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The renin–angiotensin–aldosterone system as a link between obesity and coronavirus disease 2019 severity

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Summary

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory distress coronavirus 2 (SARS-CoV2), is a rapidly evolving pandemic challenging the world and posing unprecedented public health issues. Current data show that COVID-19 is associated with increased disease severity in individuals with obesity. Obesity is usually associated with dysregulated renin–angiotensin–aldosterone (RAAS) axis. RAAS has also been implicated in acute lung injury as well as myocardial injury and has thus attracted interest as a potential regulator of COVID-19 severity. Whilst research all over the world is still struggling to provide a detailed characterization of the biology of SARS-CoV2 and its associated disease profile, it has become evident that SARS-CoV2 uses the membrane-bound form of angiotensin-converting enzyme 2 (ACE2) as a receptor for cell internalization. ACE2 is a protective component of the RAAS axis and is downregulated after SARS-CoV2 infection. The RAAS axis could thus be a link between obesity and COVID-19 severity; therefore, more accurate understanding of the underlying mechanisms would be needed with the hope of proposing efficient therapeutic interventions.

KEYWORDS

ACE2, angiotensin, COVID-19, obesity, RAAS

1 | INTRODUCTION

The Coronavirus disease 2019 (COVID-19) is a rapidly evolving pandemic.[1] Despite intensive research on the field, self-isolation measures and supportive treatment remain the mainstay of prevention and treatment, respectively.[2] Interestingly, the aetiologic agent behind COVID-19, severe acute respiratory distress coronavirus 2 (SARS-CoV2), interacts with angiotensin-converting enzyme 2 (ACE2), a part of the renin–angiotensin–aldosterone (RAAS) axis, suggesting therapeutic implications for this axis.[3–5]

Obesity, usually defined by body mass index (BMI) > 30 kg/m^2, is characterized by visceral adipose tissue (AT) expansion and inflammation.[6] As such, the waist-to-hip ratio has been proposed as a more accurate marker of visceral obesity, although less used in clinical practice.[7] Inflamed AT secretes pro-inflammatory cytokines, adipokines and other molecules with broad pathophysiological effects.[7–12] Indeed, visceral obesity is associated with conditions such as hypertension, diabetes and dyslipidaemia.[9,13] Evidence suggests that RAAS signalling is upregulated in obesity, potentially being a target in obesity-associated diseases.[14–16]

Observational findings indicate that COVID-19 severity is associated with the presence of co-morbidities such as hypertension, diabetes and obesity.[17–20] However, the possible independent association of obesity with COVID-19 clinical features has not been examined in large appropriately designed patient cohorts.[17] Optimal interventions in COVID-19 patients with obesity are controversial because of lack of underlying mechanism characterization. We hereby discuss the potential role of RAAS in COVID-19 patients with obesity, focusing on lung and myocardial injury, the main causes of adverse outcome in COVID-19.

2 | OVERVIEW OF RAAS

RAAS regulates fluid balance, blood pressure and cardiorenal function.[21] RAAS activation is initiated upon secretion of renin, an enzyme produced in the pericytes of the glomerular afferent arterioles and the juxtaglomerular apparatus of the nephron.[21] Secretion stimuli include reduced glomerular blood flow, reduced tubular sodium flow and sympathetic stimulation.[21,22] Renin converts angiotensinogen to angiotensin I (AngI), which is transformed to angiotensin II (AngII) via angiotensin-converting enzyme 1 (ACE1),[21,23] causing vasoconstriction, adrenal aldosterone secretion and renal retention of sodium and water.[14,16]

Several pathogenic mechanisms are able to bypass the physiological RAAS loop.[24–26] Reduced effective circulating blood volume (as in congestive heart failure) is sensed as virtual hypovolaemia by the kidneys, which, coupled with sympathetic activation, leads to inappropriate RAAS activation.[27] Pro-inflammatory conditions such as atherosclerosis and obesity-related AT inflammation may also increase AngII and aldosterone secretion by macrophages and adipocytes.[28–31] RAAS overactivation, in turn, regulates macrophage M1 activation, oxidative stress, fibrosis and pro-inflammatory cytokine production.[32,33]

ACE2 regulates RAAS by degrading AngII to Ang (1–7) as well as by alternatively cleaving AngI to Ang (1–9) instead of AngII,[34] inhibiting downstream AngII signalling.[33] Interestingly, Ang (1–7) has its own receptor, Mas, which can reduce pro-inflammatory cytokine release, facilitate vasorelaxation and ameliorate tissue fibrosis in experimental models of atherosclerosis, obesity, asthma and heart failure.[35–37]

RAAS is pharmacologically modifiable by angiotensin type 1 (AT1) receptor blockers (ARBs) and ACE1 inhibitors, which are widely used in clinical practice.[33] By blocking downstream AngII signalling, ARBs and ACE1 inhibitors may have a stimulatory feedback effect on ACE2, although in vivo studies on this are inconsistent.[33,38,39] Currently, pharmacological RAAS inhibition is assumed to increase ACE2, particularly after long-term treatment, although the clinical relevance of this is controversial.[33]

3 | RAAS IN OBESITY

Although inter-individual differences may be observed, obesity usually induces RAAS activation via complex mechanisms.[15] Obesity results in dysregulated AT, which secretes angiotensinogen, mineralocorticoids and mineralocorticoid releasing factors such as leptin, enhancing the angiotensin/aldosterone axis and further stimulating the adrenal glands towards aldosterone production.[14,15,30] Furthermore, obesity is associated with endothelial dysfunction and hyperinsulinaemia, which may further exaggerate endothelial dysfunction.[40] These result in disturbed renal blood flow and elicit a renal response similar to that of hypovolemia, leading to enhanced RAAS activation.[15,30] AT may also secrete cathepsins, which promote enzymatic conversion of AngI to AngII.[30]

Obesity also interacts with RAAS via neurohormonal mechanisms. Firstly, obesity is associated with sympathetic nervous system activation, a potent stimulator of renin secretion.[41] Leptin is an adipokine that is upregulated in obesity and acts in various regions of the central nervous system such as the hypothalamus and the brainstem, inducing sympathetic activation as well as food intake, further stimulating renal renin secretion.[15,42] Interestingly, AngII increases adrenal catecholamine secretion and target organ sympathetic specificity via AT1 receptors,[26,43] whilst it may modulate food intake via hypothalamic effects,[44] suggesting a bidirectional neurohormonal crosstalk with obesity that warrants further investigation in humans.

Obesity is also associated with reduced expression of ACE2 in AT, which has been linked with a variety of obesity-associated complications such as exaggeration of heart failure, hypertension and renal failure.[36,45,46] ACE2 may exert direct anti-obesity effects by promoting AT browning and lesser white AT accumulation[46] and ameliorating AT inflammation[36,47] as evidenced in mechanistic studies, warranting further investigation in humans.

4 | RAAS AND ALI

The RAAS axis is implicated in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) via AngII signalling. In *in vitro* studies, AngII induces collagen production in lung fibroblasts via transforming growth factor beta (TGFβ) and induces pneumonocyte apoptosis.[48] In an *in vivo* mouse model of ALI, AngII induced lung fibrosis, which was reversed by losartan, an ARB.[49] In a rat model of lipopolysaccharide-induced sepsis, losartan upregulated lung ACE2 and reduced histopathological lung damage and production of pro-inflammatory cytokines such as interleukin 6 (IL6) and tumour necrosis factor alpha (TNFα).[50] Similarly, losartan reduced nuclear factor kappa beta (NFκB) signalling in lung tissue and plasma IL6, TNFα and interleukin 1 beta (IL1β), improving ALI/ARDS in mice.[51] Losartan may reduce alveolar cell permeability, attenuating pulmonary oedema in mouse models of ALI/ARDS.[52]

Importantly, ACE2 may have protective effects in the context of ALI and ARDS, as evidenced by *in vivo* mouse models.[53] In mice, ACE2 deletion worsened ALI via increased alveolar cell permeability and pulmonary oedema,[54] whilst ACE2 demonstrated anti-inflammatory effects in sepsis-related ALI.[55] ACE2 may regulate alveolar cell permeability by antagonizing the effects of vascular endothelial growth factor alpha (VEGFα).[56]

In human studies, genetic polymorphisms of the ACE1 gene have been linked with adverse outcome following ARDS.[57,58] AngII plasma levels have been linked with ALI severity following other viral infections such as H7N9 influenza infection[59]; however, the biomarker potential of AngII is compromised by its large between-patients variability.[60]

5 | RAAS AND MYOCARDIAL INJURY

RAAS affects cardiac function owing to multiple mechanisms as described by various experimental mechanistic studies. AngII and

aldosterone induce myocardial remodelling and fibrosis, adversely influencing the pumping ability of the heart.[61] AngII also contributes to arrhythmogenic re-entry substrate formation via myocardial fibrotic mechanisms, which increase arrhythmia risk.[62] Whilst the previous mechanisms may become established over time, RAAS also has short-term effects on the myocardium, which may be of particular relevance in acute conditions such as COVID-19 infection. Such effects include fluid retention and peripheral vasoconstriction by AngII and aldosterone, which increase ventricular afterload, worsening cardiac function[61,63] and induction of myocardial inflammation by AngII signalling.[64] In animal models of acute myocarditis, RAAS blockage may rapidly and directly reduce myocardial inflammation, suggesting an involvement of RAAS in the pathophysiology of myocardial injury secondary to acute viral infections.[65,66]

A large number of randomized clinical trials in humans have clearly documented a beneficial role of RAAS inhibition (using ACE1 inhibitors and ARBs) with regard to management of hypertension, chronic renal disease and heart failure, improving myocardial function and cardiovascular outcomes indirectly or directly via the aforementioned mechanisms.[61,67–69] Furthermore, the potential protective role of RAAS blockade in atrial fibrillation is actively investigated in human randomized clinical trials.[62] The exact involvement of RAAS in human myocardial injury secondary to viral infections such as COVID-19 has not been directly investigated, albeit highly plausible.

6 | RAAS AND COVID-19

COVID-19 is caused by SARS-CoV2, a coronavirus with >70% genomic homology to SARS-CoV, another coronavirus responsible for the SARS pandemic in 2003.[70,71] The mechanism of SARS-CoV2 infection is unclear. Haemoglobin has been proposed to be a docking protein for the virus, which is in consistence with the observation that haemoglobin levels are reduced in COVID-19 patients; however, this is mainly based on in silico studies.[72,73] However, the predominant theory involves spike protein S of the viral capsule interacting with surface ACE2 of host cells to facilitate cell infection.[71,74] Importantly, its receptor-binding domain (RBD) shows improved affinity to human ACE2 compared with SARS-CoV, as revealed by crystallographic visualization of RBD–ACE2 interactions.[4,74,75] Genetic polymorphisms of the ACE2 gene influence susceptibility to disease severity following SARS-CoV infection[53]; if this is also the case for SARS-CoV2 needs further investigation.

SARS-CoV cell infection causes subsequent downregulation of membrane ACE2 in the infected cells *in vitro*, probably via transcriptional regulation secondary to virus infection.[53] Similarly, SARS-CoV2 appears to also downregulate ACE2 upon cell entry *in vitro*.[76] It is unclear whether ACE2 contributes to COVID-19 pathophysiology via its downregulation, beyond its SARS-CoV2 receptor properties. ACE2 is expressed in both alveolar cells and cardiomyocytes, which may explain the severe lung and myocardial injury observed in COVID-19 patients.[53,77]

Given the role of ACE2 in regulating both COVID-19 infection and RAAS activation, it has been speculated that RAAS may be of importance in SARS-CoV2 severity. In a small cohort of COVID-19 patients, plasma AngII levels were positively correlated with SARS severity and viral load.[78] Recombinant ACE2 reduces AngII levels and improves ALI in experimental models of influenza A H5N1 and respiratory syncytial virus infections,[79,80] whilst it may reduce ARDS severity in humans.[81] Based on these observations, recombinant ACE2 may be a modifiable RAAS regulatory factor with beneficial effects in COVID-19.

7 | OBESITY AND COVID-19: IS RAAS A MODIFIABLE LINK?

Obesity is a significant risk factor for mechanical ventilation and adverse outcome in a number of viral pneumonias.[17] The Centers for Disease Control and Prevention consider patients with morbid obesity (BMI > 40 kg/m^2) as being at high risk for influenza complications.[82] During the 2009 H1N1 pandemic, more than 50% of patients requiring hospitalization suffered from obesity (BMI > 30 kg/m^2), which was recognized as an independent risk factor for adverse outcome.[17,82]

Consistently, current clinical experience indicates that obesity is associated with increased COVID-19 severity and adverse outcomes.[17,83] As many as 40% of COVID-19 patients being hospitalized in intensive care units are believed to have BMI > 30 kg/m^2.[84] Importantly, a recent metanalysis of clinical COVID-19 series reports that patients with obesity graded by BMI have a three-fold increase in the odds ratio for critical disease compared with patients without obesity.[85] Further retrospective studies have shown that obesity is an independent risk factor for mechanical ventilation need in COVID-19, as well as a prominent risk factor in patients under 60 years of age.[86,87] On the other hand, obesity is also associated with a number of comorbidities including hypertension and diabetes,[83,88,89] whilst there are no specific clinical signs foreshadowing the progression from a mild COVID-19 infection to a severe form.[90] Further studies are needed to quantify the independent risk for COVID-19 severity posed by obesity.

Acute lung and myocardial injury are the main direct causes of death in COVID-19.[77,83] ALI and ARDS are hallmarks of COVID-19 infection, whilst ~20–30% of patients also have acute myocardial injury, marked by elevated high sensitivity troponin I circulating levels, an adverse predictor of COVID-19 severity and mortality.[91] RAAS, usually overactivated in patients with obesity, has been linked with SARS-CoV2 cellular infection as well as lung and myocardial injury (as explained above). Based on these considerations, it is plausible to hypothesize that RAAS is a mechanistic factor of particular importance in the context of obesity, driving COVID-19 severity via increased AngII signalling and loss of ACE2/Mas function[17,33,47] (Figure 1). To this end, there are still no appropriate studies to directly address this issue in the context of COVID-19, although the interacting mechanisms presented earlier make this hypothesis highly possible.

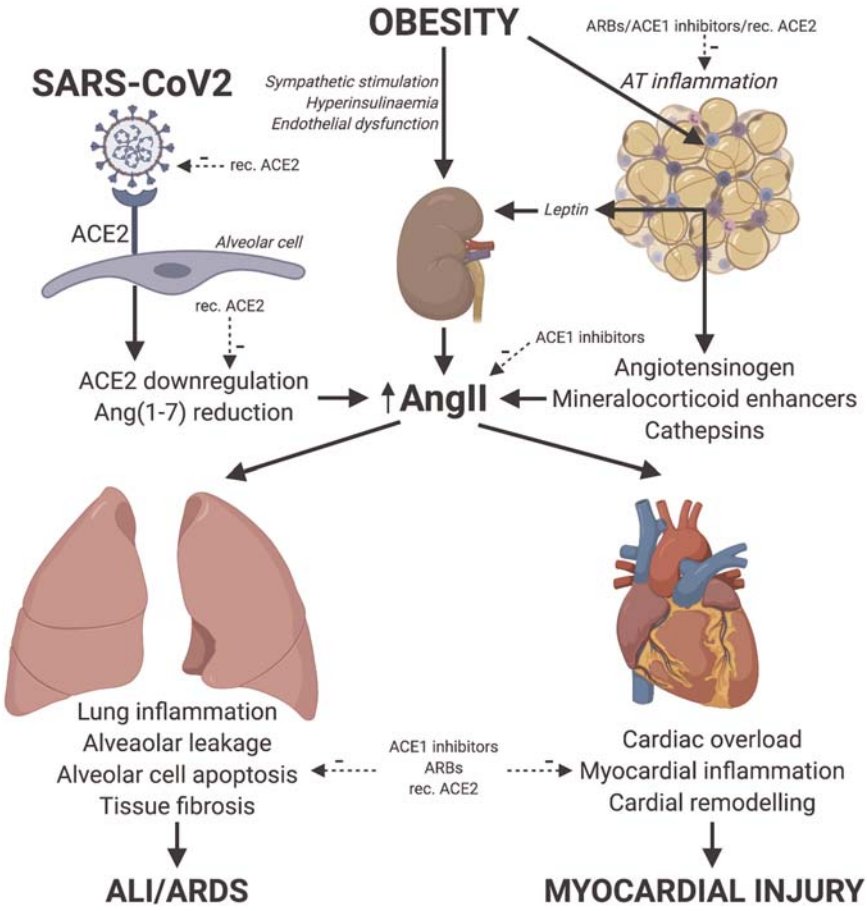

FIGURE 1 The renin–angiotensin–aldosterone (RAAS) axis as a link between obesity and coronavirus disease 2019 (COVID-19) severity. Obesity is associated with adipose tissue (AT) inflammation, which leads to the secretion of angiotensinogen, mineralocorticoid enhancers and cathepsins. Obesity also induces renal RAAS activation via neurohormonal signals mediated by leptin, sympathetic activation and renal vasomotor effects of hyperinsulinaemia and endothelial dysfunction. SARS-CoV2 infects host cells such as alveolar cells via angiotensin-converting enzyme 2 (ACE2) and causes downstream ACE2 and angiotensin (1–7) (Ang [1–7]) downregulation. The above synergistically result in increased levels of angiotensin II (AngII) in the lung, leading to increased alveolar cell permeability and apoptosis, fibrosis and inflammation. These pathogenic mechanisms enhance the severity of pulmonary oedema, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Enhanced AngII signalling in the myocardium also causes heart overload, myocardial inflammation and cardiac remodelling, which contribute to adverse outcome in COVID-19. Recombinant ACE2 (rec. ACE2) may scavenge SARS-CoV2 virions and also inhibit AT inflammation, AngII formation and downstream events. ACE1 inhibitors reduce AngII formation, whilst angiotensin receptor blockers (ARBs) reduce the downstream effects of AngII. Thus, in theory, these drug classes may decrease the adverse effects of COVID-19 in lungs and the myocardium

With definitive mechanistic studies still pending, the most relevant question is whether the interaction between obesity, RAAS and COVID-19 is modifiable. Efficient targeting of obesity is achievable via lifestyle changes, pharmacological agents such as glucagon-like peptide 1 agonists and bariatric surgery in humans.[92–94] Weight loss by as little as 5% may result in meaningful RAAS inhibition in humans.[95] Interestingly, dietary sodium restriction as well as exercise may be effective in RAAS blockade in humans.[95,96] Obesity-targeting lifestyle, dietary and pharmacological interventions may thus cause rapid changes in RAAS activation in patients at risk for COVID-19.

As mentioned earlier, RAAS is subject to direct modification by ACE1 inhibitors and ARBs, which have been extensively used in clinical practice against diseases such as hypertension and nephropathy.[33] On the other hand, the use of such agents in COVID-19 is controversial, because of their potential to upregulate ACE2, thus increasing SARS-CoV2 infection susceptibility.[5,33] However, this is hypothetical, with recent meta-analyses showing no increased risk of ACE1 inhibitors or ARBs with regard to COVID-19 severity.[97] Considering the detrimental effects of AngII on lung and myocardial biology, it has been hypothesized that ACE1 inhibitors and ARBs may actually protect against severe COVID-19 disease.[33] A retrospective study in hypertensive patients with COVID-19 showed that in-hospital use of ACE1 inhibitors and ARBs was, in fact, associated with reduced mortality.[98] Inhibition of the strong detrimental effects of AngII by ACE1 inhibitors and ARBs may be more important than the questionable effect of these drugs on ACE2 levels. The latter seems unlikely to drastically affect COVID-19 severity given the exponential multiplication of the virions and the small dependency on absolute ACE2 levels.

AngII signalling may also be modified by indirect ways besides ACE1 inhibition and ARB blockade. In the presence of AT1 blockade by ARBs, AngII may cross-activate angiotensin type II (ATII) receptors, which could convey protective effects in the context of ALI, although this is only hypothetical at this point.[99] Furthermore, it has been proposed that recombinant ACE2 infusion could improve outcome in COVID-19 via a two-fold mechanism involving neutralization of virions prior to membrane ACE2 binding and cell entry as well as enzymatic reduction of AngII, shifting the balance from AngII towards Ang (1–7).[53,99] To this end, preliminary clinical trials are being conducted to explore the role of recombinant soluble ACE2 in COVID-19 (NCT04287686) and the role of losartan in COVID-19 in patients having not received ACE1 inhibitor or ARB treatment previously (NCT04312009, NCT04311177).[33]

8 | CONCLUSION

The COVID-19 pandemic is spreading all over the world, causing significant morbidity and mortality and posing serious threat to national health systems worldwide. Obesity affects a great number of people worldwide, and importantly, it has been associated with increased COVID-19 severity. The RAAS axis is a pathophysiological mechanism that is upregulated by entities such as obesity and hypertension and is possibly implicated in COVID-19, with its inappropriate activation promoting ALI and acute myocardial injury. RAAS targeting may be of particular importance in COVID-19 patients with obesity, via behavioural, dietary and pharmacological means. Clinical evidence about direct RAAS blockade in COVID-19 is controversial to date, although latest work suggests a neutral or even protective effect that may rise from AngII signalling inhibition. Ongoing clinical trials are going to shed light to clinical RAAS-targeting interventions in COVID-19, which could prompt more focused interventions in patients with obesity.

CONFLICT OF INTEREST

TDF reports lecture honoraria from Boehringer Ingelheim, Mylan, Astra Zeneca, Lilly, Recordati, Bausch Health and Servier. IA reports no conflict of interest.

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