

April 16, 2014

Dear Editors,

RE: Alcoholic cardiomyopathy. No.8467

Thank you very much for your letter and the reviewers' comments concerning our recently submitted manuscript. We have revised the manuscript to address reviewers' comments and provide a detailed description of the changes below.

Reviewer 1 (Reviewer 02510354)

I have enjoyed reading this article. Some of the paragraphs are too long. Hereby my remarks:

1. Please revise the entire manuscript for English language edits.

The manuscript has been reviewed by a native English scientific editor.

2. The paragraph "Amount of alcohol required to produce ACM" is too long. Please shorten and stress the most important message.

This paragraph has been shortened.

3. The sentence "has been considered that an amount of 80 grams a day during at least 5 years is sufficient to produce the disease (9-12)". Has been repeated 2 times, redundant please remove.

Sentence has been removed from page 6.

4. The paragraph "Epidemiological studies" is too long. Please summarize.

Paragraph was summarized.

5. Under “ Experimental studies” you used the term “pre-load and post-load conditions”. You mean pre-load and after-load?

After-load is the correct term. We have changed it in the revised version of the manuscript.

6. ‘PEP/LVET’ is an abbreviation of ?

‘PEP/LVET’ stands for pre-ejection period/left ventricular ejection time ratio. As this abbreviation is not widely used, we have deleted it and the entire term appears in the new version.

7. In general there are many authors names, number of patients, years of follow up etc in each paragraph. Although correct, it makes such paragraph less interesting for the reader. In general readers are interested in summarized positive findings against the negative and a conclusion. For example: Paragraph “ Echocardiographic and haemodynamic studies in alcoholics” Paragraph “Natural History of Alcoholic Cardiomyopathy” Paragraph “Effects of Alcohol withdrawa”

We agree with the reviewer that our manuscript contains much information regarding previous published studies in the field. It was our aim to capture all available information in an extensive review, as there has not been a comprehensive appraisal in the field for some years. Nevertheless, following the suggestion we have removed some of the data from several papers in an attempt to make the text more appealing to readers.

Reviewer 2 (Reviewer 02457934)

The review written by Guzzo-Merello, title “alcoholic cardiomyopathy”, is very interesting. I have some comments as follow:

1. As the author mentioned in the Tab. 1, the two clinical trials (Prazak, Eur Heart J. 1996;17:251-7; Gavazzi, Am J Cardiol. 2000 ;85:1114-8.) used the LVEF<50% as enrollment standard as ACM, do you think it is still suitable now to diagnose DCM (or ACM) or LVEF<45% is more suitable? It is better to add such information on the definition left ventricular systolic dysfunction in DCM.

We feel that a LVEF <50% is suitable and reflects the threshold used in current clinical practice. Anyway, this is the definition used by these authors, and is described in the text as such.

2. As you mentioned in the review, there was some ACM patients among IDCM patients, is there some data to show the difference in prognosis between patients with ACM and patients with ACM+IDCM?

ACM excludes itself from idiopathic DCM because a cause (alcohol) is identified in these patients. Therefore, it would be impossible to study patients with IDCM who suffer also from ACM. Regarding other forms of DCM, to the best of our knowledge there are no data available from patients with other forms of DCM (as for example genetic DCM) who are also alcohol abusers. There are some data regarding prognosis of ACM compared to IDCM subjects. Those data are discussed in pages 17 and 18 of our manuscript.

3. The genetic factor in ACM might need be added, such as genetic polymorphisms, gene mutation like the ADH1B(*)2 , ALDH2(*)2, CYP2E1 c2, ect.

A quote regarding a possible genetic influence in ACM was added to the paragraph “Basic studies on molecular mechanisms of myocardial damage”. We have already pointed out the influence of genetics in the sentence: “The suspicion that there may be an individual susceptibility to this disease is underscored by the finding that only a small group of alcoholics develop ACM, and that a proportional relationship between myocardial damage and alcohol intake has not been proven.”

To underline the genetic factor we have added following sentence in page 16: “Regrettably, the role of gene mutations in alcohol or aldehyde dehydrogenase and genetic polymorphisms including ADH1B(*)2 , ALDH2(*)2 in humans have not been studied yet.”

Minor problems

1. There is just one sentence in some paragraphs, maybe it is more suitable to conmerged into another one;

We have done this.

2. There are a few mistaken typographical errors in the manuscript such as PEP/LVET (page 12, line 15).

See answer 6 to Reviewer 1

3. Oz is refer to ounce and 1oz=28.35g or 1 oz=28.41 ml, maybe it is need to explain for reader to understand.

It is explained: 8oz of alcohol (200g or 20 standard units)

4. In the paragraph (page 10, line 10)- “Evidence linking excessive Alcohol Consumption and DCM-In the past, the existence of a direct causal link between excessive alcohol consumption and the development of DCM was a controversial issue. While some considered that this toxin alone was able to cause such a disease, others contended that it was just a trigger or an agent favouring DCM”, it will be better to add the references.

References have been added.

5. The P value will be added in the sentence, “This is the only study describing the existence of a direct linear relation between accumulated alcohol consumption throughout life and left ventricular mass($r=0.42$), fractional shortening ($r=0.35$), and ejection fraction($r=0.46$).” (page 6, line 20).

P value was added to the sentence.

Reviewer 3 (Reviewer 00227375)

This is a systematic review about the alcoholic cardiomyopathy. The authors reviewed the definition, evidence, epidemiology, treatment, and prognosis. Though this manuscript is nicely structured and well written, several minor mistakes remained in this manuscript. Please consider the following comments. (Comments)

1.Text Regarding individual susceptibility based on alcohol metabolism, data are scarce but provocative findings arose from a study published in 2002 in which it was shown that the cardio depressive power of alcohol in mice varied according to the activity of the enzymes involved in the metabolism of alcohol (66). In this study, alcohol caused a greater impairment of cardiomyocytes in genetically modified mice with higher alcohol dehydrogenase activity. The mechanism by which cardiac damage occurred was not fully elucidated but it was proposed that it was due to the accumulation of acetaldehyde. Furthermore, mice that received an aldehyde dehydrogenase inhibitor suffered an additional impairment of contractility (66). I think the authors probably make a mistake. These contents relate to reference No. 67.

Reference number has been changed.

2.Reference No. 40 Mathews EC Jr GJ, Henry WL, Del Negro AA, Fletcher RD, Snow JA, Epstein SE. Correct to "Mathews EC Jr, Gardin JM, Henry WL, Del Negro AA, Fletcher RD, Snow JA, Epstein SE."

Reference 40 has been corrected.

3.Figure 2 Correct "Glucogen" to "Glycogen"Correct "American heart Association" to "American Heart Association"

Figure 2 has been corrected.

Reviewer 4 (Reviewer 01964825)

Dr. Guzzo-Merello and colleagues have to be congratulated for the well-structured and well-written review article on alcoholic cardiomyopathy. The manuscript should merit publication, only few comments:

1. The authors should think of restructuring the beginning of the manuscript, since the very interesting and well-written historical part could be an interesting point to start from, then continuing with the epidemiology etc.

Following this suggestion, we have modified the manuscript and we have moved the historical perspective section to the beginning of the manuscript.

2. Section Epidemiology: Some redundancy, if no redundancy in the following two statistics, they should be differentiated more precisely. Is it really 3-47% or did you mean 23-47% (see fig 1). Is it really 23-37% or did you mean 23-47% (see fig. 1).

Differences in epidemiology have been explained more precisely at the epidemiology section. The lowest prevalence of ACM (3.8%) was obtained from a series of 673 patients admitted due to HF in the state of Maryland (22). This study included not only idiopathic DCM but also all causes of left ventricular dysfunction, including hypertensive heart disease, ischemic cardiomyopathy and heart valve disease. Studies including only "real" idiopathic DCM cases with current accepted ACM definition have found a 23-47% prevalence of ACM. We have clarified this point with the following sentence:

"In contrast, European studies that focused on the prevalence of ACM included only subjects diagnosed with DCM and applied the consumption threshold of 80 g/day for ≥ 5 years, have found an ACM prevalence of 23-47% among idiopathic DCM (9-12) (Figure 1)."

3. Historical Section: in the last paragraph lit#27 was cited, the authors should mention that the facts are based on n=14 and the article concluded recovery in "most" but not "all" patients after withdrawal.

We have modified the sentence. Now it reads: "Some of these papers also have described a LVEF recovery in many subjects after a period of alcohol withdrawal (25-27)."

4. Epidemiological section: The authors should think of a similar comparison in the Fernandez-Sola data, e.g. 1:200 - 1:400 versus 1:2000 - 1:3000 or both in percent.

We have transformed the values into percentages. Sentence now reads: "Specifically, among alcoholics they found a prevalence of DCM of 0.43% in women and 0.25% in men, whereas the described prevalence of DCM in the general population is 0.03% to 0.05%."

5. Withdrawal effects section: in the last paragraph the authors should discuss potential useful biomarkers for drinkers and adherence of abstinence, further the authors could suggest standardized assessment of conceivable confounders, e.g. nicotin, neoplasia etc. The authors could add a limitations section or address the following points in the manuscript separately: how about the impact of social status / gender? how about compliance of alcoholics with comorbid conditions, especially myocarditis. Is it not possible, that alcoholics more often have untreated myocarditis of unknown origin resulting in DCM? was the abstinence controlled effectively enough in the DCM controls?

We have endeavored to cover the points raised by the reviewer by including a limitations section in the new version of our review (Page 23).

6. Table 1: Typo: LVEDV and not EDLVV

We have corrected the Table 1 legend.

7. Fig 1: Abbreviations need to be explained in the legends Is it "Prevalence of ACM among IDCM" or is it not more correct "Prevalence of heavy alcohol intake among patients with IDCM"?

Abbreviations are now explained in the legend. Regarding the title of the Figure we consider that current description (Prevalence of ACM among IDCM) describes better the message of the Figure. Although definition of ACM varied across studies (as described in the text some studies required less amount of alcohol than the amount currently accepted to consider ACM), all studies investigated the prevalence of ACM in an IDCM cohort.

Reviewer 5 (Reviewer 00214269)

The authors present a timely and important summary concerning the research on alcoholic cardiomyopathy. While potentially suitable for publication in the journal, the manuscript in its current form suffers from extensive non-idiomatic use of English. Examples include: "Alcohol is the most frequently consumed drug", "Globally, and especially over the age of 65 years", and "only a few studies have investigated the effects of alcohol at heart level". The authors are encouraged to revised their manuscript to reflect a more standard use of English

The manuscript has been reviewed by a native English editor.

We would like to thank the reviewers for their valuable comments and suggestions that have clarified and improved our manuscript. Please find enclosed the revised manuscript.

We hope that the changes that we have made will make our manuscript acceptable for publication in the **World Journal of Cardiology.**

This manuscript has not been submitted nor is under consideration for publication by another Journal.

We look forward to hearing from you soon.

Yours sincerely,

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