Can J Diabetes xxx (2017) 1–8

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Early Metabolic Improvement After Bariatric Surgery: The First Steps Toward Remission of Type 2 Diabetes

Thomas Grenier-Larouche, Anne-Marie Carreau MD, André C. Carpentier MD *

Department of Medicine, Division of Endocrinology, Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CHUS), Université de Sherbrooke, Sherbrooke, Quebec, Canada

ARTICLE INFO

Article history:
Received 17 March 2016
Received in revised form
23 August 2016
Accepted 24 October 2016

Keywords:
Bariatric Surgery
Type 2 Diabetes
Glucose Homeostasis
Insulin Resistance
Diabetes Remission
Caloric Restriction

ABSTRACT

The introduction of bariatric surgery into clinical practice in the 1980s was followed by a relatively long watch-and-wait period before the very rapid accumulation of scientific literature, over the past decade, concerning its clinical effectiveness and safety and its mechanisms of action in the treatment of obesity. These surgical procedures now emerge as the most effective therapeutic modality to induce long-term remission of type 2 diabetes. Recent research has shed light on the potential mechanisms leading to the profound improvement of glucose homeostasis following most bariatric surgery procedures. These mechanisms can be classified as weight loss dependent and independent, both playing sequential and then synergistic antidiabetes roles. Many groups, including our own, have contributed to our understanding of the relative roles of these mechanisms at differing time periods following these procedures. Here we summarize what we currently know about the mechanisms underlying the very rapid, weight loss-independent improvement in glucose homeostasis after bariatric surgery. Beyond its impact in the field of bariatric surgery, this new knowledge about the very rapid in vivo "reverse engineering" of type 2 diabetes actually provides unique insights into the intricate and complex mechanisms linking nutrition and obesity with the development of this disease.

Mots clés :
chirurgie bariatrique
diabète de type 2
homéostasie glucidique
insulinorésistance
rémission du diabète
restriction calorique

RÉSUMÉ

L'introduction de la chirurgie bariatrique dans la pratique clinique au cours des années 1980 a été suivie d'une période d'observation et d'attente relativement longue avant l'amoncellement très rapide, au cours de la dernière décennie, de la littérature scientifique sur son efficacité clinique et son innocuité, ainsi que sur ses mécanismes d'action dans le traitement de l'obésité. Ces interventions chirurgicales apparaissent désormais comme la modalité thérapeutique la plus efficace pour obtenir une rémission à long terme du diabète de type 2. Les récentes recherches ont élucidé les mécanismes pouvant mener à une grande amélioration de l'homéostasie glucidique après la plupart des interventions de chirurgie bariatrique. Ces mécanismes qui peuvent être classifiés comme étant dépendants et indépendants de la perte de poids jouent des rôles séquentiels, puis synergiques contre le diabète. Plusieurs groupes, y compris le nôtre, ont contribué à notre compréhension des rôles relatifs de ces mécanismes à différentes périodes après ces interventions. Ci-après, nous résumons nos connaissances actuelles sur les mécanismes sous-jacents à l'amélioration très rapide et indépendante de la perte de poids de l'homéostasie glucidique après la chirurgie bariatrique. Au-delà de ses répercussions dans le domaine de la chirurgie bariatrique, ces nouvelles connaissances concernant la très rapide « ingénierie inverse » *in vivo* du diabète de type 2 offrent actuellement un aperçu unique des mécanismes complexes associant la nutrition et l'obésité au développement de cette maladie.

Introduction

Type 2 diabetes is a multifactorial disease characterized by a progressive reduction in glucose-stimulated insulin secretion. This relative deficiency in insulin secretion is a fundamental condition for the progression of asymptomatic insulin resistance to prediabetes and, later, to type 2 diabetes. The magnitude of beta-cell compensation translates into an integrated beta-cell function index defined by the reciprocal relationship between insulin sensitivity and secretion (referred to as the disposition index) (1,2). A low disposition index stands for failure of insulin secretion in response to increased insulin resistance (2–5). Genetic and/or epigenetic risk

* Address for correspondence: André C. Carpentier, MD, Division of Endocrinology, Centre hospitalier universitaire de Sherbrooke, Sherbrooke, Quebec J1H 5N4, Canada.
E-mail address: andre.carpentier@usherbrooke.ca

1499-2671 © 2016 Canadian Diabetes Association.
http://dx.doi.org/10.1016/j.jcjd.2016.10.013

factors explain about 70% of the susceptibility to impaired beta-cell function (6). However, interaction with a sedentary lifestyle, a chronic positive caloric balance or obesity, is often required for disease progression. The development of insulin resistance takes place in several organs, including skeletal muscles, liver, heart and adipose tissues. Insulin resistance may occur unevenly in these organs (7), leading to a heterogeneous combination of metabolic alterations.

Diabetogenic Effects and Dysregulation of Fatty Acid Metabolism and Transport in Prediabetes and Type 2 Diabetes

Increased plasma nonesterified fatty acids (NEFAs) and saturated fatty acids in circulating triglycerides (TGs) predict the development of type 2 diabetes independent of the degree of beta-cell dysfunction (8,9). Reduction in plasma NEFAs after an oral fat load is associated with improved glucose tolerance independent of change in total and visceral adiposity after a lifestyle intervention causing weight lost (10). There is also ample experimental evidence to support the notion that excess exposure of lean tissues to fatty acids is a key factor leading to insulin resistance and impaired beta-cell function (see [11–13] for reviews). The most recognized in vivo marker of this "lipotoxicity" (14) is excess intracellular deposition of TGs in lean tissues (13–15). TG deposition in lean tissues does not, per se, lead to insulin resistance (16–19), but it is a marker of intracellular accumulation of fatty acid-derived diabetogenic metabolites, such as long-chain fatty acyl coenzyme A (CoA), diacylglycerols and ceramides, cellular inflammation and oxidative stress (13).

Excess exposure of lean tissues to fatty acids involves 3 mechanisms (12). The first relates to defective lean tissue fatty acid metabolism, including impaired NEFA oxidation in the skeletal muscles and increased de novo lipogenesis in the liver. The second mechanism is adipose tissue metabolic dysfunction and impaired expansion (12) associated with excess intracellular lipolysis of prestored TGs, the major contributor to the plasma NEFA appearance rate during fasting, and impaired adipose tissue storage of fatty acids produced by lipolysis of TG-rich lipoproteins (20–22), a process referred to as *NEFA* spillover, and that also contributes to the total NEFA appearance rate in the postprandial and postabsorptive states. Prediabetes and type 2 diabetes are associated with increased NEFA spillover (23,24). Disordered adipose tissue storage of dietary fatty acids may be secondary to impaired insulin signalling or other metabolic abnormalities, such as adipose tissue oxidative stress, that may be rapidly triggered and reversed upon modulation of dietary fatty acid intake (13). It is also possible that impaired adipose tissue storage of dietary fatty acids occurs as a consequence of hypertrophic adipocyte remodelling during weight gain (12). The latter possibility is supported by the fact that reduced dietary fatty acid uptake in the central adipose tissues of individuals with prediabetes is improved after weight loss (25) but not after 7-day caloric restriction that reduces insulin resistance (26). The third mechanism, excess lean-tissue uptake of dietary fatty acids, clearly occurs in the myocardium of prediabetic individuals and is associated with impaired adipose tissue postprandial storage of dietary fatty acids in central adipose tissue depots (26–28).

Bariatric Surgery and Remission of Type 2 Diabetes

In Canada, 4 types of bariatric surgeries are commonly performed for the treatment of severe obesity: gastric banding, vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion with duodenal switch (BPD). Gastric banding is considered a purely restrictive procedure, whereas all the other surgeries exclude nutrients from various parts of the gastrointestinal tract, leading to profound modifications in the digestive processes, secretion of gastrointestinal peptides and nutrient sensing. In RYGB and BPD, the alimentary tract excludes the duodenum and the proximal small intestine, leading to bypass of biliopancreatic secretions and lipid malabsorption. Mixed surgeries, which combine restriction and malabsorption, induce greater initial weight loss and prevent weight regain more efficiently. Pories et al reported metabolic improvement after the gastric bypass for the first time in the late 1980s (29). During the following decades, many studies have shown that bariatric surgeries are valuable options for treatment of the metabolic comorbidities associated with severe obesity. The most striking effect remains the improvement of glycemic control in patients with type 2 diabetes. Several randomized control trials have reported lower glycated hemoglobin (A1C) levels and a reduction in the use of glucose-lowering medications in the first years following VSG, RYGB and BDP compared to conventional medical therapy (30,31). Bariatric surgery is superior to medical treatment for the induction of remission of type 2 diabetes. In 2009, a consensus group concluded that diabetes remission should be defined as a fasting glucose level less than 7.0 mmol/L and an A1C level lower than 6.5% for at least 1 year in the absence of any glucose-lowering medication. This remission can be either partial or complete, depending on whether glucose parameters reach the normal levels established by the American Diabetes Association (32). Some authors have considered these criteria too strict, stipulating that this definition would be likely to underestimate the metabolic benefits of bariatric surgery (33,34).

BPD is considered the most effective of the metabolic surgery procedures, showing a type 2 diabetes remission rate of over 90% (35). One possible explanation for this phenomenon is the greater weight loss observed after BPD. Retrospective analysis of the Swedish Obesity Study shows that patients who achieved greater weight loss over 2 years invariably presented higher likelihood of remission of type 2 diabetes (36). Moreover, beta-cell function and insulin sensitivity are equally restored after RYGB and gastric banding when normalized for the percentage of excess weight loss (37), suggesting that weight loss itself is primarily responsible for the long-term antidiabetic effects. However, a recent randomized control trial reported that patients undergoing RYGB and BPD are not completely protected from diabetes relapse (35). Partial remission rates of 75% and 95% were observed 2 years after RYGB and BPD, respectively. Relapse of type 2 diabetes was observed in 58% of patients 5 years after RYGB, compared to 37% 5 years after BPD (35).

Acute Effects of Bariatric Surgery on Glucose Homeostasis

Peripheral insulin sensitivity, hepatic insulin sensitivity and the disposition index improve during dynamic weight loss or after weight stabilization (38–40). Fasting plasma glucose levels and oral glucose tolerance are also improved a few days to a few weeks after BPD (39,41), RYGB (38) and VSG (42), suggesting weight-loss-independent effects on glucose homeostasis. Metabolic investigations in humans show that hepatic glucose output is drastically reduced quickly after bariatric surgery, but peripheral (muscle) insulin sensitivity, measured by euglycemic-hyperinsulinemic clamp, normalizes only after significant weight loss (38,40). It has been proposed that the proximal Roux limb significantly increases its glucose uptake and utilization shortly after RYGB (43,44). Increased gut metabolism may contribute to the increase in systemic glucose clearance after RYGB. The proposed mechanism is an increase in the expression of glucose transporter 1 and glycolytic flux directed toward the pentose phosphate pathway to support the biosynthetic pathways necessary for hyperplasia and hypertrophy of the jejunum (43,44). A very different phenotype has been observed after VSG, in which hypertrophy of jejunal mucosa is absent, and jejunal