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OPINION
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Spironolactone: An Anti-androgenic and Anti-hypertensive Drug That May Provide Protection Against the Novel Coronavirus (SARS-CoV-2) Induced Acute Respiratory Distress Syndrome (ARDS) in COVID-19

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INTRODUCTION

At the onset of the COVID-19 pandemic, mortality following infection of severe acute respiratory coronavirus (SARS-CoV-2) was thought to be solely associated with aging and pre-existing conditions; however, as the pandemic ensued, several large scale epidemiological observations eluded to additional atypical risk factors, particularly hypertension, obesity, and male gender (1–11).

SARS-CoV-2: CURRENT KNOWLEDGE ON THE MECHANISMS OF ACTION

The peculiarities and complexity of SARS-CoV-2 infection patterns precluded definitive findings regarding the mechanisms of infectivity. Current literature suggests that angiotensin-converting enzyme-2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) are the key for SARS-CoV-2 cell entry (12–19). While ACE2 is the coupling site of the spike protein of SARS-CoV-2, TMPRSS2 facilitates SARS-CoV-2 spikes and ACE2 for viral cell entry. Although ACE2 expression is present diffusely, up to 80% of its expression is located in the type-2 pneumocytes (12, 17), which may explain why COVID-19 is predominantly pulmonary, although SARS-COV-2 may affect any organ and system. TMPRSS2 activity is modulated by androgens, which may justify why males are overrepresented among severe COVID-19 infected patients (20).

Current understanding of SARS-CoV-2 allows the division of COVID-19 into two phases (12–18). In a first, early phase, which corresponds to the period of SARS-CoV-2 cell entry, lung membrane-attached ACE2 expression seems to be positively correlated with virus infectivity, while the balance between circulating ACE2, that could protect from lung infectivity by coupling with SARS-CoV-2 and precluding from the entry into the pneumocytes (13–16), and membrane-attached ACE2, may also be relevant.

In a second phase, represented by the inflammatory and immunological responses to SARS-CoV-2 infection, ACE2 is downregulated due to the entry into cell cytoplasm when coupled with the virus. In opposition to the first phase, in the second phase, lung-attached ACE2 expression may be positively correlated with better clinical outcomes, since ACE2 may limit the cytokine storm that underlies the Acute Respiratory Distress Syndrome (ARDS) in COVID-19, while the

balance between proinflammatory angiotensin II–angiotensin receptor type 1 (AT1) axis, and the anti-inflammatory angiotensin 1–7—G-coupled Mas receptor (angiotensin 1–7 receptor) axis may also be crucial for level of severity of the second phase (13, 15–19).

SARS-CoV-2: THE LINK BETWEEN MECHANISMS OF ACTION AND RISK FACTORS

The Renin-Angiotensin-Aldosterone System (RAAS) has been shown to be central in COVID-19, since three of the key modulators of SARS-CoV-2 infectivity–angiotensin 1–7, ACE2, and AT1—belong to the RAAS, in addition to the TMPRSS2 expression (12–19).

Disruption of RAAS and ACE2 expression abnormalities are likely the underlying mechanism that links hypertension and obesity as important risk factors for COVID-19 (21–29). Conversely, TMPRSS2 overexpression in response to exposure to androgens may justify the higher occurrence of COVID-19 complications in males (30–33), which can be reinforced by the fact that males under androgen deprivation therapies such as for prostate cancer may experiment decreased risk for ARDS when compared to age-, sex-, and comorbidities-matched subjects (33).

A pro-thrombotic state, and endothelial, hematological, kidney, hepatic, cardiovascular, gonadal, neurological, and gastrointestinal manifestations in COVID-19 are at least partially mediated by ACE2 and TMPRSS2 expressions (34–60).

In summary, aberrancies in ACE2 expression, unbalance between angiotensin II and angiotensin 1–7 levels, and overexpression of TMPRS22 seem to be key factors for the severity of clinical manifestations in COVID-19.

SPIRONOLACTONE AS A CANDIDATE AGAINST COVID-19

Drugs that address ACE2, any sight of the RAAS, or TMPRSS2 expression are potential candidates for COVID-19. In this context, the use of old drugs against COVID-19 may present major potential benefits over novel drugs for some reasons, including: (1) The well-established long-term safety profile (2) Extensively described risks and contraindications, which allows to prevent its use when contraindicated and monitor for risks directedly; and (3) The lower cost of old, non-patented drugs allows its massive use in public health systems, when clinically indicated.

These observations combined with our understanding of SARS-CoV-2 molecular mechanism of infectivity lead us to believe that spironolactone is an ideal candidate drug for the prophylactic treatment of SARS-CoV-2.

Spironolactone is a safe and well-tolerated anti-hypertensive and anti-androgenic drug used since 1959, that is effective to maintain normal blood levels (61–63), address heart function, and provide cardio- and renoprotection (64–68).

While spironolactone is a safe and unexpensive option, it may act in multiple sites against COVID-19, including: (1) Favorable patterns of ACE2 expression, including potential increase of circulating ACE2, enhancing its potential protective role in SARS-CoV-2, once plasma ACE2 may couple to SARS-CoV-2 and avoid its entry in the cells (24, 69–74); (2) Downregulation of the androgen-mediated TMPRSS2 due to its antiandrogenic activity (75–77), without the adverse events of male sexual castration; (3) Mitigation of the deleterious effects of obesity on the RAAS, possibly reducing obesity-related COVID-19 complications (78, 79); (4) Direct anti-inflammatory and anti-viral effects that could directly avoid pulmonary complications of COVID-19 (80–90).

Hence, spironolactone meets corresponding epidemiological data, mechanistical plausibility, and sufficient safety profile to become a candidate against COVID-19.

For the proper management of spironolactone during COVID-19, since spironolactone mostly targets the virus entry in the cells, which is the hallmark of the first phase of Covid-19, spironolactone should be preferably started during the earlier stages of the infection, prior to the complications of respiratory manifestations, but could also be employed in the second phase, when the inflammatory and immunologic responses become clinically relevant, due to its anti-inflammatory effects (91).

CONCLUSION

Abnormal ACE2 expression, angiotensin II and angiotensin 1–7 imbalance, and TMPRSS2 androgen-mediated overactivity seem to be key regulators of SARS-CoV-2 infectivity, in accordance with epidemiological observations of hypertension, obesity, and male sex as being major risk factors. Since spironolactone is a long used safe drug that exhibits concurrent actions in the modulation of ACE2 expression that could avoid SARS-CoV-2 cell entry, attenuation of the harms caused by the overexpression of angiotensin II-AT-1 axis, discloses anti-androgenic activity that can decrease viral priming through TMPRSS2 activity, and has anti-inflammatory effects in the lungs, spironolactone seems to be a plausible candidate for the prophylactic and early treatment of SARS-CoV-2.

AUTHOR CONTRIBUTIONS

FC, CW, and AG developed the underlying theories on the present paper, wrote, and reviewed the manuscript in its final format for submission. All authors contributed to the article and approved the submitted version.

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