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Impact Of Dexamethasone On COVID-19 Patients

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Abstract

The coronavirus infection 19 (COVID-19) is an extremely contagious as well as infectious agent's viral illness generated by the extreme acute respiratory disorder coronavirus which called (SARS-CoV-2) virus, which first appeared in Wuhan as well as China, and has since spread throughout the world. The 2019 Coronavirus Infection (COVID-19) is linked to diffuse lung injury. Corticosteroids can help to prevent respiratory damage as well as death by modulating inflammation injury occurs in the lung. The method of this study is based on an analysis of past studies' literature; the aim of a literature review is to obtain a knowledge of current studies as well as debates related to this specific research subject, as well as to address that information in the form of a research. The objectives of this research were to look at the anti-inflammatory effects of corticosteroids (particularly dexamethasone) in individuals with COVID-19-induced moderate-to-severe ARDS.

It also described the pathway of glucocorticoid metabolic effects as well as illustrated some adverse effects of dexamethasone on various organs in COVID-19 patients. According to the findings, small quantities of corticosteroids (dexamethasone) can minimize mortality in patients with serious COVID-19 disorder, but they have no effect on the death rate in patients with such a mild type of the illness. Patients with moderate symptoms should avoid dexamethasone. Further randomized clinical trials on this treatment are required to further develop our knowledge of the variables as well as effect of glucocorticoids on people with SARSCoV-2 disease.

Keyword: *Impact, Dexamethasone, COVID-19, Patients, infection.*

1- Introduction

Respiratory viruses continue to cause problems within the general population, as a result of frequent acute and chronic infections, including occasional epidemics. Infection by these viruses can occur by inhalation or [1]directly contact with a mucosal surface of respiratory tract. Coronaviruses are a group of related viruses which have a pandemic power involving humans as well as animals (Oh et al., 2021). The disease was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in the ongoing 2019–20 coronavirus pandemic (coronavirus disease-19 (COVID-19) , or SARS-CoV-2) (SARS-CoV-2 - Wikimonde, 2021).

The virus can transmitted via direct contact with the contaminated surfaces or air transport between persons close to each other (Carinci, 2021). Once COVID-19 contaminates the environment, it can penetrate the mucous membranes of the nose, eyes and/or mouth and then reach the vital organs including the lung (Huh, 2021).

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Human COV-19 are divided into low pathogenic and highly pathogenic; however, infection is not necessarily followed by the characteristic symptoms, but can be silent (MQ et al., 2021). Low pathogenic CoV-19 infects the upper respiratory tract and causes mild respiratory diseases, similar to colds; on the contrary, highly pathogenic onescause severe acute respiratory distress syndrome (ARDS), multisystem organ failure, and death. The virus mainly infects the lower airways with consequent pro-inflammatory cytokine release and pneumonia, which can be fatal, especially in debilitated subjects or those suffering from relevant pathologies. Severe pneumonia caused by coronavirus is often associated with rapid virus replication, infiltration of inflammatory cells and elevated responses to inflammatory proteins such as cytokines, resulting in damage of internal organs and acute respiratory stress syndrome consisting of hypoxemic respiratory failure associated with neutrophilia, mucus deposition in bronchi, and bronchiectasis (PMC, 2021).

CoVID-19 infection is catered for by a large replication of the virus in respiratory epithelial cells provoking acute inflammation and violent respiratory disease. Inflammation is mediated by pro-inflammatory cytokines which worsen the clinical picture of the disease, including interlukins: IL-1β, IL-6, TNF and IL-8 (Borthwick, 2021 and SK et al., 2021). IL-1β is mediating lung inflammation, fever and fibrosis, and provoking severe respiratory problems. Immune cells are attracted to the place of infection by IL-8, a chemokine that is generated at the inflammatory site (Borthwick, 2021).Studies have shown that most cases infected with COVID -19 have lymphocyte penia with significant increases in neutrophil levels. Their blood urea levels are also significantly high (Griffin et al., 2021).

In addition, the inflammatory response triggers multiple signaling pathways that result in goblet cell differentiation and hyperplasia in the airway, leading to the synthesis of mucin, the main protein component of mucus, followed by mucus hypersecretion which can obstruct the respiratory tract, limiting airflow and thereby aggravating the already declining lung function (PMC, 2021). A study by Prompetchara et al. (2021) showed that COVID 19 can activate the inflammatory response and induce increased secretion of respiratory mucosa.

Several existing antiviral medications are being evaluated for treatment of COVID-19, including remdesivir, chloroquineand hydroxychloroquine, lopinavir/ ritonavirand lopinavir/ ritonavir combined with interferon beta (Kupferschmidt, K., & Cohen, J. (2020)). However; at this time, there are no specific treatments for COVID-19. So, there is an urgent need to discover novel therapy to eradicate this serious virus.

Corticoids seemed to be an ideal therapy for the acute lung injury, given their potent anti-inflammatory and antifibrotic properties (Rhen and Cidlowski, 2021). They switch off genes that encode pro-inflammatory cytokines and switch on genes that encode anti-inflammatory cytokines. It has been reported that low doses of corticosteroids prevent an extended cytokine response and might accelerate the resolution of pulmonary and systemic inflammation in pneumonia (Villar et al., 2021).

Dexamethasone is a corticosteroid that prevents the release of substances in the body that cause inflammation.The potent anti-inflammatory and immunosuppressant properties of dexamethasone render it useful in various inflammatory and autoimmune diseases. In addition, dexamethasone is used to prevent vasogenic edema secondary to cerebral tumors, in conjunction with other chemotherapeutic agents in multiple myeloma and as a replacement hormone in adrenal insufficiency.

(Villar et al. 2021) recently published a clinical trial enrolling 277 patients with established moderate-to-severe ARDS who received either low-to-moderate doses of dexamethasone for 10 days or usual care (Villar et al., 2021). The study demonstrated that corticosteroid therapy is associated with a sizable reduction in duration of mechanical ventilation and hospital mortality (Annane et al., 2021). The dysregulated inflammation and coagulation observed in COVID-19 (Borthwick, 2021), is similar to multifactorial ARDS and thus may be amenable to corticosteroid treatment to down regulate inflammation-fibro proliferation and accelerate disease resolution (Annane et al., 2021), so it can postulate that treatment with dexamethasone in the early phase established moderate-to-severe ARDS caused by COVID-19 may changes the pulmonary and systemic

inflammatory response and thereby reduces mortality. This may have a large impact on patients with COVID-19 since the drug is cheap and widely available.

1.1. Aim of the Work:

The aim of this study was to focuse on the antiinflammatory effect of corticosteroids (specifically dexamethasone) in patients with moderate-to-severe ARDS caused by COVID-19. Also; it highlighted some side effects of dexamethasone on different organs of COVID-19 treated patients and explained the mechanism of metabolic effects of glucocorticoids.

2. Methodology:

The method of this study is based on an analysis of past studies' literature; the aim of a literature review is to obtain a knowledge of current studies as well as debates related to this specific research subject, as well as to address that information in the form of a research.

3. Theoretical Framework

3.1. History of Coronaviruses

Unlike viruses such as influenza, smallpox, and polio, coronaviruses have only recently been discovered to infect the human population. When they were first discovered in the 1960s, there was almost no epidemiological, genomic, or pathogenic information about these viruses – only that they contained RNA surrounded by a membrane composed of 'spike'-shaped proteins (Vabret, Mourez, et al 2005) As of 2020, the US-based Centers for Disease Control and Prevention (CDC) recognizes seven coronavirus strains that can infect humans(COVID, Team et al 2020)

The first identified coronaviruses in the human population were human CoV-229E (HCoV-229E) and HCoV-OC43(Wevers & van der Hoek 2009) . These viruses were found to cause common upper respiratory tract diseases, such as the common cold, and infections caused by the viruses have low levels of severity. After the emergence of the first two coronavirus strains, two other strains were identified: HCoV-HKU1 and HCoV-NL63(Gaunt, Hardie et al 2010) Three other coronavirus strains that have been identified in the human population since are SARS-CoV, MERS-CoV, and SARS-CoV-2(COVID, Team et al 2020). All three of these coronavirus strains vary from the four common strains as they can cause severe illnesses that may result in death.

One characteristic that distinguishes HCoV-229E, HCoV-C43, HCoV-HKU1, and HCoV-NL63 from the severe strains of coronavirus is their extremely low basic reproduction numbers (R_0) (Delamater, Street et al 2019).

The basic reproduction number is used to describe how transmissible or contagious a pathogen is(Terefe, Gaff et al 2018).The value is not fixed and can be affected by intervention methods such as social distancing and vaccination. The R0 value is used to signify the potential amount of people a single infected person can infect(Andreasen, V. 2011)

The higher the R0 number is, the higher the chance that infected individuals will spread the pathogen to others.

Thus, pathogens that are deemed extremely infectious have R0 values greater than 1, while some pathogens that have low R0 values can be contained without any need of isolation of known cases and potentially infected individuals (Dietz K ,1993)

While coronaviruses have only been known in the human population for six decades, they have come to the forefront of research and news due to the outbreak of SARS-CoV(Su, Wong et al 2016),which demonstrated in the early 2000s that this virus family has the potential to cause a pandemic(Singhal, T. 2020). The four common, nonsevere human coronaviruses are distributed globally, with a low density in any given local population (Su, Wong et al 2016).

Regarding the three severe coronavirus strains, infections from the SARS-CoV strain were localized in China, with small outbreaks in other countries. MERS-CoV infections, which have been ongoing since 2012, are localized in the Middle East. SARS-CoV-2, which causes COVID-19 disease, is a global pathogen of pandemic proportions (Singhal, T. 2020).COVID-19 originated from a Chinese city, Wuhan, in the Hubei province and spread to the rest of the globe (Adhikari et al., 2020).

3.2. COVID-19 Virus Structure

The coronaviruses have crown-like appearance of the surface 'spike' proteins and gave the virus family the name – 'corona' being Latin for crown (Kahn JS & McIntosh K 2005).Viruses with that specific shape and structure belong to the family of Coronaviridae, which are grouped into four genera using their phylogeny: alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV (Siddell SG, Anderson R, Cavanagh D 1983),(Su, Wong et al 2016). In general, they are classified as single-stranded, positive-sense RNA genome-bearing viruses(Su, Wong et al 2016). Their genome is estimated to be around 26–32 kilobases (for comparison, the human genome is 3 000 000 kilobases) (Masters, P. S. 2006).

The spike glycoprotein (red) is the protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor of host cells and mediates viral entry. Additionally, this protein is what gives the virus its crown-like (Latin 'corona') appearance. The membrane proteins (yellow) and the envelope small membrane proteins (blue) are important structurally as well as mechanistically. The genomic RNA (white) comprises the genetic material that the virus uses to propagate itself once inside its host **(Figure 1)** (Atzrodt et al., 2020).

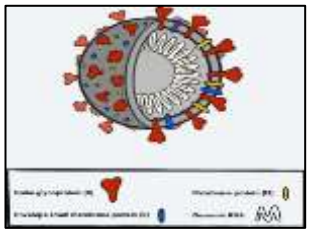

Figure 1: Structure of SARS-CoV-2 virus.(Atzrodt et al., 2020).

3.3. Symptoms and Transmission

Like previous coronaviruses, the novel coronavirus causes respiratory disease, and the symptoms affect respiratory health. According to the Centers for Disease Control and Prevention (CDC), the main symptoms of COVID-19 symptoms can be very mild to severe and include a fever, cough, and shortness of breath. Many people are asymptomatic. Current information suggests that the virus can cause mild, flu-like symptoms, as well as more severe disease. Most patients seem to have mild disease, and about 20% appear to progress to more severe disease, including pneumonia, respiratory failure, and, in some cases, death **(**Gu, J., Han, B., & Wang, J. 2020)

Signs and symptoms of COVID-19 may appear 2 to 14 days after exposure and can include: • Fever • Cough • Shortness of breath or difficulty breathing. Other symptoms can include: • Tiredness • Aches • Runny nose • Sore throat • Headache • Diarrhea • Vomiting • Some people have experienced the loss of smell or taste (Lai, Shih, et al 2020),(Yang, W., et al 2020). Multiple reports have confirmed human-to-human transmission of the COVID-19. When person-to-person spread has occurred with MERS-CoV and SARS-CoV, it is thought to have happened mainly via respiratory droplets produced when an infected person coughs or sneezes, similar to how Influenza and other respiratory pathogens spread. Data has shown that it spreads from person to person among those in close contact (within about 6 feet, or 2 meters). The virus spreads by respiratory droplets released when someone infected with the virus coughs, sneezes or talks **(Figure 2)** (- Bai, Y., et al., 2020.)(Peeri, N.C., et al., 2020)

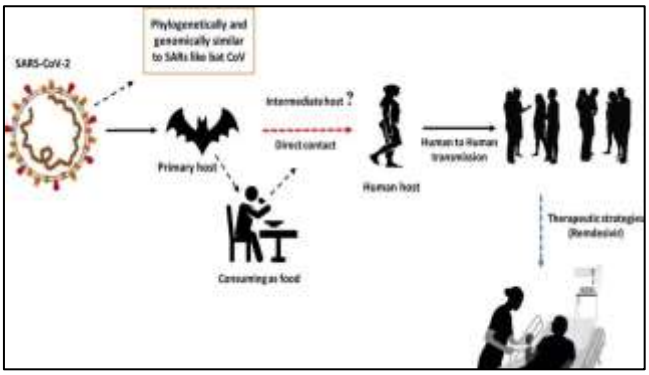

Figure 2: Transmission of the virus from animals to humans (Shereen, M.A., et al., 2020)

3.4. Etiology

In detecting the origin of Covid-19, researchers from the China CDC exposed 585 environmental samples from theWuhan Seafood Market in Wuhan, Hubei province, China, to test(Wang et al., 2020). 33 of these samples were found to contain SARS- CoV-2 traces, associating the diseases' origin to wild animals traded in the market. Using blood, lung fluid, and throat swab samples of 15 patients, researchers established the existence of a virus-specific nucleic acid sequences in the samples, differing from the known human coronavirus species.As of this laboratory test, results revealed that the SARS-CoV-2 is identical to bats beta coronavirus strains. (M Shereen, S Khan, A Kazmi, N Bashir, R Siddique, 2020)

3.5. Epidemiology

The initial outbreak was reported in the Chinese city, where four people were diagnosed with acute respiratory syndrome connected to a local seafood market (Brüssow, 2020). Most of the early cases were said to have some contact with the novel seafood market (Adhikari et al., 2020).

However, the transmission between humans through close contact was associated with a secondary infection source (Li et al., 2020). The infections increased, and yet there was no connection to wildlife exposure or visitation to Wuhan (CDC, 2020). Covid-19 disease became a factor of exposure to the virus predominantly, and the regular and immune-suppressed persons appeared susceptible. The results of early surveys suggested that males (59%) were the most vulnerable, and the median age was 59 years (Hamer, 2020). The persons with poor immunity, such as the elderly, the renal and hepatic dysfunction ailing persons, were the most vulnerable of this infection.

Compared to SARS-CoV, COVID-19 was characterized by excessive transmissibility and pandemic risk. Such a trend is a factor of the viruses' adequate reproductive number(R), which is higher than that of SARS at the virus's early stage. According to WHO, COVID-19 continues to emerge and represents a severe public health issue (Srivastava et al., 2020). The disease spread rapidly from China and across other cities, with growing spikes in Italy, Spain, Germany, France, Iran, Korea, and elsewhere across different continents **(Figure 3).**

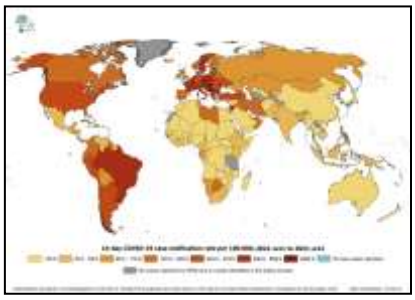

Figure 3: Illustration of the geographical spread of confirmed COVID-19 "COVID-19 (Situation Update Worldwide, as of Week 12, Updated 1 April 2021)

3.6. Prevelance of COVID-19 in Saudi Arabia

Saudi Arabia stood out among the first nations to proactively develop and implement strategies to counter the COVID-19 outbreak. The country's Ministry of Health, in collaboration with other stakeholders such as the Food and Drug Administration (FDA), Interior, and education, developed and issued measures before the first case that was reported in the country on March second, 2020. The government issued a directive halting all the direct flights between the country and China while at the same time suspending the global Umrah pilgrims and tourists' activities and monitoring the Makkah and Madinah entry points. Further measures encompassed the banning of inbound travels of persons from SARS-CoV-2 affected nations (Algaissi et al., 2020). Such steps were critical in minimizing the spread of the SARS-CoV-2 virus to the country.

Despite such measures, the country reported the first Covid-19 case in second March 2020, a case of a traveler returning from Iraq through Bahrain. By March fourth, the government ultimately suspended Umrah.

Furthermore, digital health such as the "my Health" app was activated, allowing individuals to seek medical help and access medical prescriptions without necessarily visiting health care centers. With 500 numbers, the Saudi government issued a national curfew and coupled it with a strict penalty on violators (Algaissi et al., 2020). The government also ordered for a lockdown on all main cities and provided free health care to all locals.

Previously in 2012, the country had experienced MERS-Co outbreak which remains endemic to date. Following such experience, the government had already established the Saudi Centre for Disease Control and Prevention, which remains responsive and promptly responded to the SARS-CoV-2 outbreak. The nation's Ministry of Health instituted the National Health laboratory as a designated point for advanced diagnostics to communicable ailments with high bio-containment laboratories. Also, the government set over 25 hospitals for the segregation and treatment of MERS victims, and such hospitals were adequately equipped to handle Covid-19 cases(Algaissi et al., 2020). All the measures were critical in reducing the spread of the disease. Covid-19 leads to breathing complications, mainly which weakens the lungs and may cause death if left untreated.

Concisely, COV ID-19 is a respiratory syndrome whose origin is associated with bats and whose transmission is through humans and contact. The disease that originated from Wuhan to China has several strains and spread vastly across different countries. With different countries taking measures to curb its spread, the disease still poses a threat to public health. The Saudi Arabia nation government took adequate measures to curb the spread. With previous experience in handling MERS patients, the country stood out as prepared to deal with the Covid-19 pandemic. The success of containment depended on the government's pro-activity to control the spread factors.

3.7. Mechanism of COVID-19 and Inflammatory Response

The incubation time of the new coronavirus is between 3 and 7 days but may be up to 14 days in some cases (She J, Jiang J, et al. 2019). The most common symptoms of SARS-

CoV-2 infection are dry cough, fever, weakness and anosmia. The main laboratory findings include a raised white cell count with lymphopenia, elevated C- reactive protein (CRP), ferritin and increased D-dimers. (Chen G, Wu D, et al. 2019).

A dysregulated host immune response to SARS-CoV-2 lung infection leading to exuberant cytokine release (such as IL-1, IL-6 and TNF-α) and immune-mediated lung injury has been postulated as a critical pathogenetic factor in the progression to adult respiratory distress syndrome (ARDS). (Pedersen SF, et al. 2020).

ARDS starts to develop about after 7 days of the disease, because of an explosive host immune response due to uncontrolled viral replication. The SARS-CoV-2 infection has sequential stages, with the progression, from one stage to the next, causing the deterioration in the health of the patient.

In phase I, which occurs at the time of inoculation and the initial introduction of the disease, patients begin to show nonspecific symptoms: most commonly, a dry cough and fever. During this period, the virus multiplies and establishes residence in the host tissues by binding to the ACE-2 receptor in cells, with the respiratory system being primarily affected. As proliferation of the virus occurs, the immune system is simultaneously attempting to expel it from the lungs, and, in some cases, causing immune-mediated damage of the pulmonary structures, in the process (Wan Y, Shang J, et al. 2020). Look at **(Figure 4)**.

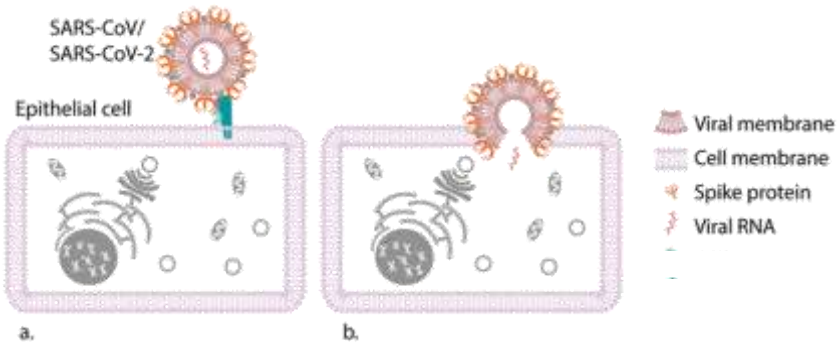

Figure 4: Phase I, start with SARS-CoV-2 gains entry to epithelial cells by binding to the ACE2 receptor(H. Roma Levy, MS 2020)

Phase II is caused by the uncontrolled replication of the virus. This process is driven by the direct cytotoxicity of ACE-2 which acts as a catalyst for further activation of the immune system and therefore worsens the hyperinflammatory state. (Singh AK, Majumdar S, et al. 2020).

In addition to the other symptoms, the patient begins to demonstrate severe hypoxemia with a PaO2/FiO2 ratio (the ratio between arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2)) of less than 300 mmHg. (Siddiqi HK, Mehra MR. et al. 2020).

In phase III, granulocyte colony-stimulating factor (GCSF); inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7 and TNF-α (tumour necrosis factor-α); macrophage inflammatory protein 1-α; D-dimer; CRP; and ferritin are remarkedly elevated in patients who are critically ill. During this phase, patients are susceptible to developing shock, respiratory failure and even cardiopulmonary collapse. (Mehta P, McAuley DF).

3.8. Diagnosis for COVID-19

Patients with suspected infection, the following diagnosis techniques are utilised: performing real-time fluorescence (RT-PCR) to detect the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretions of the lower respiratory tract samples. (Lippi G., Simundic A.M., et al 2019). In patients with COVID-19, the white blood cell count can

vary. Leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common. (Lippi G., Simundic A.M,).

Elevated lactate dehydrogenase and ferritin levels are common, and elevated aminotransferase levels have also been described. On admission, many patients with pneumonia have normal serum procalcitonin levels; however, in those requiring intensive care unit (ICU), they are more likely to be elevated. High D-dimer levels and more severe lymphopenia have been associated with mortality. Imaging findings Chest computed tomography (CT) in patients with COVID-19 most commonly demonstrates ground glass opacification with or without consolidative abnormalities, consistent with viral pneumonia.

Others study have suggested that chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. Less common findings include pleural thickening, pleural effusion, and lymphadenopathy. (Ai T., Yang Z., et al 2020), (Bai H.X., Hsieh B., et al. 2020). Chest CT may be helpful in making the diagnosis, but no finding can completely rule in or rule out the possibility of COVID-19. Serologic tests, once generally available and should be able to identify patients who have either current or previous infection. (Ling Y., Xu S.B., et al. 2020),(Lim J., Jeon S.). Coinfection with SARS-CoV-2 and other respiratory viruses, including influenza, has been reported, and this may impact management decisions.

3.9. COVID-19 Treatment

As SARS-CoV-2 is a recent virus, there are, currently, no specific anti-viral drugs which has been proven to treat COVID-19 infection **(**Ahmed, M. H., & Hassan, A. 2020). Several studies have sought to evaluate the effect of corticosteroids on the natural course of the disease (Zhu N, et al., 2020).

The rationale for the use of dexamethasone in patients with severe infection is based on this premise that the damage caused by the disease is strongly related to the aggressive infammatory response triggered (Huang C, et al., 2020).

Thus, the use of drugs with a potent antiinfammatory effect could reduce the catastrophic effects generated by the overactivation of the immune system, helping to speed up the recovery of these patients (Saghazadeh A, &Rezaei N. 2020)

3.10. Corticosteroids and COVID-19

Corticosteroid drugs are a class of synthetic steroid hormones that are produced in the adrenal cortex in healthy individuals. Corticosteroids include glucocorticoids and mineralocorticoids; they are used to treat a wide range of diseases and symptoms (Ramamoorthy S, &Cidlowski JA. 2016). One of the main roles of glucocorticoids, to consider, is the fact that they cause immunosuppression and are anti-inflammatoryn (Cruz-Topete D, &Cidlowski JA. 2015)-(Montón C, Ewig S, et al., 1999). As they suppress the adaptive immune response, glucocorticoids play an important role in the modulation of several biological functions in immune cells and in different organs and tissues in the human body (Strehl C, et al., 2019).

The latest research suggests that glucocorticoids could have both stimulatory and inhibitory impacts on the immune response depending on their concentration in the blood and how long it is taken (Singh AK, et al., 2020). Clinically, the primary reason for the use of glucocorticoids is that it might be beneficial in preventing damage of structures, like pulmonary in the case of SARS-CoV-2, by inhibiting cytokine production (Solinas C, et al., 2020).

3.11. Dexamethasone as a COVID-19 Treatment

Dexamethasone is a steroid compound, belonging to the corticosteroid class (more precisely a glucocorticoid). It is used in the treatment of numerous conditions, including chronic obstructive lung disease, severe allergies, rheumatic problems, asthma, several skin conditions, brain swelling and alongside antibiotics in tuberculosis (Ahmed, M. H., & Hassan, A. 2020).

3.12. Chemical and Physical Properties of Dexamethasone

Dexamethasone is a white, odourless crystalline powder. It is stable when exposed to air. It is practically insoluble in water (≤ 0.1 mg/mL) (Dexamethasone product package inserts. In: Daily Med. Bethesda). The molecular formula is $C_{22}H_{29}FO_5$. The molecular weight is 392.47 Da and is also chemically known as 1-dehydro-9α-fluoro-16α-methyl hydrocortisone, and the structural formula is shown in **Figure (5).**

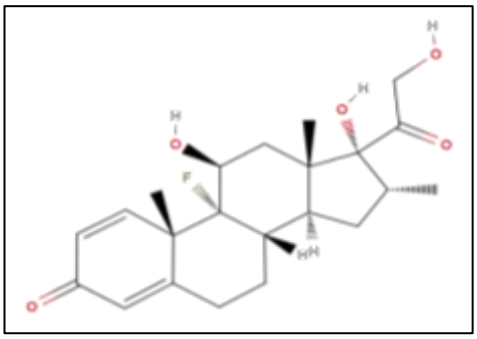

Figure 5: Structural formula of dexamethasone (Ahmed, M. H., & Hassan, A. 2020).

3.13. Posology

Dexamethasone is given in doses, ranging from 0.5 to 10 mg daily, with the dose being dependent on the disease being treated. In more acute conditions, a dose higher than (10 mg/day) may be required. The dose, also, depends on the patient's response. In order to reduce the side effects, the lowest effective dose should be used (Wallace, Chan et al., 2021). Dexamethasone exerts a good inhibitory effect on inflammatory factors and is predominantly used as an auxiliary treatment for viral pneumonia. The action of dexamethasone mimics the action of the compounds the body produces to quell inflammation, naturally. It is about 25 times more active than other corticosteroid compounds (Zoorob RJ, &Cender D. 1998).and this higher potency might be one of the reasons as to why dexamethasone has been shown to be effective in treating SARS-CoV-2 patients. Moreover, dexamethasone is also stronger than nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin. Dexamethasone is, both, anti-inflammatory and immunosuppressive, whilst NSAIDs only inhibit the vascular stage of inflammation (Becker DE,. 2013). The main antiinflammatory effect of dexamethasone is to inhibit a pro-inflammatory gene that encodes for chemokines, cytokines, cell adhesion molecules (CAM) and the acute inflammatory response (Cruz-Topete D, &Cidlowski JA. 2015). Dexamethasone possesses strong antiinflammatory effects with weak mineralocorticoid property compared with other corticosteroid compounds (Saraya MA, &Amal Abd El-Azeem I, 2012). Dexamethasone produces its antiinflammatory effects by affecting two aspects: chemotaxis and vasodilation. Additionally, as aforementioned, following entry into cells, coronaviruses result in systemic AhR activation syndrome (SAAS) and medications, like dexamethasone, that are currently being researched appear to downregulate both the Aryl hydrocarbon receptors (AhR) and indoleamine 2,3-dioxygenase1 (IDO1) genes and so further diminishing inflammation (Li F, Li W, et al., 2005).

3.14. Mechanism of Action

The mechanism of action of dexamethasone depends on the dose used: the genomic (in the case of low doses) and nongenomic mechanisms (with high doses of dexamethasone). Most effects of dexamethasone are via the genomic mechanism which require a longer period,

whereas dexamethasone effects through the non-genomic mechanism occur more rapidly, at the risk of more side effects (Chikanza IC. 2002)-(Lecoq L, et al., 2009).

3.14.1. Genomic Mechanisms: Being small, lipophilic substances, dexamethasone can easily pass through the cell membrane by diffusion and enter the cytoplasm of the target cells and proceed by binding to glucocorticoid receptors (GR) in the cytoplasm. Dexamethasone binds to the GR on the cell membrane, and the formation of this complex leads to translocation of the corticosteroid into the cell, where it travels to the nucleus. Here, it reversibly binds to several specific DNA sites resulting in stimulation (transactivation) and suppression (transrepression) of a large variety of gene transcription (Croxtall JD, et al., 2000). It can inhibit the production of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF, IFN-gamma, VEGF and prostaglandins (Chikanza IC. 2002)-(Newman SP, et al., 1994). Importantly, five of these are linked to SARS-CoV-2 severity (Zhong J, et al., 2020). At the same time, it can also induce the synthesis of glucocorticoid response element resulting in the activation of antiinflammatory cytokine synthesis, notably IL-10 and lipocortin-1.

3.**14.2. Non-Genomic Mechanisms:**
At high doses of the medication, dexamethasone binds to the membrane-associated GR on cells, such as T lymphocytes, resulting in the impairment of receptor signalling and a T lymphocyte–mediated immune response (Mitre-Aguilar IB, et al., 2015). The glucocorticoid receptor combines to integrins, leading to the activation of focal adhesion kinase (FAK) **(Figure 6**). As well as that, a high dose of dexamethasone also interacts with the movement of Ca^{+2} and Na^{+} across the cell membrane, resulting in a rapid decrease in inflammation (Grzanka A, et al. 2011).

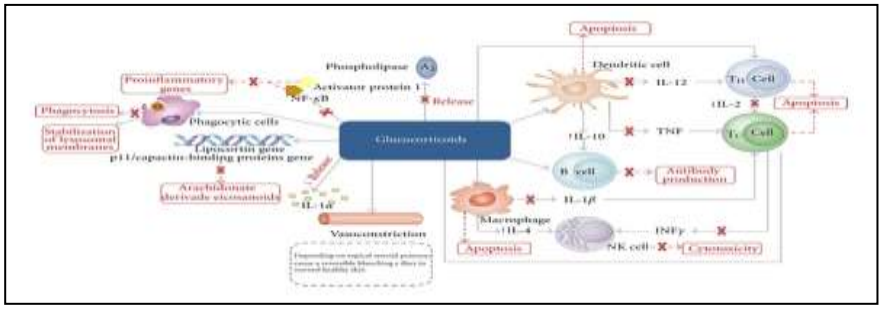

Figure 6: Anti-inflammatory, immunosuppressive, and vasoconstrictive effects of corticosteroids (E. M. Sternberg, 2006)-(J. D. Ference and A. R. Last, 2009).

3.15. Impact of Dexamethasone on COVID-19 Patients
A number of studies have been conducted on the use of this drug for treating hyperinflammatory states secondary to viral infections caused by the respiratory syncytial virus (RSV); MERS; influenza; and, now, SARS-CoV-2. In the primaeval stage of inflammation, glucocorticoids decrease inflammatory cell exudation, phagocytosis and capillary dilation. Whilst in the severe inflammatory stage, it can inhibit the fibroblasts and its excessive proliferation, which are normally responsible for fibrosis (Yang Z, et al., 2020). In vitro studies showed that corticosteroids are able to inhibit respiratory syncytial virus and rhino virus induced cytokine release (Oliver BGG, Robinson P,2014). An in vitro study found that the addition of 0.1 μM of dexamethasone to a cultured sample of human alveolar epithelial cells, H441 and A549, could delay cell proliferation and also resulted in a shorter recuperation time when compared to the untreated cultured cells (Nalayanda DD, et al., 2014). Moreover, earlier studies showed that low doses of dexamethasone (0.4 mg/kg per day, given in four doses over 48 h) had a positive impact in patients with lung infections caused by the RSV (Van Woensel JB. Et al., 2003). Furthermore, a similar dose of dexamethasone (0.6 mg/kg day) was given to patients with bronchiolitis, again, caused by

RSV, and results were approved of in terms of having positive benefits. In further investigations, glucocorticoids have been given in combination with other medical compounds, like antimalarial drugs, serine protease inhibitors, anti-viral and IL blockers, to estimate if those medications, together, have a synergistic effect (Solinas C, et al., 2020). Recently, a clinical trial carried out in France compared the use of hydroxychloroquine alone, with the use of hydroxychloroquine (600 mg/day for 10 days) in combination with dexamethasone (20 mg/day for 5 days and 10 mg/day for the next subsequent 5 days) in the treatment of patients with ARDS caused by SARS-CoV-2 (phase III). The primary outcome report showed that the patients who took the combination of hydroxychloroquine and dexamethasone had a mortality rate of 46%. The report also presented the mortality rate to be 61.8% in patients who received hydroxychloroquine alone (Stephan F, Lamrani L, Dexamethasone treatment for severe acute respiratory distress syndrome induced by COVID-19). A team of front-line physicians from China stated that the use of corticosteroids (methylprednisolone or equivalent) for patients who were critically ill was beneficial. They, however, were against the liberal use of the drug and only recommended short courses (less than 7 days) of corticosteroids (0.5–1 mg per kg per day), used prudently, for critical patients with SARS-CoV-2 pneumonia (Shang L, et al., 2019). On the other hand, Russel and his co-workers in February 2020, based on results of previous studies on the use of steroids in MERS, SARS and influenza patients, support that corticosteroid treatment should not be used for the treatment of SARS-CoV-2-induced lung injury or shock, unless it is for a clinical trial due to the lack of substantial clinical evidence proving their efficacy (Russell CD, et al., 2020). As well as that, Ling et al. carried out a study on 66 patients out of the 292 patients who had tested positive for SARSCoV-2, in January 2020, in Shanghai. The authors compared the presence of RNA in various secretions and excreta in a group receiving glucocorticoid treatment to a group receiving standard supportive treatment. The results demonstrated that the throat swabs were negative for the viral RNA after a median time of 9.5 days (6.0–11.0 days), whereas the stool samples showed to be clear of the viral RNA after 11.0 days (9.0– 16.0) of onset of symptoms. The study also reported that viral RNA detection in both oropharyngeal and faecal samples was longer in the glucocorticoid group than in the nonglucocorticoid group. Consequently, the authors concluded that glucocorticoids are not a suitable for the treatment of COVID-19, especially in those with mild symptoms. This may be due to dexamethasone suppressing the cytokine storm. The findings of clinical trials as reported in the Henry Ford Health System (HFHS)–centralized clinical microbiology laboratory indicated that an early short course of methylprednisolone (0.5 to 1 mg per kg per day in two divided doses for 3 days) in patients with moderate-to-severe COVID-19 reduced the need for escalation of care and improved clinical outcomes (Fadel, Morrison et al 2020). The latest recovery trial of using dexamethasone has been performed in the UK by a team of researchers at Oxford University. Six milligrammes of dexamethasone once daily for up to 10 days was given to 2104 patients, and the results were compared with those of 4321 patients who were not given dexamethasone. The average age of the participants was 66.1 years, and 36% of patients were female. The preliminary findings demonstrate that dexamethasone reduced the 28-day mortality by 35% in patients receiving invasive mechanical ventilation and by 20% in patients receiving supplementary oxygen. As the treatment was only used at a low- to medium dose for up to10 days, no side effects have been noted thus far. The benefits of the drug were clearer in patients who were treated for more than 7 days after the initial onset of symptoms, when inflammatory lung damage is likely to have been more common. According to these latest findings, the WHO has welcomed the preliminary results regarding the use of dexamethasone in the treatment of SARS-CoV-2 patients, as this drug treatment was proven to save lives (WHO report 16 June 2020). On the other hand, it was observed that this medication had no benefit on the outcomes of patients who had mild symptoms and so corticosteroids is only suitable for patients who are in hospital, under mechanical ventilation (severe situation) (Horby P, et al., 2020). In addition to reducing the mortality ratio of patients with a severe form of COVID-19, using corticosteroids has

prohibited the worsening of ventilator parameters, and subsequent ventilation; it has also reduced the duration of hospital stay and improved oxygenation status (Wang Y, et al., 2020).

3.16. Dexamethasone nanomedicines for COVID-19

It has been proposed that nano-formulate dexamethasone can improve the management of COVID-19 complications. At the preclinical level, several different diseases have already been successfully treated with dexamethasone nanomedicines, including, for example, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, liver fibrosis, wound healing and cancer (Quan, L. et al. 2014) (Gauthier, A. et al.2018).

The proposition that dexamethasone nanomedicines are useful for the treatment of COVID-19 is based on the widely recognized notion that nanoparticles potently accumulate in macrophages, upon intravenous administration as well as upon inhalation **(Figure 7)** .

In this context, it is worth mentioning the liposomal amikacin product Arikayce, which was approved by the US FDA in 2019 for treating Mycobacterium avium complex lung disease.

As a nanomedicine formulation, Arikayce efficiently targets the pulmonary macrophages where the bacterial pathogen resides and it has been shown to thereby improve disease treatment as compared to free amikacin (Zhang, J. et al. 2018).

Along the same line of thinking, pulmonary delivery of dexamethasone liposomes may outperform free dexamethasone when targeting alveolar macrophages as a strategy to intervene in the (sub)acute phase of COVID-19. Intravenous administration, on the other hand, provides the possibility of using liposomes and other nanomedicine formulations to target dexamethasone to myeloid and lymphoid tissues that are enriched with phagocytes, such as the spleen and bone marrow. It furthermore enables efficient and relatively selective delivery of the potent corticosteroid drug to sites of inflammation where the vasculature is leaky and where large numbers of phagocytes have infiltrated, attenuating the production of proinflammatory cytokines, of matrix degrading enzymes and of other signalling molecules that contribute to oedema formation and progressive tissue damage in COVID-19. It is crucial in this regard to impart long-circulating behaviour (for example, via PEGylation) upon the intravenously injected nanomedicines, as this promotes accumulation in inflammatory macrophages infiltrated at the pathological site, while avoiding rapid capture by the liver- and spleen-resident macrophage populations that are responsible for clearing nanomedicine formulations from the blood stream (Metselaar, J. M., Wauben, M. H. M., et al. 2003).

It is well known that COVID-19 infection causes several acute and longer-lasting life-threatening symptoms, including cytokine storm, oedema formation and fibrosis development. Dexamethasone nanomedicines may help to better manage the severity of these disease manifestations, promoting better control of life-threatening symptoms at the acute and intermediate phase, and more rapid and more complete recovery in the post-ICU phase.

Dexamethasone nanomedicines are nowhere near a vaccine in terms of global impact and control of COVID-19 disease burden. In a number of cases, however, dexamethasone nanomedicines may help in the day-to-day management of the disease:

(1) Nanomedicine formulations can help to target the potent corticosteroid drug to inflammation-initiating and -propagating phagocytic cells in the lung, in the blood, and in myeloid and lymphoid tissues. This assists in better controlling MAS and cytokine storm, which have been implicated in COVID-19-related fatalities (Merad, M. & Martin, J.et al. 2020).

As a consequence, critically ill patients on ventilation or on oxygen therapy are expected to recover faster and more efficiently than upon treatment with the free drug.

(2) Dexamethasone is a highly active anti-oedema agent. Its potent anti-swelling properties contribute to its mechanism of action in multiple different diseases, including in high-grade inflammatory disorders and in glioblastoma, and this assumingly also contributes to its activity in COVID-19. Nanoformulating dexamethasone could further potentiate this effect, by increasing drug availability and drug activity over time in

hyperactivated immune cell populations in the inflamed parts of the lung. Dexamethasone nanomedicine formulations may furthermore help to sustain antiinflammatory and anti-oedema drug activity in the days and weeks after patients have been released from the hospital.

(3) Dexamethasone is a highly potent anti-fibrotic agent. Multiple preclinical studies, in various different disease models, have shown that the anti-fibrotic effects of dexamethasone can be potentiated by reformulating it as a nanomedicine formulation (Gauthier, A. et al. 2018). In this context, dexamethasone nanomedicines have been shown to be particularly useful for preventing fibrosis. Since pulmonary fibrosis has recently emerged as a key complication in the long-term follow-up management of COVID-19 (especially in patients that have been ventilated for prolonged periods of time) (George, P. M., Wells, A. U.et al. 2020). inhaled or intravenously injected dexamethasone nanomedicines could meet an urgent medical need also at this level of COVID-19 management.

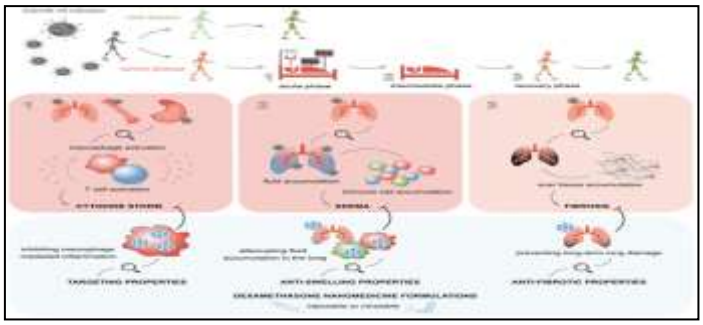

Figure 7: Dexamethasone nanomedicinesfor COVID-19 (Metselaar, J. M., et al.,2003)

When realistically reflecting upon the potential of dexamethasone nanomedicines for the treatment of COVID-19, money and time are critical issues to consider. The fact that dexamethasone is an already widely available and very cheap drug with — now proven — life-saving capability in COVID-19 substantially raises the bar for any new nanomedicine product based on dexamethasone. A dexamethasone nanomedicine product obviously entails a higher level of complexity in terms of composition and manufacturing, and it would first have to be clinically tested and registered before it becomes available on the market, where it would have to fetch at least US$100 per treatment to make it economically viable. We believe that the key undertaking here is to carefully design the clinical studies with the nanomedicine product so as to unambiguously prove what the actual added value is. If targeted delivery of dexamethasone in COVID-19 patients using a nanomedicine formulation leads to better outcomes, for instance in terms of a reduction of the number of days that patients need mechanical ventilation and/or require costly ICU hospitalization (Kaier, K., Heister, T., Wolff, J et al. 2020) (Dasta, J., McLaughlin, T. et al. 2005). then this is already a huge gain that can easily offset against the higher level of complexity and cost of the nanodrug. And if in these clinical studies, dexamethasone nanomedicines would also turn out to be able to outperform the free drug in terms of improving the survival of critically ill patients, then that would be another major leap forward in the worldwide battle against COVID-19.

3.17. Side Effects of Corticosteroids:

3.17.1. Long term use of corticosteroids

Long term use of corticosteroids is generally avoided, given the risks of serious acute complications such as infection, venous thromboembolism, avascular necrosis, and fracture as well as chronic diseases such as diabetes mellitus, hypertension, and osteoporosis (Dessein PH, Joffe BI, et al. 2004) (Davis JM 3rd, , Maradit Kremers H et al. 2007). Chronic use of corticosteroids can also lead to cataract formation and glaucoma.

Corticosteroids increase the risk of contracting certain infections and reduce the capacity to respond to serious infections (Evans, Ronald M et al.1988)

High doses of corticosteroids may cause more harm than good, especially if the treatment is given at a time when there is uncontrolled viral replication but with a low level of inflammation. Although there are potential hazards associated with high doses of corticosteroids when treating patients with SARS-CoV-2 pneumonia, including secondary infections and prolonged virus shedding, but in severely ill patients, if the hyper-inflammatory state is not controlled,
cytokine related lung injury could cause rapidly progressive pneumonia, the outcomes of which can be long-term and irreversible (Shang L, Zhao J.et al. 2020).

Use of high doses, particularly over a prolonged period of time, is associated with changes in appearance including a weight gain, centripetal redistribution of fat, muscle wasting, acne, bruising, thinning of the skin, and stretch marks.

All these adverse events are not associated with short term use (with the exception of hyperglycemia that can worsen diabetes). Low doses of corticosteroids downregulate pro-inflammatory cytokine transcription by consequently preventing an extended cytokine response and accelerating the resolution of pulmonary and systemic inflammation in pneumonia (Horby P. et al, 2020)

3.17.2. Short term use of corticosteroids

Short term use is much less understood, and evidence is generally oral corticosteroids are often used to treat conditions such as asthma, chronic obstructive lung disease, rheumatoid arthritis, and inflammatory bowel disease little is known about the prescribing patterns of short term use of these drugs in the general adult population, or their potential harm (Waljee, Akbar K., et al. 2017).

3.18. Mechanism of metabolic effects of glucocorticoids

The administration of glucocorticoids causes a signifcant change on the metabolism of carbohydrates, which can lead to insulin resistance, hyperglycemia and glycosuria. One of the frst well-elucidated effects of this drug was its role in increasing hepatic gluconeogenesis, which seems to be related to the inhibitory effects of glucocorticoids on the conversion of pyruvic acid to acetyl-coenzyme A, leading to an accumulation of pyruvic acid and resulting in glucose resynthesis (Binder C. et al. 1969) (Thorn GW, Renold AE,et al. 1957). Increased induction of enzymes related to gluconeogenesis, such as glucose6-phosphatase, fructose-1,6-bisphosphatase and phosphoenolpyruvate carboxykinase contribute to this efect (Cassuto H, Kochan K, et al. 2005). An increase in hepatic glycogen deposition can be observed from three to twenty-four hours after the administration of glucocorticoids (Ashmore J, Morgan D. et al. 1967). In addition, the use of glucocorticoids plays an important role by augmenting glucose production and decreasing peripheral glucose utilization, maintaining high serum glucose levels (De Feo P, Perriello G,et al. 1989) This action, which in physiological situations is fundamental for maintaining euglycemia during periods of fasting, may be exacerbated with the administration of exogenous corticosteroids, leading to hyperglycemia **(Figure 8)**. The chronic use of corticosteroids also increases fasting insulin levels (Ashmore J, Morgan D. 1967.). This effect is related to a metabolic response of the pancreatic beta cells to hyperglycemia, which results in reduced peripheral sensitivity to insulin. In addition, glucocorticoids also alter insulin secretion by reducing the effect of incretins, even though this action has not yet been fully understood (Lenzen S, Bailey CJ. 1984, Karlsson S, Ostlund B 2001). Experimental studies have shown that glucocorticoids have a pro-adipogenic function. The lipogenic effect of these drugs seems to be mediated by the genetic expression of pathways that lead to the maximization of insulin efects. When evaluating animal models after exposure to the use of corticosteroids, high levels of these drugs in adipose tissue were associated with increased deposition of abdominal fat, reduced glucose tolerance and hypertriglyceridemia. Moreover, there was a reduction in adiponectin levels and an increase in serum TNF-α levels, which are related to insulin sensitivity and resistance,

respectively(Richter G, Göke R, Göke B. 1990– Sato T, Hayashi H, Hiratsuka M, Hirasawa N.. 2015). Glucocorticoids also have a lipolytic action, especially pronounced in peripheral fat. This function is mediated by the induction of transcription factors that regulate the function of lipases, increasing the action of these enzymes(Knox WE, Auerbach VH, 1956. – Fasshauer M, Klein J, Neumann S,. 2002). However, the acute and longterm efects of corticosteroids on lipolysis are still not entirely clear. Glucocorticoids play a role in controlling liver metabolism mediated by the genomic regulation of glucocorticoids receptors. More than 50 target genes for this regulation have been identifed so far (Peckett AJ, Wright DC, Riddell MC. 2011). These genes codify enzymes responsible for lipogenesis and triglyceride synthesis, and the consequences of the activation of these enzymes can lead to the development of hepatic steatosis even before the establishment of insulin resistance in the metabolic syndrome. In relation to other lipoproteins, in vitro and in vivo studies have demonstrated that animals treated with dexamethasone showed an increase in serum very-low density lipoproteins (VLDL) and high-density lipoproteins (HDL). This effect is believed to be due to increased production of apolipoprotein B (ApoB), associated with increased synthesis of triglycerides and apolipoprotein A-I (ApoA1) respectively, which are stimulated by the use of corticosteroids. In the case of low-density lipoproteins (LDL), the analyses so far are not conclusive, and further studies are needed to determine what the effect would be on these molecules. Protein metabolism is also signifcantly affected by corticosteroids, which have shown to stimulate catabolism, resulting in inhibition of growth, osteoporosis, muscular atrophy, reduction in skin thickness and reduction in the amount of lymphoid tissue. Protein catabolism is the process by which proteins are broken down to their amino acids. Consequently, a greater uptake of amino acids in the liver occurs. These amino acids will be predominantly deaminated and converted to glucose or, less frequently, transformed into new proteins Regarding calcium metabolism, glucocorticoids have a direct and indirect effect on bone remodeling . They inhibit the formation of the bone matrix, which seems to be related to the reduction of the osteoblast's recruitment and to the accelerated apoptosis of osteocytes. Another effect that can be observed is the increase in the expression of receptor activator of nuclear factor-κB ligand (RANKL), which leads to increases in the number of bone-resorbing osteoclasts. This condition may be accompanied by other changes, such as reduced muscle mass, which can be present due to protein catabolism, and with cataract-related visual impairment, which is more prevalent in corticosteroid users. These three factors combined result in a signifcant increase in the risk of falls and fractures even before observation of bone mineral density reduction. Other indirect effects that can be observed are the reduction in calcium reabsorption in the kidney, changes in sex hormones and changes in the parathyroid hormone pulsatility, factors that are fundamental for adequate bone homeostasis. Water and sodium retention and the reduction in serum potassium are complications of the use of corticosteroids, especially those with mineralocorticoid action and when high doses are administered. There are currently several formulations available with a predominance of glucocorticoid effect and practically negligible mineralocorticoid effect, with dexamethasone as an example of this category. Despite this, the efect on water regulation remains, regardless of the mineralocorticoid effect. Glucocorticoids act indirectly in the proximal tubule, increasing the cellular response of sodium transporters stimulated by angiotensin II. In the distal tubule, the effect is more direct and seems to be related to crossover binding to mineralocorticoid receptors. As a result, there is an increase in sodium and water retention, increasing the circulating volume and causing an increase in blood pressure levels. Another indirect effect of glucocorticoids that results in arterial hypertension is the magnifcation of the circulating vasoconstrictors' response, since it acts upregulating the expression of receptors to many vasoconstrictors and downregulating the effects of potential vasodilators (Ebbert JO, Jensen MD.. 2013..– Van den Berghe G. 1991). Thus, glucocorticoids have the potential to alter both circulating volume and vascular resistance.

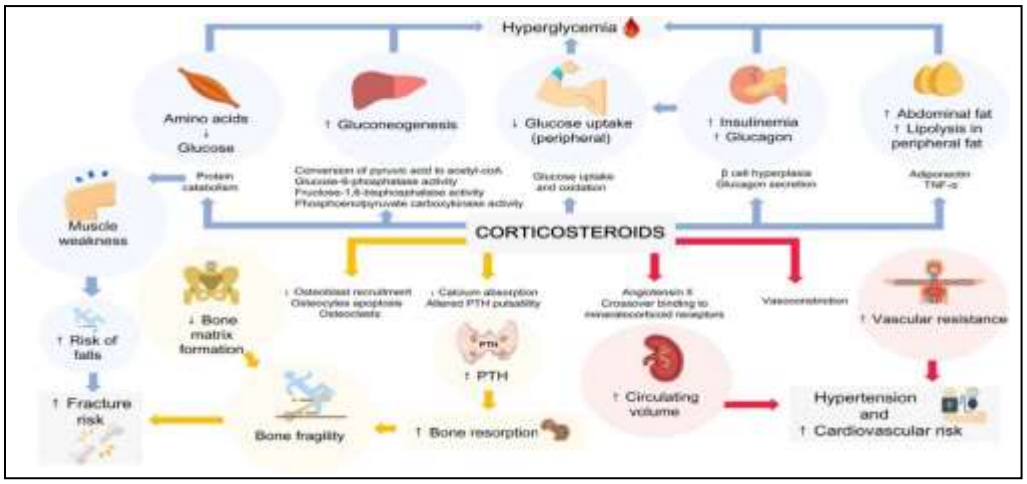

Figure 8: Efect of the use of corticosteroids on diferent functions of the body (Alessi, Oliveira et al 2020)

3.19. WHO and CDC Recommendation

WHO and CDC recommend following these precautions for avoiding COVID-19 (13, 14): • Avoid large events and mass gatherings. • Avoid close contact (within about 6 feet, or 2 meters) with anyone who is sick or has symptoms. • Keep the distance between yourself and others if COVID-19 is spreading in your community, especially if you have a higher risk of serious illness. • Wash your hands often with soap and water for at least 20 seconds, or use an alcohol-based hand sanitizer that contains at least 60% alcohol. • Cover your mouth and nose with your elbow or a tissue when you cough or sneeze. Throw away the used tissue. • Avoid touching your eyes, nose, and mouth. • Clean and disinfect surfaces you often touch on a daily basis. Vaccination.

4. Conclusion

The outcome data regarding the use of corticosteroids, especially dexamethasone, for SARS-CoV-2 so far, although not conclusive, are promising with some findings suggesting that low-to-moderate doses of dexamethasone could lower the mortality rate in patients with a severe form of the condition. It is, however, not recommended for patients with mild symptoms. To further improve our understanding of the parameters and the effect of glucocorticoids on patients with SARSCoV-2 infection, more randomized clinical trials on this treatment are necessary.

5. Ethical Considerations:

The researchers acknowledge the research does not contains any experiments on humans or animals.

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