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Functional state of kidneys in patients with clinical manifestations of hypothyroidism

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Abstract: The research *goal* is to study the function of kidneys and serum concentration of immunoregulatory cytokines (IL-1ß, IL-6, IL-8, IL-10) in conditions of thyroid hormone deficit. *Methods* – The character and severity of renal dysfunction were investigated in patients with primary hypothyroidism. The clinical examination included study of serum concentration of creatinine, urea level, potassium and natrium in blood serum, blood and urine analyses, total cholesterol, high and low density lipoproteins, daily microalbuminuria, the performing of Zimnitsky test, urinary excretion of chemokines MCP-1, RANTES, rate calculation of glomerular filtration, thyroid hormone state. *Results* – The renal function in clinical hypothyroidism without concomitant kidney disturbances was characterized by normal parameters of the concentrational kidney function, reduction of glomerular filtration rate, increased of serum creatinine, urea excretion level of chemokine MCP-1 and level of cytokines IL-6, IL-8 in patients with autoimmune hypothyroidism were revealed. *Conclusion* – It was revealed that autoimmune hypothyroidism effected balance disturbance of cytokine-producing activity of Th1 and Th2 type therefore developing autoimmune state and disease progression.

Keywords: thyroid hormones, renal function, speed of glomerular filtration

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Introduction

Primary hypothyroidism is frequent syndrome, which prevalence is 0.5–2.0% among women and around 0.2% among men [1]. According to several authors, recently the number of patients with autoimmune deceases with hypothyroidism increased by 2.1% [2]. Deficit of thyroid hormones leads to various pathologies of the whole body, including violation of kidneys [3]. Data about the character, mechanisms of occurrence, clinical significance of renal dysfunction in case of overt hypothyroidism (OH) are infrequent and controversial, what often leads to unjustified diagnosis of chronicle pyelonephritis in case of hypothyroidism patience [4]. According to some authors [3, 4] there is so-called hypothyroid tubulopathy, which includes violation of osmoregulation, ion regulation and acid renal excretory function. In case of overt hypothyroidism patients a decrease in renal blood flow and speed of glomerular filtration was revealed as well [4, 5].

Recently a lot of attention is paid to the immunological mechanisms involved in kidney damage [5]. The results of recent research prove that the cellular immune system may cause glomerular damage [5-7]. The study of renal function in terms of thyroid hormones deficit with autoimmune process in thyroid gland and without it presents a certain interest.

The purpose of the work is a clinical and functional analysis of kidney condition and the reveal of immunological characteristics in case of the patients.

Material and Methods

In a cross-sectional cohort study there were 80 primary overt hypothyroidism patients included. The inclusion criteria were: patients' age from 18 to 50 years, first identified or decompensated primary hypothyroidism. The presence of any acute chronic kidney disease, arterial hypertension II, III stage, coronary artery disease were exclusion criteria.

The diagnosis was established on the basis of complaints, anamnesis, characteristic clinical picture of overt hypothyroidism and was confirmed by the results of hormone studies (thyroid-stimulating hormone above 4 mME/L and free thyroxin below 10.3 pmol/l). The comparison group consisted of 52 people without the dysfunction of thyroid gland, comparable by sex and age.

A survey of all persons included laboratory and instrumental methods. Anamnestic data of all individuals was analysed. Required laboratory parameters: complete blood count, blood chemistry (total protein, glucose, total cholesterol, low-density lipoproteides (LDL)), urinalysis, cumulative samples (Nechiporenkos sample).

Mandatory instrumental examination included the measurement of blood pressure, ultrasound study of the urinary system, Doppler ultrasound of renal blood flow.

To assess the nature of renal functions disorders a special methods of research were used: 1) the methods to identify the condition of glomerular apparatus (Rehbergs sample); proximal tubules (urinary excretion of glucose, daily microalbuminuria); distal tubules (ability to osmotic concentration (Zimnitskys

sample), 2) methods that detect total violation of summary of the nephron (Definition of serum levels of creatinine, urea, potassium and sodium ions), also a velocity calculation of glomerular filtration rate (GFR) was made by the MDRD formulas.

To determine serum levels of thyrotropin hormone (TTH), free thyroxine (T4), triiodothyronine (T3), thyroid peroxidase antibodies (TPA), ELISA kits produced by "Alcor Bio" (St. Petersburg) were used on unit by StatFax firm (USA, 2003).

For assessment of cytokines: interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), growth factor of vascular endothelial (VEGF) in the serum used commercial diagnostic kits test systems IL-1β IL-6, IL-8, IL-10, VEGF (CJSC "Vector-Best", Novosibirsk firm, Russia), for the determination of urinary excretion of the chemokine MCP-1 (chemo-attractive protein-1 monocytes) by ELISA analysis used reagents by Bender MedSystems firm (Austria), to study RANTES (chemokine expressed and secreted by T-cell with activation) – Biosource (Belgium). Investigations were carried out on the basis of Saratov State Medical University.

Statistical processing was produced by Statistica 6.0 software package using non-parametric statistical criteria. When comparing independent groups by variables

Fishers test (Z) was used. Data are presented as Me (25%, 75%) (median, interquartile range). The critical level of significance when testing statistical hypotheses took 0.05.

Results

In order to identify the characteristics of renal function in presence of the autoimmune process, all patients with overt hypothyroidism (n=80) were divided into two groups: the first group consisted of 48 patients chronic autoimmune hypothyroidism (CAH), the second – 32 patients with postoperative hypothyroidism (PH) emissions. A comparison group consisted of 52 people, without thyroid gland dysfunction, matched by sex and age.

Metabolic, intercurrent and hemodynamic risk factors facilitates onset and progression of renal dysfunction under thyroid hormone deficiency.

Serum levels of urea in the group patients with CAH significantly exceeded these figures in comparison to the control group: urea - 5.7 (4.3, 6.4) and 3.8 (3.6, 4.9) mmol/L (p=0.015); similar trend was observed in the group of patients with PH: 5.1 (4.0, 6.1) and 3.8 (3.6, 4.9) mmol/L (p=0.04). In this case, the median of this indicator in both groups of patients exceeded the upper boundary of appropriate reference interval (8.3 mmol/L for urea) (*Table* 1).

Despite the fact that the level of serum creatinine in Rothko's blood was within the reference interval (males 123.7 mcmol/L, women 97.2 mcmol/L for creatinine), showed statistically significant differences in patients with CAH compared to the control group: 83 (72, 90) and 70 (66, 80) mcmol/L (p=0.03); similar was observed in case of patients with PH compared to controls: 85 (70, 98) and 70 (66, 80) mcmol/L (p=0.04). In this case, patients with CAH level in three patients creatinine greater than 110 mcmol/L, and all patients of the group with PH did not exceed 100 mcmol/L.

The level of potassium in blood serum of patients with hypothyroidism and in clinically healthy individuals was within the normal range and not significantly different: in the CAH group: 4.6 (4.2, 4.8) and 4.75 (4.5, 4.9) mmol/L (p=0.18); in the group with PH: 4.5 (4.0, 5.03) and 4.75 (4.5, 4.9) mmol/L (p=0.31). When studying the levels of sodium in the blood serum in case of both groups of patients with hypothyroidism, it was within the reference range (135-145 mmol/L sodium), but the median concentration of sodium ions in both groups statistically differed significantly compared to control: in CAH group: 137 (134, 140) and 142 (141, 144) mmol/L, respectively (p=0.0001); in the group with PH: 136 (135, 140) and 142 (141, 144) mmol/L (p=0.0001).

Along with that, the calculation of GFR by MDRD formula by sex, age and body weight an insignificant decrease was identified, in the group of patients with CAH to 79.41 (68.33, 91.65) mL/min/1.73 m^2, was a statistically significant difference on the indicator to the control group: 107.96 (94.14, 112.68) ml/min/1.73 m^2, (p=0.02); in case of PH patients there was as a decrease in GFR: 84.81 (71.07, 95.28) compared to control 107.96 (94.14, 112.68) ml/min/1.73 m^2, (p=0.02).

In the patients with CAH (n=48) marked reduction of renal filtration function would correspond to I-II stages of chronic kidney disease (CKD) on National Kidney Foundation, 2002 criteria. However, the assessment of the appropriate stage of CKD was not carried out, as the identification of CKD symptoms kidney damage (structural or functional abnormalities) is set when it is lasting 3 months or more.

In assessing the results of the urinalysis study (protein, glucose) abnormalities were not detected. During the ultrasound studies of renal Doppler ultrasound renal blood flow pathology were not identified.

Total cholesterol (reference interval is 3.63-5.20 mmol/L) were determined by enzymatic colorimetric method on the biochemical photometer StatFax 1904 + (Awareness Technology, USA). We also investigated the level of LDL. Reference interval for LDL is 0.0-3.4 mmol/L.

The total cholesterol level study showed a significant increase of the indicator in two groups of patients with hypothyroidism compared with a group of healthy individuals: in patients with CAH: 5.8 (5.2, 6.2) and 4.9 (4.8, 5.2) mmol/L, (p=0.01); in patients with PH: 5.7 (5.4, 6.1) and 4.9 (4.8, 5.2) mmol/L, (p=0.015). In this case, the median of this index in both groups of patients exceeded the upper limit of the corresponding reference interval.

A similar trend was observed in the groups of patients with hypothyroidism on the level of lipoproteins of low density compared to healthy individuals: a group of patients with CAH: 3.66 (3.2, 3.88) and 2.79 (2.49, 2.98) mmol/L, (p=0.001); patients with PH: 3.82 (3.60, 4.06) and 2.79 (2.49, 2.98) mmol/L, (p=0.001).

This distribution levels of total cholesterol and LDL levels corresponds with the literature on the fairly high prevalence dyslipidemia in case of patients with hypothyroidism [3-5].

The results showed that progression of renal dysfunction in case of the overt hypothyroidism is facilitated by the presence of risk factors in patients - hyperlipidemia and hyponatremia, more severe in patients with CAH.

It is known that cytokines play an important role in the pathogenesis of CAH. However, the question of the activity of Th1 cells and Th2 cell is poorly understood, because at different stages of development of the immunological process a switch from one type of immune response to the other may occure [8]. If one considers CAH from a point of view of the regulation of immune disorders, given increasing the function of T-helper cells and the initiation of a response from the autoreactive B-cells to the self-antigens even with the normal function of T-suppressor cells, are

expected to increase pro- induction of some cytokines of T-helper cells in autoimmune thyroiditis [8, 9]. Most of the authors in their studies show a predominance of Th2-cells and increased production of IL-6 and IL-10 peripheral mononuclear cells by CAH [7, 8]. To evaluate the activity of cells and Th1-Th2-cell proinflammatory cytokines (IL-1β, IL-6, IL-8) and anti-inflammatory cytokine (IL-10) levels were studied.

IL-1β – lymphocyte-activating factor, the endogenous pyrogen, leukocyte endogenous mediator, has two forms: IL-1α and IL-1β, is a group of pro-inflammatory cytokines, and it shows its biological properties by activating T- and B- lymphocytes, macrophages, and by increasing cell adhesion and proliferation activity, acute phase reactions, and fever [5, 6].

IL-6 is produced by activated monocytes and macrophages, endothelial cells, fibroblasts, activated T-cells, and a number of non-immune cells. The main effect of IL-6 is associated with its participation in the differentiation of B-cells, their maturation and transformation into plasma cells secreting immunoglobulins-regulating. To the variety of cell sources of products and target the biological effects of interleukin-6 (IL-6) is one of the most active cytokine involved in the immune response and inflammatory reaction [7].

IL-8 – neutrophil-activating protein-1, neutrophil-activating factor, an inhibitor of leukocyte, granulocyte chemotactic protein, belongs to the chemokines group and chemotactic effect on all migratory immune cells, activates neutrophils, phylum, regulates the synthesis of IgE by B-cells [6, 8].

IL-10 is anti-inflammatory cytokine, produced mainly by T-helper lymphocytes of type 2. Inhibits the function of T-helper of type 1 and monocytes, reducing production of immunocytokines (gamma-interferon, IL-1β, IL-8) [5, 8].

Among the growth factors, one of the key is vascular endothelial growth factor, which is involved in the induction and regulation of both the normal and pathologically altered angiogenesis-independent, stimulates the proliferation of endothelial cells [10]. At physiological concentrations of vascular endothelial growth factor acts as a factor that ensures the survival of the endothelium [6]. The ability of VEGF to initiate the growth of vessels can be considered as promising tools to improve vascularization of the thyroid tissue, including in areas of activation of apoptosis in thyroid epithelium. Usage of immunohistochemical analysis revealed that in the unaltered cells endothelial growth factor localised in the cytoplasm of the ship, where it is bound. This contributes to the rapid release of the growth factor in the case of cells damage [2, 10]. In addition, hyperproduction growth factor may increase the characteristic of hypothyroidism anemia [5], and therefore is a subject of interest to study the role of vascular endothelial growth factor activity and angiogenesis in Chait and GHGs. Our research in accordance with the criteria included patients without renal disease, which was confirmed by laboratory and instrumental studies, therefore the study of urinary excretion of VEGF is not advisable, since, according to the literature, reflects the severity of the morphological changes in the kidney [10].

Table 1. Clinical-laboratorial and biochemical readings of the patients with chronic autoimmune thyroiditis and post operational hypothyroidism, Me (25%, 75%)

Parameters	*Patients with hypothyroidism*		*Control group (n=52)*
	CAH patients (n=48)	*PH patients (n=34)*	
Age, years	44 (36, 50), p=0.82	48 (38, 50), p=0.36	48 (36, 50)
BMI, m^2/kg	29.2 (24.9, 34.8), p=0.14	29.3 (23.4, 33.2), p=0.08	27.1 (22.9, 31.2)
Creatinine, mcmol/L	83 (72, 90), p=0.03	85 (70, 98), p=0.04	70 (66, 80)
Urea, mol/L	5.7 (4.3, 6.4), p=0.015	5.1 (4.0, 6.1), p=0.04	4.1 (3.6, 4.9)
Total protein, g/L	67 (62, 70), p=0.89	65 (61, 69), p=0.32	66 (64, 72)
Total cholesterol, mmol/L	5.8 (5.2, 6.2), p=0.01	5.7 (5.4, 6.1), p=0.015	5.1 (4.8, 5.2)
LDL, mmol/L	3.7 (3.2, 3.9), p=0.001	3.8 (3.6, 4.1), p=0.001	2.8 (2.5, 3.0)
Potassium, mmol/L	4.6 (4.2, 4.8), p=0.01	4.5 (4.0, 5.0), p=0.31	4.8 (4.5, 4.9)
Sodium, mmol/L	137 (134, 140), p=0.0001	136 (135, 140), p=0.0001	142 (141, 144)
GFR, mL/min (MDRD)	79.4 (68.3, 91.7), p=0.02	84.8 (71.1, 95.3), p=0.57	108.0 (94.1, 112.7)

p – differences credibility in comparison with control group.

Table 2. Immunoregulatory processes readings of the patients with clinical hypothyroidism, Me (25%, 75%)

Parameters	*Patients with hypothyroidism*		*Control group (n=52)*
	CAH patients (n=48)	*PH patients (n=34)*	
IL-1β, pg/mL	4.9 (3.7, 8.9), p=0.16	4.3 (2.9, 6.2), p=0.31	3.6 (2.5, 5.5)
IL-6, pg/mL	13.2 (8.8, 19.6), p=0.001	6.3 (3.1, 9.4), p=0.019	3.7 (1.2, 4.8)
IL-8, pg/mL	11.3 (8.8, 14.6), p=0.01	9.7 (8.0, 12.2), p=0.03	7.4 (6.4, 9.5)
IL-10, pg/mL	12.1 (6.8, 15.5), p=0.001	7.3 (4.6, 8.9), p=0.015	5.4 (1.6, 8.0)
VEGF, pg/mL	51.2 (26.1, 84.4), p=0.005	43.1 (29.9, 74.9), p=0.012	32.3 (18.8, 40.3)

Reference interval of normal values for IL-1β, IL-6, IL-8, IL-10 is 0–10 pg/mL; for VEGF it is 0–40 pg/mL.

p – differences credibility in comparison with control group.

Table 3. The urinary excretion of MCP-1, RANTES chemokines, of the patients with clinical hypothyroidism, Me (25%, 75%)

Parameters	*Patients with hypothyroidism*		*Control group (n=52)*
	CAH patients (n=48)	*PH patients (n=34)*	
CMP-1, pg/mL	167.5 (92.3, 202.6), p=0.004	67.7 (51.2, 144.1), p=0.13	86.5 (69.3, 101.5)
RANTES, pg/mL	4.5 (2.7, 6.5), p=0.61	5.3 (3.8, 6.5), p=0.16	3.9 (2.5, 6.9)

Reference interval of normal values for MCP-1 is 0–100 pg/mL; for RANTES it is 0–10 pg/mL.

p – differences credibility in comparison with control group.

According to several authors, increasing the concentration of VEGF is accompanied by stimulation of endothelial cell proliferation, which are the active producers of IL-1β [2, 7]. In addition, the important role that IL-1β plays in pathogenesis of CAH, which is used for radiator IU lymphoid infiltration of the thyroid, and the only cytokine capable of inducing cell-thyroid receptor expression of apoptosis (Fas-antigen), which is further evidence of the role of this cytokine in the development of autoimmune reactions [8]. We considered it necessary to examine serum levels of this cytokine to identify the likely changes in the relationship of concentrations of IL-1β and VEGF in the OH.

Median, and 25th and 75th percentiles, describes the distribution of the concentration of IL-1β raw knob blood in those with CAH and PH compared to healthy people are not significantly different. In the CAH group, IL-1β was 4.9 (3.67, 8.89) and 3.59 (2.47, 5.45) pg/L (p=0.16); in PH group: 4.29 (2.94, 6.18) and 3.59 (2.47, 5.45) pg/L (p=0.31), is within the Lakh reference value range of indicators (0-10 mg/L), which confirms the absence of time-differences between the examined groups of patients with OH and healthy individuals.

In the group of patients with CAH the increasing level of IL-6 serum was observed and statistically significantly different compared to the control: 13.2 (8.8, 19.6) and 3.69 (1.24, 4.8) pg/mL (p=0.001).

Statistically significant differences were found in the study of IL-8 serum in the group of patients with PH compared with control: 9.7 (8.0, 12.2) and 7.4 (6.4, 9.5) pg/mL (p=0.03). The media in this indicator did not exceed the upper limit of the respective reference interval (*Table* 2). There were statistically significant differences in levels of IL-8 in patients with CAH compared to healthy individuals: 11.3 (8.8, 14.6) and 7.4 (6.4, 9.5) pg/mL (p=0.01). These results give a reason to believe that this chemokine takes an active part in the formation of an autoimmune process in the thyroid, directing antigen-cells, which secrete a range of pro-inflammatory cytokines in the blood of thyroid tissue, leading to the death of thyrocytes, and, apparently, IL- 8 can be used as an early biomarker for the diagnosis of CAH.

Results of the study anti-inflammatory cytokine IL-10 in the serum revealed statistically significant differences in this indicator in patients with CAH compared control: 12.1 (6.8, 15.5) and 5.4 (1.6, 8.0) pg/mL (p=0.001); in patients with PH: 7.3 (4.6, 8.9) and 5.4 (1.6, 8.0) pg/mL (p=0.015). In this case, increase of IL-10 content were only in patients with CAH, in patients with PH this figure correspond to the values of the reference interval.

The content of VEGF in the serum of patients CAH and PH was increased (51.2 (26.1, 84.4) and 43.1 (29.9, 74.9), respectively) and statistically significantly different compared to control 32.3 (18.8, 40.3) pg/mL (p=0.005), (p=0.012). Increase in levels of VEGF in serum is due, apparently, stimulation of angiogenesis in all the hot spots of thyrocytes death. This increase in the level of VEGF was detected in both groups of patients – with CAH and PH. However, PH patients with increasing concentration of the growth factor is less pronounced than in patients with CAH. This fact is probably related to the presence of-zan autoimmune process in patients. CAH and the ongoing destruction of thyrocytes, is accompanied by the release of VEGF.

Based on the above, we can assume the following sequence of "events" occurring in the immune system by CAH: in the initial stages of the disease when the cue is determined by the high-titer antibodies to TPO, but thyroid hormone levels are in the range of reference values in the immune of the patient an increase of IL-1β occurs. Then, as a deficit of thyroid hormones appears, the production of IL-1 is normalised to the age level, while in production exceeds the pro-and anti-inflammatory IL-6, IL-8, IL-10, presumably due the accumulation of IL-1β in the body precedes the stages of the disease.

Data of foreign authors suggests that chemokine (chemoattractant cytokines properties for a wide range of effector cells) play a major role in triggering and maintaining of the autoimmune process [2, 7]. It is noted that thyroid follicular cells are directly related to the development of HAIT as they are capable of inducing chemokines, including RANTES, infiltration trier thyroid tissue immune cells [6]. Literature describes the significant changes in the levels of RANTES in serum and urine in autoimmune diseases in humans when in oxidative stress and other factors violation filtering ability of the kidneys occurs [8]. Simultaneously there is an increase in expression of chemokine receptors, and then production of chemokines themselves including RANTES, in renal tubules and mesenchymal elements of kidneys. As a result, the inflamed sites of kidney migrate a large number of white blood cells, mainly monocytes / macrophages, which secrete a variety of pro-inflammatory cytokines electrons, causing destruction of cells and tubules the surrounding connective tissue elements, leading to glomerular sclerosis and interstitial fibrosis of social tissue [2, 7, 8]. CMP-1 (chemoattractant monocyte protein-1) is produced in the by kidney tube-epithelial cells in response to pro-inflammatory cytokines and proteinuria, in particular IL-1β, tumor necrosis factor-α (TNF-α) and others [7, 9].

Thus, it presents interest to research urinary excretion of RANTES and CMP-1 as a marker ditch the renal changes in the overt hypothyroidism of autoimmune etiology.

The levels of urinary excretion of RANTES in groups CAH patients and healthy people statistically were not significantly different: 4.5 (2.7, 6.5) and 3.91 (2.4, 6.8) pg/mL (p=0.61), no differences were detected and comparing performance in patients with PH and control group: 5.3 (3.8, 6.5) and 3.91 (2.47, 6.89) pg/ml (p=0.16). The obtained data indicates exist about the absence of renal changes in microgravity, as well as the functional

character of violation of the filtration function of the kidney (*Table* 3).

However, a statistically significant increase in urinary excretion of CMP-1 in the group with CAH to 167.5 (92.3, 202.6) pg/mL vs. a group of healthy men: 86.4 (69.3, 101.5) pg/mL (p=0.004), which was not observed in the group of patients with PH: 67.7 (51.2, 144.1) and 86.4 (69.3, 101.5) pg/mL (p=0.13). Increasing concentrations of pro-inflammatory chemokine CMP-1 in the urine of CAH patients due to the influence of IL-6 on the differentiation of B-cells, participating during maturation of B-lymphocytes in the antibody-producing cells.

Discussion

Thus, when there is CAH against high titers of antibodies to TPO identified laboratory symptoms of autoimmune inflammation, which is expressed in reliable increase in serum concentrations of pro-inflammatory cytokines in the serum (IL-6, IL-8) and urine (CMP-1). Maintaining immune homeostasis in the body of patients with MG is provided by complex immune mechanisms of feedback, the most important of which are the activation, proliferation and differentiation of cells, producing pro-inflammatory cytokines and an increase in the concentration of anti-inflammatory mediators, most pronounced in patients with CAH. The balance of pro-and anti-inflammatory cytokines may ultimately be the key point, is caused clinical-mechanical state of the patient at the CAH.

The results showed a number of indicators in patients with PH and CAH and reflecting the functional state of the kidneys and the immune system is significantly different from those of practically healthy individuals.

Currently treatments of hyperthyroidism are directed at correcting the functional state of the thyroid gland, and the value of immune-trope pathogenetic treatment of non-underestimated in clinical practice. This assumption is the determining the development of additional therapies that act on the main elements of the pathogenesis of CAH, that is actively and selectively affecting the immune and endocrine systems, restores the normal course of metabolic processes.

Conclusion

1. Increased serum concentrations of pro-and anti-inflammatory cytokines were detected in patients with overt hypothyroidism compared to clinically healthy individuals.

2. Levels of pro-inflammatory cytokines such as IL-6, IL-8, and the anti-inflammatory cytokine IL-10 were significantly higher in patients with CAH, indicating misbalance cytokine-producing activity of Th1 and Th2 types.

In patients with PH levels of pro-inflammatory cytokines such as IL-6 and IL-8 were also significantly different from healthy individuals, but do not exceed the limit values.

3. A significant increase in the content of the vascular endothelial growth factor levels in patients with CAH compared to healthy individuals was identified.

Conflict of interest

Work is done in the framework of Department of endocrinology (the number of state registration is 01200959764).

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