Endocrine Disorders in Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- The kidney is the site of synthesis and degradation of several hormones.
- CKD patients are characterized by the deficiency of hormones like erythropoietin, calcitriol, insulin-like growth factor, and testosterone.
- In contrast, the accumulation of insulin, prolactin, aldosterone, and growth hormone occurs in these patients.

20.1 Introduction

Endocrine abnormalities in patients with chronic kidney disease (CKD) may arise from a number of different causes, which are summarized in Table 20.1. Kidney plays a crucial role in the synthesis and degradation of several hormones. Moreover, different concomitant conditions like inflammation, malnutrition, and metabolic acidosis participate in the pathogenesis of endocrine alterations in these patients.

In CKD patients estimation of many hormones' serum concentration *per se* often fails to provide a correct assessment of the adequacy of patient's hormonal status (e.g. hormone concen-

Table 20.1 Selected pathomechanisms leading to endocrine abnormalities in chronic kidney disease

Type of defect	Example
Abnormalities of hormone production	
Reduced hormone production by the kidney	Erythropoietin, $1,25(OH)_2D_3$
Reduced hormone production in endocrine organs	Testosterone, estrogen
Abnormal secretion pattern (pulsatility; circadian rhythm)	PTH, GH, LH
Reactive hypersecretion of hormone to reestablish homeostasis	Erythropoietin, PTH, FGF 23
Inappropriate hypersecretion due to disturbed feedback	LH, prolactin, corticotropin
Abnormalities of hormone catabolism	
Decreased metabolic clearance	PTH, insulin, gastrin, leptin, adiponectin, vasopressin
Abnormalities of hormone action	
Disturbed activation of prohormones	Proinsulin, thyroxin (T_4)
Increased isoforms with potentially less bioactivity (due to posttranscriptional modifications)	LH
Increased hormone-binding proteins in serum reducing availability of free hormone	IGF
Decreased hormone-binding proteins increasing availability of free hormone	Leptin
Changed receptor number, structure, modification	Vitamin D receptor
Disturbed postreceptor cellular signaling	Insulin, GH

$1,25(OH)_2D_3$ 1,25-dihydroxyvitamin D_3, *PTH* parathyroid hormone, *GH* growth hormone, *LH* luteinizing hormone, *FGF 23* fibroblast growth factor 23, *IGF* insulin-like growth factor

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trations may be inappropriately high or low in the context of the magnitude of stimulating, or suppressing signals, the test may detect inactive hormone isoforms, or the response of the target organ may be altered—either aggravated or blunted—the so-called hormonal resistance frequently seen in uremia). It is therefore necessary to interpret serum hormone concentrations with the consideration of underlying clinical context (e.g. insulin concentration in relation to glucose concentration, parathyroid hormone—PTH concentration in relation to serum ionized calcium concentration).

20.2 Abnormalities in the Erythropoietin Secretion

In the adults, kidneys produce ca. 85–90% of circulating erythropoietin (EPO). The liver is the source of the rest 10–15% of circulating EPO. Within the kidneys, EPO is synthesized by peritubular, interstitial cells found mainly in the renal cortex and outer medulla. The main stimulus for EPO synthesis is renal hypoxia, which is caused by anemia or hypoxemia. Hypoxia stimulates the stabilization of hypoxia inducible factor (HIF), which is quickly degraded in normoxemic conditions. Among a wide set of genes activated by HIF the *Epo* gene is regulated with particular receptiveness—resulting in an extensive EPO-mRNA transcription. Besides hypoxia, also angiotensin II stimulates EPO production.

Conversely, inflammatory proteins (interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α)) inhibit EPO secretion. The serum EPO concentrations in anemic CKD patients are usually comparable to those obtained in non-anemic subjects with intact kidney function, but they are inappropriately low taking into account actual blood hemoglobin concentrations. Moreover in CKD patients the erythropoietin resistance also occurs [1, 2]. Anemia is the direct clinical consequence of EPO deficiency in CKD patients. The measurement of serum EPO concentration in CKD patients is not useful in clinical practice. Decisions concerning treatment with erythropoiesis-stimulating agents (ESAs) in CKD patients should be based on blood hemoglobin concentration and whole clinical status, and not on serum EPO concentration (see Chap. 15).

20.3 Abnormalities in the Vitamin D Metabolites

In the general population, vitamin D deficiency has been linked to increased prevalence of albuminuria, hypertension, cardiovascular diseases, metabolic syndrome, insulin resistance, and obesity. The prevalence of 25-vitamin D_3 deficiency increases with the progression of CKD and reaches 80% in CKD stage 5 patients. Moreover, in patients with nephrotic syndrome, the 25(OH)D_3 is lost with the urine and in CKD patients treated with peritoneal dialysis is lost with the peritoneal fluid (dialysate). Vitamin D supplementation in CKD patients is considered safe. In patients with clinical signs of vitamin D deficiency, i.e. hypocalcemia and hyperparathyroidism, such therapy may be recommended.

25(OH)D_3 is transported to the kidneys for further hydroxylation, resulting in the production of the active metabolite 1,25$(OH)_2D_3$. With worsening of kidney function, decline in the activity of 1α-hydroxylase, the enzyme converting 25(OH)D_3 to 1,25-dihydroxyvitamin D_3 (calcitriol) is observed. Moreover, less of 25(OH)D_3 is delivered to the kidney. Additionally, increased serum concentration of fibroblast growth factor 23 (FGF 23) may directly inhibit renal 1-α-hydroxylase, thus reducing the conversion of 25(OH)D_3 to 1,25$(OH)_2D_3$, and stimulating 24-hydroxylase which in turn increases the conversion of 25(OH)D_3 to biologically inactive 24,25 $(OH)_2D_3$. Therefore, in CKD stage 5 patients, serum 1,25$(OH)_2D_3$ concentration is reduced. Moreover, CKD patients develop organ resistance to the action of 1,25$(OH)_2D_3$, because of the decrease in the density of 1,25$(OH)_2D_3$ receptor (VDR). Recently, there is evidence growing that hypomagnesaemia is a potent factor in the development of vitamin D deficiency, as 1-α-hyroxylase, 24-hydroxylase and 25-hydrox-

ylase, as well as vitamin D binding protein activity are all dependent on the presence of Mg^{2+}.

The $1,25(OH)_2D_3$ deficiency in CKD patients plays an important role in the pathogenesis of secondary hyperparathyroidism, defective intestinal absorption of calcium, skeletal resistance to the calcemic action of PTH, defective mineralization of bone, growth retardation in children, and proximal myopathy. Clinical studies suggest that $1,25(OH)_2D_3$ deficiency increases cardiovascular and general mortality in CKD patients. The results of the small interventional studies suggested that treatment with calcitriol or other VDR agonists may reduce the mortality among these patients. Some published studies show that $1,25(OH)_2D_3$ deficiency increases proteinuria and paricalcitol treatment reduces proteinuria in CKD patients. However, these studies enrolled only modest number of patients, and therefore more, larger studies are needed in the abovementioned areas [3–5]. It is noteworthy though, that the recently published results of large placebo-controlled studies (VIDA and VITAL) showed no benefit of vitamin D intervention in patients from the general population.

The other abnormalities in the endocrine regulation of calcium and phosphate metabolism (among others, PTH and fibroblast growth factor 23) in CKD are discussed in detail in Chap. 16.

20.4 Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis in Men with CKD

Men with CKD are characterized by a variety of derangements of the hypothalamic–pituitary–gonadal axis (Table 20.2). The most important abnormalities are related directly to the gonadal function.

20.4.1 Luteinizing Hormone

In CKD patients, the lack of appropriate cyclic release and decreased amplitudes of the secretory bursts of gonadotropin-releasing hormone (GnRH) by the hypothalamus lead to a loss of normal pulsatile luteinizing hormone (LH) release by the pituitary. The causes of impaired cyclic release of GnRH are hyperprolactinemia and high serum GnRH and LH concentrations caused mainly by their reduced renal clearances [5, 6].

Table 20.2 Abnormalities in the hormones of hypothalamic–pituitary–gonadal axis in chronic kidney disease

	Male	Female
LH	↑	↑
FSH	↑	N
Prolactin	↑	↑
Testosterone	↓	–
Estradiol	–	↓
Progesterone	–	↓

FSH follicle-stimulating hormone, *LH* luteinizing hormone, *N* normal

In the majority of CKD patients, basal serum LH concentrations are elevated. High serum LH concentrations in CKD patients result from a decreased rate of catabolism and lack of testosterone inhibition (due to low serum testosterone concentration in CKD) of GnRH secretion and secondarily also LH secretion.

20.4.2 Follicle-Stimulating Hormone

In CKD patients, serum concentrations of follicle-stimulating hormone (FSH) are in the upper normal range, or elevated. FSH is an important factor in spermatogenesis. It stimulates testicular growth and increases the production of testosterone-binding protein by Sertoli cells. In CKD patients, spermatogenesis is impaired despite elevated blood levels of FSH. This is probably due to the resistance of the testis to the action of FSH, due to primary testicular dysfunction, and also by the reduced serum inhibin concentration [5, 6].

20.4.3 Prolactin

Serum prolactin concentrations are elevated in the majority of male hemodialysis patients. Apart from elevated basal prolactin concentrations, the

circadian rhythm of prolactin secretion is also disturbed. Moreover, the sleep-induced secretory bursts are not observed, although episodic secretion occurs during the daytime. It seems that both diminished prolactin clearance and increased production rate (probably due to inadequate dopaminergic inhibition of prolactin release from pituitary) contribute to hyperprolactinemia in CKD patients [7, 8]. Prolactin accumulation leads to inhibition of GnRH pulsatile secretion and testosterone synthesis which resulted among others with sexual dysfunction and infertility. Interestingly, in some CKD patients, correction of the hyperprolactinemia by bromocriptine caused improvement of sexual function. There is evidence, suggesting that hyperprolactinemia may participate in the endothelial dysfunction frequently observed in CKD patients. The association between hyperprolactinemia and negative cardiovascular outcome was found in CKD patients. In a small clinical study in patients with CKD, it was found that reduction of serum prolactin concentration with bromocriptine reduced blood pressure and left ventricular hypertrophy [6–8].

20.4.4 Testicular Hormones

In most male hemodialysis patients, serum testosterone concentrations are low. The normal circadian rhythm of serum testosterone concentrations, with a peak at 4–8 a.m. and nadir at 8–12 p.m., is maintained in CKD patients. The response to 4 days administration of human gonadotropin is sluggish and delayed; no increase in testosterone concentration was seen after 8 h, but a two to threefold increase was seen after 4 days.

With respect to the other androgens, decreased serum concentration of androstenedione and dehydroepiandrosterone sulfate has been reported in men with CKD. The Sertoli cells in the testis are responsible for production of other hormones, such as inhibin and anti-Müllerian hormone. Concentration of both of these factors is reduced in CKD—which as it was already mentioned leads to the increase of serum FSH concentration *via* impaired negative feedback loop. This suggests that probably uremic damage of the testis is the primary cause of androgen deficit in men with CKD. Also, malnutrition participates in the reduction of serum testosterone concentration in men with CKD, and low-protein diet, essential amino acid, and keto amino acid analog supplementation tends to raise serum testosterone concentration [6, 7, 9].

Androgen deficiency in CKD males may cause changes in body composition: body fat increases, while lean body mass (mainly muscles mass) is reduced. Androgen deficiency leads also to CKD-related bone disease and higher incidence of bone fractures, anemia, and ESAs hyporesponsiveness (due to reduced growth of differentiated stem cells and decreased sensitivity of erythroid progenitors to EPO), depression, decreased libido, and impairment of sexual function. Finally, it was recently shown that low serum testosterone concentrations were associated with worse outcomes in male hemodialysis patients [6, 9].

Therapy with exogenous testosterone is not exempted from risks, but results of recent studies seem to suggest that transdermal testosterone replacement therapy might be safe and effective in reversing the symptoms of testosterone deficiency and improve life quality of life in men with CKD [8, 9].

20.5 Abnormalities in the Hormones of the Hypothalamic–Pituitary–Gonadal Axis in Women with CKD

Women with CKD present a variety of derangements of the hypothalamic–pituitary–gonadal axis (Table 20.2). The consequences of these abnormalities are anovulatory menstrual cycles and infertility.

20.5.1 Luteinizing Hormone

Serum LH concentration is elevated in most premenopausal CKD patients. In healthy premenopausal women, the secretion of LH is pulsatile. In

women with CKD, the lack of appropriate cyclic release of GnRH by the hypothalamus leads to a loss of normal pulsatile LH release by the pituitary. In healthy women, estradiol lowers the amplitude of LH pulses. In women with CKD, estradiol fails to influence the LH surge, suggesting impaired feedback loop which results in impaired ovulation. The clinical consequence of the loss of normal pulsatile LH release by the pituitary in CKD women is infertility [6, 10].

20.5.2 Follicle-Stimulating Hormone

In contrast to the abnormal serum LH concentration, the serum FSH concentration is normal in most premenopausal CKD female patients. Therefore the FSH/LH ratio is decreased. The decreased FSH/LH ratio suggests the occurrence of severe hypothalamic–hypophyseal axis dysregulation [10].

20.5.3 Prolactin

Serum prolactin (PRL) concentrations are often elevated in women with CKD and the increase of serum prolactin after the administration of thyrotropin-releasing hormone (TRH) is blunted. Also, improper diurnal rhythm of prolactin secretion is usually seen and the sleep-induced bursts of PRL secretion are usually absent, although episodic secretion of prolactin in the daytime was noted [6, 8, 10]. Hyperprolactinemia in women with CKD is mostly caused by the reduced renal clearance of PRL and to some extent, by the increase of PRL secretion in the pituitary gland, which is caused by inadequate dopaminergic inhibition. Thus, in CKD woman with hyperprolactinemia, amenorrhea occurs frequently.

20.5.4 Estrogens

In women with CKD, serum estradiol concentrations may be normal, but more often are decreased and are consistently lower in woman with CKD and concomitant hyperprolactinemia. In the second half of the menstrual cycle, serum progesterone concentrations are low because of the defective luteinization of the follicles. The hormonal derangements in CKD women are clearly the consequence of deregulation of the hypothalamic–pituitary–ovarian axis [10].

A major consequence of low serum estrogen concentration concerns bone disease [11]. Amenorrheic patients had not only lower serum estrogen concentrations but also lower bone mineral density, compared to normally menstruating women requiring dialysis. Small clinical interventional studies suggest that treatment with transdermal estradiol and cyclic addition of norethisterone acetate or treatment with raloxifene, a selective estrogen receptor modulator (SERM), may increase bone mineral density of the lumbar spine in hemodialysis postmenopausal women. Nonetheless taking into consideration the potential adverse cardiovascular effects of hormone replacement therapy, it must be emphasized that currently long-term studies of safety of hormone replacement or SERM therapy in women with CKD are not available.

20.5.5 Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) is a 140 kDa glycoprotein, which is mostly synthesized by the granulosa cells that are surrounding the oocyte in the maturing follicles. The most important physiological function of AMH is the inhibition of excessive recruitment and growth of other follicles. This leads to the selection of a dominant follicle and takes place in the follicular phase of the menstrual cycle. Serum AMH concentration tends to be constant during the entire menstrual cycle. It reflects the number of growing follicles and is proportional to the pool of primordial follicles. This is why serum AMH concentration is considered to be one of the best markers of ovarian reserve. The highest serum AMH concentration is found in women around 25 years of age, then it decreases with age, until circulating AMH is usually undetectable in postmenopausal woman. The diminishing serum AMH concentration may be an indicator of either physiological

or premature aging of the gonads. CKD women are characterized by significantly lower serum AMH concentration, which seems to suggest that a decrease in AMH secretion by the damaged granulosa cells and a reduction of ovarian reserve are the most pronounced causes of diminished fertility in women with CKD [6].

20.6 Abnormalities in the Growth Hormone/Insulin-Like Growth Factor (Somatotropic) Axis

The somatotropic axis comprises growth hormone (GH), insulin-like growth factor 1 and 2 (IGF-1 and -2), six IGF-binding proteins (IGFBP-1 to -6), and the IGFBP proteases (BP-Pr). All are involved in the modulation of somatic growth, cellular proliferation, and metabolism. Several abnormalities (Box 20.1) in the somatotropic axis have been reported in children and adults with CKD [12, 13]. The clinical consequence of these abnormalities is growth retardation and reduced final height in CKD children. It was also shown that growth failure in CKD patients is associated with increased morbidity and mortality [12, 14].

Box 20.1 Abnormalities in the Growth Hormone/Insulin-Like Growth Factor Axis in Chronic Kidney Disease

Growth hormone
Increased serum GH concentration
Peripheral resistance to GH due to defect in GH intracellular signal transduction
Insulin-like growth factor
Decreased IGF-1 serum concentration
Reduced free IGF-1 serum concentration
Increased IGFBPs (IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6) serum concentration
Presence of low molecular weight (1000 Da) inhibitor of IGF-1 in serum
Peripheral resistance to IGF-1 due to postreceptor defect in IGF-1 action

GH growth hormone, *IGF- 1* and *IGF- 2* insulin-like growth factor-1 and -2, *IGFBP* IGF-binding protein

20.6.1 Growth Hormone

In children and adult CKD patients, serum concentration of GH may be normal, or elevated, depending on the extent of glomerular filtration decrease. The increased serum GH concentration in CKD is caused by both a reduction of renal clearance and an increase of GH secretion. Also the half-life of GH in CKD patients is prolonged. Hyperglycemia induced by glucose infusion suppresses GH secretion in healthy individuals, not in CKD patients. Moreover, in CKD, the response of GH secretion to the administration of GHRH is exaggerated.

In CKD patients, high serum GH concentrations are counteracted by peripheral resistance to GH. The GH resistance appears to be both at the receptor and at the postreceptor level. Determination of the concentration of serum growth hormone-binding protein (GHBP), which is a cleaved product of the GH receptor, may be used to assess GH receptor density in tissues. GHBP serum concentration is low in children and adults with CKD. Resistance to GH is also due to defective intracellular signal transduction. The impaired phosphorylation and nuclear translocation of GH-activated STAT protein were also found. Hyperparathyroidism, metabolic acidosis, and inflammation may participate in the pathogenesis of GH resistance in CKD [12–14]. Noteworthy, recent data suggest a direct involvement of excess GH concentrations in the development of albuminuria, glomerular sclerosis, hypertrophy, and hyperfiltration, which is mostly caused by podocyte damage [14].

20.6.2 Insulin-Like Growth Factors

GH promotes linear growth partially by stimulating systemic and local concentrations of IGFs. IGF-1 and IGF-2 are produced locally by most tissues, including the growth plate, but the liver is the main source of circulating hormones. IGF-1 mediates most of the growth-promoting effects of GH. Serum IGF-1 forms complexes with six IGF-binding proteins (IGFBP-1 to IGFBP-6).

In advanced CKD, the serum concentration of IGF-1 is decreased and of IGF-2 is increased. In patients with advanced CKD, the resistance to the metabolic effects of recombinant human IGF-1 was found. Moreover the so-called somatomedin bioactivity in blood, an index of IGF activity measured by sulfate incorporation into porcine costal cartilage, is reduced in uremia. The discrepancy between normal or elevated total IGF serum concentration and its low bioactivity in CKD may be explained by increased serum concentration of IGFBPs, circulating IGF inhibitor and receptor or postreceptor defect.

Serum concentrations of four of the six IGF-binding proteins (IGFBP-1, IGFBP-2, IGFBP-4, and IGFBP-6) are markedly higher in CKD patients. The increased binding capacity of IGF-1 decreases the concentration of free IGF-1. This imbalance between serum IGF-1 and serum IGFBP concentrations is relevant in the pathogenesis of growth failure in CKD.

A low molecular weight (1000 Da) inhibitor of IGF-1 has been identified in the serum of CKD patients, but molecular details have not yet been characterized.

Resistance to IGF-1 in CKD is also due to defective intracellular signal transduction (both autophosphorylation of the IGF-1 receptor tyrosine kinase and activity of the IGF-1R tyrosine kinase to the exogenous insulin receptor substrate 1) [12–14].

20.6.3 Growth Hormone Therapy

Demonstration of the resistance to the action of GH and IGF-1 in CKD provides the rationale for the use of GH in the treatment of CKD children with retarded growth despite normal or elevated hormone concentrations. Administration of recombinant human GH in prepubertal children with CKD caused an increase in growth rate and in standardized height without undue advancement of bone age or significant side effects. In adults, recombinant human GH administration stimulates muscle mass gain and may be used in the treatment of protein energy wasting [12–14].

20.7 Abnormalities in the Adrenocorticotropin–Cortisol Axis

The adrenocorticotropin–cortisol axis is only mildly affected in CKD. In CKD patients, serum adrenocorticotropin (ACTH) and cortisol concentrations are normal, or modestly elevated. The cortisol half-life is prolonged in CKD patients, and decreased catabolism may contribute to the mildly elevated serum cortisol concentrations in CKD [15].

Clinical consequences of the abovementioned modest hormonal alterations are unclear, but hypercortisolemia may cause osteopenia, disturbed distribution of adipose tissue, and increased protein catabolism.

In CKD patients, ACTH secretion cannot be suppressed by standard oral doses of dexamethasone, but higher doses of dexamethasone suppress ACTH secretion. Therefore, when Cushing syndrome is suspected in CKD patients, a 2-day dexamethasone test is recommended.

20.8 Abnormalities in Arginine Vasopressin

In CKD patients, the plasma arginine vasopressin (AVP) concentration is elevated. The major cause is decreased metabolic clearance rate. The main physiologic stimuli for AVP secretion are increased serum osmolality and decreased cardiac output or arterial vasodilation. The osmotic and nonosmotic regulation of AVP secretion in CKD is intact. In hemodialysis patients, the plasma AVP concentration increases during ultrafiltration and plasma volume contraction and decreases during hypervolemia. The clinical significance of the elevated plasma AVP concentration in CKD is still uncertain. Experimental and observational human studies suggest that high plasma AVP concentration may participate in the CKD progression [16, 17].

Copeptin (CT-proAVP) is the C-terminal part of the vasopressin prohormone. CT-proAVP is secreted with AVP, and it is easier to estimate than AVP itself. In patients with diabetic nephrop-

athy, high plasma CT-proAVP copeptin concentration predicts cardiovascular mortality [16, 17].

20.9 Abnormalities in the Thyroid Gland and Hypothalamic–Pituitary–Thyroid Axis

Abnormalities in the function of the thyroid gland and in the serum concentrations of thyroid hormones are common in patients with CKD. A detailed profile of the indices of thyroid status in CKD as compared to primary hypothyroidism and chronic nonthyroid, nonkidney illness is presented in Table 20.3 [18, 19].

20.9.1 Thyroid Hormones

The serum concentration of thyroxin (T_4) is usually normal. In contrast, triiodothyronine (T_3) concentration is frequently reduced in CKD patients. Low T_3 syndrome is the most common laboratory finding in patients with CKD and subclinical hypothyroidism is the most common thyroid disorder found in this group of patients. The reduction of serum T_3 concentration in CKD patients occurs due to the impaired conversion of T_4 to T_3 caused by the suppression of iodothyronine deiodinase activity. This results from, e.g. malnutrition, chronic metabolic acidosis, or inflammation. Furthermore, reduced clearance of inflammatory cytokines such as TNF-α and IL-6, which inhibit the extrathyroid expression of 1, 5′-deiodinase may also contribute to the decreased serum T_3 in CKD patients.

Noteworthy, patients with CKD and concomitant low serum T_3 concentrations appear usually clinically euthyroid. In this group, the decreased concentrations of thyroid hormones may not necessarily be the indicator of thyroid dysfunction, but are probably a reflection of the chronic illness and/or malnutrition.

Traditionally low serum concentrations of T_3 were regarded as an adaptive response to severe acute or chronic disruptions (e.g. starvation, sepsis, trauma, surgical procedures such as coronary artery bypass grafting, and apparently CKD) that allowed to diminish the basal metabolic rate to save energy. This state is classically called the "euthyroid sick syndrome," or in concordance to the latest suggestions the nonthyroidal illness syndrome (NTIS).

Table 20.3 Abnormalities of hypothalamic–pituitary–thyroid axis in chronic kidney disease, chronic nonthyroidal, nonkidney illness, and primary hypothyroidism

	T_4	T_3	rT_3	TSH
Chronic kidney disease	N, ↓	↓	N	N
Chronic nonthyroidal, nonkidney illness	N, ↓	↓	↑	N
Primary hypothyroidism	↓	↓	N	↑

N normal, *TSH* thyroid-stimulating hormone, *T4* thyroxin, *T3* triiodothyronine, *rT3* reverse triiodothyronine

There is evidence, however, suggesting that low serum T_3 concentration in CKD patients is related to the endothelial dysfunction, atherosclerosis, and cardiac abnormalities. In clinical studies low serum free-T_3 has been linked with the increased cardiovascular mortality in hemodialyzed patients. In contrast to the other chronic nonthyroid diseases, rT_3 serum concentration is normal in CKD patients. Clinical, as well as experimental studies conducted so far concerning levothyroxine supplementation in patients with NTIS yielded conflicting results. Therefore, there is still need for large studies to be conducted and evidence of benefits of a therapy in CKD subjects must be provided before it can be unequivocally recommended in these patients [19, 20].

20.9.2 The Thyroid-Stimulating Hormone

Despite a tendency to low serum concentrations of T_4 and T_3, the serum concentration of thyroid-stimulating hormone (TSH) is usually normal in CKD patients. The normal serum TSH concentration despite low serum concentrations of the thyroid hormones suggests an abnormal regulation of the hypothalamic–pituitary–thyroid axis. The TSH response to TRH is usually blunted. In CKD patients, the normal diurnal rhythm of TSH with a peak in the late evening or early morning is blunted, and the nocturnal TSH

surge is reduced. The pattern of pulsatile TSH secretion is also altered [8, 19].

20.9.3 Primary Hypothyroidism and Hyperthyroidism

Primary hypothyroidism is two to three times more frequent in CKD patients than in the general population. The diagnosis of hypothyroidism in patients with CKD is challenging since the typical signs and symptoms of hypothyroidism, such as pallor, hypothermia, and asthenia, are also common in the clinical picture of advanced CKD. The only reliable procedure to diagnose hypothyroidism in CKD is the finding of an elevated serum TSH concentration and clearly low serum T_4 concentrations. Heparin competes with T_4 at the binding site of the hormone-binding protein, causing an increase of serum T_4 concentrations for at least 24 h. Therefore, blood for the determination of thyroid hormones should be sampled before heparin administration at the beginning of a dialysis session. Clinical consequences of hypothyroidism in CKD are exacerbation of muscle wasting, anemia, and depression [19, 20]. Interestingly, despite the fact that no direct link between thyroid and kidney was elucidated, it seems that there is a reciprocal influence of these two organs. There is growing evidence that thyroid hormones have a direct impact on kidney structure and function, and if hypothyroidism is left untreated may exacerbate the course of CKD.

The prevalence of hyperthyroidism in CKD is similar to that found in the general population.

20.10 Aldosterone

Serum aldosterone concentrations are elevated in CKD patients when GFR is lower than 70 mL/min, and a correlation between serum aldosterone concentration and the rate of CKD progression is found [21].

The results of the small interventional studies suggest that treatment with spironolactone reduces proteinuria in CKD patients. Some new study results showed benefits of such treatment in patients with CKD and heart failure. However, these studies enrolled modest number of patients so no definitive conclusions can be drawn. Also, the recent systematic reviews of Cochrane database did not result in unequivocal conclusions in that matter. Conversely, the results of FIDELIO-DKD Study showed that treatment with finerenone can reduce the risk of CKD progression and cardiovascular events in type 2 diabetes patients. This only emphasizes the need of such large studies to definitely assess the safety and efficacy of aldosterone antagonist treatment [22, 23].

20.11 Abnormalities in Insulin and Glucagon

In patients with chronic kidney disease (CKD), abnormalities in carbohydrate metabolism are encountered at different levels of the insulin–glucose cascade (Box 20.2) [24, 25].

Box 20.2 Insulin Metabolism in Chronic Kidney Disease

Fasting hyperinsulinemia with prolonged insulin half-life and elevated blood levels of proinsulin and C peptide
Usually decreased early, but exaggerated late-insulin response to hyperglycemia induced by oral or intravenous glucose administration
Decreased peripheral sensitivity to insulin action, but normal suppression of hepatic glucose production by insulin

20.11.1 Insulin Secretion and Clearance

Insulin secretion is impaired in CKD. Causes of this impairment are among others high PTH and low serum $1,25[OH]_2D_3$ concentration.

The kidney plays an important role in insulin clearance. Insulin is filtered by the glomeruli and reabsorbed in the proximal tubule. In healthy subjects the renal clearance of insulin is about 200 mL/min. This value exceeds the glomerular

filtration rate (GFR), indicating that, in addition, peritubular uptake of insulin takes place. It is estimated that 6–8 U of endogenous insulin are daily removed by the kidney, accounting for 25–40% of the total removal of endogenous insulin. A decrease in the metabolic clearance rate of insulin is documented in patients with GFR <40 mL/min. In CKD patients, diminished insulin clearance accounts for fasting hyperinsulinemia. It also accounts for decreased insulin requirements in diabetic patients with impaired kidney function [25, 26].

20.11.2 Insulin Resistance

Peripheral resistance to insulin occurs frequently even in early stages of chronic kidney disease and is found in the majority of patients with advanced CKD. The main sites of decreased insulin sensitivity are skeletal muscles. It was demonstrated that the defect is located not only at the level of the insulin receptor but presumably at the postreceptor level. Impairment of phosphatidyl-inositol 3-kinase activity (PI3-K) was documented in CKD patients. Higher serum insulin concentrations are required to increase glucose uptake by skeletal muscle. The main factors responsible for insulin resistance in CKD are metabolic acidosis, inflammation, and oxidative stress. Those abnormalities act mainly through the promotion of expression of signal regulatory protein alpha (SRIPα) which impairs insulin signaling in skeletal muscles by dephosphorylation of tyrosines in the insulin receptor and insulin receptor substrate 1 (IRS1). Additionally, serum concentrations of insulin antagonists like glucagon and growth hormone are frequently elevated in CKD patients and may participate in the development of insulin resistance in those patients.

The resistance to the peripheral action of insulin is markedly improved after several weeks of hemodialysis or peritoneal dialysis. Presumably, besides the correction of metabolic acidosis, also yet unidentified dialyzable uremic "toxins" are involved in the pathogenesis of deranged insulin action. Such compounds with a molecular weight of 1–2 kDa are specific for CKD, because they are not found in nonuremic patients with insulin resistance.

A number of other factors have been identified which are involved in the pathogenesis of insulin resistance in CKD patients and which are potential targets for intervention. In hemodialysis patients, insulin resistance is ameliorated by treatment with erythropoietin or $1,25(OH)_2D_3$. Lifestyle changes like more vegetable oriented diet, protein restriction, and also antidiabetic medications like metformin, SGLT2 inhibitors, or GLP1 agonists may help in overbearing the insulin resistance in CKD patients [25, 26].

20.11.3 Clinical Consequences of Hyperglycemia and Insulin Resistance

Hyperglycemia and insulin resistance in CKD patients contribute to increased cardiovascular risk and CKD progression. Insulin resistance may also participate in the pathogenesis of the malnutrition often found in these patients. Insulin deficiency (or resistance) stimulates breakdown of muscle and activates a common proteolytic pathway via the ubiquitin–proteasome system. Insulin resistance also increases salt sensitivity through increased tubular sodium reabsorption and therefore contributes to hypertension [25, 26].

20.12 Abnormalities in the Cardiac Natriuretic Peptides

Serum concentrations of atrial natriuretic peptide (ANP) and brain or B-type natriuretic peptide (BNP) usually are elevated in CKD patients. Moreover, in these patients, the pulsatile secretion of ANP and BNP is characterized by abnormally high amplitude. The causes of high serum concentrations of ANP and BNP in CKD are an increase in intravascular filling and atrial distension, concomitant heart failure, and diminished renal clearance. The removal of fluid by ultrafiltration during dialysis therapy is associated with a decrease in the serum ANP and BNP concentrations.

The measurement of ANP and BNP serum concentration was used as a biochemical marker of volume overload in CKD patients. The weight of evidence indicates that measurements of serum

ANP and BNP concentration add little to the clinical examination of these patients. However, high serum concentrations of cardiac natriuretic peptides, particularly BNP, were strong predictors of cardiovascular mortality in CKD patients.

The estimation of serum concentrations of cardiac natriuretic hormones (BNP and N-terminal proBNP) could be useful for a differential diagnosis of heart failure in general population. In CKD patients, most studies indicate that the upward adjustment of diagnostic cut points preserves the usefulness of BNP and N-terminal proBNP for the differential diagnosis of heart failure [27].

20.13 Abnormalities in Cardiotonic Steroids

Cardiotonic steroids (ouabain and marinobufagenin) act as physiological regulators of sodium pump activity and are implicated in regulation of natriuresis and vascular tone. In CKD patients, the serum marinobufagenin but not ouabain concentration is elevated. Such an elevation seems to be of pathophysiological relevance because it was shown that in CKD patients erythrocyte Na/K-ATPase was inhibited, and serum marinobufagenin concentration exhibited a negative correlation with this enzyme activity [28]. The clinical significance of the elevated serum marinobufagenin concentration in CKD is uncertain. Results of experimental studies suggest that high serum concentration may participate in the pathogenesis of hypertension, diastolic dysfunction, and both cardiac and renal fibrosis in CKD.

20.14 Abnormalities in Gastrointestinal Hormones

An elevated serum gastrin concentration is found in CKD patients. The kidney is the main site of gastrin biodegradation; therefore, hypergastrinemia in uremic patients is mainly due to reduced renal degradation of this hormone. Hypergastrinemia in CKD patients is due predominantly to "big" gastrin (G34), but not "little" gastrin (G17) accumulation. G34 is biologically less active than G17. Postprandial gastrin secretion in CKD patients is similar to that in normal subjects, but the peak values were attained later and the response was more prolonged [29].

Elevated serum ghrelin levels were observed in CKD. Increased ghrelin serum concentration in CKD is due to the decreased degradation of ghrelin by the kidney. There are two forms of circulating ghrelin: acylated and des-acyl ghrelin. Acylated ghrelin promotes food intake, whereas des-acyl ghrelin induces negative energy balance. However, only serum des-acyl ghrelin concentration was elevated in CKD. It is suggested that elevated des-acyl ghrelin serum concentration may be involved in the pathogenesis of anorexia in CKD patients. The results of small interventional clinical studies suggest that ghrelin treatment in CKD patients enhanced food intake and may improve nutritional status [30].

The serum concentrations of other gastrointestinal hormones, such as cholecystokinin, gastric inhibitory peptide, pancreatic polypeptide, secretin, gastrin releasing peptide, vasoactive intestinal polypeptide, and motilin, are elevated in CKD patients. The pathophysiological importance of these findings remains to be elucidated.

20.15 Abnormalities in the Hormones of Adipose Tissue

The adipose tissue is an important endocrine organ producing biologically active substances (adipokines). An elevated serum concentration of different adipokines is found in CKD patients (Box 20.3). It was proved that some of them (such as leptin, adiponectin, resistin, and visfatin) are characterized by systemic actions [31].

Box 20.3 Abnormalities in the Hormones of Adipose Tissue in Chronic Kidney Disease

Leptin	↑
Adiponectin	↑
Resistin	↑
Visfatin	↑

Patients with CKD are characterized by increased serum leptin concentration. The decreased leptin clearance by failed kidneys leads to its accumulation in the circulation. Leptin stimulates the proliferation and the differentiation of hematopoietic stem cells. It is likely that the effects of leptin and erythropoietin are synergistic. Apart from this, hyperleptinemia stimulates the activity of the sympathetic nervous system and therefore likely plays a pathophysiological role in the CKD progression, pathogenesis of hypertension, and cardiovascular diseases [31].

Patients with CKD are characterized by increased serum adiponectin concentration. The increased serum adiponectin concentration in CKD patients is owing to the disturbances of its biodegradation and elimination by the failed kidneys. Clinical consequences of increased serum adiponectin concentration in CKD are not clear [31]. It seems however that in CKD patients due to the receptor resistance, the unique antiatherosclerotic actions of adiponectin are reduced.

Serum concentration of resistin is increased in CKD patients. The main cause of high serum resistin concentrations in CKD is its reduced renal clearance. Resistin, at concentrations seen in CKD patients inhibits neutrophil activity. Therefore, it may participate in the pathogenesis of the increased risk of infections in CKD patients. Resistin also appears to have a potential role in the pathogenesis of cardiovascular disease in CKD patients. Hemodialysis patients with the low serum resistin concentration had poor hospitalization-free survival [31].

The serum concentration of visfatin gradually increases with the loss of kidney function and is related positively to endothelial dysfunction. This adipokine stimulates adhesion of monocytes to endothelial cells. Visfatin may also play a role in the pathogenesis of malnutrition in CKD. A high serum visfatin concentration predicted mortality in CKD patients [31].

Box 20.4 What the Guidelines Say You Should Do [32]

- In patients with CKD stages 3–5D, 25(OH)D (calcidiol), levels might be measured; vitamin D deficiency and insufficiency may be corrected using treatment strategies recommended for the general population.
- In children and adolescents with CKD stages 2–5D and related height deficits, treatment with recombinant human growth hormone when additional growth is desired, after first addressing malnutrition and biochemical abnormalities of CKD–MBD, is recommended.

Box 20.5 Relevant Guidelines

***1. KDIGO Guideline*:** KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7:1–59.

Erratum in: Kidney Int Suppl (2011). 2017;7:e1.

Available at: https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf

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- The main clinical consequences of endocrine abnormalities in CKD patients are anemia, bone disease, and infertility.
- Decisions concerning treatment with erythropoiesis-stimulating agents (ESAs) in these patients should be based on blood hemoglobin concentration and whole clinical status, and not on serum EPO concentration.

- Vitamin D supplementation in CKD patients with clinical signs of overt vitamin D deficiency, i.e. hypocalcemia and hyperparathyroidism is recommended.
- Therapy with exogenous testosterone is not exempted from risks, but results of recent studies seem to suggest that transdermal testosterone replacement therapy might be safe and effective in reversing the symptoms of testosterone deficiency and improve life quality of life in men with CKD.
- There is no data from the large, clinical studies concerning the safety and efficiency of the estrogen therapy in women with CKD. The decision of hormone replacement therapy in female CKD patients should be individualized and made after discussion with gynecologist.
- The administration of recombinant human GH in prepubertal children with CKD causes an increase in growth rate without undue advancement of bone age or significant side effects.
- Blood samples for the assessment of thyroid hormones concentration should be taken before heparin administration at the beginning of a dialysis session.
- In CKD, decreased thyroid hormone concentrations may not necessarily indicate a state of overt hypothyroidism, but rather the nonthyroidal illness syndrome (NTIS) which is a reflection of the state of chronic illness and/or malnutrition.

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