



# Public health concerns and increased risk of severe COVID-19 disease through androgen use

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## **Purpose of review**

Given governmental policy responses to the COVID-19 pandemic include various foci on establishing preventive measures to increase the health and constitution of populations (i.e. through renewed efforts to tackle obesity), the use of androgens in a recreational manner requires attention because of existing medical evidence related to their role in immunosuppression.

## **Recent findings**

Whilst a broad body of work exists that outlines the mechanisms that underpin COVID-19 and public health responses, as well as the use of androgens in both recreational and medicinal contexts, the recent nature of the disease has left an area requiring greater investigation and clarification. There is emerging literature that highlights the potential complications that existing androgens use may bring to those infected with COVID-19, as well as the start of empirical evidence detailing this.

## **Summary**

In this article, we outline the latest viewpoints and literature related to how the use of androgens may contribute to less robust immunoresponses.

## **Keywords**

anabolic-androgenic steroids, androgens, hyperinflammatory responses, immunosuppression, increased mortality risk, testosterone

## **INTRODUCTION**

Coronavirus disease 2019 (COVID-19) was announced as a novel coronavirus on 1 December 2020 by the WHO [1]. It presents a wide variety of symptoms (as well as asymptomatic infection), which vary from mild to hyperinflammatory responses and triggering critical disease responses [2,3]. Declared a worldwide public health emergency, initial attempts by the majority of world governments to reduce transmission (i.e. through lockdowns), mitigate the severity of infection through medicinal purposes and availability (such as ensuring ICU did/do not exceed capacity), and establish effective vaccination programmes, are now being supported by a range of policies and strategies that seek to lower comorbidities and concurrent risk factors through proposed health programmes (i.e. increased activity, cardiovascular efficiency, and lower obesity levels).

As part of this approach to ensuring healthier populations are less susceptible to some of the critical disease that COVID-19 can trigger, the use of androgens (also referred to as anabolic-androgenic steroids or AAS), for potential medicinal recovery as well as the literature related to increasing comorbidities,

needs consideration. In this article, we present a more detailed outline of the above, and a review of literature related to existing understanding of androgen supplementation and the physiological, and psychiatric, costs it can manifest. We also outline a review of recently published articles that position androgen supplementation as possibly increasing the risk of increased risk of COVID-19 disease severity.

## **CORONAVIRUS DISEASE 2019, HYPERINFLAMMATORY RESPONSES, AND EMERGENCY PUBLIC HEALTH RESPONSES**

The emergence of COVID-19 as a worldwide pandemic has instigated a succession of public health

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## KEY POINTS

- Public health response to the COVID-19 pandemic has included movement and travel restrictions, social distancing, increased sanitary guidance and legislation, and dedicated monitoring and notification systems, as well as longer term strategies to increase population physical activity levels.
- Existing medical evidence recognizes the role of androgen use in immunosuppression, hyperinflammation, and acute respiratory distress, and constituting potentially dangerous and exacerbating comorbidities to COVID-19 infection.
- Emerging evidence is now implicating an increased uptake of androgen use within the pandemic, including increased first-episode drug usage incidence, across several nations including the UK.
- Recent and converging evidence is suggestive of a link between increased androgens and an increased severity in response and symptoms to COVID-19 infection, whereas antiandrogen therapy is provisionally demonstrating a comparative reduction in disease severity and duration.
- As the broader public health agenda adapts to the transition of COVID-19 from pandemic to endemic status, a fuller consideration can now be implemented to include a specific strategy for this superficially healthy but deceptively vulnerable group.

measures. To reduce transmission and health service burden, there have been a range of measures from the various lockdowns, travel guidance and regulations, physical distancing, sanitary measures, the use/promotion of facemasks, and test, trace, and isolate systems. Innovations in medicinal treatment, such as the use of dexamethasone (a corticosteroid that reduces mortality for patients receiving ventilation or oxygen supplementations) [4], reduced-cost ventilation, and antibody cocktails, such as Regeneron's REGN-COV2 were implemented. The urgency at which this has taken place is in response to the high transmissibility of COVID-19, the multiorgan hyperinflammatory responses it elucidates [2,5], and an estimated Infection Fatality Rate (IFR) of approximately 0.5–1% [6,7], and most particularly in older adults consequential to age-related decline in sex steroid hormones [5].

### **PUBLIC HEALTH RESPONSES: LONGER TERM POLICY AND STRATEGIES TO MITIGATE EXCESS MORTALITY THROUGH FITNESS AND PHYSICAL ACTIVITY**

Alongside these policies and laws that have sought to decrease transmission and the development of

novel medicinal treatment, a range of public health strategies seek to fight and reduce known risk areas for those infected with COVID-19. These risk areas include, but are not exhaustive to, obesity, diabetes, poor cardiovascular fitness, and a variety of chronic health conditions. The more novel, pressing, types of discourse related to future-proofing public health policy is particularly germane when many western countries identify so many of their populations as clinically vulnerable or as clinically extremely vulnerable. In England [the four home nations (England, Northern Ireland, Scotland, and Wales) of the United Kingdom have different legislative powers as devolved nations, and thus, there are some divergences in their responses to COVID-19), for instance, there were approximately 2.2 million people who were identified as clinically extremely vulnerable in summer 2020 [8]. And since this, in early 2021 following a COVID-19 population risk assessment, a further 1.5 million people have been added to the government's Shielded Patient List (SPL) [9].

Given these numbers (i.e. in England, there are 3.7 million people on the SPL from a population of circa 56 000 000), it is not unreasonable to frame how the emerging policy and discourse related to health in the context of COVID-19, is taking an approach that includes – within any shaping the health research and policy agenda – assessing health trends, and articulating evidence-based policy options that can reduce the population numbers identified as clinically vulnerable or as clinically extremely vulnerable. In England and the UK, examples include the £2 billion package (announced in May 2020) to create more cycle and walkways [10], and Sport England's new 10-year strategy, *Uniting the Movement* (released in January 2021), that in much part is specifically centred on supporting an increase in physical activity through promoting development and strengthening systems (i.e. through enhancing partnerships, capacity building, and innovative projects), in order to address inequalities in exercise provision that have been highlighted by the pandemic [11].

### **ANDROGEN USE, MEDICINAL PROBLEMS, AND DIRECTING AND COORDINATING AUTHORITY FOR RELATED HEALTH MATTERS**

Placing physical activity support at the heart of post-COVID-19 recovery is paralleled by existing health policies that seek to ensure higher levels of population fitness through planning with a special emphasis on various health inequalities. Smoking cessation and control, for instance, has long been targeted as a way of improving the resilience of health systems.

This is primarily achieved through a combination of prevention through higher taxation, smoke-free areas, and antismoking campaigns [12]. Similarly, antidrug campaigns, to reduce illicit drug use and support recovery from drug dependency, are commonplace through western countries, that is, the UK's Drug strategy 2017 [13].

In part, through similar types of programmes and strategies, the use of Image and Performance Enhancing Drugs (IPEDs) is also oftentimes acknowledged to be problematic, particularly the negative health implications resulting from androgen use. Examples of these implications include multiorgan damage [14] and related negative cardiac effects [15]. Indeed, there are a variety of specific health risks associated with androgens and other IPEDs [16], and a relatively well understood increase in mortality risk for users [17]. Despite this knowledge and a variety of public health campaigns that have sought to reduce androgen and associated IPED use, their usage has perhaps been reinforced by the disruption of the pandemic. In a study using an international online questionnaire for 3161 (65% women) adults in various European countries, *Dores et al.* [18<sup>\*</sup>] found that lockdowns increased first time usage of IPEDs by 6%, a potentially worrying finding that warrants serious consideration.

### ANDROGEN USE AND POTENTIAL MEDICINAL BENEFITS

In the context of COVID-19 recovery, *De Lorenzo et al.* [19] highlight the specific deleterious effects of bedrest for patients who have required hospitalization. This includes, but is not exhaustive to, those who necessitated support through ventilators/intubation and who have been placed in induced medical comas. Because of this, *De Lorenzo et al.* [19] outlined some of the nutritional demands and supplementation, as well as physical therapy and motor rehabilitation, that is necessary for recovering patients. In light of this article's specific purpose, and in the context of androgen use and COVID-19, there is also emerging evidence (although conceptual/suppositional) that testosterone, and potentially estrogen, repurposing may be particularly useful for those recovering from severe COVID-19 symptoms as an anabolic agent [20,21]. This argument is, perhaps, especially relevant when the work of *Rastrelli et al.* [22] is taken into account. Here, they analysed data related to 31 male patients affected by COVID-19 pneumonia who had subsequently recovered. Whilst a limited sample, *Rastrelli et al.* [22] indicated that patients who had lower testosterone concentrations were subject to worse outcomes from COVID-19 infection, especially

within older adults for whom hormone replacement therapy may be indicated [21,23–25].

### ANDROGEN USE AND POTENTIAL PROBLEMS WITH CORONAVIRUS DISEASE 2019

In a recent commentary article [26<sup>\*\*</sup>], we outlined the fact that (alongside existing knowledge related to various known health detriments) androgens act as immunosuppressors through reducing immune cell number and function [27]. Given that the specific nature of COVID-19 characteristically elicits immune responses that can lead to hyperinflammation, we took the position – from a suppositional basis – that the use of androgen could conceivably accelerate, exacerbate, or even initiate significantly more dangerous responses to COVID-19. Of note, whilst at the time of press, there was some emerging anecdotal and journalistic evidence, there were no widely available case studies or peer reviewed resources that had clearly demonstrated a link between androgen use and increased risk of mortality or disease severity from COVID-19, as well as associated mental health challenges [25].

As outlined previously, *Cadegiani* [20] had already posited that testosterone may well be useful for those recovering from severe COVID-19 symptoms within the first calendar year of the disease. Interestingly, however, he forms part of a team that has presented more recent evidence and medical practice outlining the potential risks that androgen use may present to otherwise healthy (including young) patients who have COVID-19. In a 2021 case study, *Cadegiani et al.* [28<sup>\*\*</sup>] outline how an otherwise healthy 28-year-old male recreational bodybuilder who was using 40 mg/day of oxandrolone (an androgen), presented severe COVID-19 symptoms. The patient was given a single 600 mg dose of a novel antiandrogen, proxalutamide, and within 24 h demonstrated a significant improvement in symptoms. Given this experience, and noting that previous studies [29] have highlighted how androgen use in younger users has solicited acute respiratory distress (and pneumonia), *Cadegiani et al.* [28<sup>\*\*</sup>] strongly suggested that the severe response and symptoms to COVID-19 that the androgen user in their case study (an otherwise healthy man), was highly likely owed to androgen use.

Furthermore, a randomized controlled trial [24] investigated the effects of supplementing standard treatment with a 30-day course of dutasteride on adult patients presenting with early COVID-19 symptoms. Compared with placebo controls, treatment-arm patients ( $n=43$ ) evidenced reduced disease duration, as well as lower reported fatigue and

inflammatory markers, by day 7. Mitigating disease severity through antiandrogen therapy then, seems to highlight the potential risks that excess amounts of androgens may pose in the context of COVID-19. Indeed, whilst the work of Rambhatla *et al.* [30] declared that men who contracted COVID-19 who were also undertaking testosterone replacement therapy (TRT) were not subject to worse clinical outcomes, MacDonald and Wambier [31], in a riposte to this, stated that the TRT group in the study exhibited significantly higher hospitalization and fatality rates than comparable age groups in the USA.

Certainly, the fact that there is a gender-related distinction in COVID-19 infection, with male individuals experiencing higher morbidity and mortality rates, may in part be attributable to hormonal (androgenic) differences [32,33]. According to emerging but triangulating viewpoints [34<sup>■</sup>,35], this is in part perhaps because of the manner in which COVID-19 viral spread is articulated through the mechanism of androgen receptor activation and the transcription of the transmembrane protease, serine 2 (*TMPRSS2*) gene. Using androgen receptor inhibitors then, is considered a possible therapeutic strategy to address the vulnerability of male individuals to severe COVID-19 responses [34<sup>■</sup>].

## CONCLUSION

Given the very recent advent of COVID-19, it is of no surprise that there is presently a relative dearth of literature available within the context of androgen use. However, the fact that androgen use can adversely affect immune responsiveness, something that is critical in relation to mitigating COVID-19 morbidity and mortality, justifiably suggests medicine and healthcare systems may need to develop new policies and procedures specific to this population. Furthermore, as it is not immediately obvious as to whether an individual is actively using, or has a history of IPED use, and some individuals will conceal this information, some adaptations to risk-factor assessment protocols may need to occur.

Whilst, as mentioned, there is already a growing journalistic and anecdotal reportage of some bodybuilders and strength athletes (who may or may not have been androgen users) who have passed from COVID-19, despite sitting well outside of at-risk age categories, we anticipate that the recorded case report by Cadegiani *et al.* [28<sup>■</sup>] of a severe case of COVID-19 in an otherwise healthy 28-year-old androgen user, will likely be joined by others. We further posit that medical literature and practice, alongside any explicit goals and strategies to mitigate and/or reduce severe COVID-19 disease symptoms, will likely be

influenced by a general consensus and understanding of how androgen use will/can contribute to severe COVID-19 responses.

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## Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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