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Standards, Guidelines and Recommendations of The International Society for The Study of the Aging Male (ISSAM)

Investigation, treatment and monitoring of late-onset hypogonadism in males

Official Recommendations of ISSAM

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INTRODUCTION

The field of hormonal alterations in the aging male is attracting increasing interest in the medical community and the public at large. Simultaneously, industry has realized the growing importance and enormous potential of the impact of a rapidly mounting population of males over the age of 50 years. This population will be positioned for special health needs in the first quarter of this century and probably beyond. Among these needs, hormone replacement therapy will find its proper place, as it has for postmenopausal women over the last 25 years.

It is fully recognized that the endocrinological changes associated with male aging are not limited to sex hormones. On the contrary, profound changes occur in other hormones such as growth hormone, dehydroepiandrosterone (DHEA), melatonin and, to a lesser extent, thyroxin. However, androgen decline in the aging male (ADAM), or partial androgen deficiency of the aging male (PADAM), also widely known as andropause, is a fast-developing field (since there is no consensus on nomenclature, the terms late-onset hypogonadism, PADAM and male climacteric are acceptable and used interchangeably). The understanding of ADAM among large sections of the medical profession dealing with mature men (i.e. primary care, internists, urologists, etc.) has not kept pace with the developments in the field. The International Society for the Study of the Aging Male (ISSAM) believes that it is somewhat premature to provide guidelines for the diagnosis, treatment and monitoring of men diagnosed with or suspected of suffering from ADAM. On the other hand, a great deal of confusion and misunderstanding exists surrounding the same three issues (diagnosis, treatment and monitoring) of the condition. Therefore, ISSAM – in fulfilling its mandate – considers that this is an opportune time to provide factual information on the various

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clinical aspects of the andropause in the form of a set of practical recommendations dealing exclusively with ADAM and androgen replacement therapy (ART). It is anticipated that further recommendations and guidelines on other similar areas of competence for ISSAM will be produced in the future.

Opinions on the need for and effects of hormone replacement in aging change frequently and long-held views are now being vigorously challenged. The material in these Recommendations represents recent information on the andropause; however, it may require frequent updates as new and relevant data become available. At the appropriate time, they may also be upgraded to guidelines for the evaluation and treatment of ADAM.

A draft of Society's Recommendations was previously published in this Journal[1] to give the opportunity for discussion at the 2002 biannual meeting of ISSAM. The Recommendations were reviewed by a panel of experts, a number of suggestions were submitted by well-informed physicians as well as representatives of industry and the document was presented and discussed in Berlin during the regular meeting of ISSAM. They were approved in principle. Further opportunity was given to the membership for criticisms. Some were received and incorporated when deemed appropriate by the authors.

DEFINITION

In men, gonadal function is affected in a slow progressive way as part of the normal aging process[2]. This process, leading to hypogonadism is variously known as male climacteric, andropause or, more appropriately, ADAM or PADAM. The terms andropause and male climacteric are biologically wrong and clinically inappropriate, but they adequately convey the concept of emotional and physical changes that, although related to aging in general, are also associated with significant hormonal alterations. The clinical manifestations of male secondary hypogonadism have been well defined over 50 years[3] but ART was not widely accepted, in part due to unrealistic expectations and adverse effects due to improper management of early androgen preparations. The diagnostic criteria are presently better understood. For instance, recently, a couple of validated questionnaires[4,5] have been proposed for either screening, diagnosing and/or assessing response to therapy[5]. More sophisticated diagnostic and monitoring questionnaires are in development. Although they may prove useful for screening and diagnosis of ADAM, all require further, wider experience, particularly in their transcultural applicability.

RECOMMENDATION 1

Definition: A biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems.

DIAGNOSIS

Clinical

The clinical picture is described in the definition below. It should be remembered that there is significant interindividual variability in the onset, velocity and depth of the androgen decline associated with age, and no factors have emerged that predict the characteristics or effects of the age-related hypogonadism. As a rule of thumb, the mean serum testosterone level decreases after the age of 50 years at a rate of approximately 1% per year. This is by no means a constant phenomenon: biochemical hypogonadism is detected in only about 7% of the age group less than 60 years old but increases to 20% in those over 60 years of age[6]. It may be argued, therefore, that only a minority of individuals develop ADAM. This may not be the case. Associated with advancing age, there is also an increase in the levels of sex hormone binding globulin (SHBG) which translates into a further decrease in bioavailable testosterone (free plus albumin-bound fractions). When the diagnosis is based on the measurement of bioavailable testosterone, up to 70% of men over the age of 60 were found to be hypogonadal[4]. To compound the difficulties in establishing biochemical and clinical correlates, there are three important areas that require further elucidation:

(1) It is not yet known what level of serum testosterone defines deficiency in an older man, although it is generally accepted that 2 standard deviations below normal values for young men is conclusively abnormal (11 nmol/l total testosterone or 0.255 nmol/l free testosterone when using methods described by Vermeulen and colleagues[7]. For bioavailable testosterone the value of 3.8 nmol/l has been recommended. A tool for calculating free and bioavailable testosterone can be found on the ISSAM website at www.issam.ch). Since normal ranges vary significantly from laboratory to laboratory, the results from each patient should be compared with the normal ranges established by each laboratory.

(2) In older men, there may be variable responses by the target organs (brain, bone, prostate, muscle, etc.) to the levels of androgens.

(3) The response by target organs may be influenced by a variety of endocrine disruptors, the nature of which is only beginning to be explored in men.

The combination of these three uncertainties is important: deficiency may become clinically apparent at different points within an individual or a population, depending on the marker used (e.g. androgen levels, bone mineral density).

RECOMMENDATION 2

ADAM or the andropause is a syndrome characterized primarily by:

(1) The easily recognized features of diminished sexual desire and erectile quality, particularly nocturnal erections[8];

(2) Changes in mood with concomitant decreases in intellectual activity, spatial orientation ability, fatigue, depressed mood and irritability[9];

(3) Decrease in lean body mass with associated diminution in muscle volume and strength[10,11];

(4) Decrease in body hair and skin alterations[12];

(5) Decreased bone mineral density resulting in osteopenia and osteoporosis[13];

(6) Increase in visceral fat.

(These manifestations need not all be present to identify the syndrome. In addition, the severity of one or more of them does not necessarily match the severity of the others, nor do we yet understand the uneven appearance of these manifestations. Moreover, the clinical picture may or may not be associated with low testosterone. Therefore, the clinical diagnosis should be supported by biochemical tests confirming the presence of hypogonadism).

Biochemistry

Establishing the presence of slight hypogonadism on a purely clinical basis is, in most cases, difficult and unreliable. Only the more severe cases lead to clinical suspicion. Despite this, there is some controversy as to the need for hormonal evaluation of the aging man. For instance, hormonal evaluation in men with erectile dysfunction has been questioned on the basis that it is not cost-effective[14]. Although this scepticism is not shared by others[15,16], there are several reasons to justify, at least, basic hormonal assessment of men with erectile dysfunction. It is commonly accepted that the combination of low sexual desire and erectile difficulties may be the result of serious hormonal abnormalities. The reality is not as simple or clear-cut as that. Not only may hypogonadal men be capable of adequate sexual erections but hormonal supplementation resulting in normal testosterone values does not always result in restoration of libido and improvement in the quality of erectile function[17].

In men at risk, or suspected of having hypogonadism, the ideal test would be the measurement of free testosterone by the equilibrium dialysis method. This method, however, is difficult to perform, not automated and largely inaccessible to most clinicians. Measurement of 'free testosterone' by radioimmunoassay is widely available but should be discouraged due to its unreliability. Determination of bioavailable testosterone is attainable in some parts of the world but it is expensive and not readily accessible. Measurement of total testosterone is readily available but the results need to be interpreted with caution, particularly in the elderly and the obese in whom elevations of SHBG may result in a factual hypogonadism that is not disclosed by the results of a total testosterone determination.

The calculated free testosterone is an adequate compromise when only determinations of total testosterone and SHBG are available[7]. The formula for calculated free testosterone is available from the Society's web page. Calculated free testosterone is an indirect but reliable method. 'The evaluation of aged men's androgenicity should rely on at least one of these assessments' (bioavailable testosterone or calculated free testosterone)[18].

It should be remembered, however, that the methodology for assessment of SHBG is not standardized and that the results of calculated free testosterone may vary among different areas of the world.

RECOMMENDATION 3

In patients at risk or suspected of hypogonadism the following biochemical investigations should be done:

(1) Serum sample for testosterone determination between 08.00 and 11.00. The most reliable and widely acceptable parameter to establish the presence of hypogonadism is the measurement of bioavailable testosterone or, alternatively a calculated free testosterone.

(2) If testosterone levels are below or at the lower limit of the accepted normal values, it is prudent to confirm the results with a second determination together with assessment of follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin.

OTHER ENDOCRINOLOGICAL ALTERATIONS ASSOCIATED WITH ADVANCING AGE

It is important to dispel the concept that endocrinopathies of elderly men are narrowly focused on testosterone. Although hypotestosteronemia is the most widely recognized and investigated hormonal alteration associated with the aging process, the production of several other hormones is also profoundly affected by age. Increasing attention is being paid to these hormones because changes in their levels can be responsible for some of the manifestations previously attributed exclusively to testosterone deficiency.

DHEA and DHEA-S

The decline in both DHEA and its sulfate DHEA-S is a more constant feature of advancing age than hypogonadism. By the fifth decade, the levels of DHEA decrease to less than 30% of those in men under the age of 30 years[19]. There is a widespread belief that declining levels of DHEA run in parallel with a decrease in well-being and that supplemental exogenous DHEA results in an improvement in quality-of-life parameters[20]. More recently, a study in healthy aging men found no beneficial effect of DHEA over placebo[21].

DHEA and DHEA-S are weak androgens secreted primarily by the adrenal glands. Their role in the maintenance of an adequate androgen milieu is not known with certainty but appears to be limited. Limited trials[22] have shown that exogenous DHEA does not have a detrimental effect on prostate-specific antigen (PSA) values; however, only properly controlled long-term studies will provide a clear picture on the effectiveness and safety of adrenal androgens in the treatment of global androgen deficiency states. Behavioral correlates of DHEA and DHEA-S in the male are inconsistent[23] and consensus on their usefulness does not exist[24].

Growth hormone

The production of growth hormone (GH), after puberty, also decreases with age, about 14% per decade[25,26]. Since the production of circulating insulin-like growth factor-I (IGF-I) is controlled by GH levels, both decline together. This reduction is associated with changes in lean muscle mass, bone density, hair distribution and the pattern of obesity also described in hypogonadal states[27,28]. Administration of GH can reverse these alterations[29] and does so more efficiently in eugonadal men than in their hypogonadal counterparts[30]. Whether the possible clinical improvement after GH administration will be outweighed by undesirable side-effects and whether the improvements would be sufficient to justify the financial burden, deserve further inquiry. The same applies to the use of the newer, orally active GH-releasing peptides and related non-peptide secretagogues.

Melatonin

Melatonin secretion by the pineal gland in response to hypoglycemia and darkness also decreases with age regardless of these stimuli[31]. The physiological role of the pineal gland is not completely understood but it is involved in gonadal function and regulation of biorhythms[32]. Other physiological effects ranging from analgesic and antioxidative[33] to immunomodulating[34] properties have been attributed to melatonin. Olcese presented evidence indicating that administration of melatonin slows the growth of cancer cells in rodents[35]. However, the large popular enthusiasm around the hormone has a precarious scientific basis. It is likely that administration of melatonin may improve the significant sleep disorders frequently seen in the elderly. As mentioned before, profound hypogonadism is associated with alterations in melatonin production[11], therefore making difficult the attribution of some symptoms (sleep disturbances) exclusively to deficits of one or the other hormone. Evidence is emerging of a wide range of direct and indirect activities of melatonin on many human organ systems[36].

Thyroxin

With aging, there is an increase in serum thyroid stimulating hormone (TSH) levels and a decrease in thyroxin, although TSH levels in the elderly who have hypothyroidism are lower than in younger patients with the same disease. Hypothyroidism should be suspected if there are occurrences of unexplained high levels of cholesterol and creatinine phosphokinase, severe constipation, congestive heart failure with cardiomyopathy and unexplained macrocytic anemia. In the elderly there may be overt and subclinical thyroid deficiency. The diagnosis may not be clinically evident, and only an index of suspicion supported by biochemical evidence confirms the diagnosis. Symptoms of hypothyroidism may mask those of hypogonadism[37].

Leptin

The production of corticosteroids and estradiol in males, remains fairly constant throughout life. In contrast, leptin, a relatively recently described hormone from adipocytes, is altered in hypogonadism which explains, in part, some the changes in fat distribution observed in these men[38]. Levels of leptin can be brought down by androgen supplementation[39] that usually results in a decrease in the degree of obesity[40].

The following recommendation is put forward regarding other endocrine alterations associated with aging:

RECOMMENDATION 4

It is recognized that significant alterations in other endocrine systems occur in association with aging but the significance of these changes is not well understood. In general terms, determinations of DHEA, DHEA-S, melatonin, GH and IGF-I are not indicated in the uncomplicated evaluation of ADAM. Under special circumstances, or for well-defined clinical research, assessment of these and other hormones may be warranted.

TREATMENT

Indications

It is common clinical wisdom that a firm diagnosis is desirable prior to embarking on any therapeutic plan. This also applies to the treatment of the hypogonadal man. The goals of treatment most commonly include the restoration of sexual functioning as well as libido and sense of well-being. Equally important, androgen replacement can prevent or improve already established osteoporosis and optimize bone density, restore muscle strength and improve mental acuity and normalize GH levels, especially in elderly males[32,41]. Testosterone replacement therapy should maintain not only physiological levels of serum testosterone but also the metabolites of testosterone including estradiol, to optimize maintenance of bone and muscle mass, libido, virilization and sexual function. Since some of the manifestations of ADAM are shared with other conditions independent of a man's androgenic status, appropriate biochemical confirmation of hypogonadism should be sought out prior to initiation of treatment.

This recommendation is considered mandatory before consideration of ART:

RECOMMENDATION 5

A clear indication (a clinical picture together with biochemical support) should exist prior to initiation of androgen therapy.

Age

As mentioned previously, aging of the pituitary–gonadal axis is progressive. Hence, age more likely correlates with the severity of the biochemical changes and clinical manifestations. These aging men, however, because of associated infirmities and other socioeconomic reasons, are less likely to be considered for treatment. Therefore, the following recommendation applies:

RECOMMENDATION 6

In the absence of defined contraindications, age is not a limiting factor to initiate ART in aged men with hypgonadism.

Preparations

Current, generally available treatment options include buccal and oral tablets and capsules, intramuscular preparations, both long- and short-acting, implantable long-acting slow-release pellets and transdermal scrotal and non-scrotal patches and gels. Neither injectable preparations nor slow-release pellets reproduce the circadian pattern of testosterone production by the testes. This is accomplished best by the transdermal preparations, although oral testosterone may also approximate a circadian rhythm by dose adjustments. The relevance of reproducing a circadian rythmicity during ART remains unknown. Common testosterone preparations and their recommended doses are shown in Table 1.

Oral preparations

Oral androgen preparations have become popular because of their convenience aspects (such as dose flexibility, possibility of immediate discontinuation, self-administration). However, they demand special consideration because they undergo rapid hepatic and intestinal metabolism. Therefore, special precautions may be necessary in order to achieve adequate serum androgen levels.

An oral preparation that is widely used throughout the world (and which is currently in clinical development in the USA) is testosterone undecanoate. As the only effective and safe oral testosterone ester, it circumvents the first passage through the liver, it is free of liver toxicity and brings serum testosterone levels within the physiological range. It is liposoluble and for this reason it must be taken with meals. Studies have shown that oral testosterone undecanoate

Table 1 Most frequently used testosterone preparations

	Generic name	*Trade name*	*Dose*
Injectable	testosterone cypionate	Depo-testosterone cypionate	200–400 mg every 3–4 weeks i.m.
	testosterone enanthate	Delatestryl Testoviron, Testosterone depot	200–400 mg every 2–4 weeks i.m.
	mixed testosterone esters	Sustanon 250	250 mg every 3 weeks i.m.
Oral	fluoxymesterone*	Halotestin	5–20 mg daily
	methyltestosterone*	Metandren	10–30 mg daily
	testosterone undecanoate	Andriol	120–200 mg daily
	mesterolone	Proviron Vistinon, Vistimon	25–75 mg daily
Subcutaneous	testosterone implants	—	1200 mg every 6 months
Transdermal	testosterone patches	Androderm	2.5–7.5 mg daily
		Testoderm	10–15 mg/day
	testosterone gel	Androgel	5–10 g

*17α-alkylated testosterone preparations fluoxymesterone and methyltestosterone are both associated with serious liver toxicity; i.m., intramuscularly

improves libido, erectile function and general well-being, increases bone mineral density and improves body composition[42,43].

In order to prevent the rapid metabolic breakdown in the liver, some oral agents available in some countries (particularly in the USA) are chemically modified. These alkylated androgens generally provide erratic androgenic activity and exhibit a potential for significant liver toxicity which includes hepatocellular adenomas and carcinomas, cholestatic jaundice and hemorrhagic liver cysts[44].

Finally, the oral dihydrotestosterone (DHT) derivative mesterolone is available in some countries. The compound is not aromatizable and cannot therefore be biotransformed into estradiol. As a consequence, it only exerts a partial androgenic effect, making it a suboptimal treatment option.

None of the oral medications results in a faithful reflection of the circadian level variations. However, careful selection of the timing and amount of the dosing may ameliorate this problem.

Parenteral preparations

Injectable esters of testosterone have been available for the longest time and their effects are well recognized. They are inexpensive and safe but their use carries several major drawbacks which include:

(1) The need for periodic (every 2–3 weeks) deep intramuscular injections.

(2) Wide swings in serum levels, initially (in about 72 h), result in supraphysiological levels of serum testosterone followed by a steady decline over the next 10–14 days[45].

(3) The steady decline frequently results in a very low nadir immediately before the next injection. This phenomenon translates in wide swings in mood and well-being – the roller-coaster effect – which is disconcerting and upsetting to both patients and their partners.

(4) Parenteral androgens do not provide the normal circadian patterns of serum testosterone and the intermittent supraphysiological levels that they produce may result in the development of breast tenderness and gynecomastia.

The most widely used parenteral preparations are the 17β-hydroxyl esters of testosterone which include the short-acting propionate and the longer-acting enanthate and cypionate. The propionate is rarely used because its short half-life requires administration every other day. The enanthate and cypionate esters of testosterone, on the other hand, can be administered at the dose of 200–400 mg every 10–21 days to maintain normal average testosterone levels[46]. Higher doses will not maintain testosterone levels in the normal range beyond the 3-week limit. Another option is a preparation containing a mixture of four testosterone esters (propionate, phenylpropionate, isocaproate and decanoate), each with a different elimination half-life, which is claimed to prolong the duration of action.

Appropriate treatment of hypogonadism with injectable esters of testosterone has been shown to improve libido, sexual function, energy levels, mood and bone density if they are caused by an androgen deficiency[47]. Persistent supraphysiological levels of serum testosterone may result in infertility due to suppression of LH and FSH production[48]. Although concern exists about the psychosexual effects of markedly elevated levels of testosterone in serum, evidence has been presented indicating that, even in eugonadal men, amounts up to five times the physiological replacement doses of testosterone cypionate have only minimal psychosexual effects[49].

Transdermal preparations

Transdermal testosterone therapy (TTT) offers a close reflection on the variable levels in testosterone production manifested in normal men over the 24-h circadian cycle. TTT is available in both scrotal and non-scrotal patches and in a gel form. The scrotal TTT lost its appeal due to inconveniences such as the inability to remain in place and the need for frequent shaving of the scrotal skin. In addition, due to the high concentrations of 5α-reductase in the scrotal skin, they produce abnormally high levels of DHT[50]. Transdermal non-scrotal patches produce normal levels of estradiol but, as opposed to the scrotal ones, result in normal levels of DHT[51]. In addition, to producing physiologically appropriate serum levels of testosterone, they lower levels of SHBG, promote virilization and increase bone mineral density[52].

Also, the testosterone patches, as compared to injectable forms, minimize excessive erythropoiesis and suppression of gonadotropins[53]. Most common side-effects of the body patches are related to the need to use enhancers to facilitate absorption; this frequently results in various degrees of skin reactions, occasionally reaching significant chemical burns. This may be prevented with the use of triamcinolone. The testosterone gel offers all the advantages of the patches[54], without the frequent skin reactions. Its only drawbacks reside in the potential for contamination of others and the lack of long-term studies with its use. The efficacy of transdermal DHT therapy has been reported recently[55,56].

Regarding the widely available forms of therapy, the following two recommendations are included:

RECOMMENDATION 7

Currently available preparations of testosterone (with the exception of the alkylated ones) are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the advantages and drawbacks of each preparation.

RECOMMENDATION 8

The purpose of ART is to bring and maintain serum testosterone levels within the physiological range. Supraphysiological levels are to be avoided.

ADVERSE EFFECTS

Like most medications, androgens have a potential for undesirable side-effects. These concerns are, primarily in regard to the liver, the prostate, lipid profile and cardiovascular system, hematological changes, sleep patterns and social behavior and emotional state.

Liver

Reports of liver toxicity manifested by jaundice and alteration of liver function, as well as the development of hepatic tumors, have been limited almost exclusively to cases in which the alkylated forms of testosterone have been used. Invariably, inserts of commercial preparations mention the potential for liver toxicity. Therefore, regardless of the form of ART employed, this recommendation is proposed:

RECOMMENDATION 9

Liver function studies are advisable prior to onset of therapy, quarterly during the first year and on a yearly basis thereafter during treatment.

Lipid and cardiovascular safety

The relationship between hypogonadism and alterations of the lipid profile remains to be completely resolved. Evidence is emerging supporting the concept that hypogonadism is associated with potentially unfavorable changes in triglycerides and high-density lipoprotein cholesterol and that such abnormalities can be corrected by restoring a physiological androgen milieu[57]. Other studies support the view that low testosterone is a significant risk factor for coronary artery disease[58–60]. Although most recent evidence continues to support the concept of a beneficial effect of androgens in coronary artery disease[61], the relationships between androgens and cardiovascular risk factors are complex and still understood only imperfectly. Similarly, the relationships between androgen levels in the serum and other lipoprotein sub-fractions have not been fully investigated[62]. Therefore, caution is advisable when supplementing androgens in men with significant risk factors for cardiovascular disease. The picture is further blurred by the fluid retention associated with androgen administration; this may add to any possible adverse effect of androgen therapy to the cardiovascular system.

This recommendation was approved on the issue of lipid alterations:

RECOMMENDATION 10

A fasting lipid profile prior to initiation of treatment and at regular intervals (no longer than 1 year) during treatment is recommended.

Prostate safety

It is well established that, in the absence of sufficient androgens the prostate gland fails to develop. Most studies, however, have shown no significant increases in PSA or prostate volume following administration of androgens to hypogonadal men[63]. Evidence from placebo-controlled studies of men receiving androgen supplementation indicate that the differences between the men on hormones and those on placebo were insignificant

in regard to prostate volume, PSA or obstructive symptoms[64,65]. Although testosterone has not been implicated in the development of benign prostate hypertrophy (BPH), nevertheless, in the presence of severe lower urinary tract obstructive symptoms (LUTOS), the administration of testosterone may result in the development of urinary retention. Whether testosterone promotes the development of prostate cancer remains to be elucidated. Current evidence indicates that serum levels of sex hormones bear no relation to the development of prostate cancer and there is either no change or only a modest increase in PSA levels after testosterone administration[66]. The suspicion of prostate cancer is, however, an absolute contraindication for androgen therapy. On the other hand, prostatic biopsies prior to onset of ART in the absence of an abnormal digital rectal examination (DRE) or PSA level are not indicated. However, a rapid increase in PSA or the appearance of abnormalities in the DRE are clear indications for a thorough evaluation of the prostate to rule out the presence of carcinoma. In this situation the administration of testosterone may have served as an early warning to the presence of an occult prostatic malignancy[67].

The issue of prostate safety and exogenous androgens is, perhaps, the gravest concern. The topic was recently reviewed[68]. The following three separate recommendations were considered and approved:

RECOMMENDATION 11

Digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA) are mandatory in men over the age of 40 years as baseline measurements of prostate health prior to therapy with androgens, at quarterly intervals for the first 12 months and yearly thereafter. Transrectal ultrasound-guided biopsies of the prostate are indicated only if the DRE or the PSA are abnormal.

RECOMMENDATION 12

Androgen administration is absolutely contraindicated in men suspected of having carcinoma of the prostate or breast cancer.

RECOMMENDATION 13

Androgen supplementation is contraindicated in men with severe bladder outlet obstruction due to an enlarged, clinically benign prostate. Moderate obstruction represents a partial contraindication to ART. Once the urinary obstruction has been successfully treated, these men are candidates for androgen supplementation.

Mood and behavior

The consequences of testosterone deficiency in mood regulation are widely accepted[69,70] to the point that, recently, a hypothesis has been advanced suggesting that perinatal androgen deficiency promotes deficient cognitive development[71]. However, concerns exist regarding the promotion of sexually aggressive behavior following testosterone administration. Significant behavioral changes can be observed with supraphysiological levels of androgens. Proper treatment, aimed at maintenance of physiological plasma levels, makes this a rare occurrence and certainly not a sufficient cause to withhold treatment[72].

RECOMMENDATION 14

ART normally results in improvements in mood and well-being. The development of negative behavioral patterns during treatment calls for dose modifications or discontinuation of therapy.

Hematology

The stimulatory effect of testosterone administration on bone marrow has long been recognized even in the presence of advanced malignant disease[73]. Testosterone therapy in older men often can result in a significant increase in red blood cell mass and hemoglobin levels[74]. In younger, healthier individuals, such as those receiving androgens for sexual dysfunction, the effects can also be marked[75]. Therefore, dose adjustments or phlebotomies may be necessary. Rarely, ART has to be discontinued due to polycythemia.

RECOMMENDATION 15

Polycythemia occasionally develops during ART. Periodic hematological assessment is indicated. Dose adjustments may be necessary.

Sleep apnea

Other possible effects of testosterone treatment include exacerbation of sleep apnea[76] although hypotestosteronemia has been cited as a cause of the condition[77].

RECOMMENDATION 16

There is insufficient evidence for a recommendation regarding safety of ART in men with sleep apnea. It is suggested, therefore, that good clinical judgement and caution be employed in this situation.

MONITORING PATIENTS ON ART

Hormonal replacement may be initiated for a variety of indications but treatment is normally for life. Monitoring of these patients is also a lifetime commitment that cannot be taken lightly. Monitoring, of course requires to be tailored to the indications and the individual needs of the patient. For instance, if the indication is osteoporosis, serial bone mineral density determinations are the method for monitoring therapeutic response. In this regard, the studies by Behre and colleagues[78] provide an elegant and graphic illustration on the effectiveness of chronic testosterone supplementation in increasing bone mineral density and in moving older men out of the range of high fracture risk. Another common indication for testosterone administration is for treatment of sexual dysfunction. In this situation, a simple and effective rule of monitoring is that, frequently, the patient's report is the most reliable indicator of treatment effectiveness[59]. In addition to the specific areas of interest, long-term monitoring of these patients centers on six domains in which concerns have existed for possible serious adverse events: the liver, lipid profile and cardiovascular disease, erythropoiesis, the prostate, sleep disorders and social behavior and emotional state.

RECOMMENDATION 17

Monitoring during ART is a shared responsibility. The physician must emphasize to the patient the need for periodic evaluations and the patient must agree to comply with these requirements. Since ART is normally for life, monitoring is also a lifetime mutual duty.

CONCLUSIONS

There is clear evidence that advancing age is associated with a decline in the production of several hormones. The most prominent alterations are related to the sex steroids but other hormones such as growth hormone and melatonin are also profoundly affected. The clinical syndrome of ADAM or andropause has been described but a direct causality between its manifestations and the alterations in a specific hormone are not yet fully established. There is, however, a growing body of literature supporting the concept of a clinical picture associated with hypogonadism in aging men that impacts significantly on the quality of life. Equally, there is sufficient evidence to support the concept that appropriate treatment of these men results in alleviation of some of the manifestations of the andropause. It behoves a variety of medical specialties to be familiar with the consequences of this condition, its investigation, treatment and monitoring.

Our understanding of ADAM is still incomplete and there exist a number of controversial issues in regard to hormonal replacement in elderly men. Standards or guidelines on the subject are, therefore, premature. Recommendations, however, are justified with the present state of knowledge. Recommendations[79] and guidelines[80–82] in the area of ART require frequent updates as further information emerges. We provide this set of Recommendations for physicians interested in the diagnosis and treatment of aging men with symptoms of hypogonadism. Recommendations, guidelines and standards are, normally, work in progress. They will be discussed again at the biannual meeting of ISSAM in Prague, February 2004.

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