INTRODUCTION
Stone formation in the urinary organs is a common phenomenon with a complex pathogenesis and not fully clarified etiology. Usually the process takes place with scant latent symptoms and it is difficult to diagnose that determines the permanence of the risk factors of nephrolithiasis. Currently the known pathogenetic risk factors for urolithiasis (ULD) can be conditionally divided into internal and external, interacting with each other. In its turn, the internal risk factors of the ULD are divided into extra- and intra-renal. Extra-renal include the following: Genetic, including gene mutations of somatic cells; dysfunction of hormonal regulation of phosphorus-calcium metabolism with reduced adaptation to stress; systemic reduction of bioenergetics and antioxidant protection (30% of the population). Great importance also has a degree of expression and prolongation of endogenous intoxication. Intra-renal risk factors include the following: anomalies of the urinary system with a disturbance of urodynamics; dysembryogenesis of the renal tissue with a violation of its functions; gene mutations of the transport systems of the tubular epithelium, as well as violations of bioenergetics in the cells of the renal epithelium. The most recognized external risk factors of the ULD besides the internal factors are stress, including climatic, psycho-emotional, pain, physical as well as the immobilization and reduction of age state of hormonal activity. Among extra-renal internal risk factors of the ULD are the genetic and the changes of the hormonal regulation of calcium-phosphorus metabolism are the main ones.

GENETIC FACTORS
The greatest attention of researchers is directed to the study of the calcium nephrolithiasis problem, which compose 90–95% of all ULD cases. Most authors note that this main group of patients should be referred to multifactorial and only a few part of diseases (according to the catalog of Makkusik V.A.) accompanied by urolithiasis, have the monogenic nature of inheritance (syndromes of Dent, Barter, Lesch-Nihan and others). The authors point at the difficulties in deciphering the polygenic etiology of stone formation.
the ULD as dozens of genes are involved in the development of each specific form of the disease. “Genes of predisposition (polymorphisms) are compatible with life, but under the influence of adverse environmental factors can cause disease.” Polymorphisms of genes number associated with the place of their expression in the ULD are presented: In the proximal, distal convoluted tubules of the kidneys, loop of Henle, collecting tubes. All 12 genes currently described control the regulation of mineral metabolism in the kidneys and in the parathyroid gland for which the kidney is the target organ. Extra- and intra-renal dysfunction of hormonal regulation of phosphoric-calcium metabolism (parathormone, calcitonin, calcitriol) are also included to the polymorphic factors. Gene mutations in somatic cells that are not inherited, particularly in the exchange metabolism of purines with hyperproduction of uric acid are also important. Hyperuricuria, hyperuricemia occurs with the mutation of the hypoxanthine–guanine phosphoribosyl transferase (HGPRT) gene in somatic cells, one of the main enzymes of the biosynthesis of purine nucleotides, whose gene is located on the X chromosome, and it is susceptible to point mutations. A significant amount of xanthine and hypoxanthine, a substrate for the enzyme xanthine oxidase (XO) is released. On the one side, it sharply increases the synthesis of reactive oxygen species, and on the other side, it raises the uric acid. In addition to heat shock, the cause of mutations in the HGFRT gene is hypoxia, particularly with immobilization, increasing with age and relevant for metabolic syndrome and cardiovascular diseases. It is noted that the impairment of purine metabolism is combined with an increase in urinary excretion of oxalates and oxalate-calcium crystals. In addition, there is a sharp increase in the content of “stressor” hormones - catecholamines, glucocorticoids, regulators of mineral metabolism (parathyroid hormone) in response to stressful effects in the body. There is a mobilization of energy and structural resources, gluconeogenesis is activated, the number of mitochondria in muscles is changed, lipid peroxidation is started to work, and lipid metabolism is activated, cardiac remodeling occurs.

HORMONAL REGULATION OF PHOSPHORUS-CALCIUM METABOLISM

A variety of risk factors for the formation of calcium calculi in the organs of the urinary system cause a violation of the mineral homeostasis. Its regulation is controlled by the intra- and extra-cellular content of three ions - calcium, magnesium and phosphates (Ca, Mg, Ph) with the help of three hormones: Parathyroid hormone (PTH), calcitonin (CT) and calcitriol (1,25-dihydroxyvitamin D) acting on the three target organs (bones, intestines and kidneys). However, the other ions are involved in this process: pH levels, sodium, potassium, chlorides, bicarbonates and sulfates - all affect the cellular composition of calcium, magnesium and phosphates. In addition, other hormones and a variety of cytokines are important components in the regulation of mineral homeostasis.

The functions of parathyroid hormone and calcitonin in normal and pathological conditions are presented in Tables 1–3. As can be seen from Tables 1–3, the biological (physiological and pathophysiological) functions of parathyroid hormone and calcitonin have a wide range. Research of the relationship between the ULD and changes in the functions of the two main hormones regulating the mineral homeostasis - PTH and calcitonin (CT). The kidney is the target organ and the main site of their metabolism and elimination for PTH and CT. This allowed to demonstrate significant changes in the level and circadian rhythm of their content in the blood in comparison with the indices in the group of healthy kids of the same age (10–15 years). In addition, there was a change in the ratio of PTC/CT in individual daily periods (Table 1). It is known that PTH is produced in the parathyroid glands (in response to hypocalcemia) and vitamin D, which turns into a hormone in the kidneys (1,25 (OH)2D3) synergistically act on the exchange of calcium, phosphate, magnesium metabolism: increase Ca in the blood and reabsorb it in the kidneys, and PTH in addition reduces the reabsorption of phosphate in the tubules of the kidneys. However, PTH increases Ca in blood by increasing bone resorption, while vitamin D3 increases Ca in the blood due to increased adsorption in the intestine (reducing bone resorption at the same time). In addition, PTH in the norm potentiates the hydroxylation of vitamin D3 in the kidneys to form its hormonal form.

The opposite effect on calcium metabolism is caused by thyreocalcin (TCT), a hormone which is secreted in parafollicular C-cells of the thyroid gland in response to hypercalcemia, and it is suppressed the resorptive effect of osteoclasts on the bone. As a result, TCT reduces hypercalcemia and increases excretion of both Ca and phosphate in the kidneys. Thus, both PTH and TCT increases the excretion of phosphates. TCT as well as PTH is rapidly metabolized in the kidneys (and in the liver), the time of their circulation in the blood does not exceed 5–7 min (PTH) - 10 min (TCT). The sign of increased activity of the parathyroid gland is an increase in the activity of xanthine oxidase. The increase in xanthine oxidase activity in serum with an increase in PTH was observed in kids with USD: PTH 6.8 ± 0.1 pmol/l, calcitonin 9.0 ± 1.2 pg/ml and xanthine oxidase 554 ± 41 mmol/L/min. at a rate of 04.0 ± 0.3 pmol/l, PTH), 1.0 ± 0.1 pg/ml (calcitonin) and 120 ± 11 mmol/L/s (xanthine oxidase), respectively. This dependency was tested in an auto-experiment on four adult authors: With the injection of 20 units of PTH subcutaneously, a 6- to 8-fold increase in xanthine oxidase activity was observed after 2 h and 2–4 times increase after 24 h after PTH injection.
<table>
<thead>
<tr>
<th>Object</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>PTH: Increase of the synthesis in parathyroid glands in response to a decrease of calcium in the blood&lt;sup&gt;2,7,10,12,38&lt;/sup&gt;</td>
<td>Increased osteoclast activity, bone resorption, increased Ca and phosphate levels in the blood, increased activity of alkaline phosphatase, collagenase, xanthine oxidase.</td>
</tr>
<tr>
<td>PTH: Circulation in the blood</td>
<td>4–5 min.</td>
</tr>
<tr>
<td>PTH and kidney&lt;sup&gt;1,7–9,11,22,40,41&lt;/sup&gt;</td>
<td>Increased reabsorption of Ca, reduced reabsorption of phosphate, increased excretion of hydroxyproline, phosphate and magnesium in the urine. Activation of the hydroxylation of D&lt;sub&gt;3&lt;/sub&gt; to 1,25(OH)&lt;sub&gt;2&lt;/sub&gt;D&lt;sub&gt;3&lt;/sub&gt;, reduction of acidogenesis, increased vasopressin, arterial pressure (AP), excretion of K, Na, polyuria. Reduction of Reduction level of glomerular filtration (LGF), concentration function, inhibitors of crystal formation.</td>
</tr>
<tr>
<td>PTH: Effect on purine metabolism&lt;sup&gt;2,13,17–19,42–44&lt;/sup&gt;</td>
<td>Activated by PTH xanthinoxidase (XO) dramatically increases the synthesis of active forms of oxygen (AFO) and uric acid, which itself becomes a pro-oxidant factor in elevated blood concentrations (more than 0.25 μmol/l) and causes hyperuratermia and hyperuraturia and easily precipitates in acidic pH urine. A sharp increase in peroxidation processes often leads to gene mutations in somatic cells (lymphocytes) in the hypoxanthine–guanine phosphoribosyl transferase (HPRT) gene, which are not inherited. As a result, purine nucleotide synthesis is reduced and the content of xanthine and hypoxanthine - substrates for XO that synthesizing uric acid is significantly increased in the blood. This path is especially characteristic for kids in regions with hot, dry climate (heat shock) in the summer when they have a massive release of large aggregated crystals of uric acid of a varied caliber in their urine. During this period, all these kids show a significant increase in the activity of XO.</td>
</tr>
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### Table 2: Functions of parathyroid hormone. Norm and pathology (part II).

<table>
<thead>
<tr>
<th>Object</th>
<th>Effect</th>
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<tbody>
<tr>
<td>PTH: Membrane-destabilization, peroxidation processes&lt;sup&gt;2,13,14,25,32,34,39,45&lt;/sup&gt;</td>
<td>A sharp increase in peroxide processes under the action of activated by PTH xanthine oxidase with the formation of active forms of oxygen (AFO) causes damage of the phospholipids of cell membranes with the release of a large number of oxalate’ precursors (ethanolamine and serine), which are easily metabolized into oxalate. This process is especially active in the phospholipids of the apical membranes of the renal epithelium (the formation of oxalates “in situ”). There is a mopping of the apical membranes and their accumulation in the lumen of the dilated tubules with the deposition of calcium. The excretion of lipid (phospholipid) mediators of inflammation increases.</td>
</tr>
<tr>
<td>PTH: Bioenergetic metabolism&lt;sup&gt;2,11–14,25,39&lt;/sup&gt;</td>
<td>The increase of peroxide processes has a negative effect on the structural and functional state of mitochondria with a decrease in the synthesis of ATP, a violation of the functions of the tricarboxylic acid cycle (Krebs), which causes a deficit in the products of bioenergetic processes: inorganic pyrophosphates and citrates—inhibitors of Ca-oxalate and Ca-phosphate crystals in the urine. Damage of the mitochondria structure is accompanied by the release of calcium and phosphate from the “calcium depots” of the mitochondria, increasing the content of crystalloids in the urine. Decrease of the ATP synthesis in the renal epithelium is a risk factor for the disruption of energy-dependent transport in the renal tubules for Ca, Pi, amino acids, proteins and their concentration increasing in the urine.</td>
</tr>
<tr>
<td>PTH: The daily rhythm level in the blood&lt;sup&gt;40,46&lt;/sup&gt;</td>
<td>There was a significant deviation of the circadian periodicity of PTH in the blood under the ULD: there was no difference in the level of the hormone in the night and daytime with bilateral recurrent nephrolithiasis.</td>
</tr>
<tr>
<td>PTH: Endogenous intoxication in ULD and hyper-parathyroidism&lt;sup&gt;22,25,39,47–49&lt;/sup&gt;</td>
<td>Increased PTH in the blood and its numerous effects on metabolic processes (mineral, bioenergetic, oxidative, on kidney function, gene mutations) cause the increased endogenous intoxication in the blood, conformational rearrangement of proteins with a risk of autoimmune inflammation.</td>
</tr>
</tbody>
</table>
Table 3  Functions of calcitonin. Norm and pathology.

<table>
<thead>
<tr>
<th>Object</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin (CT): metabolism of CT&lt;sup&gt;5,25,38,50–53&lt;/sup&gt;</td>
<td>The synthesis of CT in the thyroid gland increases with hypercalcemia. Ca in the blood decreases and the excretion of Ca and phosphate in urine increases under hypercalcemia.</td>
</tr>
<tr>
<td>Biological effect&lt;sup&gt;5,25,38,50–53&lt;/sup&gt;</td>
<td>The activity of osteoclasts is decreased and the osteoblasts are activated (bone resorption decreases). The circulation time in the blood is 5–10 min. The absorption of Ca reduces in the intestine. It is metabolized in the kidney till the inactive peptides, which are quickly excreted in the urine.</td>
</tr>
<tr>
<td>Biological effect&lt;sup&gt;5,25,38,50–53&lt;/sup&gt;</td>
<td>cAMP is increased in osteoclasts, CT is acted on the central nervous system (pituitary gland), blood pressure is reduced. CT has anti-inflammatory, analgesic effect, it accelerates the healing of wounds and fractures, and it has a uricosuric effect. Glucose tolerance is reduced in large levels CT. There is an increase in CT in acute and chronic renal failure. The calcitonin gene-related peptide (CGRP) is an anti-inflammatory mediator in the lungs in bronchial asthma.</td>
</tr>
</tbody>
</table>

Signs of increased activity of the parathyroid gland is an increase in the activity of xanthine oxidase. An increase in xanthine oxidase activity in serum with an increase in PTH was observed in children with ICD: PTH 6.8 ± 1.0 pmol/L, calcitonin 9.0 ± 1.2 pg/ml and xanthine oxidase 554 ± 41 mmol/L/min. at a rate of 4.0 ± 0.3 0 pmol/L (PTH), 1.0 ± 0.1 (calcitonin) and 120 ± 11 (xanthine oxidase), respectively. This dependency was tested in an auto-experiment on four adult authors. A 6- to 8-fold increase in xanthine oxidase activity was observed in 2 h and 2–4 times at 24 h after the administration of 20 U of PTH subcutaneously.<sup>40</sup>

Furthermore, there was an increase of excretion of peptides-bound and free hydroxyproline (metabolites of collagen), as well as cystine and phosphate in the urine. This occurs not only because of the exit from the bone of mineral salts, but it is also due to collagen breakdown. Collagen degradation occurs under the influence of collagenase, its activity increases under the influence of PTH<sup>1,10,12,16,21,39</sup>.

Peptides-bound oxyproline as a part of the destroyed collagen when bone is resorbed under the influence of PTH, is released in increased amounts with calcium nephrolithiasis. It can serve as one of the nucleating components, most often the crystals of calcium oxalate are deposited on these components<sup>8,14,17,39</sup>. The anomalies of the structure and function of the kidneys can lead to the delay of these hormones in circulation and prolong their effect on the mineral exchange under stress due to the fact that the kidneys are not only the target organ for the action of PTH and CT, but also the place of their degradation to inactive peptides and the removal of fragments<sup>1,2,7,11,22,38</sup>. Violation of the balance between PTH and CT can also be a risk factor for the ULD and the crystallization of calcium and phosphate in the urine. In addition, normally hormones provide a circadian periodicity of functioning of the transport systems of cells in the tubular kidney epithelium, which is disturbed by ULD<sup>13,38,39,49</sup>.

In children with stones in the ureters, bladder or in two kidneys, the level of CT in the blood is approximately the same day and night, and in children with a stone in one kidney it is 1.6 day higher than at night. The content of PTG in the blood of healthy children at night is 2.1 times lower than in the daytime. The PTG content in the blood of children with stones in the bladder is 14 times lower, and with stones in the ureters is 2.5 times lower at night than during the day. PTH content in the blood of children with stones in one or two kidneys is the same both day and night.<sup>37</sup>

In children with stones in the ureters, bladder or in two kidneys, the level of CT in the blood is approximately the same day and night, and in children with a stone in one kidney it is 1.6 day higher than at night. The content of PTG in the blood of healthy children at night is 2.1 times lower than in the daytime. The PTG content in the blood of children with stones in the bladder is 14 times lower, and with stones in the ureters is 2.5 times lower at night than during the day. PTH content in the blood of children with stones in one or two kidneys is the same both day and night.<sup>37</sup>

**RENAL RISK FACTORS OF THE ULD**

Along with the genetic and hormonal risk factors of the ULD, according to all researchers opinion, such factors include anatomical abnormalities of the urinary system and disemembriogenesis of the renal tissue<sup>3,16,39,53–55</sup>. Among the anatomical anomalies the most often found are: One- and two-sided hydronephrosis, constriction (stenosis) of the ureteropelvic anastomosis (pass), an additional vessel, a narrowing of the distal ureter, a doubling of the kidney, a violation of urodynamic<sup>55–57</sup>. Constriction (stenosis) of the tubal-ureteric anastomosis. Histomorphologic examination of the biopsy specimens in all kids with ULD revealed abnormalities in the renal histostructure, the intensity of which correlated with the severity of the course of the disease and the age of the patients (the changes were more pronounced among younger kids in the age of 3–7 years old). All the patients noted changes in the epithelium of the convoluted tubules with desquamation of the apical...
membranes, with dilated tubular lumen and the deposition of calcium in it. Kids with ULD of older age (10–15 years old) experience pronounced interstitial sclerosis, a thickening of the stroma interlabels between the tubules (Henle loop) with diffuse interstitial hypercellularity in the medulla of the kidney. A significant number of anomalous (underdeveloped), sclerosed glomerulus, ischemia of the cortex of the kidney tissue is detected. With bilateral recurrent nephrolithiasis, embryonic sclerized renal elements, lympho-histiocytic infiltration are more common. Lympho-histiocytic infiltration is more common under bilateral recurrent nephrolithiasis, embryonic sclerized renal elements. The same changes in renal tissue are detected with primary hyperparathyroidism: focal atrophy and tubular necrosis, signs of chronic inflammation in the interstitium and focal sclerosis of the glomeruli. Thus, the ULD is characterized by the following: Diffuse numerous signs of renal dysembryogenesis, cystic tubule changes, pronounced destruction and atrophy of the tubular epithelium, calcium deposition in the lumen of the tubules, lympho-histiocytic infiltration and sclerosis of the renal elements.

Besides the genetic, anatomical and morphological risk factors of the ULD, three theories of stone formation that take into account changes of contents in the lumen of the renal tubules, including the following: (1) Increased precipitation and crystallization of calcium and phosphate at their increased concentration in the urine; (2) matrix formation - nucleation from a number of organic substances, including microproteins, collagen, mucopolysaccharides and others; (3) lack of inhibitors of crystal formation (citrates, inorganic pyrophosphates and others).

The kidney stones with increasing PTH by chemical composition are more often calcium/oxalate, and less often calcium/phosphate, or magnesium/phosphate. According to our data and a number of authors’ opinion, urinary excretion of increased amounts of uric acid does not contradict the diagnosis of hyperfunction of the parathyroid glands.

However, practically there are no discussions of the sources, the causes of the appearance of such risk factors in the body as an increase in the content of calcium and other crystalloids, matrix substances in the tubules, reduction of crystal formation inhibitors or the appearance of its promoters. The periodic appearance in increased amounts of these changes with ICD risk is undoubtedly inherent to stresses, adaptation to which in predisposed people to nephrolithiasis is reduced.

Normally, the nonspecific stress-response of cells, organs and systems and the co-ordination of these functions in the whole body are developed to adapt to living conditions, increase its resistance and prevent disease in response to any significant changes in the environment and underlies the adaptation-disadaptation of the organism to changing conditions. Such conditions include physical overload, altitude or immobilization hypoxia, heat shock, psychoemotional, emotional-pain shock and others. Common signs of disadaptation are hypersensitivity to external and internal adverse effects, polygenic nature of pathology, small mutations including somatic cells (lymphocytes), impaired immune functions, increased frequency of rare forms of polymorphic proteins (HLA), autoimmune pathology, signs of energy deficiency, increase processes of peroxidation with the formation of lipid mediators of inflammation and its chronicization, a violation of the endocrine glands function. These features are characteristic of chronic stress.

In addition, the leading exogenous causes of the increase in the frequency of ICD in recent years is the relative increase in the percentage of elderly and older population groups, as well as nutritional mistakes, especially among those living in the risk zones of the ICD.

The difference in responses to damaging agents can depend on such factors as slowing the rate of antioxidant protection, weak antioxidant protection (30% of the population) from toxic oxygen radicals, slow acetylation reaction. These options under adverse conditions can lead to disruption of adaptation. For example, hypersensitivity to oxidative stress and toxic oxygen radicals, hyperthermia, hypoxia leads to gene mutations in somatic cells that are not inherited but underlie chronic diseases, secondary immunodeficiency disorders of mineral metabolism in cells, for example, under ICD, and also - to chronic stress.

AUTOIMMUNE INFLAMMATION

THE ENDOGENOUS INTOXICATION

A powerful risk factor for aseptic autoimmune inflammation in the kidneys under ULD is the endogenous intoxication due to the numerous effects of PTH on metabolic processes: mineral, oxidative, bioenergetic, bone, effects on kidney function, the effect on genetic, endocrine glands function, inflammation and its chronicization, a violation of the metabolism, signs of energy deficiency, increase processes of peroxidation with the formation of lipid mediators of inflammation and its chronicization, a violation of the endocrine glands function. These features are characteristic of chronic stress.

This mechanism of the development of aseptic autoimmune inflammation of the renal tissue can explain...
the occurrence, but also the chronicization of inflammation as a result of chronic oxidative stress and the accumulation of endogenous toxicants in the body\textsuperscript{18,63}.

Confirmation of the risk of aseptic inflammation in the kidneys is a decrease in the ability of urine to lyse fibrin in the fibrin film, which indirectly indicates a decrease in the fibrinolytic ability of urine, and increase fibrinogene excretion is the risk of inflammation and the formation of calculus (fibrinolytic reaction of urine). A substantial change in this index was revealed in comparison with the control during different periods of the day, more noticeable among kids with concrements in the kidneys, and reflecting the risk of an inflammatory response\textsuperscript{19,46,59,62}.

**STRESS**

**DISADAPTATION**

However, practically there are no discussions of the sources, the causes of the appearance of such risk factors in the body as an increase in the content of calcium and other crystalloids, matrix substances in the tubules, reduction of crystal formation inhibitors or the appearance of its promoters\textsuperscript{13,14}. The periodic appearance in increased amounts of these changes with ULD risk is undoubtedly inherent to stresses, adaptation to which in predisposed people to nephrolithiasis is reduced (disadaptation)\textsuperscript{67–70}.

Normally, the nonspecific stress-response of cells, organs and systems and the co-ordination of these functions in the whole body are developed to adapt to living conditions, increase its resistance and prevent disease in response to any significant changes in the environment and underlies the adaptation--disadaptation of the organism to changing conditions\textsuperscript{17,32,33,36,37,67,68}.

Such conditions include physical overload, altitude or immobilization hypoxia, heat shock, psychoemotional, emotional-pain shock and others. Common signs of disadaptation are hypersensitivity to external and internal adverse effects, polygenic nature of pathology, small mutations including somatic cells (lymphocytes), impaired immune functions, increased frequency of rare forms of polymorphic proteins (HLA), autoimmune pathology, signs of energy deficiency, increase processes of peroxidation with the formation of lipid mediators of inflammation and its chronicization, a violation of the endocrine glands function\textsuperscript{7}. These features are characteristic of chronic stress\textsuperscript{17,12,33,36,37,67,68}.

In addition, the leading exogenous causes of the increase in the frequency of ULD in recent years is the relative increase in the percentage of elderly and older population groups, as well as nutritional mistakes, especially among those living in the risk zones of the ULD\textsuperscript{18,47,52}.

The difference in responses to damaging agents can depend on such factors as slowing the rate of antioxidant protection, weak antioxidant protection (30% of the population) from toxic oxygen radicals, slow acetylation reaction. These options under adverse conditions can lead to disruption of adaptation. For example, hypersensitivity to oxidative stress and toxic oxygen radicals, hyperthermia, hypoxia leads to gene mutations in somatic cells that are not inherited but underlie chronic diseases, secondary immunodeficiency, disorders of mineral metabolism in cells\textsuperscript{47}, and also--to chronic stress, in that number for nephrolithiasis\textsuperscript{59–61,65,66}.

**OXIDATIVE STRESS**

One of the characteristic features of chronic stress is oxidative stress with the accumulation of significant amounts of toxic active forms of oxygen (AFO: superoxide anions, peroxides, free radicals, lipid peroxides) combined with a decrease in the function of antioxidant protection\textsuperscript{29,64,71–73}. The antioxidant protection system (APS) includes both enzymes and non-enzyme low-molecular compounds. The enzymes of APS include superoxide dismutase (SOD), catalase, glutathione peroxidase, glutathione reductase, glutathione-S-oxidase and others\textsuperscript{45,64}. Non-enzymatic components of APS include reduced glutathione, vitamins A, E, C, carnosine, uric acid in physiological quantities and others\textsuperscript{64,74}. Hormonal stimulation of oxidative processes takes place in all in three phases of adaptation to stress\textsuperscript{65,66}. Protective mechanisms against oxidative stress are most active in the phase of resistance (stability phase) and they are reduced in the phase of depletion, when peroxide products and other endogenous toxicants, are especially actively accumulated, causing the risk of inflammation, destructive processes, a decrease in bioenergetics, apoptosis of mitochondria and the cell as a whole, violation of calcium phosphorus metabolism\textsuperscript{16,64,66,70,72,74}.

Among the protective mechanisms of oxidative stress is the ability of the organism, including the kidneys, to eliminate not only peroxidation stimulants (PTH), but also its metabolites: AFO, lipid mediators of inflammation, products of lipid peroxidation (LP)\textsuperscript{75}. First of all the accumulation of AFO is accompanied by peroxide damage of phospholipids of cell membranes, including mitochondrial and endoplasmic with violation of cellular homeostasis of calcium\textsuperscript{9,46,69,71,72,74}. Genetic and congenital (primary) functional and structural kidney abnormalities reduce the protection from oxidative stress, disrupt the transport of calcium and phosphate in the renal tubules, particularly due to a delay in the circulation of PTH, calcitonin, and various endogenous toxicants, which is detected in kids with bilateral and unilateral concrements in the kidneys, in contrast to healthy kids and patients with concrements in the bladder\textsuperscript{18,39,70–72}. The oxidative stress in the kidneys is accompanied by a powerful membrane-destructive process due to lipids of the brush margins and other membranes of the tubular epithelium, a decrease in the activity of energy-dependent tubular transport systems (including calcium and phosphate), and also by...
an increase in the synthesis of oxalates from the components of collapsing phospholipids (ethanoamine, serine)\textsuperscript{19,72}. As a result of long-term observations of patients with calcium nephrolithiasis, it was shown that the oxidative stress under disadaptation to negative effect is characterized by marked dismetabolism with disruption of the circadian periodicity and the maintenance of calcium in the blood of regulating hormones (PTH, CT), and by increased LDH activity, alkaline phosphatase (AP), XO, decrease of SOD, catalase, as well as lipidaemia and increased uric acid in the blood. Besides, a whole complex of pathological features is revealed in urine with calcium nephrolithiasis: large aggregated crystals of calcium oxalates and/or phosphates, and also - magnesium phosphate (struvite) and periodically uric acid mostly without significant increase in the excretion of crystal formers. The following things are noted: A decrease in inhibitors of crystal formation (citrate, inorganic pyrophosphate), an increase in the excretion of markers of endogenous intoxication - medium molecules, microproteins overloaded with trace elements, lipid hydroperoxides and other peroxidic compounds (H\textsubscript{2}O\textsubscript{2}), Lipiduria (including lipid mediators of inflammation), antioxidant activity decrease and fibrinolytic activity of urine, fermenturia (lactate dehydrogenase, gamma-glutamintransferase, gamma-glutamtransferase, AP, phospholipase A and C), signs of aseptic or infectious inflammation are typical\textsuperscript{19}.

CONCLUSION

Usually calcium nephrolithiasis develops in individuals who have a number of genetic and congenital disorders of the structure and function of the kidneys (polymorphism), reducing their homeostatic ability to the organism adaptation to the acute and chronic negative effects (stresses). Each phase of stress is characterized by an increase in the activity of oxidative processes, the activation of oxidases (xanthine oxidase), whose action goes beyond physiological norms by intensity and exposure duration, especially when disadaptation with the formation of toxic active forms of oxygen, the development of “oxidative stress”.

The activity of xanthine oxidase under oxidative stress is stimulated not only by the parathyroid hormone, but also by products of peroxide damage to the synthesis of purine nucleotides (xanthine, hypoxanthine) with the formation of uric acid.

Active forms of oxygen, stimulated by xanthine oxidase (and other oxidases), cause a membrane-destructive process in the apical (brush border) membranes of the renal tubular epithelium, in the membranes of its mitochondria and endoplasmic reticulum with disruption of cellular homeostasis of calcium and the release of calcium from the mitochondrial depot (the risk of apoptosis). The synthesis of macroerges and inhibitors of the calcium crystals formation (inorganic pyrophosphates, citrates) and the inhibition of energy-dependent transport systems, including for Ca and phosphates, the main components of urinary stones, is reduced.

Acidified phospholipids of cell membranes are a source of synthesis of lipid mediators of inflammation as well as modified by products of the peroxidation of microproteins with cytotoxic properties and the risk of autoimmune inflammation.

Active forms of oxygen and numerous products of their activity (lipid, protein, amino acid, homocysteine, middle molecules) are endogenous toxicants, creating additional conditions for toxic damage of the structure and the kidneys function: fermenturia, oxaluria, crystalluria.

The increases of Ca and phosphates with a decrease of the inhibitors synthesis in the urine contributes the formation of large aggregated crystals settling on various organic products of destructive processes and create a high risk of stone formation in the kidneys.

The presence of chronic oxidative stress signs in the urine is a relevant reason of the inclusion in the traditional complex of conservative ULD treatment, its recurrences and secondary stone formation, active antioxidants (mexidol), detoxicants and immunomodulators (polyoxydionium), inhibitors of calcium crystals formation (bisphosphonates, citrates), medicines that reduce stress.

REFERENCES


