The treatment of late-onset hypogonadism

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ABSTRACT

Late-onset hypogonadism (LOH) in aging men is a clinical and biochemical syndrome caused by an age-related decline in testosterone. Despite published in guidelines and recommendations, uncertainty surrounds the profile of clinical symptoms as well as the biochemical threshold of diagnosis. The only evidence-based treatment of late-onset hypogonadism is testosterone replacement therapy. The actual available evidence of the long-term risks and outcomes of testosterone-replacement therapy remains very limited, and carefully designed placebo-controlled trials of testosterone administration to assess the risks and benefits of such a therapy are required. Until such evidence is available, testosterone treatment should be restricted to elderly men with very low testosterone levels in the presence of clinical symptoms, and the advantages and disadvantages need to be accurately assessed. Careful monitoring of potential side effects is necessary. The purpose of this review is to discuss what is known and what remains unclear with respect to the benefits and risks of testosterone replacement treatment.

Key words: Aging male; late onset hypogonadism; testosterone replacement therapy.

International Society of Andrology (ISA), and The International Society for the Study of the Aging Male (ISSAM), and European Association of Urology (EAU) defined late-onset hypogonadism (LOH) as a clinical, and biochemical syndrome in men secondary to aging.^[1] In the clinical picture of this syndrome which biochemically manifests itself as a decrease in serum testosterone levels, symptoms, and impairment of quality of life can be also seen due to multiple organ involvement.^[2] Although various terminologies as andropause, male climacterium, Androgen Deficiency in Aging Male (ADAM) have been used for this syndrome which affects physical, social, psychological, and cognitive functions, currently 'late-onset hypogonadism' has been most widely used, and recommended terminology.^[3]

Number of aged individuals (>65 yrs) has increased 10-fold from 1900's, and elderly population is predicted to increase consistently. This increase in aged population has brought the issue of healthy aging into agenda.^[4] In females, menopausal symptoms which are related to the rapid decline in the production of ovarian hormones, are frequently seen in women aged 50 years, and over.^[5] Therefore, the etiology, and diagnosis of menopause have been inves-

tigated, and its treatment protocols have been determined in the past.. LOH in men, with its slower progression, and diversity in its symptoms has been recently analyzed anew, while aged population are increasingly growing in number. Establishment of diagnostic, and therapeutic standards is being investigated. From the biochemical perspective, starting from 40 years of age, annual decreases in total, and bioactive testosterone in male population have been shown to be at a rate of 0.8, and 1.6%, respectively.^[6] Decrease in total testosterone which is at a lesser extent than a decrease in bioactive and free testosterone, has been attributed to increase in sex-hormone binding globulin (SHBG) with aging.^[3] The incidence of hypogonadism in these patients has been reported at various rates in different age groups as follows: 2-30% (40-59 yrs), 20-45% (60-69 yrs), 34-70% (70-79 yrs), and in most of the male population over 80 years of age.^[7]

Pathophysiology

In various studies, decrease in hormone (especially androgens) production in adrenal glands with aging has been already demonstrated. Besides, in aging men diurnal pulsatile release pattern of testosterone is impaired, response of

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testosterone to luteinizing, and also human chorionic gonadotropin hormone generally attenuates. All of these factors are influential on the decrease in the testosterone levels with aging. In a study where the effect of aging on Leydig cell level was investigated, decreases both in steroidogenic ability at cellular level, and concentrations of some enzymes with aging were found, which was related to the drop in the production of testosterone.^[8]

Symptoms, and questionnaire surveys

Diagnosis of late-onset hypogonadism should be based on clinical symptoms, and supportive biochemical data. The most prevalent symptoms of LOH included in guidelines are summarized in Table 1. The presence of at least one of these symptoms, and detection of a decrease in total testosterone levels are sufficient to make a diagnosis of LOH.^[9] The abovementioned symptoms can emerge as a result of decrease in testosterone levels, and direct impact of aging. Decrease in total testosterone most frequently leads to weakening of libido, and decrease in morning stiffness, and erectile function.^[10] In order to evaluate these symptoms better, and use them for the monitorization of the treatment, different symptom questionnaire forms have been designed. Short Form-36 (SF-36),^[11] European Male Aging Study (EMAS),^[12] ADAM questionnaire form,^[13] International Index Erectile Function (IIEF)^[14], and Aging Males' Symptoms Questionnaire (AMS-Q)^[15] are most frequently used questionnaire forms. Among them the most frequently used one is AMS-Q whose Turkish version has been also validated.^[16] AMS-Q comprises total of 17 items which are subdivided in psychologic, somatic, and sexual domains. Therefore it is possible to determine severity, and type of the symptoms using this questionnaire form. This form has a 73.6% sensitivity, and 70.4% specificity in demonstrating the improvement of the disease after testosterone replacement therapy (TRT). In addition, its use has been recommended as a means to monitor these patients after initiation and/or termination of hormonal therapy.^[17]

Biochemical evaluation

In patients with late-onset hypogonadism, serum testosterone levels should be evaluated. All guidelines have arrived at a consensus which requires at least two serum testosterone analyses in blood samples drawn between 8:00 AM, and -10:00 AM. Testosterone replacement is recommended for symptomatic individuals with total testosterone levels below 8 nmol/L (231 ng/dL). As a generally accepted knowledge, total testosterone levels above 12 nmol/L (346 ng/dL) are considered to be normal physiologic levels. However in patients with total testosterone levels between 8, and 12 nmol/L, and typical LOH symptoms, investigators have indicated the necessity of treatment.^[9] Especially in symptomatic LOH patients analysis of only total testosterone can fail to diagnose LOH. A 50% of the total testosterone is

bound to albumin, 45% of it to SHBG, and the remaining small proportion to freely circulating testosterone. Biologically active testosterone forms in the body consist of albumin-bound bioactive testosterone, and free testosterone. Since levels of SHBG increase with aging, total testosterone concentrations can be within normal limits, even if concentrations of bioactive testosterone fall down. Therefore, in symptomatic patients with total testosterone levels within normal range or between 8-10 nmol/L, measurement of free, and also bioactive testosterone levels is recommended so as to reinforce the established diagnosis (these levels can be estimated using the on-line calculator available on website: www.issam.ch/freetesto.htm).^[3,18] Free testosterone levels below 225 pmol/L (6.5 ng/dL) strongly suggest hypogonadism in patients with low-normal total testosterone levels.^[19] Threshold value for bioactive testosterone is reportedly 281 pg/mL.^[20]

Treatment

Challenging issues in the diagnosis of late-onset hypogonadism are also reflected on the selection of the patients eligible for treatment. Supplemental hormone therapy is recommended for the patients with tabulated (Table 1) symptoms, lower testosterone levels in whom we conceived diagnosis of LOH also based on AMSQ assessment criteria.^[18] Unfortunately, in the urology practice, it is not always easy to recommend TRT for these patients. The abovementioned cases are typical LOH patients, and TRT can be initiated unless a contraindication exists. However in some of these patients testosterone levels are within normal limits, despite presence of symptoms, and other patients have not any complaints despite lower testosterone levels. This wider patient profile indicates that lower testosterone level is not the only etiological factor of LOH which complicates our decision to perform testosterone replacement therapy. Because of all these related factors, and its potential adverse effects, TRT was not favoured in the past. However, nowadays, relevant studies have been conducted on this issue, treatment algorithms have been developed, and professional associations interested in this subject recommend TRT in the treatment of LOH. (Table 2). An updated algorithm for the diagnosis, and treatment of LOH is presented in Figure 1.^[18]

Table 1. The most prevalent symptoms seen in LOH^[9]

Symptoms
Decrease in libido
Decrease in muscular mass, and strength
Decrease in bone mineral density, and osteoporosis
Reduce in vitality
Depressive mood
Increase in body fat

Table 2. Review of the guidelines which recommend testosterone replacement therapy^[18]**ISSAM**

Personal expert opinion

1996 Morales et al.

Endocrine Society

Recommendations based on evidence-based guidelines

2006 Endocrine Society Clinical Practice Guideline.

2010 Endocrine Society Clinical Practice Guideline.

Institutional recommendations of ISSAM

2002 ISSAM

2004 ISSAM, ISA, EAU, and KOSAR

2006 Korean J Aging Male

2008 Korean J Androl

Recommendations of evidence-based guidelines

2008 ISA, ISSAM, EAU, EAA, and ASA

2009 Park NC. Korean J Androl

ISSAM: International Society for the Study of the Aging Male; ISA: International Andrology Society; EAU: European Association of Urology; EAA: European Association of Andrology; ASA: American Society of Andrology; KOSAR: Korean Society for the Aging Male Research

Figure 1. Diagnostic algorithm for hypogonadism in the aging man**Treatment Alternatives**

Therapeutic goal in the treatment of late-onset of hypogonadism is to replace deficient amounts of testosterone. Any other evidence-based treatment except TRT has not been recommended so far. With this treatment we priorly expect improvement in libido, and erectile functions.^[21] Theoretically, the product we will use should be natural, endogenous, and it should kept the concentration of the relevant hormone at physiological

levels. Besides, its active metabolite should be used safely, and relieve the symptoms without causing any major adverse effects. However, such a medication which contains all of the enumerated features is not available currently.^[18] Testosterone formulations used for TRT, their modes of usage, and treatment regimens are given in Table 3. A standard treatment modality has not been formulated, yet. Appropriate treatment modality should be determined based on the request of the patient, and

Table 3. Current testosterone replacement treatment regimens for late-onset hypogonadism^[18]

Route of administration	Formulation	Active ingredient	Dose	Advantages	Disadvantages
Oral	Capsule	Testosterone undecanoate	40 mg x 4/gün	User-friendly	Variable serum concentrations, increased DHT/T ratio
Buccal	Bioadhesive tablet	Testosterone	30 mg x 2/gün		Gingival adverse effects (16%)
		Testosterone enanthate	250 mg 1/2-3 weeks		Fluctuations in T levels
Intra-muscular	Oily suspension	Testosterone cypionate	200 mg 1/2 weeks		
		Testosterone undecanoate	1000 mg 1/2-3 months frequency	Decreased application	Extra volume (4 mL)
Subcutaneous	Pellet/rod	Testosterone	3-6 (each contains 200 mg) 1/6 ay	Decreased application frequency	Need for a surgical procedure
	Scrotal patch		10-15 mg, 1/day the treatment	Ease in termination of	Increased DHT/T ratio
Transdermal	Non-scrotal patch	Testosterone	2.5-5 mg, 1/day	Ease in termination of the treatment, user-friendly	Tissue irritation
	Gel		1%, 10 g/day	user-friendly, improved tissue tolerance	Contamination potential during sexual intercourse

the physician, cost of the treatment, and evaluation of the advantages, and disadvantages of the treatment.^[18]

Negative feedback of exogenously administered testosterone on hypothalamic-pituitary-testicular axis, risks, and adverse effects of various testosterone formulations will be described later. Because of these inconveniences related to TRT, other alternatives have been searched for the treatment of LOH. Among these alternatives, currently, anti-estrogen treatment is used. Active substances like clomiphene citrate which binds weakly to estradiol receptors, and stimulates hypothalamic-pituitary-testicular axis with its negative feedback, and increase release of endogenous testosterone have been investigated. In the past this drug was used three times 50 mg a week for 3 months, in a current study it has been prescribed at daily doses of 25 mg for 3 months. At the end of the treatment, mean testosterone value rised from 310 ng/dL up to 669 ng/dL. The outcomes of the study have been found to be favourable as for efficacy (especially improvement in libido), and side effects, however conduction of further has been recommended.^[22]

Beneficial effects of TRT

Normalization of testosterone levels might improve most of the effects of hypogonadism. TRT makes the patient feel himself more energetic, and well. It exerts favourable effects on his emotional state, sexual functions, body mass index, cardiovascular system, bone mineral density, and erythropoiesis (Table 4). Thanks to these favourable effects of testosterone, its use has

been increased in recent years. In the United States of America a 500% increase in the sales of testosterone formulations has been reported.^[23]

Improvement in Sexual Desire, Function, and Performance

Normal sexual function in men, is a complex phenomenon made up of psychological, neurological, vascular, and hormonal factors.^[24] Impact of many independent factors including age, prostatic hyperplasia, body mass index, diabetes, chronic diseases (heart disease, hypertension etc.), concomitant medications, depression, and anxiety on sexual function has been demonstrated in many studies.^[25] Decrease in sexual desire caused by a drop in testosterone levels with aging, and significant improvement in libido with TRT have been indicated in various studies.^[26,27] Some studies have emphasized lack of any clear-cut association between erectile function, and testosterone levels.^[28] In a recent study, association between the decrease in the level of testosterone with aging and sexual symptoms was determined, and this correlation has been clearly demonstrated for testosterone levels below 8 nmol/L.^[29]

As indicated above, and in many literature studies, elderly hypogonadal patients regain their sexual drive following testosterone replacement therapy. In the meta-analysis of placebo-controlled studies, significant improvement in the libido of hypogonadal men has been demonstrated, while inconsistent responses obtained by oral agents have been emphasized.^[30] Another striking point is that response to treatment is insignificant and incon-

Table 4. Testosterone replacement therapy in the aging male, and its potential benefits^[28]

Potential benefits of the testosterone replacement therapy	Administration of testosterone replacement therapy
Effects on body	
Improvement in muscular mass	
Decrease in fatty mass	
Increase in muscular strength in lean or moderately fat elderly men	
Probably a little benefit in lumbar spine bone mineral density	In individuals with low-trauma fractures or osteoporosis, evaluate bone mineral densities of lumbar spine, femur neck, and pelvis 1-2 years after the treatment
Sexual function	
A favourable effect on sexual life in patients with lower pretreatment testosterone levels	Assessments at the beginning, and at 3., and 6. months of the treatment, then annually Also evaluate its effect on erectile dysfunction
Mood state, and quality of life	
A favourable effect on mood state in patients with lower pretreatment testosterone levels	Assessments at the beginning, and 3., and 6. months of the treatment, then annually
A significant impact on libido could not be found	
Components of type 2 diabetes mellitus, and metabolic syndrome	
A minor positive effect on HbA1c, and insulin resistance (a few number of findings in favour of contrary opinions have been also asserted)	Lack of any specific recommendations

sistent in individuals with low-normal testosterone levels.^[31] As a cause for this inconsistency, variable bioactive testosterone concentrations in individuals with low-normal total testosterone levels. have been implicated.^[18]

As mentioned above, the only reason for erectile dysfunction in patients with late-onset hypogonadism, is not decreased testosterone levels, but aging, and additional diseases also affect erection at a vascular level Therefore testosterone monotherapy fails in the treatment of LOH or yields inconsistent outcomes. Because of all these reasons, in the treatment of erectile dysfunction in this patient group, combined use of TRT, and PDE5 inhibitors has been brought into agenda.^[18] In animal, and human cell culture studies, it has been shown that pathogenesis of erectile dysfunction in hypogonadism induces a significant deterioration in the peripheral mechanism.^[32] Favourable effects of testosterone especially on penile smooth cells, decrease in smooth musculature caused by post-castration testosterone insufficiency which is replaced by connective matrix tissue have been demonstrated in many studies.^[33] It has been demonstrated that testosterone favourably increases nitric oxide synthase transcription, and PDE5 expression.^[34,35] Briefly, the effect of testosterone on erectile function is complex, and still debatable. Lack of any significant correlation between hypogonadism, and erectile dysfunction in already healthy population supports this phenomenon.^[27] Because of all these factors, in LOH patients with erectile dysfunction, combined use of testosterone, and

PDE5 inhibitors has been revived.^[36] Clinical studies have planned combination therapy in especially patients with hypogonadism refractory to PDE5 inhibitors. However, since, LOH patient group consists of elderly patients, and individuals with concomitant diseases, difficulties have been encountered in the definition of the the target population. Further long-term studies with homogenous groups are recommended to better determine its efficacy, and indications.^[37]

Effects on bone mineral density

Although osteoporosis appears to be the disease of the elderly women, it is also an important health problem in the aging male. Mortality rates of hip fractures are 2-fold higher in men when compared with women.^[38] Many studies have emphasized direct impact of testosterone, and estradiol on bone mineral density in men, and reported relevant hip fractures, and symptomatic vertebral fractures in 50, and 20% of the patients with hypogonadism, respectively.^[39] Various studies have emphasized the important role of estradiol on bone mineral density in men. As an etiological factor of osteoporosis in LOH patients, decrease in estradiol levels which is a metabolite of testosterone, relative to drop in testosterone levels with aging has been implicated. Therefore, maintenance of the bone mineral density in aging men requires both of these steroidal sex hormones.^[4] Osteoporosis, and rapid bone mineral loss following castration reinforce this information^[40] In a placebo-controlled study where post-TRT effectiveness was evaluated, investiga-

tors reported significant improvements in spinal bone mineral density in patients with baseline testosterone levels below 10 nmol/L, while they couldn't find any effect of 3-year-long TRT on bone mineral density of elderly male patients with baseline mean total testosterone level of 12.8 nmol/L.^[41] A more recent study demonstrated lack of any effect of TRT on bone mineral density in patients with low-moderate testosterone levels.^[42] Two meta-analyses with inconsistent outcomes are available on this issue, and as a causative factor for this inconsistency, use of different preparations have been implicated.^[43,44]

Effects on body-build, muscular mass, and strength

Increase in testosterone levels, in the elderly men, has been shown in many studies to enhance body mass, and decrease adipose tissue of arms, and legs. Contrary to this favourable effect, the effect of TRT on muscle strength is controversial.^[4,41] Similarly, in two recent randomized placebo-controlled studies, improvements with testosterone therapy in moderately or severely incapacitated elderly patients with restricted range of mobility have been demonstrated.^[45,46] In placebo-controlled studies where testosterone therapies were used for 36, and 6 months, testosterone treatment in healthy elderly men could not improve muscle strength in these individuals.^[41,42]

Effects on mood, and quality of life

Generally sex hormones are thought to effect cognitive functions, and mood state. Lower testosterone levels in the old age are associated with depression, worsened cognitive function or even Alzheimer's disease. In experimental studies, neuro-protective effects of testosterone have been asserted.^[4] In men with testosterone levels below normal, favourable effect of testosterone therapy on mood state has been demonstrated. This effect could not be detected in individuals with low-normal testosterone levels.^[9] In these patients, the effects of sexual dysfunction on psychological condition, mood state, and quality of life have critical importance. Outcomes of randomized placebo-controlled studies have demonstrated inconsistent effects of testosterone on quality of life, and depression. Miscellaneous quality of life questionnaire forms used, are thought to result in inconsistencies among outcomes.^[42,45]

Effects on components of type 2 diabetes, and metabolic syndrome

Metabolic syndrome includes clinical conditions as central obesity, hypertension, impaired glucose metabolism, worse lipid profile with a higher risk of type 2 diabetes, cardiovascular disease, and atherosclerosis. Its incidence in both genders, especially in men increases with age.^[23] Low level of testosterone is prevalently seen in males with type 2 diabetes and/or metabolic syndrome. In many studies, an inverse correlation has been reported between testosterone level on one hand, and obesity, insulin resistance, and dyslipidemia on the other hand. This phenomenon can be explained partly by increased

aromatase activity induced by conversion of testosterone into estradiol. (increased testosterone-estradiol conversion is related to subcutaneous adipose tissue).^[47] An increase in the risk of development of type 2 diabetes, and metabolic syndrome in hypogonadal men has been asserted.^[48,49] However, in a small number of placebo-controlled studies performed so far, minimal (if any) impact of TRT on insulin resistance, and HbA1c has been demonstrated.^[50,51] Therefore, large-scale randomized controlled studies are needed to be able to speak on the impact of TRT on the components of metabolic syndrome.

Potential risks of TRT

Risks of testosterone replacement therapy are correlated with age, living conditions, and other medical states of the patient. In the presence of prostate cancer, benign prostatic hyperplasia (BPH) symptoms, liver toxicity, tumour, sleep-apnea symptoms, congestive heart failure, gynecomastia, infertility, and skin diseases, TRT conveys risk(s) for these patients. If this individual plans to be a father, TRT which inhibits hypothalamic-pituitary-testicular axis is not appropriate for him. Risk factors for TRT are summarized in Table 5.^[23]

Effects on prostate cancer, and BPH

Prostate is dependent on, and sensitive to androgens. Testosterone is required for the development of prostatic hyperplasia, and it might play an etiological role in carcinogenesis of prostate.^[52] Androgens are needed for the development of BPH, and antiandrogens can decrease prostate volume.^[53] Since the mainstay of the treatment of advanced prostate cancer constitutes androgen withdrawal, as reports have indicated, TRT in these patients might induce disease progression.^[54] In consideration of this information, the question "Is higher testosterone level a risk factor for prostate cancer?" has raised concerns about usage of TRT. In a study conducted by 18 study groups, any evidence concerning correlation between serum sex hormones, and risk of development of prostate cancer was not detected.^[55] A 3-year-follow-up data of a placebo-controlled study performed recently could not yield outcomes demonstrating TRT as a risk factor in the development of prostate cancer.^[56]

Table 5. Potential risks of testosterone replacement therapy^[23]

Induction of the progression of breast, and prostate cancer
Symptomatic worsening of benign prostatic hyperplasia
Induction of hepatic tumours, and toxicity
Induction of gynecomastia
Induction of erythrocytosis
Induction of infertility, and testicular atrophy
Induction of skin diseases
Worsening or induction of sleep-apnea

In a randomized controlled study which investigated the effects of testosterone replacement therapy on prostatic tissue, any treatment-related change in prostatic histology, tissue biomarkers, gene expression or the incidence of prostate cancer could not be found.^[57] Another study couldn't detect any impact of TRT employed for prostate cancer patients with hypogonadism, on the disease progression.^[58] All these data have demonstrated that TRT can be safely used in individuals without suspect prostate cancer, without any cancerogenic effect. Even the latter study is very promising for the use of TRT in prostate cancer, testosterone monotherapy is not effective *per se*. Indeed, TRT is absolutely contraindicated in prostate cancer patients, provided that contrary claims are strongly proved to be true in larger-scale, long-term, and evidence-based studies.^[23]

Many literature studies have indicated that short-term use of testosterone did not induce lower urinary tract symptoms. Even TRT has been assertedly provided symptomatic improvement in hypogonadal males.^[59] On the contrary, a meta-analysis demonstrated that TRT increases prostate-specific antigen (PSA) levels, aggravates acute urinary retention, and International Prostate Symptom Score (IPSS).^[60] These diverse results indicate the need for large-scale, and long-term studies. Nowadays, in the light of this information, as relative contraindication for TRT, IPSS scores of ≥ 19 points, presence of severe BPH, and lower urinary tract symptoms have been indicated. In addition, TRT might have ameliorating effects in mildly symptomatic patients.^[5]

Since unfavourable effects of testosterone replacement therapy on prostate, raise concerns in TRT users, attempts at decreasing its adverse effects have been always kept up-to-date. The main influential factor in prostatic hyperplasia, and increased PSA is not testosterone, but its tissue metabolite dihydrotestosterone. Therefore inhibition of 5-alpha-reductase is thought to eliminate potential adverse effects, and recently a meta-analysis concerning this issue has been published. In this meta-analysis, TRT, and 5-alpha-reductase inhibitors were used in combination to investigate if inhibitory effects of TRT on prostatic enlargement, and increased PSA levels could be prevented by this combination. Short-term (6 months) combination treatment has reportedly no impact on prostatic enlargement, while it might decrease PSA levels, and its long-term use will slow down progression of prostatic enlargement.^[61]

Effects on hematocrit

It has been acknowledged that endogenous androgens stimulate hematopoiesis, increase hemoglobin levels with apparently opposite effects in castration. However in testosterone insufficiency, 10-20% decrease in hemoglobin levels with resultant development of anemia has been already demonstrated. Therefore, TRT has been also proposed for the potential treat-

ment of anemia in hypogonadal men.^[62,63] However this incremental effect of testosterone on hemoglobin also constitute one of the risks which restricts application of TRT. In clinical studies, increase of hematocrit levels over 50% is the most frequently encountered side effect of TRT. In a meta-analysis which included 19 randomized studies, a 4-fold increase in the incidence of this adverse effect was reported in TRT patients when compared with placebo users. Although the clinical significance of this increase is not clear-cut, regular follow-up of hematocrit levels in these patients should be performed.^[60]

Effects on liver

Hepatic diseases related to testosterone replacement therapy include benign, and malignant liver diseases, intrahepatic cholestasis, hepatotoxicity, and hepatic failure. However these hepatic conditions are not seen when transdermal, intramuscular, and oral formulations (except for testosterone undecyrate) are used.^[23]

Cardiovascular effects

Once, potential presence of an inverse correlation between testosterone levels, and occurrence of cardiovascular disease had been conceived, and potential beneficial effects of TRT for hypogonadism patients had been indicated. However, reports of the studies published more recently have yielded inconsistent results. In a meta-analysis comprising nineteen clinical studies, any difference was not detected between patients who had or had not received testosterone regarding incidence of a cardiovascular disease.^[60] Later meta-analyses which could not find either favourable or unfavourable effect of testosterone treatment on cardiovascular disease have provided further support for this assumption.^[64] However in a more recent placebo-controlled study, withdrawal of TRT in elderly patients with restricted mobility because of more prevalent cardiovascular side effects have been reported.^[45] This surprising outcome does not comply with the results of the study performed so far. These findings have made us to be suspicious about usage of TRT in elderly patients with restricted mobility, and cardiovascular disease. Because of these inconsistent results, further studies

Table 6. Contraindications of Testosterone Replacement

Prostate cancer
Breast cancer
Prostatic nodules of induration
Unexplained increased PSA levels
Erythrocytosis (>50%)
Severe lower urinary tract symptoms together with benign prostatic hyperplasia (IPSS>19)
Unstable congestive heart failure (Class 3 or 4)
Serious, but untreated sleep-apnea syndrome

Table 7. Follow-up of the Testosterone Replacement Therapy^[66]

Indication	Timing
Compliance	At baseline, and every visit to define potential causes
Adverse effects - General	At 3 rd month, then annually
Adverse effects- specific	Buccal: In case of any change in taste, examination of gums, and buccal mucosa Injection: Especially in older patients, interrogation of fluctuations in mood state, and libido, and hematocrit test to determine (if any) excessive erythrocytosis Patch: Search for signs of tissue reaction on the application site Gel : The patient should be warned about transmission to other people through contamination of clothes and/or skin contact
Bone mineral density	Every 1 or 2 years in hypogonadal men with bone fractures, and osteoporosis
Hemoglobin, hemotocrit	At baseline, 3-4 th months, annually thereafter. If hematocrit >50%, then treatment is stopped till it reaches to normal levels, sleep apnea, and hypoxia are evaluated, and the TRT therapy is restarted at a lower dose.
Lipid profile	At baseline, 6 th , and 12 th months, then annually
Liver enzymes	At certain intervals
Prostatic examination	Digital rectal examination, and PSA test at baseline, and 3. months , then at time intervals recommended in guidelines.
Treatment response	At 3.-4. months, then annually
Testosterone level	At baseline Transdermal gel: 2 weeks after the treatment At 3. months from the initiation of the treatment; <ul style="list-style-type: none"> • Cypionate/enanthate: in the mid-interval between injections • Transdermal patch: 4-8 hours after application of the patch • Buccal tablet: immediately before application

should be performed concerning application of TRT in patients with cardiovascular disease.^[65]

Contraindications

Contraindications for testosterone replacement therapy are given in Table 6. These conditions should be evaluated with a detailed anamnesis, physical, and laboratory examinations before initiating testosterone replacement therapy. For example, prostate cancer constitutes an absolute contraindication for TRT. Prostate cancer should be ruled out using relevant examinations as PSA tests, and digital rectal examination, and then TRT should be initiated. A definite recommendation has not been proposed for debatable condition which is related to TRT in patients who had been treated successfully without any clinical, and laboratory evidence for a residual tumour.^[23]

Follow-up

Before the treatment baseline, and then periodic evaluations should be absolutely performed in patients in whom we have initiated testosterone replacement therapy. Many sources recommend follow-up of the patients in order to protect them from adverse effects, and risks of TRT. Before initiation of the recommended therapy, total testosterone, PSA, liver enzymes, lipid profile, hemoglobin, and hematocrit should be analyzed, and posttreatment risks, and adverse effects should be evalu-

ated, and these tests should be repeated at certain intervals. We target a testosterone value of 350-1050 ng/dL. However in some patients low-normal values can be obtained. Follow-up protocol for TRT in the presence of various risk factors or adverse effects is summarized in Table 7.^[66]

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