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Biochemical investigation of steroids on metabolic sequelae and neurobiological effects

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Abstract: Steroids are hormone mediators that are synthesized commercially by humans and are used extensively in medicine. The cortex of the adrenal glands produces them naturally. They're used to treat steroid-responsive illnesses and dermatoses, which are a group of maladies. Corticosteroids are a two-edged sword: when used correctly and for a short period, they can provide significant benefit with a low incidence of side effects; however, the wrong dose and/or duration, as well as unmindful withdrawal after prolonged administration, can have disastrous consequences. Corticosteroids are employed in a variety of medical fields. In this review, we will discuss in detail all the metabolic sequelae and neurological effects of steroid use. Moreover, we are also going to discuss the adverse events associated with prolonged steroid use.

Introduction

Steroids are the most common group of drugs that were synthesized commercially by humans and used extensively by physicians for anesthetic practices. In humans, they are produced from the adrenal glands situated above the kidneys and can be further classified into glucocorticoids (e.g. cortisol), mineralocorticoids (the most common one is aldosterone), and androgenic sex hormones (1).

If taken in higher doses than the prescribed ones these groups of drugs can significantly affect the normal functionality. In conditions such as patients with eczema and asthma, these drugs are used along with some other dermatological conditions. Steroids also lower the immune system's functioning, which is the body's natural defense against disease and infection. This can aid in the treatment of autoimmune diseases such as rheumatoid arthritis and lupus, which are caused by the immune system attacking the body incorrectly (2).

Cortisone was first used in a bed-ridden woman who was suffering from rheumatoid arthritis in 1948 and within 3 days after the administration of the drug the patients were able to walk. This was the first reported case of the use of steroids in humans and hence the research on this drug and its application to different conditions made significant progress (3).

Presently a group of glucocorticoids is produced synthetically that have various functions including anti-proliferative, immunosuppressive, and anti-inflammatory effects. The metabolic and electrolyte-regulating actions of corticosteroids and their physiologically active synthetic aanalogsdiffer (4).

The corticosteroids are also associated with the alterations in carbohydrate, lipid, and protein metabolism, preservation of normal function of the renal, immune, and skeletal muscles, maintaining the normal cardiovascular system, and the water-electrolyte balance. When endogenous production is compromised, these drugs are used at physiological dosages for replacement therapy. Furthermore, glucocorticoids decrease inflammation well, hence they are widely used in several autoimmune illnesses and inflammatory conditions making them one of the most commonly prescribed pharmacological classes (5).

With the increase in the use of steroids the abuse of these drugs has also been increased. The prevalence of steroid abuse has increased significantly in the last two decades a previous meta-analysis reported that abuse of androgenic steroids areisdewidespreadis study reported that being male and athletes are the most common predictor of AAS abuse (6).

Anabolic steroid misuse has also been reported among male weightlifters who are in their 20s. Moreover, it was also reported that among high school students steroid misuse is more prevalent. In a study conducted in, Germany it was reported that most of the revisit visits centers received their supply from the healthcare providers (7). The most common problem arising due to steroid abuse is that makers take up unsafe practices of taking all these steroids and almost 13% have resharing to share their needles or vials with others and reusing needles (8).

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Around 30% of androgenic steroid users develop a dependency, which is defined as long-term use of the drug despitunfavorablele consequences and negative impacts on physical, psychosocial, or occupational functioning (9). In the model of anabolic androgen steroid dependence model, high-dose AAS is utilized with dietary and intensive weight training in stage 1, which is referred to as the "my active" phase occurs. On the other hand, stage 2 is characterized by long-term and high-dose AAS usage, which leads to the establishment of a brain reward system, which contributes to misuse and dependency. The modern world's day-to-day lives and customs have been thrown into disarray by the internet and social media. The spread of misconception, along with a lack of knowledge regarding the limits on AAS, causes young athletes to engage in risky behaviors (10).

In this present review, we are going to discuss the effect of steroid use in humans and its biochemical effects on normal physiological processes, and also the neurological effect of these drugs. This review will try to address the effect of steroid use and its physiological outcome.

Alteration in blood and Biochemical parameters

Past studies reported that long-term use of steroids can result in several changes in the biochemical parameters including blood count, renal function test, level of serum electrolytes, and lipid profile.

Blood count and hematological changes

Bordin et al reported that in steroid users the level of Haematocrit and mean corpuscular hemoglobin concentration (MCHC) increases significantly compared with the non-users. This study also reported that among steroid abusers the MCV levels also increased, but this had no statistically significant difference with the non-users. This study reported that erythropoiesis is higher in the steroid abusers compared to the non-users (11).

In a previous study conducted among COPD patients who use inhaled corticosteroids, it was observed that users with inhaled corticosteroids have changed hemogram parameters. This study also reported higher MCV and mean MCHC levels among ICS users. The level of neutrophil counts, and WBC were significantly lower in the ICS users (12).

Previous studies have reported that testosterone increases the level of hemoglobin in replacement therapy. It was reported that corticosteroids increase the RBC count and hemoglobin mainly by decreasing erythrophagocytosis. They were also shown to affect the level of WBC (13).

They also affect white blood cells in circulation. Glucocorticoid therapy causes an increase in polymorphonuclear leukocytes in the blood due to an increased rate of entry from the marrow and a decreased rate of clearance from the vascular compartment. Glucocorticoids, on the other hand, reduce the number of lymphocytes, eosinophils, monocytes, and basophils. When a single dosage of cortisol is given, lymphocytes are lowered by 70% and monocytes are reduced by 90%. The number of cells in the body increases 24 to 72 hours following treatment (14).

Although certain lymphocytes also experience glucocorticoid-induced apoptosis, the decrease in several lymphocytes and other associated cells is assumed to be the result of redistribution (15). T lymphocytes are more susceptible to glucocorticoid-induced apoptosis than B lymphocytes, and glucocorticoid sensitivity varies by T-cell subpopulation.

Level of Sodium potassium, electrolyte, and water balance

Mineralocorticoids are associated with the regulation of water and electrolyte balance through the kidney. Treatment with aldosterone causes an increase in sodium reabsorption as well as potassium and hydrogen excretion in the renal tubule (16).

Mineralocorticoids' systemic activity is accounted for by similar effects on cation transport in most other tissues. Among the several symptoms of mineralocorticoid excess increased extracellular fluid volume, hypokalemia, positive sodium balance, and alkalosis are the important ones. Hypocorticism causes salt loss through the kidneys along with a decrease in the extracellular fluid volume and hydration (13).

The changes that happen in hypercorticism cause profound cardiovascular changes that can eventually result in renal failure and if not treated can eventually result in death. The mineralocorticoid receptors present in the distal tubules get activated by the Aldosterone. This increases the permeability of the apical membrane of the collecting tubular cells. There is also a rapid mechanism that has been reported that is independent of the activation of mineralocorticoid receptors (17).

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Aldosterone also increases the activity of enzymes such as ATPase that are present in the serosal membrane. The driving forces for increased potassium and hydrogen excretion as a result of these alterations include increased sodium reabsorption and a larger negative potential in the lumen (18).

Calcium and magnesium excretion is also increased by mineralocorticoids, most likely due to volume expansion. Sodium "escaping," or the cessation of sodium alterations, occurs with long-term aldosterone treatment, whereas potassium and hydrogen loss continue. The mechanism for this action is uncertain, however, it could entail downregulation of mineralocorticoid receptors and subsequent loss of hormone reactivity (19).

The effects of glucocorticoids on the kidney differ from those of mineralocorticoids. Water diuresis, glomerular filtration rate, and renal plasma flow are all increased by glucocorticoids. Cortisol increases sodium retention and potassium excretion but does not appear to increase hydrogen excretion. Increased renal calcification, renal stone disease, and increased stone formation as a result of elevated urinary calcium and uric acid are the most common renal side effects of glucocorticoid drugs. (20).

Renal Biomarkers

It was observed that in individuals who had steroids the blood retention of urea, uric acid, and creatinine increased and reaches up to 60.6 mg/dl, 7.5 mg/dl, and 1.9 mg/dl is much higher than the normal level and commonly found in individuals with renal disorders. It was reported that bodybuilders who use higher doses of protein supplements and steroids have a higher number of amino acid metabolism in the liver (21).

The increased steroid doses are also associated with the increase in creatinine levels. As per the recommendation of the international Renal Association the determination of the glomerular filtration rate can provide information about renal functionality (22).

Bordin et al reported that in steroid users the value of GFR varies from 89ml/min to 79 ml/min which is lower than the normal GFR of 90 ml/min. This decreased GFR if persisted for a longer period can eventually result in CKD. However, there is no change in the uric acid level that was reported in this study (11).

Daher et al reported that androgens cause direct toxicological effects on the glomerular cells and thus resulting in the accumulation of the mesangial matrix. This eventually results in acute kidney injury (23). Moreover, it is also reported recently that long-term use of steroids can cause focal segmental glomerulosclerosis (24).

Lipid profile and Liver functions

The exact pathophysiological basis of corticosteroid-induced liver damage is still unknown and is only linked to HBV infection in some patients. Though modest dosages of corticosteroids are thought to be safe for the liver, long-term use of these medicines has been linked to steatosis and steatohepatitis (25).

In the previous studies, it was reported that steroid dose increase can significantly increase the risk of non-alcoholic fatty liver diseases. In this study, the authors have reported a case where an increase in the steroid dose increases the level of Serum aspartate aminotransferase (AST) and alanine aminotransferase levels (ALT). Further analysis revealed that women had NAFLD. Liver biopsy results showed the presence of fatty liver (26).

Another study by Coelho et al reported one case of hepatitis in a patient with inflammatory bowel disease. In this study, one patient with IBD was prescribed steroids. After a few days, the liver parameters showed significant changes. The level of ALT, AST, GGT, and alkaline phosphatase levels increased significantly. They have concluded that this is associated with steroid use as the patient had a normal level of liver enzymes the admission. After the steroids were withdrawn the liver function tests became normal (27).

Metabolic effects of steroid use

Glucocorticoid essential cortisol is an important regulator of nucleic acid, protein, lipid, and carbohydrate metabolism. Cortisol will increase blood glucose degrees by stimulating gluconeogenesis inside the liver (28). The loss of protein stores, which are required in all body cells except those of the liver, is one of the most significant effects of cortisol on the body's metabolic system. This is due to a decrease in protein synthesis and an increase in the catabolism of already present proteins in the cells. Cortisol enhances fatty acid mobilization from adipose tissue and boosts fatty acid oxidation in cells; nevertheless, too much cortisol induces fat deposition in the neck and chest, giving the torso a "buffalo" appearance (29).

The exact dosing and the effect of corticosteroids in individuals differ. This difference is mainly based on the difference in their preparations and their pharmacokinetic effects. Further, the condition of the underlying

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disease for which the drugs are been used also varies. The response to corticosteroid treatment also depends on the interactions of these drugs with the other non-steroid agents and their responses.

In a study conducted among patients with rheumatoid arthritis, it was shown that low doses of glucocorticoids have similar adverse events as that of the placebo group. This indicates that in low doses these drugs defy the common belief of abuse and its adverse events on individuals (30). The most significant effects of these steroids are described in detail in the below section.

Intermediary Metabolism

Metabolism of protein, carbohydrate, and lipid all are influenced by the glucocorticoid. Storage of carbohydrates as glycogen and gluconeogenesis is also promoted by glucocorticoids. The mobilization of amino acids from protein and subsequent breakdown as a source of carbon during gluconeogenesis causes an increase in urine nitrogen after an increase in glucocorticoids (31).

Availability of food most importantly free amino acids helps the adrenalectomized animals to function correctly. However, when these animals are starved, they are unable to mobilize amino acids from muscle or serum protein, demonstrating that cortisol is involved in the mobilization process. Hepatic gluconeogenesis is stimulated by glucocorticoids, which in turn increases the concentration of plasma glucose. This results in the deposition of liver glycogen (32).

Long-term glucocorticoid exposure results in a diabetic-like state due to increased plasma glucose, whereas low glucocorticoid levels result in hypoglycemia, decreased glycogen storage, and insulin hypersensitivity (33).

On lipid metabolism, glucocorticoids have two well-known impacts. The first is that hypercorticism causes body fat redistribution, and the second is that it makes lipolytic medication effects easier. Glucocorticoids cause fat redistribution to the upper trunk and face, as well as fat loss in the extremities when taken in large amounts. The mechanism behind this action is unknown, however, variations in the number of glucocorticoid receptors in different types of fat cells could explain these seemingly opposing effects (34).

Adrenal suppression

Exposure of the HPA axis to the glucocorticoid can cause adrenal suppression. However, the dose of the medications and duration is not always the sole predictor of adrenal suppression (AS) in any individual (35).

It was shown that even exposure to glucocorticoid therapy for 5 days can result in the development of AS. Therefore, it is important to note that even topical, intraocular, and inhaled glucocorticoid can effectively absorb systematically and results in AS (28). Long-term use of glucocorticoids has been reported to be associated with an increased risk of developing AS. The timing of glucocorticoid administration is also important. This is because studies have shown that morning administration of the drug is less inhibitory than evening administration (36).

It was also reported that the physiology of the HPA axis is less suppressed in a daily dose of glucocorticoids compared with the alternate-day therapy. However, there is currently no substantial clinical evidence to support this claim (36). Cortisol has a wide range of physiological functions, which are especially significant during times of physiological stress such as in surgery or any disease. Many of the clinical symptoms of AS are non-specific, and they might be mistaken for symptoms of intercurrent illnesses or the underlying condition being treated with glucocorticoids.

Weight gain and Cushingoid appearance

Long-term usage of corticosteroids can lead to weight gain and adipose tissue redistribution. As a result, abdominal adiposity, moon face, and adipose tissue deposition in the dorsocervical region emerge. In a study conducted on 2167 glucocorticoid users, the most common complication was weight gain (37). In another study of people suffering from rheumatoid arthritis, glucocorticoid users showed a 4-8% increase in the body weight who were on prednisone doses for more than 2 years (30).

Hyperglycemia

Exogenous corticosteroid use has been associated with hyperglycemia, and increased therapy exacerbates insulin resistance in persons with diabetes, including pre-existing and newly diagnosed. The effects of that same GC injection on glucose levels appear to be dose-dependent and noticeable within hours of exposure to the steroid. As the daily steroid dose was raised, the probability of hyperglycemia increased significantly. GCs appear to have a greater influence on postprandial glucose concentrations than they do on fasting glucose levels (38).

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Neurological effect

Patients taking glucocorticoids frequently develop a feel-good feeling after starting the medicine; moderate exhilaration or anxiety are also possible side effects. Early in therapy, hypomanic reactions and activated states are more common than depression; nevertheless, depression is more common in individuals who have been in therapy for longer. It was also reported that the use of corticosteroids can result in different neurological and psychiatric disturbances in individuals having these medications for a longer period (39).

Psychiatric and cognitive disturbances

The use of corticosteroids can result in a wide range of cognitive and psychiatric problems. Patients undergoing GC treatment for a longer period have reported agitation, anxiety, mood changes, memory impairment, lethargy, irritability, and worse cases of psychosis. All these adverse events can start as early as 1 week after the treatment regimen is started and changes with the duration and dose of the corticosteroid (40). Psychiatric side effects are widespread during systemic corticosteroid medication, according to a review article. According to two extensive meta-analyses, severe responses occurred in approximately 6% of patients, whereas mild to moderate reactions occurred in roughly 28%. Although short-term corticosteroid medication can cause mood, cognition, sleep, and behavior disorders, as well as outright delirium or even psychosis, the most prevalent side effects, are euphoria and hypomania (41).

It was also reported that GC-related adverse events are more common among patients with a family history of depression or alcohol abuse. Patients who reported having psychiatric effects after short-term use of the corticosteroids had depressive symptoms and euphoria among the other neurological manifestations (42).

Sleep difficulties have been reported, particularly with dual dosages, suggesting that the cortisol production cycle may be disrupted. Akathisia is a common glucocorticoid side effect (motor restlessness). Patients who have had a previous neuropsychiatric condition may be more likely to acquire one after using glucocorticoids. Pseudotumor cerebri has also been connected to the usage of glucocorticoids (43).

The use of more than 20 mg of prednisone or equivalent for lengthy periods is usually the only way to develop GC-induced psychosis. Low serum albumin levels in SLE patients may also be a predictor of GC-induced psychosis. Antipsychotic therapy may be necessary for patients who have chronic psychotic symptoms (44).

Neuropsychiatric Adverse Effects

Children with acute lymphoblastic leukemia who were given dexamethasone or prednisone for treatment induction and maintenance have reported neuropsychiatric adverse effects with glucocorticoid therapy. Children under the age of six are more vulnerable, and symptoms usually occur during the first week of glucocorticoid treatment (45).

Glucocorticoid-induced acute neuropsychiatric impairment might manifest as euphoria, hostility, mood variations, loss of sleep, depression, and even severe psychosis. Although these psychological aberrations normally fade away after ceasing glucocorticoid therapy, a small percentage of patients may still experience symptoms after stopping the prescription (46).

Other complications

Cardiac and arterial complications

Glucocorticoids also increase the renal excretion of several electrolytes including phosphate and potassium. On the other hand mineralocorticoids, particularly cortisol and cortisone are associated with fluid retention, hypertension, edema, weight gain, and arrhythmias. However, hypertension only arises in higher doses. Long-term usage of medium-high dose glucocorticoids results in a dose-dependent pattern of premature atherosclerosis (47).

Heart arrhythmias and rapid death have also been connected to pulse GC treatment. These events, on the other hand, are rare and have usually occurred in persons who have underlying kidney or heart disease. Although it is unclear whether these substantial AEs are due to GC use or the underlying condition, some doctors advise that patients undergoing pulse therapy who have significant cardiac or kidney problems have constant cardiac monitoring (48).

Gastrointestinal complications

The use of corticosteroids increases the risk of gastric ulcer, GI bleeding, and gastritis. The use of NSAIDs also increases the chance of GI effects if they are used in combination with corticosteroids. Among other

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complications visceral perforation, fatty liver, pancreatitis, and cirrhosis have been positively associated with the use of GC (49).

Muscular complications

Corticosteroids have direct catabolic effects on skeletal muscles, resulting in decreased muscle protein synthesis and catabolism, as well as muscle weakening. Myopathy usually appears after a few weeks or months of GC use. Muscular weakness and atrophy in both the upper and lower extremities are common in these patients. However, no myalgias or muscle soreness was reported (50).

Although the dose and duration of GC medication can vary drastically before the start of myopathy, it is more common in persons who are taking less than 10 mg of prednisone per day or comparable. Furthermore, the bigger the GC dosage, the faster muscular weakening develops (51).

In patients who require large doses of intravascular GC and neuromuscular blocking agents, myopathy is a common complication. Diffuse and severe weakness develops after several days from the doses received. This usually is a reversible condition and often results in frequent ICU admissions. These patients also develop severe myopathy and increase the risk of mortality (52).

Immune suppression and increased infection

Corticosteroid administration is associated with immunosuppression. The exact mechanism of this immunosuppression is not known. This immunosuppression often predisposes patients to infection. In a meta-analysis consisting of 2000 patients, it was reported that systemic application of GC increases the chances of infection in patients compared to the placebo (53).

Moreover, it was also reported that patients who received GC are more susceptible to viral and fungal infections, mostly in patients who are undergoing a transplant. Aged patients with other functional impairments have a higher risk of developing infections compared to the younger lot (54).

Ophthalmic complications

Patients who took more than 10 mg of prednisone per day for more than a year had a significantly higher incidence of cataracts, with a dose-dependent relationship. Low-dose glucocorticoids have also been related to a higher risk of cataracts. Cataracts usually affect both eyes and progress slowly (1).

Intraocular glucocorticoids and high-dose systemic glucocorticoids cause increased intraocular pressure, especially in patients with a family history of open-angle glaucoma. Glaucoma is a condition that causes vision field loss, cupping of the optic disc and atrophy of the optic nerve. The increase in intraocular pressure normally goes away within a few weeks after stopping systemic therapy, but the damage to the optic nerve is often irreversible (55).

Central serous chorioretinopathy is a unique adverse effect of systemic or even topical glucocorticoid treatment, in which the retina separates from its underlying photoreceptors due to the development of subretinal fluid in the macular region. This sickness is characterized by central visual blur and reduced visual acuity (56).

Conclusion

The benefit of the use of systemic corticosteroids is well established within the clinical system. It has been successfully employed to treat various inflammatory and autoimmune diseases. However, its prolonged use and use at a higher dose (commonly known as steroid abuse) may create severe adverse events that affect different physiological systems such as cardiovascular, musculoskeletal, endocrine, neurological, and gastrointestinal.

In addition, its metabolic effect brings in different perturbations in biochemical parameters in blood and other organs. However, these adverse effects can be minimized through the implementation of proper clinical monitoring and management that involves a well-informed patient. The patient must be informed by clinicians about all the possible AEs of systemic steroid therapy and made aware to take medical advice whenever feels any adverse event is taking place.

It is very useful and important to decide the lowest effective dose of a lower potency agent to treat a prospective patient. The clinician must follow all the existing guidelines to implement the steroid therapy and must monitor several parameters such as risk factors or pre-existing conditions that may potentially be exacerbated by steroid therapy.

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A careful examination of physical parameters, past medical history, and presence of co-morbidities such as hyperglycemia, CVD, GI dysfunction, dyslipidemia, osteoporosis through measurement of different blood parameters, and other associated laboratory assessments. For children, careful assessment of nutritional status and pubertal factors may help in keeping control of adverse events. As steroids may cause birth defects like cleft palate, women of childbearing age must be questioned about the planning of pregnancy before administration of steroids.

The neurologic and metabolic sequelae can be improved by deciding the lowest effective steroid dose for the minimum period required to achieve treatment goals. Intermittent monitoring of treatment outcomes and planned withdrawal by dose-tapering may help in a better treatment outcome and fewer adverse events.

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