Review Article

Hypogonadism and renal failure: An update

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ABSTRACT

The prevalence of both hypogonadism and renal failure is increasing. Hypogonadism in men with renal failure carries with it significant morbidity, including anemia and premature cardiovascular disease. It remains unclear whether testosterone therapy can affect the morbidity and mortality associated with renal failure. As such, in this review, we sought to evaluate the current literature addressing hypogonadism and testosterone replacement, specifically in men with renal failure. The articles chosen for this review were selected by performing a broad search using Pubmed, Embase and Scopus including the terms hypogonadism and renal failure from 1990 to the present. This review is based on both primary sources as well as review articles. Hypogonadism in renal failure has a multifactorial etiology, including co-morbid conditions such as diabetes, hypertension, old age and obesity. Renal failure can lead to decreased luteinizing hormone production and decreased prolactin clearance that could impair testosterone production. Given the increasing prevalence of hypogonadism and the potential morbidity associated with hypogonadism in men with renal failure, careful evaluation of serum testosterone would be valuable. Testosterone replacement therapy should be considered in men with symptomatic hypogonadism and renal failure, and may ameliorate some of the morbidity associated with renal failure. Patients with all stages of renal disease are at an increased risk of hypogonadism that could be associated with significant morbidity. Testosterone replacement therapy may reduce some of the morbidity of renal failure, although it carries risk.

Key words: Dialysis, end-stage renal disease, replacement, testosterone

INTRODUCTION

The prevalence of hypogonadism in the general population has been estimated to be between 6 and 12%.[1] Only 23% of patients with end-stage renal failure had normal testosterone values (>14 nmol/L).[2] Several conditions such as obesity, cardiovascular disease, osteoporosis, HIV, chronic obstructive pulmonary disease (COPD) and renal failure[3] have been associated with hypogonadism. Patients with end-stage renal disease are found to be at increased risk for hypogonadism. In one report, testosterone (T) deficiency (<10 nmol/L) was present in 44% of the men with renal failure, while 33% showed testosterone insufficiency (10–14 nmol/L), and only 23% had normal testosterone values (>14 nmol/L).[2] Hypogonadism in patients with renal failure carries with it significant morbidity, including anemia, and premature cardiovascular disease - therapy with testosterone replacement could improve some of these effects. As such, in this review, we sought to thoroughly assess the current literature addressing hypogonadism, specifically in men with renal failure.

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MATERIALS AND METHODS

The articles chosen for this review were selected by initially performing a broad search using PubMed, Embase and Scopus from 1990 to the present. Initially, the terms "hypogonadism" and "renal failure" were used as search terms. This produced 195 results, of which approximately 60 titles and abstracts seemed relevant, as judged by the primary author. The dates of publication of these abstracts spanned from 1970 to 2014. Of these 60 titles, the below-referenced articles were most appropriate for inclusion. Eleven articles specifically addressed hypogonadism in the renal failure population. Of those, six articles [Table 1] contained primary data focused on hypogonadism in renal failure. The information below

Table 1: Summary of studies that demonstrated association between renal failure and hypogonadism

Reference	Study type	Number of patients	Findings
Carrero *et al.*, 2011[2]	Cross-sectional	260	In men with renal failure, testosterone deficiency (<10 nmol/L) was present in 44%, while 33% showed T insufficiency (10–14 nmol/L) and only 23% had normal T values (>14 nmol/L) T deficiency was associated with cardiovascular co-morbidity, independent of age, diabetes or inflammation
Dunkel *et al.*, 1997[4]	Cross-sectional	9	Serum from boys with renal failure showed inhibitory activity preventing LH receptor activation This inhibition is dependent on stage of disease
Carrero *et al.*, 2009[5]	Prospective observational	126	Independent of age, patients with T in the lower tertile of patients with ESRD were at increased risk of cardiovascular disease at baseline Lower T values were associated with higher likelihood of having cardiovascular disease Independent of age and creatinine, lower levels of T were correlated with higher levels of inflammatory markers, including IL-6, and CRP Patients with lower T levels had a higher rate of death from cardiovascular disease and all-cause mortality
Yilmaz *et al.*, 2011[6]	Cross-sectional	239	Total and free T levels gradually decreased across increasing CKD stages (ranging from 17% in CKD stage 1 to 57% of the patients with CKD stage 5)
Canguven *et al.*, 2010[7]	Prospective longitudinal	102	Patients on hemodialysis with both hypogonadism and erectile dysfunction achieved therapeutic T levels after 1 month of supplementation with 5 g of T gel T gel improved IIEF scores and frequency of intercourse at 6 months of therapy
Johansen *et al.*, 1999[8]	Randomized, double-blind, placebo-controlled trial	29	Dialysis patients given nandrolone decanoate weekly were found to have increased lean body mass and improved outcomes on exercise measures when compared with placebo

T=Testosterone, LH=Luteinizing hormone, ESRD=End-stage renal disease, CRP=C-reactive protein (CRP), CKD=Chronic kidney disease

comes from both primary sources as well as other review papers.

Pathophysiology of renal failure and hypogonadism

Multiple factors are responsible for hypogonadism in renal failure [Figure 1]. Pituitary and gonadal alterations seen in many men with renal failure lead to disruption of the hypothalamic -- pituitary -- gonadal axis and contribute significantly to hypogonadism. Renal failure is associated with decreased luteinizing hormone (LH) production[4] as well as a decreased clearance of prolactin.[9] Reduction in clearance of prolactin leads to hyperprolactinemia that can inhibit LH production and in turn lead to decrease in testosterone production.

Uremia, commonly seen in men with advanced renal failure, inhibits the LH receptor in the Leydig cells,[4] thereby impairing testosterone production. Several medications commonly used by patients with renal disease may interfere with the synthesis of sex hormones.[10] These medications include angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), spironolactone, ketoconazole, statins and glucocorticoids.

Renal failure results in a reduced clearance of gonadotropin-releasing hormone (GnRH), LH and follicle-stimulating hormone (FSH), leading to elevated serum levels of both LH and FSH. Although elevated levels of stimulatory hormones should cause increased testosterone (T) production, this is not observed in patients

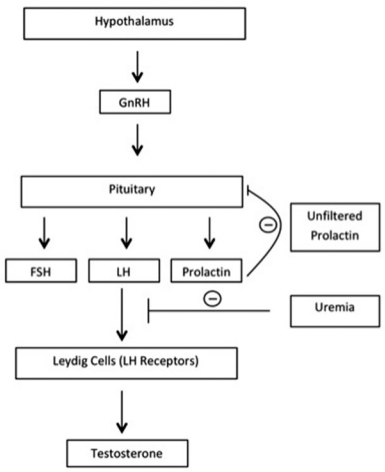

Figure 1: Pathophysiology of association between renal failure and hypogonadism

with renal failure.[9] This unexpected outcome could be due to uremia inhibiting the action of LH. Luteinizing hormone receptors (LHR) interact with membrane-associated G proteins in order to increase adenylyl cyclase activity and are only found on Leydig cells. The increase and accumulation of cAMP resulting from LH stimulation leads to increased androgen production. It is possible that Leydig cell resistance is responsible for the moderately decreased T production despite the mildly elevated gonadotropin levels. Additionally, decreased T levels fail to stimulate gonadotropin production. Because low T should produce an increase in gonadotropins, there is likely additional distortion of the positive-feedback mechanism at the

hypothalamic–pituitary level. Hemodialysis and peritoneal dialysis do not reverse the inhibitory effects on LHR in men with renal failure.[4]

In addition to uremia, a variety of medications commonly prescribed to end-stage renal disease (ESRD) patients contribute to hypogonadism through direct inhibition of sex hormone synthesis. T biosynthesis is inhibited by spironolactone and cimetidine through competition for androgen receptors. Additionally, spironolactone and ketoconazole reduce 17-α hydroxylase and C17-20 lyase activity, which also contribute to a reduction in T synthesis.[9] Glucocorticoids interact both at the gonadal steroid receptors and at the hypothalamic–pituitary axis to decrease T synthesis. The immune suppressants cyclosporine A and tacrolimus alter the function of both Leydig cells and the hypothalamic -- pituitary -- gonadal axis. Tricyclic antidepressants, benzodiazepines and opiates induce secondary hypogonadism by inhibiting LH and FSH signaling.[9]

Screening and diagnosis of low testosterone in men with renal failure

The signs and symptoms of hypogonadism in men with renal failure can be particularly slow in onset and non-specific.[10] These symptoms may include fatigue, increased sleepiness, decreased energy and negative mood states.[10] More specific symptoms include decreased libido and erectile dysfunction. Erectile dysfunction has been noted in 20 -- 87% of patients with renal failure, but the cause is multi-factorial and not always due to hypogonadism.[11] Physical exam may reveal increased abdominal fat, reduced muscle and bone mass, decreased body hair, gynecomastia and small testicles.

After a thorough history and physical exam, a measurement of total testosterone is required to diagnose hypogonadism. Testosterone, along with other hormonal studies, should be obtained early in the morning, as this is when testosterone peaks.[1] However, this circadian rhythm may be blunted in older patients (over 60 years of age).[1] The measurements should not be obtained during acute illness as this may distort true values. In addition, two values at different times should be obtained to verify the diagnosis.[1] Most studies have used a total testosterone of less than 10 nmol/L (300 ng/dL) as a cut-off level for low testosterone.[2,5] However, free testosterone could be a better marker than total testosterone. This is especially true in the elderly population, when sex hormone-binding globulin (SHBG) increases and binds more testosterone, leading to a decrease in the percentage of free testosterone.[10] Other conditions may alter SHBG as well including liver disease, thyroid dysfunction, HIV, the use of anticonvulsants, obesity, diabetes and nephrotic syndrome. If a suspicion for altered SHBG is present, a free testosterone and SHBG level should be obtained.

Although currently all patients with renal failure are not screened for hypogonadism, certain findings support the adoption of this practice. In a study of 260 patients with ESRD, Carrero *et al.* found that only 23% of these patients had a truly normal testosterone level. Testosterone deficiency (<10 nmol/L) was found in 44% of patients, and testosterone insufficiency (10 -- 14 nmol/L) was found in another 33% of patients.[2] This high incidence of low testosterone levels is not only limited to patients with ESRD but also to different stages of chronic kidney disease (CKD). In a cross-sectional study of 239 male patients with varying stages of CKD, Yilmaz *et al.* demonstrated that total and free testosterone levels gradually decreased across increasing CKD stages.[6] In fact, the prevalence ranged from 17% in CKD stage 1 to 57% of the patients with CKD stage 5. This supports the fact that a deterioration of kidney function can progressively lower testosterone levels. However, it is important to note that hypogonadism cannot be diagnosed with laboratory values alone and that patients need to be symptomatic as well.

Morbidity of hypogonadism in men with renal failure

Recently, evidence has surfaced that may link low testosterone to increased morbidity and mortality, specifically in the ESRD population. In a prospective study, Carrero *et al.* followed 126 patients with ESRD treated with hemodialysis.[5] Cardiovascular morbidity accounted for over 50% of premature deaths in this population, and Carrero *et al.* hypothesized that low testosterone may play a role. Patients with testosterone in the lower one-third of this population (which was set at the level of 8.1 nmol/L) were found to have an increased presence of cardiovascular disease at baseline. This association held true independent of age. The data also demonstrated that the lower the testosterone, the higher the odds ratio of having cardiovascular disease (CVD). Compared with patients with testosterone levels above 12 nmol/L, patients with testosterone levels between 8 and 12 had a 2.6 OR of having CVD, and those with levels below 8 had an OR of 3.32. This general trend also held true for free testosterone and SHBG. Lower levels of testosterone were correlated with higher levels of inflammatory markers, including interleukin (IL)-6, and C-reactive protein. These correlations also held true independent of patient age and creatinine.[5] Lastly, patients with lower testosterone levels had a higher rate of death from CVD and all-cause mortality. In a larger cohort of patients with ESRD, Carrero *et al.* reproduced the correlation of testosterone deficiency being associated with cardiovascular co-morbidity, independent of age, the presence of diabetes or inflammation.[2] The finding was again replicated by Shores *et al.*, who found an increased risk of mortality in the male veteran population with low testosterone levels.[12]

Management of hypogonadism in men with renal failure

Multiple options exist for modalities of testosterone replacement, including transdermal gels, intramuscular injections, transbuccal tablets, oral tablets and subcutaneous

implants.[13] Intramuscular injections of T are associated with very variable serum levels, including significantly supratherapeutic levels initially and subtherapeutic levels prior to repeat dosing. The supratherpeutic peaks have also been associated with significant polycythemia, which presents a concern for ESRD patients who are at increased risk for cardiovascular events. Subcutaneous testosterone implants (pellets) have the longest duration of action of all forms and create relatively stable levels. T pellets are implanted into the subdermal fat of the lower abdominal wall or the deltoid, proximal thigh or buttocks, and are changed about every 6 months. They are generally well tolerated, but side-effects include pellet extrusion, minor bleeding, infection or fibrosis around the implantation site. For patients with renal failure, gels or pellets are likely to be safer given their steadier testosterone values with therapy.

Benefits of testosterone therapy in men with renal failure

Given the potential benefits, testosterone therapy should be initiated in patients with clinical hypogonadism. Different formulations of testosterone have been investigated in men with renal failure. Canguven *et al*. assessed a group of 102 patients who had been on hemodialysis for at least 6 months and had both hypogonadism and erectile dysfunction.[7] The patients were given 5 g T-gel per day for 6 months, with testosterone levels tested every 3 months, and international index of erectile function (IIEF) retaken by patients on Days 30, 90 and 180 of the study. They found that after 1 month, patients achieved therapeutic testosterone levels. In addition, both IIEF scores and frequency of intercourse improved after therapy. The IIEF scores remained stable and elevated at 6 months of therapy.

In a randomized, double-blind, placebo-controlled trial, Johansen *et al*. assessed nandrolone decanoate to placebo in a population of 29 patients on dialysis.[8] The study aimed to determine whether anabolic steroids could improve malnutrition and decrease muscle mass in patients on dialysis. It is important to note that hypogonadism was not part of the inclusion criteria for this study. After administering nandrolone decanoate or placebo in weekly injections, subjects were found to have increased lean body mass and improved outcomes on exercise measures when compared with subjects receiving placebo.

Unfortunately, further investigation into the benefits of testosterone replacement is still lacking. It has been documented that testosterone replacement in this population can improve sexual function and anemia. In the general population, treatment of hypogonadism with testosterone has been shown to also have metabolic benefits with regard to insulin resistance and obesity, as well as improvements in bone health.[3] However, to the best of our knowledge, these findings have not been assessed or replicated in an ESRD population.

Risks and Adverse Effects of Testosterone Therapy

Current controversy exists regarding the cardiovascular morbidity of testosterone. It is contraindicated in patients with prostate cancer, although no data support this currently.[10] Testosterone therapy has many side-effects, including weight gain, edema, gynecomastia and polycythemia.[9] Although polycythemia may be heralded as an adverse effect in the general population, it is therapeutic in a renal failure population.[10] Before the development of epogen, testosterone was used for renal failure patients with anemia.

It is important to be mindful of an individual patient's risk of adverse effects when beginning T therapy. Although polycythemia is a risk of T therapy and may be associated with thrombotic events, most patients with ESRD are profoundly anemic, and the resultant increase in hematocrit may be therapeutic. Most patients with ESRD have risk factors for CVD, such as diabetes, high blood pressure and peripheral vascular disease. As such, the etiology of the patient's ESRD should be considered when initiating testosterone therapy. For example, a 25-year-old male with ESRD from adult polycystic kidney disease does not carry the same cardiovascular risk as a 65-year-old patient with diabetes, hypertension and coronary artery disease. As such, the first patient could be started on testosterone therapy with a low likelihood of having an adverse event, but the second patient should be counseled extensively and all risk factors should be investigated thoroughly.

CONCLUSIONS

Patients with ESRD are found to be at increased risk for hypogonadism. Hypogonadism in patients with renal failure carries with it significant morbidity; therefore, physicians treating renal failure should evaluate the symptoms of hypogonadism. Therapy with testosterone replacement may reduce some of the morbidity of hypogonadism in renal failure and should be pursued only in patients with symptomatic hypogonadism. Based on the reviewed literature, it appears likely that preparations such as testosterone gels, subcutaneous depot injection and pellets that provide more stable levels of testosterone would be safer in men with renal failure. Testosterone therapy is not without significant risk, but the risk to the individual patient should be considered in the context of their overall medical health and relevant risk factors.

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