A Narrative Review on Dynamic Aspects of Remission in Type 2 Diabetes Mellitus along with Nutritional approaches.

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DOI: https://doi.org/10.63001/tbs.2024.v19.i02.S.I(1).pp782-787

Received on:

19-09-2024

Accepted on:

25-12-2024

ABSTRACT

Diabetes is becoming more widely acknowledged as a serious worldwide health epidemic and is considered to be chronic and progressive. Diabetes-related complications are a substantial cause of morbidity and mortality. The long-term effects of diabetes include microvascular diseases like nephropathy, neuropathy, and retinopathy as well as macrovascular complications like stroke, cardiovascular disease, and peripheral artery disease. With a lifelong commitment to monitoring and treatment, the traditional treatment strategy has been one of regulating glycemia and related cardiovascular disease risks. Only in the last decade have terms like "remission," "reversal," and even "cure" been mentioned in relation to the management of type 2 diabetes (T2DM), typically in the context of dramatic blood glucose improvements brought on by metabolic and bariatric surgery, aggressive medical weight loss methods, or carbohydrate restriction (with corresponding weight loss). Over the past few years, the idea of T2DM remission and the return of diabetes markers to normal levels has gained popularity. Various international guidelines are starting to recognize T2DM remission progressively. The development of evidence-based dietary recommendations has advanced, although there is still disagreement and uncertainty among the health professionals. This narrative review discusses through much detail about the various theories of diabetes remission as well as the methods that can be used to achieve T2DM remission, including dietary and lifestyle changes, exercise, bariatric surgery, and medicinal nutrition therapy. Although the idea of T2DM remission has become a practical possibility, it may not be possible to put it into routine clinical practice until long-term research establish the effectiveness of various techniques in this area.

INTRODUCTION

According to details from the WHO and International Diabetes Federation, 537 million people worldwide have diabetes, and because there are so many people at the prediabetes stage, this number is likely to quadruple in the coming decades. These numbers are troubling and would put a significant strain on national health systems around the world. ¹

T2DM is one of five major noncommunicable diseases (cardiovascular disease, diabetes, cancer, chronic respiratory diseases and mental health disorders). T2DM is an insulin-resistant disease with concomitant beta-cell dysfunction. Initial compensation involves a rise in insulin release, which keeps blood sugar levels within the usual range. As the illness worsens, beta cells alter, making insulin secretion unable to keep glucose homeostasis in check, leading to hyperglycemia. The majority of T2DM patients are obese or have a greater body fat percentage, which is primarily distributed in the abdominal area. Through numerous inflammatory processes, including increased FFA release and dysregulated adipokines, this adipose tissue itself encourages insulin resistance. Physical inactivity, history of GDM (Gestational Diabetes mellitus) among individual with

hypertension, or dyslipidemia raises the chance of developing T2DM. Increasing evidence points to adipokine dysregulation, inflammation, altered incretin biology with decreased incretins such glucagon-like peptide-1 (GLP-I) or incretin resistance, hyperglucagonemia, increased renal glucose reabsorption, and alterations in gut microbiota as contributing factors. ²

T2DM has long been seen as a chronic, inexorably progressing condition. This opinion has been altered by several studies, including Counterpoint, Counterbalance, and the Diabetes Remission Clinical Trial (DiRECT). It has been shown that effective diet-induced weight loss results in long-term remission of T2DM. ³ The predictive usefulness of the term "remission" in terms of time to problems and absence of antidiabetic therapy is what gives it relevance today. Of course, type 2 diabetes (T2DM) patients face the danger of a shorter life expectancy as well, although the risk of early death in this patient population is significantly reduced while receiving optimal care, even in the absence of remission. Importantly, extensive research on the predictive significance of the cutoff level in terms of the risk of late diabetic problems is the foundation for the current use of HbA1c values to define effective therapy. ⁴

However, despite the fact that the concept of diabetes remission has emerged, there is still very minimal data available regarding diabetes remission and different strategies for obtaining diabetes remission. Given the high level of interest in the possibility of remission among patients living with T2DM, a practical, adequately informed review can assist practitioners in delivering individualized advice, care, and effective implementation in a therapeutic setting.

Methodology:

We performed a narrative review of the current literature. We used PubMed and Google Scholar and other relevant sites for this purpose. The search terms were diabetes mellitus, diabetes remission, obesity and diabetes remission, polycystic ovary syndrome (PCOS) and diabetes remission, cardiovascular disease and diabetes remission, bariatric surgery and diabetes remission and other relevant terms related to the topic discussed. Duplicate articles were removed. We only considered articles written in English, with no restrictions on the date of publication.

Background:

Pathophysiology of Remission in T2DM

The twin cycle hypothesis was put up in 2008 in an attempt to predict the pathophysiology and an etiology of the onset and remission of T2DM. Several research looked into this, all of which emphasized the significance of extra fat in the liver and pancreas in an etiology of this disease. In the setting of ordinary primary care, DiRECT had demonstrated that T2DM remission is feasible and long-lasting with dietary weight loss in the context of routine primary care. Furthermore, it has been demonstrated that the ability of beta-cells to regenerate after the elimination of this metabolic burden is maintained, and that a reduction in both hepatic and intrapancreatic fat is a requirement for diabetic remission. Recently, it was demonstrated that T2DM remission and redevelopment are both correlated with the important role of hepatic lipoprotein export on intrapancreatic fat storage and beta -cell function. Furthermore, there was a correlation between the increased enrichment of palmitic acid in the lipoproteins exported from the liver and the resurgence of diabetes.³ The predominant saturated fatty acid in the human body is palmitic acid (16:0, PA), which can be obtained through the diet or produced endogenously. PA is a major component of palm oil (44% of total fats), but it can also be found in margarine, cereals, candies, baked goods, meat, and dairy products. De-novo lipogenesis (DNL), which results in an increase in the tissue content of PA and a disruption of the homeostatic control of its tissue concentration, can be effectively induced by physiological pathological circumstances and dietary variables. Dyslipidemia, insulin resistance, and dysregulated fat metabolism are the results of metabolic dysregulation and systemic inflammatory response caused by DNL's overproduction of PA, which is triggered by physiological pathological circumstances and chronic dietary

The twin cycle hypothesis of the etiology of type 2 diabetes

Any extra glucose must go via de novo lipogenesis, which encourages the liver to store fat. Individuals with relative insulin resistance in muscle (caused by hereditary or lifestyle factors) can develop liver fat more easily due to greater plasma insulin levels since insulin encourages de novo lipogenesis. The increasing liver fat will lead to resistance to insulin's ability to reduce hepatic glucose production. Over a long period of time, a small rise in fasting plasma glucose will trigger higher basal insulin secretion rates. Hyperinsulinemia that results will hasten the translation of extra calories into liver fat. Hyperinsulinemia and a weakened inhibition of hepatic glucose production develop into a vicious cycle. Additionally, export of VLDL-triglycerides will boost the supply of fat to all tissues, including the brain. Postprandial hyperglycemia will eventually develop because of the impaired acute insulin secretion caused by the increased availability of fatty acids in and around pancreatic islets. Continuously elevated blood sugar levels throughout the day will boost insulin secretion rates and boost hepatic lipogenesis, which will speed up the liver cycle and stimulate the pancreatic cycle. The trigger level is eventually reached by the fatty acid and glucose inhibitory effects on the islets, causing a rather abrupt onset of clinical diabetes.⁷ Discussion:

Defining Diabetes Remission

The terminology used has an impact on both policy and clinical practise. People who have been declared free of a previously identified illness state have been given a variety of names. When referring to T2D, the terms "resolution," "reversal," "remission," and "cure" have all been used to denote a successful outcome of interventions that leaves a patient in a state of health. ⁸

The American Diabetes Association (ADA) developed a consensus statement in 2009 that addressed these concerns. It was recommended to use the term "remission," which means 'abatement or disappearance of the signs and symptoms," as a descriptive term. There were intended to be three types of remission. "Partial" remission was defined as the persistence of hyperglycemia below the diagnostic levels for diabetes without the use of active medication for at least a year. "Complete" remission was defined as normal glucose readings for a full year without the need of medication. A full remission that lasted for five years or longer without the use of medication is referred to as a "prolonged" remission. A partial remission was defined as HbA1c 6.5% (48 mmol/mol) and/or fasting plasma glucose (FPG) 100-125 mg/dL (5.6 to 6.9 mmol/L), whereas "normal" levels of HbA1c and FPG (<100 mg/dL [5.6 mmol/L]) were needed for a complete remission. 5

The ADA assembled a global, multidisciplinary expert panel to build on this statement and subsequent publications in accordance with more current experience. There were representatives from the Endocrine Society, the American Diabetes Association, the European Association for the Study of Diabetes, Diabetes UK, and the Diabetes Surgery Summit. The panel of experts also included an oncologist to provide a different viewpoint. The phrase "diabetes remission" is the most appropriate, according to this expert panel. It strikes the right balance between acknowledging that diabetes may not always be present and progressing and indicating that a significant improvement might not last permanently. The concept that a person could need continuous assistance to prevent relapse and regular monitoring to enable intervention should hyperglycemia recur is consistent with this information.

Diagnostic standards for Remission in T2DM

HbA1c, FPG, 2-hour plasma glucose following an oral glucose challenge, and mean daily glucose as assessed by continuous glucose monitoring (CGM) are examples of measurements frequently used for the diagnosis or glycemic treatment of T2D. As the primary defining marker, the committee preferred HbA1c below the existing cutoff of 6.5% (48 mmol/mol) for the initial diagnosis of diabetes and maintaining that level for at least three months without the continued use of the standard antihyperglycemic medications. Strict quality control measures must be in place for assays used to test HbA1c, and they must be standardized to meet standards that are in accordance with international reference values. ^{7,11,12,13}

Measurement of the 24 h mean glucose concentrations by CGM has been recommended as an alternative to HbA1c in situations when it may not be reliable. 14 The term "estimated HbA1c" (eA1C) or, more recently, "glucose management indicator" (GMI) refers to a glycated hemoglobin result that has been determined to be equal to the observed mean glucose by CGM. 15 The usage of CGM can be utilized to evaluate the relationship between mean glucose and HbA1c and detect patterns that fall beyond the typical range of normal in situations when the accuracy of HbA1c results is questionable. ^{16,17} In some instances, an FPG below 7.0 mmol/l (126 mg/dl) may be used as an alternative criterion for remission, just as a value over that level indicates active disease. The panel strongly supported the use of the HbA1c < 48 mmol/mol (6.5%) defining criterion as the most straightforward and commonly accepted defining criterion under typical conditions. In certain situations, an eA1C or GMI.8

Obesity Management and Diabetes Remission

Obesity is increasingly regarded as a condition that increases mortality and is linked to substantial morbidity. Type 2 diabetes is one of its primary metabolic consequences, as the two illnesses share important pathophysiological pathways. ¹⁸

Additionally, losing 5-10% of one's body weight is an effective means to prevent diabetes, even over the long term, and may significantly improve the lives of those who already have type 2 diabetes by lowering risk factors and improving measurements of

feeling and functioning. In fact, weight loss brought on by negative energy balance and the resulting weight loss has profound and complex impacts on a variety of physiological parameters that may bring about a remission of the type 2 diabetes disease process. It is widely established that weight increase is a major contributor of cardiometabolic comorbidities. Only recently has the relationship between weight loss and its significant improvements in these comorbidities been investigated and explained. ¹⁹

Clinically, it is well documented that individuals can enjoy glycemic and other health benefits with BMIs as low as 25 kg/m2 or even 30 kg/m2. ²⁰ A major study found that the liver and intraabdominal adipose tissue losses from weight loss are disproportionately larger. Total fat mass decreased by 10, 18, and 27%, intra-abdominal adipose tissue decreased by 9, 23, and 30%, and intrahepatic triglycerides decreased by 13, 52, and 65%, respectively, when total weight decreases of 5, 11, and 16% were included. This preferential loss of body fat from organs and storage locations that are known to be linked to harmful "lipotoxicity"—the proinflammatory and prothrombotic cytokines and other products of adipose tissue that drive cardiometabolic risk-could explain why improvements in cardiometabolic risk have been made without completely normalizing body fat stores. The study suggested that improvements in muscle, fat, and liver insulin sensitivity as well as beta cell activity can result from weight loss due to the elimination of visceral fat in the liver, muscles, and pancreas. These changes, achieved by a decrease in the lipotoxic effects of visceral adiposity, would be essential in bringing about the remission of type 2 diabetes. 21

PCOS and Diabetes Remission

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, which is characterized by irregular menstruation, infertility, hirsutism, and polycystic ovarian morphology (PCOM). In the long run, PCOS is more likely to cause complications like diabetes, cardiovascular disease, and endometrial cancer. Depending on the demographic investigated and the diagnostic criteria applied, the prevalence ranges from 6% to 21%. ²²

Metabolic disorders such as insulin resistance (IR) and ß-cell dysfunction is linked to PCOS. Hyperinsulinemia, which is the outcome of IR, is a key factor in the pathophysiology of excess androgen in PCOS. In fact, insulin functions as a cogonadotropin to augment theca cell androgen production caused by luteinizing hormone (LH) and can increase GnRH-mediated gonadotropin release. Additionally, insulin raises the number of bioavailable androgens by decreasing the synthesis of hepatic SHBG (sex hormone binding globulin). (Arianna and others, 2020) In comparison to control women of a comparable age and body composition, insulin action was lowered by 35-40% in both lean and obese women with PCOS. ²³

Up to 70% of PCOS patients with prediabetes will eventually develop type 2 diabetes (T2DM), with an estimated 30% to 40% of PCOS people having this condition. These patients have a higher risk of negative cardiovascular events because of their prediabetes. Additionally, early-pregnant women with PCOS and IGT are more likely to develop gestational diabetes. ²⁴

The Endocrine Society has recommended OGTT over A1C to detect prediabetes in PCOS patients because IGT (which can be missed by A1C) is specifically linked to an increased risk of cardiovascular disease in women, despite the fact that OGTT and A1C are equally suitable test options for prediabetes in the general population. (2002) Tao et al. Endocrine and reproductive problems can be restored to normal with an increase in insulin sensitivity. According to clinical evidence, PCOS women's endocrine and metabolic profiles may be improved by using insulin sensitizing medications such metformin (MET), inositols, and lifestyle changes. ²⁵

Therapies based on incretins are frequently utilized to treat T2DM. Exenatide (EX), a glucagon-like peptide (GLP)-1 analogue, increases beta cell insulin production in an oral glucose-dependent way to lower plasma glucose levels. They also result in reduced body weight and increased insulin sensitivity. When combined with MET, EX, or the DPP4 inhibitor sitagliptin, improves glycemic control and beta cell function in patients with type 2 diabetes in comparison to MET monotherapy. Chronic

inflammation linked to T2DM may be reduced by long-term EX and MET combination therapy, which may also enhance the adipocytokines profile. According to the results of a randomized controlled experiment, EX alone or in combination with MET is linked to a higher rate of prediabetes remission in patients when compared to MET monotherapy, EX alone or in combination with MET is associated with higher remission rate of prediabetes among patients with PCOS by improving postprandial insulin secretion. 24 The primary line of treatment for PCOS in women is lifestyle modification, which is not a substitute for medication management. For many years, one of the treatments for PCOS patients has included nutritional counselling. Strict calorie limitations, however, fail to provide the desired long-term results. In comparison to high GI (HGI) diets, low GI (LGI) diets reduced fasting insulin, total and low-density lipoprotein (LDL) cholesterol, triglycerides, waist circumference, and total testosterone. The LGI diet is an efficient, acceptable, safe solution for reducing IR. The study revealed that the majority of PCOS-affected women have an unbalanced diet with deficiencies in folic acid, vitamin C, vitamin B12, and vitamin D as well as fibre, omega 3, calcium, magnesium, and zinc. Sucrose, salt, total fats, saturated fatty acids, and cholesterol were all found to be in excess. However, adding supplements to the diet is a topic that must be discussed specifically with the patient regarding diet, and active participation and adherence are preferred for the overall improvement of the metabolic balance. The primary component of PCOS treatment should be a healthy diet and lifestyle. 2

Cardiovascular Disease and Diabetes Remission

About 90% of diabetes cases are T2DM, and cardiovascular (CV) events in people with T2DM are a key contributor to the increased risk of early death and have evolved into a growing danger to human health on a global scale. ²⁶ Diabetes mellitus type 2 (T2D) increases the risk of heart failure while tending to preserve the ejection fraction. Diabetes cardiomyopathy, a condition associated with T2D, manifests early in the course of the disease and advances covertly. Exercise intolerance is a predictive factor for type 2 diabetes and an early sign of heart failure. ²⁸

Ischemic heart disease, heart failure, stroke, coronary artery disease (CAD), and peripheral artery disease are the main cardiovascular illnesses (CVDs) linked to type 2 diabetes (T2DM), and these consequences can cause death in at least 50% of T2DM patients. 27 Insulin resistance and hyperglycemia, which are frequently but not always accompanied by impaired lipid metabolism, are characteristics of T2DM. Insulin resistance typically develops early in T2DM and CVD development. 29 Importantly, a larger relative risk of CV events is linked to insulin resistance. Furthermore, an excessive buildup of lipids may cause diastolic dysfunction, fibrosis, and insulin resistance in the heart. Also mentioned as a concern is hypoglycemia, which is commonly acknowledged as a negative side effect of glucose decline, has also been noted as a risk factor for CVD among patients with T2DM. To sum up, CVD linked to diabetes is a significant cause of death and disability among T2DM patients. 30

Concentrating on preventing CVD events in high-risk populations may lower mortality and the financial toll of heart attack and stroke. Controlling blood sugar, blood pressure, and cholesterol as well as making lifestyle changes including giving up smoking, eating well, and exercising more can prevent or delay CVD. Primary prevention entails preventing or delaying newly developing CVD in T2DM patients. Early diagnosis of T2DM in people without CVD and early detection of CVD-related risk factors in community-based high-risk groups are required. Treating risk factors in diabetics with established CVD is secondary prevention. ³⁰

Achieving type 2 diabetes remission is linked to a decreased risk of microvascular complications, especially in younger populations and those with fewer coexisting conditions. Targeted therapies that aim to boost remission in these populations may lessen the negative effects of microvascular problems and their related medical expenses. ³¹ Reduced cardiovascular events were observed after a median follow-up of 9.6 years in the Look AHEAD study among people who lost weight during the intensive lifestyle intervention. ³² Similarly, remission of T2D was linked in a cohort study to a reduction in cardiovascular risk factors, although

changes in heart structure and function or exercise capacity were not investigated. $^{\rm 33}$

Approaches for to achieving T2DM Remission

According to the available evidence, T2DM remission can be accomplished with lifestyle changes, physical activity, and bariatric surgery. The US Preventive Services Task Force's 2014 recommendations emphasize the necessity for nutritional counselling and physical activity for persons at risk of cardiovascular diseases (CVDs). ^{34,35}The American Heart Association (AHA) advises using behavior modification strategies to encourage lifestyle changes, such as goal setting and self-monitoring. ³⁶ The ADA advises sending high-risk diabetics to health programs that emphasize improving physical activity and weight loss. ³⁷

According to the available research, T2DM remission is possible with sufficiently drastic lifestyle changes.³³ Medical nutrition therapy (MNT) and a low-carbohydrate, low-calorie diet (LCD) are two lifestyle changes being investigated for the treatment of diabetes. Calorie restriction helps to restore normal levels of visceral fat, hepatic glucose output, beta cell function, particularly secretory capacity, and insulin sensitivity.^{38,39}

Medical nutrition therapy (MNT) is a supporting treatment that aids in setting objectives, prioritising tasks, and developing tailored action plans to encourage self-care in diabetics. Nutrition screening and referral, assessment, diagnosis, intervention, documentation, monitoring, evaluation, and outcome management systems are the MNT's constituent parts. It's vital to understand that MNT differs from diabetes self-management training and may need to be modified for ethnicity. 38,40 The Diabetes Remission Clinical Trial (DiRECT), which revealed that weight loss along with lifestyle management resulted in diabetes remission in 46% of study participants after one year, proved the efficacy of MNT in T2DM.4

Furthermore, long-term weight control requires consistent daily physical activity. For people with diabetes, the Nutrition Practise Guideline (NPG) suggests developing a personalized physical activity schedule. The recommendation is to engage in at least three days per week of moderate intensity aerobic physical activity (50-70% of maximal heart rate) for a total of 150 minutes without a break of more than two days. Additionally, it's crucial to advise against starting an abrupt workout regimen when you're trying to lose weight and to keep up your regular physical activity. 42,43

Bariatric Surgery and Type 2 Diabetes Mellitus

Achieving adequate glycemic control is a key component of standard T2DM treatment, which is primarily accomplished by medical management. This helps reduce cardiovascular and other risks. This medication, however, can be difficult for obese individuals because many pharmaceutical treatments might actually make them gain weight, which exacerbates their insulin resistance. Bariatric surgery is then used in this situation. Bariatric surgery has shown considerable impacts in reducing rates of T2DM in addition to improving cardiovascular health and lowering morbidity and mortality, despite being initially classified as a surgical procedure for weight loss. 44

With regard to the reversal of the metabolic imbalances causing overt T2DM, bariatric surgery appears to be promising because it addresses a number of complementary pathogenetic pathways. The goal of bariatric surgery has gradually changed from weight loss alone to improving cardiometabolic health, and the indications have been expanded to encompass those with a range of adiposity and poorly managed T2DM. ⁴⁵

The main contributing elements can be divided into those that are related to weight reduction and those that are independent of weight loss, even though from a clinical point of view it is not always practicable or necessary to distinguish between the different mechanisms of metabolic improvement after surgery. Losing weight consistently improves glycemic levels, which increases the likelihood that T2DM will go into remission. Results from the Diabetes Remission Clinical Trial (DiRECT), which incorporated lifestyle changes mostly consisting of strict dietary restriction and increased physical activity, serve as a stunning illustration of this idea. ⁴⁶

The observation that an improvement in glycemic indices can be noticed as soon as a few days after surgery, before any clinically

significant weight loss is achieved, suggests that there are metabolic improvement mechanisms following bariatric surgery that are independent of weight loss. Since it may help patients with T2DM normalize their plasma glucose levels, improve their beta cell activity, and increase their hepatic insulin sensitivity, acute severe calorie restriction in the post-operative period may partially account for these outcomes. ^{47,48} Additional factors having a potential impact in metabolic improvement following surgery without regard to weight reduction include changes to the gut bacteria and an increase in glucose absorption from the intestine. ⁴⁹

Cohort research among French people found that the rate of remission was 50% and the prevalence of relapse was very low. ⁵⁰ In general, bariatric surgery is regarded as a secure and reliable method of treating T2DM in those who are battling with obesity. Prior to any significant weight reduction, the effects can be observed rather quickly, demonstrating the interaction of hormonal factors that increases insulin sensitivity by activating pancreatic cells. The success of bariatric surgery in achieving diabetes remission has been demonstrated in a number of studies, including randomized clinical trials with 1, 3, 5, and even 10 years of follow-up. BPD-DS and RYGB have shown some evidence that certain bariatric surgery techniques are more successful than medication therapy for controlling T2DM. ^{51,52}

T2DM Remission as the Primary Treatment Objective

The paradigm for managing and treating diabetes has been continuously changing. The advent of concepts and practices including bariatric surgery, continuous glucose monitoring systems, and the scope of diabetes treatment are examples of how the methodologies for managing diabetes, measuring glycemia, and determining glycemic objectives have changed. Similar efforts have been made to evaluate the possibility of achieving diabetes remission using various modalities in actual clinical practice. As clinical evidence has steadily accumulated, expectations for achieving diabetic remission have increased. 53 Recent research found that short-term intense glucose-lowering medication, weight loss, specialized diets, and comprehensive lifestyle changes were all linked to the accomplishment of diabetes remission in up to 50% of individuals. Because of this, establishing diabetic remission is practicable and can be thought of as an alternative to conventional diabetes therapy. However, more clinical research and a thorough comprehension of the mechanisms producing diabetes remission with various approaches are needed. 38,54

Conclusion:

Diabetes mellitus has a serious negative impact on both health and finances worldwide. Despite being incurable, the field of diabetes care has embraced solutions like diabetes prevention, delaying the start and course of the disease, and remission or reversal. The growing number of clinical trials shows that the idea of T2DM remission has been on the rise for more than ten years. Although the definition of remission is unclear, efforts have been undertaken to accurately identify and measure remission in T2DM patients. The combination of bariatric surgery and lifestyle changes, such as dietary and exercise adjustments, is essential for establishing T2DM remission. To lose weight and improve their lifestyles, newly diagnosed T2DM patients should undergo formal nutritional counselling and lifestyle advice. One size does not fit all, and individualization needs to be taken into account, like many medical therapies. Population interventions are required but not yet widely accessible. These include education, dietary recommendations, and empowerment to make healthy food choices, such as clear food labelling.

Lasting remission is brought on by long-term maintenance of weight loss, however this is more challenging to accomplish than weight loss. The development and rigorous testing of strategies to best prevent weight regain over the long term in all groups is necessary. Population-based efforts are also necessary to promote better eating options and stop the current trend of excessive weight rise among both children and adults. To ascertain whether type 2 diabetes also lowers the incidence of vascular events and cancer linked to excess weight, long-term monitoring of those with the disease in remission is required.

Additionally, dietetics and other areas of diabetes care must fully embrace the potential of diet and nutrition to significantly

enhance glycemic control and result in remission. Then, this can be used to encourage persons with T2DM in reaching their goals and start a discussion about the possibility of T2DM remission.

References:

- International Diabetes Federation.IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org
- Goyal R, Jialal I. Type 2 Diabetes. [Updated 2023 May 8]. In: StatPearls [Internet]. StatPearls Publishing; 2023 Jan
- Al-Mrabeh, Ahmad. Pathogenesis and remission of type 2 diabetes: what has the twin cycle hypothesis taught us? Cardiovascular Endocrinology & Metabolism 9(4):p 132-142, December 2020.
- American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes—2019. Diabetes Care. 2019:4
- Kalra, S.; Singal, A.; Lathia, T. What's in a Name? Redefining Type 2 Diabetes Remission. Diabetes Ther. 2021, 12, 647-654
- McInnes, N.; Hall, S.; Sultan, F.; Aronson, R.; Hramiak, I.; Harris, S.; Sigal, R.J.; Woo, V.; Liu, Y.Y.; Gerstein, H.C. Remission of type 2 diabetes following a short-term intervention with insulin glargine, metformin, and dapagliflozin. J. Clin. Endocrinol. Metab. 2020, 105, dgaa248
- Taylor R. Pathogenesis of Type 2 diabetes: Tracing the reverse route from cure to cause. Diabetologia 2008; 51: 1781-9.
- Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, Rothberg AE, le Roux CW, Rubino F, Schauer P, Taylor R, Twenefour D. Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes. Diabetes Care. 2021 Aug 30;44(10):2438-44.
- Buse JB, Caprio S, Cefalu WT, et al. How do we define cure of diabetes? Diabetes Care 2009:32:2133-2135
- Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). Br J Diabetes 2019;19:73-76
- The American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation (2007) Consensus statement on the worldwide standardisation of the HbA1c measurement. Diabetologia 50:2042-2043.
- Jeppsson J-O, Kobold U, Barr J et al (2002) International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Approved IFCC reference method for the measurement of HbA1c in human blood. Clin Chem Lab Med 40:78-89.
- EurA1c Trial Group (2018) EurA1c: the European HbA1c trial to investigate the performance of HbA1c assays in 2166 laboratories across 17 countries and 24 manufacturers by use of the IFCC model for quality targets. Clin Chem 64:1183-1192.
- Danne T, Nimri R, Battelino T et al (2017) International consensus on use of continuous glucose monitoring. Diabetes Care 40:1631- 1640.
- Bergenstal RM, Beck RW, Close KL et al (2018) Glucose management indicator (GMI): a new term for estimating A1C from continuous glucose monitoring. Diabetes Care 41:2275-228
- Shah VN, DuBose SN, Li Z et al (2019) Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. J Clin Endocrinol Metab 104:4356-4364
- Beck RW, Connor CG, Mullen DM, Wesley DM, Bergenstal RM (2017) The fallacy of average: how using HbA1c alone to assess glycemic control can be misleading. Diabetes Care 40:994-999.

- Lingvay Ildiko, Sumithran Priya, Cohen Ricardo V, Le Rou Carel. 2022 .Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. The Lancet, Volume 399, Issue 10322, 394 - 405
- Donna H. Ryan; Energy Balance and Weight Loss for Diabetes Remission. Diabetes Spectr 1 May 2020; 33 (2): 117-124
- Ryan DH, Yockey SR. Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over. Curr Obes Rep 2017;6: 187-194
- Magkos F, Fraterrigo G, Yoshino J, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab. 2016; 23:591-601
- Shang Y, Zhou H, Hu M, Feng H. Effect of Diet on Insulin Resistance in Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2020 Oct 1;105(10):dgaa425. doi: 10.1210/clinem/dgaa425. PMID: 32621748.
- Dunaif, K. R. Segal, W. Futterweit, and A. Dobrjansky, "Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome," Diabetes, vol. 38, no. 9, pp. 1165-1174, 1989
- Tao T, Zhang Y, Zhu YC, Fu JR, Wang YY, Cai J, Ma JY, Xu Y, Gao YN, Sun Y, Fan W, Liu W. Exenatide, Metformin, or Both for Prediabetes in PCOS: A Randomized, Open-label, Parallel-group Controlled Study. J Clin Endocrinol Metab. 2021 Mar 8;106(3):e1420-e1432.
- Arianna Pani, Ilaria Gironi, Giacoma Di Vieste, Elena Mion, Federico Bertuzzi, and Basilio Pintaud. From Prediabetes to Type 2 Diabetes Mellitus in Women with Polycystic Ovary Syndrome: Lifestyle and Pharmacological Management. International Journal of Endocrinology, Hindawi, 2020, 1687-8337
- Szczuko M, Kikut J, Szczuko U, Szydłowska I, Nawrocka-Rutkowska J, Ziętek M, Verbanac D, Saso L. Nutrition Strategy and Life Style in Polycystic Ovary Syndrome-Narrative Review. Nutrients. 2021 Jul 18;13(7):2452
- Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):83-83.
- Bilak JM, Yeo JL, Gulsin GS, Marsh AM, Sian M, Dattani A, Ayton SL, Parke KS, Bain M, Pang W, Boulos S, Pierre TGS, Davies MJ, Yates T, McCann GP, Brady EM. Impact of the Remission of Type 2 Diabetes on Cardiovascular Structure and Function, Exercise Capacity and Risk Profile: A Propensity Matched Analysis. J Cardiovasc Dev Dis. 2023 Apr 24;10(5):191.
- James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol. 2021.
- Ma, CX., Ma, XN., Guan, CH. et al. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovasc Diabetol 21, 74 (2022).
- Hounkpatin H, Stuart B, Farmer A, Dambha-Miller H. Association of type 2 diabetes remission and risk of cardiovascular disease in pre-defined subgroups. Endocrinol Diabetes Metab. 2021 Jun 19;4(3)
- Baum A, Scarpa J, Bruzelius E, Tamler R, Basu S, Faghmous J. Targeting weight loss interventions to reduce cardiovascular complications of type 2 diabetes: a machine learning-based post-hoc analysis of heterogeneous treatment effects in the Look AHEAD trial. Lancet Diabet Endocrinol. 2017;5(10):808-815
- Dambha-Miller H., Day A., Strelitz J., Irving G., Griffin S. Behaviour change, weight loss and remission of Type 2 diabetes: A community-based prospective cohort study. Diabet. Med. 2020;37:681-688.
- Kelly, J.; Karlsen, M.; Steinke, G. Type 2 Diabetes Remission and Lifestyle Medicine: A Position Statement

- from the American College of Lifestyle Medicine. Am. J. Lifestyle Med. 2020, 14, 406-419.
- LeFevre, M.L. U.S. Preventive Services Task Force. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: U.S. Preventive Services Task Force Recommendation Statement. Ann. Intern. Med. 2014, 161, 587-593.
- Artinian, N.T.; Fletcher, G.F.; Mozaffarian, D.; Kris-Etherton, P.; Horn, L.V.; Lichtenstein, A.H.; Kumanyika, S. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: A scientific statement from the American Heart Association.
- American Diabetes Association. Standards of Medical Care in Diabetes-2015. Diabetes Care 2015, 38, s1-s93
- Kalra S, Bantwal G, Kapoor N, Sahay R, Bhattacharya S, Anne B, Gopal RA, Kota S, Kumar A, Joshi A, Sanyal D, Tiwaskar M, Das AK. Quantifying Remission Probability in Type 2 Diabetes Mellitus. Clin Pract. 2021 Nov 9;11(4):850-859. doi: 10.3390/clinpract11040100. PMID: 34842637; PMCID: PMC8628725.
- Bhatt, A.A.; Choudhari, P.K.; Mahajan, R.R.; Sayyad, M.G.; Pratyush, D.D.; Hasan, I. Effect of a Low-Calorie Diet on Restoration of Normoglycemia in Obese subjects with Type 2 Diabetes. Indian J. Endocrinol. Metab. 2017, 21, 776-780.
- Kelly, J.; Karlsen, M.; Steinke, G. Type 2 Diabetes Remission and Lifestyle Medicine: A Position Statement from the American College of Lifestyle Medicine. Am. J. Lifestyle Med. 2020, 14, 406-419
- Lean, M.E.; Leslie, W.S.; Barnes, A.C.; Brosnahan, N.; Thom, G.; Mc Combie, L.; Peters, C. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. Lancet 2018, 391, 541-551.
- Taylor, R.; Barnes, A.C. Can type 2 diabetes be reversed and how can this best be achieved? James Lind Alliance research priority number one. Diabet. Med. 2019, 36, 308-315
- Franz, M.J.; MacLeod, J.; Evert, A.; Brown, C.; Gradwell, E. Academy of Nutrition and Dietetics Nutrition Practice Guideline for Type 1 and Type 2 Diabetes in Adults: Systematic Review of Evidence for Medical Nutrition Therapy Effectiveness and Recommendations for Integration into the Nutrition Care Process. J. Acad. Nutr. Diet. 2017, 117, 1659-1679
- Courcoulas AP, Gallagher JW, Neiberg RH, Eagleton EB, DeLany JP, Lang W, Punchai S, Gourash W, Jakicic JM. Bariatric Surgery vs Lifestyle Intervention for Diabetes

- Treatment: 5-Year Outcomes From a Randomized Trial. J Clin Endocrinol Metab. 2020 Mar 1;105(3):866-76.
- Rubino F., Nathan D.M., Eckel R.H., Schauer P.R., Alberti K.G., Zimmet P.Z., Del Prato S., Ji L., Sadikot S.M., Herman W.H., et al. Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations. Diabetes Care. 2016;39:861-877
- Tsilingiris D, Koliaki C, Kokkinos A. Remission of Type 2
 Diabetes Mellitus after Bariatric Surgery: Fact or
 Fiction? Int J Environ Res Public Health. 2019 Aug
 30;16(17):3171.
- Lean M.E., Leslie W.S., Barnes A.C., Brosnahan N., Thom G., McCombie L., Peters C., Zhyzhneuskaya S., Al-Mrabeh A., Hollingsworth K.G., et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. Lancet. 2018;391:541-551.
- Lim E.L., Hollingsworth K.G., Aribisala B.S., Chen M.J., Mathers J.C., Taylor R. Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54:2506-2514.
- Jackness C., Karmally W., Febres G., Conwell I.M., Ahmed L., Bessler M., McMahon D.J., Korner J. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and betacell Function in type 2 diabetic patients. Diabetes. 2013
- Chondronikola M., Harris L.L., Klein S. Bariatric surgery and type 2 diabetes: Are there weight loss-independent therapeutic effects of upper gastrointestinal bypass? J. Intern. Med. 2016;280:476-486.
- Conte C, Lapeyre-Mestre M, Hanaire H, Ritz P. Diabetes Remission and Relapse After Bariatric Surgery: a Nationwide Population-Based Study. Obes Surg. 2020 Dec;30(12):4810-4820. doi: 10.1007/s11695-020-04924-3. Epub 2020 Aug 31.
- Chumakova-Orin M, Vanetta C, Moris DP, Guerron AD. Diabetes remission after bariatric surgery. World J Diabetes. 2021 Jul 15;12(7):1093-1101
- Kalra, S.; Singal, A.; Lathia, T. What's in a Name? Redefining Type 2 Diabetes Remission. Diabetes Ther. 2021, 12, 647-654
- McInnes, N.; Hall, S.; Sultan, F.; Aronson, R.; Hramiak, I.; Harris, S.; Sigal, R.J.; Woo, V.; Liu, Y.Y.; Gerstein, H.C. Remission of type 2 diabetes following a short-term intervention with insulin glargine, metformin, and dapagliflozin. J. Clin. Endocrinol. Metab. 2020, 105, dgaa248