Energy Balance and Weight Loss for Diabetes Remission

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Diabetes remission—the occurrence of durable normoglycemia without antidiabetic medications—has been demonstrated in some patients with type 2 diabetes who have achieved and sustained weight loss through lifestyle intervention or metabolic and bariatric surgery. Although this pursuit would represent a paradigm shift in our diabetes chronic care model, could diabetes remission become a routine treatment strategy in patients with type 2 diabetes? This article reviews the mechanisms by which weight loss can drive improvements in insulin sensitivity and β-cell function sufficient to normalize glycemia, treatment approaches that provide evidence for diabetes remission, and avenues for developing the research and discovery that will be required to make diabetes remission possible as part of the routine medical management of type 2 diabetes.

Type 2 diabetes has long been considered a chronic disease, and the classical approach to treatment has been one of managing glycemia and associated cardiovascular disease risks, with a lifelong commitment to monitoring and treatment. It is only in the past decade that "remission," "reversal," or even "cure" have been discussed in the context of type 2 diabetes treatment, usually in the context of dramatic glycemic improvements produced by metabolic and bariatric surgical procedures, intensive medical weight loss approaches, or dietary restriction of carbohydrate (with associated weight loss). To reduce confusion around these terms, the American Diabetes Association (ADA) in its 2019 consensus statement on nutrition therapy for adults with diabetes or prediabetes (1) defined remission as the maintenance of euglycemia (complete remission) or a prediabetes level of glycemia (partial remission) with no diabetes medication for at least 1 year. This article provides a state-of-the-art review of our knowledge of remission of glycemic abnormalities in patients with established type 2 diabetes achieved through negative energy balance and resulting weight loss.

Mechanisms by Which Weight Loss Can Result in Diabetes Remission

Obesity and type 2 diabetes are biologically linked, with obesity being a primary driver of insulin resistance and also implicated in β-cell decompensation (2). Furthermore, weight loss of 5–10% is a proven means of diabetes prevention (3), even over the long term (4–6), and can dramatically improve the lives of people with established type 2 diabetes, bringing positive improvements in risk factors and measurement of feeling and function (7). In fact, negative energy balance and the weight loss it produces have powerful and protean effects on many physiologic factors that could lead to remission of the type 2 diabetes disease process. The association between weight gain as a driver of cardiometabolic comorbidities is well known. The association between weight loss and its powerful effects in improving these comorbidities are only now being explored and explicated.

Clinically, it is well known that patients need not achieve a BMI ≤25 kg/m² or even ≤30 kg/m² to experience glycemic and other health improvements (8). First, weight loss is predominantly fat loss in ambulatory patients, and initially, fat is disproportionately mobilized from visceral, as opposed to subcutaneous, stores. An important study (9) of patients with obesity and insulin resistance who achieved different degrees of weight loss illustrated this point, and some of its results are shown in Figure 1 and Table 1. In this study, weight loss was associated with disproportionate loss of body fat across multiple compartments (Figure 1). Weight losses of 5, 11, and 16% were associated with reductions in total fat mass (in kg) of 10, 18 and 27%, respectively, and reductions in intra-abdominal adipose tissue (in cm³) of 9, 23, and 30%, respectively (9). Even more disproportionate were reductions in intrahepatic triglyceride (measured as a percentage via MRI) of 13, 52, and 65%, respectively. Thus, it appears that with total body fat loss, the stores of intra-abdominal and intrahepatic fat are preferentially lost. This preferential loss of fat from organs and from storage sites that are known to be associated with adverse "lipotoxicity"—the

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proinflammatory and prothrombotic cytokines and other products of adipose tissue that drive cardiometabolic risk—may explain the achievement of improvement in cardiometabolic risk without completely normalizing body fat stores.

Magkos et al. (9) also showed that body composition changes were associated with a variety of improvements in clinical end points, but that different tissues responded to different degrees of weight loss. At 5% weight loss, there was significant improvement in some risk factors for cardiometabolic disease (i.e., glucose, insulin, triglyceride, alanine transaminase, and leptin), but a 5% weight loss did not affect others (i.e., free fatty acids, LDL and HDL cholesterol, and adiponectin). With greater degrees of weight loss, there was greater improvement in these end points, but only after 16% weight loss did C-reactive protein concentrations decrease and the plasma adiponectin concentration increase significantly. Thus, for some end points, greater degrees of weight loss are needed.

In their study, Magkos et al. (9) performed sophisticated tests of multiorgan insulin sensitivity (a two-stage hyperinsulinemic-euglycemic clamp with infusion of stable isotopically labeled tracers) and demonstrated that liver and adipose tissue insulin sensitivity improved at 5% weight loss and then plateaued, whereas muscle insulin sensitivity continued to improve as weight loss increased to 11 and 16%. β-Cell function also improved in a step-wise manner with progressive weight loss (9).

Magkos et al. (9) also examined adipose tissue expression of genes involved in cholesterol flux, lipid synthesis, extracellular matrix remodeling, and oxidative stress and again found a step-wise improvement in function with progressive weight loss. The clinical takeaway message from this study is that, for diabetes remission, it is not necessary to achieve a "normal" BMI or even total normalization of body fat stores. It is important to achieve enough weight loss to reduce ectopic body fat stores so as to affect the adverse clinical end points driving risk for type 2 diabetes, and this study's findings suggest that the aim be at least 16% weight loss (9). This study proposes that the effect of weight loss through loss of visceral fat in liver, muscle, and pancreas can produce improvements in muscle, fat, and liver insulin sensitivity as well as β-cell function (9). These improvements, achieved through reduction in the lipotoxic effects of visceral adiposity, would be crucial in bringing about the remission of type 2 diabetes.

Diabetes Remission With Metabolic and Bariatric Surgery

That metabolic and bariatric surgery produces immediate and dramatic improvement in glycemia has been known for many years (10). In fact, all common procedures, including gastric band, Roux-en-Y gastric bypass, gastric sleeve, and biliopancreatic diversion, have been associated with diabetes remission (11). However, even with remission after metabolic and bariatric surgery, relapse is an issue. Weight regain with gastric band has been problematic, and this procedure is now rarely done.

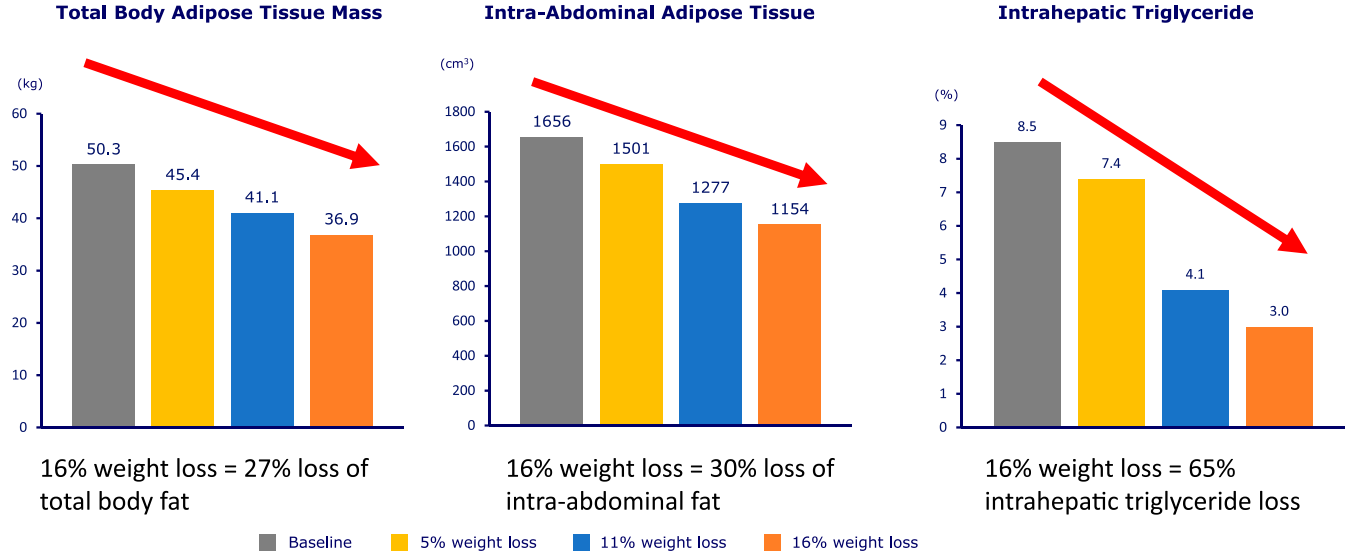

FIGURE 1 Weight loss produces disproportionately greater loss of intra-abdominal and liver adipose tissue. Total weight losses of 5, 11, and 16% were associated with reductions in total fat mass of 10, 18, and 27%, respectively; reductions in intra-abdominal adipose tissue of 9, 23, and 30%, respectively; and reductions in intrahepatic triglyceride of 13, 52, and 65%, respectively. Adapted from ref. 9.

TABLE 1 Effects of Moderate and Subsequent Progressive Weight Loss on Metabolic Function and Adipose Tissue Biology in Humans With Obesity

	5% Weight Loss	10% Weight Loss	15% Weight Loss
Risk factor/mediator improvement: glucose, insulin, triglycerides, and alanine transaminase	+	++	+++
Risk factor/mediator improvement: LDL and HDL cholesterol, adiponectin, and free fatty acids		+	++
Risk factor improvement: C-reactive protein			+
Adipose tissue insulin sensitivity	+++	+++	+++
Liver insulin sensitivity	+++	+++	+++
Muscle insulin sensitivity	+	++	+++
β-Cell function	+	++	+++
Upregulation of genes involved in cholesterol flux and downregulation of genes involved in lipid synthesis, extracellular matrix remodeling, and oxidative stress		+	++

+, ++, and +++ indicate progressively greater effects. Adapted from ref. 9.

In the subgroup analysis of 343 patients with type 2 diabetes at baseline in the Swedish Obesity Subjects (SOS) study (12), metabolic and bariatric surgery (predominantly vertical sleeve gastrectomy) brought 72% into remission (i.e., blood glucose ≤110 mg/dL on no diabetes medications) compared with 16% in remission in medically treated control subjects at 2 years. By 15 years, these remission rates had decreased to 30% in the surgery group versus 7% in control subjects. At 2 years, mean weight loss was 26.3 kg (21.2%) in the surgery group and 3.0 kg (2.4%) in the control group ($P < 0.001$). The corresponding mean weight losses from baseline to 10 years were 22.5 kg (18.0%) for surgery and 4.4 kg (3.6%) for the control group ($P < 0.001$).

Because of the dramatic improvements in glycemia seen with surgery, guidelines (13) have recommended metabolic and bariatric surgery for patients with diabetes and a BMI as low as 30 kg/m^2; however, higher BMI (along with higher C-peptide and shorter duration of diabetes) seems to be a predictor of successful diabetes reversal with metabolic and bariatric surgery (14). In the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) clinical trial, patients with severe, poorly controlled diabetes and a BMI ≥30 kg/m^2 were randomized to medical therapy, gastric sleeve, or Roux-en-Y gastric bypass. Remission rates (A1C ≤6% on no diabetes medications) were 0, 27, and 42% at 1 year for these interventions, respectively (15), with approximately half relapsing in 5 years (16). One could presume that the amount and durability of weight loss would predict diabetes remission. Some studies indicate this is true (17,18), whereas others (19,20) have not supported the predictive value of amount of weight loss achieved with surgery with regard to diabetes remission.

The overall message for clinicians is that metabolic and bariatric surgery can be an excellent and life-extending option for some patients with type 2 diabetes, but these procedures are associated with perioperative risk, permanently change patients' relationship with food, sometimes elicit the emergence of psychiatric disorders, and require lifelong nutritional support and medical monitoring. A full discussion of the risks and benefits of bariatric and metabolic surgery is beyond the scope of this article. Instead, the focus here is on what these surgeries demonstrate: that diabetes remission is possible and that we may be able to replicate the success of surgical procedures with medical approaches to diabetes remission.

Diabetes Remission With Intensive Medical Approaches

The Look AHEAD (Action for Health in Diabetes) trial (21,22), DiRECT (Diabetes Remissions Clinical Trial) (23,24), and a commercial continuous care model from Virta Health (25) provide examples of weight loss and diabetes remission achieved through intensive medical approaches. These interventions are discussed in more detail below and are summarized, along with exemplary surgical approaches, in Table 2.

Weight Loss Achieved Through Intensive Lifestyle Intervention

In the Look AHEAD trial (21), patients with overweight or obesity and established type 2 diabetes were randomly

TABLE 2 Exemplary Studies Demonstrating Weight Loss and Diabetes Remission With Intensive Medical or Surgical Approaches

	Effects on Weight and Diabetes Remission		
Study and Characteristics	1 Year	2 Years	≥4 Years
Look AHEAD (22): intensive lifestyle intervention delivered to 2,241 patients with type 2 diabetes, mean age 51 years, and mean BMI 35.8 kg/m^2	8.6% mean weight loss; 11.5% achieved complete or partial diabetes remission		At 4 years, 4.7% mean weight loss; 7.3% with complete or partial diabetes remission
DiRECT (23,24): total meal replacement for 3–5 months and long-term follow-up in primary care practices of 149 patients with type 2 diabetes	10-kg mean weight loss; 46% achieved complete or partial diabetes remission	5.4-kg mean weight loss; 36% with complete or partial diabetes remission	
Virta Health (26): continuous care intervention with ketone monitoring and a low-carbohydrate diet in 262 patients with type 2 diabetes	13.8-kg mean weight loss; 72% achieved an A1C <6.5% on no medications or only on metformin	10% mean weight loss; 17.6% with partial remission and 6.7% complete diabetes remission	
STAMPEDE (15,16): 150 patients with poorly controlled type 2 diabetes and mean BMI 37 kg/m^2 randomized to:			
Gastric bypass surgery	29% mean weight loss; 42% achieved complete diabetes remission		At 5 years, 23% mean weight loss; 22.4% with complete remission (A1C <6% without diabetes medications)
Gastric sleeve surgery	25% mean weight loss; 27% achieved complete diabetes		At 5 years, 19% mean weight loss; 14.9% with complete diabetes remission
Medical therapy	5.4-kg mean weight loss; 0% achieved complete remission		At 5 years, 5% mean weight loss; 0% with complete remission
SOS study (12) bariatric surgery (predominantly vertical sleeve gastrectomy) in 343 patients with type 2 diabetes		21.2% mean weight loss; 72% achieved complete or partial diabetes remission	At 10 years, 18.0% mean weight loss; at 15 years, 30% with complete or partial diabetes remission

assigned to intensive lifestyle intervention (ILI, n = 2,241) or diabetes support and education (DSE, n = 2,262). ILI consisted of weekly group and individual counseling in the first 6 months followed by three sessions per month for the second 6 months and twice-monthly contact with regular refresher group sessions and campaigns in years 2–4. The DSE group attended three group sessions per year on diet, physical activity, and social support. Complete and partial diabetes remission were defined by the ADA consensus definition discussed above (1).

The ILI group was significantly more likely to experience any remission (partial or complete), with prevalence of 11.5% during the first year and 7.3% at year 4, compared with 2.0% for the DSE group at both time points (P <0.001 for each) (22). The prevalence of complete remission was more common in the ILI group than in the DSE group but was low overall, at 1.3% for ILI versus 0.1% for DSE (P <0.001) in year 1 and 0.7% for ILI versus 0.2% for DSE in year 4 (22).

These diabetes remission results are best understood in the context of the modest weight loss achieved and sustained in this study. Participants in the ILI group lost, on average, 8.6% of their body weight versus a mean loss of 0.7% for those in the DSE group at year 1, and by year 4, mean weight lost was 4.7% in the ILI group and 0.8% in the DSE group. Furthermore, the patients in Look AHEAD were predominantly middle-aged or older (mean age 59 years), with a mean BMI of 35.8 kg/m^2, and the median time since type 2 diabetes diagnosis was 5 years. As shown in Table 2, the rate of diabetes remission with the Look AHEAD ILI was unimpressive compared with the improvements seen with metabolic and bariatric surgery, but what is impressive is that at least some patients could achieve remission, or even partial remission, with lifestyle intervention alone. Furthermore,

the weight loss achieved in Look AHEAD produced a host of positive benefits, including improvements in glycemia and cardiovascular risk factors, reduction in the need for antidiabetic and lipid-lowering medications, and improvements in feeling and function (7).

Weight Loss Achieved Through a Meal Replacement Diet

The DiRECT trial by Lean et al. (23) generated great interest by targeting diabetes remission using a structured liquid diet approach to weight loss in primary care practices in the United Kingdom. In that study, 306 individuals with diabetes of <6 years' duration enrolled from 49 (23 intervention and 26 control) general practices. The intervention required withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (a formula diet of 825–853 kcal/day for 3–5 months), stepped food reintroduction (over 2–8 weeks), and structured support for long-term maintenance of weight loss. Diabetes remission at 1 year (defined as A1C ≤6.5% after at least 2 months off all antidiabetic medications) was achieved in 68 participants (46%) in the intervention group and 6 (4%) in the control group (P <0.0001) (23).

The coprimary end point in this study was the proportion of participants achieving a 15-kg weight loss, which was accomplished by 24 participants in the intervention group and none in the control group. At 1 year, mean weight change in the intervention group was −10 kg versus −1 kg in the control group.

Remission varied with weight loss in the whole study population, with achievement in none of the 76 participants who gained weight, 6 (7%) of the 89 participants who maintained a weight loss of 0–5 kg, 19 (34%) of the 56 participants with a loss of 5–10 kg, 16 (57%) of the 28 participants with a loss of 10–15 kg, and 31 (86%) of the 36 participants who lost ≥15 kg (23). However, in a follow-up study (24), effects on relapse were demonstrated. At 2 years, 17 intervention participants (11%) and 3 participants in the control group (2%) had a weight loss of ≥15 kg, and 53 intervention participants (36%) and 5 control participants (3%) had diabetes remission (P <0.0001).

This study has had an impact on U.K. public health policy. Based on its results, the U.K.'s National Health Service announced that the structured low-calorie liquid diet will be piloted in up to 5,000 patients with diabetes in primary care practices (26).

Weight Loss Achieved With a Low-Carbohydrate Diet and Continuous Care Approach

One commercial entity promoting diabetes remission is Virta Health, which, with its stated mission "to reverse diabetes in 100 million people by 2025," has raised millions of dollars toward achieving that goal (25). This company is based on a program that uses a continuous care intervention (CCI) consisting of home monitoring (weight, blood glucose, β-hydroxybutyrate [BHB], and blood pressure), online coaching, and online group support. Patients are counseled to achieve "nutritional ketosis" through a low-carbohydrate diet and to maintain ketosis by monitoring BHB levels in blood.

Results for 262 patients have been reported at 1 and 2 years (27,28). Of the 262 patients receiving CCI, 88% were on medications for type 2 diabetes. A total of 218 (83%) completed the first year (27), and 194 (74%) completed 2 years. On average, completing participants had lost 13.8 kg after 1 year (27) and 10% of their initial body weight at 2 years (28). At 1 year, 72% (156 of 218) achieved an A1C <48 mmol/mol (6.5%), and 60.3% (117 of 194) achieved this A1C while, in either case, taking either no diabetes medication or only metformin (27). If one takes an intention-to-treat approach, of the 262 patients in the CCI at entry, 60% at 1 year and 47% at 2 years met the criterion of A1C <6.5% on no medications or metformin only. The traditional definitions of complete or partial diabetes remission (off medications) were not reported at 1 year, but at 2 years, 17.6% of participants met the traditional definition of partial diabetes remission (A1C ≤6.5% on no diabetes medications), and 6.7% met the traditional definition of complete remission (A1C ≤6.0% on no diabetes medications) (28).

How much the low-carbohydrate approach contributes is uncertain, but diets that eliminate large numbers of foods and food classes result in reduction in food intake and weight loss. This diet may be a way for patients to navigate the modern obesogenic environment by avoiding highly processed foods and simple carbohydrates. Clearly, more data are needed on outcomes of this approach, now that it has been scaled up for wide delivery.

Other Approaches to Diabetes Remission

Two additional studies have demonstrated partial or complete diabetes remission, albeit at low rates of success. In a study of patients newly diagnosed with type 2 diabetes who were randomized to a low-carbohydrate Mediterranean diet (n = 107) or a low-fat diet (n = 108) (29), the low-carbohydrate Mediterranean diet showed superior rates of complete and partial diabetes remission. However, these rates were low. For any remission (partial or complete), 14.7% (95% CI 13.0–16.5) of those on the low-carbohydrate Mediterranean diet achieved remission during the first year, decreasing to 9.7% (95% CI 8.6–10.7) during year 3 and to 5.0% (95% CI 4.4–5.6) during year 6. Only 4.6%

achieved complete remission in year 1, with declining rates thereafter. Similarly, in another study (30), patients in the Veterans Affairs system were randomized to receive group medical visits with intensive weight management and a low-carbohydrate diet (n = 127) or group medical visits alone (n = 136). The intensive group in this study had superior results in glycemic control and reduction in use of diabetes medications and even some cases of diabetes remission, albeit at an overall low rate.

Can Diabetes Remission Be Accomplished in Clinical Practice?

In 2017, 228,000 metabolic and bariatric surgery procedures were performed in the United States; however, this number represents only 1% of patients who meet eligibility criteria (31). There are still financial barriers to accessing surgical treatment, and even patients who have insurance coverage are often hesitant to take this step. Still, our primary care providers need to discuss this option and refer patients with type 2 diabetes and obesity more proactively.

To have an impact on diabetes remission on a national scale, the opportunity lies in achieving and sustaining successful weight loss in primary care. Toward that end, a low-calorie liquid diet has been successfully implemented in primary care in the United States. The LOSS (Louisiana Obese Subjects Study) trial (32) demonstrated that primary care practices in Louisiana could successfully implement office-based weight management that included a low-calorie-liquid diet and behavioral counseling similar to that in the DiRECT trial, but also used medications indicated for weight management. However, the problem encountered in LOSS was weight regain. As shown in Table 2, if weight regain occurs, diabetes relapse occurs. Thus, successful approaches to the maintenance of lost weight in primary care are much needed.

One solution to the issue of weight regain is to use antiobesity medications. We know that medications have been successful in diabetes prevention. With the advent of medications approved as an adjunct to lifestyle intervention for chronic weight management, efficacy in diabetes prevention has been shown with orlistat (33), phentermine/topiramate (34), liraglutide (35), lorcaserin (36), and naltrexone/bupropion (37). One of the greatest values of these medications is not that they produce so much weight loss, but that, as long as they are taken, they support weight loss maintenance.

The issue of metformin also needs to be raised. This medication is indicated in the treatment of type 2 diabetes and, although it does not have an indication for weight management, it does produce and sustain modest weight loss. In fact, in the Diabetes Prevention Program trial, over 10 years of follow-up, participants who were highly adherent to using metformin 1,700 mg/day lost almost 5% and maintained it without regain for 10 years (38). The question arises, though, of whether we should consider diabetes to be in remission for patients who are taking metformin, an antidiabetic medication, for weight loss maintenance.

The Future of Diabetes Remission Through Weight Loss: Research and Discovery Needs

Approaches to Delivering and Sustaining Sufficient Weight Loss

Successfully implementing diabetes remission strategies in primary care will require improvement in two areas. First, we need an educated and competent workforce skilled in medical weight management. Obesity standards of care (39) and obesity medical education competencies (40) have recently been published and will advance this concept. There is also a growing cadre of obesity medicine specialists who have been certified by the American Board of Obesity Medicine (41). An educated and competent specialist medical team can support primary care providers. Second, providers need better tools to produce and sustain weight loss that is sufficient for diabetes remission. One such tool could be semaglutide 2.4 mg weekly, which is now in phase 3 studies for an obesity indication. Phase 2 studies with this drug (42) suggest that we can expect twice as much weight loss as is now achievable with antiobesity medications. More medications with different mechanisms of action are also needed for obesity, which is a heterogeneous disease, so we can better achieve weight loss in all patients.

Randomized Comparisons of Surgical and Medical Approaches With Health and Economic Outcomes

If we are successful in developing medical approaches that can deliver weight losses similar to those achieved with metabolic and bariatric surgery, then it will be important to compare medical and surgical approaches in terms of their effects on diabetes remission and other outcomes. We are not at the level of equipoise yet, but with more efficacious antiobesity medications becoming available, equipoise will make such comparisons important. Will it be less costly and equally safe to invest in metabolic and bariatric surgery or should we invest in intensive medical management with pharmacotherapy for the long term? We will need randomized comparisons to answer this question.

Should We Focus More on Diabetes Prevention Than on Its Reversal?

It appears that a weight loss of 10% produces maximal benefit in terms of preventing the progression of impaired glucose tolerance to type 2 diabetes (43). Because microvascular disease is established during the course of type 2 diabetes, we need to be more proactive in trying to achieve normoglycemia in the disease state of prediabetes (44). Our goal should be long-term normoglycemia achieved with weight loss, whether patients have prediabetes or established type 2 diabetes.

Conclusion

Diabetes remission—the occurrence of durable normoglycemia without antidiabetic medications—is currently achievable in some patients. Gastric sleeve and gastric bypass surgical procedures can deliver diabetes remission in a substantial percentage of, but not all, patients. Medically managed weight loss approaches are beginning to show promise. However, weight loss is resisted and weight regain is expected because of adaptive thermogenesis (45,46) and biologic changes in appetite signals (47). For this reason, patients must take antiobesity medications over the long term to sustain weight loss.

This is a time of shifting concepts about type 2 diabetes as a chronic, intractable, progressive condition. Future developments likely will allow us to target weight as a pathway to both the prevention and remission of type 2 diabetes, shifting the current chronic care model of diabetes management to a chronic care model of obesity management.

DUALITY OF INTEREST

D.H.R. has an equity interest in the following start-up companies engaged in various aspects of weight management: Calibrate, Epitomee, Gila Therapeutics, Scientific Intake, and Xeno Biosciences. She is on speakers bureaus for Bausch Health and Novo Nordisk. She has served as an advisor or consultant to Alyvent, Amgen, Bausch Health, Boeringer Ingelheim, Epitomee, Gila Therapeutics, IFA Celtic, Janssen, Kensai Therapeutics, Novo Nordisk, Phenomix, real appeal (United Health), ReDesign Health (Calibrate), Sanofi, and Scientific Intake. She also serves on the steering committee for the SELECT cardiovascular outcome trial for Novo Nordisk's investigational semaglutide product. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

D.H.R. is the sole author of this article. She is the guarantor of this work and, as such, had full access to all the data included and takes responsibility for the integrity of the review.

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