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Steroid-induced diabetes in the paediatric population

Cukrzyca posteroidowa w populacji pediatrycznej

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Abstract

Steroid-induced diabetes is a rare disease in the paediatric population. High doses of corticosteroids are used in diseases such as acute lymphoblastic leukaemia (ALL), lymphomas, or connective tissue diseases.

Post-steroid hyperglycaemia arises as a result of increased gluconeogenesis and increased glycogen synthesis. Steroid-induced diabetes most often is asymptomatic; therefore it is important to monitor the glycaemic level in patients receiving systemic glucocorticoids. So far, no separate guidelines for steroid-induced diabetes have been developed, so the criteria for diagnosing drug-related diabetes mellitus do not differ from the criteria for diagnosing type 2 diabetes. Hyperglycaemia adversely affects the immune system: it impairs the function of granulocytes, immunoglobulins, and also causes T-lymphocyte apoptosis. A hyperglycaemic environment favours the development of bacterial and fungal infections. Numerous studies confirm that hyperglycaemia increases the risk of infection and severity of infection.

There have also been reports of adverse effects of steroid-induced hyperglycaemia in the course of treatment for the underlying disease in the adult population. Reports related to the paediatric population are not as numerous. There are studies that have proven an increased risk of infection in paediatric patients with ALL and steroid-induced diabetes, as well as studies that proved an unfavourable effect of diabetes on survival in children with ALL and as well the studies that proved that risk of life-threatening infection and survival does not differ statistically in the group of patients with hyperglycaemia and in the group of patients who did not develop diabetes.

Key words:

glucocorticosteroids; oncohaematological children; transient hyperglycaemia, steroid-induced diabetes.

Streszczenie

Cukrzyca posteroidowa to rzadkie schorzenie w populacji pediatrycznej. Należy do grupy cukrzyc polekowych. Wysokie dawki kortykosteroidów stosuje się w takich schorzeniach, jak ostra białaczka limfoblastyczna (*acute lymphoblastic leukemia* – ALL), chłoniaki czy choroby tkanki łącznej.

Hiperglikemia posteroidowa powstaje wskutek wzmożenia glukoneogenezy oraz wzmożenia syntezy glikogenu. Cukrzyca posteroidowa najczęściej przebiega bezobjawowo, dlatego ważne jest monitorowanie stężenia glikemii u pacjentów otrzymujących glikokortykosteroidy ogólnoustrojowo. Dotychczas nie opracowano oddzielnych wytycznych dla cukrzycy polekowej, zatem kryteria rozpoznania cukrzycy posteroidowej nie różnią się od kryteriów rozpoznania cukrzycy typu 2. Leczeniem z wyboru cukrzycy posteroidowej w populacji pediatrycznej jest insulinoterapia. Ponadto należy wdrożyć odpowiednią dietę oraz wyedukować pacjenta i jego opiekunów. Hiperglikemia wpływa niekorzystnie na działanie układu immunologicznego: upośledza funkcje granulocytów, immunoglobulin, a także powoduje apoptozę limfocytów T.

Środowisko hiperglikemiczne sprzyja rozwojowi infekcji bakteryjnych i grzybiczych. Liczne badania potwierdzają, że hiperglikemia zwiększa ryzyko infekcji oraz powoduje ich cięższy przebieg. Opublikowano również doniesienia o niekorzystnym wpływie hiperglikemii posteroidowej na przebieg leczenia choroby podstawowej w populacji dorosłych. Doniesienia odnoszące się do populacji pediatrycznej nie są tak liczne i istnieją zarówno badania, w których udowodniono zwiększone ryzyko infekcji u onkologicznych pacjentów pediatrycznych z ALL z rozpoznaną cukrzycą posteroidową, oraz niekorzystny wpływ cukrzycy posteroidowej na przeżywalność u dzieci z ALL, jak i badania, w których udowodniono, że ryzyko wystąpienia infekcji zagrażającej życiu oraz przeżywalność nie

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różnią się statystycznie w grupie pacjentów z rozpoznaną hiperglikemią posteroidową oraz w grupie pacjentów, u których powikłanie to się nie rozwinęło.
Słowa kluczowe:
glucocorticosteroids, oncohaematological children; transient hyperglycaemia, steroid-induced diabetes.

Introduction

Diabetes is a group of metabolic diseases with a diverse aetiology characterised by chronic hyperglycaemia resulting from a defect in action and/or excretion of insulin.

Among children diagnosed with diabetes about 90% suffer from type 1 diabetes and about 10% suffer from type 2 diabetes (although this percentage is currently increasing), and less than 5% are other cases of diabetes, including drug-induced diabetes [1].

Large doses of steroids in paediatrics are used mainly during oncological treatment of such cancers as: acute lymphoblastic leukaemia, and both Hodgkin's and non-Hodgkin's lymphomas. These drugs are also used in other haematological diseases: severe aplastic anaemia, immune thrombocytopaenia, autoimmune haemolytic anaemia, or haemophagocytic syndrome. In addition, corticosteroids are used in transplantology, nephrotic syndrome, and connective tissue diseases [2].

It should not be forgotten that steroids are also administered topically, in the form of inhalants (in the treatment of bronchial asthma, laryngitis, and tracheitis) as well as in the form of drops, ointments, or intra-articular injections in various inflammatory conditions

It is well known that steroid therapy is burdened with numerous complications such as: hyperglycaemia, hypertension, psychiatric disorders, glaucoma, cataracts, osteonecrosis, osteoporosis, abnormal distribution of adipose tissue, or immunosuppression.

The side effects of topical corticosteroids are much less common than with systemic steroids. However, it should be remembered that with long-term use of high doses of the topical drug, we can also observe the above-mentioned complications [3].

Mechanism of steroid-induced diabetes formation

The mechanism of hyperglycaemia formation during corticosteroid therapy is complex. Hyperglycaemia after using glucocorticosteroids (GK) is caused by increased gluconeogenesis in the liver. Glucocorticosteroids stimulate the expression and activity of phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase. Both of these enzymes play A key role in gluconeogenesis. In addition, GK, by stimulating the lipolysis of adipocytes and proteolysis of proteins, increase the amount of substrates for gluconeogenesis [4]. It has been proven that GK, both in short-term and long-term therapy, impairs the inhibitory effect of insulin on endogenous glucose production by as much as 50% [2]. Glucocorticosteroids-induced insulin resistance is also observed in skeletal muscles; in studies in rats, reduced glucose uptake and increased glycogen synthesis after steroid administration have been reported [5]. The mechanism of insulin resistance in skeletal muscles may be associated with an increase in the level of non-esterified fatty acids and the lack of lipolysis inhibition by GK. Attention should also be paid to the effect of GK on pancreatic cells. In connection with insulin resistance induced by steroids, the level of fasting insulin and insulin secretion after glucose stimulation increase, which, with long-term exposure to GK, may cause pancreatic beta-cell dysfunction in genetically predisposed individuals [2]

Steroids may also stimulate pancreatic alpha cells for enhanced glycogen synthesis – this phenomenon is however observed only at high doses of GK (30 mg of prednisolone daily); this effect can be observed after administration of single high doses of the drug [6].

Steroid-induced hyperglycaemia most commonly causes postprandial glycaemia increase at normal fasting glycaemia level due to the pharmacokinetics of glucocorticoids, which have their maximum effect from 4 to 13 hours after administration. Of course, if during intensive treatment the patient receives steroid doses in the evening or at night, fasting glycaemia levels will also be abnormal [7].

The risk of steroid-induced diabetes occurrence increases with the dose of the drug and the length of the time of its use. However, not all patients develop this type of diabetes; the risk factors for the development of hyperglycaemia include age $>$ 10 years, body mass index (BMI) $>$ 90th percentile, and family history and personality history for carbohydrate metabolism disorders [8].

Diagnosis and treatment of steroid-induced diabetes

The symptoms of steroid-induced diabetes are non-specific because they resemble type 2 diabetes and very rarely have the characteristics of ketoacidosis. However, some cases of patients with steroid-induced diabetes who have experienced hyperglycaemic coma, ketoacidosis, or nonketotic hyperosmolar hyperglycaemia have been described [9, 10].

Therefore, it should be taken into account that the patient may not present any clinical symptoms, although hyperglycaemia is in progress.

So far, no separate guidelines for the diagnosis of drug-induced diabetes mellitus have been developed; therefore, the criteria for the diagnosis of steroid-induced diabetes do not differ from the criteria for diagnosis of type 2 diabetes according to the Polish Diabetes Association 2017.

Pilot studies were carried out to create algorithms for the recognition and treatment of steroid-induced diabetes. Most of these studies, however, were conducted on a group of adult patients, such as the Valderhaug *et al.* study in patients after renal transplantation or Burt's study in patients with chronic obstructive pulmonary disease [7, 11]. A significantly smaller number of studies were conducted in children. One of the proposed algorithms for the treatment of children with oncohaematological diseases was created at the Department of Paediatrics, Haematology, and Oncology of the Medical University of Gdańsk in cooperation with the Department of Paediatrics, Diabetology, and Endocrinology. In this algorithm, the authors draw attention to the need to search for factors predisposing to steroid-induced diabetes and for the necessity of systematic monitoring of glucose levels in all children with cancer, who receive GK [12].

In contrast to adults, in whom steroid-induced diabetes can be treated with oral antidiabetic agents, the treatment of choice for steroid-induced diabetes in children is insulin therapy. One should also remember about the necessity of introducing a proper diet, and education of the patient and his/her caregivers. However, introducing a diet based on a low glycaemic index is extremely difficult in paediatric patients during steroid therapy. Corticosteroids stimulate the hunger centre, and therefore patients constantly feel hungry. Due to the young age, cooperation on the issue of rational nutrition with a limited amount of food is often impossible. Care of children with steroid-induced diabetes should be performed by a multidisciplinary team consisting of a haematologist, a paediatric diabetologist, and a dietician.

Steroid-induced diabetes usually disappears in patients after the end of GK treatment. Children who have been diagnosed with hyperglycaemia after using steroids, however, have an increased risk of developing type 2 diabetes in the future.

The effect of hyperglikaemia on the immune system

Hyperglycaemia impairs phagocyte function and granulocyte germicidal activity by inhibiting such functions as cell migration to the site of infection, cell adhesion, oxidative burst, and the killing of absorbed bacterial particles [13]. Hyperglycaemia also causes the inhibition of interleukin 2 production, which stimulates T cells and NK cells. High serum glucose level also causes excessive lymphocyte apoptosis and inhibits T-cell proliferation due to decreased expression of adenosine kinase [14].

Mechanisms that impair the immune response due to hyperglycaemia include the acceleration of non-enzymatic glycosylation of human body proteins. One of the proteins subjecting to non-enzymatic protein glycosylation is immunoglobulin G. Glycosylation impairs the functions of immunoglobulins, which are involved in the immune response to encapsulated bacterial infection. Immunoglobulins stimulate phagocytosis by coating the bacteria and presenting the Fc region to phagocytes [15]. Subsequent proteins that undergo non-enzymatic glycosylation due to hyperglycaemia are components of the complement. This process also impairs their function thereby inhibiting the immune system [14].

Patients undergoing steroid therapy are immunocompromised patients due to the mechanism of corticosteroid activity and also due to underlying diseases such as acute lymphoblastic leukaemia, severe aplastic anaemia, or lymphoma. Immunosuppression in combination with steroid-induced hyperglycaemia may lead to an increased risk of severe bacterial and fungal infections.

Hyperglycaemia and bacterial and fungal infections

Bacterial infections

Glucose is a very good medium for many bacteria; moreover, a high level of glucose in the environment favours the change of gene expression by bacteria, which results in their greater virulence. It should not be forgotten that by impairing the immunological mechanisms, which are described above, the killing of bacteria by the human body is significantly inhibited.

Fungal infections

Candida albicans is a pathogen that produces a protein induced by glucose. This protein is structurally and functionally homologous to the complement receptor on mammalian phagocytes. This protein promotes the adhesion of fungal cells to the epithelium and mucosa, and impairs phagocytosis of the host [16].

Both mononuclear and polymorphonuclear phagocytes are involved in the control of fungi of the order *Mucorales* by activating oxidative metabolites and through the participation of cationic peptides – defensins 33, 166, and 169. Clinical data indicate that phagocytes are the main defence mechanism of the host against mucormycosis. Hyperglycaemia impairs the ability of phagocytes to migrate and negatively affects the destruction of microorganisms by inhibiting the oxygen response [17].

The immune system fights against infections with fungal aetiology from the genus *Aspergillus*, including *Aspergillus fumigatus*, through the mechanism of an oxidative burst [18]. Hyperglycaemia impairs the functions of phagocytes, and hence also the reactions of an oxidative burst, which means that patients during hyperglycaemia are also at greater risk of developing an infection with fungal aetiology from the genus *Aspergillus* spp.

Increased risk of infection development and more severe infection course in hyperglycaemia patients

The influence of hyperglycaemia on all the above-described mechanisms gives rise to the conclusion of a significant risk of developing infection of diverse bacterial and fungal aetiology in patients with steroid-induced diabetes.

Numerous studies have been carried out on the adult population and fewer on the paediatric population, which not only prove an increased risk of infection in this group of patients but also a more severe course in patients with steroid-induced diabetes.

Patel *et al.* report that hyperglycaemia in adult patients without diabetes mellitus, diagnosed within 48 h of the observed increase in *P. aeruginosa* in the blood is an independent risk factor increasing mortality in these patients [19]. However, Rueda *et al.* in their study prove that hyperglycaemia in adult patients without diabetes causes a more severe course of the disease and increases mortality in patients diagnosed with infection of *Streptococcus pneumoniae* [13].

Other authors also prove the adverse effect of hyperglycaemia on morbidity and mortality from infection. Marik *et al.* proved that in critically ill surgical patients with hyperglycaemia induced by stress, the risk of infection of various aetiologies increases, while Schuetz *et al.* in their study prove that hyperglycaemia in adult patients with acute diabetes-free infection without organ failure in the course of the infection is a risk factor for death, longer hospitalisation and the need to transfer to the intensive care unit [20, 21].

In the case of fungal infections, Bader *et al.* have proven that severe hyperglycaemia (Glc > 13.9 mmol/l) is a factor increasing the risk of death due to *Candida* infection [22].

In a study published in 2005 on invasive aspergillosis in children treated for acute lymphoblastic leukaemia, hyperglycaemia is also mentioned as a risk factor for the development of this infection [23].

The effect of treatment of steroid-induced diabetes on the course and complications of underlying disease

In children receiving chronically GK, there is always impairment of the immune system. Particularly noteworthy is the group of oncological patients, in whom, in addition, deep myelosuppression is usually observed as a result of the applied chemotherapy. This group of children is particularly vulnerable to the development of life-threatening infections. Hyperglycaemia is an additional factor that increases this risk. It should not be forgotten that oncological patients are at risk of developing hyperglycaemia not only as a complication of steroid therapy but also as a consequence of the use of cytostatics such as asparaginase preparations or, more rarely, anthracycline preparations.

Based on data from the literature, it can be concluded that maintaining normoglycaemia in oncological patients diagnosed with steroid-induced diabetes significantly reduces the risk of many complications, including the risk of death.

Many authors show that in critically ill patients with hyperglycaemia the risk of mortality increases as does the period of hospitalisation, including time in the intensive care unit, in comparison to patients with normoglycaemia [20, 24, 25].

Van den Berghe *et al.* in their study prove that maintaining normoglycaemia in this group of patients reduces the risk of death from 8.0 to 4.6% [26].

Weiser *et al.* also showed that patients who had normoglycaemia maintained by normal diabetes treatment compared to patients who did not receive such careful glycaemic control showed shorter periods of respiratory therapy, renal failure, hyperbilirubinaemia, and septic fevers [27].

Again, it is worth paying particular attention to the group of oncological patients, especially those with acute lymphoblastic leukaemia (ALL), because hyperglycaemia may also cause an increase in proliferative activity of lymphoblastic cells. Stimulated metabolism characterised by increased glucose uptake through increased glucose usage in the nucleic acid synthesis process and suppression of glucose oxidation facilitates the proliferation of tumour cells.

In a study conducted by Weiser *et al.*, hyperglycaemia was found to be an independent risk factor for death and to develop early ALL relapses in adults treated with the Hyper-CVED protocol. The same study also showed a relationship between hyperglycaemia and the development of severe infections (sepsis, pneumonia, invasive fungal disease) [27].

It should be emphasised that in paediatric patients, the authors disagree about the effect of steroid-induced hyperglycaemia on the course of treatment of acute lymphoblastic leukaemia. In their studies, Weiser *et al.* and Zhang *et al.* demonstrated an increased risk of infection in ALL paediatric patients diagnosed with steroid-induced diabetes [28] and the effect of steroid-induced diabetes on survivability in children with ALL [29]. However, there are studies on a group of paediatric patients diagnosed with acute lymphoblastic leukaemia, which prove that the risk of life-threatening infection and survivability do not differ statistically in the group of patients diagnosed with steroid-induced hyperglycaemia and in the group of patients who did not develop this complication. Undoubtedly, it is necessary to conduct tests on a larger group of paediatric patients in order to determine the effect of hyperglycaemia on the obtained results of treatment of ALL children [30].

Summary

Steroid-induced diabetes is rare in the paediatric population. However, this is a condition that can be extremely dangerous for the patient in immunosuppression. It is necessary to emphasise the necessity of routine glycaemic measurements in patients during steroid therapy, in order to quickly recognise steroid-induced diabetes and to use proper treatment. It should be assumed that maintaining normoglycaemia in immunosuppressed patients reduces the risk of serious infections and the risk of death.

Paediatric patients after steroid-induced diabetes require further diabetes care because the risk of developing type 2 diabetes increases in this group of patients.

Conducting tests in paediatric patients will allow the development of an algorithm of treatment in children diagnosed with steroid-induced diabetes, and to analyse the complications of hyperglycaemia in the paediatric population.

Close co-operation of a haematologist and a paediatric diabetologist is a key element in improving care of children with steroid-induced diabetes complicating anticancer treatment.

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