Reviewer's report

Title: Prevalence of Non-Alcoholic Fatty Pancreas Disease (NAFPD) and Its Risk Factors among Adult Medical Check-Up Patients in a Private Hospital: A Large Cross Sectional Study

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Reviewer: Gabor Firneisz

Reviewer's report:

In this paper by Lesmana et al. studied the presence of non-alcoholic fatty pancreas disease (NAFPD) in 1054 adult patients recruited at their medical check-up in Indonesia in a cross-sectional study.

NAFPD was diagnosed using ultrasonography and the authors reported that many of the known metabolic risk factors are also increasing the risk for having NAFPD, that occurred with a 35% prevalence in their study population and also showed a strong correlation with the presence of NAFLD.

Such studies are important as the prevalence of metabolic diseases, including type 2 diabetes mellitus are still increasing and it is awaited that both NAFPD and NAFLD plays a role in the pathogenesis and also in the development of diseases such as the pancreatic cancer that occurs with a higher risk in diabetic individuals.

Nevertheless there are a few concerns that may be raised regarding the paper:

Major points:

1. The discussion about the different radiologic modalities in determining the intrapancreatic fat content is completely missing, despite that these days likely more accurate radiologic diagnostics became available such as the MRI/MRS based methods (Dixon’s two point technique corrected by the magnetic resonance spectroscopy – e.g.: Sijens et al. World Journal of Gastroenterology 2010;16:1993-1998.) and also the EUS (that is obviously less feasible for such purpose due to its invasive nature). In contrast authors cite a reference which is more than 30 years old (from 1980) by Marks et al. when describing the method they used. I suggest to briefly compare the methods in the introduction section with a reasoning that why they have selected the US based diagnosis (in comparison with the more accurate MRI/MRS based methods). Also please update the literature referenced for US to a more recent review.

2. In the view that BMI is a metabolic risk factor, but also a confounding factor in ultrasound based visualization of the pancreas (in line with abdominal circumference) – I suggest to implement a separate Limitations section where they discuss that one of their most important outcome result as a risk for having NAFPD is also a confounding factor of the method they used for the diagnosis of NAFPD. In the limitation section point 1. may also be included.
3. Did they measure abdominal circumference or BMI only? If there is no data please include a reasoning why.

4. In table 2 – it is somewhat unexpected to have the cholesterol levels (total, LDL, low HDL) to be so significant and pose such a high OR for having NAFPD – also very unusual and highly unexpected for systolic blood pressure that poses a higher OR for having NAFPD than diabetes mellitus itself – so please re-check data and if no change is OR and p-values discuss it extensively (i.e. why systolic bp is a stronger risk factor for NAFPD than DM).

5. Were routine liver tests done? Specifically a relation of NAFPD to AST/ALT ratio or to gGT levels would be expected (possibly stronger than that of with systolic and diastolic blood pressure). If there were no liver test measures please indicate why.

6. Despite that 62 patients with diabetes mellitus (I assume type 2, but please clearly indicate it) participated in the study there is a complete lack of data on their drug use. Specifically PPARg agonist, statin, DPP-4 inhibitor and GLP-1 analouge/mimetic drug use and its relation to NAFPD would be interesting (and possibly metformin also, yet we do know that metformin fails to upregulate adipokine hormone levels therefore not specifically beneficial in NAFLD). So please include drug use in the analysis.

7. How was the lack of having diabetes mellitus diagnosed? 75g carbohydrate OGTT, normal HbA1c level? if none of these, and it was based only on medical history and fasting glucose levels, than this should be discussed in the limitations section, as in this age group a single fasting glucose level may not always be sufficient to exclude diabetes mellitus or IGT and this has an impact when authors calculate OR of DM for NAFPD.

8. Were there any data on HbA1c levels in the group of patients with DM? If so please do a calculation if the mean of the last 3-5 HbA1c levels do correlate with the presence of NAFPD.

9. Data presentation is misleading in table 2, in terms that when authors indicate relative proportions (as %) it should be calculated otherwise: i.e. if they do have 31 patients with T2DM in the NAFPD group of 315 individuals and they have 31 patients with T2DM in the normal pancreas group of 586 individuals the relative proportion should not be 50-50% as they currently indicate - rather the relative prevalence of T2DM should be: 9.8% in the NAFPD group in contrast to 5.3% among patients who were with normal US pancreas morphology. Please do correct the relative proportions accordingly for all 11 (or if extended with liver tests than for all) variables assessed.

10. Authors do make substantial conclusions – even in the abstract – about NAFPD’s role in malignancy, despite they do not have any cancer or cancer related outcome measure. I agree with mentioning this in the discussion section and refer to results by other study groups as pancreatic malignancy is still posing an unresolved problem and its relation to diabetes mellitus is well established,
yet authors are supposed to make conclusion about their own observations – i.e. without any cancer or cancer related outcome I would remove it from the conclusion and much more moderately mention it in the discussion section in the view of the results by others.

11. Isn’t Beta-cell lipotoxicity and subsequent Beta-cell dysfunction important from the point of diabetes mellitus when there is an excessive ectopic fat deposition also in the pancreas? Why do authors only mention insulin resistance, when the association between diabetes mellitus and NAFPD is discussed?

Minor comments:

1. How was the fasting glucose levels measured? Capillary blood glucose level or venous plasma? if the latter please use the term FPG (fasting plasma glucose level) instead of FBG.

2. Any further explanation for why their results on NAFPD prevalence (35%) deviate so significantly from the regional Taiwanese study (US based diagnosis with more than 8000! participants – Ou et al. Plos One 2013 May 3) and from the Hong Kong study (an MRS based diagnosis in 685 individuals – Wong et al. Gastroenterology 2014;109:589-97) as both measured a 16% NAFPD prevalence? Please discuss this difference more extensively.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests