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<p>The individual and societal burdens of living with a chronic disease are a global issue. Diabetes directly increases health care costs to manage the disease and the associated complications and indirectly increases the economic burden through long-term complications that hinder the productivity of humans worldwide. Thus, it is crucial to have accurate information on diabetes-related costs and the geographic and global economic impact when planning interventions and future strategies. Health care systems must work with government agencies to plan national-level pre diabetes and diabetes strategies and policies. Public health services must focus on diabetes screening prevention and remission.</p>	
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<p>Obesity and its association with metabolic syndrome are implicated in many disease states. Research has focused on the role of diet and lifestyle modifications in the evolution of prediabetes to diabetes seeking ways to intervene and improve outcomes. Proven nutritional include leaner proteins, an abundance of vegetables, extra-virgin olive oil, and controlled portioning of carbs and starches. The transition from a sedentary state to an exercise routine of moderate intensity has shown efficacy in lowering metabolic risks. The synergy of dietary and physical activity modifications are the building blocks for lifestyle modifications examined in this review as a means of preventing obesity-related diabetes.</p>	
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<p>Type 2 diabetes is characterized by progressive decline in pancreatic <math>\beta</math>-cell function. Studies in adult subjects with newly diagnosed type 2 diabetes have reported that intensive insulin therapy followed by various antihyperglycemic medications can delay <math>\beta</math>-cell decline. However, this improvement is lost after cessation of therapy. In contrast, youth with type 2 diabetes experience a more rapid loss in <math>\beta</math>-cell function compared</p>	

with adults and have loss of  $\beta$ -cell function despite being on insulin and other antihyperglycemic medications. In part one of this two-part review, we discuss studies aiming to achieve diabetes remission with insulin and oral antidiabetic medications.

**Intervention with Therapeutic Agents, Understanding the Path to Remission to Type 2 Diabetes: Part 2**

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Shuai Hao, Guillermo E. Umpierrez, and Priyathama Vellanki

Type 2 diabetes is characterized by progressive decline in pancreatic  $\beta$ -cell function. Newer agents, such as glucagon-like peptide-1 receptor agonist (GLP-1RA) and dual incretin agonists, can augment  $\beta$ -cell function and delay the need for additional antihyperglycemics. However, the effect on  $\beta$ -cell function ceases after stopping the medications. When combined with intensive lifestyle modifications, higher doses of GLP-1RA than those used for diabetes treatment can be used to induce weight loss. More research is needed on whether the weight loss achieved with GLP-1RA can be sustained after stopping medication and in turn can sustain diabetes remission.

**Physiology Reconfigured: How Does Bariatric Surgery Lead to Diabetes Remission?**

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Vance L. Albaugh, Christopher Axelrod, Kathryn P. Belmont, and John P. Kirwan

Bariatric surgery improves glucose homeostasis and glycemic control in patients with type 2 diabetes. Over the past 20 years, a breadth of studies has been conducted in humans and rodents aimed to identify the regulatory nodes responsible for surgical remission of type 2 diabetes. The review herein discusses central mechanisms of type 2 diabetes remission associated with weight loss and surgical modification of the gastrointestinal tract.

**Remission with an Intervention: Is Metabolic Surgery the Ultimate Solution?**

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Zubaidah Nor Hanipah, Francesco Rubino, and Philip R. Schauer

Long-term remission of type 2 diabetes following lifestyle intervention or pharmacotherapy, even in patients with mild disease, is rare. Long-term remission following metabolic surgery however, is common and occurs in 23% to 98% depending on disease severity and type of surgery. Remission after surgery is associated with excellent glycemic control without reliance on pharmacotherapy, improvements in quality of life, and major reductions in microvascular and macrovascular complications. For patients with type 2 diabetes, early intervention with metabolic surgery, when beta cell function still remains intact, provides the greatest probability of long-term remission as high as 90% or more.

**Can the Future be Bright with Advances in Diabetic Eye Care?**

89

Samantha Paul, Christian Kim, Mohamed Kamel Soliman, Warren Sobol, Jose J. Echegaray, and Shree Kurup

The prevalence of diabetic retinopathy is steadily increasing as the population of patients with diabetes grows. In the past decade, the development of anti-VEGF agents has dramatically changed the treatment landscape for diabetic retinopathy and diabetic macular edema (DME). Newer agents in development aim to reduce the treatment burden of diabetic retinopathy.

**Diabetic Kidney Care Redefined with a New Way into Remission** 101

Nour Hammad, Mohamed Hassanein, and Mahboob Rahman

Diabetic kidney disease has been a leading cause for end-stage kidney disease. Traditional methods to slow progression include tight glycemic control, blood pressure control, and use of renin–angiotensin axis inhibitors. Finerenone and sodium glucose co-transporters have shown proven benefit in diabetic kidney disease regression recently. Other potential targets for slowing the decline in diabetic kidney disease are transforming growth factor beta, endothelin antagonist, protein kinase C inhibitors, advanced glycation end product inhibition, Janus kinase-signal transducer and activator of transcription pathway inhibition, phosphodiesterase 3 or 5 inhibitors, and Rho kinase inhibitor. These targets are at various trial phases and so far, show promising results.

**Nagging Pain and Foot Ulcers Can be Treated into Remission** 119

Craig B. Frey, Richard Park, Rachel Robinson, and Courtney Yoder

Lower extremity ulcerations are very common in patients with diabetes. These wounds lead to amputation in a surprisingly large percentage of patients with diabetes. The mortality rate following amputation in a patient with diabetes is alarmingly high. Preventive treatment is pivotal to avoid the numerous complications associated with diabetic ulcerations. However, at the onset of ulceration, early treatment under the supervision and guidance of a specialist can result in remission. Diabetic peripheral neuropathy is also a life-altering and debilitating disease. Although some patients experience numbness, some experience pain that can be sharp, shooting, and tingling. Although treatment is challenging and often requires medication, newer modalities, such as stimulation and physical therapy, have shown promise in reversing the devastating effects of peripheral neuropathy.

**Ameliorating Cardiovascular Risk in Patients with Type 2 Diabetes** 135

Issam Motairek and Sadeer Al-Kindi

Patients with type 2 diabetes (T2D) are at an increased risk of cardiovascular disease (CVD), which constitutes the most common cause of morbidity and mortality in these patients. Intensive CVD risk factor control can ameliorate the elevated CVD associated with T2D. In this review, we provide an overview of CVD risk factor control, including traditional (blood pressure, glycemia, lipid, thrombosis, and lifestyle modifications) and nontraditional (social and environmental determinants of health) in patients with T2D, including evidence on management and outcomes.

**Nonalcoholic Fatty Liver Disease** 149

Scott Isaacs

Management of nonalcoholic fatty liver disease (NAFLD) is crucial for type 2 diabetes (T2D) remission because they are linked through the common pathophysiology of insulin resistance and lipotoxicity. One in three patients with T2D has nonalcoholic steatohepatitis leading to fibrosis, cirrhosis, and hepatocellular carcinoma. Noninvasive testing with imaging and/or serum biomarkers can assess the risk for advanced liver disease. A liver biopsy is

only necessary in select patients where there is diagnostic doubt. Treatments for NAFLD parallel T2D remission strategies focusing on weight loss and managing comorbid conditions through lifestyle modification, anti-obesity medications, and/or bariatric surgery, and T2D medications with proven efficacy.

### **Remission in Ketosis-Prone Diabetes**

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Nupur Kikani and Ashok Balasubramanyam

Heterogeneous forms of Ketosis-prone diabetes (KPD) are characterized by patients who present with diabetic ketoacidosis (DKA) but lack the typical features and biomarkers of autoimmune T1D. The A-β+ subgroup of KPD provides unique insight into the concept of “remission” since these patients have substantial preservation of beta-cell function permitting the discontinuation of insulin therapy, despite initial presentation with DKA. Measurements of C-peptide levels are essential to predict remission and guide potential insulin withdrawal. Further studies into predictors of remission and relapse can help us guide patients with A-β+ KPD toward remission and develop targeted treatments for this form of atypical diabetes.

### **What Is a Honeymoon in Type 1, Can It Go into Remission?**

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Anuradha Viswanathan, Jamie R. Wood, and Betul A. Hatipoglu

Type 1 diabetes is a chronic autoimmune disorder that results in destruction of insulin-producing cells in the pancreas. The autoimmune process is thought to be waxing and waning resulting in variable endogenous insulin secretion ability. An example of this is the honeymoon phase or partial remission phase of type 1 diabetes, during which optimal control of blood glucoses can be maintained with significantly reduced exogenous insulin, and occasionally exogenous insulin can be temporarily discontinued altogether. Understanding this phase is important because even fairly small amounts of endogenous insulin secretion is associated with reduced risk of severe hypoglycemia and microvascular complications.

### **Islet Cell Therapy and Stem Cell Therapy for Type 1 Diabetes: There Will Always Be a Hope**

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Betul A. Hatipoglu and Julia Blanchette

To date, people living with type 1 diabetes depend on external subcutaneous insulin while waiting for a cure, or a feasible method to preserve, replace, and generate fully functioning β cells that secrete appropriate insulin in response to glucose. Current work includes evaluating renewable sources of β cells, transplantation methods without immunosuppressives, and methods to preserve β-cell function. Such methods include β-cell encapsulation, scaffolding, immune modulation, gene editing, and disease-modifying therapies. The purpose of this article is to review the progress and describe β-cell therapies over the past 5 years.