

## Response to reviewer comments

We thank the reviewers for their comments. The necessary changes have been made accordingly.

### Reviewer#1

1.The core tip and as well as adverse effects look like paragraphs taken from a leaflet.

Ans: The core tip as well as adverse effects both have been modified with the following references added in adverse effects.

Both the sections were modified with the following references added in the adverse effects section.

- a) Wierman ME, Kiseljak-Vassiliades K. Should Dehydroepiandrosterone Be Administered to Women? *J Clin Endocrinol Metab.* 2022 May 17;107(6):1679-1685. doi: 10.1210/clinem/dgac130. PMID: 35254428; PMCID: PMC9113789.
- b) Panjari M, Bell RJ, Jane F, Wolfe R, Adams J, Morrow C, Davis SR. A randomized trial of oral DHEA treatment for sexual function, well-being, and menopausal symptoms in postmenopausal women with low libido. *J Sex Med.* 2009 Sep;6(9):2579-90. doi: 10.1111/j.1743-6109.2009.01381.x. Epub 2009 Jul 10. PMID: 19619146.
- c) Maggiolini M, Donzé O, Jeannin E, Andò S, Picard D. Adrenal androgens stimulate the proliferation of breast cancer cells as direct activators of estrogen receptor alpha. *Cancer Res.* 1999 Oct 1;59(19):4864-9. PMID: 10519397
- d) Arnold JT. DHEA metabolism in prostate: For better or worse? *Mol Cell Endocrinol.* 2009 Mar 25;301(1-2):83-8. doi: 10.1016/j.mce.2008.10.019. Epub 2008 Nov 1. PMID: 19013497; PMCID: PMC2667103.
- e) Srinivasan M, Irving BA, Dhatriya K, Klaus KA, Hartman SJ, McConnell JP, Nair KS. Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. *J Clin Endocrinol Metab.* 2009 Mar;94(3):761-4. doi: 10.1210/jc.2008-1774. Epub 2008 Dec 9. PMID: 19066301; PMCID: PMC2681274.

2.The search strategy does not represent a real search strategy.

Ans: The search strategy has been modified accordingly.

Reviewer#2

1.The abstract is short and does not represent the manuscript in its full. Please add the conditions which are listed in the manuscript

Ans: The abstract was edited and all the conditions described in the manuscript were listed in the abstract.

2. The cardiovascular section deserves more attention. There have been reports about DHEAS and fatal arrhythmias and other risk factors.

Ans: The cardiovascular section was further modified with focus on arrythmias as well as other risk factors and metabolic derangements associated with DHEA supplementation. The following references were added in the cardiovascular section:

- a. Golden SH, Maguire A, Ding J, Crouse JR, Cauley JA, Zcur H, et al. Endogenous postmenopausal hormones and carotid atherosclerosis: a case-control study of the atherosclerosis risk in communities cohort. *Am J Epidemiol.* 2002 Mar 1;155(5):437–45.
- b. Wu FCW, von Eckardstein A. Androgens and coronary artery disease. *Endocr Rev.* 2003 Apr;24(2):183–217.
- c. Ng MKC, Nakhla S, Baoutina A, Jessup W, Handelsman DJ, Celermajer DS. Dehydroepiandrosterone, an adrenal androgen, increases human foam cell formation: a potentially pro-atherogenic effect. *J Am Coll Cardiol.* 2003 Dec 3;42(11):1967–74.
- d. Srinivasan M, Irving BA, Dhatariya K, Klaus KA, Hartman SJ, McConnell JP, et al. Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. *J Clin Endocrinol Metab.* 2009 Mar;94(3):761–4.
- e. Qin Y, O Santos H, Khani V, Tan SC, Zhi Y. Effects of dehydroepiandrosterone (DHEA) supplementation on the lipid profile: A systematic review and dose-response meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis NMCD.* 2020 Aug 28;30(9):1465–75.

3. Table 1 has little sense as there is only one column. Please add other columns such as trials which indicated that there is an effect, or possible effects and side effects.

Ans: Table 1 was modified with another column added and the current evidence on each of the indications has been referenced and highlighted.

4. "Therefore, DHEA and DHEAS are useful markers of adrenal androgen secretion and the onset of adrenarche. Thereafter, levels of DHEA and DHEAS progressively" Therefore is used repeatedly, change to another term.

Ans: The sentence has been modified and the term therefore has been changed to another term.

5. "Can add mechanism: intracrinology Current recommendation ???" I believe that this requires editing.

Ans: This line has been edited and the paragraph has been completed in full.

6. There are multiple type mistakes.

Ans: The typographical mistakes have been corrected.