

## PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 74895

**Title:** Anabolic androgenic steroids-induced liver injury: An update

**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 06076623

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Croatia

**Manuscript submission date:** 2022-01-11

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-01-12 02:00

**Reviewer performed review:** 2022-01-20 09:14

**Review time:** 8 Days and 7 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

The authors reviewed an update of anabolic androgenic steroid-induced liver injury in this paper. They focused on the pathogenesis, diagnosis, treatment and prognosis of several diseases that may be caused by the use of AASs by summarizing the relevant clinical reports and basic molecular mechanism research. This is a meaningful review, but requires major revision. 1.The authors mentioned “latest case reports regarding adverse effects of AASs in dietary supplements” in Core tip, but there are few case reports in the main text. 2.The discussion on the disease mechanism is not deep enough. 3.Figure 1 is poor to explain the detailed molecular mechanism of the diseases, and needs to be refined and embellished. 4.Some references, such as the literature cited by the data of epidemiological survey, are too old and may not be enough to represent the current situation. 5.NFKB is not cytokine.

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**Peer-review model:** Single blind

**Reviewer's code:** 02461833

**Position:** Peer Reviewer

**Academic degree:** MD, PhD

**Professional title:** Professor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Croatia

**Manuscript submission date:** 2022-01-11

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-01-12 13:40

**Reviewer performed review:** 2022-01-21 05:15

**Review time:** 8 Days and 15 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

This article reviews the latest knowledge in the epidemiology and pathological mechanism of liver injury induced by anabolic androgenic steroids (AAS). AASs are beneficial in medical conditions such as hypogonadism, while they are misused for skeletal muscle building and performance-enhancing effects. The retrospective clinical cases reveal that AASs are closely related cholestasis, liver cirrhosis, HCC and steatohepatitis. The mechanisms of liver injury include oxidative stress in mitochondria, immune cell infiltration of liver parenchyma, promotion of hepatocyte hyperplasia and upregulation of bile acid synthesis. Most of currently available data on AAS adverse effects in this article are based on case reports, in vitro studies, and animal model studies, while there is a lack of randomized controlled trials and systematic studies, which needs to be mentioned in the discussion. In general, the review is clear and comprehensive, which fully draws attention to liver injury and even HCC caused by improper intake of AAS, and has guiding significance for clinical practice, so it is recommended to be ACCEPTED.

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**Provenance and peer review:** Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02567669

**Position:** Editorial Board

**Academic degree:** MD

**Professional title:** Emeritus Professor

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** Croatia

**Manuscript submission date:** 2022-01-11

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2022-01-17 07:46

**Reviewer performed review:** 2022-01-26 20:38

**Review time:** 9 Days and 12 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [ ] Yes [Y] No

## SPECIFIC COMMENTS TO AUTHORS

Th is a very written review about clinical manifestation and pathophysiology of liver damage induced by anabolic steroids. I have only some minor concerns. In the Abstract: "Supraphysiologic and long-term use of AASs affects all organs leading to cardiovascular, neurological, endocrine, gastrointestinal, renal, and other disorders. It must added that testosterone induces hematological disorders. Induction of erythropoetin. Is there an iron overload as a consequence of increased EPO? In the Introduction: Unmodified testosterone is a rapidly metabolized substance with therapeutic index of 1 resulting in proportional anabolic and androgenic effects. What does that mean? Hepatotoxicity: As far as I remember Thiobarbituric acid material are sialylated glcoproteins. Is that correct? Anabolic steroids induce collagen deposition. Is Kupffer cell acitivation the sole cause? The authors mention themselves that stellate cell activation plays a major role. I suggest to include stellate cell acitivation in Fig. 1 The pathophysiology of peliosis remains rather ambiguous. Possible role of vascular growth factors? Cholestasis: Does a polymorphism of MRPs play a role?

## RE-REVIEW REPORT OF REVISED MANUSCRIPT

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**Reviewer's code:** 06076623

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Croatia

**Manuscript submission date:** 2022-01-11

**Reviewer chosen by:** Yu-Lu Chen

**Reviewer accepted review:** 2022-04-01 10:32

**Reviewer performed review:** 2022-04-01 14:28

**Review time:** 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

#### **SPECIFIC COMMENTS TO AUTHORS**

The revised manuscript is good.