Nutrafoods (2020) 2:176-185 DOI 10.17470/NF-020-0024

Commentary

COVID-19, interleukin-6, androgen receptor and the adipose organ: what are the possible targets of this association?

Abstract

On March 11th 2020, the World Health Organisation (WHO) declared COVID-19 the first pandemic due to a coronavirus. Clinical severity can vary significantly; some patients are asymptomatic, others develop mild infections of the upper respiratory tract, while others develop severe pneumonia and acute respiratory distress syndrome (ARDS). Risk factors are elderly age, a high sequential organ failure assessment (SOFA) score and chronic comorbidities. The knowledge of these factors is very important but they do not explain the disparity between the sexes or the deaths of young patients who did not have any health problems before the diagnosis of SARS-CoV-2 infection. Among the various factors that could help explain these dynamics, it is of great interest to investigate the potential contribution of the soluble androgen receptor (AR) and of the adipose organ, with particular reference to the actions of leptin.

If what was proposed in this analysis were confirmed by surveys, it would be possible to consider acting at the level of these molecular objectives, with different synthesized or extracted molecules including bicalutamide and magnolol for AR, and curcumin, silibinin and other molecules for leptin. Further studies are needed to validate this suggestion.

These studies could help to find new treatments and provide useful information for a better assessment of the risk of serious SARS-CoV-2-related disease, taking into account the susceptibility and characteristics of the host.

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Keywords: Coronavirus, SARS-CoV-2, COVID-19, adipose organ, IL-6

Introduction

Coronaviruses are very common microorganisms that can infect both human beings and other species.

These microorganisms, belonging to the *Coronaviridae* family, are enveloped viruses with a positive-sense single-stranded RNA genome. The envelope is composed of phospholipids and it contains a series of proteins that are necessary for viral functions [1]. Most coronavirus infections lead to positive clinical courses with mild symptoms. However, the most recent infections caused by *Betacoronavirus*, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), resulted in more than 10,000 cases and their mortality rates were, respectively, 10% and 37% [2–4].

In December 2019, a number of pneumonia cases of unknown origin were reported in Wuhan, Hubei, China. The symptoms resembled viral pneumonia. Analysis of lower respiratory tract samples indicated a new coronavirus, which was initially named 2019-nCoV and then SARS-CoV-2. Unfortunately, the virus developed very quickly. It started as a local epidemic, then evolved into multiple outbreaks and finally, into a pandemic. Thus far (World Health Organisation; WHO Situation Report 183, July 21st 2020), 14,562,550 people have been infected and 607,781 people have died. The mortality rate is higher in elderly people and in individuals with comorbidities. SARS-CoV-2 is a new coronavirus belonging to the *Betacoronavirus* genus, which is responsible for the third infection with zoonotic transmission caused by a coronavirus after SARS and MERS [5]. According to the collected data [6], early cases were linked to the Huanan seafood market in Wuhan, Hubei, China.

From there, the infection spread on a local and then on a global level through efficient human-to-human transmission.

On March 11th 2020, the WHO declared COVID-19 the first pandemic due to a coronavirus. Clinical severity can vary significantly. Some patients are asymptomatic, others develop mild infections of the upper respiratory tract, while others develop severe pneumonia and acute respiratory distress syndrome (ARDS) which can, eventually, lead to death [7–9]. Risk factors are an elderly age, a high sequential organ failure assessment (SOFA) score and chronic comorbidities [10, 11]. These factors do not explain, however, the disparity between the sexes or the deaths of young patients who did not have any health issues before being diagnosed with SARS-CoV-2 infection [12].

A recent study showed that a sex disparity exists for patients with severe COVID-19 infection, with male sex representing an important independent risk factor [odds ratio (OR) = 3.60; 95% confidence interval (CI) = 1.75–7.75]. Hypertension [OR = 2.71; 95% CI = 1.32–5.59] and older age (>50) [OR = 1.06; 95% CI = 1.03–1.08] [13] are also associated with increased severity of the disease.

Other studies have shown that there is a difference in severity among male and female patients with COVID-19. Wei *et al*. [14] carried out a study on 77,932 patients, of whom 41,510 (53%) were men. Their meta-analysis showed that men had a higher risk of developing severe illness compared to women [OR = 1.63; 95% CI = 1.28–2.06] and a higher mortality [OR = 1.71; 95% CI = 1.51–1.93].

Moreover, another study considered 1,099 patients, of whom 58% were male.

Out of 67 patients with severe symptoms who had to be taken to intensive care units, needed non-invasive ventilation or died, 67% were male [7]. At the same time, obesity seems to be an important risk factor, which may partially explain the higher mortality rate in Italy and in the USA compared to China [15]. Recently, a retrospective study from a French

centre has been published. It shows that the proportion of patients who needed invasive mechanical ventilation (IMV) increased along with the BMI (p<0.01). It also shows that resort to IMV was associated with male sex (p<0.05), irrespective of age, the presence of diabetes or hypertension [16].

Virus–host interaction and infection dynamics

One of the main characteristics of SARS-CoV-2 is its ability to cause lung damage, which can lead to ARDS [4]. In the first phase, the virus replicates and cytolysis occurs. During this phase, symptoms resembling influenza may appear. In the second phase, symptoms become more severe and some patients may develop pneumonia and ARDS, typically within 5–10 days from when the first symptoms appeared [17]. From a mechanism point of view, SARS-CoV-2 exploits ACE2 for entry to the cell through a surface protein called spike (S) protein (180 kDa) [18, 19]. The spike protein binds to a cellular receptor after priming through the serine protease TMPRSS2. Without TMPRSS2 the virus cannot enter the cell [20]. The binding allows for the invasion of the oropharyngeal epithelial cells [21]. However, not only can ACE2 act as the "entrance door" for the virus, but it can also be involved in the pathogenesis of the disease, given its implications in the development of ARDS [22].

ACE2 counter-regulates the formation of angiotensin II, a peptide causing vasoconstriction, by ACE (targeted by antihypertensive ACE-inhibitor drugs). ACE2 catalyzes the conversion of angiotensin into angiotensin-(1-9) and angiotensin-(1-7). According to some authors, angiotensin-(1-9) is an ACE inhibitor [23], whereas angiotensin-(1-7) has been identified as a hypotensive agent [24]. Angiotensin II can induce the activation of a number of cells within the immune system [25], such as T cells, endothelial cells, fibroblasts, macrophages and monocytes, and the production of pro-inflammatory cytokines such as IL-6 [26, 27] and TNF-α [28]. The link between the virus and ACE2 can explain several aspects of COVID-19 pathogenesis [29].

When the virus interacts with ACE2, it causes its down-regulation, local activation of immune cells, an increase in inflammation and cellular death. In the lungs, ACE2 is expressed by type 2 alveolar cells (AT2) [30], which, despite only accounting for 5% of alveolar cells, are responsible for the production of pulmonary surfactant, essential for lung elasticity.
They also give rise to type 1 alveolar cells (AT1), which are responsible for gas exchange [31].
A reduction in AT2 and surfactant deficits have been previously associated with incomplete repair of damaged alveoli in lung epithelium and fibrotic obliteration [32]. This may explain lung damage caused by COVID-19.

It is worth noting that ACE2 presence was detected in spermatogonia using transcriptome analysis, and a considerable presence was also observed in Leydig and Sertoli cells. This means that human testicles can also be targeted by the virus. ACE2-positive spermatogonia seem to express a higher number of reproduction- and viral transmission-related genes and a lower number of spermatogenesis-related genes compared to ACE2-negative spermatogonia. ACE2-positive Leydig and Sertoli cells express a higher number of genes involved in cell junction formation and in immune processes than those that are ACE2-negative. They also express a lower number of genes associated with mitochondrial activity and reproduction compared to ACE2-negative Leydig and Sertoli cells [33]. These results suggest that testicles are at risk and can be targeted by SARS-CoV-2. This factor should be taken into account when analyzing higher mortality rates in men.

The aggravating role of inflammation

As for the inflammation caused in SARS, lung inflammation caused by SARS-CoV-2 has been compared to uncontrolled immune activation, which has been observed during haemophagocytic lymphohistiocytosis (HLH) [34] or in cytokine release syndrome.

The latter has been observed during antitumoural treatments [35] and in sepsis [36]. In fact, in some cases of severe infection by SARS-CoV-2, significant immune system activation has been observed through high levels of procalcitonin, ferritin and IL-6 [10]. More specifically, increased serum levels of pro-inflammatory cytokines, such as TNF-α, IL-1 and IL-6, have been observed in patients with severe SARS-CoV-2 infections [37]. The deaths of patients with ARDS have been associated with a consistent increase in IL-6 and IL-1 levels [34]. Preliminary data suggest that the severity of the infection caused by SARS-CoV-2 can be associated with a decrease in IFN-γ production by CD4+ T cells [38], meaning that patients with a severe illness may lack a front line against the virus. As with HLH, a loss in front line antiviral defence could underlie a second wave of more aggressive immune activation headed to the tissue that includes the anomalous production of IL-6, which leads to a second cytokine storm. Preliminary trials show that blocking cascades of IL-6 by preventing interaction with the IL-6 receptor (IL-6R) using the humanized monoclonal antibody tocilizumab may prove effective [39, 40]. However, it should be noted that it is unclear whether high levels of IL-6 could be dangerous only in cases of SARS-CoV-2-related pneumonia. In experimental models IL-6 can both suppress and facilitate viral replication [41]. Further studies are needed in order to investigate its role in the infection caused by SARS-CoV-2. In light of this, the timing of potential anti-IL-6R treatment is crucial. In theory, if the treatment is administered too early, it could delay viral clearance. As has been previously shown, men seem to incur a higher risk of developing a serious form of infection by SARS-CoV-2 than women. The mechanisms that underpin this disparity between the sexes are not clear. Some studies show that oestrogens may play a protective role [42, 43], thus explaining such differences between the sexes.

Wei *et al*. [14] identified a higher percentage of ACE2, expressed by AT2, and a higher expression of IL-6ST (also called gp130, IL6ST, IL6-beta or CD130) in men. Given the pathogenetic mechanisms previously mentioned, this may explain why men are more likely to develop a serious infection than women. Another important role is played by the soluble androgen receptor (AR). When activated, it can positively regulate ACE2 expression [14].

Other studies have already shown that androgens can modulate inflammation in numerous organs [44, 45]. AR, in particular, may also play a role in the development of cytokine storms. Oncology models have shown that, by binding directly to the IL-6 gene promoter, AR can increase IL-6 transcription. This, in turn, can activate the expression of the AR gene, thus creating a circuit of mutual STAT3-mediated amplification [46, 47]. Given the higher degree of androgen expression in men, AR can be considered another important co-factor in the development of severe forms of the illness.

As previously described, transmembrane protease serine 2 (TMPRSS2) allows the virus to enter the cells. It must be noted, therefore, that the transcription of the TMPRSS2 gene requires AR activity, because no other regulatory element has been described in humans thus far for this gene apart from the AR promoter [48, 49].

Furthermore, TMPRSS2 mRNA expression seems to be regulated by the presence of androgens in prostatic cells and AR is responsible for TMPRSS2 mRNA up-regulation [50, 51].

The TMPRSS2 gene is mainly expressed in prostate cells, but it can also be expressed in other tissues such as the colon, small intestine, pancreas, kidneys, lungs and liver [52].

Should this information be confirmed, a series of add-on therapy opportunities may be contemplated. Professionals could use AR activation inhibitors such as bicalutamide, which can bind to AR without activating gene expression, thus inhibiting the androgenic stimulus [53], or magnolol, which can regulate STAT3 phosphorylation with a JAK-dependant mechanism, thus suppressing IL-6 effects without compromising JAK activation [54] (**see Fig. 1**).

The possible role of the adipose organ

Obesity has been included among the factors leading to the development of a serious infection by SARS-CoV-2 and causing a higher mortality [15]. A review by Guzik *et al*. analyzed the role of adipocytokines as potential linkers between inflammation and vascular functions. In light of data presented in the scientific literature, the review also focused on different associations between these molecules and other elements involved in the inflammatory

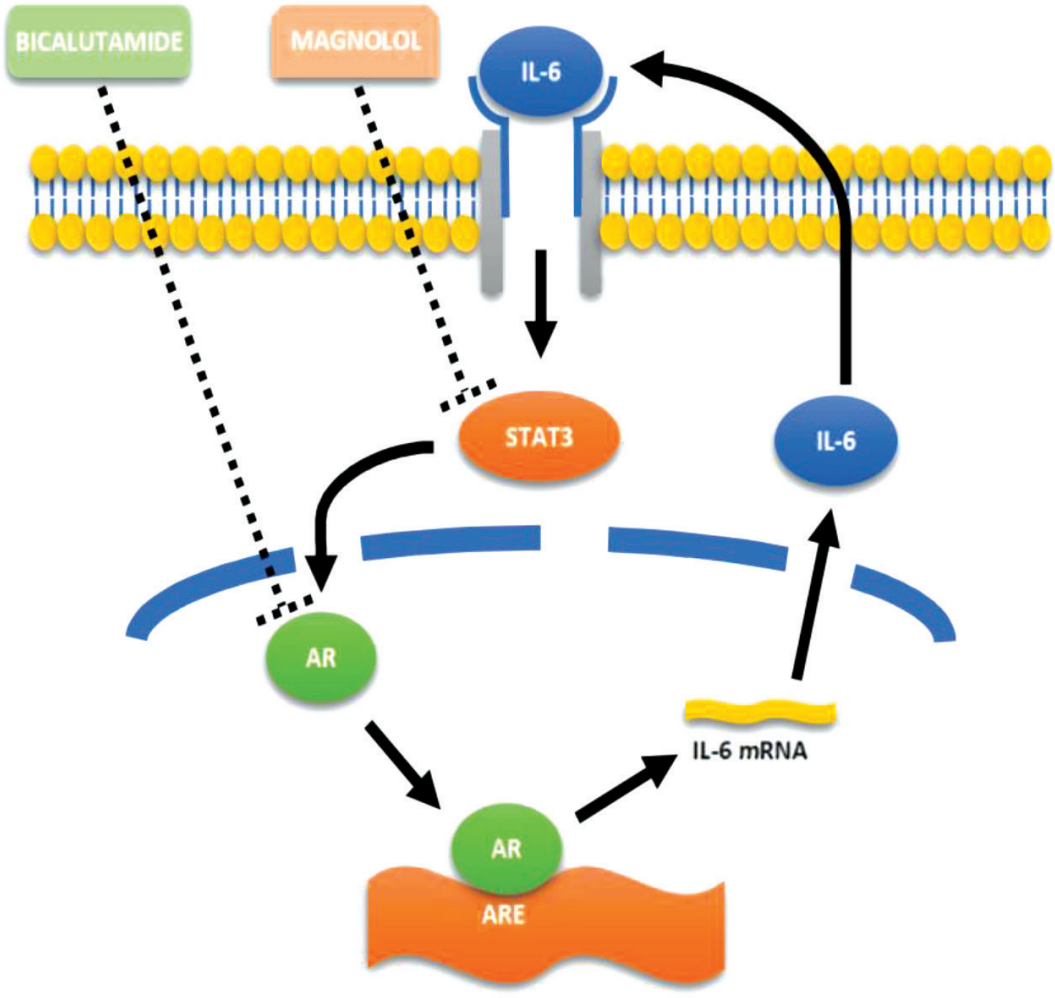

Figure 1 Potential add-on therapies for the treatment of COVID-19, targeting the soluble androgen receptor (AR) and its interaction with the IL-6 cascade

response, which could be relevant to infection by SARS-CoV-2 [55]. Obesity is characterized by a generalized subclinical inflammation, with high C-reactive protein levels and significant pro-inflammatory cytokine production, due to the atypical action of some cells within the immune system [56]. Adipose tissue is considered an organ [57] with endocrine functions [58] that can exert an effect on the immune system and on inflammatory cascades, due to adipocytokines. Adipocytokines are produced in the adipose organ, the most predominant being leptin, resistin and adiponectin. A close relationship exists between adipocytes and pro-inflammatory cytokines. Apart from being produced by immune cells present in the adipose organ [59], pro-inflammatory cytokines can be produced by adipocytes. Adipocytes can produce TNF-α and IL-6, linking obesity and inflammation dynamics. Almost 30% of IL-6 production in obese patients is due to adipocytes [60]. The production of chemokines may also be responsible for macrophagic infiltration within the adipose organ, potentially creating a self-perpetuating circuit [60]. Leptin is a protein that is mainly expressed at an adipocyte level. It can also be expressed at gastric, vascular, ovarian, placental, muscular and hepatic levels [58, 59, 61, 62].

One of the main roles of leptin is appetite regulation in what has been described as the brain–gut axis, providing satiety signals at a hypothalamic level [62–64]. Leptin levels are directly proportional to fat mass levels, increasing or decreasing according to their variation [65]. A number of cytokines such as TNF-α and angiotensin II [66] can be included among the agonists that facilitate leptin secretion by adipocytes. Leptin has a number of effects on different parts of the body, especially on the cardiovascular and immune systems [59, 61, 67, 68], and it has also been linked to cancer [69].

Leptin can exert pro-inflammatory effects because of structural similarities with cytokines such as IL-6, GM-CSF or IL-12 [60]. Moreover, several immune cells such as granulocytes, monocytes, macrophages and lymphocytes can also express leptin receptors [70–73] activating other immune cells such as monocytes, lymphocytes and neutrophils, thus linking nutritional status and the immune response [74].

In addition to the presence of the leptin receptor, it is worth noting that leptin- and STAT3 transcription factor-induced tyrosine phosphorylation has been observed in endothelial cells of human umbilical veins [75]. Should these data be confirmed, this may overlap with the AR activation mechanism associated with IL-6 in other cellular lines, demonstrating another potential element that could intervene in turning on and feeding the previously described self-perpetuating circuit. Research using several experimental models has identified curcumin and silibinin as modulators of leptin and resistin expression. These are extracted respectively from *Curcuma longa* and *Silybum marianum*. Similar effects have been observed with molecules extracted from *Capsicum annuum*, *Cinnamomum zeylanicum*, *Eugenia caryophyllus*, *Piper nigrum* and *Zingiber officinalis* [76–80]. The mechanisms underlying these effects are as yet unclear.

Conclusions

Numerous factors can explain a higher rate of severe illness in men. These encompass physiologic factors such as lower hormonal-mediated protection from cardiovascular diseases [81, 82], viral infection in the testicles [33] or behavioural factors such as differences in smoking behaviour [83] between men and women, which have already been associated with an increased severity of illness [84].

This review may prove useful in explaining the increased severity and mortality associated with SARS-CoV-2 infection in men, especially those who are obese, proposing that AR plays a

crucial role as a precipitating factor, exploiting high levels of leptin in obese patients. If this information is confirmed, a new anti-AR therapy using bicalutamide and/or magnolol may be considered. This could be a new add-on strategy to treat SARS-CoV-2 infection in male patients. This therapy could also be integrated with the aforementioned molecules, thus modulating leptin expression in obese patients. Further studies are necessary to validate this suggestion. In addition, not only may such studies find new treatments, but they could also provide useful information for a better assessment of the risk of severe SARS-CoV-2 illness, taking into account the susceptibilities and characteristics of the host.

Author contributions

Conceptualization: AB, DB, MN, ABr; writing: AB, DB; original draft preparation: AB, DB.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

The authors wish to thank Virginia Bressan for the language revision.

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