Diet and exercise in the prevention and treatment of type 2 diabetes mellitus

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Abstract | Evidence from observational studies and randomized trials suggests that prediabetes and type 2 diabetes mellitus (T2DM) can develop in genetically susceptible individuals in parallel with weight (that is, fat) gain. Accordingly, studies show that weight loss can produce remission of T2DM in a dose-dependent manner. A weight loss of ~15 kg, achieved by calorie restriction as part of an intensive management programme, can lead to remission of T2DM in ~80% of patients with obesity and T2DM. However, long-term weight loss maintenance is challenging. Obesity and T2DM are associated with diminished glucose uptake in the brain that impairs the satiating effect of dietary carbohydrate; therefore, carbohydrate restriction might help maintain weight loss and maximize metabolic benefits. Likewise, increases in physical activity and fitness are an important contributor to T2DM remission when combined with calorie restriction and weight loss. Preliminary studies suggest that a precision dietary management approach that uses pretreatment glycaemic status to stratify patients can help optimize dietary recommendations with respect to carbohydrate, fat and dietary fibre. This approach might lead to improved weight loss maintenance and glycaemic control. Future research should focus on better understanding the individual response to dietary treatment and translating these findings into clinical practice.

Prediabetes
An intermediate condition between normoglycaemia and type 2 diabetes mellitus, characterized by moderately elevated fasting or postprandial blood glucose or HbA_{1c}.

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The worldwide prevalence of type 2 diabetes mellitus (T2DM) in adults has increased from ~150 million affected people in 2000 to >450 million in 2019 and is projected to rise further to ~700 million by 2045 (REF.[1]). Genetics and lifestyle habits (such as consumption of a high-sugar diet and a sedentary lifestyle) can have a predisposing influence as T2DM occurs at varying rates in people of different racial and/or ethnic backgrounds[2]. In addition, the level of adiposity can affect the risk of T2DM. For example, the prevalence of T2DM increases proportionally with increasing BMI; however, the disease can occur even among those with body weight in the normal range[2]. The excess accumulation of adipose tissue in the body negatively affects nearly all physiological functions and organ systems, and increases the risk of cardiometabolic disease[3]. Large prospective studies have demonstrated that an increase in body weight over time considerably increases the incidence of T2DM[4] (FIG. 1). Likewise, an increase in BMI of 5 kg/m^2, from the upper limit of normal BMI (25 kg/m^2) to the lower limit of obesity (30 kg/m^2), more than doubles the risk of death associated with T2DM[5]. Evidence clearly indicates, however, that the risk of T2DM increases with increasing BMI well before clinical obesity is diagnosed[6–8].

The mechanisms responsible for the tight link between weight gain and the development of prediabetes and T2DM are not completely clear; however, excessive accumulation of fat in the body increases insulin resistance and brings about other subtle metabolic changes, well before T2DM is diagnosed[9]. For example, obesity is associated with increased fatty acid release into the circulation[10], decreased insulin sensitivity in muscle, liver and adipose tissue[11], and excessive fat accumulation in adipose tissue and liver[12], as well as potentially in other organs (for example, pancreas and skeletal muscle)[13]; these metabolic alterations can occur even before abnormalities in glucose homeostasis manifest. Early in the natural history of T2DM, metabolic alterations that are associated with fat accumulation are accompanied by gradual and only minor increases in fasting and postprandial hyperglycaemia (that is, prediabetes), owing to a compensatory increase in pancreatic insulin secretion (hyperinsulinaemia) that helps mask the effects of insulin resistance and maintains normal glycaemic control[14,15] (FIG. 2). Eventually, however, β-cells begin to fail and insulin secretion can no longer keep up with the increased demand for insulin; therefore, fasting and postprandial glucose concentrations rise further and the diagnosis of T2DM ensues[14,15] (FIG. 2). The close

Key points

- Studies show that weight loss can produce remission of type 2 diabetes mellitus (T2DM) in a dose-dependent manner.
- In patients with T2DM and obesity, weight loss of ~15 kg, achieved by an intensive management programme involving calorie restriction, can lead to remission of T2DM in ~80% of individuals.
- Long-term maintenance of weight loss and metabolic health in people who have undergone intensive lifestyle intervention is challenging.
- Carbohydrate restriction might help maintain weight loss and maximize metabolic benefits.
- When combined with calorie restriction and weight loss, increases in physical activity and fitness are an important contributor to T2DM remission.
- Preliminary work suggests that pretreatment glycaemic status could be used to stratify patients in order to optimize dietary recommendations.

relationship between increasing body fatness and T2DM has led to the connotation 'diabesity', which highlights the fact that many individuals with T2DM also have overweight or obesity and also highlights the need for combined treatment strategies[16,17].

In this Review, we highlight large randomized clinical trials that provide evidence of T2DM remission after weight loss induced by intensive diet-based lifestyle programmes, alongside findings from smaller, well-controlled and mechanistic studies. We consider the role of macronutrient composition of the diet, including carbohydrate quality and/or restriction. We also discuss results showing that physical activity can contribute to T2DM remission when combined with diet-induced weight loss. Finally, we cover preliminary findings that suggest that individuals with prediabetes can be stratified according to metabolic status to optimize recommendations of dietary composition for long-term weight loss maintenance and thereby prevent progression to T2DM.

Weight control for T2DM treatment

Studies have repeatedly shown the importance of body weight control for the management of T2DM[16]. Data from the Swedish Obese Subjects study[18] and the Scandinavian Obesity Surgery registry[19] demonstrate that major weight loss 2 years after bariatric surgery is accompanied by complete remission of T2DM in 72% and 58% of patients with T2DM, respectively. Likewise, patients with T2DM who are treated with glucagon-like peptide 1 (GLP1) analogues have associated weight loss, which is accompanied by sixfold to tenfold greater odds for T2DM remission (defined as HbA_{1c} ≤6.5%) than with placebo[20]. However, both bariatric surgery and medications can have important weight loss-independent effects on glucose metabolism. For example, GLP1 analogues stimulate insulin secretion and perhaps also increase insulin sensitivity in peripheral tissues[21,22]. Furthermore, postprandial levels of GLP1 and other incretins are substantially increased by certain bariatric surgery procedures (for example, gastric bypass and sleeve gastrectomy)[21]. Therefore, the aforementioned findings do not allow researchers to distinguish between the effects of weight loss per se and weight loss-independent mechanisms on T2DM remission.

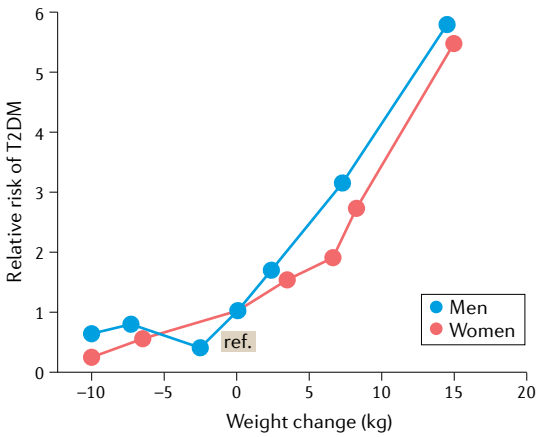

Fig. 1 | **Weight gain and risk of T2DM.** The relative risk of type 2 diabetes mellitus (T2DM) according to weight change from baseline compared with the reference category (ref.) of no weight change over 10 years in men (Health Professionals' Follow-Up study) and 18 years in women (Nurses' Health study). Data originally presented in REF.[4].

Proof of concept. Weight loss induced solely by dietary calorie restriction dose-dependently improves body composition by progressively decreasing total body fat, intra-abdominal fat (known as visceral adipose tissue) and intrahepatic lipid content[23]. Moderate diet-induced weight loss (~5% of baseline body weight) in non-diabetic individuals with obesity and metabolic dysfunction decreases fasting blood glucose and insulin concentrations, increases insulin sensitivity in the liver, adipose tissue and muscle, and improves β-cell function. Additional weight loss (11–16% of baseline body weight) further improves muscle insulin sensitivity and β-cell function[23]. Accordingly, progressively greater weight loss (from no change to >14% loss of baseline body weight) in patients with obesity and T2DM is associated with progressively increasing reductions in fasting glucose, insulin and HbA_{1c} concentrations; that is, stepwise improvements in glycaemic control[24].

Mechanistic studies showed that diet-induced weight loss (6–17 kg) in patients with obesity and T2DM decreased fasting glucose concentrations predominantly owing to augmented suppression of basal hepatic glucose production (that is, improved hepatic insulin sensitivity)[25,26]. Furthermore, the decrease in postprandial glucose concentrations occurred predominantly due to augmented stimulation of peripheral glucose uptake (that is, improved muscle insulin sensitivity)[25]. Several small but well-controlled studies in patients with obesity and T2DM have demonstrated that considerable weight loss (>15 kg or ~15% of baseline body weight) induced by calorie restriction over a fairly short period of time (1.5–6 months) brings about substantial reductions of fasting blood glucose and HbA_{1c} levels for most patients, which can lead to the normalization of these parameters in some patients[27–29].

In one such mechanistic study of 11 patients with overweight or obesity with short-duration T2DM (<4 years), a weight loss of ~15.3 kg (~15% of baseline weight) achieved over 8 weeks by a very-low-calorie diet was associated with decreased fat content in the liver and pancreas as well as increased first-phase insulin

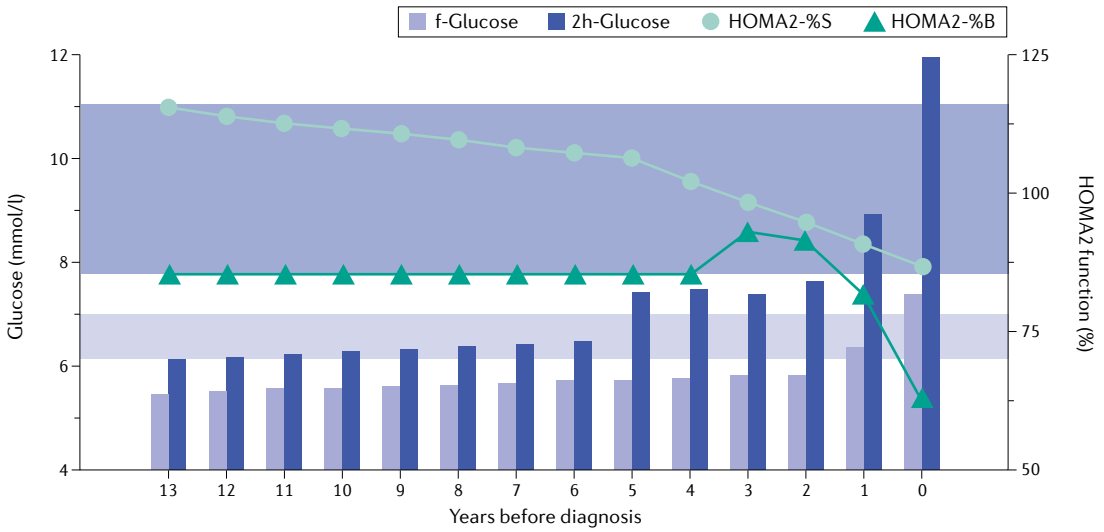

Fig. 2 | **Natural history of prediabetes and T2DM.** Trajectories of glycaemia, insulin sensitivity and insulin secretion were established by monitoring 6,538 participants without type 2 diabetes mellitus (T2DM) at baseline for a median of 9.7 years (interquartile range 7.9–14.2 years); 505 cases of T2DM were diagnosed (Whitehall II study). Fasting glucose (f-Glucose) and 2-h blood glucose (2h-Glucose) concentrations (obtained from an oral glucose tolerance test) and homoeostasis model assessment indexes of insulin sensitivity (HOMA2-%S) and β-cell function (HOMA2-%B) were evaluated retrospectively from up to 13 years before the diagnosis of T2DM. The horizontal light blue and dark blue bands represent the prediabetes range based on fasting glucose (6.1–7.0 mmol/l) and 2-h glucose (7.8–11.1 mmol/l) concentrations, respectively. Accordingly, fasting glucose levels above the light blue band and 2-h glucose levels above the dark blue band are indicative of T2DM. Data originally presented in REF.[14].

secretion, and led to remission of T2DM in all patients[30]. These results were striking because of the demonstration that weight loss can restore first-phase insulin secretion in patients with T2DM; this effect is probably an integral mechanism for remission. This hypothesis was supported by the results of several subsequent trials that assessed the effects of weight loss on T2DM remission after dietary interventions ranging in duration from 5 months to 2 years. These studies found that patients who responded to treatment were characterized by shorter T2DM duration and an increase in first-phase insulin secretion after weight loss, which did not occur in patients who did not respond to treatment despite similar weight loss[31,32]. Likewise, reductions in pancreatic fat, liver fat and hepatic very-low-density lipoprotein (VLDL) triglyceride secretion rate were more pronounced among the patients who responded to treatment than in patients who did not respond to treatment[31,32].

Interestingly, one study also reported on the characteristics of those who achieved remission at 5 months into the weight loss intervention but subsequently relapsed to redevelop T2DM at 2 years of follow-up[32]. Compared with individuals with durable remission, patients who relapsed regained more weight from 5 months to 2 years of follow-up and showed substantial rebounds in the fat content of the pancreas and liver, hepatic VLDL triglyceride secretion rate and increases in VLDL triglyceride palmitate content, as well as a complete return to baseline in first-phase insulin secretion[32]. Therefore, an increased ability of the pancreas to secrete insulin and the restoration of first-phase insulin secretion — in other words, the capacity to recover β-cell function — has emerged as a key factor for T2DM remission after weight loss.

It is less clear from the results of these studies[30–32] whether β-cell recovery in patients who respond to treatment depends in a causal manner to the decrease in ectopic fat accumulation in these individuals; similarly it remains unknown whether the rebound in ectopic fat content in patients who relapsed is the cause of β-cell function returning to baseline. The β-cells may well have a threshold for lipid-related insults and stress from various sources (for example, excess liver fat and augmented VLDL triglyceride secretion, more circulating free fatty acids and excess pancreatic fat) that renders them less responsive to weight loss, particularly with regard to longer-duration T2DM[33]. The coordinated changes in VLDL triglyceride palmitate content that accompany T2DM remission and relapse in patients who underwent diet-induced weight loss highlight a possible causal link, as palmitic acid (the primary product of hepatic de novo lipogenesis) is particularly cytotoxic against β-cells in vitro[32]. These observations support the view that the optimal time to intervene for reversing T2DM is at the time of diagnosis[34]. Nonetheless, a low-calorie intervention with total diet replacement can lead to substantial reductions in body weight and considerable improvements in glycaemic control, and thus diminish insulin burden, even among patients with long-standing T2DM who are treated with insulin[35].

Evidence from large randomized clinical trials. A few large randomized controlled trials have reported on the relationship between weight loss achieved by lifestyle modification and remission of T2DM. For example, in the Look AHEAD (Action for Health in Diabetes) study, a multi-centre trial conducted in the USA, participants were randomized to intensive lifestyle intervention,

which focused on the adoption of an energy-prudent diet (1200–1800 kcal per day) and a physically active lifestyle (175 min of moderate-intensity physical activity per week) or a control group[36]. Participants in the lifestyle intervention group lost significantly more weight during the first 4 years than participants randomized to the control group (8.6% versus 0.7%, respectively, at year 1; and 4.7% versus 0.8%, respectively, at year 4; both $P<0.001$), and had greater increases in fitness, as well as a 6.6-fold greater prevalence of T2DM remission (partial or complete, defined respectively as the transition from meeting T2DM criteria to the prediabetes level of glycaemia or to the full normalization of glycaemia, without T2DM medication)[36]. However, absolute remission rates were low (11.5% at year 1 and 7.3% at year 4 in the intervention group), which is probably owing to the modest amount of weight loss achieved and the wide range of T2DM duration at baseline (median of 5 years with an interquartile range of 8 years)[36], or even the composition of the prescribed diet[37]. Although participants in the intensive lifestyle intervention group reduced their calorie intake, this was achieved predominantly by restricting consumption of dietary fat rather than carbohydrate; as a result, the percentage of energy obtained from carbohydrate increased[38], which might have limited the efficacy of the diet (see below). Remission of T2DM at any time during follow-up was more likely for individuals with a shorter duration of T2DM (<2 years), greater weight loss (>6.5% of baseline weight) and greater improvements in physical fitness[36].

The dose–response relationship between weight loss and T2DM remission over 1–2 years was evaluated in the Diabetes Remission Clinical Trial (DiRECT), which was conducted in the UK entirely in the primary care setting. Patients with overweight or obesity with fairly short-duration T2DM (<6 years) were randomized to a best-practice care group (control group) or a structured weight-management programme that included the use of a very-low-calorie diet (~850 kcal per day) for 3–5 months, followed by stepped food reintroduction (intervention group)[39,40]. Weight loss was significantly greater in the intervention group than in the control group (8.8-kg difference at year 1, and 5.4-kg difference at year 2; both $P<0.0001$) and T2DM remission rates were several-fold greater (46% in the intervention group versus 4% in the control group at year 1, and 36% in the intervention group versus 3% in the control group at year 2; both $P<0.0001$). Furthermore, a clear dose–response relationship was demonstrated between the amount of weight lost and the prevalence of T2DM remission[39,40] (FIG. 3). Among the patients who lost ≥15 kg, ~86% and ~70% achieved complete remission of their T2DM after 1 and 2 years, respectively. These results reinforce the primary importance of weight loss in T2DM remission and should shift the clinical priority of T2DM management from methods that achieve improvements in glycaemic control to methods that induce increased weight loss and long-term management programmes to sustain weight loss.

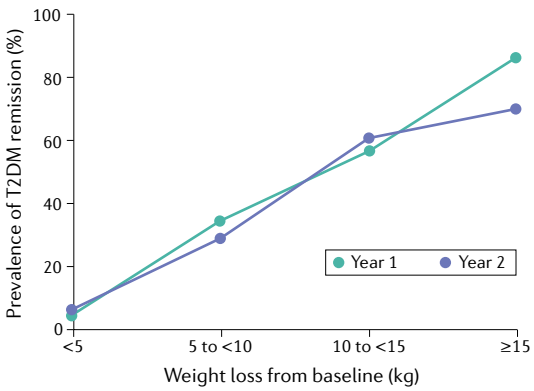

Fig. 3 | **Weight loss and remission of T2DM.** Patients with overweight or obesity and type 2 diabetes mellitus (T2DM) participated in a structured weight-management programme aiming at weight reduction (intervention) or best-practice care (control). The figure demonstrates the prevalence of T2DM remission in the overall study population according to the amount of weight loss achieved at 12 and 24 months (DiRECT study; $n=298$, dropout rate <9%). Data originally presented in REF.[40].

It should be emphasized, however, that weight loss in all the aforementioned diet trials refers predominantly to a reduction in adipose tissue mass[41]. Although no studies are currently published that evaluate remission of T2DM in relation to the amount of fat and muscle loss, it is reasonable to assume that, for a given amount of weight loss, any approach that minimizes loss of muscle tissue will optimize the beneficial effects of T2DM treatment because muscle is responsible for the majority of insulin-mediated glucose disposal and is thus a key determinant of whole-body insulin sensitivity[42,43].

The role of diet beyond weight loss

Clearly, the amount of weight loss achieved by patients emerges as the cornerstone of treatment of T2DM, which ultimately places emphasis on the cumulative energy deficit and the induction of a negative energy balance. This energy deficit can be achieved by a reduction in total calorie intake (most commonly), but also a reduction in energy absorption (for example, the medication orlistat reduces fat absorption from the gastrointestinal tract), a decrease in appetite (for example, some appetite suppressant medications decrease the sensation of hunger and/or increase the sensation of fullness), an increase in energy expenditure (for example, by taking regular exercise), or an increase in energy loss from the body (for example, some medications — gliflozins — inhibit the reabsorption of glucose in the kidneys and thereby increase glucose excretion)[44]. Different dietary regimens might have the potential to optimize weight loss in patients with T2DM such as, for example, ad libitum Mediterranean diets rich in vegetable fat and dietary fibre[45–47]. More importantly, however, diets of different macronutrient composition[48] and level of calorie restriction[49] can have different effects on the mechanisms regulating glucose homeostasis, even when weight loss is matched. Therefore, other dietary or lifestyle factors, not necessarily related to the absolute amount of weight loss, are probably also involved in the improvement of glucose control in patients with T2DM.

Other factors might also affect the T2DM relapse rate after the initial remission achieved with dietary

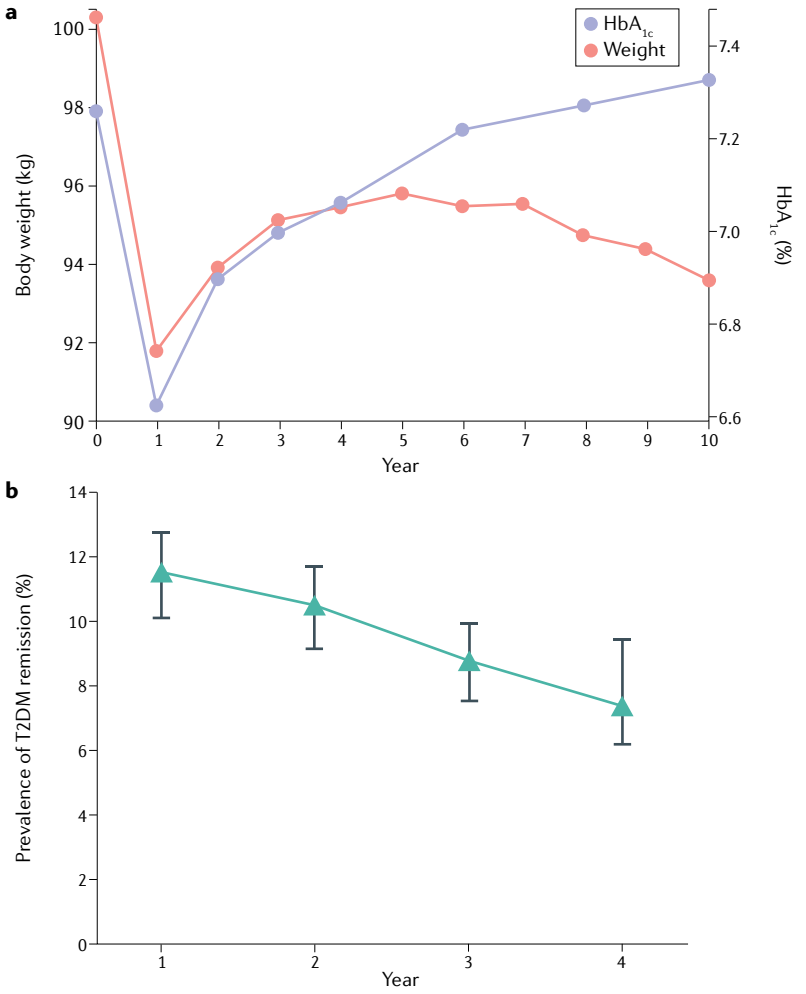

Fig. 4 | **Long-term changes induced by intensive lifestyle intervention in patients with T2DM. a** | Changes in body weight and HbA_{1c} in patients with overweight or obesity with type 2 diabetes mellitus (T2DM) who participated in an intensive intervention aiming at the adoption of an energy-prudent diet and a physically active lifestyle, and who were followed-up for ~10 years. **b** | Remission rates of T2DM in the same patient population (Look AHEAD study; $n = 2{,}570$, dropout rate <4%). Data originally presented in[50].

interventions. For example, in the patients receiving the intensive lifestyle intervention in the Look AHEAD study, weight regain occurring between years 1 and 4 of follow-up was mirrored by a rebound in HbA_{1c} levels and a progressive decline in the prevalence of T2DM remission; by 10 years of follow-up, the group mean HbA_{1c} had returned to baseline despite sustained moderate weight loss[50] (FIG. 4a,b). Even though this effect could partly reflect worsening glucose control with ageing, weight regain after weight loss is an important factor favouring T2DM relapse. Furthermore, T2DM relapse can occur even when the initial weight loss is large and much of it is maintained in the long term[51,52]. These observations suggest that some dietary or lifestyle factors are involved in tipping the balance between T2DM remission and relapse independent of effects on body weight homeostasis.

Carbohydrate restriction. In the absence of calorie restriction and consequent weight loss, modifications to the intake of dietary macronutrients can produce substantial improvements in glycaemic control and metabolic risk factors in patients with T2DM. For example, well-controlled dietary studies have shown that reducing dietary carbohydrate from 54% of total calories to 31% of total calories, whilst iso-energetically increasing fat and protein contents to maintain the same total energy intake, significantly attenuates daily postprandial glucose excursions ($P < 0.0001$) and insulin responses ($P < 0.001$) in patients with T2DM by ~14% and ~22%, respectively, even after just 1–2 days[53]. A similar carbohydrate-reduced diet (from 50% to 30% of total calories) in patients with obesity and T2DM reduces fasting glucose concentrations ($P < 0.05$) and HbA_{1c} levels ($P < 0.001$) after 6 weeks, even in the absence of considerable weight loss (that is, eucaloric feeding), in conjunction with significant reductions in the fat content of the liver ($P < 0.01$) and pancreas ($P < 0.05$)[54]. Based on these observations, it is tempting to speculate on the beneficial effects of carbohydrate-restricted diets on β-cell function, given the hypothesized link between changes in ectopic fat deposition, hepatic VLDL secretion and first-phase insulin secretion and their importance for weight loss-induced remission of T2DM[31,32,55]. For instance, restricting carbohydrate intake (particularly simple carbohydrates) under eucaloric conditions would downregulate hepatic de novo lipogenesis and decrease VLDL triglyceride palmitate, as shown by a series of studies in animal models and humans in vivo[56]. This effect, in turn, could alleviate cytotoxic stress on pancreatic β-cells, as results from in vitro and ex vivo models have demonstrated that palmitic acid is potentially the most β-cell-toxic saturated fatty acid[32].

It is true that results from randomized trials and meta-analyses regarding low-carbohydrate diets are not entirely consistent[57], which is possibly owing to variation in total energy intake and macronutrient composition, and the combination of studies with weight maintenance and weight loss interventions. In one meta-analysis, replacing carbohydrate with fat in the diet of patients with T2DM whilst keeping protein intake constant produced small but significant decreases in postprandial glucose and insulin levels, independent of energy restriction and changes in body weight[58]. Similarly, another meta-analysis demonstrated that low-carbohydrate diets (replacing carbohydrate with either protein or fat, or a combination of both, mostly in combination with calorie restriction) lead to significantly greater decreases in HbA_{1c} than high-carbohydrate diets (~0.34 percentage points or 3.7-mmol/mol difference after 3–6 months; $P = 0.02$) in patients with T2DM, even for the same amount of weight loss[47]. Importantly, the magnitude of improvement in glycaemic control increases with the degree of carbohydrate restriction. Nevertheless, these beneficial effects are no longer apparent at 12 months into the intervention[47], which could be owing to gradually decreasing adherence to dietary carbohydrate restriction. Of note, other meta-analyses did not find significant beneficial effects of lower carbohydrate intake on glycaemic control in patients with T2DM[57,58]. Several factors might confound these comparisons, such as the definition of low-carbohydrate and high-carbohydrate diets, the duration and intensity of the intervention,

Glycaemic index
A relative ranking of foods according to their ability to increase blood glucose levels relative to a reference food (glucose or white bread) for the same amount of bioavailable carbohydrate.

Glycaemic load
An extension of the glycaemic index that takes into account the actual amount of available carbohydrate present in one serving of a food or in the whole diet.

the type of carbohydrate being replaced (for example, simple or complex) and the overall 'quality' of the diets (for example, food sources and extent of processing)[59–61]. The glycaemic index and the glycaemic load of the diet are strongly associated with the risk for T2DM, independent of changes in body weight and body fat. As such, manipulation of the glycaemic index and load of the diet might have a role in the management of T2DM[62,63].

Obesity and T2DM are associated with diminished brain glucose responses (that is, blunted rises in intracerebral glucose levels) to peripheral hyperglycaemia[64]. Furthermore, brain glucose levels directly correlate with self-reported feelings of satiety and fullness[64]. These observations might therefore have important implications for feeding behaviour in response to the amount and type of carbohydrate in the diet. Given that the major satiety signal in response to simple and/or refined carbohydrate (that is, brain blood glucose levels) is weakened in T2DM, the importance of other satiety signals that are released mainly in response to dietary protein and fat (for example, cholecystokinin, GLP1 and peptide YY) might become more relevant[65]. Manipulating the macronutrient composition of the diet could therefore be important for the control of food intake in patients with T2DM.

It should be emphasized that carbohydrate restriction should not involve restriction of dietary fibre and whole grain foods, as their fermentation in the large intestine by gut microbiota has the potential to produce short-chain fatty acids (SCFAs), such as acetate, which might increase satiety as shown in some animal models[66,67]. Moreover, Mendelian randomization analyses of genome-wide genotyping, gut metagenomic sequencing and faecal SCFA data from 952 individuals suggests causal links between the gut production of the SCFA butyrate and increased insulin response after an oral glucose tolerance test, as well as a link between abnormalities in the gut production or absorption of the SCFA propionate and increased risk of T2DM[46,68,69]. Overall, targeted restriction of some dietary carbohydrates without a reduction in total energy intake could provide an alternative approach to calorie restriction to obtain and maintain metabolic benefits in patients with T2DM. In addition, carbohydrate-restricted eucaloric dietary interventions might be particularly beneficial for patients with lower degrees of obesity who cannot easily adhere to calorie-restricted diets[70] or for those with greater baseline metabolic derangements[71].

The importance of physical activity

Regular exercise is essential for the management of T2DM. Many studies have demonstrated multiple beneficial effects of progressive aerobic and resistance exercise training, prescribed alone or in various combinations (without diet modification), on body composition (for example, reduced total body fat and visceral adipose tissue), cardiometabolic risk factors (for example, improved blood lipid profile and blood pressure) and particularly on the mechanisms regulating glucose homeostasis (for example, improved insulin sensitivity and decreased HbA_{1c}) in patients with T2DM[72–77]. All the above effects of regular exercise in patients with T2DM can be independent of accompanying changes in body weight (that is, weight loss)[73,74,76]. Furthermore, the magnitude of these effects is dose-dependent with the total volume (total energy expenditure) of training rather that depending on either exercise duration or intensity alone[74–76,78], and is generally comparable to that of more conventional treatments (for example, insulin therapy and oral hypoglycaemic medications)[73]. However, available evidence suggests that exercise training alone, without any sort of dietary advice that facilitates calorie restriction and weight loss, does not readily lead to remission of T2DM in the majority of patients[72–77].

The Malmö feasibility study was among the first to provide long-term data on T2DM remission with an intervention that focused predominantly on an increase in physical activity. In this study, 41 participants with overweight or obesity with newly diagnosed T2DM, as well as generally poor physical fitness, received dietary advice and were offered the choice of individual or group-based exercise for 5 years (39 participants completed the entire study)[79]. The physical training consisted of two weekly 60-min sessions with various activities (calisthenics, walking, jogging, soccer and badminton playing) under the guidance of a physiotherapist, with exercise intensity increasing progressively, later into the programme[80]. Decreases in body weight and increases in fitness (maximal oxygen uptake) were greatest between 6 months and 2 years into the intervention and were attenuated thereafter. At the end of the 5-year study, participants had achieved a weight loss of ~3 kg and an increase in cardiorespiratory fitness of ~14% compared with baseline. Notably, the intervention brought about statistically significant reductions in glucose and insulin responses to a standard oral glucose tolerance test, so that more than half (~54%) of the participants with T2DM were in remission (defined as no longer meeting diagnostic criteria for T2DM) at the 5-year follow-up[79]. The results of the Malmö study alleviate concerns around the feasibility and long-term sustainability of lifestyle interventions that include physical activity to treat patients with T2DM. These findings are in accordance with several larger (500–3,250 participants) and equally lengthy (3–6 years) randomized trials in patients with impaired glucose tolerance (prediabetes), such as the Diabetes Prevention Program (USA), the Diabetes Prevention study (Finland), and the Da Qing Diabetes study (China), which demonstrated beneficial effects of physical activity in preventing T2DM[81].

A few shorter, non-randomized and randomized controlled trials that combined modest diet-induced weight loss with intensive exercise training for 6–12 months (5–6 sessions per week of mostly supervised aerobic and resistance exercise, resulting in an increase in peak oxygen uptake of 18–23%) reported similarly impressive T2DM remission rates (partial or complete) among previously sedentary individuals[82–84]. Overall, T2DM remission rates in studies with interventions that included an intensive physical activity component were 37–80% remission after 3–10 kg of weight loss at 0.5–5 years[79,82–84], which is seemingly greater than the remission rates achieved in DiRECT[40] or Look AHEAD[36] studies for the same amount of weight loss. Both these

large randomized controlled trials had similar weight loss to the aforementioned exercise intervention studies[79,82–84]; however, DiRECT, which did not include a physical activity component, achieved 29–34% remission after 5–10 kg of weight loss at 1–2 years[40], and the Look AHEAD study, which included a less intensive physical activity component, achieved 8–12% remission after 5–9 kg of weight loss at 1–4 years[36]. Moreover, in the Look AHEAD study, T2DM remission rates were notably higher among patients with greater improvements in fitness[36]. These findings collectively suggest that an increase in physical activity and fitness, within a comprehensive lifestyle modification programme, is probably an important contributor to T2DM remission, particularly when weight loss is moderate; the importance of exercise training may be less when weight loss becomes greater (for example, ≥15% of baseline weight induced by hypocaloric diet[39] or bariatric surgery[85]) and T2DM remission becomes nearly complete.

Diet interventions for prediabetes

Patients with overweight and obesity show considerable interindividual variability in the weight loss response across dietary treatments[86]; however, individual patients are often assumed by clinicians to respond similarly to the various diet prescriptions. Although specific dietary recommendations have been drawn up for T2DM, which are continuously being revised[87], individuals without T2DM have largely been treated by both clinicians and researchers alike as a homogeneous group. Nevertheless, variation in baseline glycaemic control in people with overweight and obesity but without T2DM, such as the presence of normoglycaemia or prediabetes, might lead to variable weight loss success and metabolic responses to dietary treatment[46]. In the USA, the prevalence of prediabetes has been progressively climbing, from 20% of the adult population in 2000 to 37% in 2012, and this figure is projected to rise to 40% in 2030 (REF.[88]). People with prediabetes have a considerably increased risk of T2DM[88]; however, weight loss induced by lifestyle modification can decrease this risk by ~50%[81,89]. This has been shown consistently in major randomized studies such as the US[90] and Finnish[91] diabetes prevention trials, which included 500–3,250 individuals with prediabetes and achieved 5–7% weight loss with a combination of dietary restriction and increased physical activity (150–210 min/week) over ~3 years. A similar reduction in the risk of T2DM was found in the Chinese Da Qing Diabetes Prevention study, which achieved only mild weight loss (2–3 kg) and focused mostly on increasing physical activity for 6 years[92]. Remarkably, the beneficial effects of lifestyle modification to prevent or delay T2DM can persist for an impressive 14 years after the active intervention[93]. Therefore, helping the growing number of patients with prediabetes lose weight (or prevent further weight gain) can be an effective strategy for reducing overall rates of T2DM.

The importance of baseline glycaemia. A review from 2018 identified a considerable number of studies that investigated preintervention measures of glycaemia and insulinaemia to determine whether they could be useful biomarkers to predict weight loss among individuals with normoglycaemia and prediabetes following specific diets[46]. To a greater extent than insulin, the level of baseline fasting glucose was found to be a potent prognostic marker of weight loss success. Furthermore, evidence suggested that, among participants with prediabetes, the overall macronutrient composition of the diet was of little importance; however, the quality of dietary carbohydrate was extremely important for weight loss and weight loss maintenance[46].

In the Supermarket Intervention study (SHOPUS, Denmark), participants with increased waist circumference (≥80 cm for women and ≥94 cm for men) were randomized either to the New Nordic Diet or the Average Danish Diet for 6 months[94]. The New Nordic Diet is based on the consumption of high-quality carbohydrates and generally comprises local and minimally processed foods (for example, berries, cabbages, root vegetables, legumes, potatoes, fresh herbs, wild plants and mushrooms, nuts, whole grains, meats from livestock and game, fish and shellfish, and seaweed), whereas the Average Danish Diet is similar to a Western control diet and comprises foods such as refined grains including pasta and rice, meat, dairy and cheese, sugary products, convenience foods and, to a lesser extent, low-fibre vegetables and imported fruit[94]. Participants were instructed to eat both diets ad libitum; to increase adherence, cookbooks and all foods were provided free of charge at a specially designed supermarket at the University of Copenhagen, and barcodes were scanned to ensure foods were consumed according to the randomization group. When stratifying by baseline fasting plasma glucose concentrations, we found that individuals with prediabetes lost 6.0 kg more on the New Nordic Diet than on the Average Danish Diet, whereas normoglycaemic individuals lost only 2.2 kg more[95]. Using a novel statistical approach for estimating truly individualized treatment effects, we found that the New Nordic Diet produces a 3.0-kg greater weight loss than the Average Danish Diet for every 1 mmol/l increase in baseline fasting plasma glucose concentration[96] (FIG. 5a,b). These findings suggest the importance of baseline glycaemic control for weight loss success.

In the Monounsaturated Fatty Acids in Obesity study (MUFOBES, Denmark), participants with overweight and obesity initially lost ~12 kg on a low-calorie diet and were subsequently randomized to one of three different ad libitum diets for 6 months[97]: a high-monounsaturated fat diet; a low-fat (20–30% of total energy intake) high-fibre (>30 g/10 MJ) diet similar to the New Nordic Diet; or the Average Danish Diet. Again, all foods were provided free of charge at a specially designed supermarket. When participants were stratified according to initial fasting plasma glucose levels, those with prediabetes did not regain any weight on the New Nordic-like Diet whereas those on the Average Danish Diet regained 4.2 kg, resulting in lower weight regain on the former diet than the latter (−4.2 kg, 95% CI −6.8 to −1.6, $P = 0.002$), whereas no such difference was observed among normoglycaemic individuals, who regained 2.1–2.5 kg on both diets[98]. Using the aforementioned novel statistical approach[96], we demonstrated that the New Nordic-like

Diet produces a 7.3-kg smaller weight regain than the Average Danish Diet for every 1 mmol/l increase in baseline fasting plasma glucose concentration (FIG. 5c,d), again highlighting the potential importance of baseline glycaemia in the body weight response to dietary treatment.

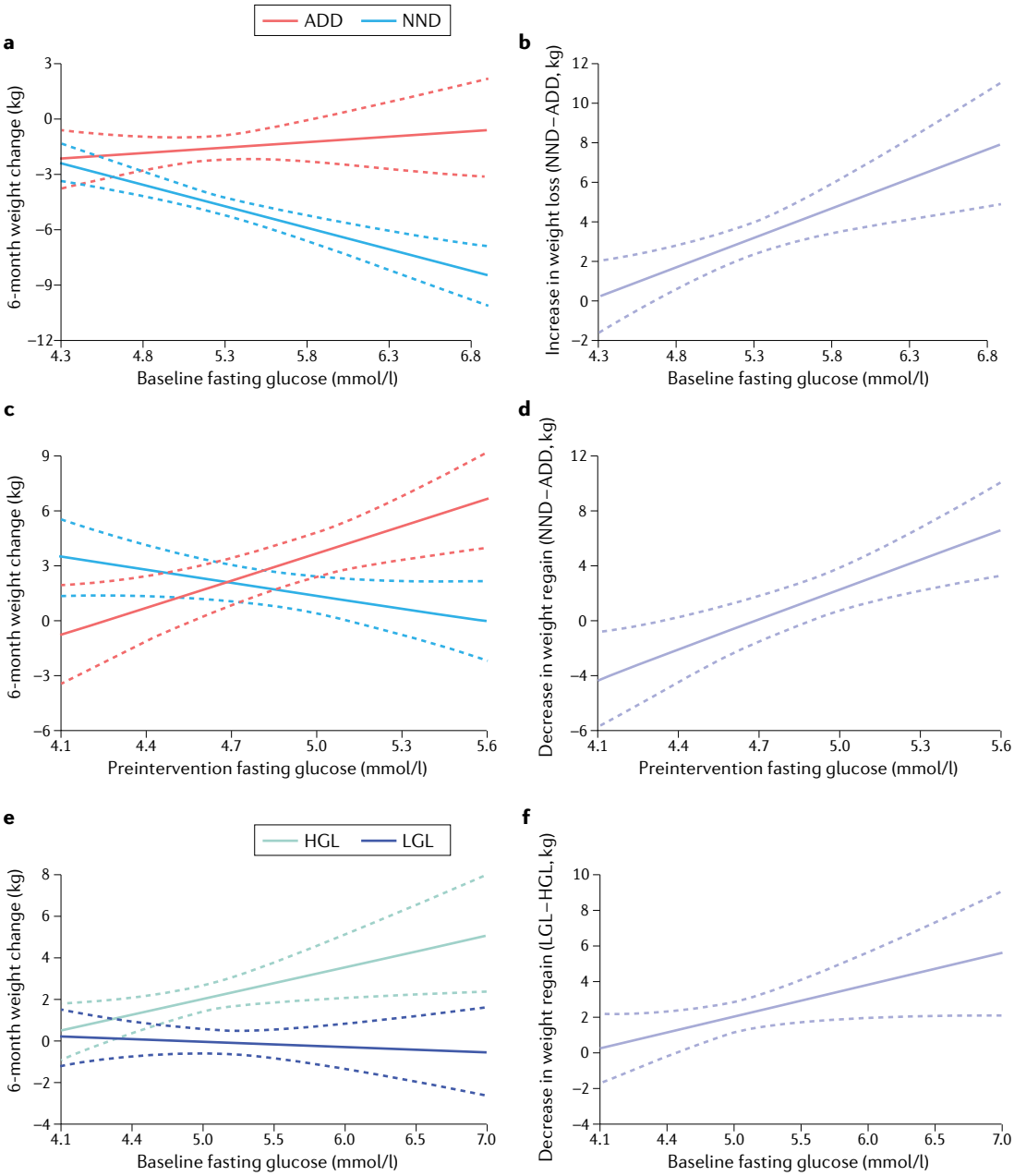

Fig. 5 | **Differences in diet-induced changes in body weight according to baseline fasting plasma glucose concentrations.** In three separate analyses (one for each of the SHOPUS[94], MUFOBES[97] and DIOGENES[99] trials), differences in changes in body weight from baseline to 6 months were estimated using a linear mixed model, which included fasting plasma glucose-by-diet interactions, as well as age and sex (and low-calorie diet in MUFOBES and DIOGENES) as fixed effects and subject-specific random effects[96]. For SHOPUS, weight changes after 6 months on the New Nordic Diet (NND) or the Average Danish Diet (ADD) in relationship to baseline fasting glucose (part **a**) were used to calculate the difference between diets (part **b**). The slope for the difference between the NND and the ADD was 3.0 kg per mmol/l (95% CI 1.2 to 4.8 kg per mmol/l, $P = 0.001$) (ADD 0.6, 95% CI −0.9 to 2.2, $P = 0.43$; NND −2.4, 95% CI −1.5 to −3.3, $P < 0.001$). For MUFOBES, weight changes after an initial period of diet-induced weight loss followed by 6 months on the NND or the ADD in relationship to baseline fasting glucose (part **c**) were used to calculate the difference between diets (part **d**). The slope for the difference between the NND and ADD was 7.3 kg per mmol/l (95% CI 3.2 to 11.4 kg per mmol/l, $P < 0.001$) (ADD 4.9, 95% CI 1.8 to 8.1, $P = 0.002$; NND −2.3, 95% CI −4.9 to 0.2, $P = 0.073$). For DIOGENES, weight changes after an initial period of diet-induced weight loss followed by 6 months on the lowest glycaemic load (LGL) diet or the highest glycaemic load (HGL) diet in relationship to baseline fasting glucose (part **e**) were used to calculate the difference between diets (part **f**). The slope for the difference between the LGL diet and the HGL diet was 1.8 kg per mmol/l (95% CI 0.1 to 3.5 kg per mmol/l, $P = 0.038$) (HGL 1.6, 95% CI 0.2 to 2.9, $P = 0.020$; LGL −0.2, 95% CI −1.3 to 0.8, $P = 0.67$).

In the pan-European Diet, Obesity, and Genes (DIOGENES) trial, individuals with overweight and obesity achieved an initial weight loss of ~11 kg by consuming a low-calorie diet for 2 months and were then randomized to one of five ad libitum diets, which differed in glycaemic index and protein content for 6 months[99]. Overall, participants who were assigned to the highest glycaemic load diet (that is, high glycaemic index and low protein) regained 1.9 kg more than those randomized to the lowest glycaemic load diet (that is, low glycaemic index and high protein)[99]. When reanalysing the results, we found that participants with prediabetes regained 5.8 kg more (95% CI 3.3 to 8.3 kg, $P<0.001$) on the highest glycaemic load diet than those on the lowest glycaemic load diet, whereas normoglycaemic individuals regained only 1.4 kg more (95% CI 0.5 to 2.4 kg, $P=0.003$), resulting in a 4.4-kg difference (95% CI 1.8 to 7.0 kg, $P=0.001$) in the responsiveness to the diets between glycaemic groups[95]. As above, we demonstrated that the lowest glycaemic diet produces 1.8-kg smaller weight regain than the highest glycaemic load diet for every 1 mmol/l increase in baseline fasting plasma glucose concentration (FIG. 5e,f). The two low glycaemic index diets in the DIOGENES trial (with low or high protein content) produced a 1.2-kg (95% CI 0.3 to 2.2 kg, $P=0.01$) smaller weight regain for every 1 mmol/l increase in baseline fasting plasma glucose concentration compared with the two high glycaemic index diets (with low or high protein content). By contrast, no significant differences were found between the two high-protein and the two low-protein diets (−0.4 kg, 95% CI −1.3 to 0.6 kg, $P=0.48$). Overall, these findings suggest an interaction between baseline glycaemic control and the amount and quality of dietary carbohydrate for optimal weight loss maintenance.

These observations are also in line with the results from a randomized, placebo-controlled, double-blind clinical trial of a novel hydrogel that was designed to mimic the viscoelastic properties of leafy vegetables (that is, cellulosic-based composition and mechanical properties)[100]. Patients with overweight and obesity were prescribed a hypocaloric diet of 300 kcal per day below their calculated energy requirements and were randomized to hydrogel or placebo for 24 weeks. Compared with patients treated with placebo, those treated with the hydrogel lost 2.1% more of their baseline weight ($P=0.0007$) and had two times greater odds of achieving ≥10% weight loss ($P=0.0107$). Notably, among the subgroup of patients with prediabetes (defined according to fasting plasma glucose levels at baseline), the odds of achieving ≥10% weight loss were approximately six times greater in the hydrogel group than in the placebo group ($P=0.0071$)[100].

Summary. Collectively, these observations suggest that patients with prediabetes might experience greater weight loss and avoid or minimize weight regain, even without being prescribed a calorie-restricted diet, when they follow an ad libitum diet that includes low-glycaemic index carbohydrate and increased amounts of dietary fibre. These observations, albeit interesting, have been produced by post-hoc analyses of data from larger trials; therefore, they should be interpreted with caution, particularly owing to the presence of many confounding factors and the absence of randomized controlled studies. In our statistical models, we adjusted for age, sex and baseline body weight, as these parameters differed or tended to differ among groups that were stratified by baseline glycaemia. Residual confounding cannot be excluded; however, these findings[95,96,98] could not be explained by differences in baseline carbohydrate or fibre intakes as these were not different between normoglycaemic participants and those with prediabetes. All the reanalysed trials were double-blinded with respect to the glycaemic status of the participants, and identified differences in dietary responsiveness therefore cannot have been influenced by researcher bias. Finally, the available measures in the three studies reanalysed indicate that fasting insulin and the homeostasis model assessment of insulin resistance, insulin secretion indexes, glucose tolerance (2-h glucose concentration measured by a standard oral glucose tolerance test) and long-term glycaemic control (HbA_{1c}) are less predictive of weight loss success than fasting glucose levels. To move this field forward, it is important to conduct randomized controlled trials of adequate size and duration, in which individuals with different levels of baseline glycaemic control are randomly assigned to different types of diets for both weight loss and weight maintenance.

Conclusions

A substantial dietary energy restriction has been proven to be a very successful method of producing rapid and major weight loss in individuals with overweight and obesity with T2DM. The achievement of weight loss in excess of 10–15 kg is key for T2DM remission; however, other factors including carbohydrate restriction and increased physical activity might help maximize the achieved metabolic benefits. Future studies should address this possibility in a systematic way. For example, exercise training is a potent intervention that improves glucose homeostasis and could also help in the control of body weight, but its contribution to T2DM remission within a comprehensive lifestyle modification programme is largely unexplored. Unfortunately, long-term maintenance of weight loss has been a major challenge owing to hunger and a lack of sufficient postprandial satiety signals, which contribute to decreasing adherence to the diet prescription over time[101–103]. This lack of adherence is probably a main reason for the generally low effectiveness observed when instructing patients to substantially alter their diet (for example, by replacing carbohydrate with fat or protein) for ≥1 year without providing the whole diet itself or at least some key food products. This observation calls for more studies to better understand factors that foster long-term adherence.

Comparisons between low-fat and low-carbohydrate diets have not led to any consistent results in unselected populations with obesity; however, retrospective analyses[95,96,98] from randomized controlled trials[94,97,99] have demonstrated the potential for much greater success in achieving satiety and body weight control among people with prediabetes, and probably also in those with T2DM, when using a personalized, precision dietary

management approach based on glucose-related metabolic traits (that is, fasting glucose levels). The effectiveness of this approach for selecting the optimal dietary treatment for weight loss and metabolic improvements in patients with prediabetes and T2DM needs to be further tested in prospective randomized clinical trials before translation of these exciting new findings into clinical practice.

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1. International Diabetes Federation. *IDF Diabetes Atlas* 9th edn (International Diabetes Federation, 2019).
2. Zhu, Y. et al. Racial/ethnic disparities in the prevalence of diabetes and prediabetes by BMI: patient outcomes research to advance learning (PORTAL) multisite cohort of adults in the U.S. *Diabetes Care* **42**, 2211–2219 (2019).
3. Magkos, F. Metabolically healthy obesity: what's in a name? *Am. J. Clin. Nutr.* **110**, 533–539 (2019). **A review of the dissociation between excess body weight and metabolic dysfunction**.
4. Willett, W. C., Dietz, W. H. & Colditz, G. A. Guidelines for healthy weight. *N. Engl. J. Med.* **341**, 427–434 (1999).
5. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. *Lancet* **373**, 1083–1096 (2009).
6. Chan, J. M., Rimm, E. B., Colditz, G. A., Stampfer, M. J. & Willett, W. C. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* **17**, 961–969 (1994).
7. Colditz, G. A., Willett, W. C., Rotnitzky, A. & Manson, J. E. Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann. Intern. Med.* **122**, 481–486 (1995).
8. Hu, F. B. et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N. Engl. J. Med.* **345**, 790–797 (2001).
9. Kendall, D. M., Cuddihy, R. M. & Bergenstal, R. M. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am. J. Med.* **122**, S37–S50 (2009).
10. Mittendorfer, B., Magkos, F., Fabbrini, E., Mohammed, B. S. & Klein, S. Relationship between body fat mass and free fatty acid kinetics in men and women. *Obesity* **17**, 1872–1877 (2009).
11. Conte, C. et al. Multiorgan insulin sensitivity in lean and obese subjects. *Diabetes Care* **35**, 1316–1321 (2012).
12. Wilman, H. R. et al. Characterisation of liver fat in the UK Biobank cohort. *PLoS One* **12**, e0172921 (2017).
13. Pienkowska, J. et al. MRI assessment of ectopic fat accumulation in pancreas, liver and skeletal muscle in patients with obesity, overweight and normal BMI in correlation with the presence of central obesity and metabolic syndrome. *Diabetes Metab. Syndr. Obes.* **12**, 623–636 (2019).
14. Tabak, A. G. et al. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* **373**, 2215–2221 (2009). **A prospective study of the temporal changes in metabolic function and glucose control along the natural history of T2DM**.
15. Weir, G. C. & Bonner-Weir, S. Five stages of evolving beta-cell dysfunction during progression to diabetes. *Diabetes* **53** (Suppl. 3), 16–21 (2004).
16. Astrup, A. & Finer, N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? *Obes. Rev.* **1**, 57–59 (2000).
17. Leitner, D. R. et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies — EASO can lead the way. *Obes. Facts* **10**, 483–492 (2017).
18. Sjostrom, L. Review of the key results from the Swedish Obese Subjects (SOS) trial — a prospective controlled intervention study of bariatric surgery. *J. Intern. Med.* **273**, 219–234 (2013).
19. Jans, A. et al. Duration of type 2 diabetes and remission rates after bariatric surgery in Sweden 2007–2015: a registry-based cohort study. *PLoS Med.* **16**, e1002985 (2019).
20. Davies, M. J. et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA* **314**, 687–699 (2015).
21. Madsbad, S. & Holst, J. J. GLP-1 as a mediator in the remission of type 2 diabetes after gastric bypass and sleeve gastrectomy surgery. *Diabetes* **63**, 3172–3174 (2014).
22. MacDonald, P. E. et al. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. *Diabetes* **51** (Suppl. 3), 434–442 (2002).
23. Magkos, F. et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab.* **23**, 591–601 (2016). **A randomized controlled trial of the effects of progressive diet-induced weight loss on body composition and metabolic function**.
24. Wing, R. R. et al. Long-term effects of modest weight loss in type II diabetic patients. *Arch. Intern. Med.* **147**, 1749–1753 (1987).
25. Henry, R. R., Wallace, P. & Olefsky, J. M. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. *Diabetes* **35**, 990–998 (1986).
26. Markovic, T. P. et al. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. *Diabetes Care* **21**, 687–694 (1998).
27. Henry, R. R., Scheaffer, L. & Olefsky, J. M. Glycemic effects of intensive caloric restriction and isocaloric refeeding in noninsulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **61**, 917–925 (1985).
28. Hughes, T. A., Gwynne, J. T., Switzer, B. R., Herbst, C. & White, G. Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. *Am. J. Med.* **77**, 7–17 (1984).
29. Steven, S. & Taylor, R. Restoring normoglycaemia by use of a very low calorie diet in long- and short-duration type 2 diabetes. *Diabet. Med.* **32**, 1149–1155 (2015).
30. Lim, E. L. et al. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* **54**, 2506–2514 (2011).
31. Taylor, R. et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for beta cell recovery. *Cell Metab.* **28**, 547–556.e3 (2018).
32. Al-Mrabeh, A. et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab.* **31**, 233–249 (2020). **A prospective study evaluating the potential mechanisms of T2DM remission and relapse following lifestyle modification**.
33. Taylor, R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. *Diabetologia* **51**, 1781–1789 (2008).
34. Taylor, R. & Barnes, A. C. Can type 2 diabetes be reversed and how can this best be achieved? James Lind Alliance research priority number one. *Diabet. Med.* **36**, 308–315 (2019).
35. Brown, A. et al. Low-energy total diet replacement intervention in patients with type 2 diabetes mellitus and obesity treated with insulin: a randomized trial. *BMJ Open Diabetes Res. Care* **8**, e001012 (2020).
36. Gregg, E. W. et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* **308**, 2489–2496 (2012).
37. Annuzzi, G., Rivellese, A. A., Bozzetto, L. & Riccardi, G. The results of Look AHEAD do not row against the implementation of lifestyle changes in patients with type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* **24**, 4–9 (2014).
38. Raynor, H. A. et al. Partial meal replacement plan and quality of the diet at 1 year: action for health in diabetes (Look AHEAD) trial. *J. Acad. Nutr. Diet.* **115**, 731–742 (2015).
39. Lean, M. E. et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* **391**, 541–551 (2018).
40. Lean, M. E. J. et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol.* **7**, 344–355 (2019). **A randomized controlled trial of diet-induced weight loss demonstrating that remission of T2DM depends on the amount of weight loss**.
41. Heymsfield, S. B., Gonzalez, M. C., Shen, W., Redman, L. & Thomas, D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes. Rev.* **15**, 310–321 (2014).
42. DeFronzo, R. A. et al. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes* **30**, 1000–1007 (1981).
43. Ferrannini, E. et al. The disposal of an oral glucose load in healthy subjects. A quantitative study. *Diabetes* **34**, 580–588 (1985).
44. American Diabetes Association. Standards of medical care in diabetes — 2020. *Diabetes Care* **43**, S1–S212 (2020).
45. Ajala, O., English, P. & Pinkney, J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am. J. Clin. Nutr.* **97**, 505–516 (2013).
46. Hjorth, M. F., Zohar, Y., Hill, J. O. & Astrup, A. Personalized dietary management of overweight and obesity based on measures of insulin and glucose. *Annu. Rev. Nutr.* **38**, 245–272 (2018). **A review of evidence supporting baseline glycaemia as a major predictor of weight loss success in response to dietary interventions**.
47. Snorgaard, O., Poulsen, G. M., Andersen, H. K. & Astrup, A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ Open. Diabetes Res. Care* **5**, e000354 (2017).
48. Kirk, E. et al. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology* **136**, 1552–1560 (2009).
49. Wing, R. R. et al. Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* **17**, 30–36 (1994).
50. Look Ahead Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N. Engl. J. Med.* **369**, 145–154 (2013).
51. Sjostrom, L. et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA* **311**, 2297–2304 (2014).
52. Wing, R. R., Blair, E., Marcus, M., Epstein, L. H. & Harvey, J. Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? *Am. J. Med.* **97**, 354–362 (1994).
53. Samkani, A. et al. A carbohydrate-reduced high-protein diet acutely decreases postprandial and diurnal glucose excursions in type 2 diabetes patients. *Br. J. Nutr.* **119**, 910–917 (2018).
54. Skytte, M. J. et al. A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. *Diabetologia* **62**, 2066–2078 (2019). **A cross-over study showing that low-carbohydrate diets can improve metabolic risk factors in patients with T2DM without much weight loss**.
55. Taylor, R., Al-Mrabeh, A. & Sattar, N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol.* **7**, 726–736 (2019). **A review of the mechanisms of T2DM remission**.
56. Hellerstein, M. K. De novo lipogenesis in humans: metabolic and regulatory aspects. *Eur. J. Clin. Nutr.* **53** (Suppl. 1), 53–65 (1999).
57. van Wyk, H. J., Davis, R. E. & Davies, J. S. A critical review of low-carbohydrate diets in people with type 2 diabetes. *Diabet. Med.* **33**, 148–157 (2016).
58. Kodama, S. et al. Influence of fat and carbohydrate proportions on the metabolic profile in patients with type 2 diabetes: a meta-analysis. *Diabetes Care* **32**, 959–965 (2009).
59. Hamdy, O. et al. Fat versus carbohydrate-based energy-restricted diets for weight loss in patients with type 2 diabetes. *Curr. Diab Rep.* **18**, 128 (2018).
60. Forouhi, N. G., Misra, A., Mohan, V., Taylor, R. & Yancy, W. Dietary and nutritional approaches for

prevention and management of type 2 diabetes. *BMJ* **361**, k2234 (2018).
61. Shan, Z., Guo, Y., Hu, F. B., Liu, L. & Qi, Q. Association of low-carbohydrate and low-fat diets with mortality among US adults. *JAMA Intern. Med.* **180**, 513–523 (2020).
62. Livesey, G. et al. Dietary glycemic index and load and the risk of type 2 diabetes: a systematic review and updated meta-analyses of prospective cohort studies. *Nutrients* **11**, 1280 (2019).
63. Livesey, G. et al. Dietary glycemic index and load and the risk of type 2 diabetes: assessment of causal relations. *Nutrients* **11**, 1436 (2019).
64. Hwang, J. J. et al. Blunted rise in brain glucose levels during hyperglycemia in adults with obesity and T2DM. *JCI Insight* **2**, e95913 (2017).
A study showing that patients with obesity and T2DM have a blunted rise in brain blood glucose levels in response to carbohydrate ingestion, and this associates with their feelings of appetite and hunger.
65. Astrup, A. & Hjorth, M. F. Classification of obesity targeted personalized dietary weight loss management based on carbohydrate tolerance. *Eur. J. Clin. Nutr.* **72**, 1300–1304 (2018).
66. Frost, G. et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat. Commun.* **5**, 3611 (2014).
67. Trajkovski, M. & Wollheim, C. B. Physiology: microbial signals to the brain control weight. *Nature* **534**, 185–187 (2016).
68. Hjorth, M. F. et al. Pretreatment prevotella-to-bacteroides ratio and salivary amylase gene copy number as prognostic markers for dietary weight loss. *Am. J. Clin. Nutr.* **111**, 1079–1086 (2020).
69. Sanna, S. et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nat. Genet.* **51**, 600–605 (2019).
70. Yamada, Y. et al. A non-calorie-restricted low-carbohydrate diet is effective as an alternative therapy for patients with type 2 diabetes. *Intern. Med.* **53**, 13–19 (2014).
71. Tay, J. et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. *Diabetes Care* **37**, 2909–2918 (2014).
72. Balducci, S. et al. Physical exercise as therapy for type 2 diabetes mellitus. *Diabetes Metab. Res. Rev.* **30** (Suppl 1), 13–23 (2014).
73. Boule, N. G., Haddad, E., Kenny, G. P., Wells, G. A. & Sigal, R. J. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* **286**, 1218–1227 (2001).
74. Snowling, N. J. & Hopkins, W. G. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care* **29**, 2518–2527 (2006).
75. Balducci, S. et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch. Intern. Med.* **170**, 1794–1803 (2010).
76. Di Loreto, C. et al. Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. *Diabetes Care* **28**, 1295–1302 (2005).
77. Balducci, S. et al. Changes in physical fitness predict improvements in modifiable cardiovascular risk factors independently of body weight loss in subjects with type 2 diabetes participating in the Italian Diabetes and Exercise Study (IDES). *Diabetes Care* **35**, 1347–1354 (2012).
78. Balducci, S. et al. Effect of high- versus low-intensity supervised aerobic and resistance training on modifiable cardiovascular risk factors in type 2 diabetes: the Italian Diabetes and Exercise Study (IDES). *PLoS One* **7**, e49297 (2012).
79. Eriksson, K. F. & Lindgarde, F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* **34**, 891–898 (1991).
80. Saltin, B. et al. Physical training and glucose tolerance in middle-aged men with chemical diabetes. *Diabetes* **28** (Suppl. 1), 30–32 (1979).
81. Nagi, D. *Diabetes in Practice* 2nd edn (John Wiley & Sons, 2005).
82. Ades, P. A., Savage, P. D., Marney, A. M., Harvey, J. & Evans, K. A. Remission of recently diagnosed type 2 diabetes mellitus with weight loss and exercise. *J. Cardiopulm. Rehabil. Prev.* **35**, 193–197 (2015).
83. Ried-Larsen, M. et al. Type 2 diabetes remission 1 year after an intensive lifestyle intervention: a secondary analysis of a randomized clinical trial. *Diabetes Obes. Metab.* **21**, 2257–2266 (2019).
84. Johansen, M. Y. et al. Effect of an intensive lifestyle intervention on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA* **318**, 637–646 (2017).
85. Vetter, M. L., Ritter, S., Wadden, T. A. & Sarwer, D. B. Comparison of bariatric surgical procedures for diabetes remission: efficacy and mechanisms. *Diabetes Spectr.* **25**, 200–210 (2012).
86. Bray, G. A., Krauss, R. M., Sacks, F. M. & Qi, L. Lessons learned from the POUNDS Lost Study: genetic, metabolic, and behavioral factors affecting changes in body weight, body composition, and cardiometabolic risk. *Curr. Obes. Rep.* **8**, 262–283 (2019).
87. Franz, M. J. & Evert, A. B. *American Diabetes Association Guide to Nutrition Therapy for Diabetes* 2 edn (American Diabetes Association, 2012).
88. Rowley, W. R., Bezold, C., Arikan, Y., Byrne, E. & Krohe, S. Diabetes 2030: insights from yesterday, today, and future trends. *Popul. Health Manag.* **20**, 6–12 (2017).
89. Gillies, C. L. et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* **334**, 299 (2007).
90. Knowler, W. C. et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **346**, 393–403 (2002).
91. Lindstrom, J. et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention study. *Lancet* **368**, 1673–1679 (2006).
92. Pan, X. R. et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes study. *Diabetes Care* **20**, 537–544 (1997).
93. Li, G. et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention study: a 20-year follow-up study. *Lancet* **371**, 1783–1789 (2008).
94. Poulsen, S. K. et al. Health effect of the New Nordic Diet in adults with increased waist circumference: a 6-mo randomized controlled trial. *Am. J. Clin. Nutr.* **99**, 35–45 (2014).
95. Hjorth, M. F. et al. Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: results from 3 randomized clinical trials. *Am. J. Clin. Nutr.* **106**, 499–505 (2017).
96. Ritz, C., Astrup, A., Larsen, T. M. & Hjorth, M. F. Weight loss at your fingertips: personalized nutrition with fasting glucose and insulin using a novel statistical approach. *Eur. J. Clin. Nutr.* **73**, 1529–1535 (2019).
This article uses a novel statistical approach to model and estimate diet-induced weight loss according to baseline levels of glycaemia.
97. Due, A. et al. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: a 6-mo randomized, controlled trial. *Am. J. Clin. Nutr.* **88**, 1232–1241 (2008).
98. Hjorth, M. F., Due, A., Larsen, T. M. & Astrup, A. Pretreatment fasting plasma glucose modifies dietary weight loss maintenance success: results from a stratified RCT. *Obesity* **25**, 2045–2048 (2017).
99. Larsen, T. M. et al. Diets with high or low protein content and glycemic index for weight-loss maintenance. *N. Engl. J. Med.* **363**, 2102–2113 (2010).
100. Greenway, F. L. et al. A randomized, double-blind, placebo-controlled study of Gelesis100: a novel nonsystemic oral hydrogel for weight loss. *Obesity* **27**, 205–216 (2019).
101. Dansinger, M. L., Gleason, J. A., Griffith, J. L., Selker, H. P. & Schaefer, E. J. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* **293**, 43–53 (2005).
102. Greenberg, I., Stampfer, M. J., Schwarzfuchs, D., Shai, I. & Group, D. Adherence and success in long-term weight loss diets: the dietary intervention randomized controlled trial (DIRECT). *J. Am. Coll. Nutr.* **28**, 159–168 (2009).
103. Sacks, F. M. et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N. Engl. J. Med.* **360**, 859–873 (2009).
The largest and longest (to date) randomized study comparing the weight loss effectiveness of diets differing in macronutrient composition shows no differences among diets.

Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
M.F.H. and A.A. are co-inventors on a pending provisional patent application on the use of biomarkers for prediction of weight loss responses and co-founders/owners of the University of Copenhagen spin-out company Personalized Weight Management Research Consortium ApS (Gluco-diet.dk). A.A. is a consultant or advisory board member for Basic Research, USA, Beachbody, USA, BioCare Copenhagen, Denmark, Gelesis, USA, Groupe Éthique et Santé, France, McCain Foods Limited, USA, Nestlé Research Center, Switzerland, and Weight Watchers, USA. A.A. and M.F.H. are co-authors of a number of diet/cookery books, including personalized nutrition for weight loss, published in several languages. F.M. declares no competing interests.

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