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REVIEW ARTICLE

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Obesity and COVID-19: A jigsaw puzzle with still missing pieces

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Summary

Apart from posing various mechanical and medical issues compromising general health, obesity is a major factor for respiratory tract infections, due to specific inflammation and immunological compromise. The burden of obesity on morbidity and mortality of SARS-CoV-2 infection/COVID-19 is considerable. Herein, we aimed to search the literature and present to the readers pathophysiologic pathways that may associate obesity and COVID-19. We present potential mechanisms, which might partly explain why patients with obesity are more prone to suffer from respiratory infections in the context of COVID-19. Better understanding of these pathways could eventually guide management strategies and therapies for COVID-19 in the future.

1 | INTRODUCTION

The world is struggling to fight the novel COVID-19 pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), previously known as "2019 novel coronavirus".[1] Per the World Health Organization (WHO), data converge that the infection fatality rate of COVID-19 is 0.5-1.0%[2]; seasonal influenza has a rate of 0.1.[2] In an attempt to identify the risk factors that might aggravate the prognosis of outpatients or hospitalized patients, obesity might be a potential suspect, since it seems to interfere with the presence or worsening of respiratory tract infections (RTIs), a major component of the mortality of COVID-19.[1]

Obesity is defined as having a body mass index equal to or higher than 30 kg/m^2 for all populations worldwide, with the exception of China, where according to the World Health Organization obesity is defined as having a BMI equal to or higher than 27.5 kg/m^2.[3] Obesity rates have almost tripled during the last 40 years, establishing it as an epidemic. Statistics from WHO in 2016, showed that 13% of the world population suffer from obesity (over 650 million subjects in total) and that 39% (more than 1.9 billion subjects) are overweight.[4] In industrialized countries, roughly half of the population is overweight or obese. In USA, the National Health and Nutrition Examination Survey (NHANES) report reported that 34% of inhabitants have obesity.[5]

In the past, from the "Spanish" influenza of 1918 onwards, in all influenza epidemics, including the 2009 Influenza A virus (IAV) H1N1 pandemic, malnutrition and obesity were associated with severe disease, complications, hospitalization, need for treatment in intensive care units (ICU) and mortality.[6] This pattern seems to be replicated with COVID-19 and the World Obesity Federation has stated that "obesity-related conditions seem to worsen the effect of COVID-19[1]; indeed, the Center for Disease Control and Prevention (CDC) reported that subjects with heart disease and diabetes are at higher risk of COVID-19 complications and that severe obesity (body mass index [BMI] of 40 kg/m^{2}or higher) poses a higher risk for severe illness[7]".

Many pathophysiological changes occurring with increased adiposity may contribute to poor prognosis of COVID-19 patients.[8,9] In the present review, we aimed to search the scientific literature for pathophysiologic pathways that associate obesity and COVID-19. We discuss published data regarding the association of obesity with the incidence and severity of respiratory tract infections (RTIs), along with RTI caused by COVID-19, focusing on molecular or hormonal pathways that may be possibly involved and drawing parallels to previous similar outbreaks of RTIs in previous epidemics.

2 | LITERATURE SEARCH

The PubMed, Google Scholar, MedRxiv and BioRxiv databases were accessed by all the co-authors to identify relevant English-language

articles published up to September 15, 2020. The search terms included "human, coronavirus, COVID-19, SARS-CoV-2, cytokine, adipokine, obesity, complications, human, humoral immunity, cellular immunity". Twenty-eight articles were initially selected and additional publications of relevance to the present article were identified by reviewing the references of the eligible articles.

3 | EPIDEMIOLOGICAL DATA

Due to the very recent and not yet well-studied outbreak of COVID-19, epidemiological data and risk factors in the normal-weight and/or populations with obesity are still lacking. While age and male sex are regarded as significant risk factors, accumulating evidence suggests a strong association with an impaired cardiometabolic profile. Initial reports from Wuhan, China, where the COVID-19 first occurred, indicated a higher prevalence of hypertension and diabetes among patients with severe compared to non-severe illness.[10] Both entities are associated with obesity, forming part of the criteria of the cluster of the metabolic syndrome. Furthermore, hypertension and diabetes, as well as cardiovascular disease were identified as risk factors associated with fatal outcomes.[11] However, most patients recruited in Chinese studies had normal BMI or a BMI compatible with overweight classification, but not obesity (please see above; in China obesity is defined by the World health Organization as having a BMI over 27.5 kg/m^2 [3]). Thus, increased BMI was not listed among the risk factors for COVID-19; however, this may reflect lower prevalence of obesity in the region due to a differential body fat distribution in individuals of Asian origin.[12] Nevertheless, it was reported that the percentage of patients with overweight BMI is markedly higher in non-survivors compared to survivors from COVID-19,[13] while most recent data have shown that in patients presenting with metabolic fatty liver disease, the presence of obesity correlated with a 6-fold increased risk for severe illness from COVID-19.[14] Results from a population-based surveillance program across 14 states representing approximately 10% of US population, have shown that among 1482 hospitalized patients in March 2020 for confirmed COVID-19, obesity was the second most common underlying condition in the general population, closely following hypertension, and first among younger individuals aged 18-49.[15] In this age group, 59% of COVID-19 patients that required hospitalization suffered from obesity and this proportion was substantially higher than any other underlying condition, suggesting that obesity might be one of the main risk factors for severe COVID-19 in young or middle-aged adults.[15] The same finding has been reported from Spain,[16] although regional data have not been officially published yet. Selected data on obesity and outcome are shown in Table 1.[17-23]

In western countries, although data from Italy have confirmed earlier Chinese reports,[24] a French study showed that patients with BMI > 35 kg/m^2 were at significantly higher risk for the requirement of intensive mechanical ventilation compared to normal-weight individuals (with BMI lower than 25 kg/m^2), even after adjusting for age, diabetes and hypertension.[25] These results were later replicated in a different hospital in France[26] and have generated more interest in the association between adipose tissue excess and disease pathophysiology. In a meta-analysis, patients with obesity and COVID-19 had a significantly elevated Odds Ratio of 1.20-7.36 to be critically ill and to be mechanically ventilated vs subjects with normal BMI. Being overweight (BMI > 25 kg/m^2) or having obesity with COVID-19 entailed an Odds Ratio of 1.22-3.68 for death compared with normal weight subjects.[27,28]

Emerging data from the UK National Intensive Care National Audit and Research Centre indicated that 7 out of 10 patients admitted to ICU were overweight or had obesity and increased body fat accumulation correlated with serious or fatal complications,[29] while in New York hospitals, patients that required mechanical ventilation were again predominantly males with obesity.[30]

It has been established that obesity may impair outcomes in patients hospitalized for respiratory infections. In a study of 1455 individuals with obesity, the latter was correlated significantly with lower RTIs (adjusted OR = 2.02, 95%CI = 1.36-3.00) and upper RTIs (adjusted OR = 1.55, 95%CI = 1.22-1.96), with a stronger association for women.[31] Influenza-like illness, bronchitis and pneumonia, pharyngitis, laryngitis but also rhinitis and sinusitis proved to occur more

TABLE 1 Selected reports on the outcome of subjects with obesity and COVID-19 vs subjects without obesity

Country of origin	N (subjects with obesity /total study subjects with COVID-19)	Outcome	Odds ratio for outcome (95% confidence interval)
United States[17]	402/3615	Severe disease	1.80-3.60 (1.20-5.30)
United States[18]	56/102	Mortality in intensive care unit	0.79 (0.41-1.53)[a]
China[b19]	37/96	Admission to intensive care unit	1.26 (NA)
China[c20]	36/95	Mortality	8.62 (0.40-184.9)
France[23]	895/5795	Mortality	1.89-2.55 (1.45-3.97)
Spain[21]	119/1000	Mortality	2.53 (1.47-4.36)
Mexico[22]	10 708/51633	Mortality	1.26 (1.11-1.43)

[a]Calculated from the data provided in the article.
[b]In this study results were noted for BMI > 24 kg/m^2.
[c]In this study results were noted for BMI > 24.9 kg/m^2.

frequently in subjects with obesity.[31] Interestingly, in a counter-intuitive fashion, a quasi-protective effect of obesity on acute lung infections has also been noted. Researchers have hypothesized that the chronic pro-inflammatory state of subjects with obesity may act towards the preconditioning of these subjects to better withstand severe lung injury or sepsis. However, this purported preconditioning may not apply for COVID-19, although experts are still debating this issue.[32-36] Of note, reports indicate that the adipose tissue may be a viral reservoir in patients with COVID-19.[37]

Since reports regarding COVID-19 are limited due to the ongoing pandemic, data can be mirrored with previous similar infectious spreads, such as the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak. In that outbreak, age, male gender and cardio-metabolic conditions including hypertension, diabetes and obesity proved to be independent risk factors for severe illness,[38] similarly to the current pandemic. This distinct pattern may suggest a shared molecular pathway between coronaviruses and pathophysiological changes occurring in metabolic syndrome related diseases. In addition, high BMI was among the most frequently identified underlying conditions in patients with pandemic 2009 influenza A (H1N1)[39] and obesity was a significant risk factor for severe illness and mortality,[40] with one third of the individuals requiring ICU being patients with obesity.[41]

4 | GENERAL CONSIDERATIONS IN RESPIRATORY TRACT INFECTIONS IN PERSONS WITH OBESITY

Patients with obesity may need a bariatric hospital bed, which is rarely found, or if so, certainly in small numbers not in all primary care hospitals/institutions. Given that COVID-19 poses a great challenge for hospitals, facilities for individuals with obesity may be in shortage.[42] They also pose a serious challenge in terms of intubations, since the excess adipose tissue on the larynx makes it technically more difficult to intubate. In patients with obesity it may be challenging to obtain a proper imaging diagnosis (there are weight limits on imaging equipment), making it less straightforward to diagnose an infection in the lung parenchyma. Moreover, patients with obesity are definitely more difficult to position and transport by nursing staff and at the same time suffer from poorer mobility; these patients may not be able to self-care and may have poor skin integrity and skin deterioration (thus becoming vulnerable to infection).[43-45] Of note, Sattar et al suggested that the higher prevalence of severe COVID-19 in the elderly population may not necessarily be associated with obesity: the relative increase in fat mass may be due to loss of muscle mass and sarcopenia (the same authors advised the need for clear public health advice regarding increased physical activity and healthy diet to reduce the burden of obesity on COVID-19, especially during lockdown measures).[46] Regarding pure respiratory characteristics of these patients, the lungs of patients with obesity exert altered mechanics, leading to compromised lung ventilation and gas perfusion, thereby lowering oxygen supply due to trunk pressure on the lung parenchyma.[47] Central adiposity limits thoracic expansion and as a result, the pulmonary parenchyma at the lung bases is suppressed, along with a potential weakness of the thoracic muscles.[47]

Obesity is often complicated by type 2 diabetes, which seems to be a risk factor for infections per se due to poor skin healing and higher vulnerability to infection.[48,49] Fat deposition in the liver may often lead to liver steatosis and possible functional impairment, thus affecting the pharmacokinetics of medications, too, while co-existence of chronic renal insufficiency, a common comorbidity in obesity, may complicate the excretion of metabolites or toxic byproducts.[50,51] In technical terms, individuals with obesity sometimes face difficulties in swallowing of medication and very often exhibit hiatus hernia or gastro-oesophageal reflux disease (GORD), which might impair proper absorption of a chemical substance.[6] Another aspect that might worsen the prognosis of an infection in a patient with obesity is an exaggerated pro-thrombotic response and increased thrombogenic risk along with increased C-Reactive Protein (CRP) and fibrinogen levels.[52,53]

5 | MOLECULAR PATHOPHYSIOLOGY OF RESPIRATORY TRACT INFECTIONS IN PERSONS WITH OBESITY

Obesity is a state of low-grade inflammation and defective innate immunity, resulting from the release of adipokines (leptin, adiponectin, visfatin, resistin), Plasminogen Activator Inhibitor-1 (PAI-1), angiotensinogen and vascular endothelial growth factor (VEGF), inflammatory cytokines [Tumour Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), IL-6, IL-10], Transforming Growth Factor- β (TGF-β) and Monocyte Chemoattractive Protein-1 (MCP-1)[54,55] (Figure 1). COVID-19 may be complicated by acute respiratory distress syndrome, caused by systemic hyper-inflammation and cytokine release, in response to increased production of CD14+ and CD16+ inflammatory monocytes (which lead to excessive synthesis of IL-6). Circulating IL-6 levels are associated with serum viral load,[56] and a meta-analysis has confirmed that increased IL-6 concentrations are associated with disease severity.[57] Monoclonal antibodies against the IL-6 receptor could be used against COVID-19 complications but large-scale relevant studies are lacking.[58,59]

Interferons (IFNs) are released in response to viral infections. Smith et al showed that diet-induced obese mice had worse clinical presentation following influenza infection, with increased mortality (42% vs 5% in lean mice).[60] In the same report, reduced lung type I IFNα/β mRNA expression, reduced natural killer cell potential and diminished lung pro-inflammatory cytokine (IL-6, TNF-α and IL-1β) and chemokine mRNA expression[60] were noted. In COVID-19 patients, expression of IFNγ was lower in patients with moderate compared to mild disease.[61]

Macrophage activation vs an antigen, along with B- and T- cell responses, are reduced in obesity. In studies of obese mice, respiratory infection disease showed increased severity and increased secondary bacterial infections, along with a delayed and barely blunted

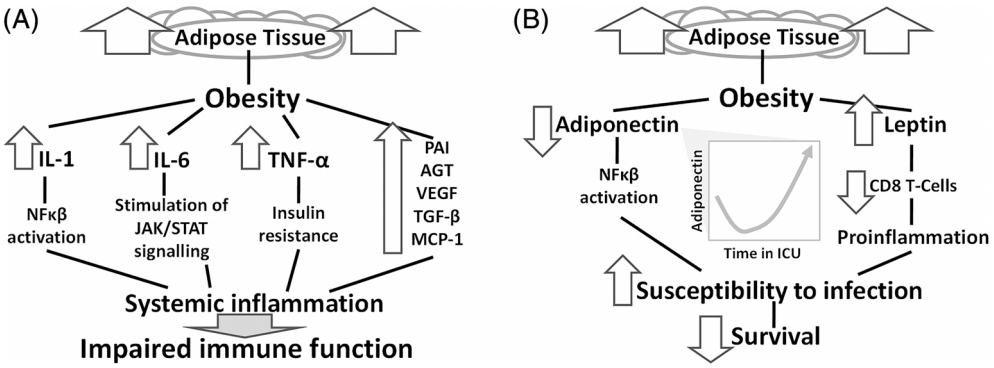

FIGURE 1 A, Cytokines and inflammation in subjects with obesity. Release of inflammatory molecules represents the cornerstone of obesity-induced inflammation. NF-κB: Nuclear Factor kappa-light chain-enhancer of activated B-cells. B, Adipose tissue and adipokines in subjects with obesity. Healthy adipose tissue secretes less leptin and more adiponectin, preventing inflammation. In obesity, this is inversed and reduced levels of the anti-inflammatory adiponectin favour resistance to leptin and subsequent susceptibility to infections. This is notable for lung infections and critical illness that requires treatment in an intensive care unit (ICU). AGT, angiotensinogen; MCP-1, monocyte chemoattractive protein-1; PAI-1, plasminogen activator inhibitor-1; TGF-β, transforming growth factor- β; VEGF, vascular endothelial growth factor

immune response and increased morbidity.[62] Obesity minimizes the response of CD8 + T cells to viruses.[6] Post-vaccination for influenza, subjects with obesity show lower antibodies' levels compared to lean subjects, and a weaker influenza-specific CD8 + T cell function; these subjects with obesity show a two- to 3fold higher incidence of influenza despite being vaccinated.[63]

The cytokine leptin is released from excess adipose tissue, signalling to the brain the amount of this tissue, albeit with no tangible effect on adiposity per se.[51] Increased leptin (caused by leptin resistance) is often seen in obesity - similarly to insulin resistance - and may predispose to a proinflammatory status. Leptin resistance compromises defence to infection and increases susceptibility to respiratory infections.[64] Zhang et al suggested that leptin resistance could aggravate outcome with 2009 A (H1N1) influenza, by exerting effects in B cell maturation, development and function.[65] Leptin binds the Ob-Rb receptor, stimulating the Janus kinase-signal transducer and activator of transcription JAK-STAT pathway, promoting the translocation of phosphorylated STAT proteins to the nucleus and subsequent gene transcription. Ob/ob and db/db mice (mice deficient in leptin signalling) present with increased rates of bacterial infections and pneumonia. Leptin has been found to be implicated in asthma, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea.[66] IFN signalling uses the same JAK-STAT pathway, thus offering a potential correlation of leptin, IFN and host defence vs viruses.[66,67]

Adipose tissue (mainly white) secretes the adipokine adiponectin. The latter promotes insulin sensitivity and is known to display anti-inflammatory effects, by reducing the inflammatory cascade induced by adipose cells, mainly via activation of NFkB.[68] Adiponectin exerts immunomodulatory actions; patients with lower adiponectin levels at admission to the ICU have lower survival rates.[69] In general, healthy (ie, non-excessive) adipose tissue secretes more adiponectin and less leptin, thus reducing inflammation. In obesity the adiponection/leptin ratio is inversed, favouring inflammation.[70] Increased TNF-α following inflammatory processes leads to the downregulation of the latter's receptors (attenuating adiponectin's inflammatory signalling and insulin sensitizing actions). Opposing roles have been attributed to adiponectin and IL-6 vis-a-vis the modulation of insulin sensitivity. Inhibition of adiponectin production by IL-6 and TNF-a, lowers adiponectin levels and perpetuates the low-grade chronic inflammation of metabolic disorders.[71,72] It would be reasonable to study levels of these or other adipokines in patients with COVID-19 and assess their clinical utility as biomarkers of disease severity and progression.

6 | OBESITY AND CORONOVIRUSES: SPECIFIC MOLECULAR TARGETS AND SHARED PATHOPHYSIOLOGY

Gattinoni et al suggested that COVID-19 pneumonia presents with two time-related main phenotypes identified based on CT findings: Type L, characterized by low elastance (ie, high compliance), low ventilation-to-perfusion ratio, low lung weight and low recruitability and Type H, characterized by high elastance, high right-to-left shunt, high lung weight and High recruitability.[73] AMong many hypotheses proposed to explain the robust epidemiological findings of severe illness from coronaviruses strains, such as SARS-CoV-2 and MERS-CoV, in patients with deteriorated metabolic profile, the role of angiotensin converting enzyme 2 (ACE2) and DPP4 receptor has gathered some attention. In specific, SARS-CoV-2 utilizes ACE2 as cell entry receptor via a serine protease termed transmembrane serine protease 2 (TMPRSS2) and TMPRSS2 blocking agents have shown to prevent SARS-CoV-2 entry.[74] ACE2 is widely expressed in many organs and particularly in the lungs, pancreas, enterocytes, blood vessel endothelium and membrane of fat cells.[75] This may explain the systemic, multi-organ damage noticed in COVID-19 patients with preferential mortality in patients with diabetes and hypertension. Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers

(ARBs) upregulate ACE2 and their role in managing hypertension or diabetes complications in patients with COVID-19 has been debated; however, in the absence of clinical evidence of any adverse effects of these agents, continuation of treatment has been advised.[76] Regarding DPP4, this receptor was shown to be a functional MERS-CoV target.[77] After binding to DPP4, MERS-CoV induces immune response by activating T-cells via NFkB pathway. Therefore, DPP4 inhibitors (DPP4i) have been suggested as potentially useful agents in the fight against coronaviruses.[78] These drugs, together with glucagon-like peptide −1 receptor agonists (GLP-1RA) exert immunomodulatory and anti-inflammatory effects and may represent tempting therapeutic targets in individuals with diabetes with respiratory or other systemic inflammation. However, SARS-CoV-2 does not bind to DPP4 and currently there is no evidence to support their use in COVID-19.[79]

Regarding COVID-19, there may be a possible direct effect of the SARS-CoV-2 virus on pancreatic insulin secretion.[80,81] In severe COVID-19 infection, cells from the lung epithelium, as well as from endothelial cells, secrete abundantly plasminogen activator inhibitor 1 (PAI-1), leading to hypofibrinolysis[82-84] and hypercoagulability and adding to the disease's morbidity. This should be more severe in patients who have obesity and suffer from COVID-19, who already are in a hypercoagulable state via the same mechanisms.[85-87]

7 | ETHNIC BACKGROUND AND THE ROLE OF VITAMIN D

Accumulating data show that ethnic and socioeconomic differences may be listed among risk factors for severe COVID-19 infection. Subjects with increased BMI are prone to be vitamin D deficient (with an odds ratio of 1.35 compared to subjects with BMI less than 25 kg/m^2).[88-90] Vitamin D insufficiency has been associated with compromised immune responses and may have an effect on ICU mortality; this is currently being evaluated in COVID-19 patients.[91,92]

Results from the UK Biobank have identified individuals of Black, Asian, Minority Ethnic (BAME) origin, and primarily Pakistani ethnicity, are at higher risk for being admitted to hospital compared to white British subjects.[93] Another implication of COVID-19 outbreak is that it occurred in late winter, with different fatality rates among countries and lower hospitalization and mortality in countries close to the Equator and southern latitudes.[94] These epidemiological data, with higher prevalence of severe COVID-19 AMong individuals with darker skin, together with genetic and social factors may contribute to this phenomenon, many investigators have suggested that vitamin D deficiency may play a role. Vitamin D receptors are found in various tissues and are present in immune cells, such as B and T- cells, suggesting an involvement in immune response.[95] Low vitamin D levels are associated with presence of several chronic diseases and impaired immunity, thereby leading to higher risk for recurrent respiratory infections.[96] A comprehensive meta-analysis has shown that vitamin D replacement can reduce the risk for acute RTIs and its protective effects were even more evident in vitamin D deficient individuals.[97,98] It is well established that individuals with obesity are more often vitamin D deficient[89] due to the soluble nature of vitamin D in fat, and therefore vitamin D supplementation, as an adjunct therapeutic approach aiming to prevent cytokine storm,[98] may be of importance in the population who suffer from obesity. This is why, at least 10 trials examining the association between vitamin D supplementation and COVID-19 outcomes are now registered with the ClinicalTrials.gov website.[99] Data collected during the early phase of the pandemic showed that lower serum 25-hydroxyvitamin D levels were associated with a higher risk for admission to ICUs due to COVID-19-related illness.[100] A thorough analysis of the UK Biobank data, using historic vitamin D levels that were collected many years before the COVID-19 outbreak, has also shown an association between vitamin D levels and COVID-19 infection.[101,102] These findings were corroborated by a recent large study from Israel, though it is still unclear whether vitamin D replacement reduces the risk of severe illness from COVID-19.[103] Thus, more studies evaluating vitamin D levels in COVID-19 are needed to examine any associations more in depth.

8 | CHARACTERISTICS OF THE CONTAGIOUS PATIENT WITH OBESITY

It seems that patients with high BMI - apart from being in danger to show a worse RTI clinical prognosis - are in fact more contagious in terms of spreading a virus or an infection, in general. As mentioned before, the immune response of an individual with obesity is compromised, partly because of reduced or delayed interferon production. This delay allows the virus to produce new potentially mutant strains, via RNA replication, thus making it more difficult for mounting a potent immune response. Moreover, adipose tissue may act as a reservoir for many viruses, and potentially for COVID-19,[104] while patients with obesity may host viruses for a slightly longer time in their body, thus extending the period of contagion.[105] Additionally, studies have shown that the viral load in the exhalation of subjects with obesity and influenza may be higher, due to increased ventilation volume, thus suggesting that these subjects can spread pathogens more easily.[106]

9 | CONCLUSIONS

Obesity favours mechanisms that apply both to innate immunity and in the development of infection, which might partly explain why patients with obesity are more prone to suffer from respiratory infections in the context of COVID-19. Future studies evaluating the role of obesity-related cytokines and adipokines, including leptin and adiponectin, are needed, to identify potentially involved shared pathophysiological pathways that can explain the already established epidemiological associations, at a molecular level. Better understanding of these pathways could eventually guide management strategies and therapies for COVID-19. Subjects with obesity are prone to be

vitamin D deficient; encouraging vitamin D replacement in subjects with obesity during winter, may be a proactive, yet reasonable, harmless and inexpensive approach against COVID-19.

CONFLICT OF INTEREST

The authors declare no financial or other relationships leading to a conflict of interest.

AUTHOR CONTRIBUTIONS

Both Kalliopi Pazaitou-Panayiotou and Grigorios Panagiotou conceived the idea for this review.

Konstantinos Michalakis, Grigorios Panagiotou, Ioannis Ilias and Kalliopi Pazaitou-Panayiotou searched the available literature and wrote the draft and final form of this article.

Kalliopi Pazaitou-Panayiotou was responsible for the co-ordination of the project.

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