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## A view of geriatrics through hormones. What is the relation between andropause and well-known geriatric syndromes?

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## Review

# A view of geriatrics through hormones. What is the relation between andropause and well-known geriatric syndromes?

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## ABSTRACT

Age related male hypogonadism, or “andropause”, is increasingly recognized as of frequent occurrence in older patients. Diagnosis requires both the presence of clinical symptoms and low testosterone levels. However, diagnosing andropause in this age group may be challenging since symptoms are frequently non specific and testosterone levels are influenced by a multitude of parameters such as lifestyle factors and chronic diseases. In this article we discuss the pathophysiology, definition and diagnostic difficulties of andropause in geriatric patients. Moreover, we review the relation between testosterone levels and frequent geriatric syndromes such as falls, osteoporosis, cognitive and mood disorders, anemia and cardiovascular disease. Finally, we examine the potential benefits and risks of testosterone replacement therapy in this age group.

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**Abbreviations:** AD, Alzheimer's disease; BMD, bone mineral density; BT, bioavailable testosterone; CV, cardiovascular; E2, estradiol; FSH, follicle stimulating hormone; FT, free testosterone; GnRH, gonadotropin-releasing hormone; IM, intramuscular; LH, luteinizing hormone; PSA, prostate specific antigen; SHBG, sexual hormone binding globulin; T, testosterone; T2D, type 2 diabetes; TRT, testosterone replacement therapy; TT, total testosterone.

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## 1. Introduction

The major circulating androgen in men is testosterone (T) [1]. T is bound to sexual hormone binding globulin (SHBG) (44%), albumin (50%) and cortisol-binding globulin (4%). Two percent of total T (TT) is unbound or free [1,2]. Bioavailable T (BT) includes free T (FT) and albumin-bound T (albumin's affinity for T is 1000 times less than SHBG) [3].

TT and FT blood concentrations peak during the third decade of life and decrease thereafter [4–7]. TT annual decrease rate is approximately 0.4–1% [5,8–10] resulting to levels beneath the reference range in 20% of healthy men over 60 and 30–50% over 80 [6,11]. In a cohort of males aged between 40 and 79 years, 17% had TT levels beneath 11 nmol/l (320 ng/dl) and 2.1% suffered from hypogonadism defined by TT below 11 nmol/l (320 ng/dl), FT below 220 pmol/l (640 pg/dl) and three sexual symptoms. Hypogonadism prevalence increased with age (0.1% and 5.1% for patients 40–49 and 70–79 years old respectively) [12]. FT and BT decrease is even steeper, probably due to the age related SHBG increase [5,13–15].

A primary testicular defect seems the most plausible cause for age related male hypogonadism [6]. Low T and high luteinizing hormone (LH) levels suggest a decrease of Leydig cell mass or lower capacity to produce T, as well as a decreased sensitivity to LH [4,14]. Moreover, age related follicle stimulating hormone (FSH) increase is steeper and independently related to an even greater androgen decline (high FSH levels have been related with low testicular volume) [6]. However, some men present with low to normal LH and FSH as a result of lower gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus also observed with older age [16].

The aim of this article is to review diagnostic particularities of andropause diagnosis, discuss its relation with well known age-related syndromes, and argue on the benefit to risk ratio of T replacement therapy (TRT) in this age group.

## 2. Clinical presentation and diagnostic criteria

Low plasma T has been associated with sexual symptoms such as diminished erectile quality, decreased libido, higher difficulty for achieving orgasms and reduced sensibility of the penis [17,18]. Heart disease, metabolic syndrome and type 2 diabetes (T2D), osteoporosis and fractures, sarcopenia, increase in abdominal fat mass, body hair and skin alterations, mood and cognitive disorders, occasional night sweats and vasomotor disturbances are also reported [4,11,13,14,18–20].

Male hypogonadism diagnosis requires the presence of both clinical symptoms and low serum T levels [18,21,22]. Wu et al. defined hypogonadism as TT serum levels below 11 nmol/l (320 ng/dl), FT below 220 pmol/l (640 pg/dl) and three sexual symptoms [12]. However, T levels interpretation is harder in this age group since they are influenced by several lifestyle factors such as body mass index (BMI) [6,13,23], physical activity [24] smoking [4,24] and alcohol consumption [24,25], as well as chronic conditions more frequently encountered in older patients [26]. Moreover, normal values of TT for elderly men are less well defined. There have also been issues with T measures standardization and reliability. TT is the most frequently used measure, even though age related SHBG modifications would make FT a more reliable marker.

Unfortunately, direct measures of BT and FT are not considered reliable enough and they are calculated from TT, SHBG and albumin values [16]. Calculated FT is mostly used to help diagnosis when TT values are between 8 nmol/l (230 ng/dl) and 11 nmol/l (320 ng/dl) [12]. Limit for low FT is under 220 pmol/l [12,22]. Finally, clinical tools for andropause screening have also been developed such as the Saint Louis University Androgen Deficiency in the Aging Male (ADAM) questionnaire (88% sensitivity and 60% specificity) [27] and the Aging Male Symptom (AMS) rating (96% sensitivity and 30% specificity) [28].

## 3. Low testosterone and geriatric syndromes

### 3.1. Musculoskeletal disorders

Falls and fractures are a major problem in older patients [29], with high morbidity and mortality [30]. After 50 years of age, the lifetime risk for a fracture is 51% for women and 20% for men [31].

Sarcopenia is a major risk factor for falls [32]. Age related T decline has been associated with low muscle mass [33–35] and strength [11,14,33], impaired balance, falls and higher dependency in activities of daily living [34,36]. FT is positively related to lean mass, muscle strength and mobility [37]. T increases amino acid re-use and protein synthesis while reducing protein breakdown in the muscular tissue [37]. It also inhibits adipocyte production and promotes muscle satellite cell proliferation [37]. Higher T is related to higher ghrelin which stimulates growth hormone release [37]. Finally, an inverse relation between LH and muscle mass and strength has been described in elderly men [38].

A positive effect of TRT on muscle mass has been observed in older patients [8,20,35–37]. Studies of TRT on muscle strength are less clear, most showing a positive effect [8,35–37,39–41] but others none [20]. The results of TRT on physical performance were also inconsistent [20,35,36,39,40,42–44]. Discrepancies between studies regarding hormonal status, physical assessment and therapeutic goals may partly explain the variety of results.

Three are the main causes of osteoporosis in 40–50% of cases in men: alcohol, glucocorticoids and hypogonadism [16]. Higher T levels are positively related to bone mineral density (BMD) and a low fracture risk [8,45]. In a study, higher BT levels were related to higher trabecular and cortical BMD [46]. Conversely, low T has been associated with low energy fractures (particularly hip and non vertebral) [47]. 20% of men with vertebral and 50% with hip fractures have low serum T levels [20]. TRT was related to an increase of BMD on the femoral neck and lumbar spine [48]. In another study, an effect on the spine appeared only when pre-treatment levels of T were low [49].

T acts on the bone partly through aromatization to estradiol (E2), which inhibits osteoclastic activity and bone resorption [50,51]. In fact, TRT combined to an aromatase inhibitor was related to a statistically significant decrease of spine BMD and a tendency for a decrease at other sites [52]. A direct effect of dihydrotestosterone through osteoblastic activity increase, has also been suggested [50].

TRT is rarely included in rehabilitation protocols in Geriatrics. Prospective studies on elderly frail populations should permit to better pinpoint patients prone to benefit from such interventions.

### 3.2. Cognitive disorders

Twenty-four million people suffer from cognitive disorders worldwide [53] with 54% of cases due to Alzheimer's disease (AD) [54]. The related human and socio-economical burden is extremely important [55,56].

In rodents, androgen receptors are found in areas vital for memory function such as the hippocampus, thalamus and deep layers of the cortex [57]. In humans, GnRH acts as a neurotransmitter in the central and peripheral nervous system. The hippocampus has among the highest concentrations of GnRH receptors [58]. Increased LH levels have been associated temporally to increased numbers of neurons at risk for degeneration and death. They have also been related to increased cell cycle alteration and oxidative stress markers, known to precede neuronal loss. Mitotic signaling pathways encountered early in AD pathogenesis seem also promoted by high LH. In fact the increased mitotic effect of GnRH and gonadotropins and the decrease of the neuroprotective effect of sex steroids could participate in the histological and biochemical hallmarks of AD, such as extracellular amyloid plaques and intracellular neurofibrillary tangles [58].

Animal and human studies support a positive effect of T on global cognitive function [8,20] and separate cognitive domains such as memory [59–61], attention [60], visuospatial ability [59,61,62] and executive function [63]. Visuospatial function seems particularly related to androgen status [62]. Memory impairment encountered in medically androgen deprived men, disappears after treatment discontinuation [64–67]. A relationship between low T levels, mild cognitive impairment (MCI) [68] and AD incidence has also been suggested [20,68]. TRT improved age related cognitive decline in mice [69]. Human studies have demonstrated a positive effect of TRT on verbal, spatial [70–72] and working memory [73] as well as visuospatial function [71,74–76] and executive functions [77] in healthy individuals and patients with dementia.

Nevertheless, the relation between cognition and endogenous T levels [78,79] or TRT [20,80,81] was not confirmed by others. In fact, studies on T and cognition are extremely heterogeneous regarding T administration, plasma levels achieved, and cognitive status at baseline. Robust evidence still lacks on the role of TRT in dementia prevention in healthy elderly or patients with MCI, as well as for the role of TRT in dementia treatment.

### 3.3. Mood disorders

Depression is common in older individuals [82]. Its prevalence is approximately 13% in general and 2% for the major depression subtype [83]. Its relation to cognitive and functional decline as well as high mortality is well established [84].

Hypogonadism shares several symptoms with depression, such as loss of energy and decreased libido. A biologically plausible relation beyond simple similarities is also suggested. T easily crosses the blood–brain barrier. It is also a neurosteroid synthesized in the central nervous system (CNS) [85]. Androgen and GnRH receptors are present in several CNS structures related to depression [57,58,82,85,86]. Animal studies have suggested an effect of T on the serotonergic, dopaminergic, noradrenergic and vasopressin/oxytocin systems, as well as the hypothalamic–pituitary–adrenal axis [85]. Finally, TRT has been associated with an increased perfusion in brain areas related to emotion, as well as mood improvement in hypogonadal depressed patients [85,87]. In a meta-analysis, greater age and T gel formulations predicted better responses of depressive symptoms to TRT [88].

Nevertheless, most studies do not show any association between T plasma levels and depression [85,89]. It has been suggested that low T is related to mild dysthymic symptoms rather than major depression [85]. In a study, elderly patients with dysthymic symptoms had lower T levels than those with the major depression subtype [90]. Others demonstrated a relation only between depression and FT or BT [86,88], or in a specific age group (patients between 50 and 65 years old) [87].

### 3.4. Cardiovascular disease

Cardiovascular (CV) disease is most prevalent in older patients. 30% of acute myocardial infarctions occur in patients over 75 and 80% of deaths from coronary disease in patients over 60 years of age [29]. Despite the widespread belief that T is associated with a high CV risk profile, this has not been confirmed by recent studies, which show mostly the contrary [91].

Metabolic syndrome and its components have been associated with low T and SHBG [9,92–95]. T levels are inversely related to insulin concentrations [92]. Androgen deprivation therapy increases the risk for insulin resistance and T2D [93]. Conversely, high T and SHBG decreased by 50% the risk for T2D [94]. The inverse relation between T and T2D seems mostly mediated by insulin related SHBG decrease [43,96]. A direct effect of low T levels has also been suggested through a higher risk for obesity [92] as well as a downregulation of genes related to glycogen metabolism and nutrient sensing in the skeletal muscle [93]. A bidirectional relation is possible where obesity and hyperinsulinemia induce a decrease in T levels, which in turn have a negative effect on body composition and insulin levels. Conversely, as supported by a study by Liu et al. [97] on non diabetic obese men, TRT has a positive effect on insulin sensitivity. TRT also improved glycemic control in hypogonadal men with T2D [98].

TRT increases the activity of hepatic lipoprotein lipase inducing a decrease in high density lipoprotein levels [20], especially in patients with higher pretreatment T levels [99]. Intramuscular (IM) T has smaller effects on HDL, probably through higher conversion to E2 counteracting T effects on lipoprotein lipase [100]. Concordantly, non aromatizable androgens decrease high density lipoprotein [43]. A decrease in total cholesterol and low density lipoprotein has also been reported with TRT [101]. Overall, actual data support a rather neutral effect of TRT on lipids [102].

Low T has been related to several markers of atherosclerosis (arterial stiffness, intima-media thickness) [103], increased incidence of abdominal aortic aneurysm [104], coronary disease [105,106], stroke, transient ischemic attack [107] and CV events [108,109]. Several studies support direct anti-anginal properties of T. T infusion has been related to coronary artery dilation and increased coronary blood flow, probably through inhibition of L-type Ca<sup>2+</sup> channels [110,111]. Intravenous T administration 30 min before exercise as well as 2 weeks of T treatment by transdermal patch had a positive effect on exercise induced ischemia [112,113]. Low T levels have been described in patients with heart failure. TRT in such patients improved symptoms and peak oxygen consumption but not left ventricular function [114]. However, T is contraindicated in case of uncontrolled congestive heart failure since it increases salt and water retention, and should be used with caution even in patients with stable disease [39,115]. Finally, concerning CV mortality, most studies support an inverse relationship with T [116–120].

Overall, most studies suggest a rather positive effect of T on CV risk factors and CV disease. Nevertheless, results remain inconsistent, and an increase of CV adverse effects has also been described [39]. TRT should be prescribed with caution in patients with CV disease history.

### 3.5. Anemia

Despite a high prevalence of chronic anemia in older patients [121] as well as its relation to high morbidity, hospitalization rate, length of stay and mortality, it is frequently overlooked and under-treated in the elderly. Causes are divided in three groups: vitamin and/or iron deficiencies; chronic disease and renal failure; anemia of unknown origin for which hypogonadism is proposed as a potential cause [122].

Low T has been related to lower hemoglobin (Hb) levels and a higher risk to develop chronic anemia in older patients [123]. Men under androgen deprivation therapy are more frequently anemic [123]. Hb levels are related to the severity of androgen deficiency [11] and increase in a linear, dose-dependent manner after TRT [124].

Androgen related erythropoietic activity seems erythropoietin independent and implicates hepcidin, a liver produced polypeptide [123,125]. Hepcidin induces a reduction of iron intestinal absorption, an increase of iron sequestration in the macrophages and reduced erythropoiesis. High levels of T rapidly suppress hepcidin in a dose dependent manner. Following TRT instauration, Hb increase is related to the decrease of hepcidin [125].

In conclusion, after frequent causes were excluded, hypogonadism should be more systematically looked for in elderly patients with chronic anemia.

## 4. Treatment

There are widespread concerns about TRT safety. Partly for this reason, only five percent of hypogonadal men receive appropriate treatment in the United States [102]. However, studies agree that serious adverse effects are rare if guidelines are followed and T levels remain within the physiologic range [18,115]. Patients should undergo a strict control before introducing TRT. Treatment is contraindicated in case of a known prostate cancer, increased PSA without urological assessment (PSA > 4 ng/ml, or PSA > 3 ng/ml in African Americans or men with a first degree relative with prostate cancer), severe low urinary tract symptoms (International Prostate Symptom Score (IPSS) > 19 [126]), hematocrit > 50%, uncontrolled congestive heart failure or ischemic heart disease in the preceding 6 months and untreated severe obstructive sleep apnea [43]. Clinical and biological assessments should be performed every 3–6 months during the first year and annually thereafter.

### 4.1. Formulation-specific complications

Oral formulations include oral T undecanoate and mucoadhesive buccal tablets, which are generally well tolerated. Oral 17 $\alpha$ -alkylated T preparations (floxymesterone, methyl-testosterone) should no longer be prescribed due to their high hepatotoxicity and potential for lowering high density lipoprotein. Transdermal formulations include T hydro-alcoholic gel and patches (genital and non-genital). High levels of dihydrotestosterone are observed with genital patches due to high concentrations of 5 $\alpha$ -reductase in the scrotal skin. On the other hand, skin reactions are more frequent with non-genital patches and should be changed at least once per week. Skin reactions are rare with gel formulations, but patients should cover the application zone with clothing because of the risk of transfer to other persons. Long acting IM T esters include T enanthate and cypionate, with similar pharmacokinetic profiles, and T undecanoate with a longer half-life. High first pass effect and potential hepatotoxicity remain serious concerns with T undecanoate. Serum T levels fluctuations with enanthate and cypionate esters may be followed by unpleasant symptom fluctuations and require adjustment of dosage or intervals between injections. Pain

at injection site and coughing following injection may also occur. Finally subcutaneous pellets may provide T for approximately 6 months. They are rarely used since they require a skin incision and they are subject to infection, scarring and spontaneous extrusion [21,102,127,128].

### 4.2. Polycythemia

Polycythemia is the most frequent adverse effect of TRT [43]. The main risk factor is older age [21,43]. It occurs more frequently with IM formulations and in the presence of conditions associated with higher hematocrit [21]. Hematocrit should be measured every 6 months for the first 18 months following treatment initiation and yearly thereafter. Treatment should be decreased or discontinued when hematocrit exceeds 52–55% [21,43], until it returns to values under 50% [43].

### 4.3. Prostate cancer

Pierorazio et al. suggested that androgens could promote typical growth and maturation in younger, but malignant transformation in older patients [129]. Studies on animals concurred that T administration stimulates growth of prostate tumors [130]. However most recent studies, including a meta-analysis, have shown no association between androgen levels and prostate cancer risk [129,131,132]. Low T levels could be surprisingly related with an increased risk, worse 5 year biochemical relapse rate, higher Gleason scores, worse pathological stages and positive surgical margins [129,133]. Concordantly, some have suggested a rather protective role of normal T in benign prostate hypertrophy and prostate cancer pathophysiology [14,134].

Actual data support a satisfying safety profile of TRT concerning prostate benign hyperplasia and cancer [17,18,21,43,102,135]. TRT seems safe, even in patients who underwent radical prostatectomy [43,135], brachytherapy [136] and external beam radiation [137]. Nevertheless, pre-treatment control and systematic follow up of low urinary tract symptoms and PSA levels remains a standard of care [18,21]. A digital rectal examination and screening for low urinary tract symptoms should be performed every 6–12 months. PSA should be measured after 3–6 months and yearly thereafter [21,102]. An annual PSA increase of 1.0 ng/dl is an indication for prostate biopsy [21,102]. PSA follow-up every 3–6 months should be programmed for annual increases of 0.7–0.9 ng/dl [21,102].

## 5. Conclusion

Low androgen levels are related to frequent conditions in older men such as metabolic syndrome, cardiovascular disease and anemia. Well-known geriatric syndromes such as cognitive, mood and musculoskeletal disorders are also related to low T [50]. Nevertheless, it is rarely looked for by geriatricians. Moreover, due to false beliefs on TRT safety, only a small fraction of patients with overt andropause receive adequate treatment. It is our strong belief that hormonal work up should be more frequently included in geriatric itineraries.

## Contributors

Nikolaos Samaras participated in the manuscript coordination, references organization and writing. Dimitrios Samaras participated in the manuscript writing, as well as in the muscle and osteoporosis chapter organization. Pierre-Olivier Lang and Patrick Meyer participated in the manuscript writing and coordination. Alexandre Forster participated in the manuscript writing and coordination of the cognitive disorders chapter. Claude Pichard



participated in the manuscript writing. Emilia Frangos participated in the manuscript writing and coordination of the anemia chapter. All the authors have seen and approved the final version.

### Competing interest

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