**Reviewer's report**

**Title:** Relationship between apolipoprotein(a) size polymorphism and coronary heart disease in overweight subjects

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**Reviewer:** Eduardo ANGLES-CANO

**Reviewer's report:**

**General**

The main objective of this study was to investigate the relationship between overweight, Lp(a) concentration and apo(a) isoforms in circulating blood. An ELISA for Lp(a) determination and a previously described agar electrophoresis/Western blot method were used. The results show that the presence of diabetes mellitus, small size apo(a) isoforms, hypercholesterolemia and BMI are significant predictors of CHD in overweight subjects. Lp(a) concentrations were relatively lower (less than 0,5 g/L) for patients at cardiovascular risk than in other studies. Even though, the concentration of Lp(a) in overweight subjects with CHD was relatively higher than in subjects without CHD (20 vs 12,6 mg/dL (median?). The frequency of small size apo(a) isoforms in both overweight/CHD and normal weight/CHD subjects was higher than in controls. The authors conclude that small size apo(a) isoforms are associated with CHD in overweight subjects.

**Comments**

Overweight is clearly associated with the development of CHD risk factors. However, studies on overweight and Lp(a) plasma concentration or apo(a) isoforms as associated risk factor are, respectively, scarce or has not been reported before. The originality of the present study resides in the fact that it analyses the relationship between these parameters and the prevalence of CHD.

The authors overemphasize the prevalence of small size apo(a) isoforms in CHD patients when suggesting that apo(a) isoform role may be independent of the corresponding Lp(a) plasma levels. However, a number of studies has establish that the effect of apo(a) isoform is related to their competitive mechanism with plasminogen for fibrin or cell binding. By definition, this competitive mechanism depends on affinities and concentration of the competing ligands. This mean that small size apo(a) isoforms must be in sufficient concentration to be of pathophysiological relevance. Therefore, ....

...in order to evaluate accurately the relevance of small versus high molecular mass apo(a) isoforms on CHD, the authors may consider to analyze the effect of Lp(a) concentration on the basis of the relative contribution of each apo(a) isoform. This can be easily made by relating the concentration of Lp(a) as determined by ELISA with the proportion of each apo(a) isoform in plasma as measured with an image analyzer such as NIH Image (http://rsb.info.nih.gov/nih-image/index.html). Furthermore, if related to the apo(a) molecular mass, concentrations can then be analyzed on a molar basis, which represents a more accurate evaluation. The advantage of this procedure is that Lp(a) concentration is directly related to the proportion of apo(a) in plasma and that a threshold concentration for the effect of small size apo(a) could probably be calculated.

Since the prevalence of small size apo(a) isoforms was similar in both overweight and normal weight
subjects with CHD, the results could also be interpreted as independency of association with CHD. The authors should therefore avoid phrases such as 'low molecular weight apo(a) isoforms seem to play a relevant role in the development of CHD in overweight subjects.' Furthermore, they should considered the word association instead of 'development' since this is not a mechanistic or pathophysiological study.

In page 3, bottom, the authors should also consider ref. Arterioscler Thromb 1992, 12: 1214-1226, one of the first to described prevalence of small apo(a) in CHD.

Page 6. Indicate anticoagulant used for blood sampling and the molecular weight of the reference apo(a) standard used for phenotyping.

Page 10 bottom "detection of apo(a) isoforms may represent a better genetic marker of CHD predisposition not influenced by environmental factors." This is certainly true for the genotype. However, as the authors indicate in the same page, several conditions may influence Lp(a) concentrations throughout life and in consequence the relative concentration of each isoform may show variations that influence apo(a) phenotyping, depending on the sensitivity of the method used.

Table 1 and 2 indicate if values of Lp(a) concentration represent the mean or the median. In Table 1 the range of Lp(a) concentrations for all overweight subjects is 2.5-19.3 whereas in Table 2 for the same subjects the range are different, 5-50.3 for CHD and 2.6-38.6 for no CHD. Please, verify these values.

The number of overweight subjects in Table 3 is 255 and not 275 as indicated in the other tables.

Is the difference overweight no CHD versus control significant?

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: A paper whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Declaration of competing interests: NONE