Author’s response to reviews

Title: Diagnostic sensitivity of carbohydrate deficient transferrin in heavy drinkers

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Author’s response to reviews: see over
16 April, 2014

Dr Ryota Masuzaki
Editor, BMC Gastroenterology

Dear Dr Masuzaki

Re: MS: 9921926711188373 “Diagnostic sensitivity of carbohydrate deficient transferrin in heavy drinkers”.

Thank you for the opportunity to submit our revised manuscript, “Diagnostic sensitivity of carbohydrate deficient transferrin in heavy drinkers”.

The reviewers have provided a careful evaluation of our manuscript and raised a number of points for attention. We appreciate the reviewers’ comments and believe they have enhanced the clarity of the manuscript. We have revised the manuscript accordingly and include a point-by-point response to the critiques, detailing the changes to the original manuscript data and text. In particular we have highlighted the novelty of our study - to our knowledge, this is the first time factors affecting the diagnostic sensitivity of CDT measurements have been analysed in a uniform cohort of subjects with sustained heavy alcohol consumption. Although one previous study reported that weight and gender could affect %CDT accuracy, the authors concluded that the effect was not clinically significant. Our results strongly indicate these effects are clinically significant.

We hope that we have satisfactorily addressed the issues raised and that the manuscript is now acceptable for publication in BMC Gastroenterology.

Yours Sincerely

Dr Elizabeth Powell
On behalf of the authors.
Referee 1:

Reviewer's report:

The article is of interest and well designed.

We thank the reviewer for his/her comments.

Discretionary revisions

The authors stated at the beginning of the introduction that CDT is the most specific biomarker of heavy alcohol consumption. Actually, during the last decade, ethyl glucuronide in hair showed a diagnostic specificity at least at the same level of CDT, and sometimes even better. Therefore I would suggest to rephrase the statement or to discuss CDT in comparison with EtG in hair.

The statement has been rephrased.

(Abstract Background and Aim) “Carbohydrate deficient transferrin (CDT) is the most specific serum biomarker of heavy alcohol consumption…”

(Introduction, paragraph 1) “The relative amount of serum carbohydrate-deficient transferrin (CDT) is currently the most specific serum biomarker of heavy alcohol consumption.…”

(Discussion, paragraph 1) “Although %CDT (determined by the HPLC assay) remains the most specific serum biomarker of…”

Minor Essential revisions

Please add to the abbreviations: OR, SPSS, SD, HCV.

These abbreviations have been added.

For a better understanding of Table 1 and 2, please add a legend describing the meaning of P.

The column title in Tables 1, 2 and 3 has been amended to “P-value” for clarity. How we performed our statistical analyses and the definition of a statistically significant p-value is described in “Statistical Methods” in the methods section.

Please be consistent with number of decimals in Table 1.

The number of decimals in Table 1 is now consistent. P values larger than 0.01 are reported to two decimal places, those between 0.01 and 0.001 to three decimal places.

Major Compulsory Revisions

The main weakness of this article is the small number of samples analyzed. Several studies, performed on a fairly greater cohort of subjects have already been published on the same issue. Therefore in my opinion the authors should discuss more in detailed what is the novelty of their study in comparison with the previously published ones.

Although we agree with the reviewer that the total number of samples analysed is small, all subjects in the study had a heavy alcohol intake, at a level expected to cause %CDT >1.7. To our knowledge, this is the first time that factors affecting the diagnostic sensitivity of CDT measurements have been analysed in a uniform cohort
of subjects with sustained heavy alcohol consumption. The novelty of the study has been highlighted in the manuscript as follows:

(Introduction, paragraph 2) “... A key limitation of our earlier study and other previous studies investigating %CDT is the inclusion of patients with a broad range of alcohol intake and a relatively small proportion of patients with a heavy alcohol intake, at a level expected to cause %CDT >1.7.

(Introduction, paragraph 3) “… The aim of this study was to determine in patients with sustained heavy alcohol intake, whether the level of %CDT is influenced by BMI or other clinical variables such as gender, age, ethnicity and smoking. To our knowledge, this is the first time that these factors have been examined in a cohort of patients with sustained heavy alcohol consumption.”

Referee 2:

Reviewer’s report:

In this study, Fagan KJ et al. investigated the factors that affect diagnostic sensitivity of carbohydrate deficient transferrin (CDT) in patients with sustained heavy alcohol intake. The authors reported that the sensitivity of CDT based on a threshold value of %CDT > 1.7 was 50% and that overweight/obesity, female gender and presence of cirrhosis were independently associated with non-diagnostic %CDT.

… the manuscript is well written and the findings are of interest …

We thank the reviewer for his/her comments.

one main concern is that the sample size is smaller than previous studies. Fifty-two patients were included in this study, however, it is too small to determine the factors that affect diagnostic sensitivity. Larger sample size would be needed to obtain any conclusive results.

See response to Reviewer 1: Although we agree with the reviewer that the total number of samples analysed is small, all subjects in the study had a heavy alcohol intake, at a level expected to cause %CDT >1.7. To our knowledge, this is the first time that factors affecting the diagnostic sensitivity of CDT measurements have been analysed in a uniform cohort of subjects with sustained heavy alcohol consumption.

Specific comments

1) Diagnostic method of cirrhosis is unclear. How did the authors diagnose as cirrhosis when liver biopsy was not performed?

When liver biopsy was not performed, cirrhosis was diagnosed on the basis of a Fibroscan® result >14 kPa or liver imaging (nodular or irregular liver surface and/or features of portal hypertension) in conjunction with other clinical and/or biochemical parameters. The manuscript has been amended to include this definition (Materials and Methods, Patients and clinical data, paragraph 4).

2) In the baseline characteristics of the patients, clinical factors such as serum aminotransferases, gamma-glutamyltransferase, platelet count, and mean
corpuscular volume, which are essential in discussing alcoholic liver injury were missing.

The median values for laboratory tests commonly used in clinical practice to suggest heavy alcohol use (serum aminotransferases, gamma-glutamyltransferase, platelet count and mean corpuscular volume) are now detailed in Table 2. The manuscript has also been amended to include the following sentence:

(Results, Characteristics of patients with %CDT ≤ or >1.7, paragraph 1) “No statistically significant differences between the two groups for laboratory tests commonly used in clinical practice to suggest sustained heavy alcohol use (serum aminotransferases, gamma-glutamyltransferase, platelet count and mean corpuscular volume) were seen. (Table 2). …”