Reviewer 2

GENERAL COMMENT

This is one of the numerous Review articles published in the last 5 years. Since the topic is hot, and this manuscript focusses on Lp(a) in childhood I am in favor of publishing. Yet there are several points that should be considered by the authors.

Thank you for your suggestions that help improve the quality of the article

SPECIFIC COMMENTS

1)The authors should explicitly mention a few of the recently published reviews on this topic. In addition, a Special Issue on Lp(a) was published last year by ATHEROSCLEROSIS, and in addition SPRINGER Nature published a whole book on Lp(a) < https://link.springer.com/book/10.1007/978-3-031-24575-6>. Either one might be worth mentioning.

We thank the reviewer for important reports. Some articles from these special issues have been cited and added to the references

-The long journey of lipoprotein(a) from cardiovascular curiosity to therapeutic target Marlys L. Koschinsky, Florian Kronenberg Atherosclerosis (2022) (new ref. 7)

-Kostner, G.M. (2023). Lp(a) Biochemistry, Composition, and Structure. In: Kostner, K., Kostner, G.M., Toth, P.P. (eds) Lipoprotein(a). Contemporary Cardiology (new ref. 11).

-Therapy of Elevated Lipoprotein(a). In: Kostner, K., Kostner, G.M., Toth, P.P. (eds) Lipopro-tein(a). Contemporary Cardiology (new ref. 45).

2. Fig.1 Only kringles are shown for apo(a) and this is actually misleading!

Figure 2 has been changed and a large caption has been added as already pointed out to the previous reviewer. Thanks to the suggestions, we think the Figure is now correct and more understandable

3. Fig.2: The disulfide bridge between apo(a) and apoB100 is not via KV but rather KIV9.

Thank you. It was an error that has been corrected

4. P.2, line 61: The question of whether the assembly of Lp(a) with apo(a) and apoB-100 takes place in the hepatocyte, on the surface or even outside is not settled yet.

We agree with the reviewer. The question is not clarified, so the text has been modified as follows in a dubitative form:

"The question of whether the assembly of Lp(a) with apo(a) and apoprotein B-100 takes place in the hepatocyte, on the surface or even outside, is not settled yet. Some studies suggest that an initial non-covalent bond between apo(a) and apoprotein B100 could be formed inside the hepatocyte [10], while the final disulphide bond that completes the formation of Lp(a) would be created outside the hepatocyte, in the Disse spaces of the hepatic sinusoids."

5. The original literature should be given in Ref. 13.

The reference has been replaced with the citation of the original study.

6. P.4, line 168: There are numerous reports indication just the opposite, namely that premenopausal women have higher Lp(a) values than man. Please consider this in the manuscript.

We thank the reviewer for his comment. Indeed, the studies on this topic do not all agree. A paragraph on this point and two references have been added (ref 56 and 57).

"Lp(a) values could also differ according to gender. However, the reports on this issue are conflicting: some authors report that males have higher values than females [52], while for others authors the opposite would be true [46]. In males, Lp(a) values would remain consistent throughout adult life [53], whereas in females there would be an increase after menopause [54-57].

7. P.5, line 205. Ref. 47 from 1991 is not the first publication on this topic. The first manuscript published is from 1991: Strobl W, Widhalm K, Kostner G, Pollak A Acta Paediatrica Scandinavica. 72(4):505-9, 1983

Thank you very much for the indication. We added the reference to the manuscript (section 5) by amending the text as follows:

"On this subject, a first study carried out in 1983 showed that Lp(a) values in neonates are very low compared to those in adults *(Acta Paediatr Scand. 1983 Jul;72(4):505-9. doi: 10.1111/j.1651-2227. 1983.tb09761.x. Serum apolipoproteins and lipo-protein (a) during the first week of life W Strobl, K Widhalm, G Kostner, A Pollak).* A subsequent study confirmed that the Lp(a) values at birth are very low and increase sig-nificantly by the seventh day of life and are still increasing even at 180 days after birth" [64].

8. Last paragraphs from line 345 onwards: There are indications that Lp(a)values rise continuously with age (Pagnan A, Kostner G, Braggion M, Ziron L Gerontology. 28(6):381-5, 1982). Together with the fact that Lp(a) is an acute phase protein and its plasma concentration is significantly increased in kidney patients certainly would justify that Lp(a) should be measured not only once in life! These facts should be elaborated in the text of the manuscript.

Based on the reviewer suggestion, we changed the text to deepen these topics (Section 2):

"Therefore, in this age group, a single Lp(a) assay may be sufficient to know the related risk profile of the individual. However, this point is a matter of debate, as it is reported that Lp(a) levels would change over time (*A. Pagnan, G. Kostner, M. Braggion, L. Ziron; Rela-tionship between 'Sinking Pre-Beta-Lipoprotein' (Lp(a) Lipoprotein) and Age in a Family Kindred. Gerontology 1 June 1982; 28 (6): 381–385. https://doi.org/10.1159/000212560*), moreover this occurs in the presence of certain diseases. First, it should be noted that Lp(a) behaves as an acute phase protein, so it increases in inflammatory states [15] and this should be taken into account when planning the measurement. In addition, nephropathies are also associated with significant increases in Lp(a) levels, which can be explained by different mechanisms depending on the type of the kidney disease. Already in the early stages of renal failure, an increase in Lp(a) can be shown, with increases proportional to the decrease in glomerular filtrate. However, in the nephrotic syndrome, Lp(a) can increase up to fourfold due to an increment of its synthesis by the liver (*Causes and consequences of lipoprotein(a) abnormalities in kidney disease Florian Kronenberg Clin Exp Nephrol (2014) 18:234–237 DOI 10.1007/s10157-013-0875-8).* Chronic kidney disease patients have a significantly increased risk of cardiovascular disease, related to the level of Lp(a) *(Relation-ship between lipoprotein(a) levels, cardiovascular outcomes and death in patients with chronic kidney disease: a systematic review of prospective studies Leandro Barbagelata, Walter Masson, Pablo Corral, Augusto Lavalle-Cobo, Juan Patricio Nogueira, Guillermo Rosa Diez J Nephrol. 2023 Apr 8. doi: 10.1007/s40620-023-01590-3*).

Comments on the Quality of English Language

Although the English is understandable, many parts of the manuscrit would gain if they were appropriately adapted

The English of the manuscript has been revised

Sixteen new citations have been