Author’s response to reviews

Title: Insulin translates unfavourable lifestyle into obesity

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Insulin translates unfavourable lifestyle into obesity

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Response to Reviewers

Reviewer #1:

1) 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.

Response:
The article has now been edited for linguistic and grammatical errors by a native speaker.

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).

Responses:

2a) The multifactorial nature of obesity including the role of neurodevelopmental genes is now pointed out on p.3, last two lines and p.4 first paragraph:

Several other pathways of promoting obesity by environmental/lifestyle factors are conceivable. For instance, the hypothalamic-pituitary-adrenal axis may be involved because increased exposure to cortisol enhances fat accumulation in visceral depots [28]. Hypothalamic circuits contribute to the regulation of appetite and energy homeostasis [29]. Recently, glial as well as endothelial cells have been reported to be contributors to metabolic disorders and obesity [30,31]. Genetic studies confirm the association between neurodevelopmental loci and obesity [32]. Another additional player is the microbiota [33]. Lipid fluxes and the liver are expected to impact the development of hepatosteatosis and obesity [34].

2b) The environmental/lifestyle factors listed in Table 1 are now described in more detail. Since the topic of the paper is on the role of hyperinsulinaemia in the development of obesity, we did not offer a detailed discussion of environmental/lifestyle factors per se but focussed on the (causal) role in modifying insulin levels or insulin resistance. The following text was added to the first paragraph on p. 3:

Calorie-rich diets were observed to cause postprandial inflammation and hyperinsulinaemia [4,5]. Continuous excess nutrition more than doubled basal insulin levels within 4 days but did not cause elevated basal glucose levels [6]. Increased physical activity or reallocation of sedentary time to physical activity lowers fasting insulin concentrations and the level of systemic inflammation [7]. Conversely, short-term decreased physical activity with increased sedentary behaviour increased whole-body insulin resistance [8]. Exposure to road traffic-associated fine
particulate matter was associated with higher levels of inflammatory markers, insulin and insulin resistance, also in an experimental setting [9]. Sleep deprivation, even for a single night, causes an increase in systemic insulin resistance [10,11] and is accompanied by systemic inflammation [12] (Table 1). The relationship between smoking, depression, stress or low socioeconomic status and inflammation or hyperinsulinaemia/insulin resistance could only be studied by epidemiological approaches, but in all cases a positive association was observed [13-18].

2c) Genetic studies might be described before intervention trials. However, the genetic studies are all animal work and thus only providing some supporting evidence. We feel that we should not switch forth and back between human and animal studies, but present human data in a coherent manner and animal studies (genetics) thereafter.

2d) Insulin therapy of diabetic patients. We had decided not to discuss insulin treatment in type 1 and type 2 diabetes. The reasons are now given on p. 5, third paragraph:

Increased systemic insulin levels are the consequence of treatment with exogenous insulin in type 2 diabetes, and this may support fat tissue growth [54]. Type 2 diabetes is heterogenous in nature, including genetics, age at onset, diabetes duration, metabolic characteristics and pharmacological therapy. It is difficult to draw conclusions on the role of insulin or hyperinsulinaemia in a healthy metabolic state, and we therefore do not include a discussion of insulin therapy in type 1 or type 2 diabetes in the current paper.

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?

Response:

We are happy to state the conclusions more strongly on p. 9, last sentence of the text:

Taken together, the data presented justify the recommendation of a lifestyle that avoids high insulin levels for much of the day in order to limit the period of anabolic fat tissue activity.

Since the paper is on pathogenetic aspects rather than on practical consequences, we did not enlarge on proposals of an appropriate lifestyle (we mentioned various diets, intermittent fasting, physical activity) but have now added one important point which should not be overlooked when giving proper advise – diurnal glucose levels not necessarily predict diurnal insulin levels. P. 9. Last paragraph:
Monitoring for diurnal glucose levels may not be sufficient to recognise periods of prolonged hyperinsulinaemia. For instance, persons with higher fasting insulin levels but normal glycaemia respond with higher postprandial insulin secretion that persons with low basal insulin [115]. In healthy adults, the oral glucose tolerance (total area under the curve) was not affected by the level of physical activity on the preceding day, but serum insulin levels during the glucose tolerance test were lower after high physical activity [116].

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?

Response:

These points represent the so-called “simple” questions that cannot be answered. In the context of the current paper, the inflammatory response is described as an example how environmental/lifestyle factors may cause the elevation of serum insulin levels. As requested, other possible pathways are now described in more detail (see response 2a above). Because the primary topic of the paper is hyperinsulinaemia, we did not discuss inflammation in more detail. We have previously argued that inflammation is a protective response but becomes detrimental if it persists for a prolonged period of time [Diabetologia 53:10 (2010); Nat Rev Endocrinol 8:183 (2012)].

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.

Response:

This is another simple difficult question touching on an aspect which is beyond the scope of the current paper. Being an anabolic hormone insulin will favour fat tissue growth. It is difficult to judge whether excess calories represent major cause of hyperinsulinaemia compared to earlier times. Dr. Corkey blames food additives, as discussed in the paper (p.8, first paragraph of the conclusion section).

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.
Response:

Thank you for pointing this out. The wording of the paragraph indeed does not resonate our view of the data. We have revised the text as follows, p. 4, lower half of second paragraph from bottom:

These results indicate that insulin levels per se may predict obesity in children and adolescents. The conclusions from the studies with adults are less clear. One important point is that these observational studies did not document and control for all lifestyle-dependent factors of obesity risk, all of which impact insulin secretion (Table 1). Dietary intake was analysed in only one study and there was an interaction between fasting insulin, total calories consumed, and with percentage of fat in the prediction of weight gain [46].

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.

Response:

The wording of the discussion was misleading. We now revised the text as described above, response to point # 6.

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.

Response:

Our description of the several trials of diazoxide lacked a proper summary. This is now added to the paragraph on diazoxide, p.4, last sentence:

Taken together, there was a reduction in body weight in all trials that achieved lowering of basal and post-challenge blood glucose levels by treatment with diazoxide.

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.

Response:
Again, we stressed the close association of lowering insulin secretion and body weight loss by adding a summary sentence to the paragraph on octreotide (p.5, end of first paragraph):

As in the trials of diazoxide, body weight reduction was only observed in association with lowering of insulin levels.

10) 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?

Response:

We now added a paragraph reported the state of knowledge for human insulin alleles (p.6, third paragraph):

Mutations of the human insulin gene have been described that affect insulin secretion. However, in all cases insulin secretion was impaired to an extent which resulted in increased fasting glucose levels or diabetes [62-64].

11) 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.

Response:

Thank you for the suggestion to include the aspect of increasing circulating insulin concentrations (by insulin therapy). We have now discussed this approach as described above, point 2d.

12) 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?

Response:
An increased level of free fatty acids may limit the benefit of low insulin levels. We therefore had included a detailed discussion of this aspect towards the end of the paper (p.8, third, fourth and fifth paragraph).

13) What of type 2 diabetes?
Response:

The focus of this paper is on obesity. It is difficult to draw conclusions on lifestyle versus hyperglycaemia and obesity in type 2 diabetes. We have now discussed this aspect as described above, point 2d.

14) 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?
Response:

The mention of inflammation in the summary is misleading since inflammation is only one aspect among several, as explained in the response to point 4 (see above). We therefore deleted the reference to inflammation in the summary.

15) 15. 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?
Response:

We have checked the narrative and find the term “risk” in all cases defined as risk of obesity or risk of diabetes. It is a relevant question how the risk of obesity relates to other health risks, but this is beyond the scope of our paper.
Reviewer #2:

1) Please briefly discuss the side effects of diazoxide and octreotide. Are some of the weight maintenance effects of these drugs related to their side effects?

Response:

The points raised have now been discussed on p.5, second paragraph:

Both compounds used for decreasing insulin secretion have additional pharmacological effects which may contribute to the weight loss observed. Diazoxide causes smooth muscle relaxation and fluid retention, octreotide treatment has a low risk of cardiac, hepatic and renal toxicity [52,53]. However, the two drugs represent quite different pharmacological approaches which share an insulin lowering effect but not adverse effects. Body weight reduction was only noted in conjunction with decreased insulin secretion.

2) I wonder whether the authors could add a paragraph about the brain as therapeutic target in the treatment of systemic hyperinsulinemia and body weight. For instance, some hope has been tied to the use of intranasal insulin in the treatment of systemic hyperinsulinemia and obesity.

Response:

2a) The importance of the brain in regulating body weight is now pointed out on p.3, last two lines and p.4 first paragraph:

Several other pathways of promoting obesity by environmental/lifestyle factors are conceivable. For instance, the hypothalamic-pituitary-adrenal axis may be involved because increased exposure to cortisol enhances fat accumulation in visceral depots [28]. Hypothalamic circuits contribute to the regulation of appetite and energy homeostasis [29]. Recently, glial as well as endothelial cells have been reported to be contributors to metabolic disorders and obesity [30,31]. Genetic studies confirm the association between neurodevelopmental loci and obesity [32]. Another additional player is the microbiota [33]. Lipid fluxes and the liver are expected to impact the development of hepatosteatosis and obesity [34].

2b) The possible intervention at the level of the brain via intranasal insulin delivery is no reported on p.5, fourth paragraph:

Increasing insulin concentrations in the brain appear to have opposite effects. Cerebral insulin is an anorexic hormone, but its actions are impaired in obese persons due to brain insulin resistance [55]. Intranasal insulin delivery has been shown to suppress food intake and enhance
postprandial thermogenesis, with concurrent lowering of postprandial systemic insulin levels [56,57].

3) Are there genetic interventions available to manipulate the gene expression of insulin in humans?

Response:

We are not aware of such attempts. In view of the role of this hormone in the periphery and in the brain such approach would be quite risky.

4) Insulin sensitivity and glucose tolerance are often worse in the evening than in the morning in healthy people (eg., 22751690), hinting that snacking late into the night may be worse for people than eating earlier in the day, and therewith predispose people to weight (re)gain. Please discuss these findings in your ms.

Response:

Thank you for bringing up this point. We have now included this aspect in the concluding discussion, p.9, second part of the second paragraph:

Dietary interventions are complicated by findings of a diurnal pattern of insulin resistance, being lowest in the morning [111,112]. Therefore, skipping breakfast has less favourable consequences than skipping dinner [113].

5) It might be worth mentioning that insulin fulfils many important physiological functions.

Response:

We now refer to the many hormonal effects of insulin and argue that the low insulin levels seen in vegetarians are apparently sufficient for proper functioning of the body. P.9, lines 3-5 of third paragraph:

Interestingly, fasting insulin levels were much lower in lean vegetarians (mean 30 pmol/l) than in a lean case control group with similar intake of energy and main nutrients (mean 44 pmol/l), and there was only a minor difference in fasting glucose values (means 4.47 vs 4.71 mmol/l) [108]. Although insulin serves physiological functions in virtually all tissues of the body, the low insulin levels seen in vegetarians are apparently sufficient to maintain hormonal effects of insulin in the body.