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Ageing, sex, obesity, smoking and COVID-19 — truths, myths and speculations

Abstract

In early December 2019, in the city of Wuhan in Hubei Province, China, the first infections by a novel coronavirus were reported. Since then, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been spreading to other cities and countries becoming the global emerging epidemiological issue and quickly reaching the status of a pandemic. Multiple risk factors of disease severity and mortality have been identified so far. These include old age, male sex, smoking, and obesity. This concise narrative review highlights the important role of these factors in the pathobiology and clinical landscape of Coronavirus Disease 2019 (COVID-19). We especially focused on their significant role in disease severity and mortality. However, in spite of intensive research, most of the presented pieces of evidence are weak and need further verification.

Key words: coronavirus infections, SARS-CoV-2, COVID-19, morbidity, mortality, risk factors

Introduction

In early December 2019, in the city of Wuhan in Hubei Province, China, the first infections by a novel coronavirus were reported. The new pathogen was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease in which it is an etiological factor for was named coronavirus disease 2019 (COVID-19) [1]. Since then, SARS-CoV-2 has been spreading to other cities and countries becoming the global emerging epidemiological issue and quickly reaching the status of a pandemic. On the 4th of March, the first SARS-CoV-2 positive patient was officially confirmed by the Polish Ministry of Health [2]. Since that time, morbidity and mortality have been increasing across the country.

The key to effective treatment of these patients is to increase knowledge about the pathobiology of the disease which does not seem to be fully understood so far.

Multiple risk factors of disease severity and mortality have been identified so far. These include old age, male sex, smoking, and obesity [3–8]. Therefore, in our considerations, we decided to cover these issues in the broad and multifaceted context of interactions, mainly focusing on its interference with the immunopathological background of COVID-19. We attempted to summarize the current state of knowledge and draw some hypotheses for further research in order to raise questions and open up a debate about analyzed issues. Figure 1 summarizes the main points discussed in the manuscript.

Beyond age…

Ageing may be defined as a progressive decline in tissue homeostasis due, at least in part, to the accumulation of replicative, oxidative, and genotoxic stress over time [9]. An increasing body of evidence suggests that ageing is associated with chronic inflammation, both pathological and physiological.

Multiple causes may contribute to ageing-associated inflammation such as pro-inflammatory tissue damage, a dysfunctional immune system, proinflammatory cytokines secreted
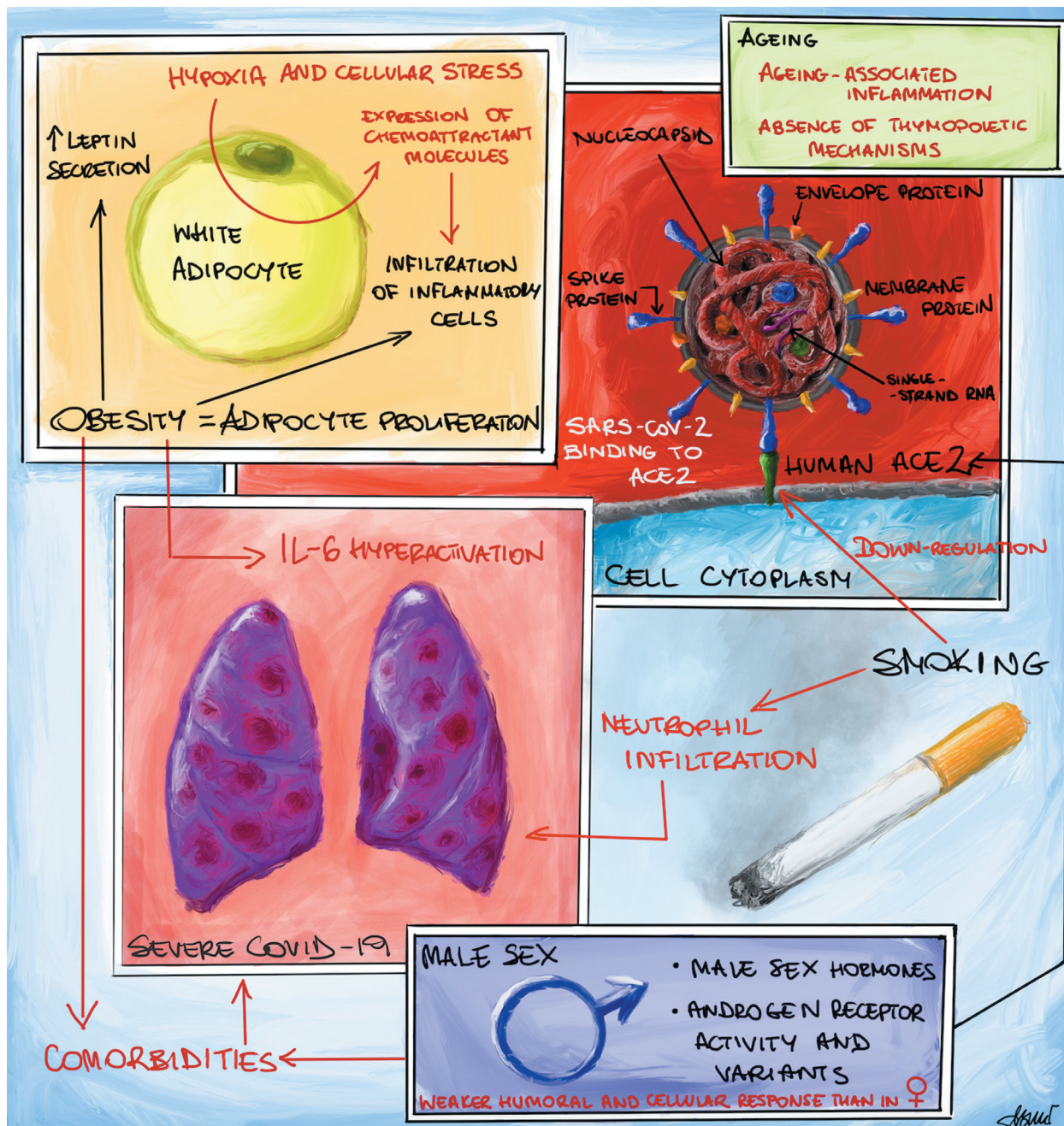
Figure 1. Graphical summary of the manuscript (author: AJ Białas)

by senescent cells, enhanced Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and a defective autophagy response. These factors enhance the activation of inflammatory pathways (i.e. the nod-like receptor 3 (NLRP3) inflammasome) and then induce the production of cytokines such as interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α), and interferons (IFNs). Long term inflammation could be a major cause of ageing-associated diseases [10]. In the SARS-CoV-2 infection, viroporin 3a has also been shown to trigger the activa-tion of the inflammasome NOD 3-like receptor protein (NLRP3) and the secretion of IL-1β in bone marrow macrophages. This condition may result in an increased release of a large number of pro-inflammatory agents. Reports suggest that a storm of cytokines is released in patients with SARS-CoV-2 disease which is mainly manifested by increased IL-2, IL-7, granulocyte colony stimu-lating factor (GC-SF), monocyte chemo-attracting protein 1 (MCP1), and TNF-α. Of all the interleu-kins, IL-6 has been found to be associated with highly pathogenic SARS-CoV-2 infection due to

increased viral replication mainly in the lower respiratory tract [11, 12].

Telomere-controlled cellular ageing

The inflammatory process associated with telomere-controlled cellular ageing can lead to reduced tissue regenerative capacity. This is probably due to the impairment of stem and progenitor cell functions.

A telomere is a region of tandem repeats of short DNA sequences at the ends of chromosomes which are important for their stability and allow for the complete replication of the ends [13, 14]. The telomere proteome consists of more than 200 proteins that are associated with different aspects of telomere functioning including their protection, elongation, or telomeric DNA synthesis [13–16]. Telomere length homeostasis is essential for the proper functioning of the cell [14, 17]. Telomeres are also an important element in the ageing of cells. As well, they are involved in maintaining immune homeostasis. They are also the main indicator of biological age and are a measurable marker of both inflammation and oxidative stress [10].

Normal ageing is, by itself, associated with telomere shortening. A significant shortening of telomeres leads to cell death. The speed of shortening can be further increased by inflammation and oxidative stress and thus, affects the ageing process. In addition, cell telomere shortening may be associated with an increase in NF-κB transcription factor activity and overexpression of inflammatory cytokines such as TNF-α, IL-6, and IFN-γ in circulating macrophages [10, 18]. NF-κB is a family of seven transcription factors (p50, p52, p100, p105, RelA/p65, RelB, and C-Rel) and plays a central role in inflammation and cell response by controlling gene network expression [19, 20]. Activation of NF-κB is redox-sensitive and can be regulated by the changes in the oxidant/antioxidant balance [19]. The members of this family may activate expression of many pro-inflammatory genes which also play a role in lung inflammation [19, 21]. This evidence justifies the reports about upregulation of NF-κB activity in both naturally aged mice and multiple progeroid mouse models of accelerated ageing [9].

The generation gap?

The specific vulnerability of older people to severe COVID-19 disease is well documented. However, let us discuss why children seem to be more protected.

Scarpa *et al.* suggest that the essential role of the thymus could be crucial in the modulation of the immune response toward SARS-CoV-2 leading to a less severe phenotype in children when compared with adult COVID-19 patients. They identify inflammaging associated with the absence of thymopoietic mechanisms as a potentially predisposing condition that sustains the surge of proinflammatory cytokines that is specifically reported in older COVID-19 patients [22]. Indeed, severe adult COVID-19 pneumonia cases are associated with a decrease in regulatory T cells and CD4+/CD8+ T cells [23]. Since the thymus is the primary lymphoid organ essential for the development of T lymphocytes, its decreased functioning could lead to a drastic decrease in these T cells [24]. Moreover, one of the age-related changes in the immune system is the impaired generation of primary T cell responses against infection [24, 25].

Some facts about fats…

White adipose tissue is an active endocrine organ consisting of mature and developing adipocytes, endothelial cells, and immune cells such as adipose tissue macrophages, neutrophils, eosinophils, mast cells, and T and B cells. Thus, people with a normal body weight have a balance between adipocytes and immune cells which maintains tissue homeostasis. In particular, eosinophils and T-regulatory cells (Tregs) secrete anti-inflammatory cytokines (IL-10 and IL-4) that direct adipose tissue macrophages towards the anti-inflammatory phenotype, thereby maintaining a tolerogenic environment. This condition is also associated with the production of adiponectin, which increases insulin sensitivity [26, 27].

In turn, obesity causes adipocyte proliferation which leads to increased leptin secretion and infiltration of inflammatory cells. Adipocyte hypoxia and cellular stress were able to induce the expression of chemoattractant molecules with a consistent recruitment of macrophages, T cells, and B cells. When T cells are activated, the number of Treg cells is reduced [28]. The phenotype of macrophages changes from M2 to M1, which in turn accumulate around adipocytes and produce large amounts of proinflammatory cytokines such as TNF-α. In addition, obesity is characterized by a dysregulated secretion of adipokines such as leptin, adiponectin, LCN2, and PGRN which have become key regulators of the innate and adaptive immune systems [27, 28].

There is a lot of evidence showing a worse prognosis in obese patients infected with the

SARS-CoV-2 virus, especially among people. It should also be mentioned that obesity is a well-known risk factor for respiratory diseases. Excessive growth of fat leads to hyperactivation of interleukin-6 and chronic inflammation which increases the risk of acquiring comorbidities such as diabetes and hypertension [27]. Again, both hypertension and diabetes are listed among the most prevalent risk factors for a worse prognosis in SARS-CoV-2 infection [12, 27].

When discussing the relationship between the inflammatory process and obesity in the SARS-COV-2 infection, we also have to discuss the role of mitochondria.

Generally speaking, mitochondria are multifunctional cellular organelles which play an important role in numerous aspects of cell morphology and physiology such as the synthesis of adenosine triphosphate (ATP), intracellular transfer of energy, redox homeostasis, regulation of cellular metabolism [29], cellular calcium homeostasis, synthesis of steroids [30], and apoptosis [31, 32]. However, mitochondria also play a key role in initiating inflammatory pathways. Mitochondrial dysfunction drives the ageing process by reducing cellular fitness, inflicting damage to other organelles, and/or causing mutations of the nuclear genome. One critical mechanism underlying the dysfunction of mitochondria is the accumulation of mutations and deletion of aged mitochondrial DNA (mtDNA), which is a consequence of the decline in mitochondrial autophagy (mitophagy). This process seems to decline in ageing individuals as the expression of several key components is decreased [33]. The dysfunction of mitophagy leads to the accumulation of damaged mitochondria, which then initiates inflammasomes and other inflammatory pathways. Mitochondria are essential for the NLRP3 inflammasome activation because they can activate NLRP3 inflammasomes by producing ROS. Furthermore, ROS-mediated mitochondrial permeability transition facilitates the release of mtDNA, which can stimulate pro-inflammatory signaling via the pattern recognition receptors RIG-I and MDA5, promoting the activation of NF-κB and interferon regulatory factors [33].

Based on the available data for SARS-CoV-2, its RNA is also located in mitochondria. It is postulated that SARS-CoV-2 transcripts found in mitochondria may affect mitochondrial function via ACE2 to avoid host cell immunity and to facilitate viral replication and COVID-19 disease [34]. Additionally, manipulation of host mitochondria by viral open-reading frames can release mitochondrial DNA (mtDNA) in the cytoplasm which can potentially serve as a potent danger-associated molecular pattern and can activate mtDNA-induced inflammasomes. This, in turn, can suppress both innate and adaptive immunity [33, 35].

Evil, damned evil and cigarette smoking…

The commonly accepted mechanism of SARS-CoV-2 cell entry is via use of the angiotensin converting enzyme 2 (ACE 2) receptor [36]. Some earlier papers suggested that smoking and nicotine are strong factors down-regulating ACE 2 expression [37]. Contrarily, results of current studies on airway epithelia are different [38, 39]. A potential adhesion site for SARS-CoV-2 is up-regulated in smokers independent of coexisting COPD. In the lung, SARS-Cov-2 infection and down-regulation of ACE2 receptors leads to increased angiotensin II activity that directly causes uncontrolled inflammation and lung damage [40, 41]. Although it has been suggested that an increase in the expression of ACE2 may contribute to the severe form of SARS-CoV-2-induced infection, it actually might be beneficial. Thus, looking for a prevalence of past or current smokers among COVID-19 patients might explain the important question both from a practical and theoretical point of view. Observational studies in China and in Italy have suggested that ARDS among smoking COVID patients is less prevalent than in patients who never smoked [42, 43]. The convincing meta-analysis of updated results from China confirms that active smoking is significantly associated with a risk of severe COVID-19 [44].

Smoking is strongly accompanied by neutrophilic airway inflammation [45]. SARS-CoV-2 infection induces biphasic immune responses. In the incubation stage, both innate and adaptive immunity are responsible for virus elimination. Therefore, inflammation can be limited, and the disease does not develop. Nearly 80% of infected people are only carriers of the infection [46].

In the second phase, when the protective response is diminished, the virus will propagate. Tissues damage develops following inflammation that is mostly mediated by neutrophils and macrophages and is especially noticeable in organs rich in ACE 2 receptors such as the lungs and kidneys. This cytokine storm seems to be mainly attributed to interleukin 6 [47].

There is no doubt that neutrophilic inflammation can be evoked and amplified by different factors. Smoking and other forms of indoor or

outdoor air pollution are two factors in the public space that can evoke neutrophilic infiltration of the lungs. Air pollutants have been shown to be important factors influencing both virus transmission and COVID development [48]. It is logical that the inflammatory process is amplified by smoking in severe stages of COVID. Controversies can arise, however, if nicotine, the stable constituent of cigarettes, is found to be protective against COVID progression. Nicotine has been found to be an agent that can prevent the onset of Acute Respiratory Distress Syndrome in animal models [49]. Nicotine has some anti-inflammatory properties due to agonistic cholinergic action [50]. Moreover, it inhibits the production of IL-6 and some other cytokines with no influence on interleukin-10 release [51]. Nicotine is approved by the FDA for medical use, but with many contraindications. Nicotine's mechanism of action might explain the controversies surrounding the influence of smoking on COVID initiation [52, 53]. However, emerging data indicate that both past and especially current smoking is an important determinant of worsening COVID-19 outcomes. This can have a positive effect on patients trying to quit smoking because the potential severity of the infection combined with the general knowledge about the harmful influence of smoking creates a situation where patients may consider smoking cessation. In fact, during the pandemic, many smokers tried to quit their smoking habit [54–56].

For individuals who use e-cigarettes, it is important to remember that they also have many harmful properties and can create a real hazard for future smoking addiction [57]. Heat-not-burn (HNB) tobacco products produce aerosol like traditional cigarettes, but with a lower level of harmful constituents, including carcinogens. It is important to remember that the impact of HNB products on population-level risk reduction will be maximized if smokers completely switch to the product (and abandon cigarettes). Individuals who use these products will find that their daily nicotine exposure remains stable or is reduced. That being said, the product will only reduce population-level risk if it does not attract non-smokers [58, 59]. To date, no study on vaping or HNB product use during COVID is available and discussing the possible result of replacing cigarette smoking with less harmful products is pure speculation. However, it seems logical that in smokers in whom all methods of smoking cessation were ineffective, new and different methods for combatting tobacco addiction should be explored.

To sum up this part of our considerations, it is evident that smoking promotes the progress of COVID-19. Paraphrasing Mark Twain, one can say that "there is evil, damned evil and cigarette smoking". Because of sociopsychological circumstances, the SARS-CoV-2 pandemic is an opportune time for smoking cessation in addicted people. The potential anti-inflammatory activity of nicotine does not seem to be significant seeing as the majority of studies show smoking as a promoting factor in the SARS-CoV-2 infection. However, nicotine replacement therapy (patches, gums) might be used during cessation therapy because of possible anti-inflammatory properties and a small risk of potential side effects. During smoking cessation, all known methods (i.e. psychosocial support, cytisine, varenicline) can be used. In smokers unable to quit smoking traditional cigarettes using these methods, using HNB products instead of traditional cigarettes may be recommended. According to a report by an independent study of Polish people trying to quit smoking, 50% of HNB product users achieved success. This is more than users of e-cigarettes, where only 25% of individuals succeeded. Moreover, in many young people, nicotine dependence starts from the use of e-cigarettes [23]. We do not recommend e-cigarettes since the balance of potential advantages and disadvantages from a public health point of view is negative.

When the lungs wear the pants…

Sex seems to be an interesting issue in the context of COVID-19. Notably, recent survival analysis performed by Li *et al.* revealed that male sex was one of the significant risk factors associated with death in patients with severe COVID-19 [6]. Chen *et al.*, in their early report from Wuhan, also reported that those who died in their cohort were more likely to be male [4]. Similarly, higher risks have been reported for men in the Italian population [7]. Another study by Jin *et al.* focused purely on gender differences in patients with COVID-19 in the context of severity and mortality and concluded that while males and females have the same prevalence, men infected with COVID-19 are at a greater risk for worse outcomes and death, independent of age [8].

In terms of analysis, we should initially examine differences in the expression of ACE2 by gender. Notably, it is activated and down-regulated by the spike protein of the virus which allows for the penetration of SARS-CoV-2 into epithelial cells and the myocardium. There is

evidence suggesting that hypertensive male mice have a spontaneously higher myocardial ACE2 expression than females, and that its levels decrease after orchiectomy [60]. This observation is concordant with the strong body of evidence indicating that ACE2 expression and activity may be influenced by sex hormones [61–65]. In light of this evidence, La Vignera *et al.* suggested that testosterone (or LH/hCG) administration could be temporarily discontinued or given at a lower posology in patients with hypogonadism, while estrogen replacement therapy may be considered in hypogonadal and postmenopausal women [60].

Male vulnerability to COVID-19 may be further enhanced by X-linked inheritance of genetic polymorphisms seeing as loci of both androgen receptors and ACE2 genes are located on the X chromosome [66].

On the other hand, ACE2 is also expressed in the testes (in spermatogonia, Leydig cells, and Sertoli cells) [67–69]. Ma *et al.* found that the level of serum luteinizing hormone (LH) was significantly increased, but that the ratio of testosterone to LH and the ratio of follicle stimulating hormone to LH was significantly decreased in males with COVID-19. This evidence, showing disturbances in male gonadal function, indicates the need for an increased focus on the evaluation of gonadal function among patients who have recovered from the SARS-CoV-2 infection, especially in reproductive-aged men [67].

Another interesting issue in the context of sex is transmembrane serine protease 2 (TM-PRSS2) which is a critical factor in enabling cellular infection by coronaviruses, including SARS-CoV-2. Notably, androgen receptor activity seems to be required for the transcription of the *TMPRSS2* [66, 70].

In turn, McCoy *et al.* hypothesized that androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia would be associated with racial variations in COVID-19 mortality. Authors also suggest that the use of anti-androgens like bicalutamide and enzalutamide or androgen modulators like finasteride and dutasteride may be beneficial [71].

Additionally, we have to emphasize that an increasing body of evidence indicates that there are dimorphic immune response differences to viral infections between males and females. These differences are unfavorable for males, who present with a higher mortality rate in epidemiological studies. Indeed, females mount a stronger immune response to viral infections due to more robust humoral and cellular immune responses.

It is suggested that estrogen and testosterone differentially alter expression of genes involved in innate immunity (i.e. those encoding TLRs and interferons) thereby contributing to sexual dimorphism in the response to viral infections. These issues may also contribute to sex differences in the natural history of COVID-19.

However, most of the above-mentioned issues are just hypotheses and should be further verified. This is especially true in terms of the specific roles and levels of androgens in the pathobiology of COVID-19.

Conclusions

This review highlights the important role of ageing, sex, and smoking in the pathobiology and clinical landscape of COVID-19. We especially focused on their significant role in disease severity and mortality. However, in spite of intensive research, most of the presented pieces of evidence are weak and need further verification.

Conflict of interest

None declared.

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