



REVIEW

Potential Adverse Effects of Dexamethasone Therapy on COVID-19 Patients: Review and Recommendations

Fei Chen · Lanting Hao · Shiheng Zhu · Xinyuan Yang ·
Wenhao Shi · Kai Zheng · Tenger Wang · Huiran Chen

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ABSTRACT

In the context of the coronavirus disease 2019 (COVID-19) pandemic, the global healthcare community has raced to find effective therapeutic agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, dexamethasone is the first and an important therapeutic to significantly reduce the risk of death in COVID-19 patients with severe disease. Due to powerful anti-inflammatory and immunosuppressive effects, dexamethasone could attenuate SARS-CoV-2-induced uncontrolled cytokine storm, severe acute respiratory distress syndrome and lung injury. Nevertheless, dexamethasone treatment is a double-edged sword, as numerous studies have revealed that it has significant adverse impacts later in life. In this article, we reviewed the literature regarding the adverse effects of dexamethasone administration on different organ systems as well as related disease pathogenesis in an attempt to clarify the potential harms that may arise in COVID-19 patients receiving dexamethasone treatment. Overall, taking the threat of COVID-19 pandemic into account, we think

it is necessary to apply dexamethasone as a pharmaceutical therapy in critical patients. However, its adverse side effects cannot be ignored. Our review will help medical professionals in the prognosis and follow-up of patients treated with dexamethasone. In addition, given that a considerable amount of uncertainty, confusion and even controversy still exist, further studies and more clinical trials are urgently needed to improve our understanding of the parameters and the effects of dexamethasone on patients with SARS-CoV-2 infection.

Keywords: Dexamethasone; COVID-19; Patients; SARS-CoV-2; Necrosis of the femoral head; Depression; Diabetes

F. Chen (✉) · L. Hao · S. Zhu · X. Yang · W. Shi ·
K. Zheng · T. Wang · H. Chen
Department of Physiology, Jining Medical
University, 133 Hehua Rd, Jining 272067, China
e-mail: chenfei123@mail.jnmc.edu.cn;
chenfei0336@163.com

Key Summary Points

It is necessary to apply dexamethasone as a therapy in critical COVID-19 patients, but its adverse side effects cannot be ignored.

Through a variety of molecular pathways, dexamethasone can interfere with normal organ functions and cause numerous clinical manifestations, intensifying the risk and severity of sequelae of COVID-19 disease, such as osteonecrosis of the femoral head, hypertension and diabetes.

Regular follow-up and evaluation of physical conditions in accordance with the time line are crucial for COVID-19 patients who have received dexamethasone treatment.

INTRODUCTION

After emerging in December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread across the world and led to high morbidity and mortality. Globally, as of 18 April 2021, there have been 140 million confirmed cases, including 3 million deaths, reported to the World Health Organization (WHO) [1]. The clinical spectrum of COVID-19 appears to be wide, ranging from asymptomatic infection to critical illness. The common symptoms of infection are fever (94%), cough (79%), fatigue (23%), loose stools (16%), anosmia and dysgeusia (70–84%) [2, 3]. Sepsis (59%) is the most frequently observed complication, followed by respiratory failure (54%), acute cardiac injury (23%) and septic shock (20%) [4]. Cytokine storm, clots, disseminated intravascular coagulation and thrombocytopenia have also been reported [5, 6]. Notably, advanced age and several comorbidities including impaired renal function and thrombosis are reportedly associated with a

worse disease course and increased mortality rate [7–9]. Hence, there is an urgent need to develop effective therapies to prevent the progression of disease. An array of drugs and therapeutic agents used to be considered as having potential efficacy against SARS-CoV-2, encompassing antiviral agents (remdesivir, chloroquine or hydroxychloroquine, azithromycin and lopinavir), blood-derived products (convalescent plasma and immunoglobulin products), anticoagulants (heparin and low-molecular-weight heparin) and immunomodulators (corticosteroids, interferons, interleukin-1 [IL-1] inhibitors, IL-6 inhibitors and kinase inhibitors) [10–14]. Disappointingly, on 15 October 2020, the interim results from the Solidarity trial coordinated by WHO indicated that remdesivir, hydroxychloroquine, lopinavir and interferon regimens appeared to have little or no effect on hospitalized COVID-19 patients [15], while dexamethasone, declared as the world's first treatment to significantly reduce the risk of death [16], is still the only therapeutic agent shown to be effective for patients with severe disease [17].

As a broad-spectrum immunosuppressor, the potency and duration of action of dexamethasone are greater and longer than those of cortisone. Its immunosuppressive effect is exerted through a variety of ways. In B cells, glucocorticoids impair upstream B cell receptor and Toll-like receptor 7 signaling while promoting significant upregulation of the genes encoding the immunomodulatory cytokine IL-10 [18]. Similarly, dexamethasone exposure causes defects in cell division for both CD4 and CD8 T cells and dampens T cell receptor signaling and cytokine expression [19, 20]. Moreover, in dendritic cells, dexamethasone could inhibit antigen presentation by increasing expression and activity of Na⁺/Ca²⁺ exchanger [21]. In parallel, the anti-inflammatory actions of glucocorticoids occur by decreasing the gene transcription of pro-inflammatory cytokines (IL-1, TNF and IL-6), chemokines and adhesion molecules [22]. Studies have demonstrated that SARS-CoV-2-induced uncontrolled cytokine storm [23], severe acute respiratory distress syndrome (ARDS) and multiorgan failure, which are the main

causes of COVID-19-related mortality, can be attenuated by the use of dexamethasone [24].

At the beginning of the pandemic, the use of corticosteroids was considered controversial, although Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial provided evidence that dexamethasone 6 mg once daily for 10 days reduced mortality in COVID-19 patients receiving oxygen therapy [16]. Some investigators noted that early corticosteroid use might lead to increased virus replication and thus higher viral loads [25]. Meanwhile, there is an analysis suggesting that the initiation of treatment in the second week of symptom onset, when the immunopathological phenomenon dominates, may be beneficial [16]. However, many researchers pointed out that, in practice, the symptom onset is usually impossible to ascertain, and the signs of severity often appear late. In a study that assessed the association between the dexamethasone initiation time and mortality benefits, Sulaiman et al. (2021) found survival benefits with the early initiation in critically ill COVID-19 patients [26]. The WHO panel concluded that it is preferable that critical COVID-19 patients receive corticosteroids (even if within 7 days of symptom onset) but non-critical patients do not (even if after 7 days of symptoms onset) [27]. Although described as ‘low-dose dexamethasone therapy,’ the dose of 6 mg per day is five to six times higher than that for therapeutic glucocorticoid replacement [28–31]. At this dose, patients suffer side effects such as skin thinning, weight gain, osteoporosis, hypertension and diabetes [20]. Hyperglycemia, gastrointestinal hemorrhage and psychosis were also considered related to dexamethasone treatment in the RECOVERY trial [16]. Recently, Weng and colleagues claimed that patients with gastrointestinal sequelae at 90 days were treated more often with corticosteroids and proton pump inhibitors than were patients without such sequelae [32]. Hence, many researchers are cautious about its extensive use for critically ill patients. Based on results of previous studies in SARS patients, avascular necrosis and osteoporosis were more likely to occur among patients with higher-dose steroid therapy. For example, in a retrospective study of 539 patients with steroid treatment

following SARS, the incidence of steroid-induced osteonecrosis of the femoral head (ONFH) was 24% [33]. Notably, all the meta-analyses found patients on corticosteroid treatment were more likely to have secondary infections such as bacterial infection, invasive fungal infection or exacerbation of pre-existing conditions [34]. Due to the immunosuppressive effect, a strong association exists between corticosteroid use and respiratory infectious disease (e.g., active tuberculosis and pulmonary aspergillosis) [35, 36]. Similarly, *Strongyloides* hyperinfection/dissemination in low- and middle-income countries induced by dexamethasone treatment cannot be ignored [37]. Moreover, short-term or protracted dexamethasone therapy might contribute to other potential side effects, such as neuromuscular weakness, psychiatric symptoms and even iatrogenic Cushing syndrome [38–40].

Although dexamethasone is recommended in critical patients infected by COVID-19, it is essential for us to develop deeper insights into the potential damage of dexamethasone in view of the large number of patients. Therefore, we searched PubMed, Scopus, the Web of Science and Google Scholar up to April 2021 for papers on the effects of dexamethasone therapy on different organs and summarized current understanding of the mechanisms of complications and sequelae induced by dexamethasone in this review. This will assist medical professionals in managing COVID-19 patients treated with dexamethasone and directing post-acute and long-term follow-up. Additionally, we hope this will provide a valuable basis for future studies. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

MUSCULOSKELETAL SYSTEM

Long-term or excessive use of glucocorticoids is the most common non-traumatic cause of ONFH [41, 42] and secondary osteoporosis [43, 44] in patients (Fig. 1). Owing to the use of glucocorticoids during the SARS epidemic in 2003, some patients had varying degrees of

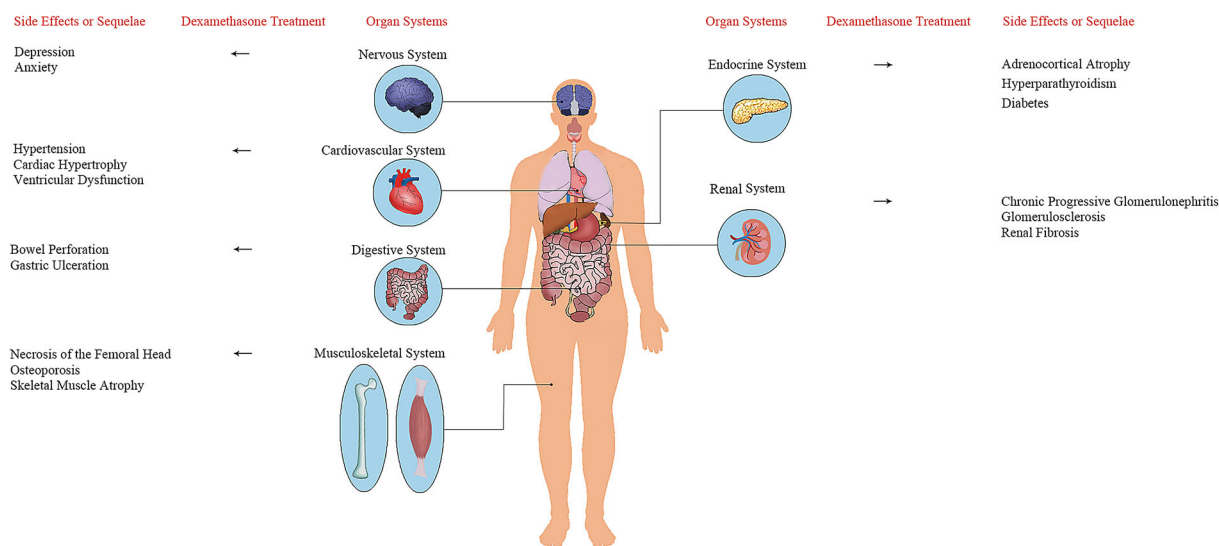


Fig. 1 Organ systems affected by dexamethasone and the side effects or sequelae

ONFH [33], and the risk of ONFH showed an aggravating trend with the increase of cumulative doses and treatment durations of steroids in SARS patients [45]. In 2014, Guo et al. found that more male SARS patients (51/129, 40%) were diagnosed with ONFH compared to female patients (79/410, 19%) [33]. Recently, a large-scale global statistical analysis revealed that while males and females are at equivalent risk of SARS-CoV-2 infection, male sex is associated with a higher risk for the development of severe disease as measured by intensive therapy unit admission [46], which indicated that male patients are more likely to receive dexamethasone treatment and suffer from ONFH. Therefore, to further explore the risk of ONFH in COVID-19 patients, we sum up the mechanisms of dexamethasone-induced ONFH. Its pathogenesis is mainly related to the differentiation of mesenchymal stem cells (MSCs) and osteoblast apoptosis. MSCs have the potential to differentiate into cells of mesodermal lineage, such as adipocytes, osteocytes and chondrocytes [47]. Yin et al. proved that dexamethasone can directly induce MSCs to differentiate into adipocytes [48]. On the one hand, adipogenesis of MSCs leads to excessive accumulation of marrow fat and increased intraosseous pressure, thus inducing venous stasis, arterial obstruction and eventually ischemic osteonecrosis [48, 49].

On the other hand, dexamethasone inhibits osteogenesis of stem cells, reducing the ability to reshape bone and repair necrotic bone and accounting for the onset of osteonecrosis [48, 50]. In addition, previous studies have demonstrated that dexamethasone could induce apoptosis of MSCs in a time- and concentration-dependent manner, which is probably the mechanism of pathogenesis of steroid-induced ONFH [51, 52]. Excessive use of dexamethasone can promote the apoptosis of osteoblasts through multiple signaling mechanisms. First, forkhead box transcription factor O1 (FOXO1) targets genes involved in apoptosis, autophagy and cell cycle arrest [53]. Dexamethasone could upregulate FOXO1 expression, inhibit the viability of osteoblasts and promote apoptosis [54]. Second, the phosphatidylinositol 3-kinase/protein kinase 3 (PI3K/AKT) signaling pathway controls many cellular functions by participating in the signal transduction pertaining to proliferation, survival and motility [55]. Dexamethasone can inhibit the activation of the PI3K/AKT pathway in osteoblasts by suppressing the expression of p-PI3K and p-AKT, thereby inducing osteoblast apoptosis [56]. Third, after dexamethasone treatment, the expression of glycogen synthase kinase 3 β (GSK3 β) in osteoblasts is significantly upregulated, which can induce mitochondrial

apoptotic and lead to ONFH [56, 57]. Zhu et al. claimed that miR-124 accumulation following circHIPK3 downregulation appears to be the primary mechanism of dexamethasone-induced cytotoxicity and programmed necrosis in human osteoblasts [58]. Therefore, to prevent dexamethasone-induced ONFH, corticosteroids should be applied only to patients in critical cases at low-to-moderate doses and short courses. In the 1st year after prescription of corticosteroids, patients with suspected ONFH should receive periodic magnetic resonance imaging examination during follow-up to diagnose and treat the disease in the early stage [59].

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [60]. As mentioned before, glucocorticoids cause apoptosis of osteoblasts and a depletion of the osteoblastic cell population, accounting for the reduction in bone formation and trabecular width [61]. On the flip side, following dexamethasone treatment, the decline in levels of the antiresorptive molecule osteoprotegerin and the increase in levels of the osteoclastogenesis-inducing molecule, the receptor activator of nuclear factor- κ B ligand, promote bone resorption by osteoclasts [62]. Taken together, these changes lead to glucocorticoid-induced osteoporosis, mainly via reduced bone formation. More recently, there have been several discoveries of key proteins that have further increased our understanding of the molecular mechanism. Dexamethasone-induced osteoporosis can be caused by suppression of the canonical Wnt signal. Secreted frizzled-related proteins (SFRPs) could compete with membrane-bound frizzled proteins for Wnt binding [63], and dickkopf-1 (Dkk-1) also mediates the inhibition of Wnt signal [64]. Then, several studies have reported dexamethasone increases the expression of Dkk-1 and SFRP1 and represses Wnt/ β -catenin signaling in human osteoblasts to reduce mineral density and trabecular bone volume [64–67]. Additionally, dexamethasone can downregulate the expression of matrix marker biglycan [68], and the lack of biglycan contributes to the reduction

in trabecular bone volume, mineral deposition rate and bone formation rate [69].

Skeletal muscle atrophy occurs also as a side effect of dexamethasone treatment [70, 71], leading to severe muscle weakness, inactivity and reduced quality of life for the patients [72]. In general, muscle atrophy results from the imbalance between protein synthesis and degradation. Qin et al. observed that the upregulation of myostatin gene expression caused by dexamethasone was associated with the myostatin gene promoter and glucocorticoid responsive element along the promoter [73], and the increased myostatin led to the changes in ultrastructure of skeletal muscle, including the inhibition of myoblast proliferation and induction of muscle atrophy [74, 75]. Moreover, dexamethasone induces depletion of myosin heavy chain protein and the upregulation of muscle RING-finger protein-1 [70, 76], which affects muscle integrity by increasing protein breakdown of an important component of the sarcomere and results in muscle atrophy [67]. Concomitantly, it has been reported that dexamethasone could induce mitochondrial dysfunction, bringing about ATP deprivation and subsequently AMP-activated protein kinase activation, which further activates the FOXO3/Atrogenes and ultimately leads to protein degradation as well as muscle atrophy [77].

CARDIOVASCULAR SYSTEM

As a common cardiovascular disease, hypertension is also the most frequent comorbidity (51%) in COVID-19 patients, followed by diabetes (19%) and atrial fibrillation (11%) [78]. At the same time, patients with severe COVID-19 infection commonly have a history of hypertension. Wu et al. (2020) reported that compared with COVID-19 patients without ARDS, patients who developed ARDS had a higher proportion of comorbidities such as hypertension (14% and 27%, respectively) and diabetes (5% and 19%, respectively) [79]. In Italy, almost 75% of patients who have died from COVID-19 had hypertension [80]. It is worth noting that dexamethasone, the first drug shown to reduce deaths from the coronavirus disease [81], can

Table 1 Organ systems of human affected by dexamethasone treatment: symptoms and sequelae

Organ system affected	Symptom/ sequelae	Subjects' characteristic	Dosage	Disease incidence	Onset time	Precaution/ therapy	Monitoring indicator or method	References
Musculoskeletal system	Necrosis of the femoral head	Multiple myeloma patients	16.7 mg/kg × 56 days (median)	7%	11.1 months (median)	Bisphosphonates, vitamin E, anticoagulants and vasodilators	MRI	[42, 59]
	Skeletal muscle atrophy	Hemiplegic patients	24 mg/day × 4 days	-	Within 10 days	1. Physical exercises 2. Vitamin D and calcium supplementation	1. Urine creatine levels 2. Muscle biopsy 3. Ultrasonography	[71, 198, 199]
Cardiovascular system	Hypertension	Infants with a birth weight of 714–1920 g (median 1087 g) and CLD	0.6 mg/kg/day × 3 days + 0.3 mg/kg/day × 3 days + taper the dose over a 3-week period	41%	Within 2 weeks	Exercise training	1. Blood pressure 2. Electrocardiogram	[82, 83, 200, 201]
	Ventricular hypertrophy	Pediatric ALL patients PI with a birth weight of 500–2054 g (median 815 g)	6 mg/m ² /day × 5 days 0.4–0.6 mg/kg/day × 3 weeks	6% 94%	4 days 2–3 days	1. Curcumin 2. Statins	1. Echocardiogram 2. MiR-30a, MiR-181b, VEGF-B	[92, 100, 101, 202–204]
		PI with CLD	0.5 mg/kg/day (taper in a standardized fashion over a total 42-day course)	57%	Within 6 weeks			
		PI with BPD	0.5 mg/kg/day (taper at successive 3-day intervals during the next 5 to 6 weeks)	-	Within 1 week			
Digestive system	Bowel perforation	PI with a birth weight of 501–1000 g	0.15 mg/kg/day × 3 days + 0.10 mg/kg/day × 3 days + 0.05 mg/kg/day × 2 days + 0.02 mg/kg/day × 2 days	13%	Within 2 weeks	1. Oral PGE2 analogs 2. Breast feeding	CT	[124, 205, 206]
Renal system	Renal calcification	PI with a birth weight of 440–990 g and CLD	3.8 mg/kg	83%	26 days	-	Sonography	[130, 131]

Table 1 continued

Organ system affected	Symptom/ sequelae	Subjects' characteristic	Dosage	Disease incidence	Onset time	Precaution/therapy	Monitoring indicator or method	References
Nervous system	Persistent nerve injury	Patients undergoing surgical procedures distal to the tibial meta-diaphyseal junction	3–4 mg	65%	2 weeks	-	Sensory neurological examination	[149]
Endocrine system	Adrenal insufficiency	Early B-cell lineage acute lymphoblastic leukemia patients	0.2 mg/kg/day × 28 days	100%	29 days	Taper doses of glucocorticoids	Adrenal stimulation testing	[156]
Diabetes		Subjects are relatives of non-insulin-dependent diabetic patients	4 mg/day × 5 days	20%	4–5 days	1. Exercise, diet therapy and oral hypoglycemic drugs (blood glucose level < 200 mg/dl)	1. Plasma glucose and insulin concentrations	[171, 172, 207]
		Non-diabetic patients with newly diagnosed gastrointestinal cancer	10–12 mg/day × 1 day + 7–8 mg/day × 2 days (+ 7–8 mg/day × 1 day) (administer every 2–4 weeks in at least three cycles)	22%	3 months	2. Insulin therapy (blood glucose level ≥ 200 mg/dl)	2. OGTT 3. IVGTT 4. Hemoglobin A1c tests	

MRU magnetic resonance imaging, *CLD* chronic lung disease, *ALL* acute lymphoblastic leukemia, *PI* preterm infants, *BPD* bronchopulmonary dysplasia, *MIR* microRNA, *VEGF* vascular endothelial growth factor, *PGE2* prostaglandin E2, *CT* computed tomography, *OGTT* oral glucose tolerance test, *IVGTT* intravenous glucose tolerance test

Table 2 Organ systems of animal models affected by dexamethasone treatment: symptoms and sequelae

Organ system affected	Symptom/sequela	Species	Dosage	Onset time	Pathogenic mechanism	References
Musculoskeletal system	Osteoporosis	Female mice (BALB/c)	1 mg/kg/day × 3 weeks	3 weeks	Osteocalcin decrease and leptin increase	[62]
		Female rats (Sprague-Dawley)	0.6 mg/kg/ 3 days × 12 weeks	12 weeks	Biglycan, LRP5, OPG and RUNX2 downregulation; Col1 α 1 upregulation	[68]
Cardiovascular system	Skeletal muscle atrophy	Female mice (Kun-Ming)	20 mg/kg/day × 8 days	8 days	Myostatin promoter activity upregulation	[73]
		Male mice (C57BL/J)	5 mg/kg/day × 18 days	6 days	Activation of AMPK/FOXO3/ agtrogene signaling	[77]
	Hypertension	Male rats (Fisher 344)	0.03, 0.3 or 3 mg/kg/day × 10 days	8, 6 or 5 days	Increased transcription of TH	[84]
		Male rabbits (New Zealand)	1000 mg/kg	Within 6 weeks	Increased transmembrane Ca ²⁺ in VSM	[85]
Cardiac hypertrophy		Neonatal rats (Wistar)	0.5 mg/kg + 0.3 mg/kg + 0.1 mg/kg	3 months	-	[127]
		Male rats (Wistar)	1.5 mg/kg/day × 8 days	2 days	Impaired expression of CBS and CSE	[90]
		Female neonatal rats (Wistar)	0.5 mg/kg + 0.3 mg/kg + 0.1 mg/kg	45 weeks	Increased promoter methylation in the CcnD2 gene	[94, 96]
		Neonatal rats (Wistar)	0.5 mg/kg + 0.3 mg/kg + 0.1 mg/kg	Within 15 months	-	[127]
Ocular system	Arrhythmias	Male rats (Wistar)	2 mg/kg/day × 7 days	1 week	Increased ROS generation	[103]
	Diastolic dysfunction	Male rats (Wistar)	35 mg/kg/day × 15 days	15 days	Impaired calcium handling and calcineurin signaling pathway activation	[102]
	Glaucoma	Mice (C57BL/6)	0.1% × (~ 20 μ l) × 3 times/day × 20 weeks	20 weeks	Myocilin, actin and ECM proteins increase	[110]

Table 2 continued

Organ system affected	Symptom/sequela	Species	Dosage	Onset time	Pathogenic mechanism	References
Digestive system	Gastric ulceration	Male rats (Wistar)	1 mg/kg	26 h	Inhibit prostaglandin synthetase and peroxidase	[121]
Renal system	Chronic progressive glomerulonephritis	Neonatal rats (Wistar)	0.5 mg/kg + 0.3 mg/kg + 0.1 mg/kg	Within 15 months	-	[127]
	Glomerulosclerosis			32 weeks	Accumulation of inflammatory factors	[128]
	Renal fibrosis			8 and 24 weeks		
	Reduction of nephron			4 weeks	Suppression of mitotic activity	[129]
Nervous system	Anxiety	Male albino mice	10 mg/kg	0.5 h	Dysregulation of the HPA axis	[136]
		Male rats (Sprague-Dawley)	5 mg/kg/day × 7 days	1 week	Excessive CREB phosphorylation and BDNF upregulation	[138]
	Depressive behavior	Male mice (C57BL/6J)	4 mg/kg/day × 21 days	20 days	GR mRNA decrease	[137]
Cerebral edema		Male mice (ICR)	60 mg/kg/day × 21 days	22 days	GR protein expression reduction	[143]
		Male rats in SE (Sprague-Dawley)	2 mg/kg	2 days	-	[150]
		Rats with acidosis (Sprague-Dawley)	3 mg/kg	4 h	AQP-1-mediated pathways	[151]

Table 2 continued

Organ system affected	Symptom/sequela	Species	Dosage	Onset time	Pathogenic mechanism	References
Endocrine system	Adrenocortical atrophy	Female rats (Wistar)	0.15 mg/kg/day × 7 days	Within 1 week	Inhibition of ACTH synthesis and secretion	[160]
	Hyperglycemia	Mice (C57BL/6J)	1 mg/kg/2 days × 2 months	Within 2 months	GR/KLF9/PGC1 α signaling pathway	[181]
	Diabetes	Rats (Wistar)	5 mg/kg/day × 24 days	Within 5 days	Insulin resistance	[182]
		Female rats Zucker (fa/fa)	0.2–0.4 mg/kg × 24 days	Promptly		

LRP-5 low-density lipoprotein5, *OPG* osteoprotegerin, *RUNX2* runt-related transcription factor 2, *AMPK* AMP-activated protein kinase, *FOXO3* forkhead box O 3, *TH* tyrosine hydroxylase, *VSM* vascular smooth muscle, *CBS* cystathionine- β -synthase, *CSE* cystathionine- γ -lyase, *CcnD2* gene cyclinD2 gene, *ROS* reactive oxygen species, *ECM* extracellular matrix, *HPA* hypothalamic-pituitary-adrenal, *CREB* anti-cAMP responsive element binding protein, *BDNF* brain-derived neurotrophic factor, *GR* glucocorticoid receptor, *SE* status epilepticus, *AQP-1* aquaporin-1, *ACTH* adreno-cortico-tropic-hormone, *KLF9* Krüppel-like factor 9, *PGC1 α* peroxisome proliferator-activated receptor γ coactivator 1 α

induce hypertension in clinical studies (Table 1) and animal experiments (Table 2) through a variety of mechanisms [82, 83]. On the one hand, dexamethasone enhances vasoconstriction. A recent study has found that dexamethasone increased synthesis of catecholamines by inducing the transcription of the rate-limiting enzyme tyrosine hydroxylase, and excessive catecholamine levels induce direct vasoconstriction [84]. Increasing calcium influx in vascular smooth muscle is also a way in which dexamethasone causes hypertension [85]. On the other hand, dexamethasone-induced hypertension is associated with reduction of vasodilating mediators such as prostacyclin, nitric oxide (NO) and hydrogen sulfide (H₂S). There have been reports indicating that dexamethasone can inhibit the biosynthesis of prostaglandins via the inhibition of phospholipase A2 activity [86–88]. Schafer et al. claimed dexamethasone could reduce NO production by means of several mechanisms including induction of oxidative stress as well as downregulation of cationic amino acid transporter-1 and endothelial NO synthase [89]. H₂S has been proposed as a candidate for endothelium-derived hyperpolarizing factor, involved in inducing vasodilation. H₂S biosynthesis could be inhibited by dexamethasone via the impairment of cystathionine-β-synthase and cystathionine-γ-lyase expression [90]. The vascular endothelial glucocorticoid receptor (GR) plays a critical role in mediating blood pressure response to steroids [91]. Although there is no report confirming the use of dexamethasone in the treatment of COVID-19 leads to hypertension, we still suggest follow-up, evaluation and close monitoring of blood pressure after recovery from SARS-CoV-2 infection, especially for the hypertensive patients who received dexamethasone treatment.

A clinical trial suggested retardation of heart growth among dexamethasone-treated infants compared with control infants [92]. Cardiomyocytes can only divide within a limited time after birth, and once the proliferation of cardiomyocytes is inhibited during this period, it will have a negative repercussion on the total number of cardiomyocytes later in life [93]. The use of dexamethasone in newborn rats

increased promoter methylation in the cardiomyocytes CcnD2 gene, which causes the decrease of D2 protein and inhibition of cardiomyocyte proliferation [94, 95]. Eventually, neonatal dexamethasone treatment in rat pups leads to a permanent decrease in heart weight, as well as reduced number, hypertrophy and early degeneration of cardiomyocytes during adult life [93, 96]. Since most COVID-19-positive newborns are mildly affected with cases of severe disease being very rare [97] and dexamethasone is mainly shown to be effective against the novel coronavirus for severe patients, we believe that dexamethasone is not suitable for the overwhelming majority of neonates. During the treatment of 66 babies with SARS-CoV-2 infection in a UK survey, only 2 (3%) were treated with corticosteroids [97]. Meanwhile, we recently indicated that SARS-CoV-2 infection poses a great threat to pregnant women and fetuses [98], and according to the above survey, of total 66 neonates, 16 (25%) were premature babies [97]. Bensley et al. claimed that cardiomyocyte proliferation can be inhibited by premature birth, which may adversely affect heart growth, cardiac function, functional reserve and repair ability throughout postnatal life [99]. Therefore, dexamethasone treatment may bring about more serious damage to the heart in preterm infants [100, 101].

Recent evidence suggests that dexamethasone treatment in adults could result in hypertension, pathologic cardiac remodeling, cardiac hypertrophy associated with maladaptive remodeling and ultimate ventricular dysfunction [102, 103]. Cardiac hypertrophy, considered an adaptive response, allows heart to withstand glucocorticoid-induced hypertension [102]. Roy et al. (2009) and De et al. (2011) reported that excess of dexamethasone treatment could induce cardiac hypertrophy, myocardial fibrosis, hypoxia and ventricular dysfunction via angiotensin II signaling pathway [104, 105]. Pathologic heart remodeling occurs at the same time as the enhanced collagen synthesis, which leads to interstitial fibrosis [104]. Fibrosis is directly responsible for reduced blood flow to the heart and increase in cell apoptosis [102]. Additionally, myocardial fibrosis increases the stiffness of the myocytes,

causing systolic or diastolic disorders [106]. However, Macedo et al. demonstrated that a short-term therapeutic regimen of dexamethasone will not decrease ventricular contractility [103]. In terms of the effect of dexamethasone on heart rate, cardiac fibrosis impairs the electrical conduction and subsequent generation of reentry circuits [107, 108]. By increasing sympathetic modulation, but reducing the parasympathetic one, dexamethasone induces autonomic imbalance, which may make the dexamethasone-treated animals more susceptible to develop harmful forms of ventricular arrhythmias through increasing reactive oxygen species generation [103].

OCULAR SYSTEM

Several ophthalmic complications, such as glaucoma and cataracts, have been demonstrated to be probably linked with the use of corticosteroids. Most patients (88%) with steroid-induced glaucoma experienced an increase in intraocular pressure (IOP), a major associated risk factor leading to glaucoma [109]. Similarly, the murine model of dexamethasone-induced glaucoma exhibited an elevation of IOP, structural and functional loss of retinal ganglion cells and axonal degeneration [110] (Table 2). This is mainly because dexamethasone treatment can increase the deposition of myocilin, actin and extracellular matrix proteins, which are relevant to the induction of endoplasmic reticulum stress. It may cause dysfunction of the trabecular meshwork, resulting in the elevated resistance to aqueous humor outflow and subsequent IOP [111–113].

The impact of corticosteroids on the incidence of cataracts remains a source of much controversy and considerable debate [114]. Posterior subcapsular cataract (PSC) has been reported in a few adults and children treated with beclomethasone dipropionate or dexamethasone aerosol, but the risk seems to be much lower than when taking these corticosteroids systemically [115]. Moreover, patients taking inhaled corticosteroids were observed to have a risk that appeared negligible, even if high doses were used [116]. Contrarily, another review

claimed that exposure to inhaled corticosteroids increased the prevalence of PSC about twofold [117]. There is even a third view, which argues that no firm link exists between them [118]. Further research is necessary to help elucidate the association between dexamethasone treatment and the incidence of PSC.

DIGESTIVE SYSTEM

Compared with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2-induced adverse effects on the gastrointestinal tract are of particular concern [119]. Patients with COVID-19 were prone to develop gastrointestinal symptoms such as nausea and diarrhea, which still bothered 44% of COVID-19 survivors at 90 days after discharge from hospital [32], even lasting \geq 6 months [120].

Even worse, it has been reported that dexamethasone makes the gastric mucosa susceptible to ulceration, but the mechanism of the ulcerogenic action remains controversial. Specifically, an earlier study indicated that dexamethasone diminishes gastroprotection and damages the mucosa by inhibiting the activity of prostaglandin synthetase and peroxidase, respectively [121]. However, Filaretova et al. held that long-lasting maintenance of blood glucose level accompanied by the signs of catabolic effects may be the reason for pathologic ulcerogenic caused by dexamethasone treatment [122].

By thinning the circumferential smooth muscle and making the bowel wall more vulnerable, dexamethasone could increase the risk of bowel perforation [123]. Stark et al. claimed that early treatment with dexamethasone has no effect on mortality or chronic lung disease but is associated with spontaneous gastrointestinal perforation and decreased growth in preterm infants [124]. In addition, dexamethasone inhibits small intestinal growth via both increased degradation and decreased synthesis of protein [125]. When dexamethasone was given to growing rats, there was a significant decrease in the weights of the stomach, small intestine and colon [126].

RENAL SYSTEM

Neonatal dexamethasone treatment might increase the risk of renal damage in adulthood. The number of glomeruli and kidney weight were lower in neonatal rats with dexamethasone administration, and the kidneys showed signs of chronic progressive glomerulonephritis with glomerulosclerosis and extensive renal fibrosis, presumably because of an early inflammatory trigger that elicits a persistent pro-fibrotic process [127–129]. On the other hand, in clinical studies, dexamethasone could contribute to renal calcification formation by increasing urinary calcium excretion [130], with nephrocalcinosis occurring in 15 (83%) of 18 infants [131] (Table 1).

NERVOUS SYSTEM

A survey of 402 adults surviving COVID-19 revealed that 42% of them suffered from anxiety, 40% from insomnia, 31% from depression, 28% from post-traumatic stress disorder and 20% from obsessive-compulsive symptoms, while females and younger patients suffered from higher levels of depression and sleep disturbances [132]. These psychiatric consequences can result from one or several combined factors. Due to the neurotropic properties with neuroinvasive activity [133], SARS-CoV-2 could induce neuronal injuries via directly infecting the central nervous system. Besides, cytokine storm involved in the immune response to coronaviruses may cause neuroinflammation, which indirectly leads to psychopathologic sequelae [134]. Simultaneously, the psychological impact of patients' fear of severe illness with a very high risk of death, uncertainty about future, stigma, traumatic memories of severe illness and social isolation in an intensive care unit setting cannot be ignored [132, 135].

Similarly, dexamethasone treatment can be associated with neuropsychiatric diseases and neurotoxicity. Peripheral administration of dexamethasone induces biphasic effects on anxiety-related behaviors: anxiolytic effects at low and anxiogenic effects at high doses [136].

According to a report from the US Food and Drug Administration, about 4% of 50,000 dexamethasone users had developed severe anxiety as an adverse effect of therapy [137]. A finding has indicated that hyperphosphorylation of cAMP-responsive element-binding protein and reduced expression of brain-derived neurotrophic factor in the cerebral cortex might be involved in high levels of anxiety-like behavior in dexamethasone-treated rats [138]. Besides, dexamethasone-treated mice demonstrated a host of depression-like behaviors, such as increased time of immobility in the forced swim test and a reduced preference for saccharin consumption. The following mechanisms are considered: first, dexamethasone treatment can cause insufficient cell energy supply through glucose inhibition [139], thereby affecting the regulation of glutamate release and reuptake. Calcium-dependent proteases, triggered by increased glutamate-mediated transmission, could cause degeneration of cytoskeletal proteins and lipases, possibly generating free radicals [140], which leads to neuronal damage and depression [141]. The second possible explanation is the hyperfunction of the hypothalamic-pituitary-adrenal axis (HPAA) caused by dexamethasone treatment, which is mainly attributed to the decreased GR mRNA [137] and protein [142, 143] expressions and consequent impairment of GR-mediated negative feedback [144]. The raised level of cortisol in the blood will exacerbate depression by impairing brain functions, such as neuronal survival, neuronal excitability, neurogenesis and memory acquisition [144]. Notably, Skupio et al. have found that the co-chaperone FK506 binding protein 51 and serum-and glucocorticoid-inducible-kinase-1 proteins increased in the prefrontal cortex, hippocampus and striatum of mice treated with dexamethasone [137], which could regulate GR sensitivity [145], mediate glucocorticoid effects on neuronal function and contribute to major depressive disorder [146].

It is worth mentioning that peripheral nerve block is often used for postoperative analgesia; however, the pain relief lasts only a few hours [147]. As dexamethasone could prolong the analgesic duration by inducing vasoconstriction, it has been used in peripheral nerve block

as an adjuvant [148]. By contrast, a recent study reported a twofold increased risk of persistent neurologic symptoms when perineural dexamethasone was applied after foot and ankle surgery [149] (Table 1). Besides, dexamethasone is widely used in clinics for alleviating cerebral edema. However, Duffy et al. (2014) found that after status epilepticus induced by lithium-pilocarpine, regional administration of dexamethasone (2 mg/kg) led to increased transverse magnetization relaxation time at 2 days and reduced hippocampal volumes at 3 weeks, representing aggravated cerebral edema and brain injury, respectively [150]. Another study observed that under acidotic conditions, dexamethasone also worsened the cerebral edema, which could be attenuated by selective blockage of aquaporin-1 channels with HgCl₂ [151]. Therefore, although recent studies demonstrated dexamethasone could slow Huntington's disease progression [152] and showed protective effects against Parkinson [153] and Alzheimer's disease-related cognitive impairments in mice [154], there is an urgent need to continue to monitor the potential influence of dexamethasone administration on mental state and damage to nerves when it is used in COVID-19 patients.

ENDOCRINE SYSTEM

A range of mechanisms that contributes to endocrine disorders has been reported in association with the use of dexamethasone, one of the most unpredictable of which is the inhibition of the HPA. Dexamethasone mainly binds to GRs in the pituitary, where it inhibits the expression of proopiomelanocortin as well as secretion of adreno-cortico-tropic-hormone (ACTH) and subsequent adrenocortical cortisol [155, 156]. Simultaneously, compared with other preparations with shorter half-lives, dexamethasone, as the most effective ACTH suppressant with a longer half-life, can lead to more serious HPA inhibition [157, 158]. For example, in cancer patients receiving chemotherapy, adrenal response suppression and adrenal insufficiency have been reported after dexamethasone use [156, 159] (Table 1). Additionally,

low-dose dexamethasone administered chronically could give rise to partial adrenocortical atrophy in rats [160]. There is evidence that the suppressive effects of dexamethasone at the hypothalamic-pituitary level are not only confined to ACTH, but the serum levels of thyroid-stimulating hormone (TSH) and prolactin (PRL) could be reduced by directly restraining the anterior pituitary [161]. Dexamethasone also attenuates the stimulation of the release of TSH and PRL by thyroid-releasing hormone [161]. Concurrently, there is a decrease in serum-3, 3', 5-triiodothyronine (T3) and thyroxine (T4) serum levels with dexamethasone treatment, which is probably the consequence of the inhibitory effect of dexamethasone on TSH secretion by the pituitary, and a direct inhibitory effect on thyroid release of T3 and T4 cannot be neglected [161]. Therefore, more detailed studies are needed to better determine the mechanism involved in these effects.

Changes in growth hormone (GH), insulin-like growth factor (IGF), melatonin and parathyroid hormone levels are associated with dexamethasone-induced endocrine disorders. Jux et al. demonstrated that GH- or IGF-1-stimulated growth plate chondrocyte growth is dose-dependently blunted by dexamethasone [162]. Melatonin is considered an output signal mediated by the circadian system. Dexamethasone could diminish melatonin synthesis by reducing the expression of the key enzymes such as tryptophan hydroxylase, arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase [163]. In parallel, previous studies have found that dexamethasone can increase parathyroid hormone synthesis, which may be an important pathogenic role in persisting hyperparathyroidism [164, 165].

It is well known that in skeletal muscle and adipocytes, insulin stimulates the translocation of glucose transporter (GLUT) 4 from intracellular vesicles to the cell membrane for glucose uptake [166]. As soon as insulin binds to its receptor, the receptor undergoes tyrosine phosphorylation and recruits insulin receptor substrates (IRSs) for tyrosine phosphorylation. Once phosphorylated, IRSs bind to and activate PI3K, acting as a molecular switch to phosphorylate downstream protein kinase B (PKB) [167].

Akt substrate of 160 kDa (also called AS160 or TBC1D4), which is phosphorylated by activated PKB, plays a crucial role in regulating GLUT4 transport [168]. In addition, PKB could inhibit glycogen synthase (GS) activity by mediating glycogen synthase kinase 3 (GSK-3) phosphorylation [169, 170].

Dexamethasone, as an exogenous glucocorticoid, can significantly influence the glucose metabolism in the human body [171, 172]. (1) In adipocytes, dexamethasone treatment affects the normal absorption of glucose by reducing the expression level of GLUT1 protein. Meanwhile, dexamethasone therapy decreases PKB expression and insulin-stimulated phosphorylation and downregulates GS expression in adipocytes [166]. In muscle, treatment with dexamethasone can not only reduce insulin-mediated PI3K and PKB activation but also increase the phosphorylation sites of GS [173, 174]. Besides, under dexamethasone treatment, the insulin-stimulated GLUT4 translocation to the cell surface decreases without altering the GLUT4 protein in total lysates in muscle and adipose tissue [175, 176]. All of these may lead to a decrease in insulin-stimulated glucose uptake, which causes insulin resistance (IR). (2) Moreover, it has been reported that elevated plasma free fatty acids (FFAs) could induce IR [177], and dexamethasone increases FFA content by interfering with fatty acid metabolism [166]. Studies have found that long-term incubation of soleus muscle strips with FFAs impaired insulin-stimulated PKB and reduced glucose uptake and glycogen synthesis [178]. Another possible mechanism involves peroxisome proliferator-activated receptor (PPAR) [179], a transcription factor activated by FFA, and Bernal-Mizrachi et al. have proven that human hepatocytes treated with dexamethasone induced PPARA gene expression and identified hepatic activation of PPAR- α as a mechanism underlying dexamethasone-induced IR [180]. Therefore, the increase in circulating FFA caused by dexamethasone use may make an important contribution to muscle IR [166]. (3) Furthermore, our previous work suggests that dexamethasone induces the expression of Krüppel-like factor 9 (KLF9) in the liver, which plays a critical role in the regulation of

hepatic glucose metabolism. KLF9 may regulate IR via KLF9/PGC1 α /TRB-3 signaling pathway and promote hepatic gluconeogenesis and hyperglycemia. Conversely, the lack of KLF9 alleviated hyperglycemia induced by dexamethasone treatment [181]. Then, due to the impaired function of insulin-stimulated glucose uptake in peripheral tissues and/or the weakened effect of insulin to suppress the liver from producing endogenous glucose, dexamethasone-induced IR can result in hyperglycemia and diabetes [182], the current common side effects in acute care settings such as emergency rooms and urgent care centers [180, 183]. (4) In addition, Guo et al. found that dexamethasone could induce apoptosis of pancreatic β cells through activation of GSK-3 β [184].

Diabetes has seriously affected the prognosis of patients with COVID-19, and according to data from Wuhan, compared with non-diabetic patients, diabetic patients have more complications and shorter overall survival time [185]. Possible explanations for this phenomenon are as follows: (1) generally, infectious diseases are more common and/or severe in diabetic patients since the hyperglycemic environment can lead to immune dysfunction, vascular disease, neuropathy and decrease in antibacterial activity of the digestive tract [186]. (2) Acute hyperglycemia has been shown to upregulate the expression of angiotensin-converting enzyme (ACE) 2 while chronic hyperglycemia reduces ACE2 expression [187]. Recently, Wijnant et al. demonstrated increased expression of ACE2 protein in the bronchi and alveoli of diabetic patients may affect the infectivity and clinical outcome of COVID-19 [188]. (3) In the case of uncontrolled hyperglycemia, the abnormally increased glycosylation of glycosylated ACE2 and the viral spike protein may promote the virus binding and inflammation [189]. (4) The fourth underlying mechanism that may explain the link between COVID-19 and diabetes involves dipeptidyl peptidase-4 (DPP-4/CD26) [190], acting as a potential receptor for SARS-CoV-2 [191]. Compared with nondiabetic subjects, DPP4 expression is enhanced on blood T lymphocytes from type 2 diabetic patients [192]. Interestingly, in 2019, Kulcsar et al. found the diabetic DPP4^{H/M} mice,

which could express human DPP4 in the non-ciliated epithelial cells and alveolar type 2 cells, exhibited more severe clinical symptoms characterized by a prolonged period of weight loss and clinical disease with a delay in the initiation of inflammation in the lung and slower inflammatory resolution after infection with MERS-CoV [193]. In addition, researchers discovered that COVID-19 may also cause hyperglycemia. The potential pathways are as follows: (1) ACE2 is expressed at high levels in pancreatic islet cells [194], and in 2003 SARS produced a transient impairment of pancreatic islet cell function. Similarly, SARS-CoV-2 may also impair β -cell insulin secretion, causing hyperglycemia, or exacerbate pre-existing diabetes [195]. (2) COVID-19 infection is accompanied by increases of many cytokines, which can induce or exacerbate IR [196].

In summary, dexamethasone has a remarkable effect on glucose homeostasis in the body, accounting for hyperglycemia and diabetes, which are risk factors for COVID-19 and adversely affect prognosis. Simultaneously, COVID-19 infection can contribute to hyperglycemia. Based on the above evidence, we make the following recommendations. (1) Blood sugar changes of COVID-19 patients treated with dexamethasone should be strictly monitored. After stopping dexamethasone therapy, IR will fall. Therefore, it is necessary to adjust insulin dose to avoid hypoglycemia. (2) More and more type 2 diabetes patients may have an increased risk for pronounced inflammatory responses, including cytokine storms, so screening for excessive inflammation is essential to improve the prognosis. (3) Regular follow-up is crucial for preventing new-onset diabetes, which may be caused by the virus and dexamethasone, and hemoglobin A1c (HbA1c), a glycosylated hemoglobin formed by the specific binding of glucose to the N-terminal valine of the hemoglobin β chain, is recommended as an annual assessment indicator for this process [197].

CONCLUSION

In conclusion, the impacts of COVID-19 are not just confined to the lungs, but lead to the involvement of almost all the organs of the body, including heart, brain, kidney and intestines. While dexamethasone can reduce the mortality in treating critically ill patients with COVID-19, consequences for various organ systems have also been reported. Through a variety of molecular pathways, dexamethasone can interfere with normal organ functions and cause numerous clinical manifestations, which may further intensify the risk and severity of sequelae of COVID-19 infection, such as ONFH, hypertension and diabetes. Hence, we suggest close monitoring of blood pressure, HbA1c and other necessary parameters when managing COVID-19 patients treated with dexamethasone and taking timely measures. Furthermore, regular follow-up and evaluation of physical conditions according to the monitoring indicators provided in this article are crucial for patients after recovery from SARS-CoV-2 infection.

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