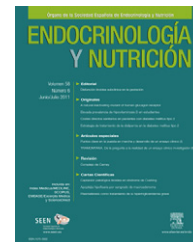




ENDOCRINOLOGÍA Y NUTRICIÓN

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EDITORIAL

Breaking therapeutic inertia: Should metabolic surgery be considered one more option for the treatment of type 2 diabetes mellitus? ☆

Rompiendo la inercia terapéutica: ¿debe considerarse la cirugía metabólica una opción más en el tratamiento de la diabetes mellitus tipo 2?

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Obesity and type 2 diabetes mellitus (T2DM) are uncontrolled health problems that have highly significant financial costs. They have reached epidemic proportions worldwide. It is estimated that there are currently 285 million people with T2DM throughout the world, and up to 438 million may be affected in 2030 if the most recent forecasts are met.¹ In Spain, T2DM prevalence is 13.8% according to the results of the di@bet.es study,² while the prevalence of obesity is 22.9%.³ Bariatric surgery, whose main objective is weight loss, is the most effective treatment for morbid obesity (body mass index [BMI] of 40 kg/m² or higher, or 30–40 kg/m² or higher in patients with obesity-related morbidity), which shows the limitations of the medical approach to this condition.⁴ Moreover, weight reduction achieved after surgery is associated with benefits regarding blood pressure, lipid profile, sleep apnea syndrome, and T2DM. Part of this metabolic improvement is considered to be independent of weight loss, and is related to its effect on levels of incretins and other hormones, and also with neural changes.^{5,6} Thus, bariatric surgery achieves remission of T2DM (fasting plasma blood glucose less than 126 mg/mL with no need for drug treatment) in 72% and

82% of patients after two years of follow-up, in up to 62% of patients in studies with follow-up longer than two years after surgery, and in 36% at 10 years.^{4,7} This remission is inversely related to T2DM duration, the degree of pancreatic reserve and insulin treatment, and more marked with mal-absorptive procedures such as biliopancreatic diversion and lower when restrictive procedures are used.⁸ In addition, bariatric surgery also decreases the specific mortality associated with T2DM.⁹ It should also be noted that, after 10 years of follow-up, the Swedish Obese Subjects Study reported an 8% incidence of T2DM in patients undergoing surgery (of whom 95% underwent merely restrictive procedures such as gastric banding and ring vertical gastropasty), as compared to a 25% incidence in non-operated obese subjects.⁴ However, only three randomized, prospective clinical trials assessing the role of surgery as compared to drug treatment have been reported to date.^{10,12} In the first of these trials, published in 2008, Dixon et al.¹⁰ assessed the effect of adjustable gastric band in a group of 60 patients with diabetes starting less than two years earlier and BMI ranging from 30 to 40 kg/m². At two years of follow-up, diabetes remission was maintained in 73% vs 13% of patients in the surgical and non-surgical groups respectively.¹⁰ In the second study, reported in March 2012, Shauer et al. compared drug treatment (n = 50) to Roux-en-Y gastric bypass (n = 50) and sleeve gastrectomy (n = 50) in 150 diabetic patients with BMI ranging from 27 to 43 kg/m² (34% with BMI less than 35 kg/m²), chronic poor metabolic control (hemoglobin A1c values ranging from 8.9% to 9.5%), diabetes onset eight or more years before, and treated with a mean of three hypoglycemic drugs (44% with insulin).¹¹ At 12 months of

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◇ The members of the Obesity Working Group of the Spanish Society of Endocrinology and Nutrition are included in Appendix A.

follow-up, 12% of patients assigned drug treatment achieved the primary endpoint of the study (hemoglobin A1c of 6% or less, with or without drug treatment), as compared to 42% in the group undergoing gastric bypass, or 37% in those undergoing sleeve gastrectomy. No significant differences were seen between the two surgical groups with regard to this goal, but it should be noted that no patients undergoing bypass required drug treatment to achieve it, while 28% of patients who underwent sleeve gastrectomy needed drug treatment. In the third study, published in the same issue of the *New England Journal of Medicine*, Mingrone et al.¹² assessed, after two years of follow-up, the rate of remission (defined in this case as blood glucose less than 100 mg/dL and hemoglobin A1c less than 6.5% without drug treatment) in 60 diabetic patients with an intermediate profile as compared to the prior two studies: BMI higher than 35 kg/m², hemoglobin A1c of 7.0% or higher, and diabetes for longer than five years. Patients were randomized to drug treatment (n = 20), Roux-en-Y gastric bypass (n = 20), or biliopancreatic diversion (n = 20). At two years of follow-up, no patient in the first group reached the remission criterion, while 75% of patients in the bypass group and 95% of those in the biliopancreatic diversion achieved the remission criterion.

Thus, two of the most relevant current questions in the field of endocrinology include (a) whether bariatric surgery controls T2DM in a much higher proportion of patients as compared to drug treatment, and if these results are better the shorter the duration of T2DM, why we do not propose surgery to obese patients with poorly controlled T2DM in an early stage of the course of their disease; and (b) why we still restrict the surgical treatment of diabetes to subjects with a BMI of 35 kg/m² or higher, excluding those with a lower degree of obesity who could also benefit from the procedure.

Various studies support the possibility of metabolic surgery (surgery mainly intended to achieve control in T2DM and other metabolic diseases) being considered a valid treatment for T2DM in patients with a BMI less than 35 kg/m². The results of the three most recent studies are worth discussing. The Scopinaro et al.¹³ group compared the effect of biliopancreatic diversion in 30 patients with T2DM for longer than three years, hemoglobin A1c levels of 7.5% or higher, and C peptide levels higher than 0.5 ng/mL. Fifteen patients had BMI ranging from 30 to 35 kg/m², and the other 15 patients had BMI values ranging from 25 to 30 kg/m². After two years of follow-up, a clear benefit was seen in glucose control, but this was less marked in overweight patients (67% and 47% respectively of patients in the first and second groups had hemoglobin A1c less than 6.5%). No excess weight loss occurred. de Sa et al.,¹⁴ in a retrospective, observational study where 27 diabetic patients with BMI ranging from 25 to 30 kg/m² and hemoglobin A1c levels of $8.36 \pm 2.05\%$ underwent Roux-en-Y gastric bypass, found complete remission in 48% of patients at 20 months, with a final hemoglobin A1c value of 5.97 ± 0.74 . Finally, Serrot et al.¹⁵ reported that in 17 diabetic patients with BMI > 35 kg/m², hemoglobin A1c decreased from 8.2 ± 2.0 to $6.1 \pm 2.7\%$ 12 months after Roux-en-Y gastric bypass, while BMI stabilized at 25.8 ± 2.5 kg/m². There are currently ongoing at least 11 randomized clinical trials registered in the US National Institutes of Health (clinicaltrials.gov) comparing several surgical procedures to

medical treatment in patients with T2DM and BMI ranging from 27 to 43 kg/m².¹⁶

What then is the place and time for metabolic surgery in the treatment of T2DM? A scientific society has positioned itself for the first time by including the surgical option in the treatment algorithm for T2DM in patients with BMI less than 35 kg/m², and not specifically in the very late stages of the disease. Thus, the International Diabetes Federation thinks that patients with T2DM with BMI ranging from 30 to 35 kg/m² should be considered candidates for surgical treatment if they have hemoglobin A1c values higher than 7.5% despite optimal drug treatment, particularly if they have progressive weight increase or other comorbidities (high blood pressure, hyperlipoproteinemia, or sleep apnea syndrome), or if the therapeutic goals recommended with conventional treatment have not been achieved.¹⁷ As regards the type of surgery, well standardized procedures for which adequate experience is available, such as Roux-en-Y gastric bypass, adjustable gastric band, and biliopancreatic diversion are recommended.

In this regard, and based on all of the foregoing, the position taken by the Obesity Working Group of the SEEN agrees with the treatment algorithm proposed by the International Diabetes Federation: in the treatment of T2DM, metabolic surgery cannot be considered as the final possible treatment option, or reserved for patients with higher BMI values only. In fact, we think that treatment of T2DM with metabolic surgery should not merely be guided by a given BMI value, but by metabolic changes in patients and their degree of control, and that these should be the main determinant factors for selecting bariatric surgery as the preferred option.¹⁸ It should not be forgotten that surgery must always be performed at hospitals with recognized surgical experience and having a multidisciplinary medical team able to provide adequate follow-up to diabetic patients for whom the surgical option has been proposed, thus minimizing the risks inherent in surgery. The medical and financial impact of this recommendation may eventually be very significant, as 6–8% of the Spanish population could be candidates for metabolic surgery, so this should not be indiscriminately performed on any diabetic patient with excess adiposity. However, just because of the low number of subjects unevenly evaluated in the available studies we definitely advocate the promotion of funding and the start of prospective, controlled, randomized clinical trials in Spain that will not only allow us to establish the safety, efficacy, and cost-effectiveness of surgery in diabetic patients with BMI less than 35 kg/m² but, above all, will also help us to better define which diabetic patients, regardless of their BMI, are the best candidates for surgery instead of drug treatment.

Appendix 1.

Members of the Obesity Working Group of the Spanish Society of Endocrinology and Nutrition (GOSEEN): José Arrizabalaga, Irene Bretón, Bartolomé Burguera, Assumpta Caixàs, Alfonso Calañas, Fernando Cordido, María Jesús Díaz, Pedro Pablo García-Luna, Albert Goday, Paloma Iglesias, Albert Lecube, Lluís Masmiquel, Susana Monereo, José Moreira, Basilio Moreno, María José Morales, Miguel Ángel Rubio, Josep Vidal, and Núria Vilarrasa.

References

1. Shawn JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010;87:4–14.
2. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: di@bet.es Study. *Diabetologia.* 2012;55:88–93.
3. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008–2010: the ENRICA Study. *Obes Rev.* 2012;4:388–92.
4. Sjöstrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* 2004;351:2683–93.
5. Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. *Cochrane Database Syst Rev.* 2009;CD003641.
6. Rubino F, R'Bibo SL, del Genio F, Mazumdar M, McGraw TE. Metabolic surgery: the role of the gastrointestinal tract in diabetes mellitus. *Nat Rev Endocrinol.* 2010;6:102–9.
7. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med.* 2009;122:248–56.
8. Schauer PR, Ikramuddin S, Gourasch W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Ann Surg.* 2000;232:515–29.
9. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753–61.
10. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *J Am Med Assoc.* 2008;299:316–23.
11. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP, Pothier CE et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med.* 2012 March 26 [Epub ahead of print].
12. Mingrone G, Panunzi S, DeGaetano A, Guidone C, Iaiconelli A, Leccesi L, et al. Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. *N Engl J Med.* 2012 March 26 [Epub ahead of print].
13. Scopinaro N, Adami GF, Papadia FS, Camerini G, Carlini F, Briatore L, et al. The effects of biliopancreatic diversion on type 2 diabetes mellitus in patients with mild obesity (BMI 30–35 kg/m²) and simple overweight (BMI 25–30 kg/m²): a prospective controlled study. *Obes Surg.* 2011;21:880–8.
14. de Sa VC, Ferraz AA, Campos JM, Ramos AC, Araujo Jr JG, Ferraz EM. Gastric bypass in the treatment of type 2 diabetes in patients with a BMI of 30–35 kg/m². *Obes Surg.* 2011;21:283–7.
15. Serrot FJ, Dorman RB, Miller CJ, Slusarek B, Sampson B, Sick BT, et al. Comparative effectiveness of bariatric surgery and nonsurgical therapy in adults with type 2 diabetes mellitus and body mass index <35 kg/m². *Surgery.* 2011;150:684–91.
16. Lautz D, Halperin F, Goebel-Fabbri A, Goldfine AB. The great debate: medicine or surgery: what is best for the patient with type 2 diabetes? *Diabetes Care.* 2011;34:763–70.
17. Dixon JB, Zimmet P, Alberti KG, Rubino F, On behalf of the International Diabetes Federation Taskforce on Epidemiology and Prevention. Bariatric surgery: an IDF statement for obese Type 2 diabetes. *Diabet Med.* 2011;28:628–42.
18. Livingston EH. Inadequacy of BMI as an indicator for bariatric surgery. *JAMA.* 2012;307:88–9.