Reviewer’s report

Title: Insulin translates unfavourable lifestyle into obesity

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Reviewer: David Leslie

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The authors describe, in this commentary, the evidence that points towards insulin being a key feature associated with obesity. In particular, they envisage obesity as a consequence of hyperinsulinemia, itself causing a low-grade inflammatory process, and that the inflammatory process in turn a consequence of lifestyle factors. The authors provide evidence that is 'High normal or slightly elevated insulin levels are sufficient to suppress lipolysis and promote lipogenesis in adipocytes, while the effect of insulin on glucose transport or hepatic glucose production requires six or two times higher hormone levels, respectively.'

They conclude that it is justifiable to propose 'a lifestyle that avoids high insulin levels in order to limit anabolic fat tissue activity.'

1. The authors should get the article edited to restructure many linguistic and grammatical errors.

2. The current headings relate to: Epidemiology; Intervention Trials; Genetic Studies; Old Findings reappraised; a larger picture; Conclusions.

I would re-structure the article since it does not give a clear sense of the multifactorial nature of obesity including the role of neurodevelopmental genes associated with obesity. That, despite Table 1 which is important in that it sets out these many factors very clearly, but they are not discussed in the text in any detail so the reader is left looking for some discussion or detail. Genetic studies might come before intervention trials. There is no mention of insulin therapy, which, notoriously, is associated with weight gain. They could then construct the article to read: Epidemiology; Genetic Studies; Effects of decreasing insulin; Effects of increasing insulin; Old Findings reappraised; a larger picture; Conclusions, (or something similar).

3. It seems justified to suggest a lifestyle that avoids high insulin levels in order to limit anabolic fat tissue activity. This conclusion is weak and could be more forcefully stated. But more to the point since all physicians currently advise lifestyle changes how does this article help them to augment their current advise?
4. Inflammation causes obesity or is it protective? How to resolve that dilemma? If inflammation was genetically determined then you might say it was predisposing - is it? Is obesity a maladaptation?

5. Obesity requires hyperinsulinaemia as a critical mediator in translating unfavourable lifestyle into body weight. Is that an advantage? Is our body weight maintained by these mechanisms on the assumption, teleologically, that we will not encounter excess calories.

6. They report that in one study, fasting hyperinsulinaemia did not predict change in body mass index (BMI), except that there was more weight gain in obese children. They then imply that risk of overweight is not simple so the role of multiple factors is important; that multilayered effect needs to be carefully stated as it does not resonate with the article as written.

7. They report that in obese children insulin levels per se may predict obesity in children and adolescents but are not enough to predict obesity in adults - that observation is left hanging without further discussion.

8. They report that Diazoxide reduces insulin and causes greater weight loss. But fasting insulin was higher in treatment than in the control group which raises the question as to whether they should cite this in this context other than to point out that the area is complicated and the results may have conflicting interpretations.

9. As above, the proposal was also true for octreotide, that is, there was a significant decrease in insulin secretion in those with weight loss but not in those without weight loss.

9. They then report genetic manipulation of insulin genes in animals which is of some interest; but what of human genetic mutants as they could be more interesting given the fact that mice have two insulin genes which both function?

10. In summary, they conclude, four different approaches of lowering insulin secretion had the same consequence, prevention of weight loss. They might balance that with the various features consequent on increasing insulin, including weight gain. These changes would, taken together, be consistent with changes in insulin not simply being a consequence of weight gain.

11. Importantly they point out the dose-dependent effect of insulin. That is, >50% of obese people have fasting insulin that inhibits lipolysis. Anabolic effect protects through insulin resistance. What of free fatty acid levels and their meaning given that low levels of insulin inhibit lipolysis?
12. What of type 2 diabetes?

13. Despite the article Summary noting the importance of inflammation there is little here of note regarding the role of inflammation in obesity. It is mentioned briefly initially and then lost. What of TNF inhibitors - do they affect weight? And what of all the other anti-inflammatory agents used in clinical practise? Line 41-42 is ambivalent and likely means that IL-1 has an effect even at a low dose rather than a decrease in IL-1 has an effect - is that correct?

14. As I see the article could read as: Obesity - risk - Insulin - inflammation or it could be: Insulin - inflammation - obesity - risk. Which is it and how do they interpret the risk profile and to what does risk relate? Is it cardiac risk, risk of obesity, risk of obesity in children or in adults or both or is it risk of cancer?

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