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# REMISSION IN DIABETES MELLITUS – A MINI REVIEW OF LITERATURE

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In 2019 *International Diabetes Federation*s aid that 463.000.000 adults and 1.100.000 children and adolescent will live with diabetes. Predictions of the same organization for the year 2030 was 578 million adults with diabetes and 700.000.000 by 2045. As a result of diabetes complications, the same organization estimates that 4.2 million adults will die in 2019. Early identification of all of diabetes (no matter of type) and its complications but also strategies for the remission of affection are considered. Partial or complete remission in diabetes is a desiderate that can reduce the cost of hypoglycemic medication, complications characteristic of the condition and improve the QoL. In the case of T1DM contrary to the efforts made the results of remission are evasive. More promising results have been published on bariatric surgery, a method that is recommended for obese patients with T2DM. More research is needed for obtaining a prolonged remission in diabetic patients.

*Keywords*: diabetes remission, bariatric surgery.

## INTRODUCTION

In 2019 International Diabetes Federation (IDF) published the 9th edition of the Diabetes Atlas which mentions that a percentage of 9.3 from the adults between 20–79 years (463.000.000 adults) have with diabetes. More than 1.100.000 youngsters have type 1 diabetes (T1DM). Predictions of the same organization for the year 2030 was 578 million people over 18 will have diabetes and 700.000.000 by 2045. IDF estimates that 4.200.000 people over 18 will die because of complications created by diabetes in 2019. Direct costs estimates are 760 billion dollars and indirect costs give 35% supplement to the annual global health expenditures associated with diabetes[1]. Obtaining a prolonged remission of this condition would allow to reduce the costs associated with the medication, but also other benefits that will be presented later[2].

In 2009 a group of experts in pediatrics and adult endocrinology, diabetes, metabolism, bariatric and metabolic surgery, hematology–oncology and transplantation agreed the following definition of remission in diabetes:

1. ***"Partial remission: hyperglycemia below diagnostic thresholds for diabetes, at least 1 year's duration, no active pharmacologic therapy or ongoing procedures;***
2. ***Complete remission: normal glycemic measures, at least 1 year's duration, no active pharmacologic therapy or ongoing procedures;***
3. ***Prolonged remission: complete remission of at least 5 year's duration [3]".***

To mention that the definitions apply to both T1DM and type 2 diabetes mellitus (T2DM).

## REMISSION IN T1DM

In newly diagnosed T1DM patients, after insulin therapy initiation, some patients have shown reduced insulin requirement due to temporary recovery of the function of beta cell along with the recovery of insulin sensitivity[4]. Most of the patients could drastically reduce the amount of exogenous insulin compared to prior dose. Complete remission is however extremely rare[5].

In children with T1DM the remission rates vary between 30 and 80% that partly reflects the inconsistency of the definition use. The rate,

duration and factors involved in the occurrence and duration of partial remission defined as a period with insulin requirement less than 0.5 U/kg body weight/day and a level of HbA1≤ 6% were studied by Abdul-Rasoul M and co-workers in 103 youngsters with diabetes (≤ 12). Partial remission was reported in 71 children and complete remission in 3 children. The duration of remission was 7.2 ± 4.8 months. Young age (under 5 years of age) concluded that high severity of the disease was associated with a lower rate of remission[6]. Bonfanti R *et al.* investigated spontaneous clinical remission in 215 youngsters with T1DM. Spontaneous partial clinical remission has been defined as HbA1c in normal ranges and insulin dose ≤0.3 U/kg body weight/day. The results of a study highlighted that remission occurred in 11% of patients at 3 months of follow-up, 8% patients at 6 months and 5% patients at 12 months; remission was more prevalent in older patients[7]. In 2009 Mortensen Hb *et al* have issued a new definition of the partial remission in children and adolescents with T1DM. The partial remission has been defined by insulin dose-adjusted HbA1c (IDAA1c) respectively HbA1c + 4 × insulin dose in U/kg body weight/day; a value of ≤ 9 imply a partial remission[8]; this definition is correlated with a level of stimulated C-peptide >300 pmol/l and it was been used also other trials[9, 10]. The rates of partial remission defined by IDDAA1c ≤ 9 was evaluated in 3657 youngsters with new-onset T1DM. Partial remission occurred in 71% patients with a median duration of 9 months. The children aged > 5 years had twice the change to develop partial remission compared to children<5 years[11]. Pecheur A and collaborators evaluated the characteristics and determinants of partial remission in 252 children with T1DM aged 0.9 to 16.4 years. The prevalence of partial remission defined by IDDAA1c ≤ 9 occurred in 56.2% of patients with T1DM without any case of complete remission[12]. A retrospective study led by Lundberg RL analysed the partial remission in 204 patients with T1DM of ages 2–14 years and compared the accuracy of total daily dose of insulin of less than 0.3 U/kg body weight/day to the gold standard IDDAA1c ≤ 9 for the detection of partial remission. The results of a study showed that the prevalence of partial remission was 42.2% by IDDAA1c ≤ 9 criterion and 40.2 by total daily dose of insulin of less than 0.3 U/kg body weight/day. There were no significant statistical differences in the parameters followed between the two evaluations[13]. Relation between age of onset of T1DM, sex and rate of remission is controversial. Abdul-Rasoul M, Bowden SA and collaborators notices that partial remission was higher in children with age over 5 years compared with under 5 years of age[6, 14]. Pubertal patients with T1DM had a low rate of partial remission[14, 15]. In contrast, results of an other studies noted that there is no correlation between rate of remission and age of onset of T1DMin children[12,16]. Relation between sex and rate of remission has been studied in multiple studies. Some studies showed no relation[17,18] but Schiffrein A and collaborators reported that girls may have better remission rates compared with boys[19] and Pollizzi P *et al.* mentioned that males have increased remission rates compared to female[20].

In the adult population incidence of partial remission ranged between 3% to 61% and complete remission was found to be more common than in the children[4]. Clinical remission in adult patients with T1DM and factors that were correlated with remission rates have been analysed in numerous studies. Agner T and co-workers evaluated the clinical remission in 268 adults patients with T1DM; partial remission was interpreted as insulin dose less than or equal to 50% of the insulin dose of the insulin dose from at discharge from the hospital and total remission as complete discontinuation of insulin therapy for at least 1 week under optimal metabolic control. During the first months of the disease 12.3% entered total remission and 18.3% partial remission. The authors suggest that relatively higher basal C peptide levels were positively correlated with remission rates[21]. Martin S *et al.* showed that higher rates of spontaneous remission is present in the first year after diagnosis and preserved beta-cell function predicts remission[22]. The results of a study published in 1999 by Schölin Aand co-workers, in which they analysed the course of clinical remission in adult patients with T1DM showed that 61% of the patients entered remission (interpreted asHbA1c ≤ 6.5% and an insulin dosage ≤ 0.4 U/kgbody weight/day for a minimum of 1 month) and concluded than "*In most adult patients with new onset of type 1 diabetes remission is induced when using multiple insulin injection therapy. Male patients seem particularly prone to remission, and the length and extent of beta-cell strain prior to diagnosis strongly influences its course*"[23].

Several agents have been studied to change the evolution of T1DM. In 2009 Rewers M and

Gottlieb P published in *Diabetes Care* a review article of interventions in primary, secondary and tertiary prevention of T1DM[24]. Primary prevention is addressed to the kids with high concentrations of human leukocyte antigen-HLA-DR, DQ genotypes and refers to elimination of the environmental triggers (nutritional such cow's milk or gluten, toxins and infectious agents). The Trial to Reduce T1DM in the Genetically at Risk (TRIG) is an international randomized double-blind controlled intervention that had compared the effects of casein hydrolysate with a conventional cow's milk in infancy with genetic disease susceptibility. 2159 infants from 2002 to 2007 in 78 study centers were recruited and the follow-up ended in 2017. The results were presented in 2018 and the authors concluded than "*Among infants at risk for type 1 diabetes, weaning to a hydrolysed formula compared with a conventional formula did not reduce the cumulative incidence of type 1 diabetes after median follow-up for 11.5 years. These findings do not support a need to revise the dietary recommendations for infants at risk for type 1 diabetes*"[25,26]. The BABYDIET was a pilot trial that assessed the effect of late begin of dietary gluten on the occurrence of islet autoimmunity on children at risk with T1DM. The results of the study suggest that delayed gluten exposure until the age of 1 year did not substantially reduce the risk for islet autoimmunity to these subjects[27]. Supplementation of vitamin D in the first years of childhood has been proposed as a possible solution in the prophylaxis measure[28,29]. Secondary prevention addresses to the preclinical period in order to avoid progression in clinical diabetes. Randomized trials and a cohort study have shown that mild asymptomatic hyperglycemia may precede by months/years overt insulin dependence among subjects with islet autoantibodies[30-32]. Large prophylactic trials have shown no benefits on the rhythm of progression to active diabetes for insulin administered orally/intranasal/parenterally as well as for oral nicotinamide[33–36]. The goal of tertiary prophylaxis T1DM is the maintenance of some insulin secretion to stimulate and maintain partial remission. There have been numerous trials and clinical studies aimed at preserving insulin secretion and/or getting remission in patients with T1DM using: antigen-specific vaccines, systemic immunomodulators, islet regeneration but contrary to the efforts made in prevention of T1DM the results are elusive[24].

## REMISSION IN T2DM

Primary prevention of T2DM require early implementation actions. Obesity (BMI over 30 kg/m$^2$), being major risk factor for stepping from normal glucose tolerance to prediabetes to diabetes**,** is clearly proven that if it is well managed can delay the evolution from prediabetes toT2DM[37–39]. The American Diabetes Association (ADA) recommended in 2020 the following measures on the management of obesity as treatment for hyperglycemia in T2DM: lifestyle strategies, pharmacotherapy and metabolic surgery[40]. Lifestyle intervention for weight control imposes the following measures: diets and physical activity. The loss of weight can be obtained using personalized programs results in a 500–750 kcal/day energy deficit, usually meaning a 1.200–1.500 kcal/day for women and 1.500–1.800 kcal/day for men. Using a the methods of systematic review and meta-analysis Franz MJ et al had published in 2015 the findings from randomized clinical trials related with weight loss programs for overweight and obese adults with T2DM concluded that weight loss of 5% is the minimum required for clinical benefits[41]. On the May 2019 the 2-year result of the Diabetes Remission Clinical Trial (DiRECT) have been published in *The Lancet-Diabetes & Endocrinology*. DiRECT is an open-label, cluster-randomized controlled trial is an open-label, cluster-randomized, controlled trial who investigated whether the offering of an intensive program for weight loss and weight loss maintenance would be advantageous for patients with T2DM. At 1 year 46% of 149 patients were in remission (meaning a HbA1c $\leq$ 6.5% after the diabetic drugs were stopped at baseline) and 24% has obtained a minimum of 15 kg weight decrease. At 2 year the program sustained remission for more than a third of patients with T2DM[42]. Sustainable weigh loss was analysed by Steven S and co-workers in a prospective, longitudinal study comprised tree phases: very low-calorie program for 8 weeks, return to isocaloric status of normal food for 2 weeks and an individualized weight control lifestyle for 6 months. A small number of patients with T2DM (30) were included in this study. The results of a study highlighted that remission occurred in 40% of patients and authors concluded than "*T2DM is a potentially reversible condition*"[43]. An observational analysis of a 4-year randomized controlled trial comparing an intensive lifestyle and education control among 2241 overweight

adult with T2DM with 2262 diabetic support and education control highlighted that intensive intervention was associated with a greater likelihood of partial remission of T2DM but the absolute remission rates were modest[44]. In contrast Ried-Larsom M *et al.* after analysing whether an intensive lifestyle intervention induced partial or complete remission in patients with T2DM mention that no significant statistical differences were observed between the control group and the standard care group[45] and similar results were also mentioned by Karter A Jand co-workers[46]. ADA recommended the following pharmacological treatment of obesity associated with T2DM: "*phentermine for short-term use and lipase inhibitor, selective serotonin (5-HT) 5-HT2C receptor agonist, sympathomimetic amine anorectic/ antiepileptic combination, opioid antagonist/ antidepressant combination, glucagon-like peptide 1 receptor agonist for long-term use*"[40]. The same association mentions that "*Metabolic surgery may be considered as an option for adults with type 2 diabetes and BMI 30.0–34.9 kg/m$^2$ (27.5–32.4 kg/m$^2$ in Asian Americans) who do not achieve durable weight loss and improvement in comorbidities (including hyperglycemia) with tested efficacious nonsurgical methods*"[40]. Several gastrointestinal operations promote long term weight loss and benefits on the control of T2DM in patients[40]. The two major surgery interventions are gastric restrictive (laparoscopic adjustable gastric banding, sleeve gastrectomy) and intestinal bypass (Roux-en-Y gastric bypass, biliopancreatic diversion) procedures[47]. First procedure involves limiting gastric volume, restrict of intake calories by inducing satiety; by this method it is estimated that patients lose 10–20% of their total body weight[47]. Dixon JB and collaborators followed 60 obese patients recently diagnosed with T2DM to determine if surgical treatment (laparoscopic adjustable gastric banding) induced better remission than conventional therapy. The remission of T2DM defined as fasting glucose level < 126 mg/dL and HbA1c < 6.2% while no taking pharmacologic therapy was achieved in 22 patients (73%)in the control group (30 patients) and 4 patients (13%) in the control group[48]. The effect of laparoscopic sleeve gastrectomy was assessed by Aminian A *et al* in 134 T2DM patients with obesity. The results of the study highlight that diabetes remission defined as HbA1c < 6.2% off medication was achieved in 26%situations, complete remission (HbA1c < 6.2% off medication) in 11% of subjects and continuous complete remission for more than 5 years in 3% of patients[49]. Vidal J. and co-workers reported that sleeve gastrectomy is effective in determining remission of T2DM also suggesting that the intervention represent an integrated strategy for the management of diabetes in obese patients[50]. A meta-analysis that looked on the efficacy of adjustable gastric banding compared with the laparoscopic sleeve gastrectomy published in 2019 by Li L. *et al.*, highlights that the second procedure is a more effective than first procedure, contributing to more weight loss and higher rates of T2DM remission. The highest concentrations of ghrelin (the only gastrointestinal hormone that stimulates food intake) are located in the gastric fundus and secretion is stopped if this area is removed due to the sleeve gastrectomy[51]. Roux-en-Y gastric bypass and sleeve gastrectomy are similar in reducing the gastric volume however only first procedure does a bypass of the duodenum and the proximal small intestine which allows an increased speed in the delivery of the food who was not digested into the small intestine with increased of the hormone glucagon-like peptide-1. A systematic review and meta-analysis of randomized controlled trials about the effect of Roux-en-Y gastric bypass and sleeve gastrectomy on remission of T2DM was published earlier this year, with the authors concluding that first procedure resulted in an increased rate of T2DM remission after 1 year in comparison with the other procedure; in studies with medium-term follow-up (2 to 5 years) there were no differences in the number of T2DM remissions between the two procedures [52]. In contrast in a meta-analysis of the medium & long-term effects of the two procedures published in 2020 Gu L. and collaborators concluded that in terms of the long-term effects of bariatric surgery the effect of Roux-en-Y gastric bypass was better than of sleeve gastrectomy[53]. Biliopancreatic diversion is a surgical intervention which results in a partial gastrectomy and a bypass of the longer segment of the small bowel resulting in malabsorption[54]. Regarding the benefits of different surgery procedures on T2DM including potential remission, Tsilingiris Dand co-workers state in a review published in 2019 that the most efficacious surgery interventions are in the following order: biliopancreatic diversion, Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding[55]. Some studies have shown that bariatric surgery reduce micro- and macrovascular complication and cardiovascular risk and improvement on quality of life[56–58]. The following

factors were correlates with an increased chance of diabetes remission and decreased risk of weight regain: age, duration of diabetes, non-use of insulin, maintenance of weight loss[40].

## CONCLUSION

Partial or complete remission in diabetes is a desiderate that can reduce the cost of hypoglycemic medication, complications characteristic of the condition and improve the QoL. In the case of T1DM contrary to the efforts made the results of remission are evasive. More promising results have been published on bariatric surgery, a method that is recommended for obese patients with T2DM. More research is needed for obtaining a prolonged remission in diabetic patients.

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