МЕДИЦИНСКИЕ НАУКИ

COVID-19 AND AUTOIMMUNE DISEASES: DRUGS USE AND PHYSICAL ACTIVITY EFFICIENCY OVERVIEW

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COVID-19 и аутоиммунные заболевания: обзор эффективности применения лекарств и физической активности

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Abstract. A new coronavirus COVID-19 become a global health emergency.

This paper touches two important topics in the context of COVID-19. First, we will essentially specify physical activity effects on immune system like defence to viral infection and upper respiratory tract infection (URTI). Second, COVID-19 is surely conditioning the treatment strategy of autoimmune disease, rheumatoid arthritis (RA), and rheumatic heart disease (RHD). Compared to the general population, the infectious risk of RA and RHD is greatly increased because the immune system of patients with autoimmune diseases, combined with the iatrogenic effect generated by corticosteroids immunosuppressive, salicylate and antibiotic drugs, are generally impaired. Thus, we analyse the evidence on either a positive or negative effect of drugs commonly used to treat RA and RHD in this particular condition, in order to optimize the current approach to RA and RHD patients.

Аннотация. Новый коронавирус COVID-19 быстро стал глобальной чрезвычайной ситуацией в области здравоохранения.

Эта статья затрагивает две важные темы в контексте COVID-19. Во-первых, мы по существу определим влияние физической активности на иммунную систему, такую как защита от вирусной инфекции и инфекции верхних дыхательных путей. Во-вторых, COVID-19, безусловно, обусловливает стратегию лечения аутоиммунных заболеваний, ревматоидного артрита (РА) и ревматической болезни сердца (РБС).

По сравнению с общей популяцией инфекционный риск РА и РБС значительно повышен, так как иммунная система больных аутоиммунными заболеваниями в сочетании с ятрогенным эффектом, создаваемым кортикостероидами иммуносупрессивными, салицилатными и антибиотиковыми препаратами, как правило, нарушена. Таким образом, мы анализируем данные о положительном или отрицательном эффекте лекарств, обычно используемых для лечения РА и РЗС в этом конкретном состоянии, с целью оптимизации текущего подхода к пациентам с РА и РЗС.

Keywords: Autoimmune diseases, COVID-19, drugs, physical activity.

Introduction

A new kind of pneumonia approved by a novel member of the family of coronaviridae called SARS-CoV-2, 'Severe Acute Respiratory Coronavirus 2 Syndromes,' developed in December 2019 from a province of China known as Wuhan [126126. This virus, as demonstrated by phylogenetic analysis, is different at a ratio of 80% nucleotide identity with SARS-CoV-1 107]. Studies show that SARS-CoV-2 causes a disease holding the characteristics of dry cough, dyspnea, fever, and fatigue with lymphopenia [40, 46,118, 123]. Clearly, more than 15-20% of infected patients show that more severe cases clinically can lead to ARDA, Acute Respiratory Distress Syndrome, and death because of the onset of interstitial pneumonia with alveolar damage [120].

As a result of the rapid global spread worldwide since the starting of the epidemic, WHO, World Health Organization, has named the disease as COVID-19 and has declared a public health emergency of international concern on January 30, 2019, and a pandemic on March 11, 2020. The epidemic is continuously evolving, and updated data on April 13, 2020, as reported by WHO shows, confirmed 1,773,084 cases and 111,652 deaths [115].

In the context of evolving this health emergency, it is critical to clarify the relationship between physical activities with COVID-19, on one side and the current virus with the negative and positive effects of drugs commonly used to treat RA and RHD in order to optimize the current approach to RA and RHD patients, on the other side.

First, an autoimmune disease is a condition arising from an abnormal immune response to a normal body part [66]. The immune system is designed to detect and destroy foreign invaders inside the body like bacteria and viruses. While working optimally, the immune system can prevent sickness when we're exposed to germs. Several factors like sleep, diet, stress, hygiene and physical activity can affect the immune system's performance. In fact, understanding how behaviours such as physical activity or exercise affect viral infection outcomes is of public health importance. Respiratory viral infections represent the most prevalent and pathogenic form of infectious disease, reporting over 7% of all deaths in both men and women in 2004 [55]. Cross-sectional and longitudinal data suggests people who engage in regular moderate intensity exercise maintain a reduced risk of self-reported respiratory symptoms [67, 85, 114, 20]. Additionally, working from the laboratories and others demonstrates moderate intensity exercise performed prior to infection [63] or infectious symptoms [26] reduces respiratory virus-associated mortality in animals. In contrast, intense exercise before or during viral infection has been associated with greater morbidity and mortality [43, 10920].

Second, the fast and uncontrolled spread of the epidemic can clearly produce even more concerns in RA, which are intrinsically characterized by an increased infectious risk due to the disease itself and to the side effects of immunosuppressive agents such as corticosteroids and synthetic or biological disease-modifying drugs [29]. Furthermore, the growing knowledge about the pathogenesis of SARS-CoV-2 infection is causing the introduction of drugs commonly used for the treatment of rheumatoid arthritis (RA) even for the management of more complex cases of COVID-19.

Third, according to World meter, those patients who comorbid cardiovascular disease experienced more risk even death compared to others who are pre-existing medical conditions [117]. In fact, as reported by WHO, there is RHD, one of the most common CVDs damage to the Heart muscle and heart valves [116]. The coronavirus can impact the heart in several ways; viruses are known to attack the heart and can cause viral cardiomyopathies in which the pumping chambers of the heart get weak and may even fail to pump blood. The coronavirus has been widely used in rabbit models to study cardiomyopathy so it is certainly capable of damaging the pumping chambers of the heart.

In addition, Dr. John Mehall, the Director of Cardiothoracic Surgery at Cantura Health in Lakewood, Colorado, stated, "Patients who have heart valve abnormalities that are well compensated and well-tolerated at baseline, are more susceptible to heart failure if they were to become infected with the coronavirus. Because of the underlying heart valve issues, if damage to the pumping chamber of the heart were to occur, patients would be less able to tolerate that." [2].

Consequently, waiting for observational data on the incidence of COVID-19 in RA and RHD, the best plan to manage RA and RHD is still far to be obvious. The goal of this study is to provide an overview of viral infectious risk in RA and RHD, with a specific focus on the knowledge about the COVID-19 and the use of anti-RA and RHD drugs in the context of the health emergency.

Immune Responses Cells to Respiratory Viral Infection

When a virus infects a person (host), it invades the cells of its host in order to survive and replicate. Once inside, the cells of the immune system cannot 'see' the virus and therefore do not know that the host cell is infected. To overcome this, cells employ a system that allows them to show other cells what is inside them – they use molecules called **class I major histocompatibility complex proteins (**or **MHC class I,** for short) to display pieces of protein from inside the cell upon the cell surface. If the cell is infected with a virus, these pieces of peptide will include fragments of proteins made by the virus.

A strong Th1 response is necessary in the early stages of viral infection, as it promotes rapid clearance of the virus. Prolonged Th1 activity, however, may lead to respiratory tissue pathology, through increased cell damage and necrosis [18]. A special cell of the immune system called a **T cell** circulates looking for infections. One type of T cell is called a **cytotoxic T cell** because it kills cells that are infected with viruses with toxic mediators. Cytotoxic T cells have specialised proteins on their surface that help them to recognise virally-infected cells. These proteins are called **T cell receptors (TCRs).** Each cytotoxic T cell has a TCR that can specifically recognise a particular antigenic peptide bound to an MHC molecule. If the T cell receptor detects a peptide from a virus, it warns its T cell of an infection.

In addition, to inducing antiviral activity in host cells, activated innate immune cells also secrete numerous pro-inflammatory cytokines including: interleukin (IL)-1, IL-6, IL-12 and tumour necrosis factor (TNF)-α which induce a local and systemic inflammatory response characterized by increased production of acute-phase opsonizing complement proteins, enhanced extravasation of leukocytes to infected tissues, and increased antigen presentation and cytotoxic capacity. These same cytokines communicate with the brain and are responsible for sickness behaviours associated with infection [74]. Respiratory viruses bind glycoproteins on the surface of mucosal epithelial cells, inducing receptor mediated endocytosis and ensuant infection of the host cell. In immunized individuals, salivary and mucosal immunoglobulins, primarily IgA, recognize and bind viral epitopes, blocking their entry into mucosal cells and reducing susceptibility to secondary infection. Virus invasion of the respiratory mucosa evokes an innate immune response through binding of pathogen-associated-molecular-patterns (PAMPs) to toll-like receptor (TLR) molecules on lung macrophages (Mϕ's), myeloid dendritic cells (mDC), and plasmacytoid dendritic cells (pDC). Specifically, TLRs 3,7, and 9 recognize single and double stranded mRNA characteristic of the viral genome and initiate signal

transduction, leading to nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κβ) transcriptional activity, which promotes the synthesis of type I interferons α/β (IFN). Secretion of (IFN-α and IFN-β) by alveolar (pDCs and Mϕ's) induces host cell upregulation of two critical antiviral mechanisms: double stranded RNA-activated inhibitor of translation (DAI) and (Mx) proteins.

The Pathophysiology of COVID-19 Infection

SARS-CoV-2, the largest virus, has its own single-stranded-RNA genome with positive-sense. The hypothetical pathogenesis of COVID-19 is shown in Fig.1

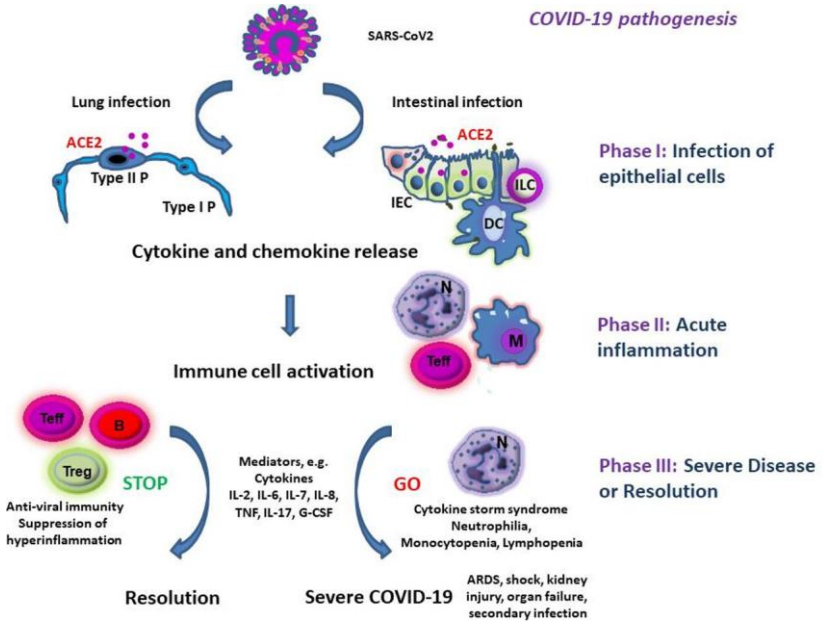

Fig. 1 Hypothetical pathogenesis of COVID-19

The SARS-CoV-2 essentially uses the SARS-CoV angiotensin-converting enzyme 2 (ACE2) for host cell entry [127]. ACE2, type I and II alveolar epithelial cells, expressed in human tissues, especially in human lung, and ACE is positive on endothelial cells [42, 125, Fig.2].

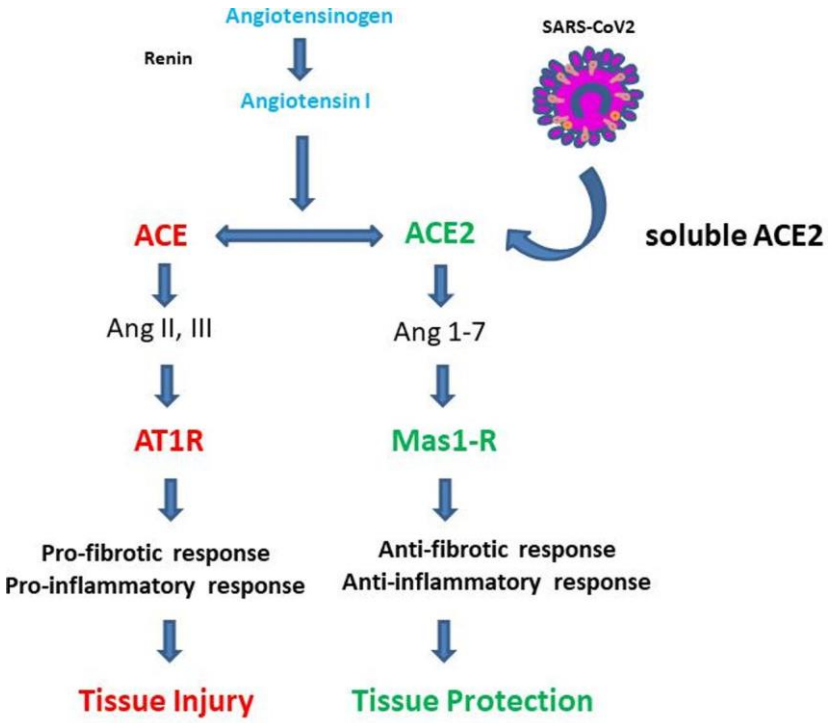

Fig. 2 The ACE/ACE2 receptor system (modified according to Zhang et al [128].

AT2 alveolar epithelial cells are specifically prone to viral infection [128]. Because of the downregulation of ACE2, which can be a result of SARS-CoV-2, angiotensin II is increased so that lung damage may increase when ACE2 expression decreases [27]. As a result of these studies, it can be suggested that the risk

COVID-19 is higher for patients who have hypertension and diabetes mellitus using ACE-inhibitors or ARBs, Angiotensin Receptor Blockers, and eventually, "the increased expression of ACE2 would facilitate infection with COVID-19 … and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19." [35].

However, there is only one contra evidence by the European Society of Cardiology, which strongly recommends, "physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the COVID-19 infection" [59].

After the virus (COVID-19, respectively) enters the cells, releasing viral RNA into the cytoplasm occurs and viral RNA translated into two polyproteins and transcription of the sub-genomic RNAs, and thus, the replication of viral genome follows [12295].

Cytokines Release Syndrome (CRS), consisting of cytokines and chemokines, is very similar to that of Secondary Hemophagocytic Lymphohistiocytosis (sHLH); in adults, sHLH includes hyperactivation of macrophages, cytotoxic T lymphocytes, and NK cells, resulting to failure in multiorgan and most common viral infections leading to death [122].

Unremitting fever, hyperferritinemia, pulmonary involvement including ARDS, and cytopenias are the most common features of sHLH [95]. A cytokine profile similar to sHLH has been reported in most severe SARS-CoV-2 infections, identified by increased levels of a number of cytokines, chemokines, and chemokines [69110]. So, the approaching of this cytokine storm regarding SARS-CoV-2 is an important need not fulfilled yet.

Physical Activity Immune Response to Viral Infection: Upper respiratory tract infection

Respiratory viruses such as influenza and rhinovirus are sub-microscopic, non-cellular infectious agents which invade respiratory mucosal tissue and replicate inside the host's living cells. Unlike bacterial infections, viruses are metabolically insufficient, depending completely on the host's cellular metabolism for replication and viral protein synthesis. Because viruses utilize host machinery, they often evade host immune surveillance, allowing rapid replication and increased viral load. The complexity of viral escape mechanisms selectively pressured the immune system to develop a broad spectrum of anti-viral responses which coordinate the recognition and clearance of viruses.

URTI is the most frequently occurring infectious disease in humans worldwide [31, 7180]. More than 200 different viruses cause the common cold, and rhinoviruses and coronaviruses are the culprits 25%–60% of the time. The National Institute of Allergy and Infectious Diseases reports that people in the USA suffer one billion colds each year with an incidence of 2–4 for the average adult and 6–10 for children [31]. URTI imposes an estimated USD40 billion burden in direct and indirect costs on the U.S. economy [71].

Low to high exercise workloads have a unique effect on URTI risk [64]. Exercise that improved survival also resulted in significantly lower cell infiltration into the lungs and draining lymph nodes and reduced (but not absent) IFN-γ mRNA and protein expression 3- and 5-days post influenza infection. Qualitative protein expression analysis (*e.g.*, antibody array) revealed a two-fold reduction in Th1 type cytokines and chemokines including IFN-γ, IL-17, IL-13, interferon-inducible T-cell alpha chemoattractant (ITAC), leptin, stromal cell-derived factor-1 (SDF-1), and lipopolysaccharide-inducible CXC chemokine (LIX). Contradicting our hypothesis, however, was an observed increase in IL-12, and no change in IL-2, both hallmark cytokines of a Th1 response. In regard to IL-12, our data revealed that the protein was expressed at extremely low levels in the lung tissue. IL-2 plays a critical role in the differentiation and maturation of T regulatory cells ($CD4^+CD25^+$), which are anti-inflammatory immune cells which play a crucial role in controlling Th1-type inflammatory responses. We conducted a further experiment to define potential mechanisms through which exercise improves survival in this influenza virus model [19].

There appears to be a point of diminishing return however; as intense, prolonged exercise leads to a suppression of inflammation and reduction in critical anti-viral effector functions, including those of alveolar Mϕ's [78] and perhaps NK cells [73] resulting in increased morbidity and mortality. Indeed, a role for exercise-induced modulation of alveolar Mϕ function in response to HSV-1 infection has been elegantly described by Murphy *et al.* [10]. In that study, intranasal treatment with clodronate liposomes (which depleted alveolar Mϕ's) completely inhibited the protective effect of exercise on HSV-1 mortality and morbidity, suggesting a critical role of lung Mϕ's in the initial recognition and clearance of that virus. This contrast between moderate intensity exercise and prolonged or high-intensity exercise is supported by numerous studies [39104] which demonstrate a highly polarized Th2 response, as observed during prolonged intense exercise may be detrimental to influenza recovery [105].

As for the direct modulators responsible for a skewing of the immune response, exercise and other physical/physiological stressors promote upregulation of stress hormones, particularly catecholamines and glucocorticoids, which are capable of binding immune cells and influencing anti-viral immune functions. Dhabhar *et al.* suggests stress hormones exert a bi-directional effect on immune function, with the slightly elevated concentrations of glucocorticoids and catecholamines observed during acute stress providing crucial immunoenhancing and anti-inflammatory effects during pro-inflammatory reactions [89]. In contrast, chronic stress, which affects circadian rhythms and significantly elevates stress hormone concentration for prolonged periods, exerts immunosuppressive effects and increases susceptibility to infection. Indeed, adrenalectomy and glucocorticoid/catecholamine blockade exacerbates

inflammatory diseases and eliminates stress-induced enhancement of skin delayed-type hypersensitivity (DTH) reactions [89]. In addition to stress hormones, exercise increases IL-6 locally in muscle and systemically in blood [83] which subsequently induces IL1-ra, sTNF receptor and IL-10 that may limit excessive inflammation induced by respiratory virus infection.

It appears that the balance between inadequate and excessive stress responses is the result of evolutionary selective pressure. Acute stressors of limited duration, such as moderate intensity exercise or being chased by a predator, stimulate "fight or flight" responses priming the immune system for potential challenges imposed by the stressor. Chronic stressors, on the other hand, may be evolutionarily adaptive in that immunosuppression conserves energy potentially utilized for coping with the stressor; albeit at the cost of increased risk for infection [83]. During moderate exercise several transient changes occur in the immune system [75798273]. Moderate exercise increases the recirculation of immunoglobulins, and neutrophils and natural killer cells, two cells that play a critical role in innate immune defences. Animal data indicate that lung macrophages play an important role in mediating the beneficial effects of moderate exercise on lowered susceptibility to infection [25]. Stress hormones, which can suppress immunity, and pro- and anti-inflammatory cytokines, indicative of intense metabolic activity, are not elevated during moderate exercise [75].

Although the immune system returns to pre-exercise levels within a few hours after the exercise session is over, each session may represent an improvement in immune surveillance that reduces the risk of infection over the long term. Other exercise-immune related benefits include enhanced antibody-specific responses to vaccinations. For example, several studies indicate that both acute and chronic moderate exercise training improves the body's antibody response to the influenza vaccine [52536581]. In one study, a 45-min moderate exercise bout just before influenza vaccination improved the antibody response [52].

Several lines of evidence support the linkage between moderate physical activity and improved immunity and lowered infection rates: survey, animal, epidemiologic, and randomized training data [5365]. Survey data consistently support the common belief among fitness enthusiasts that regular exercise confers resistance against infection [81]. In surveys, 80%–90% of regular exercisers perceive themselves as less vulnerable to viral illnesses compared to sedentary peers [20,9920]. Animal studies are difficult to apply to the human condition, but in general, support the finding that moderate exercise lowers morbidity and mortality following pathogen inoculation, especially when compared to prolonged and intense exertion or physical inactivity. Mice infected with the herpes simplex virus, for example, and then exposed to 30-min of moderate exercise experience a lower mortality during a 21-day period compared to higher mortality rates after 2.5h of exhaustive exercise or rest [76]. Another study with mice showed that 3.5 months of moderate exercise training compared to no exercise prior to induced influenza infection decreased symptom severity and lung viral loads and inflammation [87].

Regular physical activity may lower rates of infection for other types of diseases, but data are limited due to low disease prevalence. For example, women with a high frequency of walking experienced an 18% lower risk of pneumonia compared with women who walked the least [87]. In the same cohort, women who reported running or jogging more than 2h per week had a reduced pneumonia risk compared with women who spent no time running or jogging [86].

Randomized experimental trials provide important data in support of the viewpoint that moderate physical activity reduces URTI symptomatology. In a randomized, controlled study of 36 women (mean age, 35 years), subjects walked briskly for 45-min, five days a week, and experienced one-half the days with URTI symptoms (5.1 vs. 10.8) during the 15-week period compared to that of the sedentary control group [84].

The effect of exercise training (five 45-min walking sessions/week at 60%–75% maximum heart rate) and/or moderate energy restriction (1200–1300 kcal per day) on URTI was studied in obese women (n = 91, BMI 33.1±0.6kg/m^2) randomized to one of four groups: control, exercise, diet, exercise and diet [84]. Energy restriction had no significant effect on URTI incidence, and subjects from the two exercise groups were contrasted with subjects from the two nonexercised groups. The number of days with URTI for subjects in the exercise groups was reduced 40% relative to the nonexercised groups (5.6 *vs.* 9.4), similar to the level of nonobese, physically active controls (n = 30, 4.8 days with URTI) [38].

In another study, 30 sedentary elderly women (mean age, 73 years) were assigned to walking or sedentary groups [11, 14]. The exercise group walked 30–40 min, 5 days per week, for 12 weeks at 60% heart rate reserve. Incidence of URTI in the walking groups was 21% compared to 50% in the calisthenic control group during the study (September–November).

A one-year randomized study of 115 overweight, postmenopausal women showed that regular moderate exercise (166 min per week, ~ 4days per week) lowered URTI risk compared to controls (who engaged in a stretching program) [88]. In the final three months of the study, the risk of colds in the control group was more than threefold that of the exercisers.

When successful, exercise training may exert anti-inflammatory influences through a reduction in visceral fat mass and the induction of an acute anti-inflammatory environment with each bout of exercise that over time becomes chronic [4558].

The anti-inflammatory effect of near-daily physical activity may play a main role in many health benefits, containing reduced cardiovascular disease, type 2 diabetes, various types of cancer, sarcopenia, and dementia [6,8,34,49, 50, 9868]. This is an exciting area of scientific endeavour, and additional research is needed to determine how immune

perturbations during each exercise bout accumulate over time to produce an anti-inflammatory influence. As with URTI, multiple lifestyle approaches to reducing chronic inflammation should be employed with a focus on weight loss, high volume of physical activity, avoidance of smoking, and improved diet quality. Maintaining leanness and a physically active lifestyle during adulthood reduces systemic inflammation, an underlying factor in multiple chronic diseases.

Although methodology varies widely and evidence is still emerging epidemiologic and randomized exercise training studies consistently report a reduction in URTI incidence or risk of 18%–67%. This is the most important finding that has emerged from exercise immunology studies during the past two decades [67].

A one-year epidemiological study of 547 adults showed a 23% reduction in URTI risk in those engaging in regular versus irregular moderate-to-vigorous physical activity [54]. In a group of 145 elderly subjects, URTI symptomatology during a one-year period was reduced among those engaging in higher compared to lower amounts of moderate physical activity [56]. During a one-year study of 142 males aged 33–90 years, the odds of having at least 15 days with URTI was 64% lower among those with higher physical activity patterns [16]. A cohort of 1509 Swedish men and women aged 20–60 years were followed for 15 weeks during the winter/spring [101]. Subjects in the upper tertial for physical activity experienced an 18% reduction in URTI risk, but this proportion improved to 42% among those with high perceived mental stress.

Regular physical activity should be combined with other lifestyle strategies to more effectively reduce URTI risk. These strategies include stress management, regular sleep, avoidance of malnutrition, and proper hygiene [17]. URTI is caused by multiple and diverse pathogens, making it unlikely that a unifying vaccine will be developed [51]. Thus, lifestyle strategies are receiving increased attention by investigators and public health officials, and a comprehensive lifestyle approach is more likely to lower the burden of URTI than a focus on physical activity alone.

The Risk of Viral Infection and RA and RHD Patients

The relationship between RA and infectious diseases is paradoxical and includes two different directions. First, there is a dangerous connection between infections and RA in two ways; inactive anti-infectious activity characterizes patients with RA, and infections are suspected to promote autoimmunity [5]. Furthermore, virus loads RA patients are more positive compared to others (whereas 28% of RA samples were positive for two or three viruses) [3, 48]. Specifically, a study on a total of 24,117 cases of incident RA (mean age 54.7 years, 18,688 [77.5%] women) has concluded that respiratory viral infections in the population were related to a higher number of incident RA over time, specifically in women and older patients, and it suggests respiratory viral infections can be a severe risk for the development of RA [23].

In addition, patients carrying RA reported a higher risk of infections and viruses compared to the whole population. A study conducted on 609 patients with or without RA has concluded a higher risk of infections on those who carry RA [61]. Likewise, another study concluded that patients with inflammatory polyarthritis reported a higher risk of hospitalized infection compared to healthy peoples [7]. The impairment of the immune system generated above showed high risks, and higher disease activity was associated with a higher probability of developing infections [24].

Cardiovascular diseases, interstitial lung disease, diabetes mellitus, renal failure, and chronic obstructive pulmonary disease are all concomitant disorders associated with an increased incidence of infections in RA [361]. These are other factors that sometimes complicate the condition for RA [106]. Unfortunately, because of the lack of data about the risk of Viral infection in RHD patients, it stayed unknown for us whether there is viral risk on RHD or not.

The Impact of Drugs for RA, RHD on Viral Infections

Corticosteroids:

Corticosteroids prevent the immune system to respond and delay the clearance of pathogens, and also, they prevent the host inflammatory response, which may be a main factor to lung damage and occurrence of ARDS [4] MERS [102] SARS-CoV [70] outbreaks; then, that causes lung inflammation and diffuse alveolar damage [77]. Whereas, the past literature concluded the main negative effects of corticosteroids in managing this type of infection. A study in 2019, concluded that corticosteroids were associated with higher mortality (risk ratio [RR] 1.75, 95%) in patients with influenza pneumonia [94]. Thus, there is no clear evidence to prove that patients with COVID-19 infection get benefit from corticosteroids, and in contrast, they may be harmed with such therapy [91].

NSAIDs:

Nonsteroidal anti-inflammatory drugs (NSAIDs), a drug class that reduces pain, decreases fever, prevents blood clots, and in higher doses, decreases inflammation. Comparing normal rats with diabetic rats shows that ibuprofen induces an overexpression of ACE2 in diabetic rats [57]. Considering this situation to rats, the risk COVID-19 may be higher for patients because “the increased expression of ACE2 would facilitate infection with COVID-19 … and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19” [35]. However, there is not a complete certainty whether it makes COVID-19 infection worse or not.

Aspirin:

We only have one data from the NHS, British largest health website, according to which high-dose aspirin can make coronavirus (COVID-19) worse, and in contrast, low-dose aspirin does not act as an NSAID. You can continue to take this medicine as usual, whether you have symptoms of coronavirus or not.

csDMARDs:

There are some comprehensive retrospective studies about csDMARDs- such as methotrexate,

sulfasalazine, leflunomide, hydroxychloroquine, gold salts- that concluded csDMARDs are not associated with increasing infection risks [10047]. Similarly, recent study confirmed the same results in patients receiving MTX [39, 40, 41 47, 100].

bDMARDs:

Most of the studies suggest that RA patients who are treated with bDMARDs have higher risk of infection in comparison with csDMARDs [28, 92, 97]. However, a study concluded that anti-tumor necrosis factor (TNF) used to deal with patients carrying RA, may not be at any specifically increased risk of influenza [30].

tsDMARDs:

The use of Janus Kinase (JAK) is slightly safer than bDMARDs, but often, it increases the risk of viral infections either as new events or reactivation of latent conditions; specifically, the risk of HZV infection has reported an increase in patients taking JAKs compared to biological drugs [113]. However, no date including the risk of respiratory virus infections carried by JAK inhibitors is available.

The Management of COVID-19 and Anti-RA and RHD Drugs

COVID-19, similar to SARS, Middle East respiratory syndrome (MERS) virus, attacks the lower respiratory system to cause viral infection, with other impacts on the gastrointestinal system, kidney, liver, central, heart, and central nervous system, which may lead to organ failures [62]. Unfortunately, approved targeted therapies and vaccines to treat SARS-CoV-2 infection have not been found yet even though the management of SARS-CoV-2 is supportive, and some compounds are now investigated for the treatment of COVID-19 [129]. In relation to Bacterial infections, If a treatment is required for a secondary bacterial infection then a range of antibiotics can be used such as penicillin (ampicillin plus sulbactam [Unasyn], piperacillin plus tazobactam [Zosyn]), macrolides (azithromycin), cephalosporins (ceftriaxone [Rocephin]), aminoglycosides (tobramycin) and glycopeptides (vancomycin [Vancocin HCL]) for example. Often a combination of two different antibiotics is used, but there is not roky evidence to approve them as a direct treatment to COVID-19.

Lopinavir-ritonavir, interferon, and ribavirin:

The only attempt undergoing currently to manage COVID-19 is to use the same treatments (lopinavir-ritonavir, interferon, and ribavirin) of the SARS-CoV and Mers-CoV because of the similarities between COVID-19 and these viruses [60]. Lopinavir-ritonavir was given to the patients carrying COVID-19, and the viral loads and its clinical symptoms started to decrease [111]. Also, a study finding revealed that remdesivir and chloroquine have a high effectiveness in the control of COVID-19 infection in vitro [36].

Chloroquine and hydroxychloroquine:

Chloroquine and hydroxychloroquine are well known to result in a potential effect of the drugs on entry and post-entry stages of the SARS-CoV. Chloroquine used for the treatment of rheumatoid arthritis and lupus erythematosus is effective to prevent and treat malaria, and it has potential broad-spectrum antiviral activities by interfering with the glycosylation of cellular receptors of SARS-CoV, so it may have potent efficacy in treating patients with COVID-19 [37]. hydroxychloroquine treatment for COVID-19 is importantly associated with viral load reduction/disappearance in patients and its impact is increased by azithromycin [121]. In addition, hydroxychloroquine is demonstrated to be the best option in managing SARS-CoV-2 infection [22]. But in 2020 two Journals Retract Studies on HCQ, Heart Disease in COVID-19 [130].

IL-6 and IL-1 blockers:

One of the results of COVID-19 is producing release of pro-inflammatory mediators (CRS) that leads to lung damage and multiorgan failure [122]. The high level of cytokines proposed to have diverse affection of lymphocytes count, which exhausts T-cells functionality [96]. As a result, an effective immune system works against the viral infections via cytotoxic cells and viral clearance by CRS, so COVID-19 may have a worse condition. IL-6 and IL-1 have a great positive role in hyperinflammatory condition. As proposed by a study that IL-6 and IL-1 can be used as treatment options of COVID-19 without increasing adverse condition [119]. Tocilizumab, which is mainly used for treatment of RA and which includes (IL-6 receptor antagonist), has an effective role to improve clinical symptoms and repress the deterioration of severer COVID-19 patients [41].

TNF Inhibitors:

Previously stated, because of the downregulation of ACE2, which can be a result of SARS-CoV-2, angiotensin II is increased so that lung injury may happen when ACE2 expression to outside stimulus decreases [27]. Inducing the TNF-a-converting enzyme (TACE)-dependent by viral spike protein lets the virus penetrate into the cell [112]. As a result, suggesting of TNF inhibitors to COVID-19 patients may result in reducing SARS-CoV-2 infections and lung damage [44].

Janus Kinase Inhibitors:

As described before, the SARS-CoV-2 essentially uses the SARS-CoV ACE2 enzyme for host cell entry [127], and some of characterized regulators of clathrin-mediated endocytosis are part of AP2- associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) [90]. When AAK1 is inhibited, the virus cannot access lung cells [93]. However, as study has concluded that these compounds, such as sunitinib and erlotinib, result in serious side-effects, and their data infer high doses to inhibit AAK1 effectively, so according to the study, these drugs would not be a safe therapy for a population of sick and infected people [13].

By contrast, one of the six high-affinity AAK1-binding drugs, which is the janus kinase inhibitor baricitinib, also binds the cyclin G-associated kinase, another regulator of endocytosis, and the plasma concentration of baricitinib on therapeutic dosing is sufficient to inhibit AAK1, so it is suggested that it could be tested, using an suitable patient population with COVID-19, to reduce both the viral entry and the inflammation in patients [9].

Furthermore, IFN, one of the most powerful innate immune response, prevents virus to replicate, reduce tumour cell mass, and control disease symptoms, and IFNs are commonly used to in anti-HBV and HCV therapy, and it suggested that it might have the same effectiveness in SARS, COVI-19, respectively [1].

Finally, evidence still needed to be collected and tested about the use of Baricitinib, which is a drug to treat patients with RA, whether it is effective or not in the treatment of COVID-19. More study should be conducted regarding this purpose.

Conclusion

After reviewing many relevant studies, we have occluded that regular physical activity, if combined with other lifestyle techniques including stress management, regular sleep, proper hygiene, and avoidance of malnutrition, may exceedingly reduce URTI risk and viral infections, and exercise training improves body's antibody response to vaccination. Furthermore, studies about the relationship of COVID-19 and anti-RHD drugs, on one hand, and COVID-19 and anti-RHD drugs, on the other hand, even though it soon to understand the relationship in detail, but some important points can be suggested: lopinavir-ritonavir, interferon, penicillin, ribavirin-remdesivir, chloroquine, hydroxychloroquine, azithromycin, IL-6 and IL-1 blockers, tocilizumab, and TNF inhibitors may have an effective role in the treatment of COVID-19; but, sunitinib and erlotinib may not be safe to COVID-19 infections; further study should be conduct in detail with the impact of each of these drugs if we want to use them in the treatment of COVID-19 infections; anti-bacterial infection drugs need more study to approve whether they are effective or not to treat COVID-19. Even though COVID-19 is a dangerous infection and leads to damage to other major organs, including lung, brain, liver, heart and kidneys, we need patience to get approved drugs and therapy to treat the infection.

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ИЗУЧЕНИЕ ПРОЛОНГИРУЮЩЕГО ЭФФЕКТА ЗА СЧЕТ ВЗАИМОДЕЙСТВИЯ ПОЛИКОМПЛЕКСНОГО КОМПОЗИТА С ЛЕКАРСТВЕННЫМИ ВЕЩЕСТВАМИ

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Abstract. The nature of the formation of polycomplexes and polycomplex composites was investigated by IR spectroscopy, and the kinetics of the release of drugs from the base were studied by the pharmacokinetic method. Experimental data obtained under “in vitro” conditions showed a prolonging effect in comparison with the initial polymers (Na – CMC) and hydrophobic petrolatum (control), which can be explained by the interaction of drugs with polycomplexes and polycomplex composites. It was found that a high prolonging effect of drugs due to their slow release from the base layers of polycomplex composites.

Аннотация. Методом ИК-спектроскопии исследована природа формирования поликомплексов и поликомплексных композитов и изучены фармакокинетическим методом кинетика высвобождения лекарственных веществ из основы. Экспериментальные данные полученные в условиях «in vitro» показали пролонгирующий эффект по сравнению с исходными полимерами (Na–КМЦ) и гидрофобного вазелина (контроль), что можно объяснить взаимодействием лекарственных веществ с поликомплексами и поликомплексными композитами. Установлена, что высокое пролонгирующее действие лекарственных препаратов благодаря их медленному высвобождению из слоев основы поликомплексных композитов.

Keywords: sodium carboxymethyl cellulose, urea-formaldehyde oligomer, polyanion, polycation, polycomplex, polycomplex gel, dermatol, drug, ointment, structure, properties, prolongation.

Ключевые слова: натрийкарбоксиметилцеллюлоза, мочевино-формальдегидный олигомер, полианион, поликатион, поликомплекс, поликомплексный гель, дерматол, лекарственный препарат, мазь, структура, свойства, пролонгация.

К одному из наиболее значимых направлений использования полимеров медицинского назначения, несомненно, относится использование их в качестве различных матриц для доставки лекарственного вещества в организм или в определенный участок тела. Для этих целей применяется различные полимеры как природного, так и синтетического происхождения, которые используются в различных формах: капсулы, гели, мази, перевязочные материалы и т.д. Тем не менее, создание новых типов носителей лекарственных веществ и покрытий на рану, изучение их свойств и применения является весьма актуальным в связи с неуклонным развитием медицинских технологий и возрастающим требованиям к средствам отечественного производства [1,2, с. 200].

Весьма интересными, перспективными в этом аспекте являются поликомплексные композиты на основе производных целлюлозы - полианиона натрийкарбоксиметилцеллюлозы (Na-КМЦ) и синтетических мочевиноформальдегидных олигомеров (МФО) который находят применение как основы для мягких лекарственных препаратов.

В качестве основного объекта исследования использовали очищенную Na-КМЦ Наманганского химического завода, полученную методом гетерогенной твердофазной этерификации сульфитной древесной целлюлозы