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Review article

Corticosteroid induced Disorders – An overview

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ABSTRACT
Glucocorticoids are important in the treatment of many inflammatory, allergic, immunologic, and malignant disorders, and the toxicity of glucocorticoids is one of the commonest causes of iatrogenic illness associated with chronic inflammatory disease. Glucocorticoid-induced muscle atrophy is characterized by fast-twitch or type II muscle fiber atrophy. Corticosteroid (CS) therapy is widely used in the treatment of rheumatic diseases. Osteoporosis remains one of its major complications. Steroid induced glaucoma is a form of open angle glaucoma occurring as an adverse effect of corticosteroid therapy. Glucocorticoids induce hepatic and extrahepatic insulin resistance. Glucocorticoid treatment impairs both glucose transport in fat and muscle cells. Corticosteroid-induced psychosis represents a spectrum of psychological changes that can occur at any time during treatment. Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the hormone cortisol. Physicians must be aware of these adverse effects and be equipped to manage them.

Key words: Corticosteroids, Myopathy, Osteoporosis, Glaucoma, Diabetes Mellitus, Psychosis, Cushing's Syndrome.

INTRODUCTION

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and analogues of these hormones that are synthesized in laboratories**.** The corticoids have widespread actions. They maintain fluid-electrolyte, cardiovascular and energy substrate homeostasis and functional status of skeletal muscles and nervous system. Glucocorticoids are important in the treatment of many inflammatory, allergic, immunologic, and malignant disorders, and the toxicity of glucocorticoids is one of the commonest causes of iatrogenic illness associated with chronic inflammatory disease. Numerous toxicities, or adverse effects, have been attributed to glucocorticoids**.**[1]

MECHANISM OF ACTION OF CORTICOSTEROIDS

The glucocorticoid (G) penetrates the cell membrane and binds to the glucocorticoid receptor (GR) protein that normally resides in the cytoplasm in association with 3 other proteins, viz. Heat shock protein 90 (HSP90), HSP70 and immunophilin (IP). The GR has a steroid binding domain near the caboxy terminus and a mid region DNA binding domain having two "Zinc fingers", each made up of a loop of amino acids with chelated zinc ion. Binding of the steroid to GR dissociates the complexes proteins (HSP90, etc) removing their inhibitory influence on it. A dimerization region that overlaps the steroid binding domain is exposed, promoting dimerisation of the occupied receptor. The steroid bound receptor

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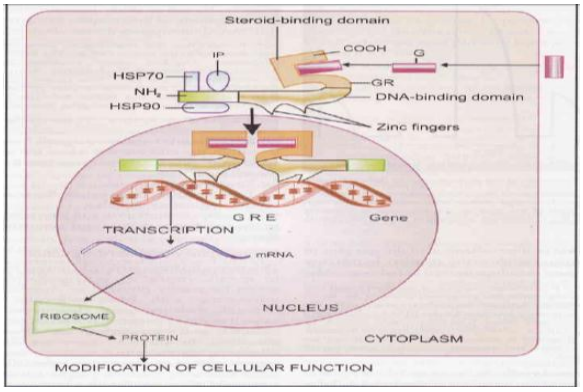
diamertranslocates to the nucleus and interacts with specific DNA sequences called 'glucocorticoid responsive elements' (GRES) within the regulatory region of appropriate genes. The expression of these genes is consequently altered resulting in promotion (or suppression) of their transcription. The specific mRNA thus produced is directed to the ribosome where the message is translated into a specific pattern of protein synthesis, which inturn modifies cell function.[2]



CORTICOSTEROIDS INDUCED MYO-PATHY[3]

Glucocorticoid-induced muscle atrophy is characterized by fast-twitch or type II muscle fiber atrophy illustrated by decreased fiber cross-sectional area and reduced myofibrillar protein content.

PATHOPHYSIOLOGY

Mechanisms of glucocorticoid-induced muscle atrophy

In skeletal muscle, glucocorticoids decrease the rate of protein synthesis and increase the rate of protein breakdown [4,5,6] contributing to atrophy. The severity and the mechanism for the catabolic effect of glucocorticoids may differ with age. For example, glucocorticoids cause more severe atrophy in older rats compared with younger rats. Furthermore, glucocorticoid-induced muscle atrophy results mainly from increased protein breakdown in adult rats but mostly from depressed protein synthesis in the aged animals[7].

Anti-anabolic action of glucocorticoids

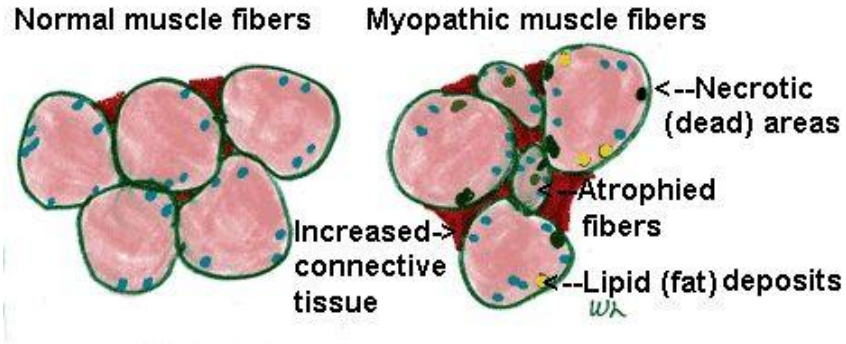
The inhibitory effect on protein synthesis results from different mechanisms. First, glucocorticoids inhibit the transport of amino acids into the muscle[8], which could limit the protein synthesis. Secondly, glucocorticoids inhibit the stimulatory action of insulin, insulin-like growth factor-I (IGF-I), and amino acids (in particular leucine), on the phosphorylation of eIF4E-binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase 1 (S6K1), two factors that play a key role in the protein synthesis machinery by controlling the initiation step of mRNA translation[9,10]. Finally, there is also evidence that glucocorticoids cause muscle atrophy by inhibiting myogenesis through the down regulation of myogenin, a transcription factor mandatory for differentiation of satellite cells into muscle fibers.

Catabolic action of glucocorticoids

The stimulatory effect of glucocorticoids on muscle proteolysis results from the activation of the major cellular proteolytic systems, namely the ubiquitin–proteasome system (UPS), the lysosomal system (cathepsins), and the calcium-dependent system (calpains). The protein degradation caused by glucocorticoids affects mainly the myofibrillar proteins as illustrated by the increased excretion of 3-methyl histidine. To activate the protein degradation, glucocorticoids stimulate the expression of several components of the UPS either involved in the conjugation to ubiquitin of the protein to be degraded (ubiquitin; 14 kDa (E2), a conjugating enzyme; atrogin-1 and MuRF-1, two muscle-specific (E3) ubiquitin ligases; or directly responsible for the protein degradation by the proteasome (several subunits of the 20S proteasome). This gene transcription activation is associated with an increased rate of protein ubiquitination and increased proteolytic activities of the proteasome itself.

Using blockers of the different proteolytic pathways, evidence was found that glucocorticoids stimulate not only the UPS-dependent proteolysis but also the calcium-dependent and lysosomal protein breakdown. The role of lysosomal system in the atrophic effect of glucocorticoids is also suggested by the increase in cathepsin L muscle

expression in glucocorticoid-treated animals[11].Because the proteasome does not degrade intact myofibrils, it is thought that actin and myosin need to be dissociated (probably by calpains) from the myofibrils before they can be degraded by the UPS. Finally, some *in vivo* data also suggest that caspase-3 can be implicated in the myofibrillar proteins breakdown induced by glucocorticoids. Indeed, in glucocorticoid-dependent muscle wasting models, such as diabetes mellitus and chronic renal failure, caspase-3 activity in muscle is increased and inhibition of caspase-3 by Ac-DEVD-CHO, a peptide inhibitor, suppresses the accelerated muscle proteolysis. However, the role of glucocorticoids in the induction of caspase-3 activity in these models has not yet been explored.



Prevention of glucocorticoid-induced muscle atrophy

Growth factors

Stimulation of IGF-I and inhibition of MSTN appear promising therapeutic tools to attenuate glucocorticoid-induced muscle atrophy[13]. Indeed, muscle IGF-I overexpression[12] or myostatin deletion[14] prevents glucocorticoid-induced muscle atrophy. Therefore, IGF-I stimulation or MSTN blockade might be beneficial for a variety of myopathies, such as the ones caused by high doses of glucocorticoids. Further experiments are needed to test this possibility.

Branched chain amino acids (BCAAs)

Provision of the BCAAs mimics the effect of a complete mixture of amino acids in stimulating protein synthesis in skeletal muscle[15]. Of the BCAAs, leucine appears to be the most important in stimulating protein synthesis. Therefore, it seems logical to propose to override the catabolic effects of glucocorticoids toward skeletal muscle by administration of BCAAs or leucine alone. However, the fact that glucocorticoids make the muscle protein synthesis resistant to exogenous BCAAs and leucine does not support this hypothesis.

Glutamine

Glutamine is a conditional essential amino acid in catabolic states. Glutamine and alanyl-glutamine have been reported to prevent glucocorticoid-induced muscle atrophy. However, attenuation of this muscle atrophy by glutamine infusion is not associated with changes in circulating IGF-I levels. In contrast, administration of glutamine prevents glucocorticoid-induced Mstn expression, which suggests that glutamine may inhibit the atrophic effect of glucocorticoids on muscle strength through inhibiting Mstn.

Taurine

Since ablation of taurine transporter gene results in susceptibility of exercise-induced weakness *in vivo*, it has been suggested that this transporter is essential for skeletal muscle function. The role of taurine in the prevention of glucocorticoid-induced atrophy is suggested by two observations. First, taurine attenuates muscle cell atrophy caused by glucocorticoids *in vitro*. Second, induction of taurine transporter prevents glucocorticoid-induced muscle cell atrophy. Although attractive, the possibility for taurine to attenuate glucocorticoid effects on skeletal muscle warrants further investigations.

Creatine

Dietary supplementation with creatine monohydrate has been shown to attenuate the muscle weight loss and the atrophy of gastrocnemius type IIb fibers caused by glucocorticoids. Furthermore, this protective effect was associated with an attenuation of the impairment of daily spontaneous running of animals receiving glucocorticoids [16]. Although further work is required to determine the specific mechanisms underlying the effects of creatine on

muscle, evidence collected *in vitro* suggests that creatine may act on muscle cells by increasing IGF-I expression.

Clenbuterol

Clenbuterol, a β2-adrenergic receptor agonist used to increase muscle mass in cattle, has been tested to prevent glucocorticoid-induced muscle atrophy. Experiments have shown that clenbuterol is able to blunt at least partially the skeletal muscle atrophy caused by dexamethasone. However, on diaphragm, attenuation of muscle atrophy was not associated with a protective effect on muscle dysfunction. Evidence collected *in vivo* suggest that clenbuterol may exert its anti-catabolic effect on muscle by increasing IGF-I expression ,while down regulating Mstn expression.

Androgens

Administration of androgens, such as testosterone or nandrolone, a minimally aromatizable analog, prevents decreased muscle mass and strength caused by glucocorticoids in animals and humans. Although the molecular mechanisms by which testosterone attenuates the effects of glucocorticoids are not fully elucidated, testosterone, like many other anabolic stimuli, appears to stimulate muscle IGF-I expression.

CORTICOSTEROIDINDUCED OSTEOPOROSIS

Corticosteroid (CS) therapy is widely used in the treatment of rheumatic diseases. Osteoporosis remains one of its major complications.

Normal

Osteoporotic bone

MECHANISM

The mechanism of CIOP is uncertain but appears different from that of post-menopausal osteoporosis. A major difference is that bone formation appears to be suppressed by CS [17]. This may be difficult to confirm in direct studies because although osteocalcin, a marker of bone formation, has been shown to be suppressed by CS therapy[18, 19], this may be due to a direct effect of CS on the osteocalcin gene promoter to antagonize the action of $1,25(OH)_2D_3$ to induce the gene [20]. The effects of CS on bone resorption are more difficult to assess because although some studies suggest that resorption is increased [18,19], others [21,22] have shown no effect.

The result of the greater depression of bone formation compared with bone resorption (remodeling imbalance) leads to differences in bone microanatomy and histology. In post-menopausal osteoporosis, the reduction in trabecular bone volume due to an increase in bone resorption appears to be due to trabecular discontinuity, whereas the reduction in trabecular bone volume due to decreased bone formation in CIOP is a result of trabecular thinning [23]. This has implications for both the diagnosis and treatment of CIOP.

Other factors involved in the development of CIOP include alterations in the calcium regulating hormones and sex steroids. Intestinal calcium absorption is reduced as a result of CS use[17]which also leads to a reduced renal tubular calcium reabsorption. Although these changes were initially thought to be due to secondary hyperparathyroidism, recent studies measuring the intact parathyroid hormone (PTH 1–84) have shown these values to be normal[19]. There is also an alteration in hypothalamic gonadotrophin releasing hormone secretion[17]with subsequent reduction in serum testosterone[24] and oestradiol levels [25]. Finally, CS therapy may influence cellular responses within the bone micro environment by modulating cytokines that act locally to regulate remodeling and these factors include interleukin1, tumour necrosis factor and insulin like growth factor.[26]

TREATMENT

Many agents used in postmenopausal osteoporosis such as activated vitamin D products, hormone

replacement therapy, fluoride, calcitonin and the bisphosphonates have been shown to maintain or improve BMD in CIOP. Primary prevention is treatment started at the time of initiation (up to 3 months) of CS therapy. Secondary prevention is treatment started >1 yr after the initiation of CS therapy or following an osteoporotic fracture and implies established bone loss. All patients should be assessed for hypogonadism and if present, HRT should be offered to women and testosterone to men[27,28,29]

CORTICOSTEROID-INDUCED GLAUCOMA

A rise in intraocular pressure (IOP) can occur as an adverse effect of corticosteroid therapy. If the ocular hypertensive effect is of sufficient magnitude, for an adequate duration, damage to the optic nerve (steroid-induced glaucoma) may ensue. Corticosteroids are believed to decrease outflow by inhibiting degradation of extracellular matrix material in the trabecular meshwork (TM), leading to aggregation of an excessive amount of the material within the outflow channels and a subsequent increase in outflow resistance.[30,31]

PATHOPHYSIOLOGY[39]

Corticosteroids cause elevation of IOP by decreasing the facility of aqueous eye flow .Steroids specific receptors on the trabecular meshwork cells may play a role in the development of steroid induced glaucoma. Recent research has elucidated the possible role of genetic influences in the pathophysiology.

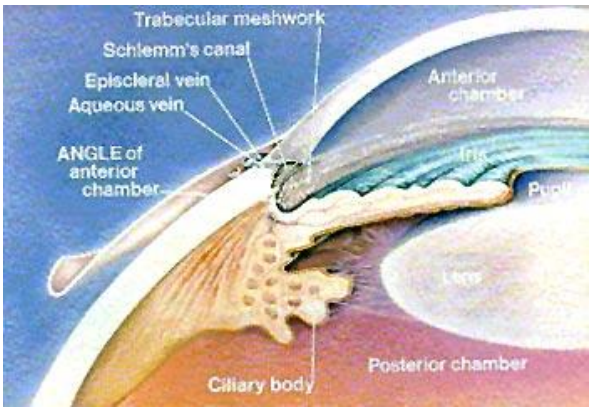
The main mechanism of action of steroids i.e; responsible for glaucoma is their membrane stabilizing action. Hyaluronidase sensitive glycosaminoglycans (mucopolysacchrides) are normally present in the aqueous out flow system. These glycosaminoglycans in the polymerised form may undergo hydration producing a 'biologic oedema'. Hence, these are constantly degraded by the hyaluronidase with in the lysosomes of the goniocytes

The steroids stabilize the lysosomal membrane of the goniocytes and thus lead to an accumulation of polymerised glycosaminoglycans in the trabecular meshwork, producing an increased outflow resistance. Glucocorticoid administration increases expression of collagen, elastin, and fibronectin with in the trabecular meshwork and induces expression of sialoglycoprotein .

Another mechanism proposed is that steroids inhibit phagocytosis by the endothelial cells lyning the trabecular meshwork. This leads to an accumulation of debris with in the meshwork. There is also extra cellular deposition of finger print like material.

Steroid use decreases expression of extra cellular proteinases including fibrinolytic enzymes and stromolysin.

A decrease in the synthesis of prostaglandins by corticosteroids, that regulate aqueous facility has also been proposed as one of the mechanisms leading to increasing IOP.



Management of corticosteroid-induced glaucoma

- Monitoring of IOP[32]
- Cessation of corticosteroid treatment[34]
- Alternative corticosteroid formulations[33,36,37]

Topical treatments can be changed to preparations such as fluoromethalone 0.1% or rimexolone 1%, which are claimed to have less effect on IOP,or in certain situations to nonsteroidal anti-inflammatory drugs (NSAIDs).

Irreversible steroid-induced ocular hypertension /glaucoma

- Medical antiglaucomatous therapy[35] Miotics, Beta-blockers, Prostaglandin analogues, Alpha agonists, Carbonic anhydrase inhibitors
- Argon laser trabeculoplasty (ALT)
- Filtration surgery[38]

Glucocorticoid-Induced Diabetes Mellitus

The mechanism of glucocorticoid-induced diabetes mellitus is multifactorial. Glucocorticoids induce hepatic and extrahepatic insulin resistance. Glucocorticoid treatment impairs both glucose transport in fat and muscle cells and the ability of glucose to stimulate its own utilization (glucose effectiveness), as well as reducing glucose clearance.

Treatment

Diet, Exercise, Self-monitoring of blood glucose concentrations[40]

Patients with mild hyperglycemia (all blood glucose concentrations <200 mg/dL)[41]

- First-line treatment: metformin (at the maximum tolerated dose, up to 2 g/day)
- Second-line treatment: sulfonylureas, meglitinides, or thiazolidenediones
- Third-line treatment: single-dose neutral protamine Hagedorn (NPH) insulin

Patients with fasting glucose concentration in goal but other glucose concentrations e200 mg/dL[42]

- NPH insulin or premixed (with rapid-acting insulin) insulin once a day; start at a generous dose (e.g., 0.2-0.4 units/kg per day)
- May need another dose of rapid-acting insulin with evening meal if bedtime blood glucose concentrations are high

Patients with fasting and daytime blood glucose concentrations e200 mg/dL[43]

- Treat like any patient who newly requires insulin but at a much higher starting dosage (eg, 0.6-0.8 units/kg per day)
- Patients often require a much larger proportion of their insulin as prandial doses

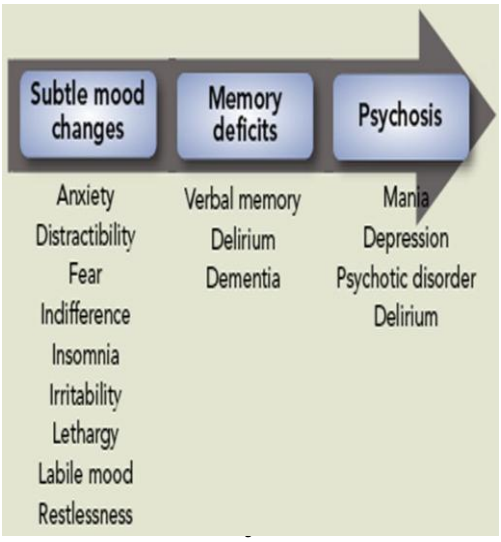
CORTICOSTEROID-INDUCED PSYCHOSIS

Corticosteroid-induced psychosis represents a spectrum of psychological changes that can occur at any time during treatment. Mild-to-moderate symptoms include agitation, anxiety, insomnia, irritability, and restlessness, whereas severe symptoms include mania, depression, and psychosis [44]

SPECTRUM OF PSYCHIATRICSYMPTOMS

Grading scale for corticosteroid-induced psychiatric symptoms

Grade	Symptoms
Grade 1	Mild, nonpathologic, and subclinical euphoria
Grade 2	Reversible acute or subacute mania and/or depression
Grade 3	Bipolar disorder with relapses possible without steroids



Pathophysiology of corticosteroid-induced psychosis

How corticosteroids cause psychosis is not well understood. One theory suggests that corticosteroids act at steroid-specific receptors and suppress filtering by the hippocampus of irrelevant stimuli.[50]

Supporting this theory of hippocampal change, a study of 17 patients receiving corticosteroid therapy for >6 months found decreased hippocampal volume compared with a control group.[51]Other possible causes include suppressed hypothalamus-pituitary axis and enhanced dopamine neurotransmission.[52]

Treatment

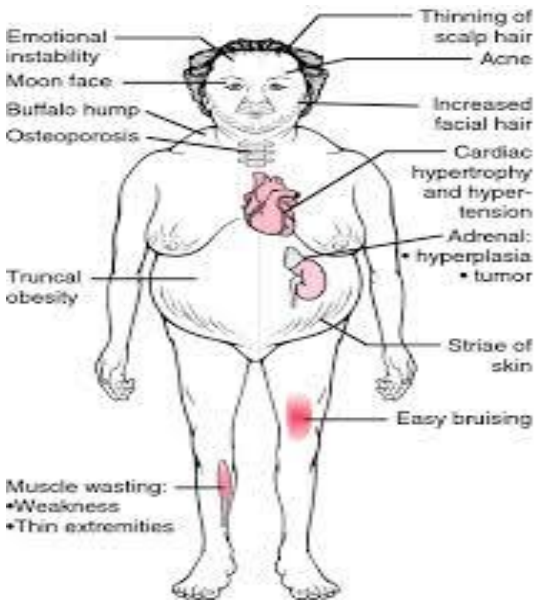
Management includes tapering corticosteroids, with or without adding medications to treat the acute state. Decreasing corticosteroids to the lowest dose possible—<40 mg/d—or gradually discontinuing therapy to prevent triggering adrenal insufficiency may improve psychotic symptoms and avoids the risk of adverse effects from adjunctive medications. Psychopharmacologic treatment may be necessary, depending on the severity of psychosis or the underlying disease, particularly if corticosteroids cannot be tapered or discontinued.[45-49]

CORTICOSTEROIDS INDUCED CUSHING'S SYNDROME

Cushing's syndrome describes the signs and symptoms associated with prolonged exposure to inappropriately high levels of the hormone cortisol. This can be caused by taking glucocorticoid drugs, or diseases that result in excess cortisol, adrenocorticotropic hormone (ACTH), or CRH levels.[64]

Pathophysiology

The hypothalamus is in the brain and the pituitary gland sits just below it. The para ventricular nucleus (PVN) of the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenocorticotropin (ACTH). ACTH travels via the blood to the adrenal gland, where it stimulates the release of cortisol. Cortisol is secreted by the cortex of the adrenal gland from a region called the zonafasciculata in response to ACTH. Elevated levels of cortisol exert negative feedback on the pituitary, which decreases the amount of ACTH released from the pituitary gland. Strictly, Cushing's syndrome refers to excess cortisol of any etiology (as Syndrome means a group of symptoms). One of the causes of Cushing's syndrome is a cortisol secreting adenoma in the cortex of the adrenal gland (primary hypercortisolism/ hypercorticism). The adenoma causes cortisol levels in the blood to be very high, and negative feedback on the pituitary from the high cortisol levels causes ACTH levels to be very low.



Treatments and drugs[53-62]

- **Reducing corticosteroid use, Surgery, Radiation therapy**
- **Medications:** Medications to control excessive production of cortisol include ketoconazole, mitotan and metyrapone. The Food and Drug Administration has also approved the use of mifepristone for people with Cushing syndrome who have type 2 diabetes or glucose intolerance. Mifepristone does not decrease cortisol production, but it blocks the effect of cortisol on tissues.

CONCLUSION

Glucocorticoids play a major role in inducing myopathy, osteoporosis, glaucoma, diabetes, psychosis, cushing's syndrome and various pathological conditions. Although there has been marked progress in the last few years in understanding the mechanisms behind corticosteroids induced disorders further research needs to be undertaken. Physician managing patients on corticosteroids should always consider the need for therapy to prevent or treat corticosteroids induced disorders. Better identification of patients at risk of corticosteroids induced disorders rises would allow them to be more closely monitored than others. The entire health care professionals should be aware of the iatragenic disease management. Early detection of these disorders can reduce the duration of hospital stay and increase the quality of life.

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