

## Endocrine disorders in chronic kidney disease

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### Abstract

**Background and Objective:** Endocrine disorders are common in patients with chronic kidney disease (CKD). The aim of the present study is reviewing available literature to give a deep understanding of complexities of endocrine disorders in chronic kidney disease.

**Methods:** A narrative reviewing method based on the available literature was approached.

**Findings:** Generally, when renal function decreases, sex hormones, hypothalamic-pituitary axis and thyroid function is commonly disrupted. The mechanisms of endocrine disorders in these patients is complex and including impaired hormonal feedback, abnormal production of hormones and disrupting hormone transmission and connect them to the receptor.

**Conclusion:** Toxic and inhibitory factors in uremic patients and also the side effects of treatment in CKD patients caused to dysfunctions in function of hormones secreted from the glands.

**Keywords:** Chronic kidney disease, thyroid hormones, Sex hormones, Growth hormone

### Introduction

Uremia interferes in the metabolism with different mechanisms and hormonal regulation and lead to change in concentration of hormones. However, this concentration sometimes decreases in uremic patients and sometimes increases in different situations.

#### Increase of plasma level of hormones

Most hormones are filtered by the glomerulus and metabolic clearance of these hormones decreases with reduction of renal function and reversely plasma level of hormones increases as a result (1). Another mechanism involved in increasing plasma concentration is increase of secretion of some hormones or hormone binding proteins in response to proliferation of stimulus factors in uremic patients such as increasing in secretion of parathyroid hormone.

#### Decrease of plasma level of hormones

Reduction of renal function is associated with

reducing in level of some hormones, especially in those whom secreted from kidney such as (erythropoietin, 1, 25-OH<sub>2</sub>-VitaminD<sub>3</sub>).

On the other hand, with production of toxic factors in uremic patients and direct effect of these materials on the performance of hormone-producing organs, concentration of these hormones reduced such as testis-testosterone, ovary-estradiol.

#### Dysfunction of hormones

##### *Disorder in the activation of prohormones*

The concentration of some prohormones in CKD patients increases; for instance, prohormone-insulin-like growth factor 1 (pro-IGF1) which is a IGF1 Precursor and not normally found in serum (2), or increase of proinsulin because of not converting to insulin in these patients, and Peripheral conversion of thyroxine (T<sub>4</sub>) to tissue-active triiodothyroxine (T<sub>3</sub>) is impaired (3). On the other hand, increase in some of these prohormones results in blocking of receptors and reducing of

function of main hormones.

#### *Change in bioactivity of hormones*

Due to problem in translation of messages for production of hormone received by the cell or disorder in metabolic clearance of some of hormone isoforms reduces bioactivity of these hormones such as what happens to the LH hormone (4).

#### *Change in binding of hormone to plasma protein*

With increasing in level of some hormone binding protein such as Insulin-like growth factor-binding protein (IGF-BP) and binding them to receptor, dysfunction of hormone is seen, even if there would be a normal plasma level of hormone IGF (5).

#### *Disorder in sensitivity of target tissues*

Different mechanism is involved in disordering of response of target tissues to hormone.

Hormone production is disorganized with some factors, including the accumulation of a series of inhibitors in uremic patients; structural changes in the receptor itself; receive the wrong messages into the cell through the hormone-receptor complex result. This is what happens to insulin and growth hormone in uremic patients (6).

#### **Gonadotropin hormones axis**

The onset of puberty in CKD patients is associated with a delay of two years. This delay also includes the onset of menarche and genital maturation and incidence of secondary characteristics (7). Investigations have shown that there is decrease in number of germ cell of testis tubules of CKD patients (8). Dysfunction of erection and decrease in libido as well as reduction of fertility has been seen in uremic patients; moreover, pregnancy is considered a rare thing in these patients.

#### **Gonadal hormones**

In CKD patients, amount of testosterone hormone decreases due to reduction in its production and increase in metabolic clearance, (9) but about Dihydrotestosterone (DHT) hormone in uremic patients there is a reduction in its concentration. As we know, the enzyme reductase-5 is responsible for synthesizing DHT from testosterone; however, its activation is declined (10), and also testis response to stimulating hormone, like human chorionic gonadotropin (HCG) is disrupted in uremic patients (11). In patients with end stage renal disease (ESRD), there is an increase in sex-hormone binding globulin. Estradiol low concentration has been seen in uremic patients; nevertheless, it has

insufficient concentration in the puberty (12).

#### **Gonadotropins**

In CKD patient, level of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) rise up (9).

Due to the low level of gonad's hormones and high level of gonadotropins result in a situation which is called hypergonadotropic hypogonadism (HH) situation but this increase is not enough to reverse hypogonadism and it means that there is a problem in gonadotropin-releasing (13).

In uremic patients, Gonadotropin-releasing hormone (GnRH) releasing from the hypothalamus and GnRH-LH signal are also impaired (14). In these patients, bioactivity of LH changes and then a series of function-inhibitors of LH are made (15).

#### **Prolactin**

Prolactin is a hormone secreted by the pituitary gland and is involved in the lactation; it is normally considered as an inhibitor of GnRH. In uremic patients, plasma level of prolactin increases because of reduction in its metabolic clearance and results in inhibiting the GnRH-LH Pulse Generator activity and it has an important role in hypogonadism (16). Circadian rhythm of prolactin release is inhibited in these patients (17).

#### **Growth hormone and IGF1**

In uremic patient, concentration of Growth Hormone increases (18); because, the metabolic clearance of this hormone reduces even up to 50%, on the other hand, occurring metabolic acidosis lead to suppress the GH secretion (19).

Post-receptors signaling are disrupted in these patients and there is a resistance to GH.

Reduction of GH receptors in the liver contributes to reduction of IGF1 production and finally, effect of GH that should be implemented by mediating the IGF, reduces (20).

It is known that effect of GH on target organs is implemented by IGF1. However, there is a resistance to IGF1 in uremic patients. While the total IGF is normal, its bioactivity has changed and serum free IGF with regarding reduction of GFR reduced even up to 50% (21).

As a result of reduction in metabolic clearance, the level of IGF binding protein such as IGFBP1,2,4 and 6 increase and result in binding to receptor as well as disrupting post receptors signaling that all of these lead to make a resistance to IGF. It should be noted that the concentration of IGFBP3 (intact) decreases (22).

### Glucocorticoid and GH-IGF axis

Corticosteroid therapy is a prevalent treatment in patients with CKD and results in different side effects, including suppressing of GH and IGF-I gene transcription, producing somatostatin which is a release-inhibiting factor and reduction of GH production as a result of somatostatin inhibitory effect (23).

Steroids have direct and negative effect on chondrocytes and enchorial bone formation (24).

### Thyroid hormone axis

Goiter is more prevalent in patients with CKD and the prevalence of hypothyroidism is between 0 to 9.5 percent, probably due to the underlying disease like cystinosis and nephrotic syndrome which effects on both thyroid and kidney (25); but about hyperthyroidism, there is no difference in its prevalence for CKD patients.

In uremic patients the plasma level of T3 and T4 is reduced and peripheral conversion of thyroxine (T4) to triiodothyronine (T3) is disrupted (26).

Inorganic iodine level increases and Thyroxine-binding globulin (TBG) decreased, especially in the severe nephrotic syndrome in which proteinuria is high (27).

TSH level is normal in these patients; however, it is expected to have an increased secretion in response to decrease in total and free T4 and T3. This suggests that there is a disorder in settings of hypothalamic-pituitary axis and releasing of TRH (28).

Clinically, CKD patients are usually euthyroid and they do not need to treatment, unless when the symptoms of hypothyroid appear and TSH increase; because of this, with considering the similarity between the symptoms of hypothyroidism and uremia, it seems logical that thyroid function tests (TFTs) are performed once in a while.

### Adrenal axis

The morning plasma cortisol level and aldosterone is normal in patients with uremia as well as the level of adrenocorticotrophic hormone (ACTH), although DHEA (Dehydroepiandrosterone) level as an androgenic hormone releasing from the adrenal decreases (29).

On the other hand, CRH- ACTH-Cortisol axis that should normally be activated in severe hypoglycemia status and led to rise up the blood sugar level, is not activated in these patients. It means that the axis has been suppressed (30).

Adrenal insufficiency may occur in treatment with steroids, amyloidosis and with coagulation

side effects in CKD patients.

Due to the similarity of the clinical symptoms of adrenal insufficiency (hyperkalemia and hyponatremia, or paleness...) and Sometimes Cushing's disease (hypertension) with the symptoms of uremia, it is necessary to check the function of adrenal in these patients.

### Hormones involved in carbohydrate metabolism

Insulin levels in uremic patients are usually normal or slightly increased and proinsulin and C-peptide level is high. Also, glucose intolerance is common in these patients (31).

Tissue sensitivity to insulin decreases in uremia and neuroendocrine regulation of insulin secretion is impaired and research has shown that the post receptor signaling is also impaired (32).

Glucagon is a hormone that stimulates hepatic gluconeogenesis and leads to increased blood sugar. In uremia glucagon's plasma level increases but its production remains normal and this is due to a decrease in its metabolic clearance. With considering high level of glucagon, function of the hormone in releasing glucose from the liver is impaired (33).

### Hormones secreted by adipose tissue (body fat)

As a result of decrease in metabolic clearance, the level of Adipose tissue hormones such as leptin which is considered as an important hormone in the catabolism of fat tissue, uremic anorexia and inflammation, increase as well as other hormones, including, Resistin, Visfatin their concentration; this increase lead to insulin resistance (34).

### Secondary hyperparathyroidism

Secondary hyperparathyroidism in uremic patient are associated with high phosphorus, hypocalcemia and disorder in production of vitamin D and leading to complications such as uremic osteodystrophy (35).

### Vitamin D

In patients with CKD, Production of 1, 25 (OH) 2D3 reduces. This hormone which is active form of vitamin D, releases from kidney and causes the reabsorption of calcium and phosphorus from the intestine. Deficiency of the hormone is revealed by the symptoms, including osteomalacia and fracture risk (36).

### Conclusion

It is evident that chronic renal failure has far-

reaching metabolic consequences because endocrine aberrations are common. Uremia may alter endocrine function through its effect on the hypothalamopituitary axis, the individual end organs, and the peripheral metabolism of various hormones. Deficiency of some hormones and excess of others coexist in patients with renal failure.

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