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Diabetes mellitus and COVID-19 in the post-acute phase patients - possible links with physical and rehabilitation medicine and balneotherapy

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Abstract

Background. The outbreak of COVID-19 - **CO**rona**VI**rus **D**isease 2019 - has become a significant threat to public health worldwide, with high contagious capacity and varied mortality in different countries. Diabetes mellitus (DM/ diabetes) is among the most frequently reported comorbidities in patients with COVID-19. In the field of physical and rehabilitation medicine and balneotherapy, specific rehabilitation procedures, natural therapeutic factors, and physical activity are known to be contributive to mitigating some of the DM clinical-patho-biological consequences.

Objective. This systematic review aims to rigorously select related articles and identify within their content, the main possible interferences between DM and COVID-19's pathological mechanisms, and to discuss the value of physical and rehabilitation medicine and balneotherapy in the post-acute COVID-19 recovery of the surviving patients.

Methods. This systematic review, based on the **P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses (PRISMA) guidelines, searched for open-access articles published in English, between January and May 2020, from the following databases: Cochrane, Elsevier, PubMed and Web of Science. The contextually searched syntax used was "DIABETES AND COVID-19". The selected articles were analyzed in detail regarding both pathologies: COVID-19 and DM. The meta-analysis proceeded was designated to estimate the prevalence of DM among COVID-19 patients.

Results. Our search has been conducted on five stages, described by a PRISMA adapted flow diagram. Within the first stage, using the syntax mentioned above resulted in **1,133** articles. After eliminating, in the second stage, all the inevitable redundancies remained **1,058** articles. In the third stage, we performed a PEDro qualitative analysis score weighted selection of all the papers and were kept **91** articles. In the fourth stage, were selected relevant issues for a meta-analysis regarding the prevalence of DM diabetes among COVID-19 cases, resulting **32** papers. The fifth stage of the PRISMA adapted flow diagram was dedicated to the analysis of the data regarding the use of natural therapeutic factors, physical exercises within the ensemble of case-specific indicated procedures used for DM, and COVID-19 patients in rehabilitation wards. For enhancing the bibliographical sources pool, we added from external, free found sources, another **15** articles.

Discussion/ Limitation. COVID-19 is an acute illness condition and DM is a chronic one. Therefore, it is difficult for now, to have enough data enabling us to see all the repercussions of COVID-19 and to completely understand the significance of physical and rehabilitation medicine and balneotherapy, which applies in COVID-19 post-acute DM patients.

Conclusions. This paper overviews the current state-of-the-art knowledge in the approach of DM /diabetes as COVID-19 comorbidity, with a focal point on the roles of natural therapeutic factors, physical exercises within the ensemble of case-specific indicated procedures used for DM and COVID-19 patients in rehabilitation wards, for possible actual and future connexions with the comprehensive management/ rehabilitation of such both chronic and post-acute survivors.

Key words: *diabetes mellitus/ diabetes, COVID-19, SARS-CoV-2, rehabilitation and physical medicine, natural therapeutic factors, balneotherapy,*

Introduction

First, China, then almost all the rest of the world faces an outbreak that is a new, significant risk for human health and a considerable challenge for the healthcare systems. The widespread distribution of the new virus has led to significant concern and changed our lives, globally.

Highly contagious and with the capability to get transmitted during the asymptomatic phase, this virus achieved rapid human-to-human infectivity, beyond geographic regions, resulting in a pandemic. The first case of COVID-2019, occurred on December 8, 2019, in Wuhan, in the Hubei Province of China (1). Since then, within a short span of just over six months, the infection has spread to more than 200 countries across the world, counting for over 12 million infected people and almost 500,000 deaths.

In Romania, from February 26, when the first case appeared, until July 10, 2020, over 30.000 COVID-19 patients have been diagnosed, with over 1.800 deaths[1].

DM is one of the leading causes of morbidity, globally: 463 million people have diabetes worldwide, respectively more than 59 million people in the EUR Region, and it is anticipated to rise substantially over the next decades. In Romania, out of 14,545,800 adults, there are 1,278,300 cases of diabetes, with a prevalence of 8,8% (data of February 2020[2]).

Several investigations have shown a higher susceptibility to some infectious diseases in diabetics, such as Staphylococcus aureus and Mycobacterium tuberculosis, probably owing to the dysregulated immune system (2)**.** The COVID-19 pandemic and diabetes have also interfering immunopathological features. The subject of our article aims to clarify the prevalence of diabetes between COVID-19 patients, to understand the mixed pathological influences of the two diseases and to find answers to the question on how natural therapeutic factors and physical exercises, within the ensemble of case-specific, indicated procedures, can be helpful for DM and COVID-19 patients' approach in rehabilitation wards.

METHOD

Search Strategy

To find relevant *open access* studies, international databases including Cochrane, Elsevier, PubMed, and Web of Science were searched for articles published from 01 January until 15 May 2020. The following search terms were used DIABETES AND COVID-19. Additionally, extra searches were performed in the reference lists of included studies, in purpose to avoid missing papers.

Inclusion and Exclusion Criteria

Any relevant articles that reported clinical characteristics and epidemiological information on COVID-19 DM patients were included in the analysis. All articles with any design (reviews, randomized controlled trials, non-randomized controlled trials, case-control studies, cross-sectional studies) were included. Articles were excluded if they didn't reach at least 50 points from 100 in our qualitative analysis using a PEDro analysis score weighted selection.

RESULTS

Our search has been conducted on five stages, described by a PRISMA adapted flow diagram (see **Figure 1**). Within the first stage, using the following combinations of keywords: **diabetes AND COVID-19**, it resulted in 1,133 articles (see **Table 1**). After eliminating all the inevitable redundancies - **75** articles (i.e., same article found in different queried databases), in the next stage, we have obtained **1,058** articles. After evaluating the full texts using a PEDro analysis score weighted selection (see **Table 2**), **967** studies were excluded due to results obtained from our evaluation. In the full-text analysis were included the remained **91 articles**, from which **32 articles**, with prevalence data, were then selected for meta-analysis. The fifth stage of the PRISMA adapted flow diagram was dedicated to analyzing data regarding the use of natural therapeutic factors, physical exercises, and other medical rehabilitation procedures for DM and COVID-19 patients. In this stage, we added from external sources another **15** citations.

[1] https://www.worldometers.info/coronavirus/

[2] https://idf.org/our-network/regions-m2embers/europe/members/154-romania.html

Meta-analysis - diabetes prevalence in COVID-19 patients, China vs other countries

OpenMeta-Analyst source (3) was used to perform the meta-analysis of data collected in **Table 3**. Non-China Studies show a diabetes prevalence of 23,4% among COVID-19 patients (see **Figure 2**) and China Studies conclude for a diabetes prevalence of 10,0% for COVID-19 patients (see **Figure 3**).

COVID-19 pathology

SARS-CoV-2 (**S**evere **A**cute **R**espiratory **S**yndrome - **Co**rona**v**irus-2) causes COVID-19 (as named by the World Health Organization - WHO), a pandemic infectious disease. Human coronaviruses are highly contagious pathogens that cause viral respiratory infections.

The human-to-human transmission was confirmed, and this disease has spread rapidly throughout the world, as there is no pre-existing immunity and also no treatment or vaccine to prevent, cure or stop, or reduce the astonishing prevalence (4).

Depending on the clinical features of COVID-19, patients are generally divided in mild (low-grade fever, cough with or without hemoptysis, malaise, rhinorrhea, sore throat, nausea, vomiting, diarrhea – but without any radiological features of pneumonia and absence of mental changes), moderate (fever, respiratory symptoms including dry cough and shortness of breath that may emerge along with the radiological features), severe (dyspnea, respiratory frequency ≥ 30/minute, blood oxygen saturation below 93%, PaO2/FiO2 ratio < 300, and/or infiltrates >50% of the lungs field within 24-48 h) and critical (usually develops after 7 days in patients with mild/moderate/severe COVID-19 with features of Acute Respiratory Distress Syndrome (ARDS) requiring mechanical ventilation along with the presence of multiorgan dysfunction failure, metabolic acidosis, and coagulation dysfunction) (5,6).

There are regional variations in the mortality rates, and these estimates are rapidly changing as more data are becoming available. Possibly, an overreaction of the immune system leading to autoimmune aggression of the lungs could be involved in the most severe cases of ARDS.

The typical pulmonary changes in the imaging appear were interstitial pneumonia with primarily bilateral involvement and multiple patchy, flocculent, or strip ground glass shadow, occur. In most patients, the leukocyte count is in the normal range and lymphocyte count is generally reduced (7).

The SARS-CoV-2 virus spreads rapidly. Originating of every index case, 2-3 people acquire the infection, the virus reproduction number (R0), or transmission rate, being 2.24 - 3.58. In contrast, H1N1 seasonal influenza, in 2009, had an R0 of 1.46-1.48.

The incubation period for SARS-CoV-2 ranges from 2 to 14 days. Asymptomatic spread occurs before the onset of the symptoms. Transmission is possible through respiratory droplets and fomites. In mid-January 2020, studies of clusters of infected family members and medical workers confirmed person-to-person transmission. Close contact with symptomatic individuals constitutes a significant risk for extensive spread.

The first transmission way is through respiratory droplets and direct contact. In one experiment, the viable virus was detected in aerosols for up to three hours, with an estimated half-life of 1.1 hours. The second is through indirect contact — this occurs when droplets containing SARS-CoV-2 land on the surface of tabletops, doorknobs, telephones, and other inanimate objects (8). The virus was detected on surfaces for days after application, with viable SARS-CoV-2 identified on plastic and stainless steel up to 72 hours. SARS-CoV-2 RNA was detected in blood and stool, and it is unclear whether the exposure to non-respiratory bodily fluids produces infection (9,10). The fecal-oral transmission was first reported in a COVID-19 case in the USA. Subsequent studies detected SARS-CoV-2 in the feces and anal swabs of COVID-19 patients. Moreover, 23.3% of COVID-19 patients remained SARS-CoV-2 positive in feces, even when the viral RNA was no longer detectable in the respiratory tract. SARS-CoV-2 has also been detected in gastric, duodenal, and rectal epithelia (11). Further studies detected SARS-CoV-2 in the tears and conjunctival secretions.

SARS-CoV-2 differs from SARS-CoV by 380 encoded amino acids; so, at the level of the binding domain of the viral protein (S) that interacts with the human angiotensin-converting enzyme 2 (ACE2) receptor, differences appear in five vital amino acids. Viral S proteins are targeted for the development of therapies and vaccines, which are significant determinants of host tropism (12–14).
Angiotensin-converting enzyme 2 [ACE2 – a component of the renin-angiotensin system (RAS)] (15)expressed by epithelial cells of the lung, intestine, kidney, and blood vessels are substantially increased in patients with type 1 or type 2 diabetes, treated with ACE inhibitors and angiotensin II type I receptor blockers (ARBs) (16). The virus uses ACE2 as a receptor for ingress into host pneumocytes (17). Thus the pathogenesis of COVID-19 entails entry of SARS- CoV-2 via the respiratory system and lodgment in the lung parenchyma (18).
After fusion occurs, the type II transmembrane serine protease (TMPRSS2), which is present on the surface of the host cell, will clear the ACE2 and activate the receptor-attached spike-like, S proteins. Activation of the S proteins leads to conformational changes and allows the virus to enter the cells. TMPRSS2 is a serine protease highly expressed within the lung and gastrointestinal tissues, including stomach, small and large bowel, pancreas, and liver. The fact that the renin/angiotensin system ACE and ACE2 are at the center of the discussion is probably due to its potential dual effect in different phases of COVID-19 (19). The primary role of the positive RAS axis, through ACE, is to augment the sympathetic nervous system's tension, causing vasoconstriction, increasing blood pressure, and promoting inflammation, fibrosis, and myocardial hypertrophy. The negative regulatory axis mediated by ACE2 can antagonize these effects (16).
The RAS system has an essential role in maintaining homeostasis in humans but also is the primary correspondent for an envelope anchored spike protein. In the RAS system, the same component can produce opposite physiological effects through different pathways. ACE2 protects against organ damage, prevents hypertension, and has beneficial effects in cardiovascular diseases - including the related pathology encountered in diabetes (16).
The renin-angiotensin-aldosterone system (RAAS) maintains plasma sodium concentration via feedback from blood pressure, baroreceptors, and sodium and potassium levels. There is particular concern about hypokalemia, which increases vulnerability to various tachyarrhythmias, in COVID-19, due to the interaction of SARS-CoV-2 with the RAAS. (20). The RAAS system is largely interferent with hypertension, heart failure, and DM, pathologies. ACE and ARB drugs, based upon substantial evidence of efficacy, are commonly used in the management of hypertension, heart failure, post-myocardial infarction care, and to slow the progression of renal disease associated with diabetes (21).

Diabetes as a comorbidity for COVID-19

Diabetes seems to be a risk factor for acquiring the new coronavirus infection, as in the case of other coronavirus infections, such as East respiratory syndrome (MERS-CoV) severe acute respiratory syndrome (SARS) (22). Supplementary, for diabetic patients, dysregulation of glucose metabolism is an aggravating factor of pneumonia, which works as an amplification loop. Meanwhile, diabetic complications signify the seriousness of diabetes, and these patients with diabetic complications showed a higher mortality rate, which further proves that diabetes is a risk factor for the prognosis of COVID-19 (23). Hyperglycemia may precede the symptoms of COVID-19 and predispose to acute metabolic complications, such as ketoacidosis and hyperosmolar coma (24).
Hyperglycaemia and diagnosis of Type 2 DM are independent predictors of mortality and morbidity in patients with COVID-19. The explanation is that these patients have a state of metabolic inflammation that predisposes them to an enhanced release of cytokines. For COVID-19, a cytokine storm (that is, significantly elevated levels of inflammatory cytokines) acts in the multi-organ failure in patients with severe disease (22). Moreover, the ”T2DM ... chronic and systemic inflammation, with the accompanying presence of circulating and dysregulated inflammatory biomarkers (... cytokine and lipid group ...); which in turn is associated with abnormal clot formation

... may in part be responsible for a hypercoagulable state and vascular dysfunction" (25). Thus, dysfunctional pro-inflammatory cytokine responses in diabetic patients might also be the underlying cause of severe COVID-19(26). This is to be emphasized as, however, "Many patients with severe COVID-19 present with coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy... Coagulopathy in patients with COVID-19 is associated with an increased risk of death."(27).

Rehabilitation, physical medicine and balneotherapy values in approaching diabetic post-COVID-19 patients

Limited physical effort while performing daily activities is one of the key factors affecting the increase in the risk of type 2 diabetes. Taking into account diabetic complications such as neuropathy, and micro-and macroangiopathy, individually planned rehabilitation programs should be considered in the treatment process (28).

The adaptive response of the human organism to exercise in respiratory physiotherapy (conditioned by many parameters, including age, sex, nutritional status, ambient temperature, body position, ability to perform the type of effort, hemoglobin mass, extracellular fluid volume, the heart condition, the lung condition) bronchial clearance and mucociliary defense mechanisms are in the center of recuperative interventions in aerosol therapy. The techniques of inhalation therapy, speleotherapy, field/forest cure are recommended in respiratory rehabilitation in many balneary resorts (29).

Pulmonary Rehabilitation has an extremely important new role and application in the treatment of COVID-19. „The purpose of pulmonary rehabilitation in COVID-19 patients is to improve symptoms of dyspnea, relieve anxiety, reduce complications, minimize disability, preserve function, and improve quality of life. Pulmonary rehabilitation during the acute management of COVID-19 should be considered when possible and safe and may include nutrition, airway, posture, clearance technique, oxygen supplementation, breathing exercises, stretching, manual therapy, and physical activity" (30). In turn, in the post-acute phase of COVID-19, pulmonary rehabilitation takes the main role in the medical assistance process and must be correctly addressed.

Besides, patients with neuromuscular diseases may have risk factors for developing severe forms of COVID-19, and receiving prolonged intensive care (31) may worsen their functional prognosis. It is essential to develop a preventive approach. Maintaining joint flexibility, muscle strength, and endurance is recommended in many neuromuscular diseases through regular in-house or office care sustained by health professionals. It is noted that some patients with neuromuscular disorders are not autonomous in daily life but have a social environment that effectively compensates for this lack of autonomy.

Physiotherapy plays an important role in the treatment process through the use of methods such as kinesiotherapy, balneotherapy, physical therapy, (in some cases) massage, and, systematic exercise. Each physical activity should be appropriately adjusted to the existing complications, and the appropriate dosage of antidiabetic – and addressed to other co-morbidities, if existing, in a specific clinical case – medication should be taken into account.

Balneotherapy is beneficial for patients whose oxidative/antioxidative balance system is damaged, such as those with DM and coronary heart disease. Also, balneotherapy has long been used for treating obesity and its comorbidities. Enlargement of adipose tissue has been linked to a dysregulation of adipokine secretion and adipose tissue inflammation. Balneotherapeutic sulfur baths have been shown to influence antioxidative status (32). The importance of antioxidant defense mechanisms in several degenerative diseases (atherosclerosis, diabetes, cataract, etc.) is largely explained and is known as normalization effects conditioned by balneotherapy, including/ especially its way of intervention represented by oral ingestion (Crenotherapy) (33).

Studies regarding balneotherapy effects in the case of obese patients induce a significant decrease in body weight, body mass index, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, glycemia, and serum levels of leptin and high-sensitivity C-reactive protein" (34). A balneotherapeutic iodine supply can contribute to an improvement of the protective mechanisms combating free-radical-induced, atherogenic, or otherwise-damaging lipid peroxidations" (35). Platelet Glutathione (GSH) synthesis appeared to be induced in response to oxidative stress; lowered glutathione peroxidase (GPX) activities indicated that the antioxidative defense system was impaired and platelet glutathione metabolism was partially improved by 4 weeks balneotherapy (36–38).

Speleotherapy and halotherapy also have positive impacts on oxidative stress balance and immunological parameters (39).

DISCUSSION

The WHO declared a global pandemic on 11 March 2020 (40). Tracking the spread of the infection indicates an exponential pattern in many countries, including Italy, Spain, USA. In comparison, sub-exponential growth patterns of COVID-19 were observed in Singapore, Korea, and many other countries as described in recent studies. (41).

The proportion of severe versus common cases of COVID-19 infection is approximately 1:4 (42). Clinical presentation of COVID-19 ranges from asymptomatic to severe pneumonia. In COVID-19 patients with diabetes, pulmonary dysfunction involving: lung volume, pulmonary diffusing capacity, control of ventilation, broncho-motor tone, and noradrenergic bronchial innervation have been reported, which account for the propensity of poor outcomes (43).

Based on the WHO analysis of 55,924 confirmed cases, fever (87.9%), dry cough (67.7%), and fatigue (38.1%) are common symptoms of the infection. Myalgia or arthralgia (14.8%) are also among typical symptoms. Another study presents symptoms in the general population as fever (98%), cough (76%), dyspnea (55%), and myalgias or fatigue (up to 44%) (17). Environmental factors such as air pollution and smoking and comorbid conditions (hypertension, diabetes mellitus, and underlying cardio-respiratory illness) increase the severity of COVID-19 (44). The prolonged neuromuscular blockade, vitamin deficiencies, electrolyte disturbances, and drug-related neuromuscular disorders were usually included in the differential diagnosis list for polyneuropathy in COVID-19 patients (45). Diabetes patients have a higher overall risk of infection that results from multiple perturbations of innate immunity and propensity to inflammatory mediated hypercoagulability and vascular dysfunction, as mentioned above. While data are emerging, it seems that the mortality rate is of the order of 1–2% (40).

Diabetes is a known risk factor for poorer outcomes in patients who develop a respiratory disease (46). Covid-19 and diabetes represent two devastating pandemics with different presentation (acute vs. chronic) and transmission (communicable vs. non-communicable), but which may be much closer than previously thought (47).

Two of the coronavirus receptors, ACE2, and DPP4 are also transducers of metabolic pathways regulating glucose homeostasis, renal and cardiovascular physiology, and inflammation. Two recent meta-analyses had shown that DPP4 inhibitors increased the risk of various infections while a third meta-analysis showed that there is no increased risk of infections with DPP4 inhibitors. Whether DPP4 inhibitors increase the susceptibility or severity of SARS-CoV-2 infection needs to be studied in future trials (48).

The interconnection between ACE2, renin-angiotensin system (RAS) signaling, aging, DM, hypertension, and severity of COVID-19 may not be as simple as it may seem. A meta-regression analysis showed that the association between DM and poor outcome was interdependent with age and hypertension. Feng and colleagues are correct when they point out that ARB treatment may increase ACE2 in possible COVID-19 comorbidities such as hypertension and diabetes. However, the speculation that such treatment enhances infection with this virus is without scientific evidence. The suggestion to replace ARB therapy with alternative anti-hypertensive medications does not take into consideration that such alternatives, like the use of calcium channel blockers, lack the major pleiotropic beneficial characteristic of ARBs. The argument that the ARB-dependent ACE2 upregulation may directly enhance SARS-CoV-2 infections ignores the complexity of ACE2 function and metabolic regulation with its inconsistent and paradoxical findings, including findings of multiple ACE2 substrates beyond Angiotensin II and SARS-CoV-2. ACE2 is not only a receptor for SARS-CoV-2, but also inhibits the Angiotensin cascade contributing to control excessive AT1R activity (49)**.**

Metabolic syndrome-related conditions such as diabetes, obesity, and atherosclerosis based hypertension and cardiovascular, diseases can be intimately linked to COVID-19 pathogenesis (50). So far, hyperglycemia was noted in 51% of COVID-19 cases. Hyperglycemia was also observed in patients with SARS in 2003, partly because the virus leads to transient impairment of pancreatic islet cell function (51).

Acute lung damage and ARDS are partly due to the host immune response (52)**.** The inflammatory caused by SARS-CoV-2 and the application of glucocorticoids resulted in fluctuations in blood glucose, which was related to pathogenesis.

Gastrointestinal symptoms caused by SARS-CoV-2 exacerbated malnutrition in elderly patients, possibly as ACE2 was also highly expressed in the digestive tract. So the gastrointestinal tract was also the main target of the SARS-CoV-2 attack. Clinically, in addition to respiratory symptoms, digestive symptoms were the most frequent in aged persons with COVID-19. Diarrhea, mild abdominal pain, nausea, vomiting, poor appetite, and other symptoms were widespread (31).

Pathophysiologically, patients with COVID-19 usually present dehydration due to fever and diarrhea, hypotension, secondary bacterial and fungal infections, and longtime bed rest. A recent publication has also discussed that patients with severe COVID-19 usually present with high concentrations of IL2, IL6, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα cytokines. The cytokine storm could be linked to disease severity and adverse outcomes. The rhabdomyolysis and the subsequent electrolyte disorder and acidosis are fatal. Previous studies have described rhabdomyolysis in patients with viral infections, such as Influenza A and SARS-associated coronavirus (53). To handle the elevated levels of IL-6, tests have been carried out using Tocilizumab, a monoclonal antibody that targets IL-6 and it seems that it can improve the prognosis in COVID-19 infected patients with severe respiratory distress. On the other hand, the efficacy of glucocorticoid and other anti-inflammatory drugs that have been used for handling the condition of COVID-19 patients has been questioned.

Inflammatory markers are elevated in COVID-19. It is of great interest that pioglitazone can produce an anti-inflammatory effect as has been assayed through high sensitive C-reactive protein within short term intervals after starting therapy (54)**.**

The umbrella term "*hyperferritinemia syndromes*" encompasses four clinical conditions, including macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS), and septic shock, all characterized by high serum ferritin and a life-threatening hyper-inflammation sustained by a cytokines storm which eventually leads to multi-organ failure(55)**.** The secretion of multiple cytokines, also termed Cytokine Release Syndrome (CRS), is closely related to the development of clinical symptoms; for example, IFN-γ can cause fever, chills, headaches, dizziness, and fatigue; TNF-α can cause flu-like symptoms similar to IFN-γ, with fever, general malaise, and fatigue, but can also cause vascular leakage, cardiomyopathy, lung injury, and acute-phase protein synthesis (56)**.**

Increased DPP4 expression was detected in pneumocytes from subjects with a history of smoking, or lung disease, including chronic obstructive pulmonary disease (47). DPP4 interacts with cellular proteins such as adenosine deaminase and caveolin-1 to generate intracellular signals governing immune responses. CD147 is a highly glycosylated transmembrane protein of the immunoglobulin superfamily that acts as the main upstream stimulator of matrix metalloproteinases (MMPs) and may be upregulated in its expression levels during asthmatic and diabetic complications. Expression levels of CD147 and MMPs are often increased in inflammatory processes. Thus, inhibition of CD147 may have beneficial effects in the prevention of diabetic complications involving inflammatory processes. However, specific studies are needed for investigating possible correlations between CD147 and diabetes mellitus in clinical complications due to COVID-19 (57).

Various antiviral drugs, corticosteroids, disease-modifying antirheumatic drugs (DMARDs) - such as baricitinib, hydroxychloroquine, tocilizumab, are being investigated for potential use in the management of COVID-19; preliminary reports are conflicting and other therapies aimed at treating COVID-19 can also have harmful effects on the cardiovascular system and electrolyte imbalances – which can occur in any critical systemic illness and precipitate arrhythmias, especially in patients with the underlying cardiac disorder – and/or other negative side effects[3].

Among infection-related biomarkers, C-reactive protein is considered. Levels of all pro-inflammatory cytokines are significantly higher (58). The cleavage of the new furin sites in the S protein of SARS-CoV-2 virus by plasmin and other proteases may enhance its infectivity by expediting entry, fusion, duplication, and release in respiratory cells (59).

Among the treatments used in COVID-19, it is known that antiviral, antibiotics for secondary sepsis, and sometimes corticosteroids are the most frequently used drugs (54). Most experts believe that the occurrence of multiple organ failure is mainly related to the sudden initiation of an inflammatory "storm" in the critically ill COVID-19 patients (60). A drug with promising results is Remdesivir, an intravenous drug that inhibits SARS-CoV-2 replication through premature termination of viral RNA (23). Until now, all treatment possibilities are still mainly due to meticulous supportive care and improve self-immunity. According to WHO interim guidance, glucocorticoids should not be routinely given systemically (61).

Hydroxychloroquine and azithromycin complex may be potent, but the adverse side effects they bring to the patients are very alarming (62).

COVID-19 comorbidities are cardiovascular and cerebrovascular diseases, endocrine system diseases, digestive apparatus system diseases, respiratory apparatus system diseases, malignant tumors, and nervous system diseases. Treatments include antiviral therapy, anti-inflammatory therapy, antibiotic therapy, hormone therapy, immunoglobulin therapy, and traditional Chinese medicines (63).

Elderly patients are more susceptible to severe disease and death, while children seem to have lower rates of infection and mortality (64). Hydroxychloroquine (HCQ) and chloroquine (CQ) act as weak bases and are known to accumulate within endosomes, lysosomes, or Golgi vesicles within cells resulting in an increase of pH within these compartments. The increase in pH could interfere with pH-dependent steps of SARS-CoV-2 replication like fusion and uncoating. As coronavirus requires acidification of endosomes for proper functioning, it is speculated that a pH increase in intracellular compartments might be one important inhibiting effect of CQ and probably of HCQ in the treatment of COVID-19 patients. An interesting new finding demonstrated that CQ has characteristics of a zinc ionophore and specifically targets the extracellular trace element zinc to intracellular lysosomes. Zinc is an essential micronutrient, with strictly regulated systemic and intracellular concentrations, and it is physiologically needed for an effective antiviral response (65). Hydroxychloroquine, used for the treatment of rheumatoid arthritis and other autoimmune conditions, it has also been used in treatment for malaria for almost 50 years.

Hydroxychloroquine is structurally and mechanistically similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of *torsade de pointes* and sudden cardiac death (66). Chloroquine exerts anti-inflammatory effects by inhibiting the release of proinflammatory cytokines, especially tumor necrosis factor-alpha, which may improve the immune reaction seen with viral infections (67). The virologic clearance day-6 post-inclusion (primary outcome) with HCQ *vs.* control was 70.0% versus 12.5%, respectively (p 0.001) (68). Controversary, another study asserts says that, while no benefit on viral clearance demonstrated by HCQ compared to the control in patients with COVID-19, a significant 2- fold increase in mortality with the HCQ was observed (69).

There are several vitamins and trace elements that are essential for the normal functioning of the immune system. Achieving recommended amounts of calories and micronutrient will be a challenge and elective micronutrient supplementations may be beneficial especially for vulnerable populations such as the elderly (70).

The current COVID-19 pandemic has forced us to reconsider how effective diabetes management is delivered during these challenging times. While

[3] https://www.pharmacists.ca/cpha-ca/assets/File/cpha-on-the-issues/DMARDs-COVID19-EN-FINAL.pdf

many of the technological opportunities are now becoming available, an improved understanding of patient behaviors and lifestyle choices is needed to achieve the full potential for emerging digital health technologies for people with diabetes (71). Close follow-up of patients can be done via telemedicine for example (72).

The presence of diabetes is linked to greater mortality and also a greater need for intensive care during COVID-19 infection. It is needed to improve physician-patient communication for better management of the disease in the era of social distancing, isolation, and quarantine. Diabetic patients need special attention and care since it seems that their disease is associated with increased severity of symptoms and complications with COVID-19 (73). Tele-consultations with registered medical practitioners and using Internet of Things (IoT) services for proper monitoring of heart rate, blood pressure, glucometer, and other activities for personalized attention. (74), would help people with DM circumvent a lot of problems imposed by lockdowns. (75).

The worse prognosis in patients with diabetes and COVID-19 could be attributed to the fact that pneumonia evolves towards clinical stages more refractory to medical therapies, oxygen administration, and mechanical ventilation, with the necessity of ICU care. In COVID-19 patients; the incidence of diabetes is two times higher in ICU/severe vs. non-ICU/severe cases (76).

Many studies have shown that the incidence of these diseases can also be caused by long exposure to air pollution, especially nitrogen dioxide (NO_2), a toxic component. (NO_2 causes an inflammatory response in the airways and these exposures may induce the synthesis of proinflammatory cytokines from airway epithelial cells which consequently play an important role in the etiology (cause) of airway diseases. High NO_2 concentration is significantly associated with respiratory mortality (77).

Regarding smoking, evidence from the literature is mixed. Initial studies suggested that current smoking increases the risk of severe infection. However, this has since been disputed with some evidence that smoking may even protect against initial infection (78).

It is also difficult to assess the true prevalence, occurrence, mortality, and spectrum of the clinical course of the disease since a proportion of inoculated individuals might be asymptomatic and were never tested (79).

Our performed meta-analysis has concluded that the diabetes prevalence among non-Chinese COVID-19 patients is more than twice the prevalence of Chinese COVID-19 patients. This is in concordance with the fact that in industrialized countries, about 50% of the population is overweight or obese, with the related prevalence increasing annually (80). A recent publication has reported the increased expression of the ACE-2 receptor in adipose tissue (81). As genes affected by SARS-CoV-2 infection are significantly enriched for other infections, they may represent a common interface, targeted by viruses. Future studies should determine SARS-CoV-2 interaction and effect on the human transcriptome, further identifying drug targets (82).

Physiotherapists who work in primary healthcare facilities are likely to have a role in the management of patients admitted to the hospital with confirmed or suspected COVID-19. Physiotherapy will have a role in providing exercise, mobilization, and rehabilitation interventions to survivors of COVID-19 (83).

It has been shown that aerobic exercises significantly increase the function of the immune system in short periods and sometimes this increase occurs after only one session (84).

The effect of aerobic exercises over-breathing exercise in the treatment of respiratory dysfunctions that occur in patients with COVID-19 can be summarized into four mechanisms: as antibiotic and antimycotic prophylaxis; effects on lung elasticity and recoil action mechanism; aging significantly decreases the function of body systems; as an antioxidant to limit free radical production and oxidative stress; decreasing cough in patients with COVID-19. Mild aerobic exercises could produce more significant effects on decreasing both cough and dyspnea, commonly seen in patients with COVID-19 (84).

Physical activity is a part and parcel of routine diabetes self-care. A total of 60 min of physical activity/day would be ideal that could be divided between aerobic activity, work-related activity, and muscle-strengthening activity. Intensity and type of physical activity should be tailored to an individual's ability and fitness level. Caution must be exercised for patients with co-existing heart diseases and a history of hypoglycemia.

Physicians could help patients choose the type and nature of the physical activity (85).

Hospitals and governments should prioritize COVID-19 testing in patients with diabetes ahead of other people without underlying diseases. (86). Besides the clinical evidence that DM is an important risk factor for COVID-19, we are still lacking research analyses. Clinical biomarkers are proposed for predicting better an adverse outcome of COVID-19, which might help clinicians for taking appropriate measures (87)**.**

As the world comes together to fight the COVID-19 pandemic, close collaboration among the global diabetes community is critical to understand and manage the sustained impact of the pandemic on people living with diabetes (88).

The pressure on researchers to develop promising therapeutic drugs for COVID-19 is very high. These drugs include cytokines, bioengineered and vector-based antibodies to block the gene expression of the virus and to develop a vaccine (89)**.** Additionally, today, the search for new molecules with a preservative power, of natural origin, is based on ethnobotanical studies which make it possible to carry out inventories of plants in a zone or a country, then on phytochemical and pharmacological studies and well other scientific aspects, thus resulting so, the importance of the use of these medicinal plants which pushed us to seek and find the molecules which can prevent SARS-CoV-2 infection (90).

Conclusions

Significant aspects of COVID-19 pandemic progression remain obscure. Further data should be urgently gathered to clarify the mechanisms underlying the pathophysiology of COVID-19 infection. The immense impact of the COVID-19 pandemic in lives lost, healthcare expenses, and economic consequences of countries and individuals is hard to evaluate because the epidemic is still rampant throughout the globe. Despite its most characteristic symptom of respiratory distress, patients with COVID-19 have also shown some residual/ remaining long-lasting manifestations; exploring the long-lasting manifestations of COVID-19 is a step towards better understanding the virus, preventing further spread and treating patients affected by this pandemic. While data are limited, and incomplete at this time, there is justifiable concern that COVID-19 may have lasting effects, including on diabetes patients. Physical and rehabilitation medicine and balneotherapy have to be prepared for this new concern, too.

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Declaration of interests. We declare no competing interests.

Figures and tables

TABLE 1 Step I: numerical search results.

	Cochrane	ISI	PubMed	Elsevier	Total
Search terms: *Diabetes AND COVID-19*	7	45	187	894	1,133
Duplicates	-	-	22	53	75
Articles selected for the systematic review:	-	34	37	20	91
Articles added for the systematic review:		14	-	-	14
Articles selected for the meta-analysis:	-	13	16	3	32

Table 2 The evaluation step form applied:

I Article title:	
II. Evaluation of article: Total Points:	
1. DATABASES (ISI – 20p/ PubMed -15p/ Cochrane -10p/ Elsevier – 5p)	
2. No. of citations (1p from each citation, over 20 – 20p)	
3. No of references (2 p from ten to ten, over 100 – 20p)	
4. The relevance of the article related to COVID – maximum 20p	
5. The relevance of the article related to DIABETES – maximum 20p	
III. This paper has reached a minimum of 50 points	**YES / NO**

TABLE 3 OpenMeta-Analyst source files

Study	N - total patients	China	Iran	Italy	Israel	Belgium	USA	Age	M	F	*diabetes*
Zhou et al (5)	191	191						over 56	119	72	36
Fang et al (15)	1291	1291									52
Li et al (8)	1527	1527						49			129
Deng et al (91)	26	26									11
Wan et al (92)	135	135						47	72	63	12
Wu et al (63)	280	280						43	151	129	34
Guo et al (2,10)	174	174						59	76	98	61
Zhao et al (10)	37	37						41	14	23	4
Emami et al (31)	3403	3403									135
Hong et al (58)	98	98						55	38	60	9
Chen et al (61)	145	145						47,5	79	66	14
Xu et al (11)	426	426						57.4	156	270	80
Li et al (64)	182	182						68.5	65	117	51
Hu et al (93)	47344	47344									3645
Roncon et al (94)	1853	1853									187
Nikpouraghdam et al (95)	2968		2968					55.50 ± 15.15	1955	1009	113
Singh et al (68)	2209	2209									232
Singh et al (6)	355			355							126
Singh et al (68)	481			481							163
Itelman et al (96)	162				162			52 ± 20	105	57	30
Lovato et al (97)	1556	1556							895	661	59
Lian et al (98)	788	788								381	57
Yan et al (99)	193	193						64	114	79	48
Guan et al (100)	1590	1590						48.9±16.3	904	674	130
Gentile (101)	1102			1102							347
Kang et al (102)	7162										780
Yang et al (103)	465	465						45(5-88)	243	222	28
Mercuro et al (66)	90						90	60.1 (16.7)	46	44	26
Wu et al (104)	201	201						51 (43-60)	128	73	22
Chow et al (105)	7162						7162				784
Bhatraju PK (106)	24						24	64±18 (23–97)	15	9	14
Orioli 1 (24)	48007	48007									2657
Orioli 2 (24)	4443			4443							1151
Orioli 3 (24)	7579						7579				894
Orioli 4 (24)	11018					11018					2336
Zhu et al (43)	9663	9663									952
	232155	122332	2968	6381	162	11018	14855	0	5488	4342	15470

Records identified through database searching (*n* = 1,133)

Records after duplicates removed (*n* = 1,058)

Full-text articles reviewed (*n* = 1,058)

Articles included in this systemical review *n* = 91 (34 *ISI Web of science* + 37 *PubMed* + 20 *Elsevier*)
Were added 14 studies related to balneotherapy and diabetes from the ISI *Web of science*.

Articles included in meta-analysis *n* = 32 (13 ISI + 16 PubMed + 3 Elsevier)

Figure 1: Flow-chart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria, a total of **32 articles** were included in the final meta-analysis.

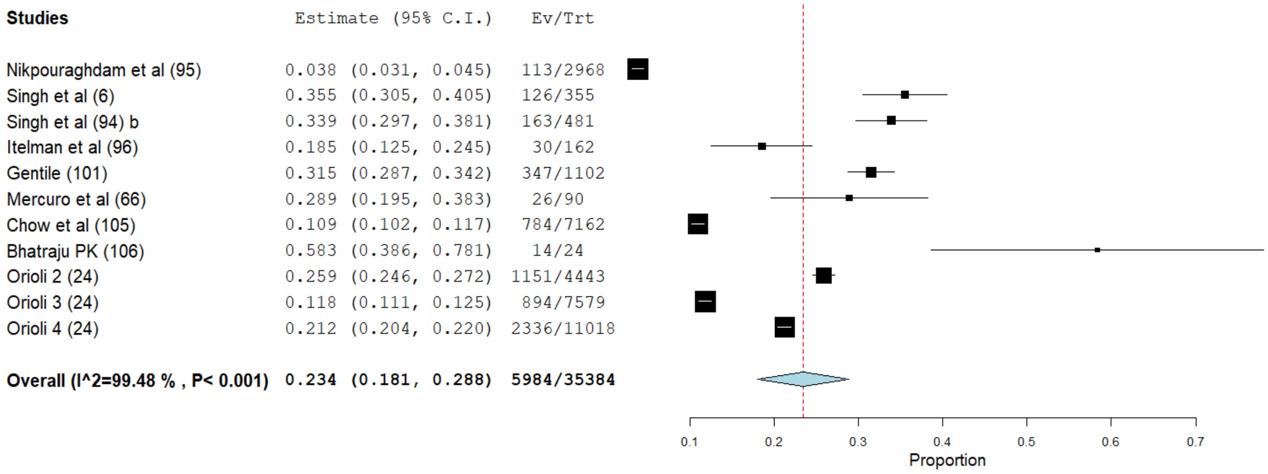

Figure 2: Non-China Studies: Diabetes prevalence : 0,234

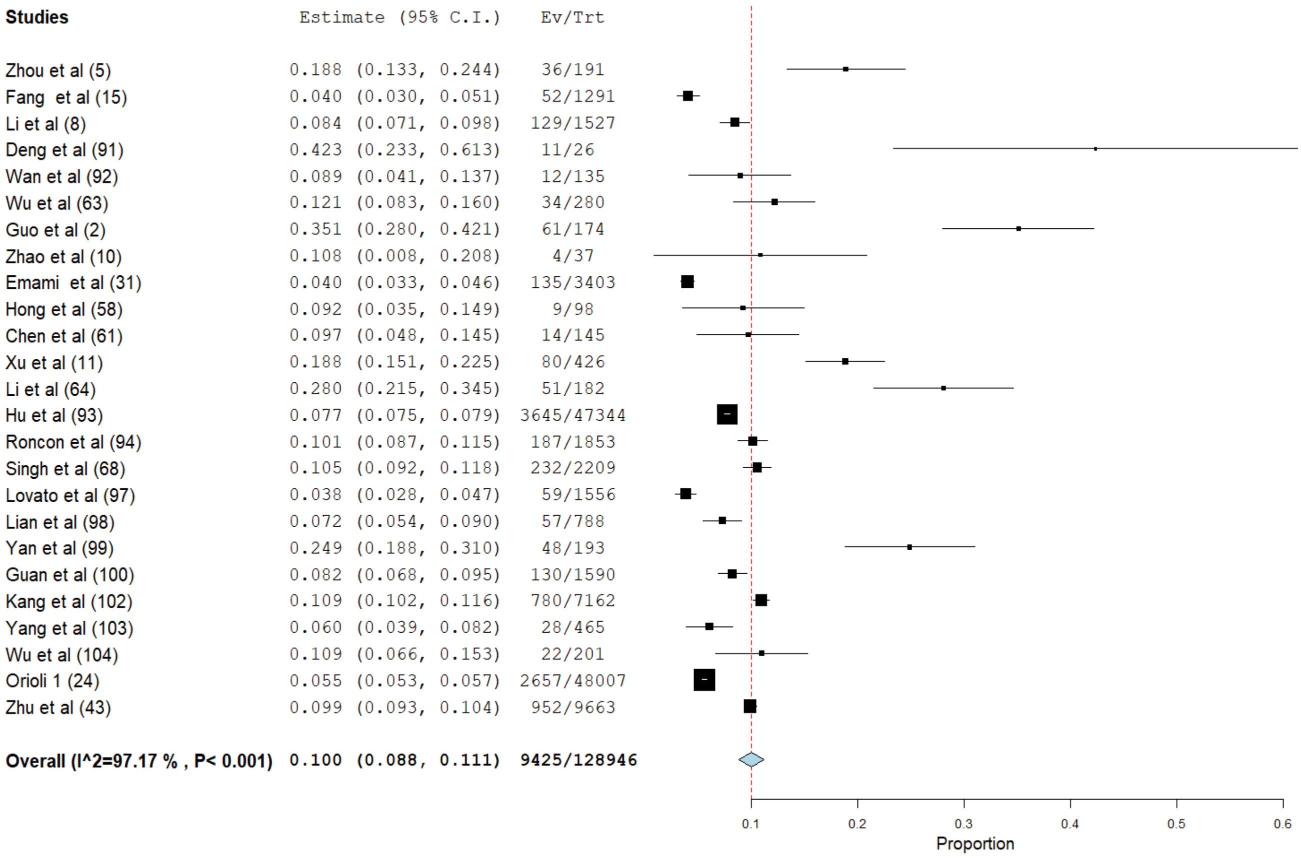

Figure 3 - China Studies: Diabetes prevalence : 0,100

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