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RESEARCH ARTICLE

NEPHROPATHIES OF EXTRARENAL GENESIS IN CHILDREN

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ABSTRACT

The review presents the main mechanisms of the formation of nephropathies in children mainly with endocrine pathology. The effect of hormones on the structure and function of the kidneys in healthy children and in children with endocrine diseases has been shown. The issues of modern diagnosis and treatment of combined renal and hormonal dysfunction are considered. Data on congenital and hereditary disorders in children with kidney and endocrine system diseases are presented

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INTRODUCTION

Much attention has been paid to the problem of the relationship between kidney diseases and hormonal dysfunctions at different times (Teodosiev, 1968; Norman, 2001; Veltischev, 2001; Demikova, 2001). However, this issue remains relevant at the present time (Ignatova, 2007, 2011). The kidneys are the most important organ performing regulatory functions. They eliminate excess and toxic metabolic products, participate in the detoxification process. The kidneys control water-electrolyte, protein, carbohydrate and mineral metabolism, regulate vascular tone. At the same time, the kidney is a target organ for many endocrine influences. Hormones regulate the processes of tubular reabsorption, secretion, membrane transport of various substances, expression of signaling molecules, metabolic processes in the interstitial connective tissue (Dedov, *et al*, A 2013; Dedov, *et al*, 2014; Dedov, *et al*, 2020; Ignatova, 2007; Gardner and Shobek, 2018; Yurieva et Dlin, 2020; Valerio, *et al*, 2018). An important role in the implementation of hormonal control of renal functions is played by the sensitivity of cellular receptors to hormones, the physiological balance between the content of antagonist hormones in the circulation, which ensures mutual regulation of their activity (Dobronravov, 2011; Valerio, *et al*, 2018).

For its part, the kidney is an endocrine organ that provides the synthesis of the following hormones: calcitriol (the hormonal form of vitamin D), erythropoietin, renin, prostaglandins. The latter have a strong vasodilatory effect. Their synthesis is stimulated by angiotensin II, vasopressin, diuretics. Prostaglandins stimulate renin secretion, participate in the regulation of renal plasma flow, regulate the excretion of sodium and water, osmolarity of urine. Prostaglandin synthesis is carried out in the thick knee of the Henle loop, distal tubules and collecting tubes in response to renal ischemia (Gardner et Shobek 2018; Ignatova, 2011). Violation of hormonal regulation of the kidney function affects its structure and contributes to the formation of kidney (Novikov, 2007; Valerio *et al*, 2018; Ravid *et al*, 1993; KDOQI_ Clinical_ Practice_Guidelines, 2004). We will consider the main pathological processes in the kidney that occur in endocrinopathies in this review. Renin (angiotensinogenase) it is a component of the renin-angiotensin system that regulates blood pressure. Renin is a proteolytic enzyme that is produced in the juxtaglomerular apparatus (JuGA) of the glomeruli of the kidneys. Thanks to renin, the kidney and the cardiovascular system provide control of the volume of circulating blood. Violation of this regulation leads to an imbalance of vasoconstrictive and vasodilating substances and the formation of arterial hypertension (Ignatova, 2011; Eckardt, *et al*, 2015;

Owen end Reisin, 2015). Renin acts on the blood glycoprotein angiotensinogen, hydrolyzing the peptide bond between leucine and valine. As a result of the reaction, an inactive decapeptide angiotensin I is formed, which is converted by the action of angiotensin converting enzyme (ACE) into the active hormone angiotensin II (hypertensin or angiotonin). The latter narrows blood vessels and stimulates the secretion of aldosterone by the adrenal glands. These two effects lead to an increase in blood pressure (Ravid *et al*, 1993; KDOQI Clinical Practice Guidelines, 2004). With a mutation of the renin gene, abnormal renin accumulates in cells, which is accompanied by apoptosis of kidney cells (Eckardt, *et al*, 2015; Ignatova, 2011). The composition of the renin-angiotensin-aldosterone system (RAS) includes, in addition to renin, aldosterone, antidiuretic hormone (ADH), angiotensin-II and catecholamines. RAS determines the volume of circulating blood and the activity of vasoconstrictor factors. Of great importance is a violation of vascular sensitivity and a change in the activity of this system in the development of vasorenal hypertension, which is caused by ischemia of the kidney (kidneys) due to narrowing of the renal artery or its branches. An increase in renin in the circulation is accompanied by damage to the renal vessels due to its direct or indirect toxic effect (Ravid, 1993).

The activation of RAS occurs with a decrease in sodium in the blood, blood loss, injuries, a decrease in blood pressure, anesthesia. Angiotensin II and bradykinin stimulate the release of prostaglandins normally, which increase the synthesis of ACE inhibitors (iACE). Prostaglandins are antagonists of the RAS system, participate in the intrarenal system of regulation of renal plasma flow: RAS is activated in response to vasoconstriction, reduced sodium intake, increased angiotensin II in the blood. Loading with sodium reduces the activity of RAS. At the same time, the level of glomerular filtration (LGF), increases of vascular tone decreases under the action of iACE, blood pressure decreases (Dedov, *et al*, 2014). An abnormal increase in the activity of RAS leads to kidney ischemia, progressive fibrosis of kidney tissue. The therapeutic effect is provided by natriuretics, ACE inhibitors, beta-blockers, blockers of slow calcium channels with the toxic effect of renin on the kidneys. Indomethacin suppresses renin synthesis (Ravid, 1993; Ignatova, 2011).

Erythropoietin: Is the second hormone that is synthesized in the JuGA of glomeruli of the kidneys in response to a decrease in red blood cells in the blood. It stimulates the differentiation and maturation of red blood cells in the bone marrow. Erythropoietin synthesis decreases in chronic renal failure (CRF) (Ignatova, 2011).

Calcitriol: Is the third renal hormone (1,25 $(OH)_2D_3$). the active form of which is formed in the proximal tubules of the renal epithelium from the precursor calcidiol (25 $(OH)D_3$). The formation of the active form of vitamin D occurs under the action of 1-alpha-hydroxylase, the activity of which is stimulated by parathyroid hormone, prolactin, estrogens, growth hormone, low levels of calcium and phosphates in serum. Its activity inhibits calcitriol. A "feet back" loop forms and regulates calcitriol synthesis (Moe , 2008; Hou *et al*, 2018). Calcitriol acts mainly on 4 target organs. These are the parathyroid gland, bone cells, small intestine and kidneys. Calcitriol circulating in the blood binds to protein and penetrates into target organ cells, where it interacts with the nuclear receptor and activates vitamin D-responses element (VDRE) in genes. In the small intestine, calcitriol regulates the adsorption of calcium and, to a lesser extent, phosphorus, suppresses the synthesis of parathyroid hormone in the parathyroid gland (PThG). In addition to participating in mineral metabolism, calcitriol performs other functions. It is involved in cellular differentiation, cell proliferation, immune system function and protects against infection. In this regard, it is used in the treatment of cancer, skin diseases, etc. (Dusso, *et al*, 2005). Hypervitaminosis D_3 is caused mainly by food or drug overload, as well as (rarely) increased sensitivity of receptors to vitamin D_3. The toxic effect of excess calcitriol in the body is characterized by an increase in calcium adsorption in the intestine, hypercalcemia, nephrocalcinosis, a sharp increase in peroxide processes. In the latter case, the lipid component of the brush edges of the tubular epithelium of the kidneys is most damaged with atrophy, destruction of the tubules, the appearance of powerful lipid mediators of inflammation with lymph-histiocytic proliferation in the interstitial of the kidneys. The content of lipids, peroxides, collagen metabolites, and medium molecules increases in urine. Microproteinuria, leukocyturi are characteristic. For therapeutic purposes, copious drinking, furosemide and other loop diuretics (blockers of K, Na / Cl metabolism in the thick knee of the loop of Henle) are used, calcitonin, bisphosphonates, calcimimetics (mimicry of high serum Ca levels and a decrease in vitamin D_3) are prescribed (Ignatova ,2011).

Vitamin D deficiency is noted with a decrease in its intake into the body, a decrease in UV radiation, malabsorption, shortening of the small intestine, a decrease in the activity of 1-alpha-hydroxylase, CRF of 3-5 degrees. Characteristic signs of rickets are hypocalcemia (decrease in ionized Ca), hypoalbuminemia, uratemia, loss of bicarbonates in urine, acidosis, leg cramps, muscle tension, Khvostek's symptom, decreased absorption of Ca in the intestine, secondary hyperparathyroidism with impaired mineral metabolism in the bones. Calcium gluconate, calcium chloride, vitamin D_3, magnesium preparations, thiazide diuretics (increase calcium reabsorption in kidney tubules), calcimimetics (to reduce secondary hyperparathyroidism) are used to treat rickets (Moe, 2008; Ignatova, 2011).

Parathyroid hormone: (PTH) is synthesized in the parathyroid glands (PTG). It, along with vitamin D_3, is a regulator of calcium-phosphorus metabolism and, supports calcium homeostasis together with the kidney. This function of PTH is carried out through (1) increasing the dissolution of bone minerals and the release of Ca and phosphates into the blood; (2) increased reabsorption of calcium in the kidneys and increased excretion of phosphates and (3) increased intestinal adsorption of Ca and P by stimulating the synthesis of 1,25 $(OH)_2D_3$ through activation of 1-alpha-hydroxylase in the cells of the proximal tubules of the kidneys. As a result, an increase in serum parathyroid hormone effectively maintains a constant level of Ca and phosphates (Dedov, *et al*, 2001; Dedov, *et al*. 2014; Novikov, 2007). Due to the fact that the kidney is one of the target organs for PTH, violations of its secretion and interaction with the kidney critically affect its structure and functions. However, kidney pathology (chronic renal failure - CRF) can also be the cause of increased PTH in circulation, since the kidney is the main organ (except the liver) that inactivates the hormone and eliminates it from the body. The primary causes of hyperparathyroidism (HPT) are PThG tumors and familial or congenital endocrinopathies

(Veltischev, 2001; Ignatova, 2011; Dedov, *et al*, A 2013). Secondary causes are hyperproduction of PTH in conditions of hypocalcemia or hyperphosphatemia, increased bone resorption, decreased calcitriol levels (with CRF). HPT is characterized by an increase in the content of Ca in the blood, an increase in its filtration and reabsorption in the kidneys. In this case, the kidney may be unable to reabsorb all filtered Ca, which leads to hypercalciuria and nephrocalcinosis (with the formation of insoluble oxalates or calcium phosphates). PTH causes ischemia of the renal tissue, a decrease in the secretion of hydrogen ions in the distal tubules, which, combined with the predominance of ammonium excretion, causes an alkaline reaction of urine. This, in turn, is a risk factor for the crystallization of tripelphosphates (ammonium-magnesium phosphates, struvite) with the formation of loose tripelphosphate stones in the kidneys. Calciuria can also cause the formation of phosphate or oxalate stones. PTH activates a pro-oxidant enzyme - xanthine oxidase, as a result of which peroxide processes in the membrane phospholipids of the brush edges of tubular epithelial cells sharply increase with the formation of lipid mediators of inflammation (leukotrienes), oxalates, various pro-inflammatory growth factors that enhance cell proliferation in PThG and in the kidneys (Arsidiacono, *et al*, 2008; Dobronravov, 2011). Nephrologists monitor hypercalcemia and renal ischemia. Calcium-sensitive receptor activators (ACE inhibitors, bisphosphonate, calcimimetics, including sansipar) are used for treatment. They allow you to reduce the synthesis of PTH. Membrane stabilizers are also used for treatment.

It is necessary to maintain a normal calcitriol content in case of its deficiency. Hypoparathyroidism may be the result of the removal of PThG, a congenital defect of sensitivity to PTH, the effects of radiation. At the same time, PThG is insensitive to low calcium content in the blood. The clinical picture of hypoparathyroidism is usually asymptomatic or there are convulsions, tetany, symptoms of Khvostek, Truss. A stress test using PTH contributes to the diagnosis. Thus, cAMP in the blood and urine and the excretion of phosphates normally increases, and with hypoparathyroidism these signs are absent. For therapeutic purposes, in acute cases, gluconate or calcium chloride is administered intravenously, calcitriol, magnesium, thiazide diuretics are prescribed (Moe, 2008; Ignatova, 2011).

Calcitonin: Is a thyroid hormone involved in the regulation of phosphorus-calcium metabolism, an antagonist of PTH. Calcitonin synthesis increases with an increase in calcium in the blood. Calcitonin is used as a medicine for hypercalcemia, it suppresses the synthesis of PTH in PThG. Lack of calcitonin synthesis may be the cause of secondary hyperparathyroidism (Yurieva et Dlin, 2020).

Adrenal hormones. **Aldosterone:** Is a mineralocorticoid hormone of the adrenal cortex. It regulates the metabolism of sodium, potassium, chlorine, and phosphates. The hormone acts directly on the distal tubules of the kidneys: it increases sodium reabsorption, potassium excretion and phosphate clearance (Dedov *et al*, 2014; Valerio *et al*, 2018). An increase of aldosterone in the blood (hyperaldosteronism - HAS) is characteristic of Conn's disease (primary HAS) and Butter's (secondary HAS). Conn's disease is caused by a malignant tumor of the adrenal glands with an increase in aldosterone synthesis, which is accompanied by nocturia, polyuria, dehydration, isostenuria, alkaline pH of urine, microproteinuria, arterial hypertension and even pyuria. There is marked hypokalemia (hypokalemic nephropathy), hypernatremia, an increased content of potassium, sodium and aldosterone in the urine. An increase in aldosterone in the blood is accompanied by edema in acute renal failure (ARF), CRF (Bochkov, 2001; Novikov, 2007; Yang Liu *et al*, 2016). Butter syndrome is caused by congenital partial resistance of the vascular wall to the action of angiotensin II, which is combined with a sharp increase in aldosterone in the blood. A decrease in blood pressure is combined with kidney hypoplasia and an increase in renin synthesis. There is hypokalemic and hypochloremic alcoholosis, lowering of blood pressure in the fetal arterioles of the kidneys, hypoxia of the kidneys, hyperplasia of the JuGA. An increase in the synthesis of renin and angiotensin II leads to an increase in the synthesis of aldosterone, which is why the content of the latter increases sharply in the blood. Hypertension is absent due to the blockade of the action of angiotensin II, unlike Conn's syndrome (Naesens, *et al*, 2004). There are significant losses of sodium and potassium in the urine. There is a lot of aldosterone in the urine. Vacuolization of tubular cells, dystrophy and necrotic changes with deposition of calcium in the tubules are characteristic for the histological picture of the kidneys in hyperaldosteronism (Novicov, 2007; Demikova, 2001; Yang Liu, *et al* 2016).

There is also receptor hypoaldosteronism (salt diabetes) with a massive loss of sodium in childhood, due to the congenital insensitivity of the tubules to aldosterone (pseudohypoaldosteronism). The disease manifests itself in the first days after birth. There is a decrease in appetite, vomiting, decreased ossification of the skeleton (hyperphosphaturia), growth retardation, lag in physical and mental development, hypovolemia, collapse, tachycardia, death from dehydration. Aldosterone excretion sharply increases, blood sodium is reduced and the potassium content in the urine is increased. For therapeutic purposes, the introduction of sodium is necessary. This defect disappears with age, as the sensitivity of the distal tubules to aldosterone is restored. Lidl syndrome is a syndrome of changing the sensitivity of the distal tubules with increased sodium reabsorption. This distal tubulopathy is characterized by a sharp increase in the sensitivity of the sodium channels of the epithelial cells of the collecting tubes, which is accompanied by a significant increase in the reabsorption of sodium and water, with simultaneous suppression of the secretion of renin and aldosterone and a significant loss of potassium in the urine. This distal tubulopathy is characterized by a sharp increase in the sensitivity of the sodium channels of the epithelial cells of the collecting tubes, which is accompanied by a significant increase in the reabsorption of sodium and water, with simultaneous suppression of the secretion of renin and aldosterone, and a significant loss of potassium in the urine. Severe volumetric arterial hypertension, delayed psycho-emotional development, muscular hypotension, increased fatigue, hypokalemia, metabolic alkalosis prevail in the clinical picture. It is necessary to limit sodium intake, prescribe potassium-sparing diuretics (amiloride, triamterene) during treatment. The lack of adequate therapy can lead to CRF up to the terminal stage (Yurieva et Dlin, 2020).

Glucocorticosteroids: (GCS) are hormones that are synthesized in the adrenal cortex. An increase in GCS in the blood is noted under stress under the stimulating influence of adrenocorticotropic hormone (ACTH), as well as with adrenal tumors.

An increase of GCS (cortisol, etc.) is accompanied by an increase flow in plasma, and the level of glomerular filtration (LGF) in the kidneys. High concentrations of GCS increase sodium reabsorption in the tubules, reduce potassium reabsorption, cause extracellular alkalosis and cell dehydration (Dedov, *et al*, 2014, Dedov et Peterkova, 2020). GCS are involved in the regulation of the circadian rhythm (circadian periodicity) of the excretion of sodium, potassium and water, the excretion of which is normally higher during the day under the influence of a high content of GCS in the blood. Most of the water is released at night (nocturia) with adrenal insufficiency. An example of hyperglucocorticism (independent of ACTH) is the Itsenko-Cushing syndrome in adrenal tumors with an increase in cortisol in the blood, 11-oxycorticosteroids (11OX) and 17OX in the urine. There is no reaction to ACTH. Kidney damage is usually asymptomatic with the exception of severe cases of hyperglucocorticism. Proteinuria, 1-3%, single erythrocytes, hyaline cylinders are detected by laboratory methods in the latter case. The release of water increases, polyuria, nocturia, a tendency to hypoisostenuria is noted, urea reabsorption decreases and its excretion increases. A decrease in renal plasma flow and LGF is characteristic. The content of potassium and sodium in the blood decreases and their excretion in the urine increases, hypokalemic nephropathy develops (extracellular alkalosis and dehydration). There is a risk of death with a prolonged course of the disease without treatment. There is a large increase in body weight, a specific increase in the abdomen, shoulders, face, bruising on the skin, poor wound healing, striae (stretch marks), loss of muscle mass, weakness, osteoporosis, kyphosis, fractures, depression, prediabetes, hypertension, blood clots (Melnichenko *et al*, 2015).

Morphological examination reveals an increase in the kidneys, thickening of the cortical layer, sometimes - foci of necrosis, thickening of capillary membranes in the glomeruli (internal hydronephrosis), sclerosis, granular destruction of the proximal tubules with a decrease in their lumen. Granular cylinders clog the lumen in the distal tubules. Sclerosis, arteriole ischemia and interstitial hyperplasia JuGA occur. Treatment of the Itsenko is Cushing syndrome is symptomatic before and after surgical removal of the tumor (Dyubkova, 2008). An example of hypoglucocorticism is Addison's disease. This is a chronic insufficiency of adrenal function (dystrophy) (Dedov, *et al*, 2014; Dedov et Peterkova, 2020). The disease is characterized by weakness, low blood pressure, hyperpigmentation of the skin and mucous membranes, loss of salts, violation of carbohydrate metabolism (flat sugar curve), decreased immunity, mental arousal, decreased appetite, back pain, muscle hypotension. There is a decrease in sodium and chlorine in the blood, an increase in potassium. The content of sodium, chlorine and corticosteroids increases in the urine. Polyuria, dystrophy of the tubular epithelium are detected. There is no response to the introduction of ACTH. Adrenaline is the main catabolic hormone of the adrenal medulla. Its synthesis increases dramatically under stress. Adrenaline acts on alpha and beta receptors, increases renin synthesis, activates the hypothalamic-pituitary system, increases blood pressure, synthesis of ACTH and cortisol, narrows the vessels of the abdominal cavity, skeletal and smooth muscles. The hormone causes tachycardia up to the development of arrhythmia, relaxes the smooth muscles of the bronchi, increases blood glucose (anti-insulin effect) (Dedov et Peterkova, 2020). It is characterized by an increase in the processes of peroxidation in the kidneys and other organs.

Adrenaline increases the catabolism of proteins, lipids, glucose. In addition to reducing bronchospasm, adrenaline has an anti-allergic and anti-inflammatory effect (reduces histamine, serotonin, kallikrein). Adrenaline lowers renal plasma flow and LGF, causes spasm of the renal veins, increases the reabsorption of sodium, potassium and water (reduces the excretion of potassium and sodium) in the kidneys, can cause oliguria. The content of medium molecules (protein catabolism), lipid peroxides, collagen metabolites in urine increases, the antioxidant protection of urine decreases. There are dystrophic changes in the epithelium of the tubules. The therapeutic effect is provided by antihypertensive agents, antioxidants, membrane stabilizers in chronic stress. Adrenocorticotropic hormone is corticotropin, it stimulates the function of the adrenal cortex. The hormone is synthesized in the anterior pituitary gland. Increased ACTH secretion is accompanied by symptoms characteristic of the Itsenko-Cushing syndrome (hyperglucocorticism). Decreased ACTH synthesis disrupts hormonal regulation of kidney function (Dedov, *et al*, 2014; Dedov et Peterkova, 2020; Efimov, 2008; Stratakis. 2016; Grossman, 2020).

Antidiuretic hormone: (ADH) is a peptide hormone, it is synthesized in the anterior lobe of the hypothalamus. The main function of ADH is the preservation of water in the body and the narrowing of blood vessels, which is why it is also called vasopressin. The transport of water in the kidneys depends on the content of ADH in plasma: the hormone activates hyaluronidase, which loosens the hyaluronic "plugs" in the intercellular spaces and enlarges the pores in the cell membranes of the epithelium of the distal tubules and collecting tubes (which are impervious to water in the absence of ADH). This is accompanied by an increase in water absorption. ADH reduces the volume of daily urine and increases its concentration (Yurieva et Dlin, 2020). The activity of hyaluronidase decreases, hyaluronic acid thickens and diuresis increases normally with a decrease in diuresis. Water transport is a passive process in all cases: it is combined with sodium transport. ADH has a hemostatic effect due to spasm of small vessels and increases the content of factor VIII of the blood coagulation system (Willebrandt factor) and the level of plasminogen activator; it enhances platelet aggregation and sensitivity of the vascular wall to the action of catecholamines (constrictor effect). ADH increases the tone of smooth muscles of internal organs (especially the digestive system) and blood vessels with increased blood pressure (Yurieva et Dlin, 2020; Starkova, 2002).

Non-sugar ("central") diabetes develops in the absence of ADH secretion (diabetes insipidus). There is a decrease in physical development in children, dehydration, polyuria, polydipsia, hypostenuria, increased osmolarity of blood. Non-sugar diabetes of nephrogenic genesis is caused by the absence of a kidney reaction to ADH (there are no receptors in the distal tubules), which leads to a decrease in water reabsorption. Mostly male children are affected: this is an autosomal dominant inheritance linked to sex via the X chromosome. The disease manifests itself from birth. Polyuria, polydipsia, decreased LGF, increased body temperature, vomiting, weight loss, mental and physical development delay are characteristic. The disease manifests itself from birth. Dehydration, albuminuria, aminoaciduria, azotemia, hypernatremia and hyperchloremia appear in severe cases. Sodium is limited for therapeutic purposes, chlortiazide is used (reducing water clearance by 20-70%), and water consumption is increased

(Demikova, 2001, Novikov, 2007). The "failure" of ADH is currently detected in patients with Covid-19 (Indian delta virus). Severe dehydration, severe hyponatremia and hypokalemia, vomiting, clonic-tonic convulsions, disorientation, polyuria with increased urine osmolarity occur in patients. These changes in the first days of the disease prevailed over the pulmonary and cardiovascular symptoms and were amenable to correction by intravenous administration of fluid or saline solution (Yousaf, *et al*, 2020; Ho, 2020). ADH secretion increases with high osmolarity of blood, with a decrease in extracellular fluid volume, with shock, trauma, bloodletting, pain, psychosis and under the influence of certain medications (Dedov *et al*, B 2013). ADH is embedded in the membrane of epithelial cells of collecting tubes (aquaporin), increases their permeability to water and increases its reabsorption following sodium reabsorption. The volume of circulating blood increases (hypervolemia, hyponatremia and hypoosmia) with an increase in ADH in the blood. Diuretics are used.

Somatotropic growth hormone: (STH) is synthesized in the anterior pituitary lobe, increases epiphyseal cartilage growth and calcium deposition in bones, increases protein content in tissues, causes hyperglycemia, glucoseuria, and fat immobilization (Dedov, *et al*, B 2013). The STH affects kidney growth, increases renal plasma flow and renal filtration, reduces the excretion of sodium, potassium and phosphates in the urine, can significantly reduce diuresis. In this regard, the volume of extracellular fluid increases, kidney function improves. An increase in STH in the blood does not have a pronounced effect on kidney function. However, there is an increase in their volume, thickening of the basement membranes, hyalinosis of the interlobular arteries, nephrosclerosis. Urine tests reveal albuminuria, single erythrocytes and leukocytes, hyaline cylinders. There is a decrease in the concentration of urea, nephrosclerosis in severe cases (acromegaly, high growth). The growth retardation, dwarfism, a decrease in renal plasma flow, glomerular filtration and urea clearance are noted with a decrease in STH synthesis. The introduction of STH for therapeutic purposes has a therapeutic effect (Dedov, *et al*, A 2013; Dedov, *et al*, 2020).

Thyroid-stimulating hormone: Is synthesized in the pituitary gland, thyroid hormones are synthesized in the thyroid gland. Thyroxine is the main hormone circulating in the blood, from which 3-iodine-tyronine and 4-iodine-tyronine are synthesized. Thyroid hormones regulate the basic metabolism of the body, performing numerous functions. They stimulate growth and development, tissue differentiation, increase oxygen demand, increase heart rate, wakefulness, mental and motor activity, body temperature, blood glucose and glycolysis, inhibit glycogen synthesis in the liver and skeletal muscles. These hormones increase lipolysis and inhibit the formation and deposition of fat in tissues, increase sensitivity to catecholamines, reduce tissue hydrophilicity and tubular reabsorption of water (Dedov, *et al*, 2014). Thyronine improves renal function, renal plasma flow, glomerular filtration and secretion in the tubules. There is an expansion of the bringing and carrying vessels of the glomeruli, the minute volume of the heart increases, hypercalcemia and a decrease in blood cholesterol are noted in patients with hyperthyroidism. Blood cholesterol increases, renal plasma flow and glomerular filtration decreases, diuresis decreases with a decrease in the minute volume of the heart in patients with myxedema (Gardner et Shobek, 2018; Larsen, 2012). Estrogens are steroid sex hormones synthesized in the ovaries and adrenal glands, regulate the menstrual cycle, sexual and physical maturation. The effect of sex hormones on the kidneys is insignificant: the excretion of sodium, chlorine, phosphates decreases, there is no effect on glomerular filtration. However, it was found that girls with pyelonephritis in prepubertal and pubertal age have a delay in the appearance of secondary sexual characteristics 3 times more often than normal, as well as 5 times more often with late menarche. Such girls with pyelonephritis have metabolic, neurovegetative disorders, decreased physical development, oligomenorrhea or amenorrhea (Dedov, *et al*, 2020; Yurieva et Dlin, 2020).

Insulin: Is a polypeptide hormone synthesized in the beta cells of the islets of Langerhans in the pancreas. It carries out the normal functioning of cells, regulates the absorption of glucose, amino acids, fatty acids in cells, suppresses the destruction of glucose, catabolism of proteins and fats. Insulin provides a stimulating effect on the synthesis of collagen and bone matrix, the functioning of cartilage. It is necessary for mineralization of the skeleton, differentiation of osteoblast functions. A decrease in insulin synthesis disrupts glucose metabolism and other functions of the hormone, causes the development of diabetes mellitus (Dedov, *et al*, B 2013; Dedov, *et al*, 2014; Dedov, *et al*, 2020; Candler, *et al* 2018). Hereditary factors (Type 1), age (type 2), insulin resistance in metabolic syndrome, eating disorders (obesity) play a role in the occurrence of diabetes mellitus (Butrova, 2013; Kalinchenko, *et al*, 2015; Schwab, *et al*, 2015). The kidney damage often occurs in diabetes mellitus for the following reasons: (1) specific vascular degenerative changes in glomerular capillaries (diabetic intercapillary glomerulosclerosis, hyalinosis); (2) atherosclerotic changes in arterioles and small vessels (arterio- and arteriole-nephrosclerosis); (3) inflammation in interstitial tissue (pyelonephritis, necrotic papillitis) (Dedov, *et al*, 2014; Valerio 2018; Candler, 2018). The frequency of diabetic nephropathy is 10-70% (the frequency ratio in men and women is 1:2). The severity of kidney pathology depends on the duration of diabetes mellitus (13-14 years), on the severity of the disease, on the regularity of treatment (diet, medications). Metabolic disorders and deposition of metabolic products (cholesterol, beta-lipoproteins, triglycerides, lipid peroxide, glycated hemoglobin and other proteins, sialic acids, mucopolysaccharides, mucoproteins) play an important pathogenetic role. These metabolic products turn into a hyaline-like substance and accumulate in the capillaries, disrupting blood microcirculation (Dedov, *et al*, 2014; Piccoli, *et al*, 2015; Valerio 2018). The morphological picture of diabetic nephropathy is nonspecific. There are nodular changes, diffuse exudative signs of damage to the glomerular capillaries, hyalinization of the basement membranes of the capillaries, fibrinoid formations on the periphery of the glomeruli (half moon). The changes in the tubules are less pronounced. They are characterized by hyalinization of small vessels, interstitial fibrosis or sclerosis. Electron microscopy reveals thickening of the glomerular basement membranes, degradation of podocytes (Yurieva *et al* Dlin, 2020; Starkova, 2002). The clinical picture of diabetic nephropathy is not always pronounced and is not specific enough. The generalized edema (nephrogenic, cardiogenic type), massive proteinuria (from 9 to 10-30 g / 24 hours), hypoisostenuria on the background of polyuria, hypertension are sometimes noted, CRF develops in late terms in severe cases.

Proteinuria is the earliest and relatively permanent sign. Severe diabetic nephropathy is more often observed in the juvenile form with signs of nephrotic syndrome. Retinally degenerative maculitis (blindness) is characteristic. There is hypoalbuminemia, increased cholesterol, lipids in the blood, glucoseuria, hyperphosphaturia, proteinuria, polyuria, hypostenuria. The hyaline cylinders, erythrocytes and leukocytes are rarely detected. Treatment of diabetic nephropathy is non-specific (the main thing is the treatment of diabetes mellitus) (Cathy Anne Pinto 2019; Dedov, *et al*, 2020, d'Annunzio 2020; Chawla, *et al*, 2020; Jenkins, *et al*, 2015). The prevention is reduced to the treatment of urinary tract infection, the exclusion of any manipulation of the bladder, diet (Dedov, *et al*, 2014; Dedov, *et al*, 2020; Piccoli, *et al*, 2015; Mehta S.*et al*., 2015, Giuseppe d'Annunzio 2020; Chawla, *et al*, 2020).

CONCLUSION

Kidney diseases and pathology of the endocrine system are interrelated, since hormones regulate the functions of the kidney, and the kidney itself is an endocrine organ. Of particular importance in the development of pathology are dysfunctions in the endocrine and renal systems in children against the background of organ maturation. It is necessary to pay attention to the determination of age-related features of hormonal functions in children, the physiology and pathophysiology of hormonal regulation of metabolic processes and their involvement in the development of kidney diseases.

Glossary of Abbreviations

ACE – the angiotensin converting enzyme
ACTH - the adrenocorticotropic hormone
ADH - antidiuretic hormone
ARF – the acute renal failure
25 (OH)D_3 - calcidiol
GCS – the glucocorticosteroids
CRF – the chronic renal failure
HAS - hyperaldosteronism
HPT - hyperparathyroidism
iACE - ACE inhibitors
JuGA - the juxtaglomerular apparatus
LGF - the level of glomerular filtration
11OX - 11-oxycorticosteroids
PThG - the parathyroid gland
PTH – the parathyroid hormone
RAS - the renin-angiotensin-aldosterone system
STH – the somatotropic growth hormone
VDRE – the vitamin D-responses element

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