UDC 616.-001.17:4
DOI http://doi.org/10.30978/GS-2023-3-79

ISSN 2786-5584 print
ISSN 2786-5592 online

Endocrine disorders in burn disease. Literature review

O. V. Kravets, V. V. Yekhalov, V. V. Gorbuntsov

Dnipro State Medical University

✉ Vasyl Yekhalov: sesualiy@gmail.com

O. V. Kravets, http://orcid.org/0000-0003-1340-3290
V. V. Yekhalov, http://orcid.org/0000-0001-5373-3820
V. V. Gorbuntsov, http://orcid.org/0000-0001-7752-0993

The purpose of the review is to highlight clinically hidden variants of hormonal dysfunctions in burn disease, which strongly determine the peculiarities of the course of the pathological condition but are often overlooked by clinicians. Based on available literary sources, this study provides a comprehensive analysis of specialised medical reports from both domestic and foreign researchers. The focus of this analysis was on compensatory and pathological shifts in hormonal regulation of the body in individuals suffering from local heat injury. The collected scientific data is expected to be useful to practitioners in the field of combustiology in their practical activities. Damage to the endocrine glands is one of the key pathogenetic factors of local thermal injury, but the intracellular mechanisms of the influence of burn disease on these processes remain poorly understood. The criticality of burn injuries often leads to hypodiagnosis of endocrine disorders, which are indeed typical and rapidly developing. The neuroendocrine response to severe burns is a multisystem coordinated response of the body, which can not only maintain homeostasis and play a protective role in critical conditions but also cause tissue damage, realising the properties of a "double-edged sword." Burns covering more than 40 % of the total surface area of the body are accompanied by a stress reaction and hyperinflammation with a steady increase in the secretion of catecholamines, glucocorticoids, and cytokines. Classic studies confirm that a sharp post-burn increase in stress hormones (adrenaline, norepinephrine, glucagon, and cortisol) contributes to the development of hyperglycemia, a systemic catabolic state, and multiple organ dysfunction. It has been established that the hypothalamic-pituitary axis is responsible for fluctuations in the content of pituitary hormones in the blood serum of patients with local thermal lesions. After severe burns, the plasma renin-angiotensin-aldosterone system is activated, and the level of some hormones increases for more than 2 months after the injury.

Keywords
burn, catabolism, endocrine disorder, hormone, inflammation.

ARTICLE • Received 2023-10-26 • Received in revised form 2023-11-18

Burns are a serious public health problem, with 11 million cases worldwide each year, resulting in more than 300,000 deaths [4]. According to the WHO, burns rank third among other injuries. Invalidation of victims, depending on the nature of injuries, is caused in (2.3—49) % of cases [39]. Studies of endocrine disorders in patients with burn injuries began in the early 50s of the last century [48]. Currently, there is increasing interest in the mechanisms of endocrine dysregulation during local thermal injury, since this system plays a leading role in the development of the body's reverse reaction to burns [31, 32]. Damage to the endocrine glands is one of the key pathogenetic factors of local thermal injury, but the intracellular mechanisms of the effect of burn disease (BD) on these processes remain poorly understood [19]. So far, most studies of such disorders have been conducted on patients with severe burns. However, modern scientific reports claim that victims of any age with mild burns also suffer from such dysfunctions [18, 21]. The criticality of burn injuries often leads to hypodiagnosis of endocrine disorders, which are indeed typical and rapidly developing [16].

Objective — to highlight clinically hidden variants of dysfunctions of hormonal regulation in BD, which strongly determine the peculiarities of the course of the pathological condition but quite often fall out of the field of view of clinicians.

During a BD, a reaction is noted on the part of all body systems, in particular the relationship between the hypothalamus, pituitary gland, and adrenal glands [38, 48, 55]. The neuroendocrine reaction to severe burns is a multisystem coordinated response of the body, which can not only maintain homeostasis and play a protective role in critical conditions but also cause tissue damage, realising the properties of a «double-edged sword» [36].

In BD, the development of adrenal gland reactions, which are crucial for catabolism and physiological adaptation to various environmental factors, is undeniably significant [33]. Severe burns cause excitation of the sympathoadrenal system (the locus coeruleus) and the adrenal medullary response, resulting in central emotional reactions (tension and alertness) and an increase in the level of catecholamines in the peripheral blood [36]. Structural changes of the adrenal glands and adenohypophysis depend on the degree of intoxication, when part of the cells die by apoptosis, necrosis, and autophagy [25]. Urinary epinephrine and norepinephrine levels after a burn injury initially increase and then decrease to normal levels approximately 2 months after the injury [24].

It is known that hormones affect the immune system. Modern data indicate numerous secondary pathologies in burn injury, which are the result of synergistic dysfunctions in these systems, and changes in endocrine homeostasis contribute to long-term suppression of immunity [4]. After a burn, there is a rapid release of proinflammatory cytokines, catecholamines, and cortisol, which initiates a hypermetabolic response and a catabolic state [28]. A recent study of children with severe burns showed that urinary norepinephrine and cortisol levels remained significantly elevated even three years after the burn [4, 28]. Burn injury disrupts endocrine homeostasis, and this has long-term consequences for immune function. Stress hormones inhibit the proliferation of lymphocytes, the activity of CD8 thymocytes, natural killer cells, and activated macrophages. They also stimulate mast cells, causing degranulation and the release of histamine, which promotes the production of T-helper type 2 (Th2) and the interleukin cytokine IL-10, resulting in further vasodilation. The stress response system suppresses the T-helper type 1 (Th1) immune response (cellular immunity, usually pro-inflammatory) and promotes the Th2 response (humoral immunity, mostly anti-inflammatory). Growth hormone levels, which decrease after burn, also modulate Th1/Th2 responses [4]. Th1-derived proinflammatory cytokines transmit their signal through three major transcription factors that promote the phosphorylation of serine residues, thereby impairing insulin receptor function. In this way, a vicious circle is formed [6].

Metabolic changes after a severe local thermal injury are similar to those observed in other major injuries. However, severe burns are characterised by a more intense and prolonged hypermetabolic response accompanied by insulin resistance [38, 48, 55]. Patients with severe burns affecting 25—65 % of their entire body surface experienced an increase in energy expenditure at rest from the 1st to the 30th day. This increase was correlated with hormonal changes [57]:

- increase in the levels of cortisol, renin, and insulin;
- decrease in the level of thyroid hormones;
- «low triiodothyronine» syndrome;
- the absence of significant changes in sex hormones.

A severe burn injury is accompanied by a deep hypermetabolic reaction that persists up to 2 years after the injury. This is mediated by a 50-fold increase in the level of catecholamines, cortisol, and glucagon in the blood plasma, which causes [59]:

- hypercatabolism throughout the body;
- increased resting energy expenditure;
- multiple-organ dysfunction.

The hypermetabolic state after a burn injury persists up to 36 months after the initial stroke. Stress hormones such as catecholamines, glucocorticoids, and glucagon increase peripheral insulin resistance, glycogen breakdown, and the synthesis of acute-phase proteins (insulin-like growth factor IGF-1, which has an anabolic effect), which ultimately leads to a catabolic state associated with organ dysfunction and death [8, 27, 28, 51]. An excess of catecholamines can suppress the secretion of prolactin, thyroxine, and growth hormone [36]. Bone and mineral metabolism is profoundly disturbed and requires correction of mineral ions (calcium, magnesium, and phosphate) to prevent bone loss and other disorders [16].

Dysregulation of the adenohypophysis causes long-term complications of BD and exhaustion of the adrenal glands, a possible path to the development of secondary hormonal insufficiency and damage to thymus cells [29, 62], which develops within a few days after thermal damage to the skin and is a prerequisite for the development of immunodeficiency [47]. Intracellular DNA damage of adenohypophysis and adrenal gland cells develops in the first days after thermal damage and is accompanied by increased apoptosis [19], which in many pathological conditions (including BD) is a mechanism of cell population renewal [20, 43]. If synthetic processes in the adenohypophysis at the subcellular level significantly decrease from the first day and

then constantly increase, reaching peak values after 21 days, then the phenomenon of apoptosis reaches a maximum after 14 days [19].

Cell damage is more pronounced in the cells of the adrenal glands compared to the adenohypophysis. Local thermal trauma impairs the functions of the adrenal cortical layer, even when the exposure is short-term. This is manifested by the hyperactivity of the adrenal cortical substance, which is characterised by increased intracellular synthesis and cell apoptosis, both of which contribute to the functional exhaustion of the adrenal glands [19]. In an animal model with skin burns, the cortical layer had significant ultrastructural damage observed mainly in the glomerular and fascicular zones. Nuclear corticocytic damage was noted as a result of:

- the growth of heterochromatin in the karyoplasms;
- the expansion of the perinuclear space;
- the formation of intussusceptions of the karyolemma;
- a decrease in the number of nuclear pores.

The cytoplasm of cells was characterised by a low electron density of lipid inclusions with cellular remodelling, a decrease in secretory activity, and regulatory capacity [33]. Burns are complex injuries that cause a stress response and lead to an increase in blood glucose levels [29]. Burns covering more than 40 % of the total body surface area (TBSA) are accompanied by a stress reaction and hyperinflammation with a persistent increase in the secretion of catecholamines, glucocorticoids, and cytokines [8, 24, 41].

Increased levels of epinephrine, norepinephrine, dopamine, and cortisol are also associated with increased hepatic gluconeogenesis and decreased insulin-mediated glucose uptake by skeletal muscle and adipose tissue. These phenomena can lead to an increase in the level of glucose in the blood in combination with a normal or increased concentration of insulin in the blood serum, forming a clinical condition that is usually defined as insulin resistance [24]. Hyperglycemia and hyperinsulinemia peaked 7—14 days after the injury. Oral glucose tolerance and insulin resistance tests further support these findings for moderate (20 % to 40 % TBSA) and severe burns (over 40 % TBSA) [55].

Classic studies confirm that a sharp post-burn increase in stress hormones (adrenaline, norepinephrine, glucagon, and cortisol) contributes to the development of hyperglycemia, a systemic catabolic state, and multiple organ dysfunction [6]. Regardless of its proximal trigger in burn pathology, peripheral insulin resistance results from impaired receptor signalling for accurate transduction of the hormonal message, resulting in hyperglycemia and catabolism. An increase in the level of stress hormones and pro-inflammatory cytokines, together with the spread of free radicals obtained from mitochondria, leads to a violation of insulin receptors, which counteracts its anabolic effect [6].

Burns are associated with a higher prevalence of complications, mortality, and hospitalisation outcomes in patients with concomitant diabetes mellitus (DM). In addition, morbidity and mortality are associated with diabetes in burn patients [61]. Critically ill patients with hyperglycemia without a previous diagnosis of diabetes face worse outcomes than patients with preexisting DM. A growing body of evidence suggests that insulin resistance and hyperglycemia worsen outcomes in burn patients with acute and transient clinical illnesses [12, 40, 46]. Population studies have shown that children and adults with mild and severe burns show an increased susceptibility to dysregulation of glucose metabolism and exacerbation of diabetes. Burn patients may suffer from impaired glucose metabolism and insulin resistance for at least three years after injury [27, 28] and are therefore at risk for premorbid diabetic pathophysiology [6, 18]. The burn cohort had 2.21 times more DM readmissions compared to the non-injured cohort. This increase was comparable between the paediatric and adult patient cohorts and remained at a high level for 5 years after the burn [4, 18].

DM can develop directly as a result of an unregulated stress response to a burn. The released adrenaline prevents the release of insulin and, simultaneously, with cortisone, promotes glycogenolysis in the liver. Growth hormone is released during stress and also counteracts the action of insulin. Prolonged hypersecretion of these hormones in response to a burn can lead to DM. As a result, if the patient does not have DM before, post-burn blood glucose must be carefully adjusted with insulin to prevent the development of DM [49].

In case of burn sepsis, there is a progressive increase in insulin resistance and a decrease in thyroid hormones and parathormones. Hyperglycemia without preexisting DM over 11 mmol/L (untreated) or insulin resistance causes a 25 % increase in insulin requirements [53].

Hyperglycemia occurs as a result of enhanced glucose synthesis, increased glucose delivery to inflamed tissues, and the development of peripheral insulin resistance or reduced glucose clearance [37, 58]. The effect of insulin resistance on glucose metabolism is manifested in two main ways [6, 59]:

- unsuppressed gluconeogenesis in the liver;
- impaired peripheral utilisation of glucose by skeletal muscles and adipose tissue.

An increase in the level of glucose in the plasma leads to a noticeable stimulation of catabolism.

Reduced effectiveness of insulin as an anabolic agent of muscle protein promotes sustained protein catabolism and whole-body proteolysis. A burn that covers more than 40 % of the TBSA can lead to a period of increased hypercatabolism and changes in insulin sensitivity that can persist for up to 3 years [54]. Catecholamine levels can increase up to 10-fold after burns and are thought to contribute to the initial stages of the hypermetabolic response. Mechanistically, catecholamines exert their effects by binding to α_1, α_2, β_1, and β_2 receptors, causing hyperglycemia and muscle catabolism. The maximum rise of catecholamines was long-lasting (11—20 days) and did not reflect changes in cortisol production [2, 6, 41]. Cortisol is a well-known stress hormone capable of contributing to hyperglycemia by mobilising energy stores. The hyperglycemic response is more intense and exacerbated when cortisol levels rise simultaneously with other counterregulatory hormones, such as catecholamines [22]. Hypercortisolemia after a severe burn injury is immediate, long-lasting, and directly related to the severity of the burn. Cortisol reduces peripheral glucose uptake by inhibiting insulin signalling [6, 34].

While insulin has the opposite effect, hyperglycemia itself can amplify the inflammatory response. The liver begins to produce pro-inflammatory cytokines. Hyperglycemia caused by insulin resistance induces the expression of pro-inflammatory cytokines, mainly in the form of mitochondrial reactive oxygen species. Each ingredient can individually increase insulin resistance and, as a result, hyperglycemia [3, 6].

Under large burns, adrenocorticotropic hormone (ACTH) is often produced in excess relative to the cortisol response, and «ACTH — adrenal» feedback may be impaired. A very high positive correlation between plasma vasopressin and ACTH levels was determined. Osmostimulants can cause stimulation of ACTH and cortisol secretion in burn patients. The release of cytokines can inhibit the synthesis of ACTH. During the long recovery phase after severe burns, a dissociation was determined between high plasma concentrations of mineralocorticoids and low levels of ACTH, which indicates that ACTH does not mediate the regulation mechanisms of the adrenal cortex [48]. Additional circulating cytokines can suppress the synthesis and secretion of ACTH. Endothelin-1 and atrial natriuretic peptide levels rise with ACTH suppression [41]. The normal circadian rhythm of serum cortisol is lost after a severe burn, so urinary cortisol is considered a more accurate indicator of total daily cortisol production [41]. The total 24-hour level of cortisol in the urine increases in the initial post-burn phase by 4—6 times. The level then declines over time, returning to the normal range 3—36 months after injury [24, 41]. The more severe the burn, the greater the dysfunction: one study found that children with burns over 80 % TBSA had higher resting energy expenditure and urinary cortisol levels than patients with lesser burns [27, 28]. Males had significantly greater increases in urinary cortisol levels that persisted approximately 40 days postburn compared to females, and declines to the normal range were similar for both groups approximately 3 months after the initial injury. No correlation was found between hypercortisolemia, normocortisolemia, and mortality or burn area at any time point [41]. As recombinant hypophysial growth hormone (rhGH) stimulates protein synthesis, it is frequently administered to burn wounds with more than 40 % TBSA, where protein synthesis is reduced and proteolysis is elevated. However, the use of rhGH is associated with an increased risk of hyperglycemia [7]. Higher levels of ACTH and cortisone were found among men after a stressful situation, which correlates with lower testosterone levels. The inhibitory effect of progesterone on the action of growth hormone in women has been confirmed [38].

Acute post-burn pancreatitis is an easily overlooked complication that occurs more often in patients with inhalation injuries and deep burns. Pancreatitis develops 3—4 weeks after an infected burn. One of the reasons for its development is ischemia of the pancreas as a result of hypovolemia after a large burn. According to this theory, acute pancreatitis should develop soon after a burn injury. Ischemia of the pancreas can provoke its cellular damage, and bacteremia due to burn sepsis can cause infectious damage to the compromised pancreas [44]. Proenzymes are activated during acute pancreatitis, resulting in the necrosis of autodigestive tissue. This necrosis is classified as mild or oedematous and severe or necrotic, ranging from oedematous and indurative to haemorrhagic and necrotic. Oedema is more pronounced in fibrous and fatty tissues. Parenchymal haemorrhages, acinar destruction and fat necrosis, dilation of ducts containing detritus, and thrombi in capillaries and vessels indicate active inflammation. Amylase and lipase levels increased in 40 % of patients with burns, and symptoms of pancreatitis were observed in 82 % of patients with TBSA over 20 % [14].

A thyroid crisis is an exacerbation of hyperthyroidism, which leads to serious systemic disorders and can end fatally. The combination of hyperthyroidism and burn injury raises the question of the need for urgent optimisation of hyperthyroid status before surgery and constant monitoring in the intensive care unit [52].

The thyroid gland in BD becomes a highly sensitive target organ among the mechanisms of neurohumoral regulation, which is documented by significant changes in the activity of its hormones. Changes in the structure and functional thyroid activity usually occur against the background of hypovolemia [31, 32, 60]. It has been proven that under BD, the organometric dimensions of the thyroid gland decrease compared to the initial ones, which, accordingly, indicates suppression of hormonal activity [42]. In an experiment on an animal model of a thermal burn in the acute period (up to the 7th day), it was proven that there were initial and adaptive-compensatory destructive changes in the histological structure of the wall of the vessels of the thyroid gland:

- thickening of the walls of arteries and arterioles;
- a certain expansion and filling of veins;
- the sludge phenomenon of erythrocytes in the microcirculatory channel.

In late toxaemia and septicotoxaemia (from the 14th to the 21st day), changes in blood vessels manifested destructive, degenerative, and sclerotic signs [31]. Trophic disturbance is manifested by the destruction of the follicles and stroma of the organ. There is a deep degeneration of thyrocytes with their necrosis and desquamation into the lumen of the follicle with dense colloid and DNA fragmentation (apoptosis) [56]. Damage to nuclear, plasma, and intracellular membranes, a decrease in the number of microvilli, and an increase in the number of phagosomes ultrastructurally reflect a decrease in the secretory activity of endocrinocytes and a hypofunctional state of the organ [39]. Histopathological examination of the thyroid gland in patients with fatal burns demonstrated morphologic changes in the thyroid gland as a result of the burn-induced hypermetabolic state, indicating a high likelihood of hypothyroidism among severely burned patients [11]. Distinct histopathological changes were observed in most specimens, including:

- mononuclear cell infiltration (65.62 %);
- distortion of follicular architecture (59.37 %);
- thyroglobulin accumulation (21.87 %);
- depletion of thyroid follicles (17.18 %).

Infiltration by mononuclear cells and follicular architecture distortion increased as the TBSA exceeded 50 % and the duration of survival extended [11]. Metabolic damage causes histopathological changes in the thyroid gland after severe burns. These changes predominantly manifest as distortion of the follicular architecture and infiltration of mononuclear cells, with the latter being a consequence of the inflammatory response after the burn [11].

A decrease in the concentration of triiodothyronine (T3) is observed in the blood plasma of burn patients during the first few days after the injury [11]. Serum levels of thyroid-stimulating hormone are increased in the late stages of BD [48]. The level of free triiodothyronine does not indicate functional hypothyroidism but may reflect adaptation to the metabolic control of the sympathetic nervous system [48]. Elevated thyroid-stimulating hormone and a reduced level of free thyroxine (T4) correspond to hypothyroidism. Establishing the diagnosis depends on the patient's presence of such characteristic signs as hypothermia, changes in mental status, laboratory data characteristic of hypothyroidism, and the exclusion of other causes [5, 11, 18].

Myxedema coma (MC) is a rare and life-threatening disease that should be recognised early to prevent morbidity and mortality. Patients with a history of endocrine disorders, especially those who do not take medication, are at high risk for endocrine complications from local thermal injury. The diagnosis is reliable when the patient is in a comatose state, especially with a known history of hypothyroidism, and has one of the symptoms of the MC triad: hypothermia, hyponatremia, and hypercapnia. On the basis of the clinical picture and an increase in the level of thyroid-stimulating hormone, a diagnosis of MC can be made [16, 26].

Carboxyhaemoglobin causes damage to the supraoptic nucleus, leading to decreased antidiuretic hormone (vasopressin) secretion. There is another combustion product, such as cyanide, that plays a role in this process [9]. Severe burns stimulate the posterior pituitary gland to release antidiuretic hormone, which promotes water reabsorption in the renal collecting duct and distal tubule to maintain sufficient circulation. At the same time, the hypothalamus-pituitary-adrenal axis is activated, stimulating the adrenal glands to synthesise and secrete glucocorticoids, allowing the body to adapt to post-traumatic inflammatory reactions and local and systemic oedema. Patients in the late stages of severe sepsis as well as those who died from severe burns due to exhaustion of the hypothalamic-pituitary system often have a significant decrease in the aforementioned hormone levels. After severe burns, the plasma renin-angiotensin-aldosterone system (RAAS) is activated, and the level of some of these hormones increases for more than 2 months after the injury [36]. The level of antidiuretic hormone (vasopressin) increases significantly in the shock stage of BD and can return to a normal level 4—5 days after the injury. Extremely elevated levels of vasopressin in the plasma contribute to vascular complications, increased systemic vascular resistance, and decreased contractility of the myocardium and cardiac output [48]. The endocrine

response is characterised by significant changes in several points of the hypothalamic-pituitary-hormonal axis. The reaction of the anterior lobe of the pituitary gland is biphasic [16, 48]:

- in the acute phase, low levels of effector hormones caused by target organ resistance are observed; these changes can persist for a long time;
- in the long-term phase, low levels of target organ hormones may occur as a result of hypothalamus suppression.

After a burn injury, hormonal regulation of metabolism occurs in two «ebb» and «flow» phases, which are described as an initial decrease and subsequent increase in metabolic activity:

- the «ebb» phase (hypometabolic response), which lasts ~72—96 hours, is characterised by a decrease in cardiac output, oxygen consumption, and metabolic rate; glucose tolerance is broken, and glycemia begins to rise;
- the «flow» phase is characterised by a gradual increase in metabolism, associated with hyperdynamic blood circulation and insulin resistance; in response to the glucose load, the release of insulin increases, and the level of glucose in the plasma rises markedly.

The hypermetabolic response (the «flow» phase) can last more than 12 months after the initial event and does not fully resolve after wound closure. Modern studies have proven the impact of the hypothalamic-pituitary axis in local thermal lesions on fluctuations in the content of pituitary hormones in blood serum [3, 27, 48]. Stimulation of this axis may be partly related to the internal cooling of the patient, which leads to increased resting energy expenditure under the influence of catecholamines to restore normal body temperature [41]. Angiotensin II receptor blockade increased insulin sensitivity in an animal model of BD [36].

In this context, proinflammatory cytokines and high levels of stress-induced hormones such as glucagon, cortisol, and catecholamines may play an important role in maintaining a catabolic state. The activity of thyroid hormones is not important for determining the degree of catabolism in BD. Exhaustion can lead to a permanent decrease in thyroid function, producing clinical signs of euthyroid disease syndrome (EDS) [3, 23]. EDS is a clinical condition characterised by low serum levels of free triiodothyronine (fT3) with characteristic elevations of:

- reverse triiodothyronine T3 (rT3);
- free thyroxine (fT4) — from normal to low levels;
- thyroid-stimulating hormone (TSH).

Such changes in thyroid hormones have been interpreted as an adaptive compensatory response to reduced energy expenditure due to hyperstimulation of the sympathetic nervous system or, alternatively, as insufficient neuroendocrine adaptation to stress, leading to an adverse effect on clinical outcome. This condition has been proposed as a prognostic factor for worse outcomes in critically ill patients, whereas definitive data on burns are lacking [23, 45].

The concentration of follicle-stimulating hormone, secreted by the anterior pituitary gland, was low on the second day after the burn. This hormone is considered a very sensitive marker of local thermal injury in both male and female patients. Low follicle-stimulating hormone levels can persist for many weeks after a major burn and correlate with very low testosterone levels in men. If a burn injury occurs in a woman during the preovulatory phase of the menstrual cycle, it disrupts the endocrine balance and ovulation [48].

An increase in the level of luteinizing hormone occurs during the first 48 hours, which significantly decreases from 14 to 30 days after the burn, returning to its normal value. The level of gonadotropin decreases significantly and still remains subnormal on the 30th day in patients with TBSA over 30 % [48].

Serum prolactin levels often increase after a burn injury. Its positive correlation with over 20 % TBSA was determined. It is known that prolactin is more sensitive to stressful stimuli than other hormones. Also, prolactin counteracts the immunosuppressive effect of cortisol, which becomes important in the late post-burn period. Thus, an increase in the level of prolactin after a burn injury can increase the patient's resistance to infection [48].

An increase in serum progesterone levels up to 2 years after the burn indicates a long-term hormonal imbalance in these patients [4, 27, 28]. Progesterone increases in patients long after the initial healing process and has an immunosuppressive effect, reducing the activity of macrophages and T-killers but promoting a type 2 (Th2) immune response [1].

Other hormonal changes occurring after burn in paediatric studies included significant decreases in serum osteocalcin, parathyroid, growth factor, insulin, protein-3 (BP3), binding insulin-like growth factor (IGF), and somatotropin that persisted for 3 years [4, 27, 28].

Burn wound healing is slower in men compared to women [50], and this gender difference suggests that sex hormones may play an important role in wound healing. Androgens exert inflammatory properties by mediating the expression of various cytokines. Furthermore, androgens prolong inflammation during wound healing by promoting both local expression of pro-inflammatory cytokines, such as TNF-α and IL-6, and wound infiltration by inflammatory

cells. A significant reduction in circulating potent androgens reduces inflammation by preventing excessive infiltration of immune cells and the production of key pro-inflammatory cytokines, highlighting the negative role of androgens as natural inhibitors of wound healing that delay the proliferative phase. At the moment, the role of safe androgens in wound healing after severe burns is not well understood, so further research is needed [10, 35, 50].

Some of the hormones are very sensitive indicators of burn stress:

- T3 levels (very low);
- testosterone in men (very low);
- angiotensin II;
- cortisol (high);
- 17-β-estradiol in men (usually elevated).

Other hormones are usually elevated, but not always (ACTH, aldosterone, prolactin, glucagon, immunoreactive insulin, β-endorphin), but there are hormones whose levels are unusually low (androstenedione, progesterone — the latter especially in women); sometimes elevated calcitonin, parathyroid hormone, and growth hormone. Levels of sensitive indicators of burn stress can be used to assess the effect of the treatment. If the burn patient is properly treated, the indicators may return to normal earlier [17].

Diabetes insipidus is a rare complication of burn injuries due to the destruction of neurons involved in the secretion of antidiuretic hormone (vasopressin) by the pituitary gland. In the literature, there are only 8 cases of diabetes insipidus in burns, which occurred in younger patients with a TBSA of more than 30 % [15, 30]. Diabetes insipidus is an endocrine disease characterised by excessive urination and polydipsia due to either insufficient release of antidiuretic hormone or resistance to antidiuretic hormone (vasopressin) in the renal collecting tubules [13]. Manifested by polyuria and urine osmolality less than 300 mosml/L, this increases plasma osmolality over 300 mosml/L, which slightly increases thirst. There are no obvious signs of dehydration if fluid intake has not been disturbed. When the volume of urine increases, the possibility of developing diabetes insipidus should be suspected after determining the level of glucose in the urine [15, 30].

Based on available literary sources, this study provides a comprehensive analysis of specialised medical reports from both domestic and foreign researchers. The focus of this analysis was on compensatory and pathological shifts in hormonal regulation of the body in individuals suffering from local heat injury. The collected scientific data is expected to be useful to practitioners in the field of combustiology in their practical activities.

Declaration of interests

The authors declare that there is no conflict of interest or their own financial interest in the preparation of this article.

Authors contributions

O. V. Kravets, V. V. Yekhalov — conceptualization, writing the original text; V. V. Gorbuntsov — editing, translation.

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Ендокринні розлади при опіковій хворобі. Огляд літератури

О. В. Кравець, В. В. Єхалов, В. В. Горбунцов

Дніпровський державний медичний університет

Висвітлено клінічно приховані варіанти дисфункцій гормональної регуляції при опіковій хворобі, які визначають особливості її перебігу, але часто не враховуються клініцистами. Проаналізовано доступні літературні джерела. Проведено узагальнення повідомлень вітчизняних та зарубіжних дослідників щодо компенсаторних і патологічних змін гормональної регуляції організму в пацієнтів із локальною тепловою травмою. Сподіваємося, що наведені дані стануть у пригоді лікарям-комбустіологам в їхній практичній діяльності. Ураження ендокринних залоз — один із ключових патогенетичних чинників локальної термічної травми, але внутрішньоклітинні механізми впливу опікової хвороби на ці процеси недостатньо вивчено. Критичність опікових ушкоджень часто призводить до гіподіагностики ендокринних порушень, які є типовими та швидко розвиваються. Нейроендокринна реакція на тяжкі опіки — це багатосистемна скоординована відповідь організму, яка може не лише підтримувати гомеостаз та відігравати захисну роль у критичних умовах, а й спричиняти тканинні пошкодження, реалізуючи властивості «двосічного меча». Опіки, що охоплюють понад 40 % загальної площі поверхні тіла, супроводжуються стресовою реакцією та гіперзапаленням зі стійким підвищенням секреції катехоламінів, глюкокортикоїдів і цитокінів. Класичні дослідження підтверджують, що різке післяопікове підвищення гормонів стресу (адреналіну, норадреналіну, глюкагону та кортизолу) призводить до розвитку гіперглікемії, системного катаболічного стану та поліорганної дисфункції. Доведено роль гіпоталамо-гіпофізарної вісі при локальних термічних ураженнях. Про це свідчать зміни вмісту гіпофізарних гормонів у сироватці крові. Після тяжких опіків активується плазмова ренін-ангіотензин-альдостеронова система, і рівень деяких гормонів підвищується протягом більше 2 міс після травми.

Ключові слова: гормон, ендокринне порушення, запалення, катаболізм, опік.

FOR CITATION

Kravets OV, Yekhalov VV, Gorbuntsov VV. Endocrine disorders in burn disease. Literature review. General Surgery (Ukraine). 2023;3-4;79-87. http://doi.org/10.30978/GS-2023-3-79.