

Endocrine alterations and cardiovascular risk in CKD: Is there a link?

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ABSTRACT

The kidney plays an important role in synthesis, metabolism and elimination of a plethora of hormones. Thus, chronic kidney disease (CKD) naturally progresses with hormonal disorders. This review will focus in emerging evidence regarding the association between CKD-associated disturbances in the hypothalamic-pituitary-gonadal axis and cardiovascular risk factors. Hormonal derangements discussed are prolactin retention, testosterone deficiency and the low triiodothyronine syndrome, all of which have traditionally been interpreted as innocent bystanders of uremia and received relatively scarce attention by the Nephrology community. We here show that these disorders share intriguing links with inflammation, endothelial dysfunction, arterial stiffness, protein-energy wasting and other cardiometabolic alterations inherent to CKD-related excess mortality. We argue that these disorders may be novel uremic risk factors with possibility to serve as therapeutic targets.

Keywords: Testosterone. Thyroid hormones. Prolactin.

¿Existe relación entre las alteraciones endocrinas y el riesgo cardiovascular en la ERC?

RESUMEN

El riñón tiene un papel importante en la síntesis, metabolismo y eliminación de gran cantidad de hormonas. Así, la enfermedad renal crónica (ERC) cursa de forma natural con diversas alteraciones hormonales. Esta revisión aborda la posible conexión entre alteraciones en el eje hipotálamo-pituitario-gonadal y factores de riesgo cardiovascular en el paciente con ERC. Las anomalías hormonales analizadas son la retención de prolactina, deficiencia de testosterona y síndrome de T3 baja, todas ellas entendidas tradicionalmente como testigos inocentes de uremia y que han recibido una atención relativamente escasa por la comunidad nefróloga. En este revisamos interesantes vínculos entre estas alteraciones hormonales y complicaciones como la inflamación sistémica, la disfunción endotelial, la rigidez arterial, el desgaste proteico-energético y otras alteraciones cardiometabólicas inherentes a la excesiva mortalidad observada en la ERC. Proponemos que estas disfunciones hormonales pueden ser nuevos o previamente no apreciados factores de riesgo en el paciente urémico, existiendo la posibilidad de que puedan servir como objetivos terapéuticos.

Palabras clave: Testosterona. Hormonas tiroideas. Prolactina.

HORMONAL ALTERATIONS IN UREMIA; NOT JUST INNOCENT BYSTANDERS

The kidney plays an important role in endocrine regulation, not only for being the producer of certain hormones, such as erythropoietin and calcitriol, but also for its implication in the

metabolism and degradation of others, such as insulin and cortisol.¹ Hence, uremia naturally courses with multiple endocrine dysfunctions, including both alterations in signal-feedback mechanisms and in production, transport, metabolism, elimination and hormonal protein binding. In addition, conditions such as protein-energy wasting, inflammation, comorbidities, common medication or metabolic acidosis, can further contribute to the development and severity of these endocrine alterations.^{2,3} Some of the hormonal derangements above described are well-described and well-therapeutically targeted. Others, such as the disturbances in the hypothalamic-pituitary-gonadal axis, have been traditionally interpreted as innocent bystanders of uremia and received relatively less

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attention.⁴ The aim of this review is to contextualize emerging evidence suggesting that these endocrines alterations share intriguing links with endothelial dysfunction and cardiovascular risk in patients with chronic kidney disease (CKD). In specific, we will discuss the clinical associates and implications of hiperprolactinemia, male hypogonadism, sub-clinical hypothyroidism and the low T3 syndrome in the context of CKD patients.

PROLACTINEMIA AND ENDOTHELIAL DYSFUNCTION

Prolactin is a hormone secreted by various tissues in addition to the anterior pituitary gland. Its biologic action in women is to control breast development and lactation. The role of prolactin in men remains still unclear. Hyperprolactinemia is a common endocrine alteration in CKD, for both men and women. Its prevalence in CKD ranges from 30% to 65% being mainly the consequence of reduced renal clearance but also increased production due to altered dopaminergic activity.⁵

Despite the high prevalence of hyperprolactinemia, little is known about the implications of this condition in CKD patients. The few studies on prolactin in the context of uremia during the last decades have mainly focused on reproductive/sexual abnormalities. There is evidence, however, suggesting in non-renal populations that prolactin may have several biologic actions that participate in the atherosclerotic process: prolactin elevations have been for instance observed in subjects with essential hypertension⁶ and during the acute phase of coronary syndromes and ischemic strokes.⁷ Prolactin may play a role in the hypertensive complications of preeclampsia,⁸ being a direct contributor to arterial stiffness in postmenopausal women⁹ and perhaps playing a causative role in the heart failure that accompanies peri/postpartum cardiomyopathy.¹⁰ Also, prolactin levels predicted major cardiovascular events in men with erectile dysfunction¹¹ and associated with cardiac remodeling.¹² It is intriguing to speculate that uremia-induced prolactinemia may relate to the increased CVD risk of this patient population.

We recently reported novel epidemiological evidence suggesting that prolactin retention in CKD may associate with atherosclerosis and cardiac risk.⁵ We observed a strong and independent association between prolactinemia, endothelial dysfunction and cardiovascular outcomes in two independent cohorts of nondialyzed and hemodialysis patients, respectively. In nondialyzed CKD patients, every 10ng/ml increase in serum prolactin concentration raised the risk of suffering a cardiovascular event by 27% (hazard ratio (HR), 1.27; 95% confidence interval (CI), 1.17-1.38). In the same way, every 10ng/ml increase in serum prolactin concentration increased the risk of mortality due to cardiovascular disease (CVD) by 15% (HR, 1.15; 1.08-1.21) in prevalent hemodialysis patients. Inter-

estingly, prolactinemia independently associated with endothelial dysfunction as measured by flow-mediated dilation (FMD), and with arterial stiffness, as assessed by pulse wave velocity.

Because of the observational nature of this study, we cannot determine whether prolactin is a risk factor *per se* or an intermediate of a larger pathophysiological pathway. Prolactin retention leads to inhibition of gonadotropic hormone production, and testosterone deficiency in male CKD patients has indeed been linked to increased intima media thickness, atherosclerotic plaque occurrence, reduced FMD, systemic inflammation, cardiovascular risk, and mortality (discussed below). Conversely, increased Prolactinemia could also be a consequence of decreased dopaminergic activity, which would in turn imply an increment in norepinephrine release and that may have adverse effects on endothelial function and on other organs, favoring myocardial hypertrophy, hypertension, and other cardiovascular comorbidities.⁵ However, there is basic research supporting the hypothesis that these associations may be causal: *In vitro*, prolactin was able to modulate the inflammatory response, to stimulate the adhesion of mononuclear cells to endothelium, and to enhance vascular smooth muscle cell proliferation.^{13,14} Also, recent data unveiled that unbalanced peri/postpartum oxidative stress is linked to proteolytic cleavage of prolactin into a potent anti-angiogenic, pro-apoptotic and pro-inflammatory 16-KDa subform that may initiate the atherosclerotic-related complications.¹⁰

If these results are confirmed in other CKD populations, we may face a new and easy to target risk factor. It would be interesting to assess whether prolactin normalization may improve atherosclerotic/cardiovascular-related outcomes in CKD patients. This is theoretically possible, because bromocriptine therapy is inexpensive, out of patent, safe and with proven efficacy, having been used for more than 70 years. In non-dialysis populations, blockade of prolactin by bromocriptine appeared successful in human pilot trials to treat peri/postpartum cardiomyopathy.^{15,16} Of note, a small study showed that bromocriptine therapy in CKD patients reduced blood pressure and regression of left ventricular hypertrophy in dialysis patients.¹⁷ Whether this effect was mediated by prolactin reduction was not tested in that study. Finally, increased prolactin secretion in CKD may be related in part to the development of secondary hyperparathyroidism. An infusion of parathyroid hormone (PTH) in healthy men enhances prolactin release, a response that can be suppressed by the administration of L-dopa.⁹ Furthermore, partial inhibition of PTH release by the administration of calcitriol led to an elevation in plasma testosterone levels, a reduction in plasma gonadotropin concentrations, and improved sexual function.¹⁸ These benefits have not been, however, fully confirmed in subsequent studies.¹⁹

TESTOSTERONE DEFICIENCY AND THE CARDIOMETABOLIC COMPLICATIONS OF CKD

Hypogonadism (i.e., testosterone deficiency) is the most common gonadal alteration in men, mainly because of reduced prolactin clearance and uremic inhibition of luteinizing hormone signaling at the level of the Leydig cells.⁴ As many as 40 to 60% of CKD stage-5 men have been reported to be hypogonadal on the basis of low concentrations of total and free testosterone.²⁰ Alterations on sex steroid production and metabolism (leading to primary hypogonadism and disturbances of the hypothalamic-pituitary axis) are already seen when moderate reductions in the GFR arise.²¹ These disorders are not normalized with initiation of maintenance dialysis treatment; instead, they often progress. Humoral factors, which accumulate in uremia, as well as other comorbid conditions that frequently accompany CKD and medications may contribute to suppressed sex hormone levels.^{4,22}

Although some efforts in the past have been made on improving sexual dysfunction and anaemia by restoring testosterone deficiency, little attention has been given to the fact that testosterone is an important anabolic hormone with many diverse effects in the organism. Testosterone is a muscle anabolic hormone and therefore testosterone deficiency predisposes to reduced muscle mass and strength in CKD patients,²³ thus contributing to the prevalence of protein-energy wasting. Intramuscular androgen supplementation in non-hypogonadal malnourished CKD patients (both male and female) has been shown to improve muscle mass and strength in both hemodialysis and non-dialyzed CKD patients.²⁴⁻²⁶

Testosterone is also involved in the induction of erythrocytosis, and at a general population level, testosterone deficiency is a predisposing factor to anemia. An increase in hemoglobin is a common adverse effect in testosterone replacement therapy and because of this, testosterone was used for the treatment of anemia before the erythropoiesis-stimulating agents (ESA). This therapy has now come in disuse, yet it is reasonable to speculate that testosterone deficient patients with CKD may be likely to develop anemia and to require higher ESA dosages. Indeed, we could recently show that hypogonadal ESA-naïve CKD patients were more likely to be anemic despite adjustment for important anemia risk-factors. Furthermore, hypogonadal ESA-treated dialysis patients were more likely to have high ESA dosages.²⁷ None of these patients were receiving treatment for their hormonal deficiency, allowing us to propose that male hypogonadism may represent a contributing factor to renal anemia. Restoration of uremic hypogonadism may result in hemoglobin increase and reduced ESA requirements, with the costs that this would convey for the Healthcare system. The exact mechanism by which testosterone stimulates erythropoiesis is unknown. Although androgens have been reported to have myelostimulating effects by inducing production of haematopoietic growth factors in bone marrow stromal cells,²² recent evidence

demonstrates that testosterone acts on iron metabolism via inhibition of hepcidin.²⁸ Indirectly supporting this hypothesis, an association between low testosterone levels and high levels of hypochromic red blood cells was reported in male dialysis patients.²⁷

Growing evidence suggests that testosterone deficiency may contribute to the onset, progression or both of CVD.^{20,21} Testosterone abnormalities have been linked to disorders in bone composition, to sRANKL levels, and to endothelial dysfunction in CKD patients.^{4,22,29} Low testosterone levels in apparently healthy male populations have been identified as a predisposing risk factor to increased mortality and cardiovascular comorbidity.²² Likewise, we could also show that low endogenous testosterone values were also associated with increased risk of death in male hemodialysis patients.²⁰ These results have been confirmed and expanded in independent cohorts throughout the world,^{29,30} and compatible results have been reported for nondialysis CKD patients.^{20,21} Yilmaz *et al.*,²⁰ for instance, found a 22% increased cardiovascular risk by every nmol/L decrease in total testosterone concentration in male nondialyzed CKD patients. All these studies report that the presence of clinical signs of CVD at the time of inclusion was accompanied by significantly lower testosterone concentration.^{20,21,30,31}

Testosterone may have direct actions in the cardiovascular system. An atheroprotective effect of testosterone was demonstrated in animal studies,³² where a high-fat diet was given to a naturally testosterone-deficient mouse model, inducing lipid deposition in the aortic root (fatty streak). Testosterone therapy in such model importantly ameliorated this lipid streak formation. Other mechanisms of action of testosterone include stimulation of endothelial progenitor cells,³³ increasing nitric oxide release from vascular endothelial cells,³⁴ or perfusion enhancement in the myocardium.³⁵

Finally, uremia is a pro-inflammatory condition, and inflammation is an established promoter of atherosclerosis.³⁶ The hypothalamic-pituitary-testicular axis is suppressed by inflammatory cytokines,³⁷ and inflammatory diseases are often associated with testosterone deficiency. Thus, low testosterone could be considered a biomarker of this illness (inflammation). In support of this, a strong inverse association between testosterone and surrogates of inflammation has been shown in various CKD populations.^{20,22,27,31} However, it is also possible that testosterone has immunomodulatory actions *per se*, because supplementation with testosterone in randomized controlled designs resulted in the suppression of cytokine production in hypogonadal men with diabetes, coronary heart disease and the metabolic syndrome.³⁸⁻⁴⁰

Surprisingly few studies have tested the consequences of restoring testosterone deficiency in the CKD patient over and above mere sexual function.²² The evidence presented in this section suggests, however, that testosterone deficiency may

contribute to, at least in part, the uremic phenotype, rendering men more vulnerable to uremia. Existing evidence makes a case for the need of more stringent screening and better management of this syndrome in the male dialysis population. Testosterone replacement therapy is nevertheless not exempted from risks and adverse events,²² and evidence in the form of interventional studies is necessary before recommending its use in hypogonadal uremic men. Yet, we are not proposing suprathreshold administration of testosterone but only treatment of deficiencies and restoration to reference ranges.

SUBCLINICAL HYPOTHYROIDISM AND THE LOW-T3 SYNDROME

A progressive reduction in renal function is linked to alterations in thyroid hormone levels and/or metabolism, resulting in an especially high prevalence of subclinical hypothyroidism and the low T3 syndrome.⁴¹ This syndrome is mainly characterized by a decrease in total (T3) and free triiodothyronine (fT3) plasma concentration, whilst thyroid-stimulating hormone (TSH) and T4 remain in the normal range.⁴² Recent reports suggest that as many as 80% of patients with ESRD⁴³ present low T3 levels and as many as 20-25% are subclinically hypothyroid.⁴⁴ A constellation of wasting, persistent subclinical inflammation and CVD, present in a large proportion of ESRD patients could be explained in part by these alterations in the thyroid system, acting as intermediate link between the inflammatory stress and the impaired cardiovascular response.⁴² The underlying pathophysiology of these derangements is likely multifactorial, involving iodine retention, altered serum protein binding capacity, systemic inflammation, malnutrition, metabolic acidosis and peripheral deiodinase activity.⁴⁵

Traditionally, these abnormalities have been considered as an attempt to save energy in response to uremic wasting. However, recent evidence suggests role of T3 in the pathophysiology of endothelial dysfunction, atherosclerosis, and cardiac abnormalities of CKD patients.⁴⁶ In nonuremic populations, the presence of overt as well as subclinical hypothyroidism has been related to accelerated atherosclerosis and coronary artery disease in many studies.⁴³ From a mechanistic point of view, T3 enters cardiomyocytes and endothelial cells, binding to nuclear receptors and regulating transcription of specific genes such as the B-adrenergic receptor, the Ca²⁺/K⁺ channels or the activation of myosin/actin.⁴⁶ In animal models, cardiac-specific elevations in T3 enhance contractility and prevent pressure overload-induced cardiac dysfunction,⁴⁷ while T3 administration enhances endothelium-dependent relaxation.⁴⁸ In line with this, intriguing and consistent associations have been reported in the recent years regarding T3 levels and inflammation, carotid atherosclerosis, arterial stiffness, flow mediated dilatation, as well as impaired cardiac function/geometry.^{21,43,49,50}

Several observational studies have reported that single measurements of T3 levels are independent predictors of all-cause and CVD mortality in patients with CKD.^{41,42,49} Furthermore, Meuwese et al.⁴⁵ evaluated the relation between trimestral variation of T3 with all-cause and cause-specific mortality in a cohort of prevalent hemodialysis patients. They observed that patients with persistently low T3 levels presented the highest hazards of dying (HR: 2.7; 95% IC 1.5-5.0) compared with that of subjects having persistently high levels. This association was mainly explained by fatal CVD events. The longitudinal design of this study adds important observational evidence—although nondecisive—that the link may underlie a causal effect.

The field of thyroid replacement therapy for the treatment of cardiac diseases is quickly developing, and up-to-date revisions discuss this topic in more detail.⁵¹ The stimulating observations above discussed and pilot trials of T3 supplementation in other nonthyroidal illnesses, including a short-term trial in patients with heart failure,⁵² suggest that supplementing T3 may have a favorable influence on clinical outcomes in dialysis patients with low T3. Near physiologic doses of T3 resulted in a negative nitrogen balance in patients with CKD,⁵³ a finding considered as a warning against thyroid hormone supplementation in these patients. However, this may only reflect correction of hypothyroidism, and any increase in protein catabolism can be prevented by adequately augmenting protein intake. Furthermore, the safety of T3 administration in patients with heart failure indicates that it is unlikely that T3 may cause harm to CKD patients with T3 depletion.⁵¹ Metabolic acidosis is causally associated with low T3 in dialysis patients,⁵⁴ which may open an interesting and safe perspective for intervention in this population to test this hypothesis.

CONCLUDING REMARKS

CKD *per se* is associated with a wide range of metabolic alterations, including disorders in the secretion of hormones and the response of target tissues, and causing endocrine dysfunctions that may contribute to worse outcomes. This review has framed recent epidemiological evidence linking alterations at the level of the hypothalamic-pituitary-gonadal axis with systemic inflammation, endothelial dysfunction, arterial stiffness, cardiovascular risk and mortality, among others. In these, there is amenability for restoration of clinical deficiencies using in most cases out-of-patent inexpensive medication that could and should be tested in the form of randomized controlled trials in patients with CKD. It is possible that these endocrine alterations are no longer innocent bystanders of uremia but instead mediators of the uremic risk. Interventional studies are warranted to confirm or refute this hypothesis so far derived from observational studies.

KEY CONCEPTS

1. CKD causes multiple endocrine dysfunctions due to changes in biologic activity of some hormones, defects in binding to carrier proteins and decreased sensitivity of target organs or tissues as a result of receptor alteration or failures of post-receptor mechanisms of cellular response.
2. Hyperprolactinemia is a frequent endocrine alteration in patients with ESRD and is associated with endothelial dysfunction, arterial stiffness as well as increased cardiovascular morbidity and mortality.
3. Testosterone deficiency associates with increased mortality risk in male CKD patients and likely predispose to endothelial dysfunction, cardiovascular comorbidity, anemia, ESA hyporesponsiveness as well as reduced muscle mass and strength.
4. Progressive reduction in kidney function renders a "non-thyroidal illness" syndrome. In this, low T3 levels appear to be independent predictors of endothelial dysfunction, arterial stiffness, carotid atherosclerosis, left ventricular hypertrophy and both all-cause and CVD-mortality in CKD patients.
5. These endocrine disorders, traditionally interpreted as innocent bystanders of uremia may constitute novel uremic risk factors with possibility to serve as therapeutic targets. Interventional studies are warranted to prove this hypothesis.

Conflict of interest

Authors declare potential Conflicts of Interest.

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Other potential conflicts: JJC is co-investigator of an ongoing intervention study to test the effects of testosterone undecanoate in male hypogonadal HD patients with partial support from Bayer Pharmaceuticals.

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