it is mandatory to ascertain prostate health prior to therapy with testosterone. To detect pre-existing prostate cancer, the prostate-specific antigen (PSA) should be determined and a digital rectal examination (DRE) should be performed at baseline in men older than 45 years. For monitoring purposes, quarterly intervals are recommended for the first 12 months followed by a yearly investigation. DRE in combination with the determination of PSA has been found to have a positive predictive value of 49% [191]. When the PSA value exceeds 4 ng/ml or the results of the DRE are suspicious, transrectal ultrasound-guided biopsies of the prostate should be performed to further verify the diagnosis (*Recommendation 10*). Various other PSA diagnostic parameters, such as free-to-total PSA density, PSA density of the transition zone, and PSA velocity, are now available improving specificity while maintaining a high sensitivity for prostate cancer detection in men with a total PSA of 2.5 to 10 ng/mL [192].

Polycythemia

High testosterone levels are knowingly associated with a rise in red blood cell mass and hemoglobin levels. Testosterone is involved in the mechanism of haematopoiesis by stimulation of erythropoietin in the kidneys and direct action on erythropoietic stem cells [193]. While the mild anemia prevalent in the elderly male population is partially linked to declining testosterone and supplementation can be beneficial [194], supraphysiological testosterone levels may become dangerous, since they can cause erythrocytosis entailing an aggravation of cardiovascular diseases. Depending on the mode of administration a wide range of risk for erythrocytosis has been reported with 3–15% for transdermal applications and 44% for injections [181]. When elevated hematocrit is detected during monitoring (*Recommendation 12*), appropriate measures are dosage reduction or withdrawal from treatment depending on severity.

Sleep apnea

Testosterone replacement therapy has been reported to worsen sleep apnea increasing the total number of disordered breathing events (apneas + hypopneas) per hour of sleep from 6.4 ± 2.1 to 15.4 ± 7.0 ($p < 0.05$) [195]. A high interpersonal variability has been observed. Replacement dosages of testosterone may reduce ventilatory drives in some individuals [196].

Mood and behavior

Testosterone levels above the physiological range may cause irritability, impulsive aggression, and signs of major depression [197,198]. A dosage of 1000 mg of intramuscularly administered testosterone undecanoate in castor oil increasing plasma testosterone concentrations from 20.7 ± 1.5 to 37.5 ± 2.2 nmol/L at week 1 and 31.6 ± 1.5 nmol/L at week 2 did not induce aggressiveness in a study with young eugonadal men ($N = 27$). Rising circulating testosterone positively correlated with anger-hostility and reduced inertia [199]. In another study, testosterone enanthate (200 mg, im, weekly for 8 weeks) did not significantly alter aggression or mood levels in eugonadal men, while testosterone treatment in hypogonadal men reduced tension, anger, and fatigue [200]. However, free testosterone levels showed significant positive correlations with measures of aggression in a trial with older men suffering from dementia [201]. Since the objective of LOH management is to sustain physiological plasma testosterone levels, the development of negative behavioral patterns is rare. Nevertheless, proper monitoring during treatment also includes the assessment of mood and behavioral changes (*Recommendation 11*).

Conclusion

Declining testosterone is certainly only one of several factors involved in the development of age-related conditions such as low BMD, sexual and erectile dysfunction, increased formation of adipose tissue, cognitive impairment, and late-onset depression. However, studies demonstrate that many older men with the biochemical evidence of testosterone deficiency experience improvement in signs and symptoms of LOH during testosterone treatment. While it is undebatable that long-term data on the effects of testosterone therapy in the older population are limited and specific risk data are urgently needed, it is also a fact that the use of testosterone supplementation in the elderly is on the rise. The physician must emphasize to the patient the need for periodic evaluations and the patients must agree to comply with these requirements. The physician's evaluation should include an assessment of the clinical response and monitoring, and certainly requires tailoring to the indications and the individual needs of the patient. The ISA and ISSAM recommendations are intended to assist the physician in the responsible management of LOH. Data helping to get a deeper understanding of the ISA and ISSAM recommendations have been provided herein.

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