Testosterone Disorders and Male Hypogonadism in Kidney Disease

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Summary: Chronic kidney disease (CKD) causes substantial alterations in the male endocrine system, which affect puberty, libido, and sexual function. A major effect of CKD is a reduction in testosterone levels because of both primary and hypogonadotrophic hypogonadism. In addition to impairment of pubertal growth and sexual maturation in children with CKD, clinical evidence suggests that uremic hypogonadism strongly contributes to several CKD complications, including erectile dysfunction, muscle wasting and frailty, anemia, decreased bone mineralization, depression, and cognitive impairment. This review focuses on a reappraisal of the physiologic role of testosterone, with an emphasis on the hypogonadal condition linked to CKD and its complications.
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Testosterone deficiency or hypogonadism is a common finding in men with chronic kidney disease (CKD), owing to decreased function of the hypothalamic–pituitary–gonadal axis and reduced androgen synthesis.[1] In addition to impairment of pubertal growth and sexual maturation in children with CKD, clinical evidence in adults suggests that uremic hypogonadism strongly contributes to several common complications, including erectile dysfunction, muscle wasting and frailty, anemia, decreased bone mineralization, depression, and cognitive impairment.[1-3] In addition, hypogonadism might contribute to all-cause and cardiovascular disease mortality.[1-3] There currently is little consideration of hypogonadism among nephrologists, therefore it often is overlooked. This review focuses on a reappraisal of the physiologic role of testosterone with emphasis on the hypogonadal condition linked to CKD and its complications.

PHYSIOLOGY OF TESTOSTERONE ACTION

Testosterone is released from testis and to some extent from the adrenal medulla. Testosterone regulates lipid, carbohydrate, and protein metabolism, and modulates the function of different cells and tissues, including hematopoietic cells, muscle, fat, bone, heart, and kidney.[4] In the kidney, testosterone promotes fluid retention by acting on aquaporin 1 and the Na^+/K^+ exchanger.[4] In vessels, testosterone favors vascular relaxation but promotes thrombocytosis and erythrocytosis.[4] Based on various studies, testosterone has vasorelaxant, anti-atherosclerotic, antihyperlipidemic, and anti-inflammatory actions. In addition, in the heart, testosterone therapy exerts inotropic effects, T-wave prolongation, and reduction in the Q-T interval.

Testosterone circulates in plasma with 2% unbound free hormone, 40% bound to sex hormone-binding globulin (SHBG), and 58% more loosely bound to albumin. Guidelines suggest that hypogonadism should be diagnosed with total testosterone less than 350 ng/dL or free testosterone less than 80 ng/dL in the presence of symptoms.[5] However, it still is unclear whether the biological actions of testosterone are best represented by the total, bioavailable, or unbound forms. The biologically active hormone is contained in the unbound and nonspecifically bound fractions. Circulating concentrations are approximately 15 to 25 times higher in adult men compared with women. With aging, men have gradual declines in average serum testosterone levels, with a 1% per year decrease in testosterone and a parallel increase in SHBG.[6] The age-related decrease in circulating testosterone is associated with decreases in sexual function, bone mass, muscle mass, and strength, and increases in body fat, depression, and fatigue.[7,8] In aging men, free testosterone appears to be a better predictor of arm and leg strength than total testosterone.[9]

African American ethnicity and a higher estimated glomerular filtration rate (GFR) are related to lower odds of having hypogonadism, while diabetes, higher body mass index, and visceral adiposity are associated with higher odds.[8,9] Therefore, hypogonadism is more frequent among men with obesity and type 2 diabetes (Fig. 1).

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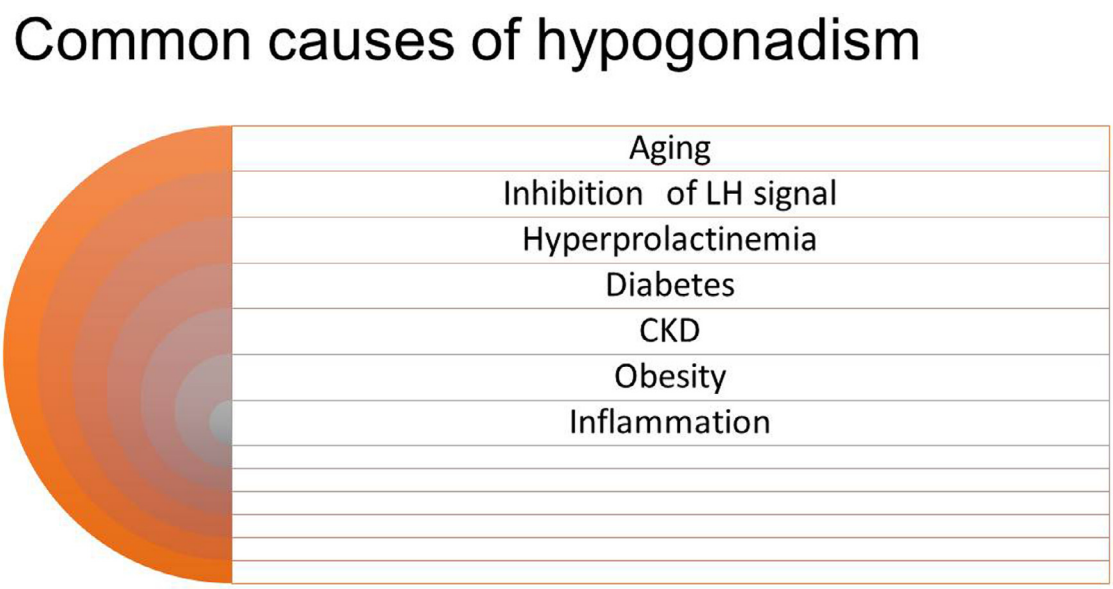

Figure 1. Causes of hypogonadism. Abbreviations: CKD, chronic kidney disease; LH, luteinizing hormone.

TESTOSTERONE AND SEXUAL DIMORPHISM OF KIDNEY DISEASES

Epidemiologic studies have shown that men have a more rapid progression of kidney disease than women.[10,11] In addition, with aging, men show greater decrements in renal function and increased glomerular sclerosis than women.[12] As shown by early studies, women with several nondiabetic renal diseases such as membranous nephropathy, IgA nephropathy, and polycystic kidney disease present with slower CKD progression.[11] Thus, men appear to be at greater risk for renal injury than women, but the underlying mechanisms are still a matter of debate.[12,13] Sex hormones have been suggested to mediate the effects of gender on CKD progression through interaction with the renin-angiotensin system, the modulation of nitric oxide synthesis, and the down-regulation of collagen degradation.[12-16] Estrogens and androgens have been shown to influence the regulation of blood pressure and renal function differently.[15] Moreover, estrogens generally have been shown to have antifibrotic and anti-apoptotic action,[14,16] while androgens have permissive effects on proapoptotic and profibrotic signaling.[17,18] Androgens may contribute to continuous loss of kidney cells by triggering an apoptotic pathway involving FAS/Fas-associated protein with death domain up-regulation and caspase-8 activation.[18,19] It is of note that Fas-dependent renal tubular epithelial cell apoptosis has been shown to mediate tubular atrophy, a hallmark of progressive renal disease. Furthermore, Fas stimulates signaling molecules that also are activated by inflammatory cytokines, such as c-Jun amino terminal kinase,[19] a key player in inflammatory stress and cell death in several chronic inflammatory diseases. Therefore, the mechanisms of cell death, which are primed by androgens, may interact with others occurring in several settings, leading to the loss of renal cells. Differences between the sexes also are apparent in their outcomes. In patients with predialysis CKD, mortality is higher in men than in women; however, this difference disappears for patients on renal replacement therapy.[12]

EFFECTS OF HYPOGONADISM

Hypogonadism is a clinical condition combining low concentrations of circulating testosterone and specific symptoms associated with impaired hormone production.[5] Many symptoms of low testosterone are nonspecific and may overlap with those of comorbid conditions (Table 1). Low libido and erectile dysfunction, gynecomastia, depression, and sarcopenia are common in men with hypogonadism. Testosterone decreases bone resorption in adults, and low levels are associated with osteopenia and osteoporosis in both men and women in the general population. In the elderly, low serum testosterone has been reported as a risk factor for all-cause mortality and cardiovascular disease (CVD) events in cross-sectional studies.[20,21] However, these results have not been reproduced in all studies,[20,21] so there is uncertainty regarding the association between hypogonadism and cardiovascular complications. It also must be considered that sex hormones might contribute differently to

Table 1. Clinical Manifestations of Low Testosterone (Hypogonadism)

Decreased libido and erectile dysfunction
Decrease in muscle mass and strength
Increase in body fat
Decrease in bone mass
Anemia
Decreased quality of life
Decrease in cognitive function
Increased cardiovascular mortality (?)

different complications and comorbidities in the two sexes. Recently, Ruth et al[22] studied the genetic determinants of testosterone levels and related sex hormone traits in 425,097 UK Biobank study participants. They observed that genetically higher testosterone is harmful for metabolic diseases in women, but beneficial in men. As an example, a genetically determined 1 SD higher testosterone level increased the risks of type 2 diabetes (odds ratio [OR], 1.37; 95% confidence interval [95% CI], 1.22−1.53) and polycystic ovary syndrome (OR, 1.51; 95% CI, 1.33−1.72) in women, but reduced type 2 diabetes risk in men (OR, 0.86; 95% CI, 0.76−0.98). Adverse effects of higher testosterone levels on breast and endometrial cancers in women and prostate cancer in men also were observed. These observations highlight the importance of specific analyses of disease risk in men and women. Addressing gender differences is an overlooked area in the care of patients with kidney disease.[12]

DERANGEMENTS IN THE HYPOTHALAMIC−PITUITARY−GONADAL AXIS IN CKD

Early studies have shown that testicular size is reduced in patients with CKD, with histologic abnormalities such as seminiferous tubular alterations, interstitial fibrosis, and tissue calcifications. The testes, in addition to impaired spermatogenesis, show evidence of impaired endocrine function.[23,24] Decreased function of the hypothalamic−pituitary−gonadal axis as well as reduced androgen synthesis are common in patients with CKD (Fig. 2).[23,24] Pituitary luteinizing hormone (LH) secretion is reduced, although its pulsatile character is maintained.[24] Both abnormal gonadotropin-releasing hormone pulsatility, together with increased levels of circulating prolactin, may lead to impairment of germinal and Leydig cell function. Despite reduced pituitary LH secretion, circulating LH levels increase, an effect that may be owing to reduced renal clearance. In addition, abnormal LH signaling can contribute to LH resistance.[24] Impaired Leydig cell sensitivity to human chorionic gonadotropin already are detectable, with only moderate decreases in the eGFR; the accumulation in serum of a factor inhibiting the LH receptor could explain the reduced response of the Leydig cell to human chorionic gonadotropin.[24] This inhibitory activity largely disappears after transplantation.

TESTOSTERONE DEFICIENCY IN CKD: PREVALENCE AND ASSOCIATIONS

Approximately 40% to 60% of end-stage renal disease patients have testosterone deficiency.[3,25-30] This

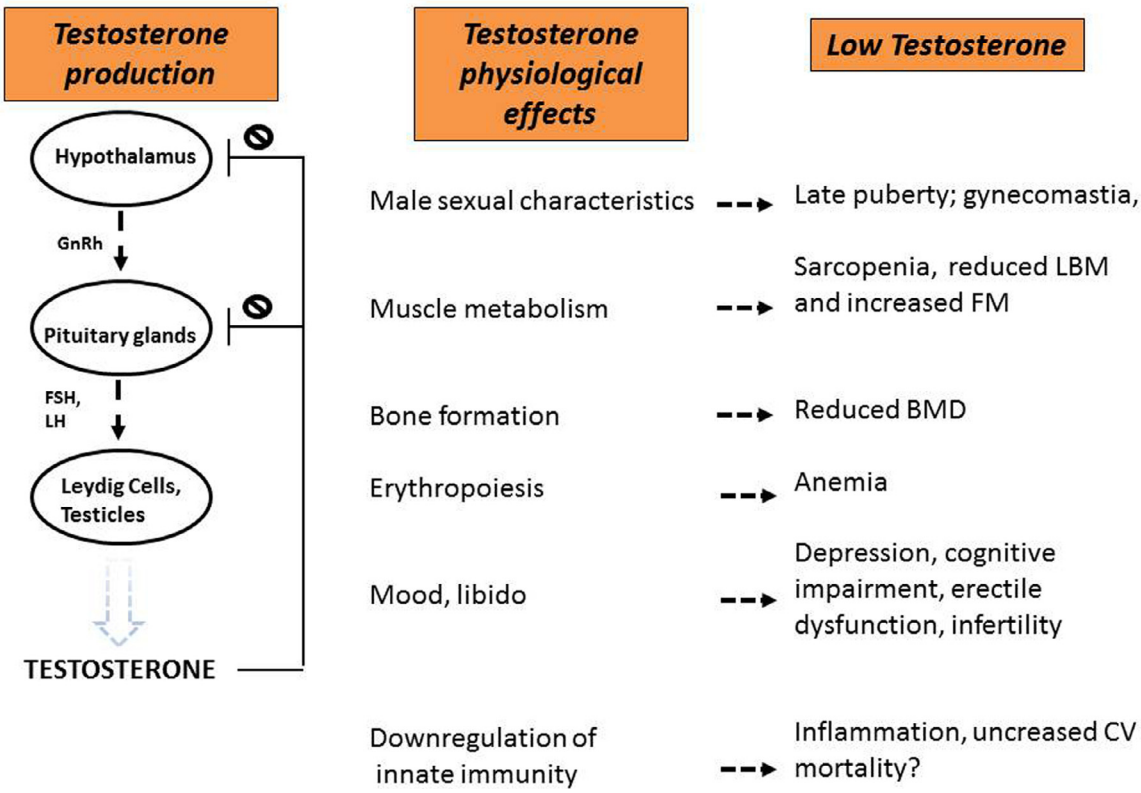

Figure 2. This graph describes how testosterone deficiency (hypogonadism) may contribute to the different components of protein-energy wasting and frailty in patients with chronic kidney disease. Abbreviations: BMD, bone mass density; CV, cardiovascular; FM, fat mass; FSH, follicle-stimulating hormone; GnRh, gonadotropin-releasing hormone; LBM, lean body mass; LH, luteinizing hormone.

prevalence is notably in excess of the general population rate. Total and free testosterone levels typically are reduced, although the binding capacity and concentration of SHBG is normal.[27,28,30] Total plasma estrogen concentrations often are increased in advanced kidney failure.[30] However, estradiol levels are normal, despite increased LH levels, in accordance with LH resistance.[30] In patients with non−dialysis-dependent CKD, hypogonadism has been linked to endothelial dysfunction,[31] impaired cognitive function and depression,[32] low muscle mass and strength,[33] increased risk of cardiovascular events,[33] and death.[2,32]

It is curious that although uremic hypogonadism is considered among the functional states,[5] it may persist even after kidney transplantation and normalization of kidney function. As shown by different cohort studies, hypogonadism is highly prevalent in kidney transplant patients, and correlates with decreased muscle and bone mass.[34,35] In addition, testosterone deficiency at the time of transplantation is associated independently with lower patient and graft survival[35]; it is unclear if hypogonadism per se, or its associations with altered body composition and function, may explain a worse outcome.

CLINICAL PRESENTATION OF HYPOGONADISM IN CKD

Symptoms and signs of hypogonadism vary according to the patient's age. Low testosterone level is associated with late-occurring puberty and reduced pubertal growth in children, and sexual dysfunction, anemia, bone fragility, infections, muscle wasting, frailty, loss of cognitive function, and accelerated cardiovascular disease in adult patients with CKD.

LATE-OCCURRING PUBERTY AND REDUCED PUBERTAL GROWTH IN CHILDREN WITH CKD

Both late-occurring puberty and reduced pubertal growth are observed commonly in children requiring long-term dialysis treatment, in those with protein-energy wasting before puberty, and in children with high glucocorticoid exposure and/or chronic kidney transplant rejection. In children with CKD stages 4 and 5, an improvement in pubertal growth may be attained by the preservation of renal function and the use of recombinant human growth hormone (see Haffner and Zivicnjak for review[36]).

SEXUAL DYSFUNCTION

The majority of adult men with end-stage renal disease (ESRD) and hypogonadism have some form of sexual dysfunction.[1] In addition, several studies also have reported significantly lower quality-of-life scores[37,38] associated with erectile dysfunction.

ANEMIA

A common effect of testosterone administration in non-renal patients is an increase in hemoglobin effect and, sometimes, the occurrence of polycythemia.[4] Androgens stimulate the production of hematopoietic growth factors and may increase iron bioavailability.[4] Hypogonadism may contribute to anemia in CKD. Testosterone and hemoglobin levels are associated negatively in CKD patients.[39] In addition, low testosterone is associated inversely with erythropoiesis-stimulating agents as well, making testosterone a possible target for patients who are hyporesponsive to erythropoiesis-stimulating agents.[39]

BONE FRAGILITY

Disturbances in the gonadal axis may contribute to skeletal fragility in men with late-stage CKD.[40] Rettew et al[41] studied the associations between endogenous levels of sex hormones and bone mineral density (BMD) in a cohort of 146 men and women with ESRD on the kidney transplantation list. In men, serum testosterone was associated positively with BMD at several bone sites, independently of age, body mass index, dialysis, diabetes types 1 and 2, parathyroid hormone, and steroid exposure. Estrogens were associated positively with BMD at the lumbar spine and femoral neck using the same fully adjusted model. In postmenopausal women, serum testosterone was correlated positively with lumbar spine BMD. Overall, these data show that high endogenous levels of sex hormones are associated with greater BMD in male kidney transplantation candidates.

INFECTIONS

Testosterone is associated with the immune system and has antibacterial activity.[41] In a large-scale, multicenter, prospective cohort study to study the role of testosterone in infection-related hospitalization, as well as in all-cause mortality and CVD events, lower levels of serum testosterone were associated with infection-related hospitalization and all-cause mortality in male hemodialysis patients.[42]

Very recently, it was shown that the severity and mortality of coronavirus disease 2019 are higher in males than in females, but the underlying molecular mechanisms are unclear. Studies have shown that viral RNA clearance is delayed in males with coronavirus disease 2019. In addition, the testis can harbor coronavirus, and, consequently, males show delayed viral clearance. Differences in sex hormone milieus also could be a determinant of viral infections because estrogen has immunoenhancing effects while testosterone has immunosuppressive effects (see Pradhan and Olsson[43] for review).

MUSCLE WASTING

Despite the progress in renal replacement therapy techniques, mortality levels remain high in patients with CKD.[44] This increase in mortality is limited not only to dialysis patients, but includes the whole range of GFR during the progression of CKD, and mainly is owing to cardiovascular disease and, at advanced stages, to infections.[44] In addition, strong associations between surrogates of muscle mass and survival have been observed in patients with CKD.[44,45] Given the high mortality and poor quality of life associated with dialysis treatment, identification of novel treatments for advanced kidney disease is a high clinical priority.[46]

The prevalence of protein energy wasting, a condition of loss of muscle and visceral protein stores not entirely accounted for by inadequate nutrient intake, increases progressively along with the loss of residual renal function, and is high in dialysis patients.[44,45] Major recent advances in our knowledge of pathophysiology of protein metabolism in CKD have allowed us to understand the mechanisms by which acidosis, insulin resistance (in CKD stages 3-5), and inflammation (in CKD stage 5D) affect different intracellular signals and pathways that promote protein degradation (Fig. 2),[47] such as caspase-3 mediation of apoptosis, myostatin, and activation of the ubiquitin−proteasome system. In addition, resistance to growth hormone/Insulin-like growth factor-I may down-regulate protein synthesis. Recently, Zhang et al[48] were able to show that CKD stimulates chromatin-modifying nucleolar protein 66, which suppresses both ribosomal DNA transcription and muscle protein synthesis via a demethylase mechanism. The control of muscle protein synthesis therefore also is impaired in CKD. Overall, available evidence underlines how the sensitive sequences of checks and balances by which protein metabolism is controlled can be influenced by the uremic state. All of these alterations may potentiate the effects of concurrent catabolic illnesses, anorexia, and physical inactivity that often are encountered in uremic patients.

It is interesting that the testosterone downward signal is positioned to counterbalance the catabolic pathways, which are primed by the uremic state. In muscle, testosterone increases protein synthesis through stimulation of androgen receptors and activation of the insulin-like growth factor-1 pathway; in addition, it promotes myonuclear accretion and satellite cell recruitment (Fig. 3).[49,50] In human beings, in the fasting state, testosterone's anabolic action is mediated via an enhancement of the efficiency of protein synthesis, that is, the rate of protein synthesis relative to the availability of amino acid precursors (Fig. 4), an effect that is not immediate, but takes a few days to occur after testosterone administration.[50] In the basal state, testosterone injection stimulates net protein synthesis but not tissue amino acid transport.[49,50] However, protein/amino acid feeding causes anabolism through greater increases in inward amino acid transport, intracellular amino acid appearance, and, subsequently, protein synthesis. Muscle

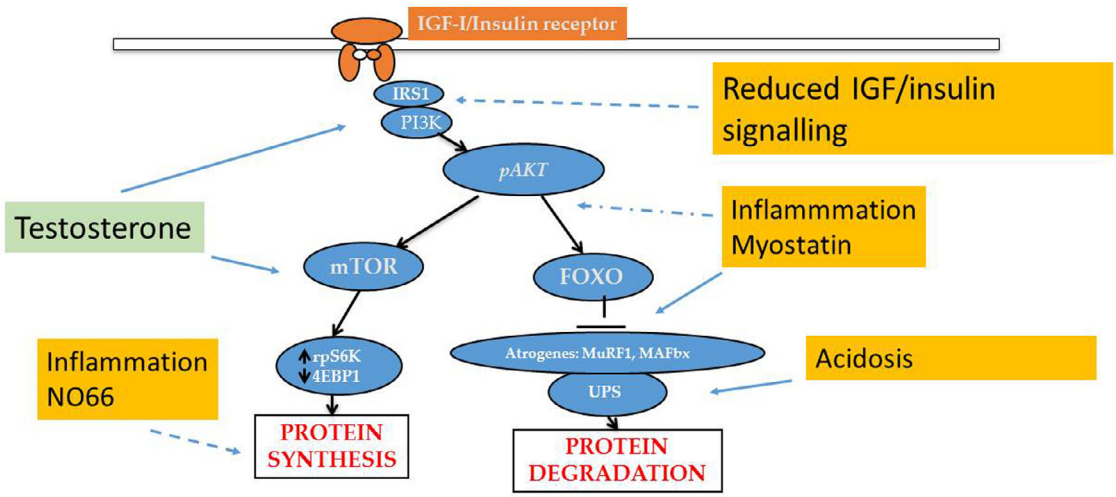

Figure 3. A schematic overview showing how testosterone may counterbalance catabolic mediators in chronic kidney disease (CKD). In the muscle of patients with CKD, acidosis, insulin resistance, and inflammation affect different intracellular signals and pathways that promote protein degradation, such as caspase-3−mediated apoptosis, myostatin, and activation of the ubiquitin−proteasome system. In addition, resistance to GH/IGF-I may down-regulate protein synthesis. Protein synthesis also is down-regulated by nucleolar protein 66 (NO66), which suppresses ribosomal DNA transcription. Testosterone anabolic signal is positioned to counterbalance the catabolic pathways, which are primed by the uremic state. Testosterone increases protein synthesis through stimulation of androgen receptors and activation of the IGF-I pathway; in addition, it promotes myonuclear accretion and satellite cell recruitment. Abbreviations: 4EBP1, 4E-binding protein 1; FOXO, forkhead box O3; IRS1, insulin receptor substrate 1; MAFbx, muscle atrophy F-box gene; mTOR, mammalian target of rapamycin; MuRF1, muscle RING-finger protein-1; PI3K, phosphatidylinositol 3-kinase; rpS6K, ribosomal protein S6 kinase; UPS, ubiquitin-proteasome system.

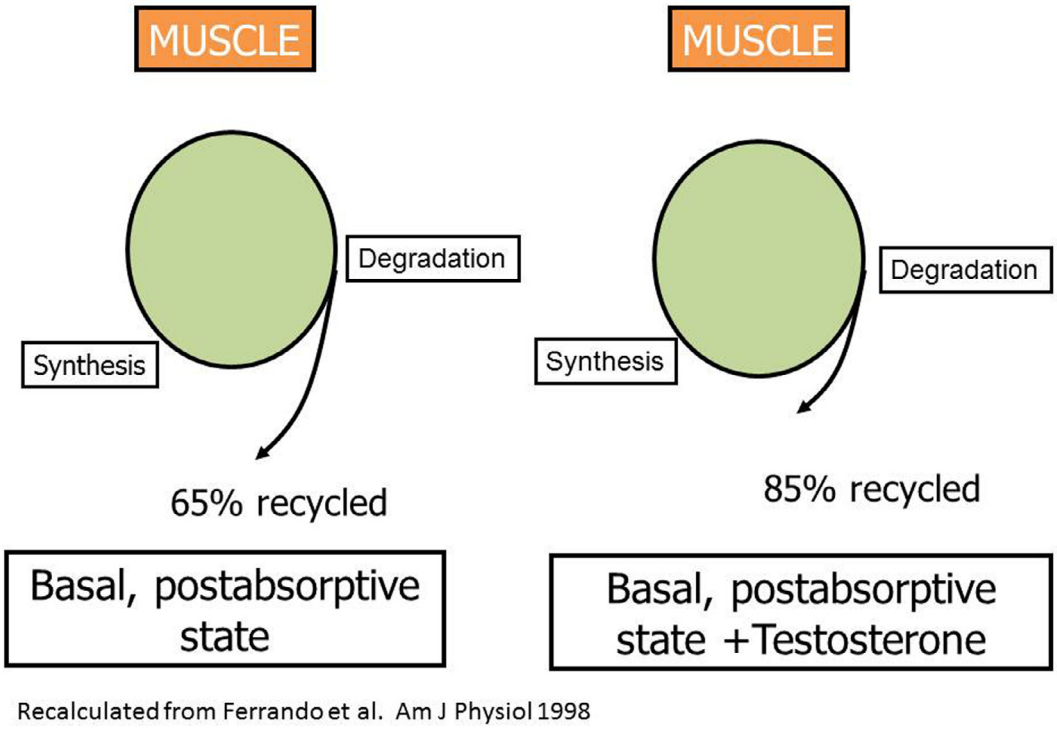

Figure 4. Testosterone's effect on the efficiency of protein turnover. On diets containing 1.1 g/kg protein, 66% of amino acids released by protein breakdown in muscle is recycled into protein synthesis (efficiency of protein turnover). During testosterone administration in healthy adults, the efficiency of protein turnover increases, with lower amounts of amino acids lost from proteins.

hypertrophy also is mediated by testosterone activation of various genomic and nongenomic pathways that act on the central nervous system.[51] Finally, there may be an androgen receptor−independent pathway through which testosterone may act.[51] Studies of long-term testosterone users have shown an increase in muscle hypertrophy of both type I and type II fibers.[52]

In keeping with the testosterone effects on skeletal muscle, low testosterone levels are associated with reduced muscle strength and fat-free mass both in CKD[53] and in hemodialysis patients.[1,54,55] Low testosterone levels in male hemodialysis patients also are associated with lower physical activity.[55] All of these findings suggest that the reduction in testosterone levels that accompany CKD may contribute further to the procatabolic environment leading to muscle wasting.[56]

FRAILTY

In the general elderly population, frailty has been defined as a condition characterized by loss of biological reserves, failure of homoeostatic mechanisms, and susceptibility to adverse outcomes, which increases vulnerability for loss of independence and death.[57,58] The term *frailty* is comprehensive of a large spectrum of stages running from the prefrail state, when individuals are at high risk of becoming overtly frail, through to extreme states in which multiple physiological systems are failing, autonomy is lost, and death is close.[57] Several aspects of frailty, including its underlying mechanisms, still are obscure. It is remarkable that some of its components are reversible, particularly in the prefrail state and after acute illnesses.[57,58] Also, although frailty is a long-established clinical syndrome, there is no uniformly accepted way of measuring it in the clinical setting.[59]

In the general elderly population, a cross-sectional association between low testosterone and/or SHBG and frailty has been observed in several studies.[60-63] The association between serum testosterone (or the change in its levels over time) and frailty also has been confirmed in prospective studies.[63,64] Because low testosterone also is associated with sarcopenia, reduced bone mass, anemia, depression, and the metabolic syndrome, hypogonadism may contribute to several different components of frailty.[63,64]

The prevalence of frailty is considerably higher among dialysis patients than among elderly community residents, and frail CKD patients are also at higher risk of morbidity and mortality.[64,65] It is interesting that the prevalence of frailty increases as CKD progresses,[62] supporting the concept of a stepwise process during which catabolic factors occurring in CKD (such as anorexia, acidosis, insulin resistance, and inflammation) progressively lead to wasting, functional impairment,

deconditioning, and thus contribute to the frail state. However, although both CKD and aging contribute to frailty, acute illnesses and anorexia are other potentially reversible contributors that can be treated.[63]

Muscle mass is an important contributor to physical function. It is interesting that the key convergent pathologic effects of frailty and wasting include loss of muscle mass and strength, which may impair mobility and have an impact on the activities of daily living. A reduced testosterone level may contribute to loss of energy, strength, skeletal and muscle mass, and favor muscle wasting, cachexia, and, in the end, contribute to frailty and mortality in CKD. Of note, many factors that are implicated in the pathogenesis of frailty, such as IGF-I and insulin resistance, inflammation, and altered androgen and glucocorticoid secretion also are common to CKD-induced wasting.[55] Johansen et al[64] observed that diabetes mellitus, certain ethnicities, and higher interleukin 6 levels were associated with worsening frailty over a 2-year follow-up period among chronic dialysis patients, whereas higher serum albumin levels were associated with improving frailty. Chiang et al,[55] in a multicenter study of 440 men on hemodialysis, observed that a 50% lower free testosterone concentration was associated with a 1.72-fold higher odds for developing sarcopenia and a decrease in muscle mass over 12 months. Further analysis showed that serum free testosterone also was associated with reduced physical function of frailty. These associations are especially noteworthy because slow gait speed and low grip strength may be important for maintaining independence and also are predictive of mortality in patients on dialysis. Therefore, the association between testosterone and low muscle mass in the CKD cohort studied by Chiang et al[55] appears to be stronger than that observed in the elderly, in which blood testosterone accounts for a small proportion (3%-11%) of the variance in muscle mass and strength.[63] These observations support the hypothesis that the measure of free testosterone may be useful for individualized patient care. Wu et al[65] in a meta-analysis of 62 study cohorts with cross-sectional designs observed that the development of frailty was associated with the emergence of cardiometabolic, musculoskeletal, and cerebral complications, and a higher risk of subsequent functional and quality-of-life impairments. Moreover, frailty in CKD patients increased health care utilization and consistently increased mortality.[65]

In consideration of the number of contributors to frailty and their effects, an individual multitargeted approach to manage prefrail and frail CKD patients is important. However, currently, there is no widely accepted treatment for frailty.[57] Clearly, the identification of treatable factors could lead to interruption of the trajectories leading to frailty; androgen deficiency appears to be an important and potentially treatable mechanism contributing to the frail state.

TESTOSTERONE DEFICIENCY AND MORTALITY RISK IN THE GENERAL POPULATION AND IN DIALYSIS PATIENTS: CAUSAL EFFECT OR REVERSE CAUSALITY?

Testosterone is a potent anabolic hormone with effects on various and important pathways in the heart and vessels. Some studies have suggested greater endothelial dysfunction in men with hypogonadism compared with men with normal testosterone levels; the underlying causes of endothelial dysfunction with sex hormone deficiency are unknown but may be related to endothelial nitric oxide synthase dysfunction and oxidative stress (for review see Khaw et al[66]). In addition to hypertension and cardiovascular disease, hypogonadism has been reported as a risk factor for systemic inflammation and all-cause mortality in the general population.[67] In the European Prospective Investigation of Cancer-Norfolk study, the risk of cardiovascular death diminished with increasing serum testosterone, with men in the highest quartile having an odds ratio of 0.53 (95% CI, 0.32-0.86) compared with men in the lowest quartile.[67] In a study with a median follow-up duration of 7.1 years, Haring et al[68] observed a U-shaped association between serum testosterone and all-cause mortality: men with total testosterone levels in the second and third quartiles (283-454 ng/dL) had a lower risk than men in the lowest or the highest quartiles. In other studies, the association between serum testosterone and mortality was not statistically significant[69] or it was not observed.[70]

Therefore, the negative association between low testosterone and mortality in the general population is still a matter of debate.[71] On one hand, population studies cannot establish causality, and they cannot exclude reverse causality. On the other hand, testosterone levels decrease in both acute and subacute illnesses; therefore, the low testosterone concentrations present in men with cardiovascular disease might be a consequence of their morbidity rather than the cause.

In summary, most, but not all, epidemiologic studies suggest that low serum levels of endogenous testosterone are a risk factor for cardiovascular events, cardiovascular mortality, and all-cause mortality in the general male population. However, the available association studies cannot establish causality or exclude reverse causality (for review, see Gagliano-Jucá and Basaria[71]).

The role of hypogonadism on cardiovascular mortality appears to be more important in patients with CKD because both low testosterone and cardiovascular complications are strongly associated. Clinical studies have suggested that low testosterone levels are associated with excess risk of CVD and mortality in high-risk elderly patients with comorbid conditions, such as those with CKD, diabetes, metabolic syndrome, and inflammatory states. In hemodialysis patients, low testosterone is strongly associated with higher cardiovascular mortality

in cross-sectional studies.[3,25,26] In a prospectively designed multicenter observational study (follow-up period, 20 mo) using data from the Canadian Kidney Disease Cohort Study, Bello et al[27] observed that higher serum testosterone levels were associated with a significantly decreased unadjusted risk of death (hazard ratio per 10-ng/dL increase, 0.58; 95% CI, 0.37-0.90); moreover, there was a statistically significant trend for higher all-cause mortality with low serum testosterone levels in adjusted analyses ($P < .001$). The strongest association was related to all-cause mortality rather than cardiovascular-specific mortality. Although the observational nature of this study does not allow us to assess whether these relationships are causal, the reported results underscore the need for increased awareness of the risks of hypogonadism among nephrologists and recommends better understanding of the effects of testosterone replacement therapy in CKD.

HOW TO CORRECT MALE HYPOGONADISM IN CKD?

Effects of Drugs and Different Dialysis Treatments

Several drugs that are used routinely in CKD stages 3 to 5d and kidney transplant patients can decrease circulating testosterone levels. An accurate check of antihypertensive treatment can be useful. Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, spironolactone, and corticosteroids,[30] which often are prescribed to patients with CKD, might interfere with testosterone production, even if there is controversy regarding the role of renin-angiotensin-aldosterone system inhibition.[75] Other agents that have anti-androgenic properties include methotrexate, cimetidine and ranitidine, glucocorticoids, cyclosporin, and tacrolimus.[30] In addition, the dialysis technique may modify circulating testosterone levels, as suggested by a lower prevalence of hypogonadism in peritoneal dialysis patients compared with hemodialysis patients.[72]

It has been shown that a change from standard hemodialysis treatment for men with CKD stage 5D to alternate nightly, longer sessions results in increased testosterone levels, while SHBG is unaffected.[73] This suggests that greater delivery of dialysis improves testosterone bioavailability but not through SHBG effects. A trial with bromocriptine in subjects with increased prolactin levels also can be feasible, although no randomized controlled trial is available.

TESTOSTERONE REPLACEMENT THERAPY IN HYPOGONADAL UREMIC MEN

Testosterone replacement in hypogonadal men leads to improvement of muscle mass and strength[74] and bone density.[75,76] An improvement in mood, sexual function, and quality of life[77] also have been shown previously in small series.[78] Administration of supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass and muscle size and strength in patients with burns, chronic obstructive pulmonary disease, cancer, and human immunodeficiency virus infection.[4] Studies involving limited numbers of frail subjects have shown that the administration of testosterone results in improved muscle mass and strength, as well as increased bone mass.[79] However, none of the studies have been of sufficient size or duration to adequately address potential risks.

The few available studies have shown that androgen replacement also may be a feasible therapeutic target in hypogonadal men with CKD stages 4 to 5D (Table 2). Interventional studies in dialysis patients have explored the effects of testosterone or testosterone derivatives on muscle mass, physical function, and quality of life. A randomized controlled trial in 29 maintenance hemodialysis patients showed that treatment with nandrolone decanoate for 6 months led to increased lean body mass and a decrease in walking and stair climbing time, as well as an increase in serum creatinine concentration compared with treatment with placebo.[80] A larger follow-up study that also incorporated exercise showed improvements in body composition with nandrolone over 3 months, but no improvement in self-reported physical function or measured strength in the absence of exercise.[81] More recently, Supasyndh et al[82] observed that oxymetholone for 24 weeks led to an increase in fat-free mass, hand grip strength, and muscle growth factor messenger RNA levels,[87] but some patients developed liver toxicity. Pampa Saico et al[83] tested transdermal testosterone on hemodialysis patients for 3 months and observed an increase in the levels of albumin and a decrease in the use of erythropoietin. An increase in free testosterone levels and an improvement in the total aging male symptom scores were observed with the use of testosterone enantholactam acid ester every 2 weeks for 24 weeks.[84] More recently, Yeo et al[77] observed that testosterone replacement improved quality of life and several symptoms of hypogonadism in a small cohort of patients with moderate-to-severe CKD. Thus, the few studies available indicated that androgens can increase anabolism, but the extent to which androgen treatment improves physical function is less clear. In addition, follow-up time was limited. Moreover, to date, frailty (as opposed to muscle strength and physical performance) has not been studied as a clinical outcome of interventional trials of testosterone replacement in CKD. Therefore, data from larger and longer interventional studies need to supplement what we have learned from currently available trials. In addition, as pointed out by a recent meta-analysis,[85] the role of sex hormone supplementation on BMD and fracture rates still needs to be addressed.

Table 2. Effects of Testosterone or Testosterone Derivatives on Muscle Mass and Physical Function in Patients on Dialysis and CKD

Drug	Administration Route	Subjects	Outcome	References
Nandrolone decanoate	100 mg IM weekly for 6 months versus placebo	29 hemodialysis patients (n = 14 treatment group versus n = 15 placebo)	1. Increase in lean body mass 2. Improvement in walking and stair climbing	Johansen et al[80]
Nandrolone decanoate	100 mg (females)/200 mg (males) IM weekly for 12 wk versus placebo (double-blinded) ± resistance exercise training	79 hemodialysis patients	1. Increase in lean body mass 2. Increased muscle cross-sectional area	Johansen et al[81]
Oxymetholone	50 mg twice-daily oral versus placebo for 24 wk	43 hemodialysis patients (treatment group n = 21 and n = 22 placebo)	Increase in fat-free mass, handgrip strength, muscle growth factor messenger RNA levels Side effect: liver toxicity!	Supasyndh et al[82]
Testosterone	50 mg transdermic daily for 3 months versus placebo	12 hemodialysis patients (n = 6 treatment group and n = 6 placebo)	Increase in testosterone concentration associated with increased albumin levels and a reduction in the needs of erythropoietin alfa	Pampa Saico et al[83]
Testosterone enantholactam acid ester	250 mg IM every 2 weeks before hemodialysis versus placebo for 24 wk	24 hemodialysis patients with late-onset hypogonadism syndrome (n = 13 treatment group and n = 11 placebo)	1. Increase in free testosterone levels 2. Improvement in the total Aging Males' Symptoms score	Inoue et al[84]
Testosterone	2% testosterone gel 60 mg/d for 3 months versus physical exercise	25 male patients with stages III and IV CKD (serum testosterone <350 ng/dL + more than 1 deficiency symptom versus 25 age-matched CKD III and IV and testosterone deficiency	1. Increase in grip strength 2. Increase in testosterone, hemoglobin, and hematocrit 3. Improvement of mental and physical quality of life and depression 4. Reduction of hypogonadal symptoms 5. Improvement of urinary function	Yeo et al[77]

Abbreviation: IM, intramuscularly.

TESTOSTERONE TREATMENT, PROSTATE CANCER, AND CARDIOVASCULAR RISKS

Even if testosterone supplementation in hypogonadism has well-defined favorable effects,[74-79] its inherent risks are undefined. Androgen deficiency in young men resulting from organic disease of the hypothalamus, pituitary gland, or testes has been treated with testosterone replacement for many years without evidence of increased cardiovascular events. In contrast to these cohort studies, some retrospective studies have shown an increased number of cardiovascular events in men who received testosterone replacement therapy, whereas other studies found either neutral or beneficial effects.[69,70] Moreover, observational studies have shown that testosterone replacement therapy might increase susceptibility to future prostate cancer.[86]

These findings, together with results of a recent study on testosterone replacement in older men with hypogonadism that was terminated early because of an excess of cardiovascular events in the testosterone group,[87] led the Food and Drug Administration to release a warning statement about the potential cardiovascular risks of testosterone replacement therapy and kindled the discussion on the cardiovascular safety of testosterone replacement.[88] However, a recent meta-analysis of 39 randomized controlled trials and 10 observational studies[86] concluded that there is no statistically significant increased risk of testosterone treatment on a composite outcome of myocardial infarction, stroke, and mortality. As a matter of fact, no trials of testosterone replacement therapy published to date were designed or adequately powered to assess prostate cancer and cardiovascular events[87,88]; therefore, the safety of long-term testosterone therapy has not been established. The Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men trial (NCT03518034) design is a trial of testosterone therapy that is adequately powered to assess cardiovascular events and the incidence of prostate cancer, but its results will take several years to become available.[88] Unfortunately, the Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy ResponSE in Hypogonadal Men trial excludes subjects at advanced (stages 4-5) CKD stages.

WHAT TO DO, WAITING FOR THE RESULTS OF NEW STUDIES?

According to current guidelines and expert opinion reports,[5,89,90] investigation of testosterone deficiency should be undertaken in men with symptoms of reduced libido, erectile dysfunction, depression, fatigue, poor concentration, and poor memory. Total and free testosterone are the most frequently used tests. However, it is

important to recognize that the clinical guideline−based cut-off value for testosterone deficiency (<350 ng/dL) does not discriminate individuals at increased risk of death[27] in hemodialysis patients. Nephrotic syndrome and diabetes are conditions that are associated with decreased SHBG levels, in which the measure of free and total testosterone is suggested.[90] Testosterone-deficient patients should be informed that low testosterone levels place them at risk for these major cardiovascular events, and clinicians should assess all testosterone-deficient patients for CVD risk factors, both fixed (eg, older age, male sex) and modifiable (eg, dyslipidemia, hypertension, diabetes, current cigarette smoking).[90] The guidelines argue against routinely prescribing testosterone therapy to all men age 65 years or older with low testosterone concentrations. In men older than age 65 who have symptoms or conditions suggestive of testosterone deficiency and consistently and unequivocally low morning testosterone concentrations, it is suggested that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits. Until the results of the new trials are available, clinicians should individualize testosterone treatment after having an informed discussion with their patients about the risks and benefits of testosterone replacement therapy.

SUMMARY

A major effect of CKD is a reduction in testosterone levels because of both primary and hypogonadotrophic hypogonadism. In addition to impairment of pubertal growth and sexual maturation in children with CKD, uremic hypogonadism contributes to several CKD complications, including erectile dysfunction, wasting and frailty, anemia, decreased bone mineralization, depression, and cognitive impairment. In addition, hypogonadism may contribute to all-cause and cardiovascular disease mortality and the progression to ESRD. It is interesting that testosterone supplementation has the potential to reverse or attenuate CKD complications. In particular, upon binding to androgen receptors, testosterone downward signal is positioned to counterbalance the catabolic pathways that are primed by the uremic state. In muscle, testosterone increases protein synthesis through stimulation of androgen receptors and activation of the insulin-like growth factor-1 pathway; in addition, it promotes myonuclear accretion and satellite cell recruitment. Testosterone replacement for androgen-deficient male CKD patients has some support from available studies on muscle mass and function, but lacks a robust evidence base and carries hypothetical risks. The safety of long-term testosterone therapy has not been established in the general population. Similarly, there is a need for clinical trials to evaluate the impact of testosterone treatment on musculoskeletal tissue, frailty, and cardiovascular and overall safety. Until the results of the ongoing long-term large trial are available, nephrologists need to individualize testosterone treatment after having an informed discussion with their patients about the risks and benefits of testosterone replacement therapy.

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