

Reviewer's report

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

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Reviewer: Rob M. van Dam

Reviewer's report:

General

The authors should be applauded for ambitiously combining data on different areas of science: information on disease distribution, evolutionary history, and metabolic studies. However, the strength of the lines of reasoning that leads to the postulated hypothesis does not appear strong to me. Based on the current manuscript, it seems that one could think of myriad other hypothesis on specific dietary components and biological pathways related to 'diseases of affluence' that are equally plausible and would be impossible to publish all.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The authors state that the global pattern of diseases of affluence suggests that some environmental factor among agricultural societies could initiate these diseases. However, they provide very few concrete examples that support that statement (Trobriand Islanders, Prakateje), and one example that does not support their statement (Amondava). The prevalence of diseases such as obesity and type 2 diabetes is strongly associated with increasing westernization and urbanization, but prevalence is very low in many poor agricultural communities. Thus, if the authors cannot provide stronger evidence for their statement, this seems to undermine most of their rationale for the hypothesis.
2. There will be many differences in diet between agricultural and non-agricultural populations, there are many biologically active components of grains, and many genes with a similar evolutionary history to leptin that potentially affect disease-related pathways. Moreover, there does not seem to be any data that shows that lectins affect the leptin receptor (in contrast to what the last sentence and the title of the section on lectin interaction with leptin suggest). Wouldn't such data be necessary before considering the proposed lectin-leptin receptor pathway an interesting candidate for explaining patterns of 'diseases of affluence'?
3. Several epidemiological cohort studies have examined the association between grain consumption and weight change and risk of type 2 diabetes. These do not suggest that higher grain consumption increases risk of obesity and type 2 diabetes. In contrast, whole grain consumption was associated with a lower risk of these conditions and increased insulin sensitivity in one randomized intervention study in humans. The authors should address this issue.
4. The statement that 'The notion that dietary lectins could inhibit binding implies that leptin binding affinity should be lower in leptin resistant humans on an agricultural diet' (Section on implications of the hypothesis) is not correct. Leptin binding affinity is per definition lower in leptin resistant humans. Thus, the observation that the proportion of unbound leptin is increased in obese humans does not provide support for a relation with agrarian diets. Information on associations between diet and leptin

levels seems highly relevant for the postulated hypothesis, but is only very briefly and incompletely referred to in the paper.

5. Although the paper contains interesting information on for example molecular evolution, the texts with general background information are much too long for the particular aims of a hypothesis paper of this type. The authors can refer to other publications for readers who are not familiar with the general principles.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Because intervention studies are prospective one tests the effect of an intervention on the incidence (not prevalence) of a disease (Abstract, 'testing the hypothesis').

Please include page numbers.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

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

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests