



COVID-19 and Anabolic-Androgenic Steroids (AAS) as Immunosuppressors: Is it Time to Revisit Government Policy and Governance Arrangements on AAS?

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Introduction

Over the last year, governmental responses to the Coronavirus disease (COVID-19) crisis have generated significant attention and deliberation in terms of public services, the experience and lessons learnt from various restrictions, and ideas for approaching possible future pandemics. Indeed, the question of how to mitigate for what is likely the now endemic nature of COVID-19, and the subsequent health implications this brings, is increasingly prevalent among both political and civic discourse. One of the main conclusions reached by many is that although initial approaches to managing the COVID-19 crisis focused on primary health measures, there are clearly significant economic implications in the short and long term that must be considered. Whilst various lockdown measures necessitated improved public engagement, understanding, and compliancy in order to successfully, if perhaps temporarily, mitigate excess mortality in comparison to taking no action, significant differences of view now exist on how best to manage the crisis. This is partially explained given we are likely following an incremental process of moving from epidemic to endemic. Because of this, alongside the latest data on low seroprevalence levels [1] and the emerging understanding of antibody reduction post-infection [2], a greater focus on individual choices and health behaviours needs to be relocated within this emerging context. In truth, whilst initial efforts to combat COVID-19 necessarily involved a focus on emergency response, economic and social considerations seem to be gradually switching the focus to ongoing management of the disease. Much of the rationale for this management quite justifiably focuses on avoiding systemic overburden and potential collapse within health systems through various interventions (i.e. social distancing, hygiene, and regional or national lockdowns), so that the Infection Fatality Rate (IFR) can be lowered through a combination of available Intensive Care Units (ICU) and, over time, both better treatments and the development of a successful vaccine.

Given that efforts within most developed countries seem to be focused on this management of the disease to buy time, importantly, and in the context of physical activity, changes in policy are now being developed and actioned. Indeed, many ideas and strategies are now being fast-tracked because of

expediency and the fact that politicians and policy makers are now having to walk a proverbial tightrope over health and economic policy. To many, as COVID-19 moved from potential epidemic, to global pandemic, and now endemic, an emphasis on the concurrent risk factors is warranted. Much subsequent and emerging health policy is now necessarily focused on dampening the transmission and spread of the disease through managing behaviours, and many governments, in response to the COVID-19 crisis, have started to actively promote programmes and strategies that emphasise physical activity, weight loss, and good nutritional habits. This is in order to combat what are known as risk areas for COVID-19 patients, for instance, obesity, poor cardiovascular fitness, diabetes, and other chronic health conditions, that place COVID-19 patients at higher relative risk of post-infection complications yet which can also be partially mitigated through healthy diet and exercise.

Strategies, such as the UK's £2 billion package (announced in May 2020) to create more cycle and walkways, seek to improve the resilience of health systems, and it is in this vein that we argue for a well-informed debate related to public health and the complex societal concerns regarding the use of Anabolic-Androgenic Steroids (AAS) and Performance Enhancing Drugs (PEDS). This is because, outside of the non-COVID-19 potential health problems that AAS use presents [3], figures on the prevalence of PED usage in the UK population are both significant and worrying. For instance, in 2016 Wales had an estimated number of 271,000 16-59-year olds who had reported lifetime use of AAS [4], in a population that in 2017 numbered 3,125,200 [5], a prevalence rate of 0.08%, equivalent to 8,000 cases per 100,000 population.

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Our position on this matter is apparent in our previous research and subsequent views related to AAS/PED use within sport [6-8]. Here, we argued against their use on both ethical, fundamentally through permanent morphological change which could leave an advantageous legacy, and health, through various known and unknown health detriments, grounds. In light of COVID-19, an infectious disease that characteristically elicits immune responses that can lead to hyperinflammation, we revisit some of our polemic regarding AAS use in athletes and recreational capacities. Our rationale for doing so is in much part because of the need to discuss the potential for increased economic burden and, indeed, the necessity of maintaining or lowering IFR and reducing additional but preventable pressure on existing ICU resource. Alongside the accepted scientific evidence that outlines the precise health risks associated with AAS and other PEDs [e.g. 3], the identification of AAS as immunosuppressors (thereby reducing immune cell number and function) has long been recognised. Specifically, the work of Fuji, Nawa, Tsuchiya, Matsuno, Fukumoto, Fukuda, and Kotani [9], for instance, demonstrated how mammalian (mice) responses to elevated testosterone confirmed suppressive activity on the immune system, and Kanda, Tsuchida, and Tamaki's [10] *in vitro* study using human peripheral blood mononuclear cells (PBMC) found that exposure to single dose of additional testosterone inhibited immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies production indicating adverse results for immune system function.

Some contrast to these findings can be found in Calabrese, Kleiner, Barna, Skibinski, Kirkendall, Lahita, and Lombardo's work [11]. Here, they used competitive bodybuilders who self-administered AAS and found that Natural Killer (NK) lymphocytes, which form part of the network of cells and molecules that comprise the immune system and work together to protect the body from infections, showed increased activity in AAS users. Crucially, however, they still supported the wider literature stating that AAS use interferes with immune responsiveness. Considered together, the evidence strongly points to the deleterious and compromising effect of AAS on immune system response. Indeed, in their review of literature related to AAS effects on the immune system, Marshall-Gradisnik, Green, Brenu, and Weatherby [12] found overwhelming evidence showing animal and human exposure to AAS resulted in "adverse side effects on immune function and several other bodily systems" (p. 28).

Given the uncertainty of how the pandemic will eventuate, mitigating COVID-19 morbidity and mortality by ensuring clinically vulnerable populations are less susceptible is warranted, in terms of increasing cardiovascular function, reducing incidence and improving management of diabetes, and reducing obesity. This is particularly salient as, for instance, the UK currently identifies 2.2 million people as clinically extremely vulnerable (high risk) [13]. Subsequently, the enormous pressure that this group (alongside the clinically vulnerable - moderate risk group) presents is extremely challenging in terms of potential deaths even without possible ICU shortage and other, emerging, long-term health effects from COVID-19. Given this, we therefore posit that a natural progression to these lifestyle edicts and contemporary governmental health advice and policy, should question the poten-

tial impact that AAS use may have in terms of compromising immune responses in individuals who would not, without AAS use, be positioned in high risk groups.

This is because in the context of personal choices regarding AAS use, any subsequent medical intervention and support package that may have been exacerbated by damaged or lesser functioning immune systems will need to be considered in terms of economic impact and resource constraints, i.e. ICU availability and hospital bed spaces. In particular, AAS use likely has the potential, in a COVID-19 endemic world, of increasing medical interventions associated with increased inflammation and lowered auto-immune responses. A well-informed public debate on AAS use then, should consider the emerging scientific evidence related to COVID-19 comorbidities and low and high-risk populations, alongside existing medical evidence in the field of AAS use and immunosuppression. This commentary calls for new advisory bodies to be established to provide a cost-benefit framework and scientific debate in order to potentially reposition government policy and governance arrangements in respect of approaches to controlling AAS use in both the context of sport (i.e. guidelines on bans) and recreational use.

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