Comments on PhD Thesis of Ivone Igreja e Sá, MSc, entitled ¨Modulation of cholesterol and bile acid metabolism via soluble endoglin and pharmacotherapy¨

The PhD Thesis is based experimental studies on the role of endoglin in metabolism of bile acids and in pathogenesis of liver diseases. This topic is very important taking into account the high and increasing incidence rate of civilization diseases such as NAFLD, NASH, overweight and obesity, diabetes or metabolic syndrome.

The PhD Thesis is written in English, has 67 pages and is structured by a standard way. The Introduction Section covers the whole field studied with a large amount of references and convincingly shows deep knowledge of the candidate. The Aims are clear, Methods, Results and Discussion are also adequate.

The Results Section is based on 4 papers (2 original papers and one review paper) published in journals with a relatively high IF, and all publications underwent a standard review process.

The PhD Thesis contains some insufficiencies, such as:

1) In the Introduction Section the candidate should have discussed the mechanism of cholesterol compartmentalization – HDL cholesterol is a source for biliary secretion of cholesterol, while LDL cholesterol is a source for bile acids. De novo synthetized cholesterol does not have bigger importance for biliary secretion of biliary lipids, which explains, why statins do not affect pathogenesis of cholesterol gallstone disease. These facts have causal relationship to the subject of the PhD Thesis and should have been discussed properly.
2) The term ¨hepatic availability of BA¨ is improper, and it is not clear, what exactly means.
3) Similarly, the term ¨absorption of BA by hepatocytes¨ is incorrect, liver cells do not absorb bile acids, these are actively transported.

Nevertheless, the PhD Thesis is well written, and my evaluation is positive, since the candidate fulfilled all the Aims. The results confirmed important contribution of endoglin in biliary lipid metabolism. The PhD Thesis is of high quality, and I recommend it as a substrate for defense of the PhD degree.

Questions to the candidate:

1) Atorvastatin in a study published in IJMS 2021 was used in a dose approximately two orders of magnitude higher, than is a common dosage used in humane medicine. Can the candidate comment, whether the data from this study can be extrapolated for use in humane medicine?
2) Are there any clinical data correlating concentrations of sEng with bile acids? If not, do the authors think about performing such a study, in particular in patients with NAFLD/NASH?

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