Reversing type 2 diabetes by dieting: does this work?

The effect of a low-calorie diet on the remission of Type 2 Diabetes Mellitus and the underlying mechanism

Sophie Bouma
S3378616

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Faculty of Science and Engineering
Rijksuniversiteit Groningen

Supervisor: Janine Kruit
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Summary

Until recently, type 2 diabetes (T2DM) was thought to be a long-life disease, with current treatment mostly focussing on improving its symptoms by lowering blood glucose levels instead of reversing it. The idea of this disease being irreversible came from the progressive nature of β-cell dysfunction, which, together with insulin resistance, is seen to be the cause of the uncontrollable blood glucose levels. These hallmarks of T2DM are a result of fat accumulation in the liver and pancreas due to prolonged excessive caloric intake. Current guidelines promote lifestyle changes, prescribing regular exercise and a healthier diet. However, only minimal support is given, and a substantial amount of weight loss is not the primary goal. Moreover, these guidelines mainly rely on anti-glycaemic drugs, such as metformin. Several studies, with more on their way, have changed the view on the incurability of T2DM. They show that losing substantial amounts of weight by following a low-calorie diet may have positive effects on the course of the disease and might even lead to remission. These studies helped to unravel the pathophysiology of the development and remission of T2DM. This research can potentially change the current guidelines that are used after diagnosis by shifting the focus toward weight loss programs. In contrast to general belief, individuals diagnosed with T2DM could be informed that they can go into remission if they are motivated enough to lose substantial amounts of weight and permanently change their lifestyle.

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Introduction

Diabetes mellitus is considered to be irreversible and is one of the most common non-communicable diseases worldwide, with the number of cases almost quadrupling since 1980 from 108 to 422 million in 2014 (WHO, 2016). This tremendous increase in the prevalence of diabetes over the last decades has closely followed the increase in obesity (Bhupthriju et al., 2016), caused by a westernized lifestyle and physical inactivity. Insulin resistance and pancreatic β-cells dysfunction in type 2 diabetes (T2DM) causes consistently high blood glucose levels that can lead to many complications, including a higher risk of heart attacks, strokes, kidney failure, lower limb amputation, vision loss, nerve damage, and in pregnancy: fetal death (WHO, 2016). Traditionally, it has been considered to be a chronic and incurable disease, with current treatments mostly focusing on the amelioration of the symptoms or slowing down its progression rather than curing it. However, with the current guidelines, within 10 years of T2DM diagnosis, approximately half of the patients need insulin therapy (Home et al., 2014). Scientific evidence has changed the view on the irreversibility of T2DM by showing remission of the disease after a gastric bypass, low-calorie diet or a low-carbohydrate diet. Even the WHO has acknowledged in 2016 that diabetes reversal can be achieved by calorie restriction if it leads to sufficient weight loss. The onset of T2DM, and its remission, is likely to be caused by the same mechanism, which is described in the Twin Cycle Hypothesis (Taylor, 2008). This hypothesis postulates that T2DM is caused by a constant positive caloric intake resulting in accumulation of fat in the liver and pancreas, leading to insulin resistance and β-cell dysfunction. This raises the suggestion that reversal can be achieved by negative caloric intake, without the use of any treatment. Scientific articles use the terms remission and reversal, all with a small difference in definition. Remission is the preferred term because reversal can imply that T2DM can be cured permanently. However, the potential of re-emergence of the disease still exists. Partial remission is reached when the hyperglycaemia threshold of the patients is below the diagnostic threshold of diabetes, which is 6.5%, for at least one year, without taking any additional anti-glycaemic drugs. Complete remission requires standard glycaemic measures below 5.7%, and prolonged remission is reached when these effects lasts for at least 5 years (Buse et al., 2009). In this review, the evidence of possible remission of T2DM by following a low-calorie diet will be discussed, the underlying mechanisms will be explained, and potential problems of low-calorie diets in achieving remission of T2DM will be addressed.

Effect of a Low-Calorie Diet on Type 2 Diabetes

Together with insulin resistance, β-cell dysfunction is one of the hallmarks of T2DM. The pathophysiology of the β-cells was long thought to be irreversible and progressive because the loss of insulin secretions was thought to be due to apoptosis induced by metabolic stress (Butler et al., 2003). On average, a decreased mass of 39% of insulin-producing β-cells was observed in autopsies of patients with T2DM compared to the control group, and it was correlated with the duration of T2DM diagnosis with a decreased mass up to 54% in individuals with a duration longer than 15 years. Moreover, an extensive variation in β-cell mass between individuals was seen (Rahier et al., 2008). However, this study hypothesizes that solely apoptosis of the β-cells cannot explain the large amount of β-cell dysfunction in T2DM, especially in the onset of the disease. Other studies have shown that metabolic stress can induce dedifferentiation, which may be a better explanation to reduced β-cell mass than apoptosis alone (Cinti et al., 2016). Mouse studies have found vital transcription factors that are related to dedifferentiation of β-cell into other endocrine lineages and not to death (Talchai et al. 2012). This suggested that β-cell dysfunction, and therefore T2DM, could potentially be reversed when metabolic stress is removed. Research on lifestyle modifications and weight loss by hypocaloric diets have shown some positive results in patients with T2DM. Several recent studies have investigated the effects of a hypocaloric diet on glycaemic control and whether this can lead to remission of T2DM.

In 2003, the Look AHEAD (Action for Health in Diabetes) study investigated the long-term effects of intensive weight-loss by low-calorie diets on the remission of T2DM in overweight participants (look AHEAD research group, 2003). 4503 adults with T2DM and a body mass index (BMI) of 25 or higher were randomized into two groups. One group received Intensive Lifestyle Interventions (ILI), which consists of a low-calorie diet and an increase in physical activity to aim at achieving and maintaining substantial weight loss. The other group received standard Diabetes Support and Education (DSE). In the first year, 11,5% of the ILI group experienced remission. However, this value decreased over time to 9,2% in the second year and to 7,3% after 4 years. Although these remission rates are relatively small, they are significantly higher than the DSE group in which only 2,0% experienced remission. Higher remission rates were seen in participants that started with a lower baseline HbA1C, lost more weight, had a shorter duration of T2DM and did not use insulin (Gregg et al., 2012).

Another study by Lim et al. (2011) tested whether a restriction of energy intake could result in the reversal of β-cell failure and insulin resistance and therefore could cause remission of T2DM (Lim et al., 2011). A small group of people (11 people) with a T2DM duration shorter than 4 years and a BMI of 33 were given a low-calorie diet of only 600 kcal a day. After only one week of the restricted diet, fasting plasma glucose reached normal proportions and insulin suppression on hepatic glucose production improved significantly. These results were observed even before substantial weight loss was observed. After 8 weeks, the hepatic triacylglycerol content dropped comparable to that of the control group and the pancreatic triacylglycerol decreased significantly. They measured an increased first-phase insulin response which came close to the values of the control group. Moreover, the maximum insulin response became normal. These results indicate that on the short-term of only 8 weeks, the β-cell dysfunction and insulin resistance can go into remission without the use of any anti-glycaemic medication. However, only participants with a short duration of T2DM were examined, so individuals with a longer duration should be tested to see if remission is possible in this group. After 12 weeks, a check-up revealed that most of the improvements were maintained, but over a quarter of the participants had relapsed. Concluding, long-term outcomes need to be assessed.

To assess the durability of the remission of T2DM up to 6 months, the same group conducted a more extensive study which involved a low-calorie diet and a period of weight stability (Steven et al., 2016). The very low-calorie diet consisted of only 624-700 kcal a day and was given over a period of eight

weeks. This diet was followed by a period of reintroduction of solid food over two weeks, and in order to avoid weight regain, a weight maintenance program up to six months was set up. In contrast to the other studies, this study used participants with a longer T2DM duration up to 23 years. Those who experienced a fall in fasting blood glucose to at least <7 mmol/L were labelled as responders, while those who did not reach this value after the diet, were labelled as non-responders. The results demonstrated that 40% of the participants that responded to the very low-calorie diet were still in remission for at least 6 months.

These outcomes led to a recent, much larger study: the primary care-based diabetes remission clinical trial (DiRECT), which determined whether a low-calorie diet in standard primary care can result in sustained remission of T2DM (Lean et al., 2018). They randomized 306 relatively healthy people with recently diagnosed T2DM (in the last 6 years and without insulin use), to either standard diabetes care or a low-calorie diet consisting of only 850 kcal a day for 3 to 5 months. After this period, the participants received a food reintroduction and support to avoid weight regain. After 1 year, 24% of the participants had lost at least 15 kg and 46% had a HbA1c lower than 6.5% without the use of anti-glycaemic medication. Thus, this study showed that almost half of the participants had either partial or complete remission of T2DM for at least 1 year without anti-glycaemic drugs. After two years, more than one third (with remission rate of 36%) sustained remission, which was linked to sustained weight loss (Lean et al., 2019).

All these studies show that remission of T2DM is possible for at least the short term, up to 2 years. Better results were seen in participants with a shorter duration of T2DM diagnosis (shorter than 6 years) and evidence shows that remission of long duration of the disease is less likely (Stevens et al., 2016; Sjostrom et al., 2014). These results required extreme lifestyle interventions to result in a sufficient level of weight loss to be able to remit from diabetes (Hallberg et al., 2019). Sticking to the diet and weight loss maintenance is still a challenge. It is crucial that future studies look at the long-term effects of low-calorie diets on the body and remission rates.

The Twin Cycle hypothesis: The pathophysiological mechanism

Clinical and pathological studies have shown that the underlying mechanism causing T2DM is mainly the result of excess of accumulated fat in the liver and pancreatic islets. The association of accumulated fat in the liver with lower hepatic sensitivity to insulin has been demonstrated at the beginning of this century (Seppälä-Lindroos et al., 2002). When fat accumulates in the liver, the suppression of insulin on glucose production in the liver is less effective, resulting in increased glucose production. In the pancreas, fat accumulation causes metabolic stress and the β-cells seem to enter a survival mode, which leads to β-cell failure. Observation of sudden negative caloric intake after bariatric surgery led to the postulation of the twin cycle hypothesis (Taylor, 2008). This hypothesis could explain the physiological changes why low-calorie diets leading to substantial weight loss can result in remission of T2DM.

This hypothesis states that chronic intake of more calories than expenditure over many years will result in fat accumulation in the liver and pancreas. A higher intake of calories than the body uses will lead to the conversion of carbohydrates into fat in the liver for storage by the de-novo lipogenesis pathway. This process is promoted by insulin, so individuals with a degree of insulin resistance, which can be caused by genetic or lifestyle factors and therefore higher plasma insulin concentrations, will accumulate hepatic fat more rapidly. High-fat content in the liver worsens hepatic responsiveness to insulin, causing liver insulin resistance. The normal suppression of insulin on hepatic glucose production is less effective, resulting in higher glucose production and rise of plasma glucose levels. To maintain euglycemia, basal insulin secretion rates rise, resulting in a vicious cycle of hyperinsulinemia and hepatic insulin resistance.

Over many years, the increased hepatic fat content will result in a higher export of VLDLs triglyceride into the circulation. As soon as subcutaneous adipose tissue storage has reached capacity, the increased fat delivery to all tissues will result in accumulation of fat in the pancreatic islets. This process is stimulated by increased plasma glucose concentrations. The pancreatic fat accumulation results in an impaired first phase insulin response to ingested glucose. The consequence is hyperglycaemia, what further increases insulin secretion rates and activates lipogenesis in the liver even more rapidly. Once this cycle has reached its trigger point, the expression of key β-cell transcription factors will be reduced (White et al., 2016) resulting in dedifferentiation of the insulin producing β-cells into other endocrine lineages. The dedifferentiating leads to β-cell failure, resulting in loss of plasma glucose control and relatively sudden development of T2DM (Taylor, 2008) (Fig.1).

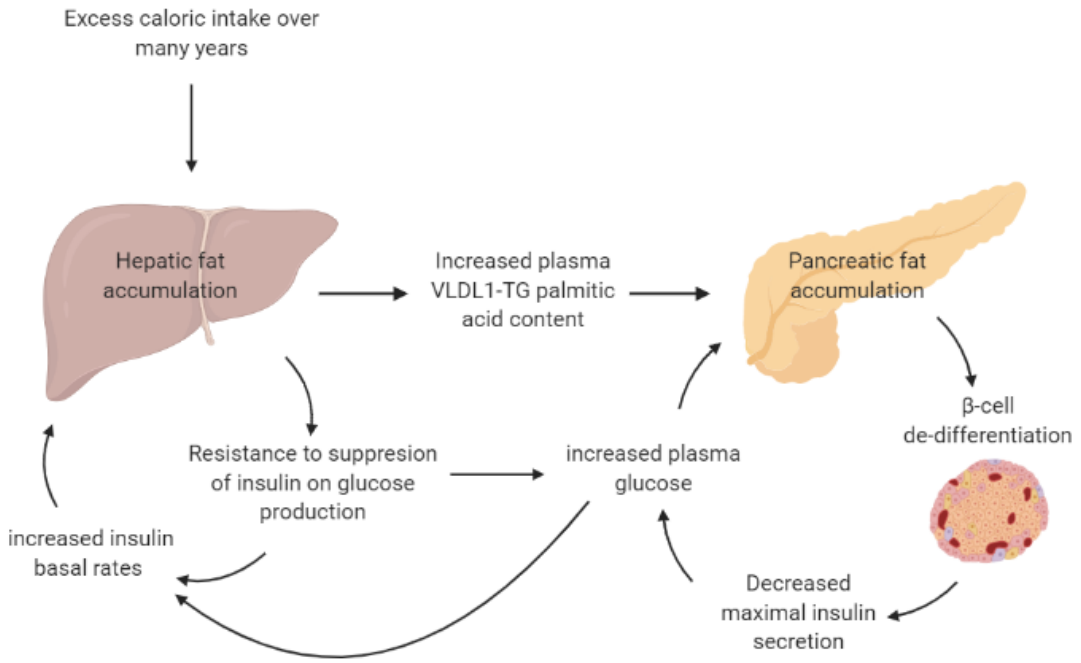

Figure 1. The Twin Cycle Hypothesis: The underlying mechanism of development of type 2 diabetes. Overnutrition can lead to fat accumulation in the liver, contributing to insulin resistance. This results in a higher VLDL export into the circulation leading to fat accumulation in the pancreas and eventually B-cells dysfunction.

The Twin Cycle Hypothesis predicts that if the main driver of T2DM is a chronic excess intake of calories, the disease can be reversed via a negative caloric balance in some, and maybe many patients. In that case, weight loss resulting in remission of T2DM should first lead to lower hepatic fat content, reversing the hepatic insulin resistance and lowering fasting glucose levels. This should be followed by falling pancreatic fat content, causing better plasma glucose control. Studies to test this hypothesis measure pathophysiological changes in liver- and pancreatic fat content, involving a low-calorie diet that resulted in remission of T2DM.

The study by Lim et al. (2011), as described before, showed that a low-caloric diet lowers hepatic and pancreatic fat, leading to remission of T2DM within 8 weeks (Lim et al., 2011). The liver fat content fell from 12.8% to 2.9% and the pancreatic triacylglycerol content from 8.0% to 6.2%. This 8-week period can be hypothesized to be too long for reversal of acute stress-induced dysfunction of β-cells and too short for β-cell neogenesis (White et al., 2016). Therefore, dedifferentiation of the pancreatic β-cells due to accumulation of fat in the pancreas is potentially an essential reason for β-cell dysfunction, and redifferentiation of the β-cell after a low-calorie diet may lead to its recovery. This study showed rapid improvement of hepatic insulin sensitivity, and a slower increase in β-cell function indicating that the Twin Cycle Hypothesis could be the reason that a negative calorie balance leads to remission of T2DM.

Additionally, the study by Steven et al. (2016) showed an initial fall in liver fat content and a lower VLDL triglyceride level in the circulation. The secondary consequence was a fall in pancreatic fat levels. The fact that there was an insulin response to arginine shows that β-cell apoptosis can not be the main reason of β-cell dysfunction, additionally β-cell dedifferentiation plays an important role (Steven et al., 2016).

In rats, research has shown that there are multiple mechanisms by which a very low-calorie diet reverses hyperglycaemic values to normal values (Perry et al., 2018). First, a reduction of diacylglycerol

content in the liver was shown, improving insulin sensitivity. Secondly, glycogenolysis rates dropped. And finally, acetyl CoA content decreased.

A very recent study demonstrated the relationship between hepatic fat, VLDL1-triglyceride production and intrapancreatic fat accumulation and the remission of T2DM (Al-Mrabeh et al. 2020). This research showed that after weight loss, the individuals that were in remission for at least 2 years, hepatic VLDL1-TG production rates, plasma VLDL1-TG concentrations and pancreatic fat content all decreased. The participants that did not achieve remission these changes were more modest and palmitic acid content remained significantly higher. This study hypothesized palmitic acid to be more toxic to β-cells than unsaturated fats, leading to β-cell dysfunction. Also, the individuals that relapsed regained some of the lost weight, resulting in an increase in these parameters. This shows that a distorted fat metabolism that can be caused by excessive caloric intake, appears to drive the development, as well as the reversal of T2DM.

Another recent study showed an increase in β-cell capacity in individuals that lost weight after a low-calorie diet, falling equal to the non-diabetic control group values (Zhyzhneuskaya et al. 2020). A gradual increase of maximum rate of insulin secretion was measured, and this approached the values of the non-diabetic control group after 12 months and this remained stable until at least 24 months. There was an increase in first phase insulin response, but this value did not return to normal, but it was enough to maintain nondiabetic blood glucose levels. This result shows that weight loss can recover the functional β-cell capacity, which is consistent with the Twin Cycle Hypothesis.

Potential problems of low-calorie diets in achieving remission

The data of recent studies on low-calorie diets and remission of T2DM seem very promising and can potentially adjust the current guidelines of treatment of the disease. However, before the low-calorie diet can be implemented several subjects need to be considered. It raises questions such as: the effect of regaining weight, who can benefit from this diet and whether it is maintainable outside controlled trial settings.

Recent studies have linked substantial weight loss to the remission of T2DM. However, maintaining the lost weight is considered to be even more challenging than losing weight in the first place. On average only 29% of the initial weight loss is maintained after a low-calorie diet after 5 years (Anderson et al., 2001). Rapid weight regain is associated with relapse of T2DM and redistribution of fat to the liver and pancreas. Re-accumulation of fat was seen in participants that gained more than 3.3kg over 12 months, while participants that gained less than 3.3 kg did not show an increase in liver fat content (Taylor et al., 2018). Other studies have shown the same results, including Zhuzhneuskaya et al. (2020) who showed that the participants that were unable to sustain remission for 2 years gained more weight than those who stayed in remission. On average, they gained 11.3 kg and 6.6 kg, respectively. Lean et al. (2018) showed that the participants that remained in remission gained around 4.3kg, while the people that relapsed after 12 months gained 7.1 kg. This was not only seen after losing weight through a low-calorie diet, but also an analysis by Chikunguwo et al. (2010) of patients who underwent a gastric bypass showed that regaining weight is correlated to the recurrence of T2DM, and that sustained weight loss is linked to the durability of T2DM remission. However, there were other factors, such as insulin use, that had bigger impact on the remission rates. Even if weight loss is maintained, many people remain overweight or even obese, but the study by Steven et al. (2016) demonstrated that if weight loss is maintained, there is no redistribution of subcutaneous fat to the liver over a period of 6 months (Steven et al., 2016). Taken together, this shows that it is highly important to maintain the new body weight to stay in remission of T2DM. However, this is challenging because not only behavioural patterns promote weight gain, also biological changes, such as a lower resting metabolic and hormonal adaptation, making it more difficult to sustain weight loss (Evert and Franz 2017; Fothergill et al. 2016).

Furthermore, research shows that not every individual with T2DM can benefit from low-calorie diets. The duration of T2DM diagnosis seems to be an important indicator to predict the effectiveness of substantial weight loss, with a longer duration (>6 years) corresponding to lower remission rates. Steven et al. (2016) included participants with a duration of T2DM up to 23 years and demonstrated that participants that responded to a low-calorie diet had a shorter duration since diagnosis than non-responders. Taylor and Steven (2015) compared the effect of a low-calorie diet on long- and short duration of T2DM and showed that similar weight loss resulted in normal fasting plasma glucose levels in half of the long duration patients (>8 years) and 87% of the short duration patients. Also, Mottalib et al. (2015) showed that participants with short duration of T2DM (<5 years) were more likely to go into remission. These results suggest that β-cell dysfunction is reversible, but only in the early stage of the development of the disease. This is likely due to the deterioration of the β-cells reaching the point of no return. Removal of excess fat in the pancreas, and releasing them from metabolic stress, will not result in expression of β-cell specific transcription factors. And redifferentiation will not occur (White et al., 2016). Other factors determining the effect of low-calorie diets include; baseline HbA1C, amount of weight loss, medicine use and age (Gregg et al., 2012; Taylor and Steven, 2015; Mottalib et al., 2015).

Some concerns about the feasibility of low-calorie diets have risen. This diet requires extreme changes in lifestyle and permanent adjustments to avoid weight regain, making it challenging to stick to. It should be carried out under medical supervision as this diet in combination with anti-glycaemic

medication can lead to hypoglycaemia. Moreover, if not executed well, this diet can lead to nutritional deficiencies and a study showed that low-calorie diets can cause heart problems after one week. However, this risk is returned to normal in week 8 (Rayner et al., 2018). This indicates that caution is needed in those with a heart disease. Rehackova et al. (2017) showed that a very low-calorie diet is perceived as feasible and acceptable, but this was studied in a controlled trial setting, with motivated participants and much support. It remains unclear how many people can undergo such intense lifestyle measures and thereby benefit from a low-calorie diet at home with fewer resources. However, motivated people have shown to turn their T2DM into remission at home (Steven, Taylor and Lim, 2013).

Conclusion

Until recently, type 2 diabetes mellitus is seen as a progressive, incurable disease, with standard diabetes care mainly focused on pharmacotherapy in combination with small lifestyle changes. However, only little guidance is given, and the effects are only modest. Present data suggests that lifestyle changes are more important than thought before, and with sufficient medical support and motivation, substantial weight loss via a low-calorie diet can be a more appropriate treatment for people with a short duration of T2DM. On short-term, this diet is associated with a decline in liver and pancreatic fat content, resulting in better glycaemic control. However, long-term effect on remission rates remain unclear and must be further explored. This diet may be challenging and requires permanent lifestyle changes to sustain beneficial effects. Future studies should look into optimizing a strategy to avoid weight regain and the effects of the low-calorie diet on the physiology of the body must be taken under consideration. This diet is focused on weight loss, but research is now on its way to investigate the possibility of using this strategy to reverse T2DM in patients with a healthy weight. To conclude, current research provides evidence that T2DM can be put into remission if the patients are motivated enough to undergo drastic lifestyle changes.

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