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Vascular Function in Diabetes After Bariatric and Metabolic Surgery

Função Vascular na Diabetes Após a Cirurgia Bariátrica e Metabólica

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Abstract

Diabetes is a chronic disease involving alterations at the vascular level, namely those at the microvascular level, such as retinopathy and nephropathy, and at the macrovascular level, namely atherosclerosis. These changes contribute to the increased risk of cardiovascular diseases in individuals with diabetes. Obesity is a risk factor for type 2 diabetes development, and both conditions often coexist along with dyslipidemia and hypertension. Bariatric and metabolic surgery has emerged as the most successful treatment for obesity and associated comorbidities when compared to non-surgical interventions. Associated with the benefits of weight loss, decreased adipose tissue mass, improved systemic, and tissue insulin sensitivity, there is evidence for changes at the vascular level. These can be assessed by the carotid intima-media thickness (CIMT) or pulse wave velocity (PWV), which measure arterial damage and stiffness, reflecting a reversal of the atherosclerotic process after bariatric surgery in most patients. A reduction in the incidence of microvascular diseases after surgery, in patients with either prediabetes or diabetes, was also evidenced in long-term follow-up studies, emphasizing the need for early successful interventions to halt the progression of microvascular complications. Obesity and chronic hyperglycemia, characteristic of diabetes, are not only associated with inflammation and oxidative stress, mainly causing dysfunction in blood vessels, but also with a loss of plasticity of the adipose tissue. Changes in the adipose tissue vascular function, along with improvements in the tissue metabolic and endocrine functions, may be one of the mechanisms contributing to the beneficial effects of the surgical treatment of obesity.

Keywords: type 2 diabetes; obesity; bariatric and metabolic surgery; vascular function

Resumo

A diabetes é uma doença crónica que envolve alterações a nível vascular, nomeadamente a nível microvascular, como a retinopatia e a nefropatia, e a nível macrovascular, como a aterosclerose. Estas alterações contribuem para o aumento do risco de doenças cardiovasculares nos indivíduos com diabetes. A obesidade é um fator de risco para o desenvolvimento da diabetes tipo 2, e ambas as condições coexistem frequentemente com dislipidemias e hipertensão. A cirurgia bariátrica e metabólica tem emergido como o tratamento de maior sucesso para a obesidade e comorbilidades associadas, quando comparada com intervenções não cirúrgicas. Associado aos benefícios da perda de peso, redução do tecido adiposo, melhoria da sensibilidade sistémica e tecidular à insulina, existe a evidência de alterações a nível vascular. Estas podem ser avaliadas pela espessura da íntima-média da carótida ou pela velocidade da onda de pulso, que medem o dano e a rigidez arterial, refletindo uma inversão do processo aterosclerótico após a cirurgia bariátrica na maioria dos doentes. Uma redução da incidência de doenças microvasculares após a cirurgia, em pacientes com pré-diabetes ou diabetes, também foi evidenciada em estudos com seguimentos prolongados, enfatizando a necessidade de intervenções precoces e bem-sucedidas para travar a progressão das complicações microvasculares. A obesidade e a hiperglicemia crónica, características da diabetes, estão associadas não só à inflamação e ao stress oxidativo, causando principalmente disfunções nos vasos sanguíneos, mas também a uma perda de plasticidade do tecido adiposo. Alterações na função vascular do tecido adiposo, juntamente com melhorias nas funções metabólicas e endócrinas do tecido, podem ser um dos mecanismos que contribuem para os efeitos benéficos do tratamento cirúrgico da obesidade.

Palavras-chave: diabetes tipo 2; obesidade; cirurgia bariátrica e metabólica; função vascular

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1. ALTERED VASCULAR FUNCTION IN DIABETES

Diabetes encompasses several types of vascular alterations in both macro and microvascular functions. The contractile/relaxation function of the main blood vessels is strongly affected by the hyperglycemic environment due to the development of oxidative stress and inflammatory processes in the vessel wall. Diabetes and metabolic syndrome often include a series of other conditions that include hyperlipidemia, lower high-density lipoproteins (HDL)-cholesterol levels, hypertension, etc. Apart from being correlated with a higher risk for the formation of atherosclerotic plaques, the metabolic syndrome is also characterized by the development of insulin resistance. Insulin is a key factor for vascular function since it regulates nitric oxide (NO) production. Insulin-resistant patients naturally have a lower NO synthesis and an increased risk for hypertension. [1] Also, hyperglycemia by itself is harmful to endothelial cells since these cells are insulin-independent and uptake glucose by gradient. This excessive glucose uptake leads to oxidative alterations that cause endothelial cell dysfunction and reduced NO synthesis. Moreover, the reactive oxygen species generated in the vessel wall react with the available NO to form peroxynitrite and further reduce its bioavailability and impair vascular function. [1]
In the smaller vessels, hyperglycemia is known for its toxic effects in the endothelial cells, but also in the pericytes, which further destabilize the capillary structure. Such mechanisms are involved in the development of diabetic retinopathy, nephropathy, and diabetic foot (together with neuropathy). In the kidney, this is further aggravated by the loss of podocytes, which are also insulin-independent cells and are particularly susceptible to hyperglycemia-induced oxidative stress. [2]
Diabetes is also characterized by an impairment of the adipose tissue vascular function. Adipose tissue plasticity is a key mechanism to its expandability and metabolic function, given that it determines the capacity to store lipids. Diabetes was shown to be associated with vascular function and adipose tissue plasticity. In fact, such mechanisms were demonstrated to be early events in the progression of metabolic dysregulation in obesity, being also correlated with the progressive development of insulin resistance. [3]

2. SURGICAL TREATMENT OF OBESITY IN DIABETES REMISSION

Compared to conventional medical and intensive lifestyle interventions, bariatric surgery (also called metabolic surgery) has shown a substantial improvement in glycemic control, and in many patients the remission of type 2 diabetes (T2D) is achieved. [4] This is observed at early time-points after surgery, sometimes even before a stable weight is attained, as also relatively maintained after several years or decades, suggesting a sustainable cure for diabetes may be possible in some individuals. [5,6] Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) are currently the most widely performed bariatric procedures for weight loss in individuals with obesity and associated comorbidities. [7] Although compiled evidence dictated that RYGB may be superior in the achievement of T2D reversal, [8] both techniques showed relevant results compared to non-surgical interventions. [9]
As for the mechanisms that may be involved, both weight loss-dependent and independent mechanisms have been extensively investigated (Figure 1). [10] Improvements in insulin sensitivity may be induced by calory restriction, weight loss and adipose tissue remodeling. [11]
Many preoperative predictors of the outcomes of bariatric surgery have been proposed, namely beta-cell function, age, diabetes duration, etc., and integrated in predictive scores for diabetes remission. [12] These are intended to help the clinical decision, aiming for a more personalized treatment of obesity and diabetes.
Long-term effects of bariatric surgery on diabetes include reduced risk of microvascular and macrovascular diabetes-related complications. [13] When considering weight loss in individuals with diabetes, it is important to recall the evidence that not only higher BMI is associated with microvascular complications, as decreasing the BMI is related with a decrease in the risk of total microvascular complications, when compared to patients with a stable (high) BMI. [14]

3. CHANGES IN VASCULAR FUNCTION AFTER BARIATRIC AND METABOLIC SURGERY

Bariatric metabolic surgery has shown beneficial effects on vascular structure and function in individuals with obesity, with a positive impact on vascular remodeling post-surgery. Considering diabetes, changes in metabolic parameters such as insulin resistance or glycemic control, were linked to improvements in macrovascular and microvascular outcomes after bariatric surgery. [15] While the remission, or at least improvements, in hypertension and dyslipidemia in patients with obesity may play a moderate role in the observed vascular outcomes, bariatric surgery impact on vascular health may extend beyond these factors, overall contributing to the decrease in the risk for cardiovascular-associated mortality.

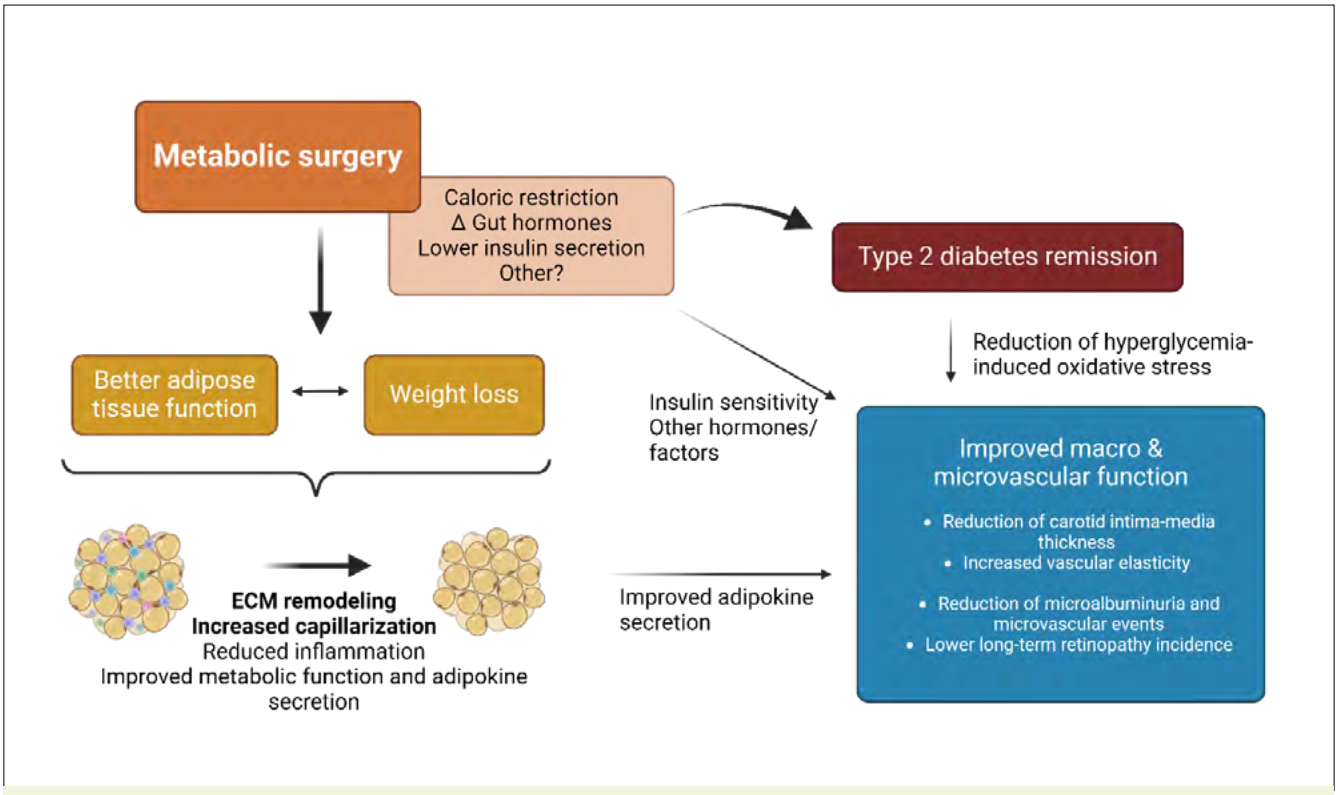

Figure 1 - The role of metabolic surgery in improving macro and microvascular function, and the potential mechanisms involved. The metabolic surgery also improves adipose tissue health, including its vascular function, a critical factor for its metabolic and endocrine activities. Abbreviations: ECM, extracellular matrix.

Obesity is a risk factor for atherosclerosis, which leads to endothelial damage. Early events of this disease include endothelial dysfunction and inflammation. Reversing atherosclerosis in its early stages will allow to decrease future cardiovascular events. Indeed, the prognosis is better for patients that still do not present an atheromatous plaque. [16] Altered lipid metabolism and/or dyslipidemias often coexist with diabetes, namely due to the buildup of circulating small-dense low-density lipoproteins (LDL) that become oxidized, which together with the chronic inflammation related to obesity, are important contributors to the development of macrovascular complications, namely atherosclerosis. [17]

Carotid intima-media thickness (CIMT) is considered a reliable non-invasive marker of arterial damage and dysfunction. A recent meta-analysis of 41 studies with 1639 patients showed CIMT was significantly reduced after bariatric surgery, which was associated with baseline CIMT. [18] This decrease may be very early observed 1-2 months after surgery, associated to the early reduction in leptin, but lost at 12 months post-surgery. [19] Similarly, increased levels of circulating adiponectin, 1 year after metabolic surgery, did not correlate with CIMT. This suggests that variations in the levels of adipokines may be more related with the metabolic changes than with the vascular remodeling. Together with increased plasminogen activator inhibitor-1 (PAI-1), C-reactive protein (CRP), thrombomodulin, and P-selectin levels, [16,20] CIMT may be one of the first detectable alterations in obesity, which could serve as an important biomarker to identify subclinical atherosclerosis and potential candidates to bariatric surgery. However, not all patients respond successfully. Indeed, a study showed that patients may show increases in CIMT after the surgical treatment of obesity, and this may be more marked in individuals diagnosed with T2D. [21]

Other clinical, vascular, or biochemical parameters are indicative of endothelial dysfunction, and may serve as useful biomarkers. Structural and functional arterial changes may be evaluated by pulse wave velocity (PWV). [21] Atherosclerosis leads to a reduction in arterial flexibility, causing them to become stiffer, which in turn results in an elevated PWV. PWV, considered an early indicator of atherosclerosis, was increased in patients with obesity and T2D. [22] After 1 year, changes in PWV were positively correlated with changes in visceral fat area (VFA) and leptin level, highlighting the connection between the loss of

fat mass and improved arterial stiffness. Although not reaching statistical significance, one study found that vascular elasticity was increased as prompt as at 3 months after bariatric surgery (reflected by a numerically lower augmentation index, which measures arterial stiffness). [23] However, these early changes might not depend on the amount of weight loss, which hinders the mechanism for the vascular improvements. A systematic review with meta-analysis highlighted a significant decrease in PWV following bariatric surgery, likewise without significant correlations between the changes in PWV and changes in body mass index (BMI). [24] Eight of the thirteen studies analyzed showed a decrease in PWV, with follow-up durations varying from 1 to 24 months. [24] However, these changes in PWV did not align with the follow-up times, suggesting that other patient characteristics may influence these outcomes. The relevance of a previous diagnose of diabetes was not discussed by the authors.

Considering the classic microvascular complications of diabetes, retinopathy, neuropathy and nephropathy, evidence indicates that bariatric surgery is effective in preventing the development and advancement of albuminuria, halting the decline in renal function. [25] In individuals with prediabetes, bariatric surgery was also associated with a reduced incidence of microvascular events, [26] highlighting the importance of pursuing weight loss before diabetes development. It was also shown that the incidence of retinopathy over 10 years after bariatric surgery was reduced independently of the glycemic status at baseline (before surgery). [26] However, there is a substantial heterogeneity of results regarding the outcomes of bariatric surgery in terms of the progression of diabetic microvascular diseases in patients with obesity and diabetes, which may be associated either with a previous advanced stage of the disease, a longer duration of diabetes or the presence of albuminuria. [27]

4. BENEFICIAL VASCULAR EFFECTS OF METABOLIC SURGERY ON ADIPOSE TISSUE

Adipose tissue vascularization is critical in maintaining tissue plasticity and its ability to store fat. For reasons that are currently under investigation, this capacity is partially lost in patients with obesity. Such loss usually involves endothelial cell death, impaired sprout formation and capillarization, which ultimately conduces to a loss of blood supply. Such mechanisms result in the well-known state of chronic hypoxia and low-grade inflammation that characterizes metabolically unhealthy obesity (MUO). [28] In hypoxic adipose tissue, the impairment of vascular function and the propagation of inflammatory signals are also associated with the progressive development of fibrosis, which further reduces plasticity. Moreover, adipogenesis and angiogenesis are mutually regulated processes, and the impairment of the vascular network also has a negative impact on preadipocyte differentiation, leading to hypertrophy of the existing adipocytes. Hypertrophic adipocytes are known for their inflammatory potential and for being associated with insulin resistance. Thus, improving adipose tissue vascular function is apparently a promising strategy to prevent the metabolic complications of obesity. Besides the endothelial cells, the vascular plasticity of the adipose tissue is controlled by the different cell types of the tissue stroma, including preadipocytes, pericytes, and resident immune cells. The loss of this capacity is associated with the metabolic complications of obesity and the onset of MUO. Such condition is associated with insulin resistance, cardiovascular diseases and T2D. [29]

Although several studies have shown the importance of the vascular network in maintaining adipose tissue metabolic and endocrine function, only a very limited number of studies have addressed the impact of metabolic surgery on such mechanisms. Most of the existing studies point out weight loss as the major outcome of the surgery, and adipose tissue function is not usually a target of interest. This is of extreme relevance since the factors that contribute to weight regain and improvement of the metabolic condition after surgery in some patients are still to be understood. Recently, it was demonstrated that the levels of Peroxisome Proliferator-Activated Receptor gamma (*PPARγ*) expression in adipose tissue before surgery were inversely correlated with weight loss after VSG bariatric surgery. [30] *PPARγ*, which is an important marker of adipose tissue function, controls adipocyte differentiation and lipid storage. Its higher expression may lead to lower adipose tissue reduction but better function, which was not evaluated in this study. Similarly, VSG was demonstrated to cause a dramatic change in adipose tissue immune cells profile in obese mice, independent of weight loss. [31] The authors observed a significant increase of CD11c- macrophages and T cells, and a downregulation of adipose tissue dendritic cells. This study highlighted the mechanisms that contribute to the reduction of inflammation after metabolic surgery but also denote structural changes, since CD11c- macrophages are known to be involved in adipose tissue remodeling. This may demonstrate the rapid adaptation of the adipose tissue to weight loss, but also the improvement of tissue plasticity. Similar findings were taken from a study in diabetic obese rats, in which sleeve gastrectomy upregulated several markers

of adipose tissue vascular function. [32] After surgery, the visceral adipose tissue levels of the Vascular Endothelial Growth Factor (VEGF) and the endothelial cell marker CD31 were upregulated, demonstrating an increase in the number of blood vessels. Moreover, the levels of the NO-producing enzyme eNOS were also upregulated, suggesting increased vascular function. All such mechanisms are known to be regulated by insulin and it is unknown whether their upregulation merely results from the observed improvement of insulin sensitivity, or if they are modulated by other mechanisms and then also contribute to improved insulin sensitivity. Interestingly, a recent study showed an increase in subcutaneous blood flow in patients submitted to metabolic surgery, which was correlated with insulin sensitivity. [33]

Although angiogenesis and blood flow are both regulated by insulin, other factors may also contribute to surgery-induced vascular remodeling in adipose tissue. One of the mechanisms currently accepted to be involved in the metabolic effects of surgery beyond weight loss is the higher release of gut hormones/incretins. Glucagon Like Peptide-1 (GLP-1) receptor agonists, such as Semaglutide, Liraglutide or Exenatide, currently prescribed for both treatment of diabetes and/or obesity, are known as regulators of vascular function and angiogenesis. Metabolic surgery was shown to upregulate the GLP-1 receptor in the adipose tissue of obese type 2 diabetic rats. [34] Also, treatment with Liraglutide led to increased capillarization in the ex vivo adipose tissue angiogenesis assay and to increased tissue irrigation in vivo. [34] Such findings are in line with other studies demonstrating that such effects of Liraglutide include the suppression of IL-6. [35] Similar pro-angiogenic effects in adipose tissue were also observed for Exenatide, which reduced inflammation and increased capillary density after 4 weeks of treatment in diet-induced obese mice. [36] In summary, metabolic surgery apparently changes the microenvironment of the adipose tissue, promoting angiogenesis and tissue remodeling. Although the mechanisms involved in such effects are unknown, the modulation of gut hormones may be important contributors. Improved adipose tissue vascular function may be involved in the proper storage, metabolic and endocrine functions of the tissue and thus be one of the mechanisms leading to the beneficial metabolic effects of the surgery. Nevertheless, the mechanisms involved should be deeply investigated.

> CONCLUSIONS

Metabolic surgery is known for its weight loss and metabolic effects, leading to T2D remission in some patients. Reduction of insulin resistance is a key target of metabolic surgery which at least partially explains its metabolic consequences. Moreover, insulin is a known regulator of vascular contractility/relaxation and angiogenesis. The existing literature suggests that metabolic surgery has a positive impact in both macro and microvascular functions and that the amelioration of insulin sensitivity may be involved in such effects. Nevertheless, the existing studies also point out that the individual metabolic condition before surgery may influence the vascular outcomes of the surgical treatment. Patients with history of diabetes may not experience the same improvements of those who have not. It is also possible that such vascular improvements after metabolic surgery may result from the better function of the adipose tissue, since adipokines are also known to regulate vascular function and angiogenesis. Regarding the adipose tissue itself, metabolic surgery was shown to improve its metabolic and endocrine function, as well as increasing its angiogenic capacity and blood flow in vivo. Some of these effects may result from improved insulin action. However, since metabolic surgery also increased the secretion of several gut hormones, these may also act in the adipose tissue to regulate vascular function. In fact, GLP-1 receptor agonists were demonstrated to increase angiogenesis and capillary density in adipose tissue. Although amelioration of insulin sensitivity appears to be a central mechanism in such effects, other mechanisms related with the upregulation of adipokines and gut hormones may also contribute to the beneficial vascular effects of metabolic surgery. Altogether, although metabolic surgery is a promising strategy to improve the vascular health of patients with obesity and T2D, their metabolic condition at baseline may be a barrier to achieve such effects, meaning more personalized approaches are needed. <

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