Author’s response to reviews

Title: The potential effects of anabolic-androgenic steroids and growth hormone as commonly used sport supplements on the kidney: a systematic review

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Version: 1 Date: 24 Apr 2019

Author's response to reviews:

♣ Michael Hughson, MD (Reviewer 1):

Comment. I am uncertain about what to say about this effort. The subject is certainly topical, and I believe it is important because of the large number of young healthy men taking body building supplements. The section on growth hormone is quite good. And the review of experiment work on possible androgenic injury to animal kidneys is decent. Their evaluation of the evidence for human androgenic injury, in my opinion, is misleading and should not be published as it is now written. The material is presented as though the question of androgenic injury in athletes is a settled matter when in fact it is not, and unless they take a more critical view of the matter, I do not see how the manuscript can be improved or have any scientific value.

Response: A number of sentences were added into the relevant subtitles of result section and also conclusion section to avoid or minimize misunderstanding and bring to a more prudent as well as practical conclusion about the potential adverse effects of anabolic-androgenic steroids on the kidney.

Comment. The reports by Daher et al. from Brazil together with 2 or more additional publications from the same group with overlap in the patient population was not related to androgen injury but was one of the initial descriptions of vitamin D injury from the injection of veterinary grade compounds. The authors describe at some length cholemic nephrosis. This needs to be mentioned but the hepatic cholestasis is an apparently idiosyncratic liver not kidney injury that occurs in > 1% of steroid abusers and resolves in almost all cases when the drug is stopped. In regards to liver pathology, it is not clear at all whether anabolics cause liver cancer. Anabolic and estrogens seem to cause adenomas (and maybe peliosis) but hepatocellular carcinoma has a latency of 10 years or more and whether it complicates steroid use without other factors such as Hep C and ETOH is not established. Similarly, rhabdomyolysis is secondary to injury at injection sites.
Response: The above study (reference 7) was added to the introduction section based on the Geraldo B. Silva Junior. He is one of reviewers of this manuscript. We are agreed with you that results of reference 7 is not directly relevant to our manuscript. If Geraldo B. Silva Junior and also the editor agree, this reference can be removed. Adding case reports regarding bile cast nephropathy due to cholestatic jaundice of anabolic-androgenic steroids were also based on the Elizabeth De Francesco Daher comment, as one of this manuscript reviewer, and they seem to be relevant and necessary.

Comment: FSGS is the androgen reaction that is thought to be specific to the kidney, but this is not proven. The Herlitz paper from Columbia reported a series of FSGS that were collected in a 10 year survey of the NYC-Boston area. This comprises a huge population, and it was not at all clear whether the number of FSGS was excessive given the population at risk. If CKD secondary to hypertension, diabetes, or of unknown origin is considered a manifestation of androgen use there is no indication that the conditions are more severe among weight athletes.

Response: We are agreed with you. We added a sentence into the relevant part of result section about additional factors including high-protein diet (via increase in renal blood flow and GFR) and elevated blood pressure (via hypertensive arterionephrosclerosis) that may have additive/synergistic adverse effects on glomeruli.

Comment: The authors mention the need for cohort studies with long-term follow up for growth hormone affects. The same is needed for androgen use. In The US, the University of Michigan and the University of Southern California, have surveyed NFL and former college football players, groups known to have used both steroids and GH, although usually surreptitiously. The numbers of participants in the U of M study is becoming fairly robust, and no excess of either renal disease or cardiovascular disease is found among former football players over the general population.

Response: The results of the following cohort study on 1,063 retired professional football players in the US were added into the conclusion section:

Comment: I am surprised that there is no data on Iranian or former Soviet athletes. They would seem to be well defined groups that could be matched with case controls. But until somebody can show a chronic injury effect for androgens, it would be inappropriate to report that it exists. In fact, at this point there is considerably more evidence for NSAIDS injury to the kidney that androgens.

Response: We are agreed with you. It is surprising. A relevant sentence was added into the introduction section.
Comment: I suggest that the authors present the experimental studies as indicating that androgens can have adverse effect on the kidney, but that aside from case reports there is no data including follow-up of college and professional athletes in the US indicating that androgen-induced kidney injury is a problem in humans. The issue of FSGS and progression of arteriolosclerosis can be mentioned together with an absence of evidence from US studies that athletes are affected any more than the general population. They could just bluntly state that the use of steroids in Soviet and Iranian athletes has not been studied. Or if it has been studied, that the results are largely negative (or not reported).

Response: To cover all the relevant studies and also adhere with the format of growth hormone section, both experimental and clinical studies were mentioned and discussed in this systematic review. In addition, a number of sentences were added into the relevant subtitles of result section and also conclusion section to avoid or minimize misunderstanding and bring to a more prudent as well as practical conclusion about the potential adverse effects of anabolic-androgenic steroids on the kidney. Finally, a sentence was added into the introduction section to highlight this odd issue that the use of anabolic-androgenic steroids in Soviet and Iranian athletes has not been studied so far.

Elizabeth De Francesco Daher (Reviewer 2):
A recent study estimated that 2.9 to 4.0 million North Americans aged from 13 to 50 years had already used AAS, 32.5% of which developed dependence. Applying such proportion to the whole North American population, around 1 million American males presented AAS dependence at some point in their lives. Those numbers are comparable to HIV infection, as well as the prevalence of type 1 Diabetes mellitus. The subject is important because of the large number of young healthy men taking body building supplements. The high prevalence is extremely alarming, for these individuals often help and guide physical activity practitioners. This manuscript brings for scientific milieu important literature review information of the potential risk effects of anabolic-androgenic steroids and growth hormone supplements abuse on kidney function.

All previously comments were answered properly by the authors but needs some minor language corrections before being published.

Response: Thanks for your valuable statements. The whole manuscript including was revised again by a native English speaking editor and all detected grammatical and vocabulary errors were corrected.