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Iatrogenic Cushing Syndrome: Management of Impaired Carbohydrate Metabolism - A Review

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ABSTRACT

Introduction and purpose: Cushing Syndrome is a condition associated with a long-term elevated concentration of cortisol in the circulatory system. The most common type of Cushing syndrome is exogenous hypercortisolism, primarily iatrogenic, resulting from long-term glucocorticoid use, which affects multiple biological systems, including carbohydrate metabolism. The aim of our work was to present the mechanisms by which glucocorticoids affect carbohydrate metabolism and compile information on strategies for its management.

Background: Glucocorticoids disrupt carbohydrate metabolism causing increased hyperglycemia, insulin resistance and diabetes mellitus. These adverse effects result from increased hepatic gluconeogenesis, reduced glycogenolysis, decreased expression of glucose transporter type 4 (GLUT4) and impaired insulin signaling. The most important factor to reduce the impact of glucocorticoids on carbohydrate metabolism is optimization of glucocorticoid therapy and ensuring proper patient surveillance. A comprehensive medical history and physical examination should be conducted prior to administration of long-term glucocorticoid therapy, with regular blood glucose monitoring throughout treatment. Another key factor is prompt implementation of appropriate pharmacologic therapy. Basal bolus insulin therapy is recommended for managing glucocorticoid-induced hyperglycemia (GIH), with metformin as the preferred oral agent. Equally significant is adopting a balanced diet and regular physical activity.

Conclusion: Iatrogenic Cushing syndrome pose a significant problem both for patients and healthcare providers. Studies outline strategies for management of glucocorticoid-induced impaired carbohydrate metabolism, however further research is required to develop evidence-

based guidelines to validate and optimize these approaches and improve the quality of life in patients with iatrogenic Cushing syndrome.

Keywords: Iatrogenic Cushing Syndrome; hypercortisolism; glucocorticoids; adverse effects; carbohydrate metabolism; glucocorticoid-induced hyperglycemia; hyperglycemia; glucocorticoid-induced diabetes;

Introduction and purpose

Cushing syndrome is a condition characterised by a variety of symptoms which are associated with a long-term elevated concentration of cortisol in the circulatory system [1]. The typical feature of this condition is change in the patient's appearance, which include: weight gain with central obesity, moon face, facial plethora, buffalo hump, limbs' muscles wasting, purple stretch marks, thin skin and hirsutism [2,3,4]. However, it is not the appearance changes that pose a serious problem for both patients and medical practitioners, but rather the effects of cortisol on many biological systems, which lead to complications such as fatigue, delayed wound healing, osteoporosis, hypertension, insulin resistance, hyperglycemia, type 2 diabetes mellitus, increased cholesterol level, depression, mood swings, loss of libido and irregular menstrual cycles [2,3].

Depending on the cause, two types of Cushing syndrome are distinguished - endogenous and exogenous [5]. Endogenous hypercortisolism is induced by excessive production of cortisol by adrenal glands. This production is adrenocorticotropic hormone (ACTH)-dependent or ACTH-independent [6]. The most common ACTH-dependent reason for cortisol overproduction is pituitary adenoma, what is called Cushing disease. It contributes to 70% of endogenous Cushing syndrome [7]. Although increased endogenous ACTH production can also be caused by neoplasms' ectopic secretion [1,3]. The adrenal glands disorders such as carcinoma, adenoma or hyperplasia are responsible for ACTH-independent cortisol excess [1,3]. However, among all causes of Cushing syndrome, the most common is exogenous hypercortisolism, primarily iatrogenic, associated with long-term use of glucocorticoids (GCs) [8]. Exogenous Cushing syndrome poses a significant problem for modern healthcare due to widespread use of glucocorticoids in many branches of medicine, such as pulmonology, rheumatology, allergology, dermatology and many others [9]. In

addition, glucocorticoids have become a pivotal treatment during the COVID-19 pandemic, as dexamethasone has proven effective in the management of severe COVID-19 cases [10]. The prevalence of glucocorticoids use depends on numerous factors including country and region, age and gender of the research population [11,12]. In the study conducted on the Icelandic population, it was found that 3.8% of the population received oral glucocorticoids annually [11], while in another research involving databases from the United States, Taiwan and Denmark, the average annual prevalence of oral glucocorticoids use was 6.8% in the United States, 17.5% in Taiwan and 2.2% in Denmark [12]. Both studies showed that there is an increasing trend in prescribing glucocorticoids [11,12].

Cushing syndrome is not a common condition but the precise data on the frequency of iatrogenic Cushing syndrome is limited and varies depending on the studied population and medical conditions [13]. Study, which was focused on patients with obstructive airway diseases, reported a prevalence of iatrogenic Cushing syndrome at 7.81% [14], which highlights the importance of monitoring for this condition in patients undergoing chronic steroid therapy.

The increasing use of glucocorticoids and their application in the treatment of various diseases contributes to the delving into their impact on the functioning of the organism and the occurrence of serious health issues. One of the serious but often under-recognised and neglected adverse effects of glucocorticoid therapy, which requires a tailored approach, is their impact on carbohydrate metabolism [15,16]. This effect compromises a patient's quality of life and may result in long-term complications [16]. Therefore, early diagnosis and efficacious treatment of iatrogenic Cushing syndrome and its metabolic consequences is essential to reduce patient mortality [8]. The aim of our work was to present the mechanisms by which glucocorticoids affect carbohydrate metabolism, as one of the most common and serious complications and collect information on strategies for its management.

Materials and methods

The literature review was conducted to identify relevant studies on the mechanisms and management of carbohydrate metabolism dysregulation in iatrogenic Cushing syndrome. Searches were performed in the PubMed open database using combinations of keywords: “Iatrogenic Cushing Syndrome”, “hypercortisolism”, “glucocorticoids”, “adverse effects”, “carbohydrate metabolism”, “glucocorticoid-induced hyperglycemia”, “hyperglycemia”, “glucocorticoid-induced diabetes”. After screening for relevance and language, a total of 32 English-language articles published through 2025 were included in this review.

Pathophysiology of iatrogenic Cushing Syndrome

Glucocorticoids are naturally produced by adrenal glands, primarily by the zona fasciculata of adrenal cortex [17]. Their production is under hypothalamic control regulated by the hypothalamic-pituitary-adrenal (HPA) axis. It means that hypothalamus by secretion of corticotropin-releasing hormone (CRH) stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn triggers the adrenal cortex to produce and release cortisol [17]. Additionally, minor amounts of glucocorticoids are produced in the thymus, vasculature, epithelial barriers and brain exerting local effects [18].

After secretion into the bloodstream glucocorticoids bind to plasma proteins, which keep them inactive. Corticosteroid binding globulin (CBG) binds 80-90% of circulating glucocorticoids [19]. Remaining free glucocorticoids exert their effects through both genomic and non-genomic pathways [20]. Their main mechanism of action depends on their binding to glucocorticoid receptor (GR), which are expressed throughout the body [19]. The glucocorticoid-receptor complex translocates to the nucleus, where it interacts with DNA and activates or represses gene-expression. This procedure leads to the regulation of various psychological processes such as metabolism, development, inflammation, cardiovascular function and reproduction [18,19,20]. In addition, there are also non-genomic glucocorticoids effects, which occur through direct physicochemical interactions with either systolic or membrane-bound glucocorticoid receptors inducing rapid signaling pathways [19,20]. Both genomic and non-genomic mechanisms of action enhance the complexity of glucocorticoid influence on cellular functions.

Exogenous glucocorticoids are structurally derived from their endogenous counterparts, meaning they participate in the same regulatory pathways by binding to the glucocorticoid receptor and influencing the HPA axis [21]. Moreover, structure modifications improve their capability to activate the receptor or prevent their deactivation. Mostly, they are also not bound by proteins [18,19].

Chronic use of glucocorticosteroids can lead to a variety of clinical symptoms and complications, such as increasing gluconeogenesis, raising levels of triglycerides and low-density lipoprotein cholesterol and suppressing immune responses [20]. Additionally, they do not remain without impact on the HPA axis, causing its disruption. Administration of exogenous glucocorticoids provides negative feedback to the hypothalamus and pituitary gland [21]. The inhibition of CRH and ACTH secretion can lead to atrophy of the adrenal

glands and in turn, lack of ability to produce sufficient amounts of cortisol can cause adrenal crisis, which is a potentially life-threatening condition [21].

Wide use of exogenous glucocorticoids for the treatment of many diseases inducing their impact on significant biological processes does not only bring benefits for patients but also is associated with adverse effects, which pose severe difficulties.

Impaired Carbohydrate Metabolism

Glucocorticoids significantly influence carbohydrate metabolism contributing to increased blood glucose level [22]. Primarily, they enhance hepatic gluconeogenesis by upregulating key enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6PC) and decreased glycogenolysis [22,23,24]. Moreover, they expand the availability of substrates for gluconeogenesis by enhancing lipolysis and promoting protein catabolism in skeletal muscle [22,23,24,25]. These actions mutually lead to elevated hepatic glucose production, contributing to hyperglycemia. Furthermore, reduction of glucose transporter type 4 (GLUT4) expression, which is stimulated by insulin, results in decreased glucose cell uptake constituting an additional mechanism of hyperglycemia [22,24]. Glucocorticoids also enhance appetite, especially for high-fat and high-sugar food, thereby promoting obesity and increasing the risk of diabetes mellitus [22].

An additional mechanism contributing to hyperglycemia is glucocorticoid-induced impairment of insulin signaling, which promotes the development of insulin resistance [22]. Elevated levels of free fatty acids, descending from increased lipolysis, accumulate in skeletal muscles, leading to the formation of lipid intermediates such as diacylglycerol and ceramides. These intermediates activate serine kinases that disrupt insulin signaling by reducing phosphorylation of insulin receptor substrate-1 (IRS-1) [15,22,23,24]. Concurrently, dysregulation of adipokines, including elevated leptin and resistin levels due to increased white adipose tissue mass, further exacerbates insulin resistance by promoting inflammation and impairing insulin action in peripheral tissues [15,22,23]. Additionally, as mentioned above, decreased translocation of glucose transporter type 4 (GLUT4) resulting in diminished glucose uptake also concurs to insulin resistance [23,24]. Moreover, glucocorticoids reduce expression of glucose transporter type 2 (GLUT2) and glucokinase receptors on pancreatic beta cells leading to decreased insulin production [18].

The incidence of glucocorticoid-induced hyperglycemia (GIH) depends on several factors including dosage, duration of treatment, history of diabetes, patient's age, Body Mass Index (BMI), abdominal obesity and hypertriglyceridemia [22]. The risk of GIH is also

elevated among hospitalized patients [15]. According to studies, the frequency of GIH is often reported to be between 20% and 30% with a relative risk approximately twice as high [15].

Prolonged use of glucocorticoids can lead to steroid-induced diabetes mellitus, especially among patients with genetic predispositions [23]. There are approximately 2% of new-onset diabetes mellitus cases worldwide, which are associated with oral glucocorticoids therapy [22], whereby over 30% of patients with Cushing syndrome will develop diabetes [23]. Glucocorticoids induce beta cell dysfunction, initially it is compensated by extension of insulin secretion and increased mass of beta cells, but long-lasting glucocorticoid therapy results in disruption of compensatory mechanisms and inducing of beta cells apoptosis [22,23]. The condition known as "relative hypoinsulinemia" reflects the direct or indirect detrimental effects of GCs on pancreatic beta cell function in Cushing syndrome or after two weeks of glucocorticoid exposure. It is characterized by elevated basal insulin levels and a blunted insulin response to glucose challenges and meals [23]. Moreover, circulating fatty acids, which accumulate in pancreas, cause beta cells impairment [15]. Collectively, these pathophysiological mechanisms facilitate the onset of diabetes mellitus.

Optimization of glucocorticoid therapy

The most effective strategy to reduce adverse effects of iatrogenic Cushing syndrome is careful management with glucocorticoid therapy [26]. It is recommended to use the lowest effective doses for the minimum period of time, which should be applied at morning hours to mimic physiological circadian rhythm of cortisol secretion [26]. This approach is intended to prevent dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. If feasible, a once-daily morning regiment and/or intermittent or alternate-day dosing should be considered [26]. However, research suggests that giving prednisolone in divided doses helps reduce GIH and lowers glycemic variability without leading to hypoglycemia [15]. Locally acting glucocorticoids are preferred to limit their effects on carbohydrate metabolism, however hyperglycemia remains a potential risk across all standard routes of administration [22].

Discontinuing glucocorticoids therapy, GCs can be tapered promptly from pharmacologic to psychologic doses if the clinicians are able to carry out the necessary tests. Nevertheless, in the absence of evidence-based guidelines, physicians may prefer gradually reducing dosage without testing to enable restore the physiological function of the HPA axis and to prevent adrenal suppression [26]. Furthermore, reducing the dose of glucocorticoids, it is necessary to modify treatment of hyperglycemia, because of increased risk of hypoglycemia [16].

Assessment and monitoring of the patient

Patients monitoring play a key role to initiate early and effective preventive treatment. Timely diagnosis and suitable management are essential to reducing morbidity and mortality [15,16]. Prior to administration of long-term glucocorticoid therapy, comprehensive medical history and physical examination should be conducted to identify risk factors or pre-existing conditions that could be aggravated by treatment [15,26]. The potential risk of glucocorticoid-induced hyperglycemia should be assessed including evaluation for pre-existing hyperglycemia or undiagnosed diabetes. Multiple other risk factors have also been identified, such as type, dosage, route and regimen of glucocorticoid administration, a family history of diabetes, advanced age, increased body weight, previous GIH events, impaired fasting glucose and glucose tolerance, elevated glycated hemoglobin (HbA1c), co-administration of immunosuppressive agents and low estimated glomerular filtration rate [15,22,27].

Initiation of glucocorticoid therapy should be accompanied by regular monitoring of blood glucose levels and if possible with HbA1c testing and oral glucose tolerance test (OGTT) [15,26,27]. Given the pharmacodynamics of GCs, postprandial glucose levels should be prioritized over fasting levels in diagnosing GIH [15]. Glucocorticoid-induced hyperglycemia is typically diagnosed when postprandial blood glucose level exceeds 200 mg/dL (11.1 mmol/L) on at least two separate occasions following the initiation of glucocorticoid therapy or an OGTT result value of 200 mg/dL (11.1 mmol/L) or more [15,16]. Studies suggest controlling blood glucose within the first 1 to 2 days for inpatients prescribed more than 5 mg prednisolone or its equivalent [15,27]. It is recommended to check blood glucose level at least one time a day preferably before lunch or dinner, whereby if the level of blood glucose is elevated above 200 or 216 mg/dL (11.1 or 12 mmol/L), depending on the source, it is advised to increase monitoring to four times daily [15,16,27,28]. Monitoring can be stopped if the level of blood glucose remains below 140 mg/dL (7.8 mmol/L) for a consistent period of 24 to 48 hours in patients without diabetes [15]. Hospitalized patients with diabetes should adhere to standard institutional protocol, which typically involves at least four measurements per day [15,16]. Outpatients should be educated about the importance of regular blood monitoring, at least twice weekly, both before and after meals and more frequently if levels exceed 200 mg/dL (11.1 mmol/L) [15,16,27]. Optimal blood glucose should be <140 mg/dL (7.8 mmol/L) for pe-meal values and <180 mg/dL (10.0 mmol/L) for post-meal values [27]. It is advised to conduct follow-up evaluations at 3- to 6-month intervals during the initial year of treatment and on an annual basis [22].

Furthermore, patients should also be informed about symptoms of hyperglycemia such as polyuria, polydipsia, weight loss and insufficient insulin production [15,26]. The diagnosis of glucocorticoid-induced diabetes mellitus is based on standard criteria including fasting plasma glucose levels, oral glucose tolerance tests and HbA1c measurement [22,26]. However, glucocorticoids have a greater influence on postprandial glucose, hence measuring postprandial blood glucose levels two hours after lunch and/or conducting an oral glucose test provides a reliable approach for diagnosing glucocorticoid-induced diabetes mellitus [22].

In addition, it is significant to remember about increased glucose variability among patients, who received glucocorticoids and their exposure to hypoglycemia, which is a risk factor for poor prognosis [15]. Continuous Glucose Monitoring System (CGMS) may be helpful to avoid especially nocturnal hypoglycemia [15]. Glucose monitoring is particularly essential when glucocorticoid therapy is reduced or discontinued and should be maintained until euglycemia is re-established [16].

Supportive pharmacotherapy

There are no clear, evidence-based guidelines for glucocorticoid-induced hyperglycemia treatment [22,29]. It is crucial to implement effective hyperglycemia management to reduce patients morbidity and mortality. It is recommended that the blood glucose levels in inpatients should be maintained between 140 and 180 mg/dL (7.8-10.0 mmol/L) [15,25]. In patients at high risk of hypoglycemia glucose levels not exceeding 270 mg/dL (15 mmol/L) may be considered acceptable [16]. Studies suggest implementing the treatment when fasting glucose levels are equal or greater than 140 mg/dL (7.8 mmol/L) including preprandial glucose level or when random glucose measurements equaling 200 mg/dL (11.1 mmol/L) or higher are observed multiple times within a day [15,25].

Individualized treatment plans are essential, taking into account the type, dosage, administration schedule and duration therapy as well as individual patients characteristics and comorbidities [22]. Short- and intermediate-acting GCs, such as hydrocortisone, prednisolone and methylprednisolone, which can lead to rapid and significant fluctuations in blood glucose levels with peaks within 4 to 8 hours and decline during night demand hypoglycemic agents with high potency and rapid onset of action to avoid risk of nocturnal low blood glucose levels [22]. Patients, who received long-acting glucocorticoids, such as dexamethasone, betamethasone or multiple daily doses demand therapeutic strategies with a prolonged duration of action and flexible dosing option [22].

Insulin is a recommended treatment for managing GIH [15]. It enables dosage adjustment for variability of glucose blood level and provides the possibility to deal with severe hyperglycemia by applying high doses [15]. Moreover, in cases of severe or persistent hyperglycemia, continuous insulin infusion may be an appropriate option [16,25]. It is advised to initiate insulin therapy in patients who experience persistent glycemic fluctuation and also in those with pre-existing diabetes mellitus type 2 when non-insulin treatments are insufficient in maintaining effective glycemic control [22]. Moreover, insulin dosage should be increased to maintain euglycemia among patients with pre-existing diabetes mellitus [15]. The preferred approach, especially in inpatients, is basal-bolus insulin therapy, which has been shown to be more safe and efficient and offer great flexibility in dose titration [15,22,25]. It is significant to align the pharmacokinetics of the glucocorticoid with the insulin regimen to optimize glycemic control and minimize the risk of hypoglycemia [25]. However, multiple daily injections, repeated glucose monitoring and risk of nocturnal hypoglycemia can be challenging in outpatients, especially when glucocorticoids are used short term. Neutral Protamine Hagedorn (NPH) insulin timed with glucocorticoid administration is a more practical option, particularly in patients receiving once-daily intermediate-acting glucocorticoids. NPH insulin's peak effect and a total duration of action align with the hyperglycemic profile induced by many GCs [15,27]. When glucocorticoids are given in divided doses, the total dose of NPH insulin can be split accordingly [15]. Although NPH insulin can be used alone in selected ambulatory patients, it is commonly incorporated into basal-bolus insulin regimen to allow for more precise glycemic control throughout the day [15,29]. Insulin sensitizers like metformin or thiazolidinediones can also be added for better blood glucose level control [22].

The role of oral hypoglycemic agents in management of glucocorticoid-induced hyperglycemia remains unclear due to a lack of sufficient evidence [15]. They are especially intended for patients with mild hyperglycemia and without a history of diabetes mellitus or with well-controlled diabetes mellitus [22]. Moreover, they may serve as adjunctive therapies to insulin [15]. There are different oral hypoglycemic treatment options. The following drugs stand out: sulfonylureas, glinides, incretin-based therapies, metformin, thiazolidinediones, sodium-glucose co-transporter type 2 inhibitors and alpha-glucosidase inhibitors [22].

Metformin is a preferred oral hypoglycemic agent in glucocorticoid-induced hyperglycemia. By increased expression of glucose transporter type 4 (GLUT-4) mRNA counteracts the effect of GCs' action [15,24]. It remains a valuable option for long-term, low-dose glucocorticoid therapy due to its ability to enhance hepatic insulin sensitivity, inhibit

gluconeogenesis, reduce intestinal glucose absorption, stimulate glucagon-like peptide-1 (GLP-1) secretion and consequently decrease insulin resistance [22,24,29]. As a result of its pharmacological effect, metformin has been shown to stabilize plasma glucose levels [24]. According to studies, metformin has been demonstrated to prevent plasma glucose elevation, improve HbA1c levels and enhance pancreatic beta cell function after 4 weeks of treatment [25]. Moreover, metformin contributes to weight reduction by decreasing appetites and subcutaneous fat, which may be particularly beneficial in patients at risk of glucocorticoid-induced weight gain [24]. Additionally, studies suggest its impact on decreasing inflammatory markers, improvement of fibrinolysis, reduction in carotid intima-media thickness and suppression of bone resorption [15,24,30]. All these additional properties of metformin are significant in mitigating the side effects of iatrogenic Cushing syndrome.

Thiazolidinediones' mechanism of action depends on insulin sensitizing without causing hypoglycemia [22]. They not only lower blood glucose level and glycated haemoglobin but also decrease total and low density lipoprotein cholesterol and leptin [31]. Additionally, they have the ability to preserve beta cell mass and function and protect it from oxidative stress [15]. Their slow onset, similarly to metformin, makes them more suitable for long-term treatment in patients with glucocorticoid-induced hyperglycemia [25]. However, thiazolidinediones are not preferable medicine due to their shared adverse effects with GCs such as weight gain, an increased risk of bone fractures and fluid retention [22,25].

Sulfonylureas may be considered in patients receiving intermediate- or long-acting GCs such as those undergoing long-term dexamethasone therapy, but due to their long duration and risk of nocturnal hypoglycemia, they are generally not recommended for managing GIH [15]. However, gliclazide is recommended as an initial treatment option in patients with pre-existing diabetes mellitus type 2 and glucocorticoid-induced hyperglycemia [16]. Glinides' rapid-acting and shorter duration of action than sulfonylureas enable flexibility in managing postprandial hyperglycemia and reduce risk of nocturnal low blood glucose level, nevertheless their frequent dosing requirements, high price and diminished efficacy in insulin resistant limit their widespread use [15,22]. Moreover, their use is impeded by associated adverse effects such as weight gain, increased cardiovascular risk and hypoglycemia, although these side effects are generally less pronounced compared to those observed with sulfonylureas [15,25].

Dipeptidyl peptidase 4 inhibitors (DPP-4) and glucagon-like peptide-1 (GLP-1) receptor agonists, which are incretin-based therapies increase insulin secretion and glucose uptake, suppress glucagon release and slow gastric emptying [15]. Their mechanisms of

action specifically target postprandial hyperglycemia without increasing the risk of hypoglycemia, which make them a promising option for managing glucocorticoid-induced diabetes, especially in patients receiving intermediate- and long-acting GCs [25]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce renal glucose absorption. Their rapid onset of action without risk of hypoglycemia and potential to reduce body weight and cardiovascular risk offers a novel approach to managing glucocorticoid-induced diabetes [22]. Both incretin-based therapies and SGLT2 inhibitors are promising medications for GIH treatment, but their efficacy and safety has restricted their widespread use, highlighting the need for further studies [15,22]. Alpha-Glucosidase inhibitors reduce postprandial glucose level by delaying carbohydrates and glucose absorption, but due to their weak hypoglycemic effect, they are preferable to be prescribed in combination with other hypoglycemic agents [22].

Lifestyle modification

Lifestyle modification in patients with iatrogenic Cushing is equally essential as medical intervention in reducing and preventing negative impact on carbohydrate metabolism [25]. Similarly as in general hyperglycemia and diabetes management patients should be educated about proper and healthy diet and regular physical activity [25]. It is recommended to avoid monosaccharides and processed food and implement a balanced, low-glycemic-index diet to help attenuate postprandial glucose excursions, improve overall glycemic control and reduce body mass index [32]. Regular physical activity is a significant factor to keep a healthy lifestyle, especially among patients receiving glucocorticoid therapy [25,26]. Aerobic and resistance exercise enhances insulin sensitivity in skeletal muscles and supports glucose utilization [32]. Furthermore, a healthy body reduces visceral adiposity, which is closely associated with insulin resistance. Additionally, patients should avoid factors which increase cardiovascular risk such as cigarettes and alcohol [26]. While pharmacological treatment may still be necessary in some cases, lifestyle modification remains a cornerstone of intervention due to its accessibility, safety and long-term metabolic benefits.

Conclusions

Cushing syndrome is a rare condition, but with increasing use of glucocorticoids pose a significant problem both for patients and their physicians. Essential role that glucocorticoids fill in contemporary medicine excludes the possibility to cease their application and creates a

challenge for medical professionals to balance positive action of glucocorticoids with their adverse effects.

Glucocorticoids impact on carbohydrate metabolism is often neglected, but entail serious consequences and can lead to long-term complications. Therefore, it is crucial to understand the mechanisms by which glucocorticoids affect carbohydrate metabolism in order to effectively prevent associated complications. The most effective strategy to minimize the adverse effect of glucocorticoids is their appropriate and carefully managed administration. It is recommended to administer the lowest effective dose of GCs, aligning the dosing regimen with the physiological circadian rhythm of cortisol secretion and prefer medications with local rather than systemic action. As significant as optimization of glucocorticoid therapy is assessment of the patient, especially with regard to identifying risk factors of glucocorticoid-induced hyperglycemia and timely surveillance of blood glucose levels. Furthermore, it is necessary to initiate early pharmacological treatment to maintain proper blood glucose level and prevent the development of glucocorticoid-induced diabetes mellitus. Equally essential as medical interventions is lifestyle modification such as a balanced, low-glycemic-index diet and regular physical activity.

Managing glucocorticoid-induced hyperglycemia presents significant challenge due to variability in glycemic responses among patients. Both glucocorticoid-induced hyperglycemia and diabetes mellitus have been associated with adverse outcomes including prolonged and more frequent hospitalizations, increased risk of infections and higher morbidity and mortality rates [16]. Existing studies predominantly pertain to hospitalized patients. Given the increasing use of glucocorticoids in clinical practice, further research is warranted to establish evidence-based guidelines to support clinicians in delivering comprehensive care for both inpatients and outpatients. These guidelines should encompass strategies for managing impaired carbohydrate metabolism and improving quality of life in individuals with iatrogenic Cushing syndrome.

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Author's contribution:

Conceptualization, PP and KR; Methodology, PP, KT and WB; Software: ZW and MT; Check: PP, OJ and JK; Formal analysis: AS and ZW; Investigation: NW, MT and JK; Resources: KR, KT and WB; Data curation: NW and OJ; Writing - rough preparation: PP, KR and AS; Writing - review and editing: WB and JK; Visualization: KT, AS and ZW; Supervision: NW, OJ and MT; Project administration: Patrycja Podlejska

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