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Review

Prevention of Type 2 Diabetes: The Role of Intermittent Fasting

Bright Test and Jay H. Shubrook *

Department of Clinical Sciences and Community Health, College of Osteopathic Medicine, Touro University California, Vallejo, CA 94592, USA; btest@student.touro.edu
* Correspondence: jshubroo@touro.edu

Abstract: Despite the progress in treatment options and improved understanding of pathophysiology, type 2 diabetes remains one of the costliest and most harmful global chronic diseases. The current guidelines encourage physicians to fight an uphill battle and react to an incubated disease state that has been propelled forward by clinical inertia. The authors completed a literature search of PubMed, ScienceDirect, and NIH, searching with the terms intermittent fasting, type 2 diabetes, and prediabetes, and excluded studies related to religion-based fasting. There is emerging evidence that intermittent fasting could be an option to aid in weight loss, reduce hepatic steatosis, and lower the level of biomarkers such as fasting glucose while improving insulin resistance. If incorporated into the lives of patients with risk factors for type 2 diabetes, intermittent fasting could prove to be a cost-effective and efficient tool for preventing this insidious disease. This clinical review examines current evidence supporting the implementation of this lifestyle to prevent the onset or exacerbation of type 2 diabetes and the hurdles that must still be overcome for physicians to confidently prescribe this to their patients.

Keywords: diabetes; intermittent fasting; prevention

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1. Introduction

1.1. Intermittent Fasting

Intermittent fasting (IF) is a popular dieting strategy that has been implemented by many to lose weight, but uncertainty remains as to whether this lifestyle change could be beneficial in the prevention of multiple metabolic disorders, including type 2 diabetes mellitus (T2DM). It is well understood that human evolution, on a biological level, lags behind rapid sociological and technological advancement. In other words, the same physical bodies our hunter–gatherer ancestors used to survive prolonged periods of fasting have not evolved to accommodate a lifestyle of working sedentary desk jobs 8 h a day with all kinds of processed foods readily available for snacking. The theory of IF is rooted in this evolutionary science and is reinforced by the biochemical processes in our bodies. When fasting, glycogenolysis activates in the short term to mobilize the glycogen stores from meals prior. After about 12 h, the stores are depleted, and the body finds energy through other metabolic pathways such as gluconeogenesis, lipolysis, and beta-oxidation (β-oxidation). As the fat stores are burned for fuel, there is a subsequent loss of weight and a decreased percentage of body fat. Alternating periods of fasting with periods of eating prevents total starvation and allows the body to function properly while still taking advantage of the above benefits. This aesthetic benefit has been one of the main incentives for people to adopt IF into their lives, but there are many more benefits to following this lifestyle than meets the eye.

Intermittent Fasting Schedules

There are different intermittent fasting schedules (Table 1). The most common one is the daily time-restricted variant (16:8), which involves fasting for about 16 h in a 24 h period [1]. During the 8 h feeding window, an individual can eat ad libitum with or

without whatever restrictions they deem fit with help from their doctor. This plan allows for much flexibility but may require a motivated attitude for long-term adherence. Due to the inherent flexibility and multitude of variables involved with this regimen, there is significant variation in its results and outcomes. The nutritional quality of the food consumed during the feasting window most likely also affects the outcomes.

Table 1. Description of common IF schedules. The varying schedules of IF may be modified based on the individual's needs and capabilities.

Schedule	Description	Possible Modifications
Daily (16:8)	All days of the week involve a 16 h fasting period of zero calories, followed by an 8 h window of ad libitum eating.	Certain dietary restrictions can be added to modify results, or the fasting period may be increased to 18 h.
Alternate-day (4:3)	Fasting is carried out every other day for a 24 h period and alternates with days of ad libitum eating.	The fasting days typically involve a 25% caloric intake compared to normal, but this can be decreased to complete zero-calorie fasting.
Whole-day (5:2)	Zero-calorie fasting is completed for two days out of the week, usually in between a few days of ad libitum eating.	While zero-calorie fasting is the standard, a modified decrease in caloric intake, such as 25% of normal, may be implemented based on individual capabilities.

IF versus other dietary plans.

Other notable intermittent fasting schedules include the alternate-day (4:3) and whole-day (5:2) schedules. The 4:3 schedule involves 4 days of ad libitum eating with 3 days of complete zero-calorie fasting or a modified 25% typical caloric intake fasting interwoven weekly. The 5:2 schedule consists of 5 days of ad libitum eating with 2 days of complete, zero-calorie, intermittently paced fasting throughout the week. In a systematic review, these two schedules were compared for improving body composition and clinical markers for disease. Alternate-day fasting trials of 3 to 12 weeks in duration appear to be effective at reducing body weight, body fat, total cholesterol, and triglycerides in normal-weight, overweight, and obese humans as compared to whole-day fasting trials lasting 12 to 24 weeks, which also reduce body weight and body fat and favorably improve blood lipids [2].

Intermittent fasting has been compared to continuous energy restriction (CER) for weight loss and related benefits. While intermittent fasting appears to produce similar effects to continuous energy restriction in reducing body weight, fat mass, fat-free mass and appetite and improving glucose homeostasis, it does not appear to improve weight loss efficiency [3]. However, a systematic review analyzing 11 comparative studies concluded that there was a significant difference in the change in body weight that favored IF over continuous caloric restriction [4]. A different 12-month trial examining insulin-resistant individuals compared the effects of modified 4:3 IF with 25% caloric intake versus daily 75% caloric intake (CR) compared to a control [5]. The research found that in this population, the weight loss was not different between the IF ($-8\% \pm 2\%$) and CR ($-6\% \pm 1\%$) groups by month 12 relative to the controls ($p < 0.0001$), and the fat mass and BMI decreased ($p < 0.05$) similarly for the IF and CR. However, IF produced greater decreases ($p < 0.05$) in fasting insulin ($-52\% \pm 9\%$) and insulin resistance ($-53\% \pm 9\%$) compared with CR ($-14\% \pm 9\%$; $-17\% \pm 11\%$) and the controls by month 12 [5]. Research has shown that IF boosts verbal memory, improves blood pressure and resting heart rate, and can help obese adults lose weight [1]. As for patients with T2DM, most of the available research shows that IF can help people lose body weight and decrease their levels of fasting glucose, insulin, and leptin, all while reducing insulin resistance and increasing levels of adiponectin [1,6,7].

1.2. Fasting for the Future

There have been studies showing the benefits of IF on animal models. In animal models, intermittent feeding improves insulin sensitivity, counters obesity caused by a high-fat diet, and ameliorates diabetic retinopathy [8].

Metabolic syndrome (MS) has been strongly linked to diabetes. Rodent studies have shown the potential for MS reversal when subjects followed a 4:3 IF schedule. Subjects experienced reductions in abdominal fat, inflammation, and blood pressure as well as an increase in insulin sensitivity and improvement in cardiovascular system functionality [9,10]. Some medications, such as metformin, show similar benefits in animal models from alternate-day IF by challenging the metabolism to switch. However, the available data from animal models suggest that the safety and efficacy of such pharmacological approaches are likely to be inferior to naturally induced metabolism switching caused by intermittent fasting [6]. In a study where mice were kept on the 4:3 IF schedule vs. ad libitum feeding, the IF group on average had significantly lower serum glucose concentrations and insulin levels compared to the control group [11].

The mice on the IF diet also exhibited a two-fold increase in the fasting serum concentration of β-hydroxybutyrate compared with mice fed ad libitum, which aligns with the knowledge that fasting raises the concentration of ketone bodies in the blood due to lipolysis. This increase in blood ketones could offer some neuroprotection as well as the added benefit of resistance to epileptic seizures [12–14]. Further, there are multiple studies examining the effects of IF on the aging process of rodents, with some showing increased lifespans by as much as 80% compared to ad libitum feeding [15–18]. The evidence for the effects of time-restricted daily 16:8 IF in human models remains relatively scarce. This narrative review will delve into the available literature and attempt to illuminate the usefulness of implementing IF alongside established drug and surgical therapies for the prevention of T2DM.

1.3. At the Core of Prediabetes and Type 2 Diabetes

1.3.1. Visceral Fat

Ongoing research has elucidated the complex pathophysiology of T2DM, from the Triumvirate to the Ominous Octet [19] to the Egregious Eleven [20]. What seems to be of the greatest clinical interest currently is the relationship between visceral fat buildup and the progression of T2DM. In patients with established type 2 diabetes, visceral fat accumulation has a significant negative effect on glycemic control through a decrease in peripheral insulin sensitivity and an enhancement of gluconeogenesis [21]. The exact mechanism of this was not investigated in this study, but correlations were seen: insulin-mediated glucose clearance was inversely related to visceral fat levels in a nonlinear fashion, and this relationship remained weakly significant after adjusting for BMI (partial r = 0.33; $p = 0.01$) [21]. To examine whether visceral fat contributed to enhanced gluconeogenesis, the percent gluconeogenesis was regressed against visceral fat levels, first purely and then after adjustment for confounders. In both models, the association between percent gluconeogenesis and visceral fat was positive (r = 0.28; $p < 0.03$ and partial r = 0.30; $p = 0.04$, respectively). When gluconeogenesis fluxes were calculated, they were more strongly associated with visceral fat in a direct fashion (partial r = 0.45; $p = 0.003$) [21]. Screening for visceral fat levels while implementing feasible exercise regimens and healthier eating habits early could be the key in keeping T2DM at bay.

1.3.2. Hepatic Steatosis

Hepatic steatosis has also been linked to the progression of prediabetes (higher likelihood of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) or both) [22]. It has been established that a fatty liver has increased hepatic glucose production due to impaired insulin signaling [23]. In this study, the adjusted liver fat metric was significantly correlated with prediabetes progression since, most notably, insulin sensitivity was inversely correlated (r = −0.44, $p < 0.0001$) and sensitivity decreased from the normal glucose

tolerance (NGT) group to the IFG+IGT group [22]. Individuals with IGT or IFG + IGT more often had a fatty liver than individuals with NGT or isolated IFG [22]. Screening for levels of hepatic steatosis could be another useful tool for patients who have a risk of developing T2DM.

Intermittent fasting has demonstrated beneficial effects on hepatic steatosis. Using MRI technology and the 5:2 IF schedule, a small study was conducted with participants with prediabetes evaluating probiotics during a 12-week IF program. The results showed that, after 12 weeks of intermittent fasting, subcutaneous fat (%) changed from 35.9 ± 3.1 to 34.4 ± 3.2, visceral fat (%) changed from 15.8 ± 1.3 to 14.8 ± 1.2, liver fat (%) changed from 8.7 ± 0.8 to 7.5 ± 0.7, and pancreatic fat (%) changed from 7.7 ± 0.5 to 6.5 ± 0.5 (all $p < 0.001$) [24]. In mice, despite being fed a high-fat or a high-fructose diet for 8 weeks, alternate-day IF for 4 weeks was effective in decreasing hepatic lipogenesis and increasing β-oxidation markers, resulting in a reduction in hepatic steatosis and inflammation [25]. In a proteomic analysis involving rats undergoing a modified daily IF schedule of 18:6 (time-restricted feeding between 1600 and 2200) for 15 weeks, the results showed that, compared with the comparison group that consumed a 60% high-fat diet ad libitum, the expression of *PPARα* (a transcription factor that is the primary regulator of liver β-oxidation) in the 6 h IF group on the same diet was significantly increased, and the lipid synthesis gene *FAS* was decreased [26]. This means that these IF rats experienced more breakdown of liver fat and stored less liver fat compared to the ad libitum group. In a human study, adults with obesity and non-alcoholic fatty liver disease (NAFLD) were randomized between four groups for 3 months: 4:3 IF with 25% caloric intake only (fasting group), 4:3 IF with 60 min of aerobic exercise five times a week (combo group), exercise-only group, and no-intervention control group [27]. This randomized controlled trial found that by month 3, the intrahepatic triglyceride content was significantly reduced in the combo group (−5.48%; 95% CI, −7.77% to −3.18%) compared with the exercise group (−1.30%; 95% CI, −3.80% to 1.20%; $p = 0.02$) and the control group (−0.17%; 95% CI, −2.17% to 1.83%; $p < 0.01$) but was not significantly different compared to the fasting group (−2.25%; 95% CI, −4.46% to −0.04%; $p = 0.05$) [27]. Also, body weight, fat mass, waist circumference, and alanine transaminase levels significantly decreased, while insulin sensitivity significantly increased in the combination group compared with the control group [27]. These studies alone highlight the importance of lifestyle changes in combating hepatic steatosis and allude to the effectiveness of intermittent fasting as an option.

Preventing visceral adiposity and liver fat accumulation could slow or prevent the onset of T2DM, relieving both the health burden as well as a significant economic burden. In the U.S. healthcare system, one out every four dollars is spent on caring for people with diabetes. And 48% to 64% of lifetime medical costs for a person with diabetes are for disease-related complications [28]. By the time someone is diagnosed with T2DM and intervention is initiated, it is already very difficult to effectively treat the disease. Maintaining a healthy and non-sedentary lifestyle proves to be the best deterrent and can be reinforced with proper patient education [29].

2. The Role of Intermittent Fasting in Combating Type 2 Diabetes Mellitus

2.1. What Is at Stake?

Diabetes has become a non-communicable pandemic. An estimated total of 37.3 million people (11.3%) in the United States have diabetes [30]. There are 96 million people (38%) who live with prediabetes at an estimated rate of progression of 1.5 million people per year [30]. The costs associated with treating this disease through classical methods are enough to prioritize treatment and prevention through affordable and straightforward interventions such as IF. According to the American Diabetes Association (ADA), the total estimated cost of diagnosed diabetes in 2017 was USD 327 billion, including USD 237 billion in direct medical costs and USD 90 billion in reduced productivity at work [31]. Understanding and effectively implementing IF into the lifestyles of at-risk patients for diabetes may prove to be beneficial before medication and insulin interventions become involved.

2.2. The Effects of Intermittent Fasting on HbA1c Levels

The INTERFAST-2 trial demonstrated safety and efficacy in reducing the total daily insulin dose and body weight in insulin-treated people with T2DM [32]. Forty-six participants were randomly assigned between a 4:3 schedule IF group and a control group for 12 weeks. The IF group spent significantly less time on average above the blood glucose range compared to the control group, significantly more time on average within this range, and a similar amount of time on average below this range as compared to the control group. There was also a significant difference between the groups for the endpoint measurements set by the trial investigators. An HbA1c reduction $\geq$ 3 mmol/mol was seen in 60% of the IF group compared to 25% in the control group ($p < 0.05$). An insulin dose reduction $\geq$ 10% was seen in 75% of the IF group compared to 0% in the control group ($p < 0.001$). A weight reduction $\geq$ 2% was seen in 80% of the IF group compared to 4% in the control group ($p < 0.001$). And all three endpoints combined were achieved by 40% of the IF group versus 0% in the control group ($p < 0.001$) [32]. While this study observed the treatment of people with T2DM, the positive benefits may be extrapolated to diabetes prevention as well. Lifestyle modification with an intermittent fasting protocol and proper diet help lower blood glucose levels, maintain body mass index, and reduce inflammation, which is the main cause of chronic diseases among the general population [33].

Intermittent fasting using a 16:8 schedule with a 25% energy restriction has shown similar results in lowering fasting glucose, insulin, and HbA1c compared to a 25% continuous energy restriction [34]. In a trial of patients with T2DM and an average HbA1c of 7.3%, a modified 5:2 IF schedule with two fasting days having a 25% calorie intake was not significantly different from CER [35]. The IF group lowered their mean HbA1c by 0.3%, while the CER group's mean was lower by 0.5% [35]. Obesity is widely known to be the most significant modifiable risk factor for developing T2DM. Calorie-restrictive regiments such as IF have been shown time and time again to help decrease weight and BMI fat mass. In an observational analysis of participants in the Look AHEAD trial, those who lost 5–10% of their body weight had 3.5:1 increased odds of decreasing HbA1c levels by 0.5% as well as seeing beneficial reductions in other metabolic markers [36]. Due to the scarcity of randomized human trials and variations in fasting schedules, there remains ambiguity about the true relationship between IF and levels of HbA1c; however, there does seem to be a positive correlation that must be explored more with long-term studies.

2.3. From Healthy to Prediabetes to Type 2 Diabetes Mellitus

Preventing the crossover from healthy to prediabetes to T2DM is difficult for many reasons, one of which is the need for consistent and accurate monitoring. This may be difficult to achieve. When should one begin monitoring for metabolic changes? When should one implement an IF schedule if they are concerned about developing T2DM? The exact beginning of elevated biomarkers is difficult to trace and varies greatly, as illuminated by the variable data from studies. As many as 183 million people globally are unaware that they have T2DM [37], and it can be present for up to 12 years in some cases before being diagnosed [38]. If a patient has a relevant family history, it is important to educate and empower them as early as possible since T2DM has a strong genetic component [39]. Despite this, genetic testing is still not clinically useful due to reasons such as the low discriminative ability of genetic testing and the non-significant added value of observable clinical risk factors [40]. The sooner the individual is made aware of these risk factors, the sooner they can begin adopting important lifestyle modifications such as IF to prevent progression from prediabetes to type 2 diabetes.

Both IFG and IGT can be used to measure and predict progression from prediabetes to T2DM. However, because IGT is more prevalent than IFG in most populations, consistently conducting 2 h oral glucose tolerance tests (OGTT) to identify those with IGT often yields a greater proportion of people at risk for developing T2DM than simply looking at fasting plasma glucose (FPG) [41]. This is not a common first-line screening tool due to its cost and inconvenience compared to other initial analyses [42]. Prediabetes and T2DM have

insidious onsets that begin to develop many years before they are diagnosed in a clinic. The exact onset varies across individuals and populations. A large retrospective analysis concluded that significantly elevated FPG can be seen 10 years ahead of a diagnosis with T2DM, and glucose dysregulation could precede a diagnosis by 20 years [43]. This inherent variability between individuals makes timely assessment and response difficult. Hopefully, though, these challenges will be resolved in the future with the development of new medical technologies in this sphere.

2.4. Current Alternative Therapies for the Prevention of Type 2 Diabetes Mellitus

It is now common knowledge that moderate weight loss, an active exercise routine, and a healthy whole food diet are all positive lifestyle changes that can aid in the prevention of T2DM [44]. There are also pharmacological interventions available for high-risk populations, such as those with IFG and IGT, that can be used in conjunction with lifestyle modifications. Metformin is the most commonly used medication in the treatment of T2DM, but it may prove useful as a method of prevention too. In the Diabetes Prevention Program (DPP) trial, 1073 participants with IGT were administered 850 mg of metformin twice a day, and 1082 participants were administered a placebo. Both groups were followed up for a median period of 2.8 years, which showed in the end that metformin reduced the incidence of T2DM by 31% compared with a placebo [45]. Some of the active participants followed up 10 years later when it was determined that T2DM incidence was still reduced more with metformin (18% compared to the placebo) [46]. The relative risk reduction (RRR) and number needed to treat (NNT) are compared to other studies examining lifestyle interventions (Table 2). In a Finnish study, 523 overweight subjects received seven sessions of nutritional and activity guidance, followed by visits every three months thereafter to help in reducing weight [47]. Weight loss and blood glucose levels were significantly improved in the intervention group and were maintained during a 3-year median follow-up period [47,48]. In a Da Qing study, 577 participants were distributed into a control group and three different intervention groups: diet, exercise, or combined [49]. Compared with the control group, those in the combined lifestyle intervention groups had a 51% lower incidence of diabetes (95% CI 0.33–0.73) during the active intervention period and a 43% lower incidence (0.41–0.81) over the 20-year period after the follow-up in 2006, controlled for age and clustering [49].

Table 2. Randomized controlled trials for lifestyle interventions for the prevention of type 2 diabetes.

Study	Country	N	Baseline BMI (kg/m^2)	Intervention Period (Years)	RRR (%)	NNT
Diabetes Prevention Program [45]	USA	3234	34.0	2.8	58	21
Diabetes Prevention Study [47,48]	Finland	523	31.0	4	39	22
Da Qing [49]	China	577	25.8	6	51	30

References. DPP Research Group. N Engl J Med. 2002, 346, 393–403 [44]. Eriksson, J.; et al. Diabetologia. 1999, 42, 793–801 [45]. Lindstrom, J.; et al. Lancet. 2006, 368, 1673–1679 [46]. Li, G.; et al. Lancet. 2008, 371, 1783–1789 [47].

Other pharmacologic agents, such as alpha glucosidase inhibitors and thiazolidinediones, have also proven to be effective in the delay of or prevention of T2DM. The STOP-NIDDM trial randomly assigned individuals with IGT to thrice daily 100 mg acarbose for a mean period of 3.3 years and demonstrated a 35.8% relative reduction in T2DM when compared to a placebo [50]. Treatment with troglitazone in the TRIPOD study delayed or prevented the onset of T2DM, wherein the protective effect was associated with the preservation of pancreatic beta-cell function [51]. The DREAM trial recruited 5269 patients with IFG, IGT, or both. The results revealed that rosiglitazone was very effective in lowering the incidence of T2DM, (60% compared to the placebo) [52]. A later study included 207 patients with IGT who received a combination of 2 mg rosiglitazone and 500 mg metformin twice

daily for a median period of 3.9 years. This low-dose combination therapy was highly effective in the prevention of T2DM, with a low incidence of clinically relevant adverse effects [53].

There are many options currently available for the prevention and treatment of T2DM. The lipase inhibitor orlistat was utilized in a randomized study. When compared to lifestyle changes alone, orlistat plus these changes resulted in a 37.3% reduction in the risk of developing T2DM in patients with obesity over the course of four years [54]. The bile acid sequestrant colesevelam has been shown to improve insulin sensitivity and β-cell function similarly in subjects with IFG and T2DM, which led to a follow-up study illustrating the positive effects of this drug in patients with prediabetes by significantly reducing A1c levels and normalizing FPG compared to a placebo [55,56].

DPP-4 inhibitors and GLP-1 receptor agonists are versatile medications implemented to combat diabetes but could also be used in prediabetes stages. Vidagliptin was compared to a placebo in 179 subjects with IGT, and the participants saw a 32% reduction in post-prandial glucose [57]. There are strong studies with GLP-1RA that could be added to this discussion. Human studies using exenatide or liraglutide have demonstrated significantly substantial weight loss and glucose tolerance improvement in patients with IFG or IGT, with benefits very apparent by about 20 weeks and, in the case of liraglutide, lasting for as long as 2 years [58,59].

Although it is not a common first-line method of prevention or treatment, metabolic surgery is another tool used to prevent type 2 diabetes among those at risk. Metabolic (bariatric) surgery is an effective and cost-effective therapy for people with T2DM and obesity. With an acceptable safety profile, it provides an appropriate treatment for people who struggle with achieving treatment goals through medication and lifestyle modifications alone [60]. Patients who undergo bariatric surgery tend to see significant improvements in A1c levels and a reduction in the number of their medications and insulin doses [61]. These findings could possibly extend to those with obesity and prediabetes. Compared to standard typical care, metabolic surgery reduces the long-term incidence of T2DM by 78% in obese individuals and by 87% in individuals with IFG [62]. This intervention is usually reserved for individuals struggling with morbid obesity, and it is unclear if the benefits seen from this surgery are merely due to the weight loss accompanied by it. Regardless, this modality is the least likely to be used in the prevention of T2DM, mainly due to the cost and risks associated with surgical procedures.

3. The Challenges to Overcome

3.1. Catching It Early

As mentioned previously, T2DM is a disease with an insidious onset, which makes early detection and intervention tremendously important. It is better to prevent the onset of a disease than to treat an ongoing one, especially when the excess lifetime medical expense is roughly USD 124,600 per person diagnosed with T2DM at the age of 40 [63]. The American Diabetes Association recommends beginning screening for diabetes in adults aged 45 years or older and then following up once every 3 years if the results are normal, with screening beginning earlier in overweight adults with one or more risk factors [64]. Compared with the ADA recommendations, the USPSTF recommendation is broader because it sets a minimum age of 35 years for screening and does not require any additional risk factors other than an elevated BMI [65]. There is a case to be made for beginning screening earlier as a US-population-based analysis found that screening for type 2 diabetes is cost-effective when started between the ages of 30 years and 45 years, with screening repeated every 3–5 years [66]. There are no established criteria for screening in healthy adults without risk factors, although visceral adiposity and hepatic steatosis could already be building up inside unaware individuals. This is where lifestyle modification, education on self-management, and patient empowerment become so crucial [67].

There are many biochemical tests conducted to monitor disease progression and diagnose T2DM. The "gold standard" is the 2 h OGTT, but it requires an 8 h fasting period beforehand and a time commitment from nursing staff that is not readily convenient, along with other limitations [68]. It is an accurate test for measuring 2 h post-prandial glucose (2hPG) and IGT, which may be a better predictor of outcomes than FPG or HbA1c. A multicenter study demonstrated that 2hPG is an independent predictor of diabetes and a novel risk assessment for cardiovascular disease, and mortality was better in this case than with FPG and HbA1c [69]. Developing a more streamlined version of the OGTT with fewer limitations could allow it to become a more common first-line monitoring tool in clinics. Combining FPG and HbA1c testing may be an optimal approach to identifying prediabetes and T2DM in clinics, but it is not used very often this way. Using both simultaneously could be more effective than choosing one over the other for initial screening. A community-based study showcased support for the clinical utility of using a combination of FPG and HbA1c levels from a single blood sample to identify undiagnosed T2DM in a population, as a high positive predictive value was seen for subsequent diagnoses of diabetes [70].

3.2. Implementing and Adhering to Intermittent Fasting

Implementing consistent and long-term lifestyle changes is a difficult task, and intermittent fasting is no exception. Helping patients go through these changes through strong motivation and support is one of the intrinsic responsibilities of a clinician. The authors provide some best practice suggestions for helping patients with therapeutic lifestyle changes (Figure 1). It is already evident that adherence to calorie-restriction diets tends to decline over time, perhaps because patients lose motivation or feel like they have reached a good point to stop [71]. A study examining the effects of four popular diets showed that, regardless of diet, about 25% of the participants adhered to a self-reported level of six out of ten by the end of the 1-year period, with adherence levels declining steadily over the 12 months [72]. On average, weight regain post-diet initiation begins about 6–9 months into the program, reflecting temporal decreases in adherence to the relevant prescribed regimen [73]. Key factors that promote adherence to IF include, but are not limited to, improvements in physical health, positive psychological impacts, and strong social support [74]. Some barriers to adherence include feelings of hunger and sluggishness, difficulties with self-monitoring, and social situations that discourage fasting schedules [74]. Most studies specifically target populations that struggle with obesity in observation of the weight-loss benefits, but other populations may see benefits as well. Although patients with certain health conditions should avoid IF, it has been linked to improving other metabolic ailments, such as dyslipidemia and hypertension [75]. Regardless, the data on the long-term effects of intermittent fasting remain very limited.

The absence of large long-term studies on the direct relationship between IF and its effects for people with T2DM is also a challenge to overcome. Most currently available published research articles, systematic reviews excluded, do not contain sample sizes in the thousands. It would be helpful to have larger sample sizes in future studies to draw more robust conclusions. Although there is a large study in progress at this time of writing known as DRIFT [71], more randomized human trials are needed.

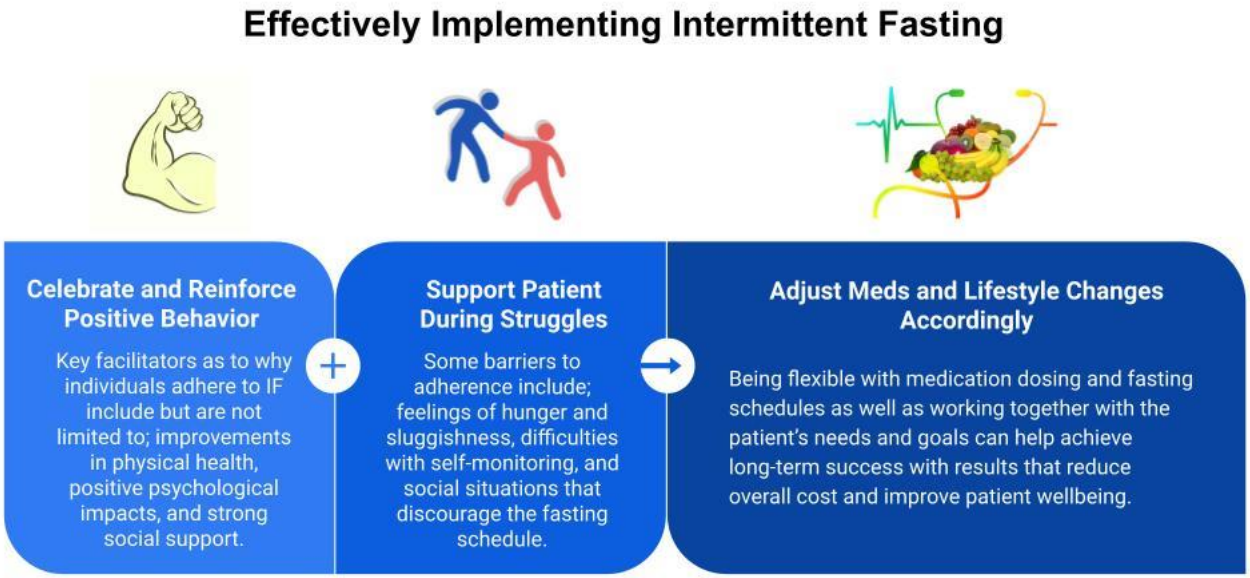

Figure 1. An example of implementing IF into the lives of patients. This represents a generalized strategy that may be modified to fit the situation.

4. Conclusions

Intermittent fasting is a popular lifestyle dietary plan that may prove to be a useful and cost-effective tool in preventing T2DM. Currently, the most pronounced results of integrating IF occur in the population of people struggling with obesity. While IF is generally a safe plan to follow, it should be avoided by individuals who require a higher caloric diet, such as children and women who are pregnant or breastfeeding, and by those who are susceptible to eating disorders like bulimia nervosa. People with type 1 diabetes who require insulin should also avoid IF, as prolonged episodes of hypoglycemia may occur. Although animal models and short-term human trials have demonstrated the positive effects of IF, more research involving long-term multi-year timelines must be conducted to examine the chronic metabolic changes associated with IF. With more established and long-term evidence, physicians can gain confidence and may be more likely to recommend IF to their patients. IF is easily assessable and affordable compared to other interventions. Since T2DM is a chronic condition, it requires a chronic prophylactic and cure, and future studies involving IF might demonstrate it to practically and effectively function as both.

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References

1. Intermittent Fasting: What Is It, and How Does It Work? Available online: https://www.hopkinsmedicine.org/health/wellness-and-prevention/intermittent-fasting-what-is-it-and-how-does-it-work (accessed on 14 June 2023).
2. Tinsley, G.M.; La Bounty, P.M. Effects of Intermittent Fasting on Body Composition and Clinical Health Markers in Humans. *Nutr. Rev.* **2015**, *73*, 661–674. [CrossRef] [PubMed]
3. Seimon, R.V.; Roekenes, J.A.; Zibellini, J.; Zhu, B.; Gibson, A.A.; Hills, A.P.; Wood, R.E.; King, N.A.; Byrne, N.M.; Sainsbury, A. Do Intermittent Diets Provide Physiological Benefits over Continuous Diets for Weight Loss? A Systematic Review of Clinical Trials. *Mol. Cell. Endocrinol.* **2015**, *418*, 153–172. [CrossRef] [PubMed]

4. Zhang, Q.; Zhang, C.; Wang, H.; Ma, Z.; Liu, D.; Guan, X.; Liu, Y.; Fu, Y.; Cui, M.; Dong, J. Intermittent Fasting versus Continuous Calorie Restriction: Which Is Better for Weight Loss? *Nutrients* **2022**, *14*, 1781. [CrossRef] [PubMed]
5. Gabel, K.; Kroeger, C.M.; Trepanowski, J.F.; Hoddy, K.K.; Cienfuegos, S.; Kalam, F.; Varady, K.A. Differential Effects of Alternate-Day Fasting Versus Daily Calorie Restriction on Insulin Resistance. *Obesity* **2019**, *27*, 1443–1450. [CrossRef]
6. De Cabo, R.; Mattson, M.P. Effects of Intermittent Fasting on Health, Aging, and Disease. *N. Engl. J. Med.* **2019**, *381*, 2541–2551. [CrossRef]
7. Redman, L.M.; Smith, S.R.; Burton, J.H.; Martin, C.K.; Il'yasova, D.; Ravussin, E. Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging. *Cell Metab.* **2018**, *27*, 805–815.e4. [CrossRef]
8. Wan, R.; Camandola, S.; Mattson, M.P. Intermittent Food Deprivation Improves Cardiovascular and Neuroendocrine Responses to Stress in Rats. *J. Nutr.* **2003**, *133*, 1921–1929. [CrossRef]
9. Castello, L.; Froio, T.; Maina, M.; Cavallini, G.; Biasi, F.; Leonarduzzi, G.; Donati, A.; Bergamini, E.; Poli, G.; Chiarpotto, E. Alternate-Day Fasting Protects the Rat Heart against Age-Induced Inflammation and Fibrosis by Inhibiting Oxidative Damage and NF-KB Activation. *Free Radic. Biol. Med.* **2010**, *48*, 47–54. [CrossRef]
10. Wan, R.; Camandola, S.; Mattson, M.P. Intermittent Fasting and Dietary Supplementation with 2-Deoxy-D-Glucose Improve Functional and Metabolic Cardiovascular Risk Factors in Rats. *FASEB J.* **2003**, *17*, 1133–1134. [CrossRef]
11. Anson, R.M.; Guo, Z.; de Cabo, R.; Iyun, T.; Rios, M.; Hagepanos, A.; Ingram, D.K.; Lane, M.A.; Mattson, M.P. Intermittent Fasting Dissociates Beneficial Effects of Dietary Restriction on Glucose Metabolism and Neuronal Resistance to Injury from Calorie Intake. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 6216–6220. [CrossRef]
12. Bough, K.J.; Valiyil, R.; Han, F.T.; Eagles, D.A. Seizure Resistance Is Dependent upon Age and Calorie Restriction in Rats Fed a Ketogenic Diet. *Epilepsy Res.* **1999**, *35*, 21–28. [CrossRef] [PubMed]
13. Gilbert, D.L.; Pyzik, P.L.; Freeman, J.M. The Ketogenic Diet: Seizure Control Correlates Better with Serum Beta-Hydroxybutyrate than with Urine Ketones. *J. Child Neurol.* **2000**, *15*, 787–790. [CrossRef] [PubMed]
14. Kashiwaya, Y.; Takeshima, T.; Mori, N.; Nakashima, K.; Clarke, K.; Veech, R.L. D-Beta-Hydroxybutyrate Protects Neurons in Models of Alzheimer's and Parkinson's Disease. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 5440–5444. [CrossRef]
15. Varady, K.A.; Hellerstein, M.K. Alternate-Day Fasting and Chronic Disease Prevention: A Review of Human and Animal Trials. *Am. J. Clin. Nutr.* **2007**, *86*, 7–13. [CrossRef]
16. Arum, O.; Bonkowski, M.S.; Rocha, J.S.; Bartke, A. The Growth Hormone Receptor Gene-Disrupted Mouse Fails to Respond to an Intermittent Fasting Diet. *Aging Cell* **2009**, *8*, 756–760. [CrossRef] [PubMed]
17. Kendrick, D.C. The Effects of Infantile Stimulation and Intermittent Fasting and Feeding on Life Span in the Black-Hooded Rat. *Dev. Psychobiol.* **1973**, *6*, 225–234. [CrossRef]
18. Goodrick, C.L.; Ingram, D.K.; Reynolds, M.A.; Freeman, J.R.; Cider, N. Effects of Intermittent Feeding upon Body Weight and Lifespan in Inbred Mice: Interaction of Genotype and Age. *Mech. Ageing Dev.* **1990**, *55*, 69–87. [CrossRef]
19. DeFronzo, R.A. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* **2009**, *58*, 773–795. [CrossRef]
20. Schwartz, S.S.; Epstein, S.; Corkey, B.E.; Grant, S.F.A.; Gavin, J.R.; Aguilar, R.B. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell-Centric Classification Schema. *Diabetes Care* **2016**, *39*, 179–186. [CrossRef]
21. Gastaldelli, A.; Miyazaki, Y.; Pettiti, M.; Matsuda, M.; Mahankali, S.; Santini, E.; DeFronzo, R.A.; Ferrannini, E. Metabolic Effects of Visceral Fat Accumulation in Type 2 Diabetes. *J. Clin. Endocrinol. Metab.* **2002**, *87*, 5098–5103. [CrossRef]
22. Kantartzis, K.; Machann, J.; Schick, F.; Fritsche, A.; Häring, H.-U.; Stefan, N. The Impact of Liver Fat vs. Visceral Fat in Determining Categories of Prediabetes. *Diabetologia* **2010**, *53*, 882–889. [CrossRef] [PubMed]
23. Samuel, V.T.; Liu, Z.-X.; Qu, X.; Elder, B.D.; Bilz, S.; Befroy, D.; Romanelli, A.J.; Shulman, G.I. Mechanism of Hepatic Insulin Resistance in Non-Alcoholic Fatty Liver Disease. *J. Biol. Chem.* **2004**, *279*, 32345–32353. [CrossRef] [PubMed]
24. Dokpuang, D.; Zhiyong Yang, J.; Nemati, R.; He, K.; Plank, L.D.; Murphy, R.; Lu, J. Magnetic Resonance Study of Visceral, Subcutaneous, Liver and Pancreas Fat Changes after 12 Weeks Intermittent Fasting in Obese Participants with Prediabetes. *Diabetes Res. Clin. Pract.* **2023**, *202*, 110775. [CrossRef] [PubMed]
25. de Souza Marinho, T.; Ornellas, F.; Barbosa-da-Silva, S.; Mandarim-de-Lacerda, C.A.; Aguila, M.B. Beneficial Effects of Intermittent Fasting on Steatosis and Inflammation of the Liver in Mice Fed a High-Fat or a High-Fructose Diet. *Nutrition* **2019**, *65*, 103–112. [CrossRef] [PubMed]
26. Deng, J.; Feng, D.; Jia, X.; Zhai, S.; Liu, Y.; Gao, N.; Zhang, X.; Li, M.; Lu, M.; Liu, C.; et al. Efficacy and Mechanism of Intermittent Fasting in Metabolic Associated Fatty Liver Disease Based on Ultraperformance Liquid Chromatography-Tandem Mass Spectrometry. *Front. Nutr.* **2022**, *9*, 838091. [CrossRef]
27. Ezpeleta, M.; Gabel, K.; Cienfuegos, S.; Kalam, F.; Lin, S.; Pavlou, V.; Song, Z.; Haus, J.M.; Koppe, S.; Alexandria, S.J.; et al. Effect of Alternate Day Fasting Combined with Aerobic Exercise on Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. *Cell Metab.* **2023**, *35*, 56–70.e3. [CrossRef]
28. Health and Economic Benefits of Diabetes Interventions | Power of Prevention. Available online: https://www.cdc.gov/chronicdisease/programs-impact/pop/diabetes.htm (accessed on 1 July 2023).
29. Galaviz, K.I.; Narayan, K.M.V.; Lobelo, F.; Weber, M.B. Lifestyle and the Prevention of Type 2 Diabetes: A Status Report. *Am. J. Lifestyle Med.* **2015**, *12*, 4–20. [CrossRef]

30. National Diabetes Statistics Report | Diabetes | CDC. Available online: https://www.cdc.gov/diabetes/data/statistics-report/index.html (accessed on 14 June 2023).
31. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care* **2018**, *41*, 917–928. [CrossRef]
32. Obermayer, A.; Tripolt, N.J.; Pferschy, P.N.; Kojzar, H.; Aziz, F.; Müller, A.; Schauer, M.; Oulhaj, A.; Aberer, F.; Sourij, C.; et al. Efficacy and Safety of Intermittent Fasting in People With Insulin-Treated Type 2 Diabetes (INTERFAST-2)-A Randomized Controlled Trial. *Diabetes Care* **2023**, *46*, 463–468. [CrossRef]
33. Tagde, P.; Tagde, S.; Bhattacharya, T.; Tagde, P.; Akter, R.; Rahman, M.H. Multifaceted Effects of Intermittent Fasting on the Treatment and Prevention of Diabetes, Cancer, Obesity or Other Chronic Diseases. *Curr. Diabetes Rev.* **2022**, *18*, e131221198789. [CrossRef]
34. Kunduraci, Y.E.; Ozbek, H. Does the Energy Restriction Intermittent Fasting Diet Alleviate Metabolic Syndrome Biomarkers? A Randomized Controlled Trial. *Nutrients* **2020**, *12*, 3213. [CrossRef] [PubMed]
35. Carter, S.; Clifton, P.M.; Keogh, J.B. Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Noninferiority Trial. *JAMA Netw. Open* **2018**, *1*, e180756. [CrossRef] [PubMed]
36. Wing, R.R.; Lang, W.; Wadden, T.A.; Safford, M.; Knowler, W.C.; Bertoni, A.G.; Hill, J.O.; Brancati, F.L.; Peters, A.; Wagenknecht, L. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals with Type 2 Diabetes. *Diabetes Care* **2011**, *34*, 1481–1486. [CrossRef] [PubMed]
37. Guariguata, L.; Whiting, D.; Weil, C.; Unwin, N. The International Diabetes Federation Diabetes Atlas Methodology for Estimating Global and National Prevalence of Diabetes in Adults. *Diabetes Res. Clin. Pract.* **2011**, *94*, 322–332. [CrossRef]
38. Harris, M.I.; Klein, R.; Welborn, T.A.; Knuiman, M.W. Onset of NIDDM Occurs at Least 4–7 Yr before Clinical Diagnosis. *Diabetes Care* **1992**, *15*, 815–819. [CrossRef]
39. Ali, O. Genetics of Type 2 Diabetes. *World J. Diabetes* **2013**, *4*, 114–123. [CrossRef]
40. Lyssenko, V.; Laakso, M. Genetic Screening for the Risk of Type 2 Diabetes. *Diabetes Care* **2013**, *36*, S120–S126. [CrossRef]
41. Shaw, J. Diagnosis of Prediabetes. *Med. Clin. N. Am.* **2011**, *95*, 341–352. [CrossRef]
42. Stern, M.P.; Williams, K.; Haffner, S.M. Identification of Persons at High Risk for Type 2 Diabetes Mellitus: Do We Need the Oral Glucose Tolerance Test? *Ann. Intern. Med.* **2002**, *136*, 575–581. [CrossRef]
43. Sagesaka, H.; Sato, Y.; Someya, Y.; Tamura, Y.; Shimodaira, M.; Miyakoshi, T.; Hirabayashi, K.; Koike, H.; Yamashita, K.; Watada, H.; et al. Type 2 Diabetes: When Does It Start? *J. Endocr. Soc.* **2018**, *2*, 476–484. [CrossRef]
44. Uusitupa, M.; Khan, T.A.; Viguiliouk, E.; Kahleova, H.; Rivellese, A.A.; Hermansen, K.; Pfeiffer, A.; Thanopoulou, A.; Salas-Salvadó, J.; Schwab, U.; et al. Prevention of Type 2 Diabetes by Lifestyle Changes: A Systematic Review and Meta-Analysis. *Nutrients* **2019**, *11*, 2611. [CrossRef]
45. Knowler, W.C.; Barrett-Connor, E.; Fowler, S.E.; Hamman, R.F.; Lachin, J.M.; Walker, E.A.; Nathan, D.M. Diabetes Prevention Program Research Group Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. *N. Engl. J. Med.* **2002**, *346*, 393–403. [CrossRef] [PubMed]
46. Diabetes Prevention Program Research Group; Knowler, W.C.; Fowler, S.E.; Hamman, R.F.; Christophi, C.A.; Hoffman, H.J.; Brenneman, A.T.; Brown-Friday, J.O.; Goldberg, R.; Venditti, E.; et al. 10-Year Follow-up of Diabetes Incidence and Weight Loss in the Diabetes Prevention Program Outcomes Study. *Lancet* **2009**, *374*, 1677–1686. [CrossRef] [PubMed]
47. Eriksson, J.; Lindström, J.; Valle, T.; Aunola, S.; Hämäläinen, H.; Ilanne-Parikka, P.; Keinänen-Kiukaanniemi, S.; Laakso, M.; Lauhkonen, M.; Lehto, P.; et al. Prevention of Type II Diabetes in Subjects with Impaired Glucose Tolerance: The Diabetes Prevention Study (DPS) in Finland. Study Design and 1-Year Interim Report on the Feasibility of the Lifestyle Intervention Programme. *Diabetologia* **1999**, *42*, 793–801. [CrossRef] [PubMed]
48. Lindström, J.; Ilanne-Parikka, P.; Peltonen, M.; Aunola, S.; Eriksson, J.G.; Hemiö, K.; Hämäläinen, H.; Härkönen, P.; Keinänen-Kiukaanniemi, S.; Laakso, M.; et al. Sustained Reduction in the Incidence of Type 2 Diabetes by Lifestyle Intervention: Follow-up of the Finnish Diabetes Prevention Study. *Lancet* **2006**, *368*, 1673–1679. [CrossRef] [PubMed]
49. Li, G.; Zhang, P.; Wang, J.; Gregg, E.W.; Yang, W.; Gong, Q.; Li, H.; Li, H.; Jiang, Y.; An, Y.; 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* **2008**, *371*, 1783–1789. [CrossRef]
50. Chiasson, J.-L.; Josse, R.G.; Gomis, R.; Hanefeld, M.; Karasik, A.; Laakso, M. STOP-NIDDM Trail Research Group Acarbose for Prevention of Type 2 Diabetes Mellitus: The STOP-NIDDM Randomised Trial. *Lancet* **2002**, *359*, 2072–2077. [CrossRef]
51. Buchanan, T.A.; Xiang, A.H.; Peters, R.K.; Kjos, S.L.; Marroquin, A.; Goico, J.; Ochoa, C.; Tan, S.; Berkowitz, K.; Hodis, H.N.; et al. Preservation of Pancreatic Beta-Cell Function and Prevention of Type 2 Diabetes by Pharmacological Treatment of Insulin Resistance in High-Risk Hispanic Women. *Diabetes* **2002**, *51*, 2796–2803. [CrossRef]
52. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein, H.C.; Yusuf, S.; Bosch, J.; Pogue, J.; Sheridan, P.; Dinccag, N.; Hanefeld, M.; Hoogwerf, B.; Laakso, M.; et al. Effect of Rosiglitazone on the Frequency of Diabetes in Patients with Impaired Glucose Tolerance or Impaired Fasting Glucose: A Randomised Controlled Trial. *Lancet* **2006**, *368*, 1096–1105. [CrossRef]
53. Zinman, B.; Harris, S.B.; Neuman, J.; Gerstein, H.C.; Retnakaran, R.R.; Raboud, J.; Qi, Y.; Hanley, A.J.G. Low-Dose Combination Therapy with Rosiglitazone and Metformin to Prevent Type 2 Diabetes Mellitus (CANOE Trial): A Double-Blind Randomised Controlled Study. *Lancet* **2010**, *376*, 103–111. [CrossRef]

54. Torgerson, J.S.; Hauptman, J.; Boldrin, M.N.; Sjöström, L. XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study: A Randomized Study of Orlistat as an Adjunct to Lifestyle Changes for the Prevention of Type 2 Diabetes in Obese Patients. *Diabetes Care* **2004**, *27*, 155–161. [CrossRef] [PubMed]
55. Marina, A.L.; Utzschneider, K.M.; Wright, L.A.; Montgomery, B.K.; Marcovina, S.M.; Kahn, S.E. Colesevelam Improves Oral but Not Intravenous Glucose Tolerance by a Mechanism Independent of Insulin Sensitivity and β-Cell Function. *Diabetes Care* **2012**, *35*, 1119–1125. [CrossRef] [PubMed]
56. Handelsman, Y.; Goldberg, R.B.; Garvey, W.T.; Fonseca, V.A.; Rosenstock, J.; Jones, M.R.; Lai, Y.-L.; Jin, X.; Misir, S.; Nagendran, S.; et al. Colesevelam Hydrochloride to Treat Hypercholesterolemia and Improve Glycemia in Prediabetes: A Randomized, Prospective Study. *Endocr. Pract.* **2010**, *16*, 617–628. [CrossRef]
57. Rosenstock, J.; Foley, J.E.; Rendell, M.; Landin-Olsson, M.; Holst, J.J.; Deacon, C.F.; Rochotte, E.; Baron, M.A. Effects of the Dipeptidyl Peptidase-IV Inhibitor Vildagliptin on Incretin Hormones, Islet Function, and Postprandial Glycemia in Subjects with Impaired Glucose Tolerance. *Diabetes Care* **2008**, *31*, 30–35. [CrossRef]
58. Rosenstock, J.; Klaff, L.J.; Schwartz, S.; Northrup, J.; Holcombe, J.H.; Wilhelm, K.; Trautmann, M. Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects with and without Pre-Diabetes. *Diabetes Care* **2010**, *33*, 1173–1175. [CrossRef] [PubMed]
59. Astrup, A.; Carraro, R.; Finer, N.; Harper, A.; Kunesova, M.; Lean, M.E.J.; Niskanen, L.; Rasmussen, M.F.; Rissanen, A.; Rössner, S.; et al. Safety, Tolerability and Sustained Weight Loss over 2 Years with the Once-Daily Human GLP-1 Analog, Liraglutide. *Int. J. Obes.* **2012**, *36*, 843–854. [CrossRef]
60. Dixon, J.B.; Zimmet, P.; Alberti, K.G.; Rubino, F. Bariatric Surgery: An IDF Statement for Obese Type 2 Diabetes. *Diabet. Med.* **2011**, *28*, 628–642. [CrossRef]
61. de la Cruz-Muñoz, N.; Messiah, S.E.; Arheart, K.L.; Lopez-Mitnik, G.; Lipshultz, S.E.; Livingstone, A. Bariatric Surgery Significantly Decreases the Prevalence of Type 2 Diabetes Mellitus and Pre-Diabetes among Morbidly Obese Multiethnic Adults: Long-Term Results. *J. Am. Coll. Surg.* **2011**, *212*, 505–511; discussion 512–513. [CrossRef]
62. Carlsson, L.M.S.; Peltonen, M.; Ahlin, S.; Anveden, Å.; Bouchard, C.; Carlsson, B.; Jacobson, P.; Lönroth, H.; Maglio, C.; Näslund, I.; et al. Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects. *N. Engl. J. Med.* **2012**, *367*, 695–704. [CrossRef]
63. Zhuo, X.; Zhang, P.; Barker, L.; Albright, A.; Thompson, T.J.; Gregg, E. The Lifetime Cost of Diabetes and Its Implications for Diabetes Prevention. *Diabetes Care* **2014**, *37*, 2557–2564. [CrossRef]
64. Vasavada, A.; Taub, L.F.M. Diabetes Mellitus Screening. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
65. US Preventive Services Task Force. Screening for Prediabetes and Type 2 Diabetes: US Preventive Services Task Force Recommendation Statement. *JAMA* **2021**, *326*, 736–743. [CrossRef] [PubMed]
66. Kahn, R.; Alperin, P.; Eddy, D.; Borch-Johnsen, K.; Buse, J.; Feigelman, J.; Gregg, E.; Holman, R.R.; Kirkman, M.S.; Stern, M.; et al. Age at Initiation and Frequency of Screening to Detect Type 2 Diabetes: A Cost-Effectiveness Analysis. *Lancet* **2010**, *375*, 1365–1374. [CrossRef] [PubMed]
67. Lambrinou, E.; Hansen, T.B.; Beulens, J.W. Lifestyle Factors, Self-Management and Patient Empowerment in Diabetes Care. *Eur. J. Prev. Cardiol.* **2019**, *26*, 55–63. [CrossRef] [PubMed]
68. Bartoli, E.; Fra, G.P.; Carnevale Schianca, G.P. The Oral Glucose Tolerance Test (OGTT) Revisited. *Eur. J. Intern. Med.* **2011**, *22*, 8–12. [CrossRef]
69. Lu, J.; He, J.; Li, M.; Tang, X.; Hu, R.; Shi, L.; Su, Q.; Peng, K.; Xu, M.; Xu, Y.; et al. Predictive Value of Fasting Glucose, Postload Glucose, and Hemoglobin A1c on Risk of Diabetes and Complications in Chinese Adults. *Diabetes Care* **2019**, *42*, 1539–1548. [CrossRef]
70. Selvin, E.; Wang, D.; Matsushita, K.; Grams, M.E.; Coresh, J. Prognostic Implications of Single-Sample Confirmatory Testing for Undiagnosed Diabetes: A Prospective Cohort Study. *Ann. Intern. Med.* **2018**, *169*, 156–164. [CrossRef]
71. Ostendorf, D.M.; Caldwell, A.E.; Zaman, A.; Pan, Z.; Bing, K.; Wayland, L.T.; Creasy, S.A.; Bessesen, D.H.; MacLean, P.; Melanson, E.L.; et al. Comparison of Weight Loss Induced by Daily Caloric Restriction versus Intermittent Fasting (DRIFT) in Individuals with Obesity: Study Protocol for a 52-Week Randomized Clinical Trial. *Trials* **2022**, *23*, 718. [CrossRef]
72. 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 ReductionA Randomized Trial. *JAMA* **2005**, *293*, 43–53. [CrossRef]
73. MacLean, P.S.; Wing, R.R.; Davidson, T.; Epstein, L.; Goodpaster, B.; Hall, K.D.; Levin, B.E.; Perri, M.G.; Rolls, B.J.; Rosenbaum, M.; et al. NIH Working Group Report: Innovative Research to Improve Maintenance of Weight Loss. *Obesity* **2015**, *23*, 7–15. [CrossRef]
74. O'Connor, S.G.; Boyd, P.; Bailey, C.P.; Nebeling, L.; Reedy, J.; Czajkowski, S.M.; Shams-White, M.M. A Qualitative Exploration of Facilitators and Barriers of Adherence to Time-Restricted Eating. *Appetite* **2022**, *178*, 106266. [CrossRef]
75. Vasim, I.; Majeed, C.N.; DeBoer, M.D. Intermittent Fasting and Metabolic Health. *Nutrients* **2022**, *14*, 631. [CrossRef] [PubMed]