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REVIEW

Hypertension and other morbidities with Cushing's syndrome associated with corticosteroids: a review

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Abstract: Corticosteroids constitute an ideal treatment for various inflammatory and autoimmune disorders due to their anti-inflammatory and immunomodulatory actions. However, corticosteroids have a considerable number of side effects, including hypertension, diabetes, lipid disorders, sleep apnea, osteoporosis, myopathy, and disorders of coagulation and fibrinolysis, which are components of Cushing's syndrome (CS). Corticosteroid-induced side effects are dependent on the formulation, route, dose, and time of exposure. However, the underlying pathogenetic mechanisms have not been clearly defined. A large body of evidence supports the role of an imbalance between vasoconstriction and vasodilation with possible links to nitric oxide, prostanoids, angiotensin II, arginine vasopressin, endothelins, catecholamines, neuropeptide Y, and atrial natriuretic peptide. Increased oxidative stress, renin–angiotensin system activation, increased pressor response, metabolic syndrome, and sleep apnea appear to be pathogenetically involved as well. The ideal treatment is the withdrawal of corticosteroids, which is most often impossible due to the exacerbation of the underlying disease. Alternatively, a careful plan, including the proper selection of the formulation, time, and route, should be made, and each side effect should be treated properly. The focus of the research should be to develop synthetic corticosteroids with anti-inflammatory effects but fewer metabolic effects, which so far has been unsuccessful.

Keywords: corticosteroids, hypertension, iatrogenic Cushing's syndrome

Introduction

It is estimated that up to 0.5% of the US population are on chronic corticosteroid therapy for various inflammatory and autoimmune disorders.[1,2] Annually, ~10 million new prescriptions for oral corticosteroids are issued in the US. A minority of patients use corticosteroids without being aware of this, due to their use in the black market. Corticosteroids have been used, along with hydroquinone and mercury, as ingredients in a variety of skin lightening (bleaching) cosmetics and toiletries that are widely used in African countries.[3] Over-the-counter combination preparations of steroids with other drugs such as antifungals may lead to unsupervised and inappropriate use of topical corticosteroids.[2,4,5] Cases of factitious Cushing's syndrome (CS) from surreptitious use of corticosteroids have been described.[6] Corticosteroids as an ingredient of a black market drug used by addicts to help them through the narcotic withdrawal stage were responsible for an outbreak of CS in Tehran in 2008.[7]

Corticosteroids have been the medication of choice in various disorders, based on their undoubted benefits from their anti-inflammatory and immunomodulatory actions. However, they are also complicated by a considerable number of side

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effects, including CS. The clinical presentation of CS often strikes with the use of high doses of corticosteroids.[1,2] Symptoms include central obesity, plethora, easy bruising, thin skin, striae, myopathy, depression or psychosis, poor wound healing, increased incidence of infection, glaucoma and other ocular disease, and hypertension (HT). Hirsutism and other virilizing features are uncommon clinical findings due to nonsignificant increases in androgens. Avascular necrosis and spinal epidural lipomatosis constitute a complication of corticosteroid-induced CS.[1,2]

All synthetic derivatives that are used clinically, including prednisone, prednisolone, methylprednisolone, dexamethasone (DX), betamethasone, and triamcinolone, have the potential for adverse effects and CS.[2] Which of these agents is most likely to cause CS has not been fully clarified due to the complex interaction of many factors involved in this process.[2] It appears that it is dependent on the formulation used, pharmacokinetics, affinity for the glucocorticoid receptor, biologic potency, duration of action, and different levels of sensitivity in individual patients.[2] Oral corticosteroid therapy has been well correlated with CS, and most physicians are aware of the dangers, having always to balance the cost–effect ratio.[2] According to accumulated data, topical, aerosol, inhaled, and injectable corticosteroid therapy may also have adverse effects, including CS.[2,8–12] There have been several cases of children who received intralesional injections into keloid scars or other wounds (such as burns) and developed CS that persisted for a long time (up to 9 months).[13] Cases of CS have also been reported in patients under treatment with paraspinal depot injections.[14] Additional unusual cases include CS induced by serial occipital nerve blocks containing triamcinolone.[15] Corticosteroid-related side effects including CS are common in patients with cystic fibrosis or HIV infection, which need combined treatments including budesonide and itraconazole or fluticasone propionate and ritonavir.[11,12,16,17]

Another critical determinant of the corticosteroid-induced side effects including CS is the dosage needed to control the disease. High doses of corticosteroids even for a short time or long-term use of agents with lower potency and short half-lives (hydrocortisone and cortisone) have been associated with CS. However, the prediction of dosages at which CS will develop is a complicated phenomenon that depends on a variety of factors.[1,2] Thus, the cost–effect ratio has to be estimated in each case, and a careful plan should be made before starting treatment with corticosteroids. This review will discuss the critical determinants and underlying pathogenetic mechanisms of CS associated with corticosteroids.

Morbidities associated with corticosteroid-related CS

Corticosteroid-induced CS and HT

HT is a prominent feature in patients with corticosteroid-induced CS, occurring in up to 20% of cases, and is dose dependent.[1,2,18,19] A variety of mechanisms has been proposed to explain its pathogenesis.[18,19]

A large body of evidence supports the theory that corticosteroids induce an imbalance between vasoconstriction and vasodilation, favoring vasoconstriction, resulting in HT.[18,19] According to in vitro, in vivo, and also human data, increased vasoconstriction is in large part mediated by increased endothelin-1 synthesis and secretion.[20–22] Increased cytosolic calcium levels downregulate the expression of the Na–Ca exchanger and increased erythropoeitin levels have also been pathogenetically involved in corticosteroid-induced vasoconstriction and HT.[23,24] Accumulating data suggest that increased sympathetic activity, reflected in the increased synthesis of catecholamines and a1β-adrenergic receptor expression, is an important underlying pathogenetic mechanism as well.[18,19] The increased synthesis of catecholamines is due to increased expression and activity of various enzymes involved in the catecholamine biosynthesis, including tyrosine hydroxylase and phenylethanolamine *N*-methyltransferase. Elevated epinephrine and norepinephrine levels in plasma and adrenal medulla and increased expression and activity of tyrosine hydroxylase have been found in hypertensive rats treated with subcutaneous injections of dexamethasone (DX; 1 mg/kg/day for 2 days).[25] Elevated levels of plasma dopamine and epinephrine have been found in humans treated with a single dose of 2 mg DX.[26] In both studies, the observed effects were blocked by the administration of alpha-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase.[25,26] Increased activity of phenylethanolamine *N*-methyltransferase has been found in both intact and adrenalectomized rats treated with subcutaneous injections of DX (1 mg/kg/day for 12–14 days).[27,28] In addition, in vitro, in vivo, and human studies suggest that corticosteroids alter the availability of α1-adrenergic receptors in vascular smooth muscles, leading to increased vascular reactivity, pressor responsiveness, and HT.[29–31]

Increased corticosteroid-induced vasoconstriction and thus HT are also mediated through enhanced synthesis and action of vasoactive substances and their receptors, including

neuropeptide Y (NPY), arginine vasopressin (AVP), and atrial natriuretic peptide (ANP).[19,20] Increased corticosteroid-induced NPY gene expression and tissue content in neuroendocrine tissue and cell lines have been associated with vasoconstriction.[32] Coadministration of AVP and DX (1.8 mg/kg/week for 2 weeks) to normotensive rats resulted in dose-dependent increases in mean arterial pressure, which can be reversed by the administration of d(CH2)5Tyr(Me) AVP, an AVP-V1 receptor antagonist, suggesting the role of the V1aAVP receptor in DX-induced HT.[31,33,34] Increased expression of atrial, ventricular, pulmonary ANP genes and plasma ANP levels have been found in both intact and adrenalectomized rats treated with DX (1 and 4 mg/kg/day for 2 days).[31,35] Higher ANP levels have been observed in atrial slices and extracts obtained from rats treated with DX (intraperitoneally, 0.1 mg/kg/day for 4 days).[36,37]

Another interesting issue is the role of renin–angiotensin system activation in the development of corticosteroid-induced HT.[18,19] Corticosteroids act directly at the liver site, enhancing the synthesis of the plasma renin substrate (angiotensinogen).[31,38] Experimental studies using saralasin, an angiotensin antagonist, and SQ14225, an angiotensin-converting enzyme, partly prevented HT in rats treated with DX (0.17–0.27 mg/kg/day), suggesting the partial contribution of angiotensin II in terms of increased synthesis or sensitivity in the development of DX-induced HT.[38]

A large body of evidence supports the theory that apart from the increased corticosteroid-induced synthesis and secretion of vasoactive substances, an increased sensitivity and reactivity of various tissues to their action, reflected in increased vascular pressor responsiveness, has also been observed.[31,39–41] A reduced threshold and increased maximal response to norepinephrine has been observed in rat mesenteric vasculatures isolated from hypertensive rats treated with DX orally (7–9.5 mg/kg/day for 28 days).[42,43]

AVP, but not norepinephrine or angiotensin II infusion, elicited increased pressor response in DX-induced hypertensive rats (257 mg/kg/day for 2 weeks).[33] Infusion of angiotensin II in humans treated with DX (orally, 3 mg/day) resulted in increased forearm vascular resistance.[39,44] These effects seem to be mediated through changes in the activity of sodium/potassium pump[45] and function of glucocorticoid[46] and mineralocorticoid[47] receptors as well. Administration of angiotensin II and AVP in DX-treated experimental animals was accompanied by a reduction in the threshold of the inositol triphosphate production and HT, an effect that was blocked by the administration of a specific glucocorticoid receptor antagonist RU38486 but not spironolactone or RU28318, type I mineralocorticoid receptor antagonists.[46,48] DX-induced stimulation of vascular angiotensin II type 1 receptor has also been observed and linked to HT.[47] Furthermore, corticosteroids seem to induce HT by binding to mineralocorticoid receptors.[49] It has been supported that although corticosteroids activate both mineralocorticoid and glucocorticoid receptors, they exhibit a higher affinity for glucocorticoid receptors than with mineralocorticoid receptors.[50]

On the other hand, corticosteroids negatively affect various vasodilatory systems.[18,19] Corticosteroid-induced HT has been associated with nitric oxide (NO) deficiency through a range of negative influences on the NO biosynthetic pathways, involving i) alteration in the activity and expression of NO synthase, ii) decreased availability of tetrahydrobiopterin (BH4), and iii) decreased NO precursor L-arginine.[51–53] NO deficiency might also be the result of NO interaction with excess superoxide to form a powerful oxidant, peroxynitrite, which leads to NO inactivation and deficit.[54,55]

According to experimental data, corticosteroids seem to negatively affect the production of other vasodilatory substances as well, such as prostacyclin, prostaglandin E2 (PGE2), and kallikrein.[56–58]

The end result of the afore mentioned alterations is hemodynamic changes in various vascular beds. A large dose of oral DX (0.5 mg/kg/day) in dogs was accompanied by a reduction in cardiac output and an increase in calculated total peripheral resistance.[31] In humans, oral DX (1 mg three times daily for 7 days) increased mean and total peripheral vascular resistance without affecting the cardiac output.[39] Limited studies support an effect of DX on the regional hemodynamics as well. Intravenous 24 h infusion of DX (125 mg/kg/h) increased the mean arterial pressure, and decreased renal and mesenteric blood flow and conductance.[59] However, it remains unclear whether this is a coexisting feature or a pathogenic mechanism of corticosteroid-induced HT.

Coexisting metabolic abnormalities appear to mediate and accentuate the corticosteroid-induced HT. Obesity is associated with a reduction in urine sodium excretion, increased plasma and extracellular fluid volume, and HT.[18,19] Insulin resistance leads to sodium and water retention, increased sympathoadrenal system activity, local renin–angiotensin system activation, vascular hypertrophy, increased vascular resistance, and HT.[18,19] Sleep apnea has also been associated with HT through increased sympathetic tone during hypoxemic episodes, insulin resistance, and diabetic autonomic neuropathy.[18,19]

It seems that corticosteroids regulate blood pressure by exerting their effects at the central nervous system as well. Subcutaneous tritium-labeled DX administration in rats resulted in localization of radioisotope in the thalamus (lateral nucleus), hypothalamus (arcuate, ventromedial, periventricular, and paraventricular nuclei), and cell bodies of locus ceruleus, area postrema, and nucleus tractus solitarii, indicating that systemically administered DX passes to the brain and cerebrospinal fluid.[60–62] An interesting theory has been developed suggesting that corticosteroids induce central nervous system activation and HT, but this has to be further evaluated.[62] This effect might be mediated through direct interaction of corticosteroids with γ-aminobutyric acid type A and B receptors and nontranscriptional activation of phosphatidylinositol 3-kinase/protein kinase Akt pathway, possibly mediated by the glucocorticoid receptor.

Corticosteroid-induced CS and osteoporosis

Osteoporosis constitutes an important component of corticosteroid-induced CS in children and adults.[1,2] Bone loss appears to be fastest in the first 6 months of therapy and persists at a slower rate thereafter, resulting in osteopenia and osteoporosis. Trabecular bone and the cortical rim of vertebral bodies appear to be more susceptible to the effects of corticosteroids, improving rapidly after their withdrawal. In addition, fractures may occur in 30%–50% of corticosteroid-treated patients independently of bone mineral density differences.[63,64] Long-term use of corticosteroids in asthmatic patients has been associated with increased rib and vertebral fractures.[65] A retrospective cohort study of 244,235 adults on oral corticosteroids documented a dose-dependent increase in nonvertebral, hip, forearm, and vertebral fractures, occurring even with low doses of corticosteroids (2.5 mg/day).[66] A meta-analysis of 42,500 men and women from seven prospective cohorts showed that current or prior corticosteroid use has been associated with increased fracture risk.[67] There is a large body of evidence indicating that inhaled corticosteroids negatively affect bone metabolism, as well as when they are taken orally.[68,69] However, the percentage of bone loss and the real fracture risk attributed to corticosteroids is difficult to be estimated in those patients, due to the multifactorial origin of altered bone metabolism.

Corticosteroids negatively affect calcium metabolism and bone remodeling, leading to decreased bone formation and increased bone resorption. Corticosteroids decrease intestinal calcium absorption and renal tubular reabsorption of calcium, resulting in hypercalciuria, secondary hyperparathyroidism, and increased bone resorption.[63,64] Corticosteroids have a negative impact on osteoblastogenesis as well by reducing synthesis of type 1 collagen and insulin-like growth factor, altering the binding and thus the anabolic effects of transforming growth factor-β, inhibiting Wnt signaling, and inducing apoptosis of osteoblasts and osteocytes.[63,64] Decreased activity of type 1-11β-hydroxysteroid dehydrogenase and increased activity of type 2-11β-hydroxysteroid dehydrogenase by circulating inflammatory cytokines, the antagonistic effect of corticosteroids on parathormone and testosterone, seem to represent underlying pathogenetic mechanisms. On the other hand, corticosteroids stimulate osteoclast proliferation by suppressing synthesis of osteoprotegerin, stimulating production of the receptor activator of nuclear factor κB and decreasing estrogen and androgen production, leading to increased osteoclastic bone resorption.[63,64,70–72]

Corticosteroid-induced CS and disorders of the coagulation/fibrinolysis system

Thromboembolic disease is an important and serious complication in patients with CS, as it is associated with increased morbidity and mortality.[1,2,73] Small clinical studies in patients with CS have shown an activation of the coagulation system reflected in higher levels of plasma von Willebrand factor VIII, factor IX, and factor XII; decreased fibrinolytic activity reflected in lower levels of PAI-1, tPA, or euglobulin clot lysis time; and increased levels of factors XII, XI, IX, and VIII plasminogen and a 2-antiplasmin.[74,75] These effects have been closely related to corticosteroids, as they were fully reversed after surgical treatment. In a similar way, exogenous corticosteroids cause disorders in the coagulation and fibrinolytic systems, reflected in increased synthesis/secretion of PAI-1, and increased levels of thrombin–antithrombin complex increased plasma factor VII, factor VIII, factor XI, and fibrinogen levels.[76–78]

Corticosteroid-induced CS and muscloskeletal disorders

Myopathy seems to be a common feature in CS, clinically expressed as the inability to rise from a crouching position, due to the adverse effects of corticosteroids on the proximal muscles of the lower limb and the shoulder girdle.[1,2,79] Corticosteroids affect type 2B or 'phasic' muscle fibers (fast twitch) causing atrophy (but not necrosis), resulting in reduced muscle protein synthesis. This effect is mediated through increased oxidative phosphorylation, inhibition

of protein synthesis, and impairment of muscle membrane excitability.[79]

The acute form of myopathy involves proximal and distal muscle weakness, is positively correlated with elevated serum creatinine phosphokinase levels, is an indicator of focal and diffuse muscle necrosis, is mediated by hypokalemia, or constitutes the end result of a direct effect of corticosteroids on skeletal muscle. This type of myopathy may take between 6 weeks and several months to resolve, even after the discontinuation of corticosteroids. The chronic form is more insidious in onset, primarily involves proximal muscle groups, and is characterized by typically normal or only slightly elevated creatinine phosphokinase levels with no evidence of focal or diffuse muscle necrosis. Although there is no direct correlation with dosage, patients who receive even small amounts of prednisone (ie, 10 mg/day) can develop myopathy.[80,81]

Corticosteroid-induced CS and metabolic syndrome

Impaired glucose tolerance, diabetes, dyslipidemia, and fatty liver disease are common findings in patients treated with corticosteroids.[82–84] Not only experimental but also human data support the theory of corticosteroids having an effect on various sites involved in protein, lipid, and glucose metabolism, including skeletal muscle, liver, and adipose tissue. Corticosteroids induce insulin resistance in skeletal muscle by directly interfering with the insulin signaling cascade. Decreased glucogen synthesis rates and glycogen synthase concentration and activity have been found in skeletal muscle biopsies of healthy subjects on 4 mg DX for 4 days[85] and patients on long-term treatment with high doses of corticosteroids following renal transplantation.[86] Skeletal muscle insulin resistance is further aggravated by corticosteroid-induced protein catabolism with concomitant atrophy-related decrease in total muscle area and elevated circulating aminoacids,[87] which negatively affect insulin signaling,[88] glucose uptake, and glycogen synthesis in muscle.[89] In addition, corticosteroids induce whole body lipolysis,[89] resulting in increased plasma levels of free fatty acids and triglycerides[90,91] with deleterious effects in skeletal muscle insulin sensitivity and glucose uptake. Corticosteroids induce hepatic insulin resistance as well, directly by interference with insulin signaling and indirectly by elevating free fatty acid and triglyceride supply to the liver.[92] Thus, increased endogenous glucose production has been observed, especially in the postprandial state, as was demonstrated in healthy subjects following short-term exposure to corticosteroids.[84,93,94] Corticosteroids increase body fat content and alter body fat distribution by regulating hormone sensitive lipase and lipoprotein lipase activity.[95] In addition, corticosteroids modulate adipose tissue biology by altering the secretion of adipokines either directly or through insulin resistance.[96] In addition to inducing insulin resistance, corticosteroids might exert an inhibitory effect on β cells, which is dependent on duration of exposure, dosage, and susceptibility of the population exposed. A prolonged exposure (2–5 days) of healthy subjects to high doses of corticosteroids resulted in fasting hyperinsulinemia and increased insulin secretion, possibly to compensate for the corticosteroid-induced insulin resistance.[97–99] However, in a susceptible population, such as people with a reduced insulin sensitivity before treatment, people who are healthy first-degree relatives of patients with diabetes, and obese women, this compensation failed, resulting in β cell failure and diabetes.[88,98–100] Thus, corticosteroids induce insulin resistance, impaired glucose metabolism, obesity, and central obesity, all of which are components of metabolic syndrome, which has been associated with increased morbidity and mortality from cardiovascular disease.

Corticosteroid-induced CS and cardiovascular disease

Patients with corticosteroid-induced CS exhibit increased cardiovascular morbidity and mortality.[1,2,101–103] Increased mortality from cardiovascular disease has been reported in patients with asthma, chronic obstructive pulmonary disease, inflammatory arthritis, and giant cell arteritis.[104–106] A population-based study showed that patients who were exposed to systematic corticosteroids in a dose greater than the equivalent of 7.5 mg of prednisolone daily had substantially higher rates of cardiovascular disease during 1–5 years of follow-up, namely myocardial infarction, heart failure, and cerebrovascular disease.[102,103] It has to be mentioned that this association was not evident in patients treated with low doses or 'nonsystemic' (eg, topical and rectal) corticosteroids.

Corticosteroids appear to have a direct causal effect relationship with cardiovascular disease, which is dependent on the dose, duration, cumulative dose of exposure, and route of administration. Whether, and to what extent, the increased risk is mediated through the disease background for cardiovascular disease and the induction of several risk factors for cardiovascular disease and represents a direct corticosteroid effect that is much higher than their anti-inflammatory and antiproliferative actions cannot be answered by the existing data.[107,108]

Corticosteroid-induced CS and fetal programming

Much interest has been focused over the last 5 years on the role of corticosteroids in fetal programming.[1,2,109] The key mediators appear to be the hypothalamic–pituitary–adrenal axis, the glucocorticoid receptor, and the expression of type 2-11β-hydroxysteroid dehydrogenase genes in a range of tissues. The administration of corticosteroids to mothers to promote maturation of organs in fetuses, to prevent a number of life-threatening complications of preterm birth, and to reduce the effects of congenital adrenal hyperplasia has undoubted short-term benefits and also potential long-term adverse effects.[109,110] A large body of experimental and human evidence supports the theory that corticosteroids appear to be involved in a dose-dependent manner in the fetal programming of adult diseases.[111] Corticosteroid-related fetal programming of adult HT is exerted through the effects on maturation of tissues involved in the control of blood pressure, such as glomerular number and kidney size, in the expression of catecholamine receptors and second messenger systems in renal and vascular tissue, and by affecting growth factors and carbohydrate and fat homeostasis. In addition, corticosteroids potentiate vasoconstrictor effects on the vasculature and regulate the synthesis of catecholamines, NO, and angiotensinogen.[112,113] HT is coupled to tissue-specific increases in glucocorticoid receptor expression and downregulation of type 2-11β-hydroxysteroid dehydrogenase activity in the placenta, kidney, and adrenal, increasing sensitivity and overexposing organs to corticosteroids. Apart from inducing HT, corticosteroids are involved in the fetal programming of type 2 diabetes, cardiovascular disease, other manifestations of the metabolic syndrome, several central nervous system functions, and psychiatric syndromes. However, the exact underlying pathogenetic mechanisms are still unclear and need to be further elucidated.

Exogenous vs endogenous corticosteroid-induced CS and HT

Although the clinical presentation of CS is quite similar from endogenous cortisol overproduction and exogenous corticosteroids, it also has some differences, mainly in the more striking clinical manifestations, due to the use of high doses of corticosteroids.[1,2] CS as a result of the long-term usage of corticosteroids has less hirsutism and other virilizing features due to nonsignificant increases in androgens. In addition, HT is less profound in exogenous corticosteroid-induced CS compared with endogenous CS, depending on the form used. In contrast, avascular necrosis and spinal epidural lipomatosis occur primarily in the setting of corticosteroid-induced CS.[1,2] In addition, a kinetic difference has to be mentioned. In contrast to cortisol, most synthetic corticosteroids bind to albumin and not to cortisol-binding globulin or circulate as free steroids with a much higher affinity for the glucocorticoid receptor. With HT, both forms of CS exhibit some similarities and some differences.

In both forms of CS, the development of HT is rapid. Supraphysiological oral cortisol doses (80 and 200 mg/day) in humans can cause HT within 24 h, with peak blood pressure occurring at day 4 or 5 of treatment.[114,115] In addition, subcutaneous DX (10 mg/day) in rats and oral DX (0.5 mg/kg/day) in dogs and humans (3 mg/day) increases blood pressure within 1–2 days.[31] According to in vitro and in vivo studies, the same pattern is observed in endogenous CS as well.[116,117] HT, in both clinical entities, is independent of mineralocorticoid activity and sodium loading or retention.[49,118] However, in endogenous CS, sodium excess can magnify the hypertensive response.[119,120] Increased oxidative stress, reflected in increased superoxide production and elevated levels of plasma F2-isoprostanes, constitutes a common underlying disorder in both forms of CS and is prevented and reversed by antioxidants (folic acid, *N*-acetylcysteine, tempol, and apocynin) but not with BH4 or allopurinol.[121–123] In both conditions, HT has been associated with decreased NO bioavailability, reflected in decreased plasma reactive nitrogen intermediates (nitrate/nitrite).[122,123]

Although HT, in both forms of CS, is associated with increased oxidative stress and NO deficiency and inactivation, blood pressure response to treatments known to modify the synthesis of NO and superoxide seems to be variable. L-Arginine treatment (500 mg/kg/day) increased plasma nitrate/nitrite concentrations but failed to prevent HT in corticosteroid-treated rats.[53,121] In contrast, in endogenous CS, HT was prevented and partly reversed by L-arginine treatment.[124] Aspirin, an antioxidant and nonselective cyclooxygenase inhibitor, prevented and partly reversed HT related to endogenous but not exogenous CS.[125] Vasopressin antagonism with an AVP-V1 receptor antagonist significantly decreased mean arterial pressure in exogenous but not endogenous CS-related hypertensive rats.[33] Both forms of HT exhibit a different response to glucocorticoid receptor antagonism, suggesting a different degree of receptor activation in both situations. Thus, dehydroepiandrosterone, an endogenous steroid with antiglucocorticoid activity, prevented corticosteroid-induced but not endogenous

cortisol-induced HT.[31,126] In summary, it appears that HT due to endogenous or exogenous CS involves either different pathophysiological mechanisms or different degree of perturbations of the same mechanisms.

Treatment

Patients with autoimmune or inflammatory disorders should be on long-term use of corticosteroids and may develop HT and other morbidities associated with corticosteroid-induced CS. The ideal treatment is the withdrawal of corticosteroids before the onset of comorbidities. However, this is practically impossible, as it is associated with exacerbation of the underlying disease. When possible, corticosteroids should be gradually withdrawn. The use of corticosteroids in low dosages or on alternative days results in fewer metabolic effects and also helps in the prevention of corticosteroid-related pathology. Thus, each patient should be treated individually, following a careful, properly designed plan. In most cases, patients should be treated for corticosteroid-related morbidities. For HT, eplerenone, angiotensin receptor antagonists, and angiotensin-converting enzyme inhibitors are indicated. Weight loss is encouraged through changes in the lifestyle. Medications that improve insulin resistance, such as biguanides and peroxisome proliferator-activated receptor agonists, should be added. Treatment of sleep apnea with a continuous positive airway pressure device appears to be generally effective in controlling not only apnea but also HT, insulin resistance, and increased risk for cardiovascular disease. Bisphosphonates are the first-line choice for prevention or treatment of osteoporosis, with teriparatide as the second-line option; calcium and vitamin D supplements should be coprescribed in the majority of individuals. Muscle biopsy is recommended in patients who require long-term corticosteroid treatment and develop weakness during therapy. Phenytoin has been suggested for treatment of corticosteroid myopathy, but this still needs further research. In the absence of prospective randomized clinical trials, there is currently general agreement that patients with CS should be treated as having a prothrombotic disorder. However, future large prospective trials are needed to evaluate the type, intensity, and duration of thromboprophylaxis in patients with either endogenous CS or iatrogenic CS.

Conclusion

Corticosteroid-induced CS constitutes a major health problem with difficult handling. A careful plan for treatment, namely formulation, route, dose, and time of exposure, should be properly evaluated individually before patients start corticosteroids use. Corticosteroid-related complications should be treated properly, if evident, and prevention strategy involves changes in lifestyle and treatment with appropriate agents. The focus of the research should be on developing synthetic steroids with anti-inflammatory but fewer metabolic effects, which so far has been unsuccessful.

Disclosure

The authors report no conflicts of interest in this work.

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