Reviewer's report

Title: Factors associated with postprandial lipemia and apo A-V levels in individuals with familial combined hyperlipidemia

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Reviewer: ROCIO MATEO-GALLEGO

Reviewer's report:

Almeda-Valés et al. have studied the effect of a fat meal on postprandial lipemia and apo A-V concentrations in 99 subjects with familial combined hyperlipidemia (FCH). They have found that baseline triglycerides levels is the main factor associated with postprandial response to a fat meal. Abdominal obesity, assessed by the waist circumference to hip ratio, also contributed to postprandial lipemia. Authors have also concluded that apo A-V postprandial response is directly related to postprandial lipemia.

To my opinion, this is an interesting topic since postprandial lipemia have been associated to a high cardiovascular risk. The study is well designed and the manuscript is correctly written although there are several major points that should be changed before considering for publication.

*** Major Compulsory Revisions ***

- As stated in “Methods” section (lines 93-94), FCH diagnosis was based on LDLc > 160 mg/dl and/or and triglycerides levels > 150 mg/dl. Why these levels have been selected for FCH diagnosis? Is there any published study in this study population with these reference levels? Depending on the sex and age, these levels could be even under percentil 90th. I consider them too low and could overestimate the presence of FCH. Authors have to justify why they have used these limits for diagnosis.

- In the same way, authors classify the subjects by presence of hypertriglyceridemia and/or abdominal obesity. Those individuals in Group 3 have triglycerides below 150 mg/dl and, according to Table 3 data, mean cholesterol levels are 206,3 mg/dl (which are among normality). LDLc levels are not provided, so do these patients meet LDLc criteria? Triglycerides > 150 mg/dl criteria is not met so I suppose it but it has to be clarify.. Mean apolipoprotein B concentration is also below 120 mg/dl. Do these patients meet FCH criteria?

- Authors make a linear regression to identify those variables associated with triglycerides postprandial response. Triglycerides levels are expressed as median [interquartile range] so I suppose that this is a variable without a normal distribution. To my knowledge, this variable can not be used for linear regression unless any kind of transformation (i.e.: logarithm, etc.) is made. Has been this variable transformed into any kind of variable with a normal distribution to be able
to be used in the regression? I have the same comment for apo A-V variable which is also expressed as median so I suppose it has not a normal distribution.

- Authors explain statistical analysis they have used to analyse data. They mention ANOVA or Pearson correlation. They are tests to use with variables with normal distribution but the vast of variables have a skewed distribution. In these cases, it should be used Friedman test instead of ANOVA for repeated measures; Spearman correlation should be used instead of Pearson, etc. Authors also state that they have used “one way ANOVA” but should “t-test” used in this case?

- Lines 198-199: Authors state that the model has been adjusted by HOMA-IR and apo B levels. What does this mean? These variables have been included in the model although they did not finally remain because of P > 0.05? Or they are in the model anyway to adjust the model by these variables for any reason? Correlations showed no statically significance. BMI was included in the model but it was not statistically significant? Correlation was significant but not the regression model? Indicate in “Methods” section and in the footnote of the regression table those variables that were initially included into the model. If any of these variables remain despite not statistically significance, specify the reason.

- I have the same comment regarding independent factors associated with postprandial apo A-V response (line 214).

- Please, review carefully statistical methods. I think it could be useful to consult with a Statistical professional for further assistance.

- I think non-HDL cholesterol should be more appropriate in these patients since LDLc is not useful when triglycerides > 300 mg/dl. Besides, the most of international guidelines include non-HDL cholesterol as main factor for clinical diagnosis. So, please, consider to include it in the results (both in tables and regression analysis).

- Table 3: Letters indicating statically significance between groups are not completely clear. There are not significant differences between group 2 and groups 3 or 4 or they have not been indicated? I.e: apo B-48 iAUC (no differences between group 2 and 3??)

*** Minor Essential Revisions ***

* Abstract:
- Line 41: Indicate “linear” in “regression model”.
- Lines 45-46: Define fasting hypertrigliceridemia and abdominal obesity. Specify the considered levels.
- Line 48: WHR abbreviation has not been previously defined.
- Lines 49-50: R2 is usually indicated as “0.22” instead of “22”. Please, consider to modify them here and across the manuscript.
- Line 54: “Fasting triglycerides levels is the main factor” has been indicated.
However, this data has not clearly provided in “Results” section of the abstract. Please, indicate the R2 of fasting triglycerides variable (solely) in linear regression for iAUC triglycerides.

- It has to be indicated anywhere in the Abstract that abdominal obesity has been assessed by waist-to hip ratio to avoid confusion.

* Background:
- Line 69: “apo” abbreviation has not been previously defined.

* Methods:
- Subjects with high alcohol consumption have been excluded? Please, indicate it.
- Line 112: “Subjects were studied…”. This sentence is confused. Please, explain clearly that patient were 12-hours fasten and meal test was provided after that. I suppose fasting triglycerides were determined in this condition but it is not completely clear.
- Line 123: “TG levels > 250 mg/dl”. This level is usually “300”. Please, correct or clarify.
- Line 148: Indicate “p” as “P”.

* Results:
- Lines 153-154: Authors state that 1 subject with high fasting TG levels were excluded. High TG concentration is not an exclusion criterion. Please, clarify.
- Line 162: “p < 0.01” is indicated although in “Figure 2” legend is indicated “p < 0.001”. Please, clarify.
- Line 171: “at the beginning and at the end”. Which time point refer to when they state “at the end”? Just finishing the meal test consumption or after 8 hours?
- Correlation between apo A-V iAUC and apo B48 iAUC is significant, as stated in lines 206-207) but the model (line 214) has not been adjusted by this variable. If this is statically significant, why the model has not been adjusted by this variable?

* Discussion:
- Lines 257-258: To my point of view, this affirmation is too speculative. Please, indicate that the “postprandial lipemia is MAINLY determined by fasting…” or specify in a similar way. R2 is 0.22 so these 2 variables explain the 22% of variability of triglycerides iAUC, as stated in lines 278-280. Please, indicate this information together to avoid confusion.

* Figures:
- In the Figure 1 and 2 legends, “during” is indicated. Do authors mean “after”?
- In the same legends, “repeated measures ANOVA” test is indicated. Please, refer to my comment of “Major comments” section for further information. In this
case, Friedman test should be performed. If statistical tests used are indicated in Figure legends, they should be also included in the tables footnotes homogenously.

- In Figure 2: Please, indicate which each Group means. I.e: High TG and WHR instead of “Group 1”. It would facilitate the comprehension of the results.

* Tables:
- Table 1: The title is not too clear.
- Table 2: In the footnote it is indicated “excluded variables: apo B and HOMA-IR”. I have previously indicated in another comment that it is not clear what “excluded variables” mean. These variables remain in the model despite not being statically significant? Or they have been excluded because they are not significant? In this case, any other variable has been included in the model?
- Table 2: “R2” of each variable has to be included in a separate row to clarify the importance of each variable into the model.
- Table 3: The titles “Group 1”, “Group 2”, etc. are not clear. Please, indicate in each row heading what it is each group. It would facilitate the comprehension of the table.
- Table 3: Triglycerides iAUC, apo B-48 iAUC, apo B-48 peak and apo A-V iAUC differences between groups are not statically significant (P < 0.05)? Data seem very different.

**Level of interest:** An article whose findings are important to those with closely related research interests

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

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have not any financial competing interests but also any non-financial competing interests that may cause them embarrassment were they to become public after the publication of the manuscript.