**LATE-ONSET HYPOGONADISM**

**AN UNDERTREATED CONDITION IN AGING LEBANESE MEN**


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**INTRODUCTION**

“The day after the first subcutaneous injection, and still more after the two succeeding ones, a radical change took place in me... I had regained at least all the strength I possessed a good many years ago.” [1]. By these words, the 72-year-old physiologist Charles E. Brown-Sequard described in The Lancet the effects of self-administered extracts of dog and guinea pig testes. Even though Brown-Sequard acknowledged the possibility of a placebo effect, his widely publicized experiments led to derision by some, but also to an unscrupulous industry of testicular transplants in wealthy old men by others. Early man-to-man transplants gave way to chimpanzee testicular transplants in Europe when few human testicle donors came forward. In the United States, goat testicular transplants were marketed as a “cure” for aging males. Sixty years later, in 1939, Butenandt and Ruzicka shared the Nobel Prize in chemistry for synthesizing testosterone from cholesterol, independently of each other [2].

The andropause, commonly used today by clinicians to denote the hypogonadal syndrome, first appeared in the literature in the 1940’s [3]. It refers to a cluster of symptoms and low testosterone levels in men over the age of 50 years. In 1944, Heller and Myers linked depression, fatigue, loss of libido and potency, and many other signs in aging males to lower than normal levels of testosterone, and found that symptoms improved when patients were administered replacement doses [3]. On Harley Street in London, synthetic testosterone replacement became a cure-all for many symptoms of aging. From these uncertain beginnings grew our understanding of the role of declining testosterone levels in the pathogenesis of certain age-related symptoms, and clinical research on hypogonadism and testosterone replacement has grown rapidly since. Was Brown-Sequard’s rejuvenating elixir the long sought-after hormonal fountain of youth? This review discusses the pathophysiology behind the age-associated decline in testosterone levels, as well as the promises, limitations, and risks of testosterone supplementation in hypogonadal males.

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**PATHOPHYSIOLOGY**

Many cross-sectional studies have shown a decline in serum testosterone levels in aging men. This decline occurs gradually – at approximately one percent per year after the age of 35 [4]. This was confirmed in a longitudinal study of older males by Morley et al. in which serum testosterone levels dropped by 100 ng/dL/decade [5]. Approximately 60% of circulating testosterone in young men is tightly bound to sex hormone-binding globulin (SHBG) and not readily available for tissue uptake. The remaining 40% constitute bioavailable testosterone, of which most is loosely bound to albumin and 1-2% circulates as free testosterone [6]. To what extent low-affinity albumin-bound testosterone is available for target tissues remains debatable, but most experts agree that it is the non-SHBG testosterone that best correlates with tissue activity. The decrease in testosterone production in aging men is accompanied by an increase in sex hormone-binding globulin. This increase is likely related to higher levels of estrogen which stimulates hepatic production of SHBG. According to the Massachusetts Male Aging Study, SHBG increases by 1.2% annually [7], and in older men as much as 75% of total testosterone is bound to SHBG. As a result, total testosterone declines at a slower rate (0.4% per year) than free testosterone (1.2% per year) and albumin-bound testosterone (1.0% per year) [8], and measurement of total testosterone will underestimate the true degree of deficiency. Age, therefore, is not only associated with a decrease in testosterone production, but also with bioavailability due to an increase in protein binding. This age-associated decline in testosterone has been referred to by a variety of names including male menopause, climacteric, andropause, ADAM (androgen deficiency in aging men), late-onset hypogonadism (LOH), or age-associated hypogonadism [9]. In this review, late-onset hypogonadism will be used.

The cause of LOH appears to be multifactorial, and age-related changes have been documented at all levels of the hypothalamic-pituitary-testicular axis. Early studies suggested testicular failure as the primary cause of LOH. Leidig’s cells have been shown to decrease in number and function in testes of older men [10]. Partial desensitization of Leidig’s cells to luteinizing hormone (LH) with age is evident by a decline in secretory bursts in response to LH stimulation [11]. In another study, after suppressing intrinsic LH production with luprolide acetate (a gonadotropin-
agree that bioavailable testosterone less than 70 ng/dL is considered diagnostic of LOH and levels above 320 ng/dL ideally be drawn between 7:00 am and 11:00 am. Actually, for consistency, serum testosterone levels should reflect testosterone levels between the young and the old than exists in late in the day may reveal a smaller difference in testosterone rhythm is markedly obtunded with age. Samples drawn in testosterone receptor activation or concentration occurs with age remains unanswered.

Evidence that older men require higher levels of circulating testosterone than younger men for libido and erectile function suggests a decline in receptor activation, but can also be due to a failure of tissue response following activation. To what extent other confounding factors and comorbidities affect the hypothalamic-pituitary-testicular axis continues to be studied.

In short, testosterone levels start to decline from the fourth decade of life due to failure at all levels of the hypothalamic-pituitary-testicular axis. Many diseases affecting the elderly may directly or indirectly contribute to hypogonadism. The increase in SHBG with age makes total testosterone an unreliable measure, and bioavailable testosterone has become the assay of choice. However, as discussed next, a diagnosis of LOH must fulfill both hematologic as well as clinical criteria.

DEFINITION, PREVALENCE AND DIAGNOSIS

The prevalence of LOH varies widely among studies. This is due to differences in measurement essays, diagnostic criteria, and general health of the population studied. Additionally, the timing of sample collection effects measurement outcome. Testosterone is secreted in a circadian rhythm with peak levels in the morning. This diurnal rhythm is markedly obtunded with age. Samples drawn late in the day may reveal a smaller difference in testosterone levels between the young and the old than exists in actuality. For consistency, serum testosterone levels should ideally be drawn between 7:00 am and 11:00 am.

Total testosterone levels below 200 ng/dL (6.9 nM) are considered diagnostic of LOH and levels above 320 ng/dL (11.1 nM) are considered normal; between these two values, ambiguity exists and bioavailable testosterone (free + albumin-bound) is a superior measure [14]. Most experts agree that bioavailable testosterone less than 70 ng/dL constitutes hypogonadism in older men. When bioavailable testosterone is used to measure gonadal function, 3-5% of 40 to 50-year-old males and 30-70% of 70-year-old males have LOH [5-13]. The Baltimore Longitudinal Study used a different essay, the free androgen index (testosterone per SHBG), and found comparable results [15]. More recently, the overall prevalence of LOH in the European Male Aging Study (EMAS) population was found to be around 2.1% [16], considerably lower than previous reports. The study population consisted of healthy males 40-79 years of age and the diagnosis of LOH was based on testosterone levels plus clinical criteria. Furthermore, the prevalence was reported for the group in toto. The EMAS authors concluded that the presence of three predefined sexual symptoms combined with a total testosterone level of less than 11 nmol per liter and free testosterone level of less than 220 pmol per liter can be considered the minimum criteria for the diagnosis of LOH in aging men. The low prevalence of LOH in this study can be attributed to the good health of the study group and the dual diagnostic criteria. Even conservative estimates make LOH the most common endocrine syndrome after female menopause. Clearly, then, clinical criteria are necessary to establish screening and treatment standards.

Clinically, the signs and symptoms of LOH are nonspecific and can vary according to the patient’s age, comorbidities, duration of testosterone deficiency, and severity of testosterone deficiency [17]. According to the recommendations of the International Society of Andrology, the International Society for the Study of the Aging Male, and the European Association of Urology, LOH must not be diagnosed solely on laboratory values. LOH is defined as “a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems” [18]. The nonspecific symptoms make the need for hematologic confirmation essential, but LOH remains primarily a clinical diagnosis. In other words, low serum testosterone without clinical findings does not necessarily warrant treatment. In 2006, the Endocrine Society provided a list of symptoms and signs suggestive of testosterone deficiency. These include reduced libido and sexual activity, decreased spontaneous erections, loss of body hair (axillary and pubic), loss of height, low-trauma fracture, low bone mineral density, and reduced muscle mass and strength. Less specific signs include decreased energy, depressed mood, poor concentration and memory, sleep disturbance, anemia, increased body fat or BMI, and diminished physical or work performance.

A number of questionnaires have been developed for LOH screening in older males. The most widely used is the Androgen Deficiency in Aging Males (ADAM) questionnaire, developed by Morley et al. as a screening tool to identify middle-aged and older men likely to have testosterone deficiency [19]. It is a simple questionnaire that can be self administered and consists of ten forced “yes” or
“no” questions (Table I). The questions pertain to the presence or absence of symptoms associated with LOH. These symptoms, however, can result from numerous other conditions commonly affecting the elderly, and hence hematologic confirmation of a positive score is necessary. Sensitivity and specificity of the ADAM questionnaire are 88% and 60% respectively [20]. Since it lacks specificity, the ADAM screen is not recommended as a tool to be used indiscriminately, but is reserved for men whose symptoms confer a high likelihood of LOH. Examples would be men who recover slowly from uncomplicated surgery, men with refractory anemia, or those with frailty beyond what could be explained by their known illness. The other commonly used tool, the Aging Male Symptoms (AMS) scale, was developed by Heinemann et al. in 1999, and is based on subjective evaluation of symptomatology [21]. It was initially intended as a descriptive tool to quantify the severity of symptoms and not as a screening tool [22]. This scale has a specificity of 49% and a sensitivity of 75% and is currently proposed for use as an outcome measurement for treatment efficacy.

**CLINICAL EFFECTS OF HYPOGONADISM AND OF TESTOSTERONE REPLACEMENT THERAPY**

**Sexual function**

Epidemiologic studies demonstrate that sexual performance, erectile capacity, and libido markedly decrease with age and correlate with declining total and bioavailable testosterone. Men with greater sexual activity have higher bioavailable testosterone levels than men with less frequent activity. It is not entirely clear, however, to what degree these findings are due to the declining testosterone. Erectile dysfunction and waning sexual desire might be related to other comorbid conditions or medications, and often have multifactorial etiologies.

Testosterone is essential for libido. Several studies have shown that androgen replacement markedly improves libido in hypogonadal men. The effect of testosterone on erectile dysfunction is less clear. Some interventional studies, but not all, suggest that testosterone replacement therapy (TRT) increases the strength or duration of erections in older men. There is recent evidence that testosterone and phosphodiesterase inhibitors (e.g. sildenafil) have an additive, if not synergistic, effect in men with low or low-normal testosterone levels. Nitric oxide plays a role in penile smooth muscle relaxation, and testosterone is necessary for the production of nitric oxide synthase. A trial of testosterone replacement is therefore warranted in men whose erectile dysfunction fails to respond to sildenafil or similar drugs.

**Bone mineral density**

Hypogonadal men have a high prevalence of osteopenia, osteoporosis, and low-trauma fractures [23]. Until recently, however, it has been difficult to demonstrate an independent correlation between LOH and bone loss because of the tight correlation between age and testosterone deficiency. In the past decade, evidence for the independent role of testosterone on bone mineral density (BMD) has accumulated. The prevalence of osteoporosis in testosterone-deficient men is twice that of age-matched eugonadal men, and patients with prostate cancer treated with anti-androgen therapy have an increased risk of osteoporotic fractures. Furthermore, testosterone esters administered biweekly to young eugonadal men increased BMD, bone turnover, and bone deposition. Testosterone appears to have a dual effect on bone – it increases osteoblastic activity, and reduces osteoclastic activity through aromatization to estrogen. Multiple studies have shown that TRT prevents bone loss at the femoral neck and increases BMD of the lumbar spine. Most studies indicate that the effect on the lumbar spine is more robust than that at the femoral neck. In a study by Snyder et al., BMD at the lumbar spine increased only in men with pre-treatment low total testosterone concentrations [24]. The pooled results of a meta-analysis of eight trials (365 patients) suggest a moderate increase in lumbar bone density and inconclusive findings on femoral neck bone [25]. None of these studies were sufficiently powered to show a reduction in fracture risk with TRT.

**Body composition, cardiovascular risk, and metabolic syndrome**

In 1981, Hanefeld and Leonhardt were the first to coin the term metabolic syndrome [26]. Since then, definitions for metabolic syndrome (MetS) have been proposed by at least four groups including the World Health Organization (WHO), the National Cholesterol Education Program’s (NCEP) Adult Treatment Panel (ATP III), International Diabetes Federation, and the American College of Endocrinology on Insulin Resistance Syndrome [27]. Most definitions include at least three of five major components: diabetes or prediabetes, elevated triglycerides (> 150 mg/dL), low high-density lipoprotein (< 35-40 mg/dL), hypertension (>130-140/85-90 mmHg) or the use of antihypertensive agents, and abdominal

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**TABLE I**

**ANDROGEN DEFICIENCY IN AGING MALES QUESTIONNAIRE**

<table>
<thead>
<tr>
<th>Androgen Deficiency in Aging Males (ADAM) questionnaire**</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have a decrease in libido or sex drive?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2. Do you have a lack of energy?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3. Do you have a decrease in strength or endurance?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4. Have you lost weight?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. Have you noticed a decreased “enjoyment of life”?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6. Are you sad or grumpy?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7. Are your erections less strong?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. Have you noticed a recent deterioration in your ability to play sports?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9. Are you falling asleep after dinner?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. Has there been a recent deterioration in your work performance?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Ref. 19. **A positive ADAM score consists of a “Yes” for questions 1 and 7, or any three other questions.
obesity (waist circumference >102 cm for males, waist-to-hip ratio > 0.9, or body mass index > 30 kg/m²). The relationship between androgen deficiency and MetS has captured attention during the last ten years as researchers begin to understand how each condition affects the other [27]. Both are related to age, and numerous studies have found an inverse association between features of the metabolic syndrome and plasma testosterone [28].

Regardless of age, MetS itself is a risk factor for hypogonadism. Tan et al. found that in men with an average age of 73 years, 64% of those with diabetes had total testosterone levels under 300 ng/dL compared with 38% of non-diabetic men [29]. Moreover, in a study by Liu et al. on aging Taiwanese men, older age, obesity, and diabetes mellitus were all found to be independent risk factors for LOH and symptomatic androgen deficiency [30]. Conversely, hypogonadism is linked to each component of the MetS. In the Massachusetts Male Aging Study, each decrease of one standard deviation in free testosterone was associated with a 1.58-fold greater risk of developing diabetes after a median interval of nine years [31]. These results were similar to those found in the Multiple Risk Factor Intervention Trial (MRFIT) and the Rancho Bernardo Study. An inverse relationship also exists between the serum testosterone levels and obesity in men. In a study of 57 men between the age of 70 and 80, Vermeulen et al. reported a negative correlation between testosterone levels and percentage of body fat and abdominal fat [32]. Other studies showed that testosterone levels correlated positively with HDL-C [33] and negatively with total cholesterol, LDL-C, and triglycerides [34]. While some studies reported an increase in lean body mass and a decrease in fat mass and serum cholesterol with TRT, others failed to show this effect, with duration of treatment possibly being a determining factor.

The link between LOH and the coronary syndrome has recently received particular attention [35-41]. The MetS by itself is a pro-coagulant condition, and serum testosterone levels were found to negatively correlate with two prothrombotic factors: plasminogen activator inhibitor-1 (PAI-1) and factor VII. The extent and progression of aortic and carotid atherosclerosis also correlates with low serum testosterone levels in aging males. Furthermore, testosterone is a systemic and coronary vasodilator that can improve ischemia in patients with stable angina. This data is consistent with the increased prevalence of cardiovascular morbidity in aging males; however, at this time, we cannot translate these observations into clinical application.

**Hematopoiesis**

It has been suggested that testosterone accounts for the 1-2 g/dL difference in hemoglobin between adult men and women. In fact, testosterone deficiency results in up to 20% decrease in hemoglobin concentration [42], and multiple studies have demonstrated that TRT results in a prompt and significant rise in hemoglobin. The mechanism by which this occurs remains poorly understood. It was previously believed that testosterone stimulates erythropoietin secretion or directly stimulates erythroid progenitor cells. Recent studies cast doubt on these pathways. In a study of 60 older men, a dose-dependent increase in hemoglobin in response to testosterone was observed, but without an associated increase in erythropoietin [43]. Furthermore, testosterone had minimal proliferative effect on purified erythroid progenitor cells in vitro [44]. Very recently, Bachman et al. proposed a separate independent mechanism, and showed that testosterone suppresses the iron regulator peptide hepcidin, resulting in increased bioavailable iron [45], but they conceded that other mechanisms are also likely to be involved. Whatever the mechanism(s), erythropoiesis is one of the most consistent and robust effects of TRT in older men, and partly explains the improved energy, endurance, and quality-of-life described by patients. In extreme cases, dangerous hyperemia has occurred necessitating phlebotomy or withholding therapy.

**Muscle mass, muscle strength, and functional activity**

Sarcopenia (the loss of muscle mass), decreased lean body fat, and decreased muscle contractile function and strength are classic features of aging. Sarcopenia can be predicted by physical activity and insulin growth factor-1, but the free androgen index was found to be the strongest predictor of muscle mass in older men. Other studies have found that bioavailable testosterone was a predictor of strength, functional decline, and frailty in older men. Many interventional studies clearly show that TRT increases muscle mass (by as much as 2 kg) or arm circumference, with no concomitant increase in body weight [46-47]. This occurs even in older eugonadal men. The effect of testosterone on muscle strength, however, is less compelling. Some testosterone replacement studies in hypogonadal men have shown improvement in muscle strength, most notably in the upper extremities. Other studies failed to show an improvement in strength, as measured by hand-grip and leg extensor strength, particularly when the subjects were not hypogonadal. Whether TRT improves physical function, or reduces the risk of falls, disability, and frailty continues to be studied. A combination of testosterone and nutritional supplement markedly reduced hospitalization and duration of admissions in undernourished older men and women. Two pilot studies of short-term testosterone replacement in supraphysiologic doses showed improved recovery and outcome in ill older men and following knee replacement surgery [48-49], but many other studies failed to show a clear and lasting benefit of standard-dose testosterone on rehabilitation in elderly males undergoing major surgeries. Current evidence does not support the routine use of testosterone replacement for rehabilitation, but in select patients it may prove promising.

**Prostate**

A major fear of using testosterone in older men is the potential adverse effect on the prostate. These concerns result from the known effects of testosterone on metastatic prostate cancer and on benign prostatic hypertrophy
(BPH); both testosterone-sensitive conditions (Table II). Indeed, a mainstay in the treatment of BPH and prostate cancer are drugs that oppose testosterone such as 5-α-reductase inhibitors (prevent activation of testosterone to the more potent dihydrotestosterone), anti-androgens, GnRH agonists/antagonists, and most recently Abiraterone. Furthermore, histopathological examination of “normal” prostate tissue at autopsy reveals a high prevalence of carcinoma in situ. Is it not reasonable, then, to expect a surge in prostate cancer with testosterone replacement?

Not necessarily. Evidence that TRT increases the risk of prostate cancer or BPH remains inconclusive. In a meta-analysis of 18 studies that included 3886 men with prostate cancer and 6438 controls, serum concentrations of endogenous sex hormone was not associated with the risk of prostate cancer [50]. Furthermore, most interventional studies show that the prevalence of prostate cancer in men receiving testosterone was similar to that in the general population. There is unequivocal evidence that testosterone can accelerate growth and aggravate symptoms of locally advanced or metastatic cancer, but there is no compelling evidence that testosterone has a causative role in prostate cancer. In another meta-analysis of 19 studies, the combined rate of all prostate events (biopsies, PSA > 4, cancer, urinary retention, etc.) was significantly higher in testosterone-treated men than in the placebo group, but differences within each event were not individually significant [51]. Most interventional studies show no significant voiding symptoms attributable to BPH, nor any difference in postvoiding residual volume or urine flow rates in the treatment group. The poor correlation between prostate volume and urinary symptoms might account for this anomaly.

Cognition, affect, and quality-of-life

Epidemiologic studies have shown a strong correlation between low bioavailable testosterone and cognitive decline in older men [13], and LOH is a predictor for the development of Alzheimer’s disease. In experimental mice, testosterone replacement reduces excessive production of amyloid protein (implicated in Alzheimer’s disease) and reverses memory deficits [13]. No such benefits have been shown in human studies. Most trials have been small and of short-duration, and failed to show improvement in cognitive function in patients with early dementia, though some report improvement in visuospatial deficits. Similarly, studies have failed to show an improvement in depression, despite the existence of an inverse correlation between bioavailable testosterone and depression in older men. Symptoms of LOH overlap with those of depression, and TRT consistently improves energy, sense of well-being, and mood, but not depression. One might be tempted to conclude that dysthymia due to the ill-effects of LOH and declining health can be partly reversed with TRT, whereas major depressive disorder is a separate entity with distinct pathophysiology. More long-term studies are needed, however, before definite conclusions can be reached. Whatever the mechanism, a subjective perception of improved well-being is a compelling reason to continue TRT.

### TABLE II

**CONTRAINDICATIONS TO STARTING TESTOSTERONE REPLACEMENT THERAPY**

| 1. | Prostate cancer |
| 2. | Prostate nodule noted on digital rectal examination that has not been worked up |
| 3. | Elevated prostate specific antigen (> 4 ng/dL) that has not been worked up |
| 4. | Severe untreated benign prostatic hypertrophy with symptoms of bladder outlet obstruction |
| 5. | Breast cancer |
| 6. | Erythrocytosis (Hemoglobin > 17.0 g/dL) |
| 7. | Moderate-severe untreated obstructive sleep apnea |
| 8. | Previous severe allergic reaction to testosterone preparation (including delivery system) |

**TESTOSTERONE DELIVERY SYSTEMS**

Intramuscular injection of testosterone esters have long been the mainstay of androgen-replacement therapy. Commonly used preparations include testosterone enanthate, testosterone cypionate, and mixed testosterone esters [52]. Lipid solubility of testosterone, and hence half-life, is determined by the ester side chain at the 17-β hydroxyl position. Testosterone propionate, with a three-carbon chain, is short acting and must be administered every 2-3 days, making it impractical for the long-term management of LOH. Testosterone cypionate and testosterone enanthate remain the treatment of choice, and are administered at 100-200 mg every 1-3 weeks; most clinicians use 200 mg every two weeks [53]. This dosing regimen strikes a compromise between the discomfort of weekly injections and the symptomatic fluctuation in testosterone levels (particularly on mood) with less frequent injections. Peak levels are attained within two days of injection, and subtherapeutic levels occur in 2-3 weeks. In order to minimize these disturbing peaks and troughs, various testosterone ester combinations have been developed. Testoviron combines testosterone propionate and enanthate and can be administered as 250-500 mg every 3-4 weeks. Sustanon is a blend of four testosterone esters and is widely used in Europe. It can be dosed once a month and, as the name suggests, provides more sustained testosterone serum level than other preparations. Finally, an injection containing 1000 mg of testosterone undecanoate has become available in the past decade [54], and studies have shown that injecting testosterone undecanoate at intervals of up to three months is an excellent alternative to testosterone enanthate and cypionate. This preparation was approved for use in Europe in 2004, but the FDA continues to have concerns with reports of post-injection anaphylactic reactions and pulmonary oil microemboli, though these observations are more likely related to injection technique and volume (4 mL) rather than to the drug itself.

Transdermal testosterone preparations include scrotal...
and non-scrotal skin patches, and topical testosterone gel. All have good absorption kinetics and provide continuous delivery of testosterone that approximates normal eugonadal levels [55-56]. Scrotal patches additionally produce higher levels of dihydrotestosterone (DHT) due to high 5α-reductase activity in scrotal skin, but require the inconvenience of scrotal skin shaving. The benefits of transdermal preparations are ease of use and the maintenance of steady serum testosterone levels, but skin rash at the site of application is a common side effect with the patch. The transdermal gel has been available since 2002 and provides flexible dosing and a lower incidence of skin irritation compared to the patch [56-57]. The longest lasting replacement option is pellets of crystallized testosterone implanted subcutaneously. Their zero-order kinetics offer steady-state testosterone delivery for many months. Implanted pellets, however, have a 5-10% rate of infection or extrusion and are difficult to remove, and so may not be suitable for the elderly.

Other delivery systems under development include testosterone nasal spray, sublingual testosterone, inhaled testosterone, and novel enteral drugs. Oral testosterone preparations have a first-pass liver effect and are potentially hepatotoxic. An exception is the oral preparation of testosterone undecanoate (Andriol) which is enclosed in an oil based capsule and absorbed as a fat through the lymphatic system, thus bypassing the liver. Andriol is used extensively outside the US and appears to have an excellent safety record [58]. No oral testosterone preparations are currently available in the US or Lebanon.

MONITORING FOR SAFETY AND SIDE EFFECTS

Based on meta-analysis and experts opinion, consensus guidelines exist for monitoring testosterone therapy [59-61]. The dual goal of monitoring is to prevent side effects and ascertain an adequate response to treatment (Table III). Some experts recommend monitoring serum testosterone every three months after the initiation of therapy, with a target range between 400 and 500 ng/dL (14.0-17.5 nmol/L). Most, however, claim that monitoring levels is unnecessary unless the patient is receiving oral or transdermal replacement therapy and/or did not improve clinically [59]. Since hematocrit level above 50% is the most frequent adverse event, hematocrit follow-up is recommended every four to six months for the first three years then at least annually [59]. The Endocrine Society recommends DRE and PSA screening three months after starting therapy, and then per routine guidelines [60]. One meta-analysis demonstrated a 3.7% increase over baseline in lumbar spine BMD after 12 to 36 months of treatment [62], thus the American association of clinical endocrinologists recommended BMD every 1-2 years [61]. Monitoring of liver enzymes is essential in patients receiving the oral forms of testosterone and should be performed no less than 2-3 times a year. Intramuscular and transcutaneous preparations are much less likely to cause hepatic toxicity or cancer, and monitoring frequency can be relaxed to once or twice a year [62]. No monitoring is recommended for cholesterol levels based on several meta-analyses [59].

Clinically, patient should also be screened for sleep apnea and hypoxia prior to starting TRT and during therapy. Obstructive sleep apnea is a well documented complication of TRT, and the patient himself may have no knowledge of the problem. Patients also should be alerted to the possibility of gynecomastia due to aromatization of testosterone into estradiol which stimulates the growth of breast tissue. Another potential side effect of TRT is water retention, which can lead to worsening heart failure and hypertension. Finally, if TRT does not result in a feeling of well-being and improved quality-of-life by 3-6 months, treatment should be discontinued. Better options exist for management of osteoporosis, and testosterone should not be used primarily for this purpose.

A WINDOW ONTO THE LEBANESE POPULATION

IS HYPOGONADISM BEING MISMANAGED?

As physicians, we must not waver from our commitment to improve the quality-of-life of our patients. Our responsibility in facilitating well-being and functional independence takes an even more central role when treating older patients with multiple chronic progressive disorders that rarely have a cure. In a subset of older males, identifying and treating LOH can be a definite step towards realizing this goal. So… is LOH being underdiagnosed and undertreated in aging Lebanese males? There is no epidemiological data to support an answer, but the unequivocal response is a resounding “certainly, without doubt”. How can we be so sure in the absence of data? In 2001, it was estimated that there were 5 million hypogonadal men in the US, 1500,000 of whom were receiving treatment –
a mere 3%. Today, the proportion is certainly higher due to improved public awareness, but still the vast majority of men with LOH remain untreated. The treatment rate in Lebanon is not expected to exceed that of the US, and in fact is likely to be much lower.

Several cultural obstacles hinder optimal management of LOH in Lebanon. The Middle East culture demands respect for older people and highly values the bonds of affection between family members. Over the past two decades, however, these values have started to erode in the Lebanese society – strained by economic constraints, demographic shifts, increasingly fragmented families, and social polarization. An inevitable health consequence of this cultural/social change is suboptimal attention to “non-critical” chronic medical conditions in the elderly such as chronic pain, depression, and LOH; conditions with big impact on quality-of-life.

Specifically, addressing LOH offers unique challenges. Asking an older man about his sex life and sexual function is still challenging in our culture, if not taboo. Moreover, relating fatigue, weakness, apathy, or depression to decreased levels of “sex hormones” requires some trust and social finesse. Some patients may withdraw if they perceived that their “manhood” is being called into question. The first step in establishing rapport is spending sufficient time understanding patients’ needs, concerns, and attitudes. This should be done in a respectful non-judgmental way, while ensuring patient’s privacy and comfort. Patient confidentiality should be explicitly communicated at the onset of the discussion, even as they are assured that LOH is a common medical problem affecting many older men. As healthcare educators, public awareness and attitudes toward LOH and TRT must be addressed. Some older males refrain from TRT for fear of being misconstrued or of a damaged reputation. Knowledge that TRT is not just for sexual needs may go a long way towards correcting misconceptions.

Finally, the nature of medical practice in Lebanon does not support optimal management of chronic conditions that require patient education, follow-up, and monitoring. Management of LOH should be the domain of qualified primary care providers, but most patients bypass this essential step and seek care directly from specialists. This approach limits physician access, and hence adequate patient education and support.

Furthermore, the only testosterone preparations available in Lebanon are injectable Testoviron and Sustanon, and occasionally these are hard to secure. Convincing patients to undergo a deep muscle injection every two weeks for symptoms they attribute to aging may be a tough sell, but once TRT is commenced, many patients willingly continue treatment due to the favorable impact on quality-of-life. For those who do opt to continue long-term TRT, the final challenge is safety monitoring since testosterone can be purchased without prescription in Lebanon and it is not uncommon for patients to eschew clinic visits, especially when feeling well.

CONCLUSION

Hypogonadism is a medical condition frequently encountered in older males. It is often overlooked since symptoms of LOH mimic those of other common conditions, or the aging process itself. LOH should be suspected in older men presenting not only with decreased libido and sexual performance, but also with any of the nonspecific signs and symptoms such as fatigue, dysthymia, anemia, osteoporosis, or failure to thrive, especially when difficult to explain by existing ailments. LOH predisposes elderly males to significant morbidities. Replacement therapy, however, has not been shown to prolong life, but does have a favorable effect on the quality-of-life of patients who respond to treatment. Thus, initiating a trial of TRT is prudent in symptomatic hypogonadal men who have no contraindications.

REFERENCES

12. Mulligan T, Iranmanesh A, Veldhuis JD. Pulsatile IV infusion of recombinant human LH in leuprolide-suppressed men unmasks impoverished Leydig-cell secretory respon-
28. Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? J Urol 2006; 176: 1524-7; discussion 27-8.