Author's response to reviews

Title: Agrarian diet and diseases of affluence - Do evolutionary novel dietary lectins cause leptin resistance?

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- Do evolutionary novel dietary lectins cause leptin resistance?

The paper has been formatted according to the manuscript formatting checklist.

Reviewer: Rob M. van Dam

- In the section 'Global epidemiologic pattern' it is suggested that the variation in coronary heart disease is puzzling, but this only seems to be true for some of the geographic variation. Although some variation in CHD rates may be puzzling, for example differences in dietary intakes of fatty acids are likely to contribute to differences between Poland and Spain and lifestyle factors have been identified that could explain variation in CHD over time in the US (Hu FB, et al. N Engl J Med. 2000 Aug 24;343(8):530-7).

The text has been changed to reflect that only some of the variation in coronary heart disease is puzzling and that known risk factors explain some of the variation.

- The section 'Molecular Evolution of Leptin' mostly refers to the leptin gene. Because the hypothesis concerns the possible effects of lectins on the leptin receptor, perhaps it would be more appropriate to refer to the leptin receptor gene.

It is reasonable to assume that leptin and leptin receptor coevolves since they are interdependent for signalling. Thus, an adaptation to avoid disturbed function between the ligands could be on either or both. It would be interesting to see results from studies on molecular evolution of the leptin receptor, but such studies are unfortunately lacking. We focus on the leptin receptor since they are known to be glycosylated, and thus have a potential binding site for lectin.

We admit that this was not clearly stated in the manuscript but it has now been clarified under the section ‘Possible direct interaction between lectin and the leptin system’.

- In the section 'Implications of the hypothesis' the final part starting with the sentence 'If dietary lectins could inhibit leptin binding, then leptin..' seems to include information on 'Testing the hypothesis'.

The part referred to have been transferred to ‘Testing the hypothesis’.

- The sentence 'If dietary lectins could inhibit leptin binding, then leptin binding affinity should be lower in leptin resistant humans on an agrarian diet.' should specify to which group the leptin resistant humans on an agrarian diet are compared, i.e. lower than whom? Lower than leptin resistant humans on a non-agrarian diet? The following sentence on the association with obesity and fasting does not directly seem to provide evidence for an effect of an agrarian diet.
The sentences have been changed to more clearly state the proposed relationships. Obese people are taken as an example of supposedly leptin resistant humans, and fasting should cause less agrarian lectins to affect the leptin system. Although the studies do not provide direct evidence for the proposed relationships, we believe that they support them.