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# CLINICAL REPERCUSSIONS OF HORMONAL DISORDERS IN CHRONIC KIDNEY DISEASE

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**Abstract: Introduction:** When the functional capacity of the kidney is chronically impaired by any mechanism, there is the manifestation of chronic kidney disease (CKD), there is the manifestation of chronic kidney disease (CKD). Unlike the role of filtration, reabsorption and elimination considered in the diagnosis of the disease, however, the hormonal regulation exerted by the kidney, which is also compromised, is usually less valued by the general or technical population. The fact is that the kidneys secrete different substances, through specific secretory cells, many of which are not yet well defined, which act as hormones that regulate the functioning of the organism and, in the face of a dysfunctional kidney, this imbalance manifests a series of other symptoms and complications. This study, therefore, aims to recognize the clinical repercussions of hormonal disorders present in chronic kidney disease in order to seek a more effective approach to the patient. **Methodology:** This is a literature review where 12 articles were selected from 2004 to 2021 correlated with different aspects of the theme, regardless of the country of origin, as the association of the descriptors used is still quite restricted. After this selection, the main hormonal dysfunctions with their respective pathogens and clinical repercussions were presented. **Results:** Calcitriol deficiency disorders, parathyroid hormone elevation, erythropoietin and iron deficiencies, ammonia production, renal nitric oxide production, and reduced sex hormone synthesis have been described. **Conclusions:** For the improvement of knowledge about the aforementioned disorders and for a better therapeutic approach to these hormonal complications, new sources of scientific production that aim to establish predictive factors and pathogenic reversion to control another aspect of the CKD spectrum are of paramount importance.

**Keywords:** Renal physiology. Chronic

kidney disease. Endocrine function. Clinical condition.

## INTRODUCTION

The kidneys make up important organs of the excretory system that perform, among other functions, the main function of eliminating waste and excess substances from the body, ending up in maintaining a water, electrolyte, acid-base, catabolite excretory and regulatory balance. hormonal.

When the functional capacity of the kidney is chronically impaired by any mechanism, chronic kidney disease (CKD) manifests – a pathology defined by: *National Kidney Foundation* (NKF), in his document: *Kidney Disease Outcomes Quality Initiative*, according to the criteria: a) Injury present for a period equal to or greater than 3 months, defined by structural or functional abnormalities of the kidney, with or without a decrease in glomerular filtration rate (GFR), manifested by pathological abnormalities or markers of kidney damage, including blood or urine changes, or imaging tests, and/or b) GFR < 60 ml/min/1.73 $m^2$ for a period greater than or equal to 3 months, with or without kidney damage. The stages of CKD are represented in table 1.

Highly prevalent diseases in the population, such as diabetes mellitus and arterial hypertension, are the main etiologies of CKD in Brazil and worldwide, accounting for more than 70% of cases. The first causes diabetic glomerulopathy (30% of cases) and the second, hypertensive nephrosclerosis (35%). In the pediatric group, obstructive uropathies are the main causes, although CKD is rare in this group.

Unlike the role of filtration, reabsorption and elimination considered in the diagnosis of the disease, however, the hormonal regulation exerted by the kidney, which is also compromised, is usually less valued by the general or technical population. The fact is that the kidneys secrete different substances, through specific secretory cells, many of which are not yet well defined, which act as hormones that regulate the functioning of the organism and, in the face of a dysfunctional kidney, this imbalance manifests a series of other symptoms and complications.

Furthermore, although the kidney is not an endocrine gland itself, the secretory portion of it seems to be located entirely in the renal cortex, especially in the juxtaglomerular complex and in medullary interstitial cells which, in addition to renin secretion, also

| **TFG Stages** | **TFG (ml/min/1,73 $m^2$)** | **Interpretation** |
|---|---|---|
| G1 | Greater than or equal to 90 | Normal |
| G2 | 60-89 | slight decrease |
| G3a | 45-59 | Mild to moderate decrease |
| G3b | 30-44 | Moderate to severe decrease |
| G4 | 15-29 | severe decrease |
| G5 | < 15 | kidney failure |
| **Albuminuria stages** | **Albuminuria (mg/day)** | **Interpretation** |
| A1 | < 30 | Normal |
| A2 | 30-300 | moderate increase |
| A3 | > 300 | severe increase |

Table 1. Staging of DRC according to KDIGO (2013).

produce other substances, such as : renal erythropoietic factor, bihydroxylated products of vitamin D, prostaglandins, kallikrein and metabolizes thyroxine (AIRES, 1999; DOUGLAS, 2002 A, B, C; GUYTON, 2002; DELAMARCHE, 2006).

This study, therefore, aims to recognize the clinical repercussions of hormonal disorders present in chronic kidney disease in order to seek a more effective approach to the patient.

## METHODOLOGY

This is a literature review, whose search terms were "renal physiology", "chronic kidney disease", "endocrine function" and "clinical picture" in the Scielo, PubMed, Lilacs and Google Scholar databases. Twelve articles were selected from 2004 to 2021 correlated with different aspects of the theme, regardless of the country of origin, as the association of these descriptors is still quite restricted. The temporal cut was not an inclusion criterion, since the selection was defined by the relevance to the theme. Therefore, studies whose discussion did not contribute to the clinical repercussions of hormonal disorders present in chronic kidney disease were excluded.

After this selection, the main hormonal dysfunctions with their respective pathogenesis and clinical repercussions were presented.

## RESULTS

### CALCITRIOL DEFICIENCY

Phosphorus balance in CKD patients is altered due to the loss of nephrons, which leads to a reduction in phosphorus excretion rates and leads to hyperphosphatemia. Phosphorus retention can also act as an indirect inhibitor of the production of the active form of vitamin D due to the inhibition of the renal enzyme 1-α-hydroxylase, which is responsible for the conversion of vitamin D to its active form (1,25(OH)2 D3). As a consequence of the decrease in active vitamin D, there is a reduction in intestinal absorption and bone resorption of calcium, favoring the development of more frequent and sustained episodes of hypocalcemia. Therefore, the progressive loss of renal mass determines a drop in the circulating levels of the active form of vitamin D and a drastic reduction in the intestinal absorption of calcium (PORTO et al., 2016).

Among the clinical manifestations of this condition, renal osteodystrophy and uremic myopathy stand out, which is still one of the most common causes of secondary hyperparathyroidism.

### ELEVATED LEVELS OF PARATHYROID HORMONE (PTH)

PTH is formed by the 4 parathyroid glands located posterior to the thyroid. The main function of this hormone is to promote the supply of calcium from the bone to the plasma, also acting on the kidneys and indirectly on the small intestine. In skeletal tissue, stimulation of bone resorption allows the grouping of osteoblasts and osteoclasts to increase bone turnover.

In CKD, especially in more advanced stages of the disease, such as in dialysis patients, the resulting tendency to hypocalcemia leads to the establishment of a condition of hyperparathyroidism, which makes it possible to maintain plasma calcium at a normal or slightly reduced level at the expense of mobilizing bone reserves. and the establishment of a negative calcium balance, resulting in progressive bone decalcification, since PTH seeks calcium from the bone reservoir that must come from intestinal absorption (PORTO ET AL., 2016). In addition, PTH acts as a uremic toxin and contributes to nearly all of the signs and symptoms of the syndrome of the same name,

including encephalopathy, cardiomyopathy, anemia, and pruritus. The manifestation most dependent on the effects of PTH is renal osteodystrophy.

## ERYTHROPOIETIN AND IRON DEFICIENCY

Anemia in CKD is mainly due to the reduction in erythropoietin production by the decreased mass of functioning peritubular fibroblasts of the renal cortex. Some studies have shown that the prevalence of anemia increases as the glomerular filtration fraction decreases, and this association is early (CANZIANI et al., 2006). This is the main pathogenic factor related to uremic anemia.

As for iron deficiency, there is an association with low intake due to dietary restrictions in patients with more advanced CKD, such as food refusal due to consumption. The role of hepicidine in iron metabolism is also studied. This peptide is produced in the liver by stimulation of several pro-inflammatory cytokines and compromises both intestinal iron absorption and iron release from organic stores. Thus, since CKD is an inflammatory disease, increased hepidine concentration may interfere with iron bioavailability.

The main manifestations include fatigue, reduced ability to exercise, reduced libido and cognitive function, increased cardiac overload due to anemia, bleeding, among others.

## DEFICIENCY IN AMMONIA PRODUCTION

The ammonia secreted by the kidney corresponds to that of renal origin, mainly from the proximal convoluted tubule cells (ALPERN and RECTOR, 1996), in an attempt to eliminate non-volatile acid radicals, products of protein degradation. With regard to renal failure, there is a reduction in the organ's ability to excrete or secrete ammonia, suggesting that nephropathy is responsible for the retention of ammonia in the body (HALL et al., 1987).

In rats with uremia, a decrease in the activities of the hepatic enzymes carbamylphosphate synthetase (CHAN et al., 1974) and ornithine transcarbamylase (SWENDSEID et al., 1975), both involved in the urea cycle, was observed. In addition to this, renal dysfunction could play a role in decreasing arginine levels, a necessary substrate of the ornithine cycle, due to a reduction in its supply by the kidney, which normally synthesizes arginine from citrulline (YOKOYAMA et al., 1996).

This state contributes to the metabolic acidosis of uremia, since in CKD, the acid-neutralizing plasma bicarbonate produced is not fully or partially regenerated due to reduced renal function. This depletion is due to the decrease in the excretion of hydrogen ions impaired by the deficiency in the production of ammonia, which generates less regeneration of bicarbonate and a greater reduction in its plasma levels (LEAL et al., 2008).

## DEFICIENCY IN RENAL NITRIC OXIDE PRODUCTION

Nitric oxide (NO) is a free, gaseous, inorganic and abundant free radical that acts in a variety of biological processes. It plays a significant role in cardiovascular control, as a modulator of peripheral vascular resistance and platelet aggregation, as well as a neurotransmitter and mediator of inflammatory processes. In the kidneys, NO has been considered in many physiological functions such as: (a) regulation of glomerular hemodynamics and tubuloglomerular function; (b) participation in pressure natriuresis; (c) maintenance of spinal perfusion; (d) inhibition of tubular sodium reabsorption; and (e) acting as a modulator of sympathetic nervous system activity.

Given these functions, the occurrence of its deficiency is associated with chronic kidney disease (CKD) in vasoconstriction and consequently glomerular hypertension, systemic arterial hypertension (SAH), proteinuria and progression of renal dysfunction (GALVÃO and CARVALHO, 2014).

The nitric oxide produced in the macula densa by activation of the nitric oxide attenuates the constriction of the efferent arteriole, consequently the absence of this action, results in vasoconstriction, retention of sodium and water inducing SAH (LEE, 2008). As probable causes of nitric oxide in CKD, limitations in the availability of the substrate (L-arginine) can be attributed, due to its decrease in renal biosynthesis and decreased transport of L-arginine in endothelial cells in uremic patients (BAYLIS, 2008). The high concentration of Nitric oxide synthesis inhibitors, in particular asymmetric dimethyl-arginines (ADMA) may also be related to the decrease in nitric oxide production in patients with CKD (BAYLIS, 2008).

### DECREASED SYNTHESIS OF SEX HORMONES

Valdivielso et al. (2019) state that lower levels of testosterone are common both at the beginning of the disease and in patients undergoing dialysis and that circulating levels of this hormone are inversely proportional to the stages of CKD involvement. It is also associated with testicular damage and impaired spermatogenesis, so that seminal analyzes of some patients indicate a decrease in ejaculatory volume as well as azoospermia or low amount of sperm with poor motility.

For Delesalle et al. (2015) decreased libido and erectile dysfunction must be related to reduced vascularization and changes in hormone levels; according to Van Ek et al. (2015) changes including bone and mineral disorders and anemia conditioned by CKD, changes in the endocrine system and testicular function, the uremic environment, the presence of preexisting diseases, medication side effects and psychosocial factors are the conditions that influence the appearance of these dysfunctions (RAMALHO, 2021).

The main complaints of these patients are related to erectile dysfunction, infertility and reduced libido.

## CONCLUSIONS

In view of all the articles and data present in this bibliographic review, it is essential to recognize the endocrinological role of renal function, as well as the clinical repercussions of hormonal disorders present in chronic kidney disease (Table 2), in order to pay attention to an approach more effective for the patient.

In order to improve knowledge about the aforementioned disorders and for a better therapeutic approach to these hormonal complications, new sources of scientific production that aim to establish predictive factors and pathogenic reversion to control another aspect of the CKD spectrum are of paramount importance.

| Disfunction | Pathogeny | Clinical repercussion |
|---|---|---|
| Calcitriol Deficiency | Phosphorus retention leads to reduced formation of active vitamin D, which compromises the intestinal absorption. | Renal osteodystrophy. |
| Elevation of PTH levels | Hyperparathyroidism secondary to hypocalcemia. | Fatigue, reduced ability to exercise, reduced libido and cognitive function, increased cardiac overload due to anemia, bleeding |
| Erythropoietin and iron deficiency | Decreased mass of functioning peritubular fibroblasts of the renal cortex and low iron intake. | Fatigue, reduced ability to exercise, reduced libido and cognitive function, increased cardiac overload due to anemia, bleeding. |
| Deficiency in ammonia production | Decreased levels of arginine, a necessary substrate of the ornithine cycle. | Metabolic acidosis of uremia. |
| Deficiency in renal nitric oxide production | Limitations in substrate (L-arginine) availability, due to its decrease in renal biosynthesis and decreased transport of L-arginine in endothelial cells in uremic patients. | Glomerular hypertension, systemic arterial hypertension (SAH), proteinuria and progression of renal dysfunction. |
| Decreased synthesis of sex hormones | Decreased vascularization and changes in hormone levels due to uremic status and extrinsic factors. | Erectile dysfunction, infertility and reduced libido. |

Table 2. Clinical repercussions of hormonal disorders present in chronic kidney disease.

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