Dear Prof. Taylor,

Thank you for sending us your paper and giving us the chance to consider your work as part of The BMJ Food for Thought 2 collection. We sent it out for external peer review, as for all the articles in this collection, and discussed it at the food 2 editorial committee meeting on 30 April. Present were Fiona Godlee, Anna Lartey, Paul Simpson, Navjoyt Ladher, Emma Veitch, and myself.

We sought advice from two peer reviewers, whose comments are enclosed below. I hope you find the reviews constructive. In the editorial meeting, the editors agreed that we would like to consider this paper further for inclusion in the proposed Food for Thought 2 collection. However, some changes would need to be made to address the specific issues highlighted by the editorial committee and the reviewers. Specifically, a more balanced argument would need to be presented, involving the inclusion of perhaps another author who may be able to provide a low-carb perspective to the article.

Therefore, we would like to invite a revision, addressing the reviewers' and editors' comments below, which would then be considered for potential publication in this collection.

We hope that you will be willing to revise your manuscript and submit it by the beginning of June. We realise this is tight, however we want to give the piece the best possible chance of consideration to time with the planned online meeting on 29-30 June. Either I or the other editors would be happy to liaise with you to discuss deadlines and how to address reviewers' or editorial feedback on this timescale.

When submitting your revised manuscript please provide a point by point response to our comments and those of the reviewers. We also ask that you keep the revised manuscript within the word count of 2500 words.

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I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely,

Diana

Diana Lucifero, PhD
Associate editor, The BMJ
dlucifero@bmj.com
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EDITORIAL COMMITTEE’S COMMENTS TO AUTHORS:

The editors would like to acknowledge the commendable efforts made in the preparation of this manuscript. We thought that this was a very interesting article and we hope that these comments will be helpful to the authors.

- As mentioned in our letter, the article would benefit from providing a more balanced discussion of the possible paths to diabetes reversal, and specifically, from the inclusion of an additional author who would be able to discuss diabetes reversal from the low-carb perspective. In the previous series, we encouraged authors to outline areas of consensus and uncertainty, and to discuss different approaches/disagreements in the text rather than come to forced compromise. We would encourage you to bring on a further author who might offer that differing view and be clear in the revision where those disagreements are rather than try and come to a forced compromise. Our editorial for the last series outlined this thinking https://www.bmj.com/content/361/bmj.k2463

One of the articles from the last series may serve as a model. The article on dietary fat presented strongly differing views and at times made this clear in the text. For example, "Here, we ourselves disagree on the significance and interpretation of these trials because...
https://www.bmj.com/content/361/bmj.k2139

- It may be worth considering a change to the structure of the article to focus on what will likely be of greatest interest to readers -- ie, which paths to diabetes reversal have been shown to be effective, and what is the real-world applicability of those results. A possible structure would be as follows: (1) a more developed introductory section that discusses how reversal has been shown to be possible now, and that several routes to reversal have been studied; (2) a pathophysiology section that gives a more rounded discussion about what we know and what we don't know about pathways to remission/reversal; (3) evidence for the research on dietary patterns, perhaps with subsections for macronutrients as currently described in the dietary advice section, but to include the data from the DIRECT study alongside other research. Low-cal, low-carb (keto), and bariatric surgery have all been studied and have evidence for reversal, with more discussion about the specific interventions and whether they were just diet alone or also included other interventions (eg, psychological support); (4) the section on ethnically diverse and
global populations; (5) long-term maintenance and dietary advice; (6) what does this mean for practice and policy?

- Please consider adding greater detail to the figure, perhaps including some of the biochemistry involved in diabetes reversal.

- Adding another box may be useful as a feature to explain remission vs reversal, or perhaps provide definitions of remission, reversal, maintenance - if there are generally agreed definitions.

Specific points:
- In the cases of reported reversals, have there been any long-term follow-ups and what have been the outcomes?
- Please consider adding mention of ketosis, fasting, bariatric surgery to the discussion
- P4 line 58: please change to "religious faith practices".
- P5 lines 32-38: several statements have been made in this paragraph which require references - please add.
- P6 para 7-15: many countries are developing food-based dietary guidelines (FBDGs) as a tool for governments to guide their citizens on healthy eating. Please consider briefly including in the discussion how national FBDGs may support people to make healthy dietary choices.

REVIEWERS' COMMENTS TO AUTHORS:

Reviewer: 1

Recommendation:

Comments:
This well-written article succinctly and clearly summarises the new paradigm of type 2 diabetes remission/reversal. It covers some of the physiology behind remission, and considers potential strategies for maintaining remission and preventing relapse.

Major points:

My major concern is the oversimplification of the pathophysiology as described - in fact one of the sections in entitled "understanding the simplicity". While the twin cycle hypothesis might fit the majority of cases of type 2 diabetes, I worry the acceptance of this hypothesis to explain the entirety of type 2 diabetes (which is now considered a heterogeneous condition) could 1) discourage further study into current unknowns and grey areas (as covered below) and 2) potentially negatively impact the clinical management of some patients.

To say type diabetes is characterised by NAFLD is misleading. About 30-70% of people with type 2 diabetes have NAFLD.

To say "type 2 diabetes is a state of excess fat in liver and pancreas" is also misleading - as the author's own excellent work has shown -there were no differences in liver fat or pancreatic fat reduction in responders (people who got remission) vs non-responders (people who did not get remission). We could assume that in these people the "functional" beta-cell failure has become non-reversible - but still this means that something other than liver and pancreatic fat is playing a role in the progression of type 2 diabetes.

In addition - in prediabetes, neither liver fat or pancreatic fat are associated with beta-cell function - and beta-cell function is the seminal event in the pathway to type 2 diabetes; and again, as the author's own work has shown, its restoration in the form of a "rebooted" first phase insulin response is the sine qua non of remission.
Beta-cell function seems to be the central player in type 2 diabetes development and remission based on this evidence. In my opinion, other potential contributors to beta-cell pathology should be mentioned such as glucotoxicity or the potential role of so-called beta-cell rest in inducing remission.

It would be of value to readers new to this area to understand some of these grey areas and unknowns, not least because many readers will be healthcare practitioners who will see patients with type 2 diabetes of long-duration and/or on insulin and it would be a disservice to think that all these patients need to do is lose 10-15kg, lose liver fat and they can get remission. Knowing the grey areas is important for a healthcare practitioner and others to understand this.

Small points:

Remission is defined and used throughout the manuscript whereas reversal is in the title and the opening paragraphs - I think sticking to one would be clearer.

Additional Questions:

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Please enter your name: Nicola Guess

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If you have any competing interests please declare them here: I have received research funding from Diabetes UK, the Diabetes Research and Wellness Foundation, the Medical Research Council, Innovate UK and Oviva. I have received consulting fees from Babylon Health, Boeringer Ingelheim, and Ways of Eating (a low carb app).

Reviewer: 2

Recommendation:

Comments:
The article by Taylor and colleagues is a brief that puts forth the idea that type 2 diabetes is etiologically linked to liver (and pancreas) fat accumulation, and can be reversed by weight loss; diabetes reversal can be long-lasting as long as weight is kept off. The second part of the manuscript discusses the dietary principles for achieving weight loss and maintaining it in the long-term.

Even though I wholeheartedly believe in weight loss induced by diet and exercise as key for the treatment of diabetes, this view does not recapitulate the totality of available evidence. I have the following comments for consideration by the authors.

1) Abstract / Standfirst statement: Even though I can align with the idea that (most) diabetes can be "reversed to normal by (much) weight loss" it is certainly a stretch to suggest that diabetes can be reversed by "avoidance of weight gain using sound nutritional principles." I presume the authors wanted to say avoidance of weight regain after weight loss (i.e. long-term weight loss maintenance) but if so, they should revise this to make it clear, because as it stands, this statement implies that one can reverse diabetes by not gaining weight.

2) Understanding the simplicity/how complete is the return to normal: These two parts suggest – on several occasions and by using relatively blunt statements – that the development of diabetes and its reversal are well-understood and straightforward processes. However, when it comes to presenting the data, the complexity of the issues comes to light.

For example, it takes 5 paragraphs for the authors to introduce the importance of diabetes duration, which essentially makes some diabetes (the long-duration one) not so simple and easy to reverse.

Also, in paragraphs 5 and 6 (page 2 lines 49-60), the authors "admit" that weight loss does not always reverse type 2 diabetes. Only 1 in 2 people with diabetes duration >10 yrs enjoy remission of their diabetes after weight loss (Steven 2016 Diabetes Care), and even in the Direct trial with relatively short-duration diabetes (<6 yrs), overall 1 in 3 patients in the intervention group achieved remission at 2 years; and even among those who maintained a weight loss >15 k, "only" 2 out of 3 achieved remission (Lean 2019 Lancet Diabetes Endocrinol).

Last but not least, regarding the purported critical importance of weight loss maintenance for long-lasting diabetes remission, I would like to bring the following studies to the authors’ attention. In the 10-yr follow up from the Look Ahead study (N Engl J Med 2013), after the initial maximum weight loss at year 1, weight regain occurred until year 5 (about half of lost weight was regained at this point) but weight stabilized thereafter and dropped again slightly until year 10. Despite this relatively successful long-term maintenance of (moderate) weight loss, HbA1c (and I presume the incidence of diabetes) after the initial drop at year 1 continued to rise towards baseline and, by year 10, it had completely rebounded (despite much of the weight loss being maintained). Even when much more
weight loss is sustained in the long term, whether by diet (Wing 1994 Am J Med) or surgery (Sjostrom 2014 JAMA), relapse does occur over time, at non-negligible rates. These data suggest that – even though weight regain is undoubtedly a risk factor for relapse (many studies have shown that) – relapse can happen even when initial weight loss is large and much of it is kept off long-term. I am mentioning these data to challenge the purported simplicity of the problem at hand.

In my opinion, therefore, the suggestion that considerable weight loss and its maintenance in the long-term cures diabetes is not as straightforward and simple as portrayed by the authors.

3) Role of liver fat: The authors state that diabetes is characterized by liver steatosis (non alcoholic liver disease, NAFLD), which causes hepatic insulin resistance (increased glucose production) and also channels fat to the pancreas via increased VLDL-triglyceride export. And this process is reversible by weight loss. First of all, NAFLD is present “only” in 2 out of 3 patients with diabetes (Stefan 2011 Diabetes) so, clearly, not all diabetes is characterized by liver steatosis. Furthermore, to the best of my knowledge, a causal relationship between liver fat and triglyceride (TG) secretion has not been convincingly demonstrated. It may well be that fat in the liver accumulates as a result of inadequate TG export (i.e. the latter being the cause of liver steatosis). Studies in humans have shown that the relationship between liver fat content and TG secretion is curvilinear; TG export rises to a plateau with increasing liver fat (Fabbri 2008 Gastroenterology) and this indicates that more liver fat is not necessarily accompanied by more TG export. Likewise, liver steatosis is not invariably associated with hepatic insulin resistance (Amaro 2010 Gastroenterology). Last but not least, even mild weight loss (5% of initial weight) reduces liver fat by about 50% (Magkos 2016 Cell Metab) but this has little beneficial effects on glucose control (fasting glucose and HbA1c) in people with diabetes (Wing 1987 Arch Intern Med). These observations, at the very least, leave room for doubting the view that excessive liver fat accumulation (and its reduction) is of such critical importance for diabetes development (and its reversal).

Page 2 Line 60: “...have been suggested...”

4) Reversal in ethnically diverse populations: This part suggests that diabetes in Whites and other ethnicities (Hispanic, African Americans, South Indians) is pretty much the same, and that weight loss is the cornerstone therapeutic approach for all populations. I believe this is a one-sided presentation of available evidence. First, the authors do not consider East Asians (Chinese, Japanese, etc.) which constitute a large part of the world’s population and a big part of the diabetes epidemic. In these populations, about 40% of newly diagnosed diabetes occurs in lean people (BMI <22 kg/m2) and in the absence of weight gain (Kuwahara 2017 Sci Rep). It seems counterintuitive to suggest weight loss of 15 kg or more to cure diabetes in these patients! Please also note that, the studies cited by the authors in South Asian populations (e.g. Indians in ref 16 and Thai in ref 18) refer to diabetic patients who are overweight and obese (i.e. only about half the diabetics in these populations); and even among those patients, weight loss was not universally effective in reversing diabetes. So, the concluding statement on page 6, lines 21-22 is, in my opinion, not adequately representative of available data and the uncertainties we still have.

Page 3 Lines 38-40: Something is missing here, in the comparison between AA to W; only one value for remission is given (I presume the value in AA) rather than two (readers cannot compare and evaluate this statement if they don’t know the value in W).

Page 3 Line 47: I think the symbol < is missing before 5.6 mM.

5) Rest of the manuscript:

Page 4 Lines 22-25: Please revise this sentence. The way the findings are presented is confusing, even though the meaning (“weight loss maintenance takes less effort over time”) is clearly stated.

Page 4 Line 52: The statement that adherence to diet is likely more important than diet composition for weight loss success need to be cited (e.g. Dansinger 2005 JAMA, Sacks 2009 N Engl J Med).
Page 5 Line 24: There is much evidence accumulating in recent years indicating that not all saturated fat is the same in terms of health effects and disease risk, including diabetes. The authors admit to that later on when they talk about dairy vs processed meat, etc. I would therefore suggest avoiding perpetuating the stigma against all saturated fat here.

Page 5 Lines 44-45: The “healthy eating index” is not a dietary pattern per se.

Page 6 Lines 24-25: In the paragraphs above (“Dietary advise”) the authors have discussed many uncertainties, unknowns, and complexities when it comes to diet, but here again they state that "the nutritional principles...can now be described with confidence"? This statement simply does not follow what was mentioned earlier in the text. (See also my comment #2 on "Understanding the simplicity/How complete is the return to normal").

The reference list needs to be formatted in a consistent manner. Some titles are Sentence case, some are Capitalizing Each Word; some journal names are abbreviated and some are not (full names), and so on.

Page 10, Text box: The statement about exercise (5th bullet point) does not make any sense to me. Why is it "important not to start a new exercise program during weight loss"?! If anything, the opposite is true (I think :)

Faidon Magkos, MSc PhD
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University of Copenhagen

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