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SIDE EFFECTS AND HYPERSENSITIVITY REACTIONS TO CORTICOSTEROIDS

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Abstract. Side effects and hypersensitivity reactions to corticosteroids. Lisiecka M.Z. *The relevance of the topic under study is due to the fact that patients receiving large or repeated doses of corticosteroids often suffer from hypersensitivity reactions or side effects from taking this category of drugs. As a result, this poses a serious problem for healthcare authorities, as the scientific understanding of this phenomenon is still at an early stage. The purpose of study is to comprehensively disclose the various types of mechanisms underlying corticosteroid hypersensitivity, as well as to develop recommendations for more accurate methods of diagnosis, treatment, and prevention of this reaction. To achieve this goal, this theoretical study used various methods, including analysis, deduction, abstraction and generalization, and the method of synthesis. The results of the study underscore the broad spectrum of applications for corticosteroid drugs in medicine, highlighting their systemic effects and potential for side effects and hypersensitivity reactions across various bodily systems. These adverse reactions encompass hyperglycemia, hypertension, respiratory issues, visual impairments, skin conditions like contact dermatitis, bone tissue complications, and behavioral disorders, notably in children. Administering corticosteroids in COVID-19 treatment necessitates caution due to the potential for life-threatening immediate hypersensitivity reactions, which may be mistaken for disease progression. The results and conclusions of this study, which were formed using the above methods, may lead to a more accurate diagnosis of hypersensitivity to drugs such as corticosteroids, and may also contribute to the development of effective preventive measures. This study is of practical importance for dermatologists, allergists and immunologists, as well as researchers working in the field of rheumatology, allergology and immunology.*

Реферат. Побічні ефекти та реакції гіперчутливості до кортикостероїдів. Лісецька М.З. *Актуальність досліджуваної теми зумовлена тим, що пацієнти, які отримують великі або повторні дози кортикостероїдів, часто страждають від реакцій гіперчутливості або побічних ефектів від прийому цієї категорії препаратів. Як наслідок, це створює серйозну проблему для органів охорони здоров'я, оскільки наукове розуміння цього явища все ще перебуває на початковій стадії. Метою дослідження є комплексне розкриття різних типів механізмів, що лежать в основі гіперчутливості до кортикостероїдів, а також розробка рекомендацій щодо більш точних методів діагностики, лікування та профілактики цієї реакції. Для досягнення поставленої мети в цьому теоретичному дослідженні були використані різні методи, зокрема аналіз, дедукція, абстрагування та узагальнення, а також метод синтезу. Результати дослідження підкреслюють широкий спектр застосування кортикостероїдних препаратів у медицині, підкреслюючи їх системну дію та потенціал виникнення побічних ефектів і реакцій гіперчутливості в різних системах організму. Ці побічні реакції включають гіперглікемію, артеріальну гіпертензію, респіраторні проблеми, порушення зору, шкірні захворювання, такі як контактний дерматит, ускладнення з боку кісткової тканини та поведінкові розлади, особливо в дітей. Застосування кортикостероїдів при лікуванні COVID-19 вимагає обережності через потенційну можливість виникнення небезпечних для життя негайних реакцій гіперчутливості, які можуть бути помилково сприйняті як прогресування хвороби. Результати та висновки цього дослідження, які були сформовані за допомогою вищезазначених методів, можуть привести до більш точної діагностики гіперчутливості до таких лікарських засобів, як кортикостероїди, а також сприяти розробці ефективних профілактичних заходів. Це дослідження має практичне значення для лікарів-дерматологів, алергологів та імунологів, а також дослідників, які працюють у галузі ревматології, алергології та імунології.*

Corticosteroids are widely used in clinical practice to treat a number of diseases, including inflammatory and autoimmune diseases. However, despite the efficacy of this category of drugs, there is considerable concern among healthcare professionals about the increased incidence of hypersensitivity reactions and side effects in patients treated with corticosteroids.

Polish researchers considered corticosteroids as a treatment for multisystemic inflammatory syndrome and noted that the drugs have a pronounced

antiinflammatory and immunosuppressive effect [1]. However, adverse reactions are a key factor when taking this group of drugs. The most common effects include increased blood glucose levels, decreased immune function, and an increased risk of infections. The researchers noted that adverse reactions include hypotension, tachycardia and bradycardia, arrhythmia, visual impairment, seizures, anaphylaxis. In addition, corticosteroids have been shown to be effective in improving the clinical course of persistent tachypnoea in infants [2]. The researchers used corticosteroids in combination with inhaled bronchodilators. However, the study did not address the issue of safe dosing and possible side effects and hypersensitivity reactions in infants, although this is a key factor in safe treatment.

To date, the use of corticosteroids in otorhinolaryngology has also been considered. M.B. Skarzynska and P.H. Skarzynski [3] emphasized the high efficacy of the drugs in the treatment of diseases such as tinnitus, sudden hearing loss, and others, as well as an adjunctive method in various otorhinolaryngological operations. It is worth noting that the efficacy of a drug should always be assessed with risks, as well as the possible development of a hypersensitivity reaction. However, previous studies have provided little information on identifying the risks of such reactions. Due to the lack of such data, the issue is a problem of past scientific research. There is also a study that demonstrates a high risk of adverse reactions due to the use of inhaled corticosteroids. P. Damiański et al. [4] believe that the risk of systemic and local side effects can be addressed by adjusting the dosage and changing the type of drug use. However, in most cases, hypersensitivity reactions are treated by stopping corticosteroids completely, so the proposed method will be ineffective. A study by A. Podlecka-Piętowska et al. [5] demonstrated the high efficacy of corticosteroids in the treatment of patients with COVID-19 and recurrent cases. However, the study does not mention adverse reactions and hypersensitivity to these corticosteroids, although these factors are key in the treatment with corticosteroids.

Hypersensitivity reactions can have various clinical manifestations and vary depending on the severity of the condition: allergic reactions, hypersensitivity of various types, and local symptoms. It should be noted that understanding the reactions and the factors that contribute to the development of these reactions is of great importance to ensure the adequate, safe and effective use of corticosteroids in medical practice [6]. The study by P. Hałubiec et al. [7] reveals the topic of fear of adverse reactions. It is worth noting that this psychological factor plays a significant role in corticosteroid treatment, as the patient's fear can significantly affect the course of the disease and treatment. The authors emphasized that adverse reactions do occur, and that corticosteroid treatment should be carried out as soon as possible. This will help to minimize and prevent the development of adverse reactions.

Today, corticosteroids remain the main group of drugs for the treatment of diseases such as asthma, allergic reactions, autoimmune diseases, arthritis [8]. Their widespread use explains the importance of studying the side effects and reactions that patients may experience, especially those who require long-term treatment. Scientists continue to investigate the mechanisms of action of corticosteroids and their complex effects on the human body. Thus, research not only expands knowledge of biological processes, but can also contribute to the development of safer and more effective medicines.

The aim of the study is to identify the prevalence and factors that cause hypersensitivity reactions and side effects to corticosteroids. In this regard, the objectives of this study are to consider the mechanism of development of reactions to corticosteroids, to describe methods of diagnosing such conditions, and to identify how to prevent the development of an allergic reaction in a patient treated with corticosteroids.

MATERIALS AND METHODS OF RESEARCH

In order to achieve the objectives of this study, various, mainly theoretical methods were used, including abstraction, analysis, deduction, and generalization. The method of abstraction was used to identify key concepts and notions from scientific publications. This method was intended to simplify the study of a large volume of literature by highlighting the most relevant information from 25 sources used to describe various aspects of corticosteroid hypersensitivity reactions and their side effects. The main themes and issues related to the topic of corticosteroid hypersensitivity reactions were formulated, and then these data were abstracted from the available literature. The analysis method was used to identify common themes, trends, and contradictions in the literature. This method also allowed for a critical review of scientific papers, highlighting key findings and identifying differences in research approaches and results. The deduction method in this study helped to clearly formulate conclusions based on the analysis and synthesis of available data. The main conclusions were drawn and presented in the context of the research objective. The method of synthesis was used to systematize and structure the information obtained. All data were divided into certain categories, including

types of hypersensitivity reactions, risk factors, mechanisms of development and treatment.

Various databases were used to systematically search for the necessary scientific literature. Among them are the following: PubMed, Google Scholar, Scopus, Web of Science, EMBASE, as well as medical databases such as MEDLINE. The search for the necessary materials was carried out using a combination of keywords and phrases related to the topic of hypersensitivity reactions and side effects from taking corticosteroids. The keywords included "corticosteroid hypersensitivity", "adverse effects of corticosteroids", "allergic reactions to corticosteroids", "adverse effects of corticosteroids", "allergic conditions", "hypersensitivity to glucocorticoids", "corticosteroids" and others.

It should be noted that this study included scientific articles, literature reviews, clinical trials, meta-analyses and books published between 2015 and 2023. To determine the relevance of each publication, a preliminary analysis of the abstract or summary was conducted. Several criteria were taken into account in order to include the literature in this study. These include subject, language, and accessibility. The study included articles and publications directly related to corticosteroid hypersensitivity reactions and side effects. In addition, the material had to have results and discussions related to the stated topic. The language of all publications is mainly English, but studies by Polish, Italian, and other foreign authors were included. In addition, the study included those publications that had access to the full text or abstracts. In case the full text was not available, abstracts or summaries were used to obtain the main information. Articles and publications that did not meet these criteria were not included in the study. The selected literature sources were analysed and systematized according to thematic categories and key results.

RESULTS AND DISCUSSION

Corticosteroids used in medicine have a variety of compounds. There are several types of corticosteroids, including glucocorticoids (regulate metabolism and have an anti-inflammatory effect) and mineralocorticoids (regulate water-salt balance). Their chemical structure has a general structure based on a steroid skeleton. It includes four carbon rings (three hexagonal and one pentagonal) forming a three-dimensional structure. Important elements of the chemical structure of glucocorticoids are: carbon skeleton (contains 17 carbon atoms arranged in the form of four rings), keto group (C=O), hydroxyl group, side chain. Examples of glucocorticoids include cortisol (hydrocortisone), prednisone, and dexamethasone [9]. Mineralocorticoids also have a steroid structure, but there are some differences. Important elements include the carbon skeleton, keto group, and hydroxyl groups. So, both types of corticosteroids share the same steroid framework, but the difference lies in the side chain and substituents. This determines the variety of biological effects and pharmacological properties of both species.

Thus, glucocorticoids have the following mechanism of action:

- binding to receptors (for example, cortisol binds to glucocorticoid receptors);
- transport to the cell nucleus (a glucocorticoid-receptor complex is formed and transported to the cell nucleus);
- regulation of gene transcription (in the nucleus, this complex interacts with genes involved in transcription regulation, which can lead to an increase or decrease in the expression of certain genes);
- anti-inflammatory effects (glucocorticoids suppress the expression of genes responsible for the inflammation process, as well as inhibit phospholipase a2 and prostaglandin synthesis, which suppresses the inflammation process);
- immunosuppressive effects (glucocorticoids suppress the activity of immune cells, such as monocytes; reduce the secretion of cytokines, including inflammatory ones).
- The mechanism of action of mineralocorticoids is significantly different, as the following processes occur:
- binding to receptors (for example, aldosterone binds to mineralocorticoid receptors, which are usually found in renal tubular cells);
- regulation of electrolyte balance (stimulation of sodium reabsorption and potassium excretion from the kidneys, which leads to an increase in vascular fluid volume and maintenance of normal blood pressure);
- effects on renal cells (mineralocorticoids affect renal tubular cells, increasing the amount of sodium reabsorbed back into the bloodstream).

Thus, both types of corticosteroids (in particular, glucocorticoids) are used in medical practice to manage inflammatory and immune processes.

Corticosteroids are divided into systemic and topical. Systemic corticosteroids are a class of steroid hormones that affect the body as a whole, rather than a specific organ or system. This mainly refers to glucocorticoids, which are the purest form of unified regulation of metabolism and the immune system. However, synthetic drugs used to treat inflammatory and immune diseases are often systemic steroids. Systemic steroids include prednisolone, dexamethasone and others. They are used in the form of tablets or injections to treat systemic inflammatory conditions, control severe allergic reactions, and treat autoimmune diseases [10].

However, due to their systemic effects, these corticosteroids carry a high risk of developing systemic side effects, including high blood pressure, osteoporosis, diabetes mellitus. Topical corticosteroids are applied topically to the skin or mucous membranes in the form of creams, ointments or lotions [11]. Topical medicines are used to treat skin conditions such as eczema, psoriasis, dermatitis, as well as itching and inflammatory reactions. This category of drugs has a limited effect, as their action is concentrated only in the area of application. However, side effects are common, particularly with long-term use of corticosteroids.

There are two main types of corticosteroid hypersensitivity reactions: delayed and immediate. It should be noted that immediate reactions occur in a short time after taking corticosteroid drugs (usually from several hours to several days). Delayed reactions to corticosteroids include the development of contact and atopic dermatitis, as well as other pathological skin conditions (often rashes) [12]. In addition, some patients experience conditions such as pneumonia, nephritis, visual impairment. Less commonly, conditions associated with circulatory system disorders occur, provoking thrombocytopenia. It has been noted that delayed reactions are much more common than immediate reactions [13]. It is worth noting that corticosteroids have a systemic effect on the body, so their effects can be quite unexpected. Among the immediate reactions, allergic anaphylaxis should be highlighted first and foremost. This condition is severe because anaphylaxis develops progressively and quickly. Symptoms include urticaria, Quincke's oedema, shortness of breath, low blood pressure, and angioedema [14]. Importantly, both types of reactions require immediate medical attention and intervention in the patient's treatment plan. Medical personnel should be prepared for the possibility of such reactions in any case, so special attention should be paid to the management of patients using corticosteroids and preventive measures.

There are three types of hypersensitivity reactions to corticosteroids: Type I, III, IV. It is worth noting that corticosteroids suppress immune activity and reduce the number of antibodies, and that is why type II hypersensitivity reactions do not occur (this type of reaction is cytotoxic and antibody-dependent) [15]. Type I hypersensitivity reactions are allergic reactions characterized by a rapid immune response to an allergen. The main mechanism of this type of reaction is the activation of immune cells, such as mastocytes and basophils, by binding immunoglobulin E (IgE) antibodies to allergens [16]. This leads to the release of inflammatory mediators, including histamine, which causes allergic symptoms. Examples of this type of reaction include allergic rhinitis, atopic dermatitis, asthma, and anaphylactic reactions.

According to R.R. Vatti et al. [17], the overall prevalence of corticosteroid hypersensitivity is estimated at 0.3-0.5%. Type III hypersensitivity reactions are associated with the formation of certain complexes in the blood that are deposited in tissues, provoking inflammatory processes [18]. According to the author, the mechanism of development of this reaction is explained by the fact that antibodies are formed when exposed to antigens, and immune complexes are formed with them. These complexes can clog small blood vessels, thereby provoking an inflammatory reaction. An example of this reaction is rheumatoid arthritis. Type IV reactions are cellular hypersensitivity reactions. They develop as a result of the influence of immune system cells, including T-lymphocytes.

Thus, T-lymphocytes are activated upon contact with antigens and begin to release cytokines, which provokes the development of inflammation and tissue damage. An example of this type of reaction is contact dermatitis. It is also worth noting the cross-reactions that can occur with long-term use of corticosteroids. This means that the body loses sensitivity to the drugs and a reaction to one drug or its component may occur when using another. Firstly, sensitivity to corticosteroids decreases, making treatment ineffective. At this point, there is a need to increase the dose of the drug, which is likely to result in an allergic reaction. Thus, transient sensitivity to one of the corticosteroids can lead to the development of allergic reactions when using another drug. Most often, such patients have allergic contact dermatitis, itching, redness and swelling. Against this background, depending on the form and type of drug used, local and systemic side effects develop. The use of topical medicines often leads to skin atrophy, and systemic effects are characterised by hypertension, hormonal disorders and hyperglycaemia.

There is currently no accurate official data on the number of cases of corticosteroid hypersensitivity reactions. However, in a study by A. Patel and S.L. Bahna [19], it was stated that according to some estimates, the prevalence of such cases is approximately 13%. The authors stressed that static data on the occurrence of such reactions in patients may be incorrect. This is due to the fact that doctors are not always able to diagnose this condition, as well as to enter a specific case into the register of official data around the world. Therefore, it is assumed that there is a high probability of underreporting. However, there is some data on the most frequent manifestation of hypersensitivity reaction to corticosteroids. Skin manifestations of hypersensitivity to this category of drugs are most common in clinical practice. Contact

dermatitis is a frequent phenomenon [20]. This type of condition manifests itself as redness of the skin and may also be accompanied by rashes and swelling. This type of reaction occurs in patients who use corticosteroid-based ointments or creams. It should be noted that the author took into account only patients with dermatological problems. Therefore, such data and results are limited and cannot be equated to the general picture of corticosteroid use.

It is also worth noting the method of taking corticosteroids, as it can affect the severity of hypersensitivity reactions and side effects. Below are Table 1 and Table 2 show the side effects of taking systemic and topical corticosteroids.

Table 1

Side effects of systemic corticosteroids (oral/intravenous/intramuscular administration)

Organ/system	Description of the side effect
Skin	Possible delay in the wound healing process
Cardiovascular system	The risk of hypertension increases, and tachycardia may develop
Endocrine system	The increased production of glucose increases the risk of developing diabetes mellitus; Due to hormonal imbalance, general disorders of the endocrine system (thyroid disorders) occur; Cushing's syndrome
Digestive organs	The risk of developing ulcerative gastritis increases due to a decrease in the protective functions of the gastric membrane; Reduced appetite can lead to a decrease in body weight
Kidneys	Possible renal dysfunction and development of renal failure
Respiratory system	Due to a decrease in immunity, the risk of developing infectious diseases of the upper respiratory tract increases significantly
Musculoskeletal system	Increased risk of osteoporosis

Table 2

Side effects of topical corticosteroids (creams/ointments/lotions)

Organ/system	Description of the side effect
Skin	Contact dermatitis often develops; Skin atrophy (skin thickness decreases, stretch marks appear); Skin regeneration processes are disrupted
Eyes	There is a risk of developing cataracts and glaucoma, especially with prolonged use of the drug around the eyes
Mucous membranes	The protective functions of the mucous membranes are suppressed, resulting in an increased risk of infections
Musculoskeletal system	Sometimes myopathy can develop with prolonged use of topical corticosteroids

It is worth noting that both tables are a general overview of possible side effects from certain organs and systems. Allergic reactions should also be highlighted separately, among which the most common are allergic contact dermatitis, systemic allergic reaction and type IV (cell-dependent) hypersensitivity. Interestingly, there are now studies that demonstrate the difference between different types of corticosteroid use. M.K. Yang et al. [21] studied the difference between oral and intravenous administration of the drug using ophthalmic patients as an example. According to the authors' research, intravenous corticosteroids were adequately tolerated, with better clinical remission and more effective prevention of inflammation relapse, unlike oral medication. Therefore, given these results, it can be assumed that

intravenous administration of the drug is completely safe and can be used effectively without causing severe adverse reactions in patients.

According to R. Patel et al. [22], oral use of corticosteroids significantly increases the risk of adverse reactions. In their study, the authors examined adverse reactions during treatment with corticosteroid medications for asthma. In some patients, a decrease in bone mineral density was found. However, the authors noted that such data are ambiguous, as this phenomenon was not detected in some patients. In addition, this group of patients was observed for a short time, so it is inappropriate to testify to the reliability of the results. Other side effects included eye diseases (cataracts) and respiratory infections. In these adverse reactions, the authors also noted a low level of confidence, as the classification was incorrect, and in most cases, it was not possible to take into account certain factors affecting the results. Therefore, such statements should be considered limited and used only as assumptions or insufficiently researched data.

However, according to K. Mahlab-Guri et al. [6], hypersensitivity reactions can occur with absolutely any route of administration. According to the study, the development of at least some hypersensitivity reactions or side effects does not depend on the route of administration, as corticosteroids are systemic drugs. It is possible that intravenous administration of drugs is to some extent safer, as the effects of corticosteroids will not directly affect some organs, such as the gastrointestinal tract and others. Therefore, such data remain only assumptions and require more detailed and comprehensive research. Currently, there are virtually no comprehensive studies comparing oral, inhalation and intravenous routes of corticosteroid administration. The availability of such data would help to more accurately assess the safety of these methods of drug administration, as well as the risk of adverse reactions depending on the listed methods. In addition, the researchers stressed the importance of diagnostic measures (subcutaneous tests, patch tests). This way, it will be possible to avoid unwanted complications in the patient's condition, as well as to change the treatment plan by prescribing alternative and safe medicines. S. Voltolini and F. Fumagalli [23] also mentioned this diagnostic method, indicating that allergy testing is useful in differentiating patients and adjusting the patient's management plan.

Diagnosing corticosteroid hypersensitivity is an essential step in managing this condition. Doctors perform two types of diagnostic tests, including *in vitro* and *in vivo* diagnostics. In order to detect a type I allergic reaction, skin tests with intradermal injection of allergens are used to determine sensitivity to allergens. You can also use a diagnostic test to determine the level of IgE in the blood. This determines the level of IgE antibodies, which indicates sensitivity to specific allergens. Diagnostics of type III allergic reaction is rarely used. In some cases (very rarely), an Allen's test may be performed (clinically assessing the patency of the arteries of the hand), but more often an analysis is performed to determine the level of immune complexes formed during allergic reactions of this type in the blood. In addition, diagnostic methods can be used to determine the effect of allergens on the endothelium and its permeability. In this way, it is possible to determine whether a type III allergic reaction is developing. To diagnose type IV allergic reactions, patch tests, skin tests with intradermal antigen injection (determining sensitivity to antigens that cause cell-dependent allergy), and tests with increased endothelial permeability are widely used.

The literature notes that for diagnostic purposes, patch tests (aimed at testing sensitivity to corticosteroids) or immunological studies (detecting antibodies and other immunological markers that help to establish the correct diagnosis) are most often used [24]. Immunological tests are aimed at finding biomarkers associated with hypersensitivity to the declared drugs. It should be noted that determining the level of immune markers can be an additional diagnostic method. In addition, other diagnostic methods are also carried out, including subcutaneous tests. They involve sensitivity tests to detect the manifestation of a reaction to medications [25].

S. Svendsen et al. [20] conducted a study involving 6823 patients. All of them underwent a patch test. The authors' study showed that 185 (2.7%) patients had a positive patch test result for corticosteroids, with no gender differences. In addition, the study noted that sensitivity to thixocortol-21-pivalate was more common in women than in men (61.3% to 34.5%, respectively). It should be noted that the rate of 2.7% is not small, and it is in this case that it is possible to assume that the frequency of hypersensitivity reactions to corticosteroid drugs is quite high. Such data indicate the need to conduct drug sensitivity tests in patients who are prescribed treatment with these drugs. However, at present, not all doctors conduct tests to determine the patient's sensitivity to corticosteroids. This may be due to a lack of awareness of the development of hypersensitivity reactions and serious side effects. Another option is uncontrollable actions of medical staff, which is already a problem for healthcare authorities. If the algorithm of actions of medical personnel were strictly controlled in accordance with certain protocols, most cases of hypersensitivity reactions in

patients prescribed corticosteroids could be avoided [26]. So, as of today, this problem is quite real and has no specific solutions.

In addition to diagnostic measures, risk factors also play an important role. It should be noted that previous researchers have hardly considered the genetic risk factor. A. Ramadan et al. [27] study only mentioned that genetic factors can generally influence corticosteroid hypersensitivity reactions. However, nothing specific was said. It is worth noting that some genes can significantly affect the body's ability to metabolize corticosteroids. Examples of such genes are cytochrome *P450* genes (e.g. *CYP3A4* and *CYP3A5*). Variations in these genes can lead to changes in enzyme activity, which can significantly affect the rate and efficiency of corticosteroid metabolism. In addition, genes that regulate the body's immune response should also be considered. Such genes are related to the function of T- and B-cells, and therefore may be involved in hypersensitivity reactions to corticosteroids. Variations in these genes can affect the body's immune response and its regulation. Genes that control allergic reactions (genes encoding IgE) may also be important, as they may be associated with the development of an allergic reaction to corticosteroids. It is worth noting that these genetic factors are considered in the context of individual susceptibility to hypersensitivity reactions to corticosteroids. However, genetic predisposition is not the only cause of such reactions, and it may well interact with other factors, such as the dosage and duration of medication, the patient's allergic history [28].

The patient's allergic history is also an important factor. This term should be understood as the history of complications that may have occurred in the patient's past. This is a rather serious risk factor when prescribing corticosteroids to a patient, as this category of drugs can lead to an increased susceptibility to allergic reactions. Therefore, corticosteroids should be prescribed to such patients with extreme caution. Unlike diagnostic measures, the treatment of hypersensitivity reactions does not currently have a single approach. Discontinuation of corticosteroids is the leading treatment, as these drugs have systemic effects on the body and can cause additional side effects. These effects can include a decrease in immune function (the danger is that due to the suppression of the immune system, the risk of at least any type of disease increases significantly), hormonal changes (a decrease in cortisol levels is common), and atrophy (reduction) of the skin [29].

S. Kulkarni et al. [30] examined metabolic reactions in patients receiving systemic corticosteroid therapy in her study. The authors identified several undesirable metabolic events associated with taking corticosteroid medications. The first place in the prevalence of cases was weight gain (13%). This rather high figure can be explained by the fact that taking medications can significantly increase appetite, as well as disrupt fat metabolism and synthesis. Hyperlipidaemia was the second most common condition (8% of patients had this condition). In fact, this figure may be reasonable, as insulin sensitivity decreases while taking corticosteroids. In addition, it can be assumed that drugs in this category can increase the synthesis of fats in the liver, which leads to an increase in cholesterol and triglyceride levels. The third most common disease was hypertension (6%). The risk of developing hypertension is often mentioned in public information. It is worth assuming that several factors may contribute to this, including insulin resistance and increased salt excretion (i.e., increased sodium excretion and water retention in the body, which increases the volume of circulating blood, causing an increase in blood pressure). Severe hyperglycaemia was the last most common condition (5% of cases). It is worth noting that the author highlighted the severe form of hyperglycaemia, so it can be assumed that mild and moderate hyperglycaemia accounted for a much higher percentage, which is quite typical for taking corticosteroid medications. Based on these data, it can be said that taking corticosteroids is likely to have certain consequences (i.e., it is not necessarily a hypersensitivity reaction) [31].

In their study, F.F. van den Brand et al. [32] also examined the development of corticosteroid side effects in patients with autoimmune hepatitis. The authors noted that 25% of patients had side effects, with low doses of the drug increasing the likelihood of bone fractures, and high doses could contribute to the development of cataracts and diabetes. However, the study did not specify the dosages in question. This is probably due to the lack of an optimal dosage and the need to individually prescribe the dosage of a corticosteroid medicine. However, based on these data, it can be argued that even low doses of corticosteroids are not safe and often lead to the development of adverse effects. A study was conducted in which E.J. Koshi et al. [33] associated the development of complications due to corticosteroids with high dosages. In the case of prednisolone, a dosage above 430 mg was indicated. In this case, the risk of side effects increases significantly. In addition, the author emphasized the increased likelihood of gastrointestinal bleeding. It is worth noting that other researchers have hardly considered this issue, so it is impossible to confirm or refute such data.

In today's reality, it would also be advisable to consider the role of corticosteroids in patients with COVID-19. It is worth noting that corticosteroids

have been and are being used quite actively to treat patients with COVID-19. M. Lafaurie et al. [34] conducted a study aimed at examining the impact of systemic corticosteroids and side effects in patients diagnosed with COVID-19. The study included 253 patients. Almost 7% of patients were prescribed corticosteroids during hospitalization, and side effects were observed in 1% of patients. However, the authors noted that there was no overall increased risk of adverse outcomes. In addition, X. Chang et al. [35] noted that acute respiratory distress syndrome caused by COVID-19 is quite effectively treated with corticosteroids, while reducing the risk of death.

M. Karn et al. [36] have also studied the impact of corticosteroids on patients with this disease. The authors focused on the acute effects of corticosteroids, which are often ignored by doctors. Since patients receive oxygen, doctors should be extremely careful when prescribing corticosteroids, as an immediate hypersensitivity reaction can occur. The problem is that this reaction can be easily confused with the progressive deterioration of COVID-19. An allergic reaction in this case implies anaphylaxis. According to the authors, such cases are quite rare, and their percentage is approximately 1%. However, it can be assumed that a certain proportion of such cases were ignored or not noticed at all. Therefore, given that there is no official data on the reported conditions, it is reasonable to assume that the frequency is higher. Another critical issue, according to the researchers, is thrombosis and cerebrovascular disease. COVID-19 damages endothelial tissue, and a corticosteroid drug can increase blood clotting and fibrinogen concentration. In this case, patients may experience clinical thrombosis [37]

In his study, K. Wang et al. [38] described the case of a 53-year-old patient treated with corticosteroids. The authors noted that the woman was diagnosed with COVID-19 by a chest computed tomography scan and a PCR (polymerase chain reaction) test for SARS-CoV-2. The patient had severe shortness of breath, poor oxygenation, and lung tissue compaction. The doctors decided to administer corticosteroid drugs in moderate doses. According to the authors, the patient's condition improved significantly within six days. No adverse reactions were noted. The patient was discharged from the hospital on the 17th day of hospitalization. Such data may indicate the effectiveness of corticosteroids in COVID-19, as many doctors treat their patients (including those in serious condition) with corticosteroids. In addition, not everyone experiences adverse reactions. It can be assumed that side effects in patients with a respiratory infection can be prevented with optimal dosage. However, if the patient is hypersensitive to the drug, treatment with this particular category of drugs is likely to be contraindicated.

X. Yang and H. Jin [39] studied the safety of corticosteroids in children with respiratory diseases. The authors noted that the group of children taking corticosteroids had a shorter hospital stay. In addition, the percentage of untreated children after 3 days of treatment was significantly lower compared to the group of children who did not take corticosteroids. There were no differences in the development of side effects between the two groups. Based on these data, it can be argued that the use of corticosteroids in children with respiratory diseases can significantly reduce hospital stays and promote faster recovery without causing adverse reactions.

A recent study by K.S. Bodum et al. [40] drew attention not only to physical, but also to behavioural side effects. The authors studied the manifestation of this phenomenon in children and adolescents with bronchial asthma. The European Medicines Agency registered 104 and the Children's Medicines Agency registered 3 reports of adverse behavioural reactions in children and adolescents with respiratory diseases (in this case, only bronchial asthma was considered). In addition, 5 out of 8 paediatricians stated that in their practice there were cases of behavioural disorders in children treated with corticosteroids during the disease. However, none of the specialists submitted official reports on these cases.

Analysing these data, it can be argued that the official figures will be significantly underestimated, as almost no one attaches importance to behavioural disorders due to corticosteroid medication. It should be emphasized that the author did not specify what kind of behavioural reactions developed in children or adolescents. It can be assumed that these were insomnia, anxiety, increased stress levels, and mood changes. This list is based on well-known facts about the effects of corticosteroids on the nervous system. However, there is currently no official data to draw any conclusions on this topic. However, a potential side effect does exist, and doctors should be informed about it.

CONCLUSIONS

1. Since corticosteroid drugs have a systemic effect and a fairly wide range of use, side effects and hypersensitivity reactions can occur in various organs and systems of the body.
2. Medicinal products can provoke hyperglycaemia (this phenomenon can also provoke other pathological conditions), hypertension and hyperlipidaemia.
3. Adverse reactions can include respiratory diseases, visual impairment, skin manifestations (e.g., contact dermatitis and other conditions accompanied

by skin rashes), adverse effects on bone tissue and even behavioural disorders, particularly in children.

4. The safety of different methods of taking corticosteroid drugs has not been studied sufficiently. However, there is an assumption that oral administration is more dangerous than intravenous administration.

5. The use of corticosteroids in COVID-19 requires special care, as there are life-threatening conditions (immediate hypersensitivity reactions) that can be easily confused with the deterioration of the condition that is characteristic of this disease.

6. In general, the literature review on the stated topic allowed comprehensively considering the possibilities of taking corticosteroids.

7. According to the material analysed, corticosteroids are used in many areas of medicine (i.e., the use of corticosteroid drugs is not limited to dermatology, immunology and other fields).

8. It was found that there are certain problems with diagnostic measures (in particular, identifying the patient's sensitivity to corticosteroids).

9. Strengthening control over the actions of medical professionals would help to avoid this problem. There are currently no effective methods to prevent side effects and/or undesirable outcomes.

10. In this regard, it would be advisable to develop methods to reduce the risk of adverse reactions.

11. The development of such methods for long-term use of corticosteroids would help to significantly improve the quality of life of patients. In addition, it is crucial to have an alternative to corticosteroids.

12. The search for and development of safe and effective alternative treatments that do not cause hypersensitivity reactions is currently a key factor in solving this problem.

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