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GLUCOCORTICOIDS AND MINERALOCORTICOIDS IN BLOOD PLASMA AS MARKERS OF EARLY DIAGNOSTIC ADRENAL CORTICAL TUMORS

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Adrenocortical tumours of the adrenal glands are formed when the cells of the cortical layer grow. The morphological and histological structure of benign adrenal tumours is variable, which complicates their early diagnosis. The study of the levels of hormones in the adrenal cortex along with the analysis of the symptoms of the disease will allow not only to differentiate hormone-producing tumours, but also to predict the direction of metabolic processes, which will make it possible to choose the right treatment regimen and prevent complications from other organs.

***The aim of the study** is to determine the level of cortisol and aldosterone and assess the state of the pituitary-adrenal and renin-aldosterone systems in patients with various types of adrenocortical adenomas.*

***Materials and methods.** The state of the hormonal status of the adrenal cortex was assessed by determining the level of glucocorticoids – cortisol and mineralocorticoids – aldosterone using a direct quantitative enzyme immunoassay. The level of adrenocorticotropic hormone (ACTH) and renin was determined by immunochemical methods using monoclonal antibodies specific for ACTH and renin.*

***Research results.** An increase in the level of cortisol was detected against the background of a decrease in the level of ACTH in patients with cortisol-producing adrenocortical adenomas. It is shown that the aldosteronism we discovered in patients with aldosterone-producing adenomas develops against the background of an unchanged renin level and an increase in the aldosterone/renin ratio.*

***Conclusions.** The development of hormone-dependent adenomas of the adrenal cortex is accompanied by an imbalance in the work of the pituitary-adrenal and renin-aldosterone systems, the direction of changes of which can serve as a criterion for early diagnosis of adrenocortical adrenal adenomas*

***Keywords:** adrenocortical adenoma, adrenal glands, cortisol, aldosterone, adrenocorticotropic hormone, renin*

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1. Introduction

One of the most urgent problems in medicine is the diagnosis and surgical treatment of neoplasms of the adrenal glands, among which adenomas [1] and pheochromocytomas [2] are the most common. These adrenal tumours are formed by the growth of cells of the cortical and medullary layers, respectively, with the formation of focal neoplasms [1, 2].

Benign tumours of the adrenal cortex are characterized by the absence of pronounced symptoms and sizes less than 4 cm. Diagnosis of adrenocortical adenomas is often accidental during instrumental examination [3]. This indicates the morphological and histological variability of benign tumours of the adrenal glands, which accompanies their various symptoms [4]. In this regard, the issue of early diagnosis of adrenocortical adenomas remains open to this day, which requires the search for reliable markers that would allow diagnosing and predicting the development of transformed tissue of the adrenal cortex at the initial stages of neoplasm development.

Since the symptoms of adrenocortical adenomas largely depend on the type of tumour – cortisol-producing adenoma, aldosterone-producing adenoma, adrenocortical incidentaloma [5], determining the level of glucocorticoids (cortisol) and mineralocorticoids (aldosterone) in blood plasma will allow establishing the direction of the tumour process. In addition, dyshormonal changes under the conditions of adrenocortical adenomas may indicate metabolic disorders not only in the hypothalamic-pituitary-adrenal system, but also in the renin-angiotensin-aldosterone system [6]. Violations of biochemical processes in these systems will be accompanied by changes in the physiological characteristics of the human body – disturbances in the regulation of blood pressure and blood volume in the body, changes in sodium and water reabsorption in the kidneys, regulation of carbohydrate metabolism [7]. Hormonally active tumours of the adrenal glands have a wide range of clinical manifestations, while inactive incidentalomas do not manifest themselves [7]. The first step after detecting an adrenal tumour should be to determine its hormonal status.

Hormonal activity of neoplasms of the adrenal cortex is an indication for surgery [8]. Today, the question of the possibility of performing organ-preserving surgical interventions on the adrenal glands, especially when part of the hormone-producing tissue in patients is preserved, is an acute issue. Therefore, the levels of glucocorticoids and mineralocorticoids in the blood can be not only diagnostic markers of the type of adrenocortical adenomas, but also indicate the effectiveness of the treatment and its long-term consequences.

The aim of the study. To determine the level of cortisol and aldosterone and evaluate the state of the pituitary-adrenal and renin-aldosterone systems in patients with various types of adrenocortical adenomas.

2. Materials and methods

The study was conducted based on the Shupyk National Medical Academy of Postgraduate Education for the period 2020–2022. The study was conducted based on the endocrinological department of the Lviv Regional Endocrinological Dispensary (LRED).

The study analyzed the results of 35 patients with adrenocortical adenomas. There were 21 (60 %) women and 14 (40 %) men among the patients. The age of patients is from 38 to 69 years (average age – 44.7±5.8 years).

All studies with patients were conducted in accordance with the provisions of the Declaration of Helsinki of the World Medical Association "Ethical Principles of Medical Research Involving Human Subjects" (Helsinki, Finland, 1964), which was revised by the 59th General Assembly of the WMA (Seoul, 2008). The Ethics Commission conducted an examination of clinical trials regarding research and monitoring of compliance with ethical and moral and legal principles during clinical trials with the presence of statements confirming the consent of all patients in the study (Protocol No. 1 dated 23.01.2022 of the Ethics Commission of the Department of Surgery and Transplantology of Shupyk National Medical Academy of Postgraduate Education).

Preoperative differential diagnosis of adrenal gland tumours included a standard set of studies: collection of complaints, history, and objective examination. Adrenal cortical adenoma in patients was detected during computed tomography (CT) of the organs of the retroperitoneal space, which made it possible to detect and clearly localize the development process of the neoplasm. In 5 (14.3 %) patients, benign tumours of the adrenal cortex were found, which had an asymptomatic course.

During the interview and objective examination of patients, special attention was paid to the known clinical manifestations of hormonal activity of the tumour, such as increased blood pressure numbers, characteristic changes in the appearance of patients, weight gain, etc. During the collection of anamneses, the presence of concomitant oncological pathology in patients was clarified. Exclusion criteria: presence of cancer of any localization and malignant neoplasm in the adrenal gland, metastatic nature of the tumour.

The content of adrenal cortex hormones was determined in the blood. Cortisol content was determined from glucocorticoids, and aldosterone content from mineralocorticoids. To determine the patient's hormonal status, to determine the level of cortisol in the blood, a test with 1 mg of dexamethasone was conducted. The content of hormones in the adrenal cortex was determined using a direct quantitative immunoenzymatic method (EIA-1887, "Cortisol ELISA", CSHA). Based on the obtained results, 2 groups were formed: group I – patients with cortisol-producing adrenocorticotropic adenomas of the adrenal glands (n=18); group II – patients with aldosterone-producing adrenocorticotropic adenomas of the adrenal glands (n=17). Controls were 23 healthy patients with an average age of 47±3.2 years, among whom there were 12 (52.2 %) women and 11 (48.2 %) men. The groups were comparable in terms of age and gender.

Blood was collected from the median ulnar vein into vacuum tubes with an anticoagulant on an empty stomach in accordance with generally accepted recommendations. Within 30 minutes of collection, blood tubes were delivered to the laboratory, where they were centrifuged at 2000 rpm for 10 minutes. To determine the state of the pituitary-adrenal system, the level of adrenal hormones and the level of adrenocorticotropic hormone (ACTH) of the pituitary gland were determined using enzyme-linked immunosorbent assay systems according to the generally accepted method using ELISA kits on the "SIRIO S" photometer analyzer. The direct concentration of renin was determined by immunochemical methods using monoclonal antibodies specific for renin.

The aldosterone-renin ratio (ARR) was calculated by dividing the plasma aldosterone concentration by the plasma renin concentration.

The obtained digital material was subjected to statistical processing using the program "Statistica", Stat Soft Inc (USA). A statistically significant difference between indicators was determined by the method of parametric statistics using the Student's test. Results between two groups were considered reliable at $p<0.05$.

3. Research results

The results of the research showed that all patients had an increase in the hormonal background in the blood at the level of glucocorticoids or mineralocorticoids, the nature of which depended on the morphological structure of the tumour.

Determination of the level of cortisol in patients with adrenocortical adenomas showed that in 18 (51.4 %) patients, the level of this hormone in blood plasma was elevated. Thus, the concentration of cortisol in these patients was at the level of (546.4±61.2) nmol/l, which was 1.4 times higher than the indicator of the group of healthy patients (392.1±41.5) nmol/l) ($p< 0.05$) (Fig. 1). The established fact indicates that this group of patients developed cortisol-producing autonomous tumours of the adrenal glands.

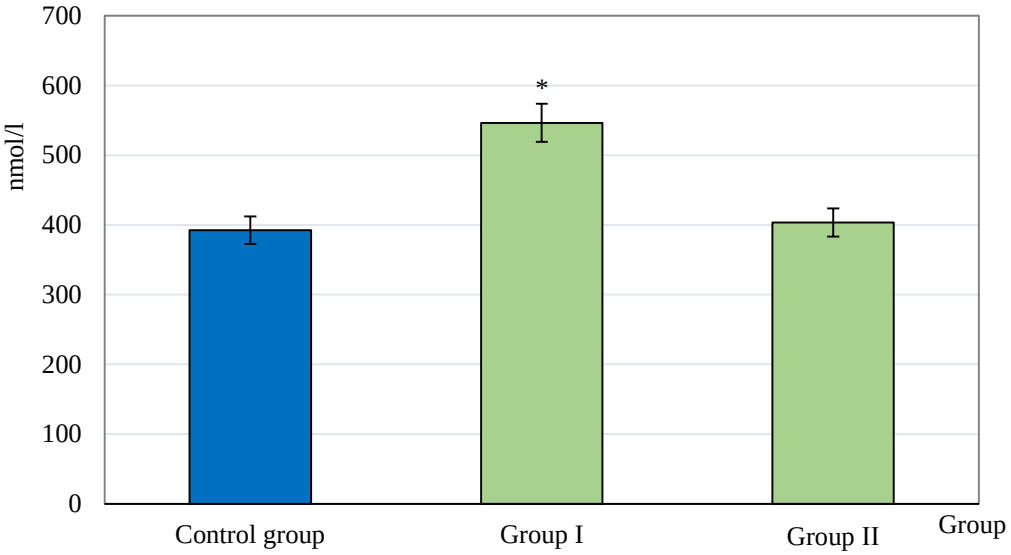

Fig. 1. The level of cortisol in the blood plasma of patients with adrenocortical adenomas of the adrenal glands: * – statistically significant difference compared to the indicators of the control group, $p<0.05$

The assessment of the morphological indicators of the adrenal glands in these patients with the help of CT showed an increase in their size, heterogeneity of the structure, but the contours were even and no signs of invasion into the neighbouring tissues were determined. There were changes in the density of the neoplasm after the injection of the contrast agent. In addition to evaluating the characteristics of the tumour itself, CT also evaluated the presence and volume of unchanged adrenal gland tissue, which in patients was at the level of 60 % to 80 %. Neoplasms in the adrenal glands were usually single and originated from the bundle layer, which obviously caused the secretion of only cortisol in excess (Fig. 1).

Determination of the aldosterone level showed its increase in 17 (48.6 %) patients, whom we allocated to group II – patients with aldosterone-producing adrenocorticotropic adenomas of the adrenal glands. It was established that in this group of patients the level of aldosterone was at the level of (22.8±1.89) ng/dL, which was 1.5 times higher than that of the group of healthy patients, whose aldosterone concentration was (15.2±1.89) ng/dL ($p<0.05$) (Fig. 2).

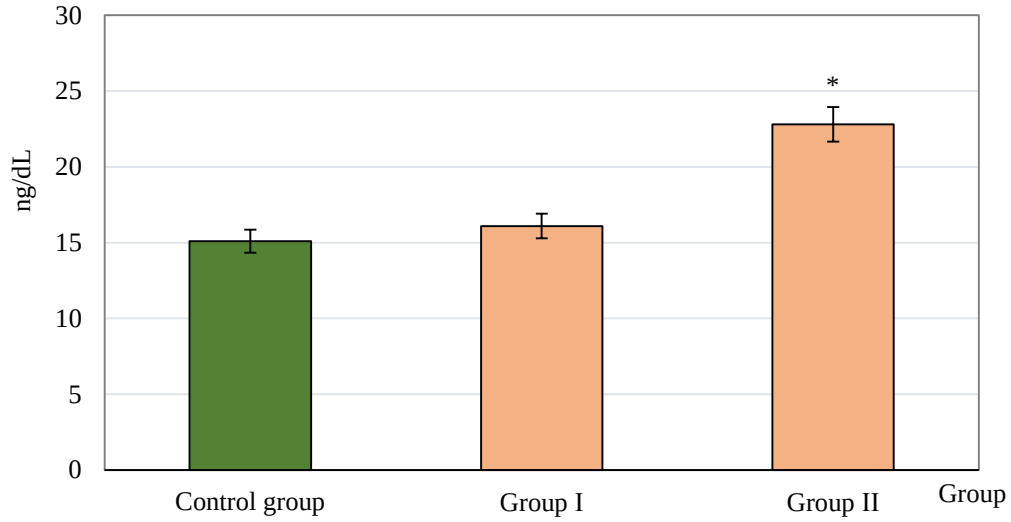

Fig. 2. The level of aldosterone in the blood plasma of patients with adrenocortical adenomas of the adrenal glands: * – statistically significant difference compared to the indicators of the control group, $p<0.05$

In all patients, neoplasms were well visualized and had a benign nature.

Since the synthesis and secretion of the studied glucocorticoids and mineralocorticoids are metabolically related to ACTH and renin, at the next stage we determined the concentration of these biologically active substances.

ACTH is a peptide hormone produced by basophilic cells of the anterior lobe of the pituitary gland and stimulates the production of cortisol by the adrenal cortex [9]. Determination of the level of ACTH showed that the concentration of this hormone did not change in the blood of patients with aldosterone-producing adrenocortical adenomas of the adrenal glands and decreased in patients with cortisol-producing adenomas. Thus, in this group of patients, the level of ACTH decreased to (15.7±1.23) pg/ml compared to the value (26.86±2.19) pg/ml typical of healthy individuals ($p<0.05$) (Fig. 3).

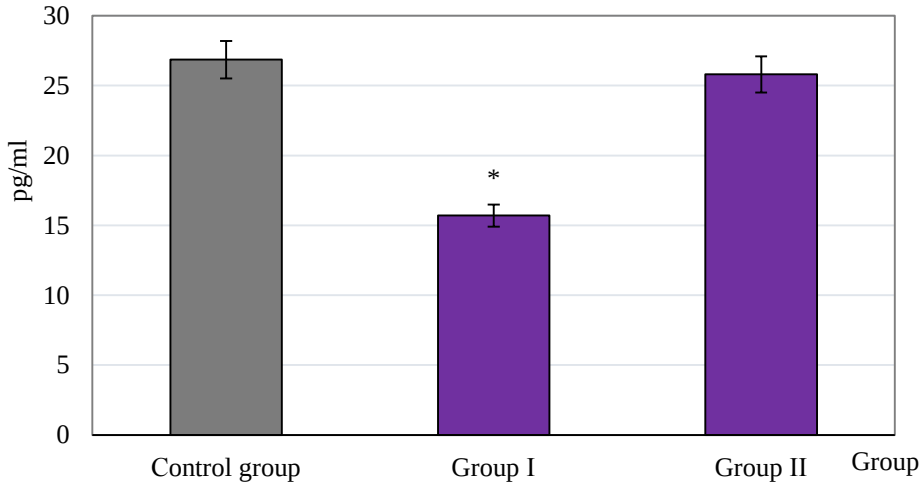

Fig. 3. The level of adrenocorticotropic hormone in the blood plasma of patients with adrenocortical adenomas of the adrenal glands: * – statistically significant difference compared to the indicators of the control group, p<0.05

The revealed inhibition of ACTH production occurs under the influence of glucocorticoids, since it is known that an increase in the concentration of cortisol in the blood inhibits the secretion of both ACTH and hypothalamic corticotropin-releasing hormone [10].

Therefore, the development of cortisol-producing adenoma of the adrenal cortex in the body leads to hypersecretion of cortisol and disruption of the activity of the hypothalamic-pituitary-adrenal system.

The state of the renin-aldosterone system was assessed by the level of renin and the indicator of the aldosterone-renin ratio. The analysis of the results showed that the level of renin in the two studied groups did not statistically significantly differ from the indicators of the control group (Fig. 4A). At the same time, an increase in the aldosterone/renin ratio was observed in the group of patients with aldosterone-producing tumours, in which the aldosterone/renin ratio was 1.3 times higher than that of the control group of patients (p<0.05) (Fig. 4 *b*).

This established fact may indicate that the hyperaldosteronemia observed in patients with adrenocortical adenomas of the adrenal glands is probably secondary in nature and is renin-independent, and physiological changes in the body with the corresponding manifestation of clinical signs occur independently of the influence of angiotensin II [11].

Thus, studies of increased cortisol and aldosterone concentrations indicate a disturbance in the adrenal cortex, which is associated with the development of adrenocortical neoplasms in this organ. Changes in the level of glucocorticoids and mineralocorticoids in the blood plasma can be the cause of a malfunction of the pituitary-adrenal and renin-aldosterone systems, respectively, which will lead to metabolic and physiological disorders in the body of patients with neoplasms of the adrenal cortex.

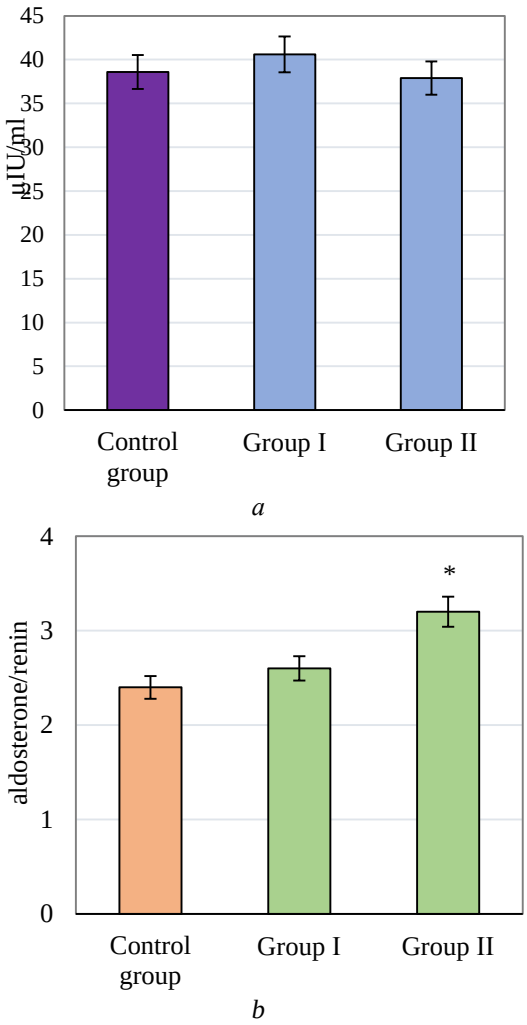

Fig. 4. Renin content and aldosterone/renin ratio in blood plasma of patients with adrenocortical adenomas of the adrenal glands: a – renin level in blood plasma; b – aldosterone/renin ratio in blood plasma; * – statistically significant difference compared to the indicators of the control group, p<0.05

4. Discussion of research results

Differential diagnosis of benign adrenal gland tumours at the preoperative stage is associated with significant difficulties. Cytological and histological examination of the material taken for fine-needle aspiration biopsy is informative only in 80–85 % of cases. This is because the main difference between different types of adrenocortical adenomas is mainly metabolic changes both in the tissues of the neoplasm and in the body as a whole, which cannot be clearly determined in these studies [12]. Given the low informativeness of preoperative morphological studies, a major role in the differential diagnosis of benign tumours of the adrenal glands is played by clinical and laboratory methods determination of hormone levels.

As revealed by our research, the increased secretion of cortisol in adrenocortical adenomas of the adrenal glands was associated with the development of Cushing's syndrome, since in patients the clinical signs were a round red face, increased blood pressure, muscle and bone weakness, abdominal obesity, specific signs for this syndrome skin, etc. [6]. It should be noted that the characteristic symptoms were manifested more intensively in those patients in whom the size of the adenoma was greater than 2.5 cm. With smaller neoplasms, the symptoms were less pronounced. The detected hypercorticism did not depend on the level of ACTH, since the level of ACTH was reduced on this background. It is worth noting that the development of ACTH-independent Cushing's syndrome with hypersecretion of cortisol was observed against the background of disruption of the pituitary-adrenal system. Thus, an excess of cortisol inhibits the release of ACTH with possible subsequent atrophy of the tissue of the adrenal gland cortex located outside the tumour [13]. In addition, when a unilateral benign tumour was detected, multiple nodules of the adrenal cortex were often visualized in the second adrenal gland, indicating nodular hyperplasia. Often, such hyperplasia had a polyclonal character, while adenomas were mainly monoclonal.

Determination of aldosterone level showed that an increase in its level in the blood plasma of patients with benign tumours of the adrenal cortex is an independent factor in the development and progression of arterial hypertension since a high level of aldosterone in the blood plasma was correlated with hyperhydration and an increase in blood pressure. Therefore, an increase in the level of aldosterone in the blood of patients with aldosterone-producing tumours should be considered not only as an early diagnostic marker of this pathology, but also as an independent risk factor for potentially fatal cardiovascular complications. The results confirm the relationship between the level of aldosterone and the severity of clinical symptoms. Aldosteronism can cause a violation of water and electrolyte metabolism, increased blood pressure, muscle weakness, hypokalemia, and alkalosis [14].

Changes in the level of renin in the blood plasma were not associated with the development of adrenocortical adenomas, however, the aldosterone/renin ratio was correlated with this pathology, the value of which increased with the studied pathology. Based on the research results, it could be stated that an increase in the aldosterone/renin ratio is one of the most likely markers of an unfavourable prognosis in patients with adrenal cortical neoplasms [15], so it could be used not only for the diagnosis of adrenocortical adenomas, but also for screening the effectiveness of various methods treatment – both operative and medicinal. At the same time, no direct correlation was found between the plasma renin level and the development of adrenocortical adenomas of the adrenal cortex.

Therefore, it could be assumed that many factors are involved in the mechanism of development of various types of tumours of the adrenal cortex, which depend on the direction of synthesis of glucocorticoids or mineralocorticoids. At the same time, all processes in the body are interconnected, may have a common pathogenetic mechanism and underlie the risk of the development of concomitant pathologies in which the hormones studied by us are involved. Clarifying the relationship between the clinical features of the course of development of different types of adrenocortical adenomas and the degree of disruption of the pituitary-adrenal and renin-aldosterone systems allows us to understand the cause-and-effect processes that develop in the body of these patients and will allow us to choose the right treatment method.

Study limitations. The level of cortisol and aldosterone and the state of the pituitary-adrenal and renin-aldosterone systems in patients with various types of adrenocortical adenomas are considered, but the quality of life of patients after organ-preserving (resection) operations on the adrenal glands is not studied.

Prospects for further research. To reveal and evaluate the quality of life of patients after organ-preserving (resection) operations on the adrenal glands and to formulate an algorithm for the preoperative assessment of the oncological risk of adrenal tumours, which will allow to determine the indications for organ-preserving operations and radical adrenalectomy (clinical signs, size, hormonal activity, signs of invasion and metastasis, biopsy data).

5. Conclusions

1. In patients with cortisol-producing adrenocortical adenomas, an increase in the level of cortisol was established against the background of a decrease in the level of ACTH, which was characterized by the development of ACTH-independent Cushing's syndrome, the severity of which was correlated with changes in the concentration of hormones in the blood.

2. Revealed aldosteronism in patients with aldosterone-producing adenomas developed against the background of unchanged renin levels, which led to an increase in the aldosterone/renin ratio. The identified changes underlie the development of water-electrolyte metabolism disorders, increased blood pressure, muscle weakness, hypokalemia, and alkalosis.

Conflict of interests

The author declares there is no conflict of interests.

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