Vascular Dysfunction in Adipose Tissue: Its Impact on Type 2 Diabetes and Cancer

Disfunção Vascular no Tecido Adiposo: Impacto na Diabetes Tipo 2 e no Cancro

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Abstract

The overgrowth of adipose tissue is a major trigger for the development of other metabolic disorders, like insulin resistance, hypertension, type 2 diabetes, cardiovascular disease, and cancer. Among the causes of this association lies the fact that increased adiposity is accompanied by a non-functioning vascular component. Accordingly, vascular dysfunction within the adipose tissue is common in obesity and associated with deregulated metabolic cues such as decreased nitric oxide (NO), increased oxidative stress and hypoxia. These will result in metabolic comorbidities, which ultimately may end up in type 2 diabetes and cancer.
The current study addresses the state-of-the-art regarding the mechanisms involved, focusing on two diseases with huge prevalence worldwide: type 2 diabetes and cancer. Understanding how adipose tissue vascular dysfunction impacts on metabolic disease is of paramount importance and may lead to innovative therapeutic approaches.

Keywords: adipose tissue; vascular dysfunction; type 2 diabetes; cancer.

Resumo

O aumento excessivo do tecido adiposo é um promotor importante de outros distúrbios metabólicos, como são o caso da insulinorresistência, hipertensão, diabetes tipo 2, doença cardiovascular e vários tipos de cancro. Entre as causas para esta associação encontra-se a disfunção da componente vascular (fração vascular estromal) do tecido adiposo. A disfunção vascular do tecido adiposo é comum na obesidade e está associada a sinais metabólicos alterados, como diminuição do óxido nítrico, aumento de stress oxidativo e hipóxia. Por seu lado, estes resultam no desenvolvimento de comorbilidades metabólicas, que culminam em doenças como a diabetes ou cancro.
O presente estudo aborda o estado-da-arte relativamente aos mecanismos envolvidos, focando-se em duas doenças com enorme prevalência a nível mundial: a diabetes tipo 2 e o cancro. Compreender como a disfunção vascular do tecido adiposo influencia as doenças metabólicas é de extrema relevância e pode levar a abordagens terapêuticas inovadoras.

Palavras-chave: tecido adiposo; disfunção vascular; diabetes tipo 2; cancro

> INTRODUCTION

Adipose tissue is a complex and highly active metabolic and endocrine organ and plays crucial functions. Beyond energy balance, adipose tissue plays vital roles in various physiological processes. It provides mechanical protection and support to organs, helps maintain body temperature, and serves as a reservoir for lipid-soluble vitamins. In addition to adipocytes, adipose tissue contains a stromal vascular fraction (SVF), consisting of various

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Recebido/Received: 06/06/2024; Aceite/Accepted: 24/06/2024.

types of cells, including adipose stromal cells (ASC), endothelial cells and adipose tissue macrophages (ATM) (DeBari & Abbott, 2020; Michailidou et al., 2021). Each cell type has distinct characteristics and functions. Adipose stromal cells (ASCs) are multipotent cells within adipose tissue that can differentiate into various cell types, such as adipocytes, osteocytes, and chondrocytes. Adipose tissue macrophages (ATMs) are crucial for tissue homeostasis, inflammation, and immune responses. Meanwhile, endothelial cells, which line the blood vessels within adipose tissue, are essential for vascular function and angiogenesis. Obesity, the excessive accumulation of adipose tissue, is a global health challenge and has aroused growing concern due to the exponential increase in its prevalence. Obesity is a multifactorial pathology mostly associated with the increasingly sedentary lifestyle of the world's population (Lin & Li, 2021). The excessive and deregulated accumulation of fat results in structural alterations and dysfunctional adipose tissue (Longo et al., 2019), making it a significant risk factor for the onset, development, and modulation of various pathologies. The interplay between the described cell types and others in obesity creates a pathological environment characterized by hypoxia, chronic inflammation, fibrosis, oxidative stress and ultimately, vascular dysfunction. These cellular interactions lead to systemic metabolic disturbances, increasing the risk of developing obesity-related diseases such as type 2 diabetes, cardiovascular diseases, and cancer (Figure 1).

A healthy vasculature network is a core basic function of normal adipose tissue remodeling. As a highly plastic organ, adipose tissue mass can shrink or expand according to the metabolic landscape, relying on angiogenesis, the growth of new blood vessels from pre-existing ones (Corvera et al., 2022). The growth of adipocyte size or number upon caloric surplus will induce a transient shortage of oxygen diffusion capacity and thus initiate a state of acute hypoxia, leading to the secretion of hypoxia-inducible factors (HIF) (Crewe et al., 2017). HIF-1α and HIF-2α will trigger the upregulation of several genes encoding for pro-angiogenic factors, such as vascular endothelial growth factors (VEGF), angiopoietins, the placental growth factor, and endothelial nitric oxide synthase (eNOS) (Fong, 2008), which ensure endothelial cells proliferation and survival.

Acute hypoxia also induces transient macrophage activation, monocyte recruitment, and increased pro-inflammatory cytokines, which display pro-angiogenic effects and favor matrix remodeling via upregulation of matrix metalloproteinases (MMPs) and transforming growth factor β (TGF- β) (Andrei et al., 2017; Crewe et al., 2017; Matz et al., 2023). Thus, the healthy expansion and retraction of adipose tissue consist of a short well-controlled interaction between acute hypoxia, inflammation, immune cells' infiltration, matrix remodeling, and angiogenesis. In an obesogenic environment, an imbalance of such features will occur and promote the aforementioned pathologies. The aim of this review is to assess the influence of vascular dysfunction, modulated by inflammation, hypoxia, fibrosis, and oxidative stress in two diseases with huge prevalence worldwide: type 2 diabetes and cancer.

> DIABETES AND CANCER

Insulin resistance and type 2 diabetes (T2D) frequently arise as part of the metabolic sequelae of obesity and have reached a concerning high prevalence worldwide (Europe, 2022). Endothelial dysfunction is a common feature of obesity and T2D and confers an increased risk for cardiovascular diseases (Deanfield et al., 2007; Powell-Wiley et al., 2021).

Obesity also represents an additional risk for various types of cancer, contributing to their onset and increased incidence, impairing their progression and prognosis, and mostly increasing mortality rates (Pati et al., 2023). However, the relationship between obesity and cancer, as well as the mechanisms underlying tumour development, are not yet fully understood. Obesity is recognized as an unfavorable prognostic marker for various types of cancer (Balaban et al., 2017; Parekh et al., 2012), since it is associated with metabolic abnormalities that can favor the growth, survival, and metastasis of tumour cells (Berger, 2018; Park et al., 2014). This association is corroborated by scientific evidence suggesting that excess weight can influence various biological processes that promote the appearance and growth of cancer cells, such as angiogenesis (Pellegata et al., 2022), oxidative stress (Jovanović et al., 2023), chronic inflammation (Deng et al., 2016), hormonal changes (e.g. insulin and estrogen) (Zhong et al., 2023), insulin resistance (Arcidiacono et al., 2012) and imbalanced metabolites (Doerstling et al., 2017) that favor the uncontrolled cancer cell growth.

> THE IMPACT OF INFLAMMATION IN THE VASCULAR DYSFUNCTION

The chronic low-grade inflammation is a common feature in obesity, being associated with type 2 diabetes and cancer as well. Vascular endothelial dysfunction is triggered by the imbalance between vasodilators and

Revista Portuguesa de Diabetes. 2024; 19 (2): 53-59

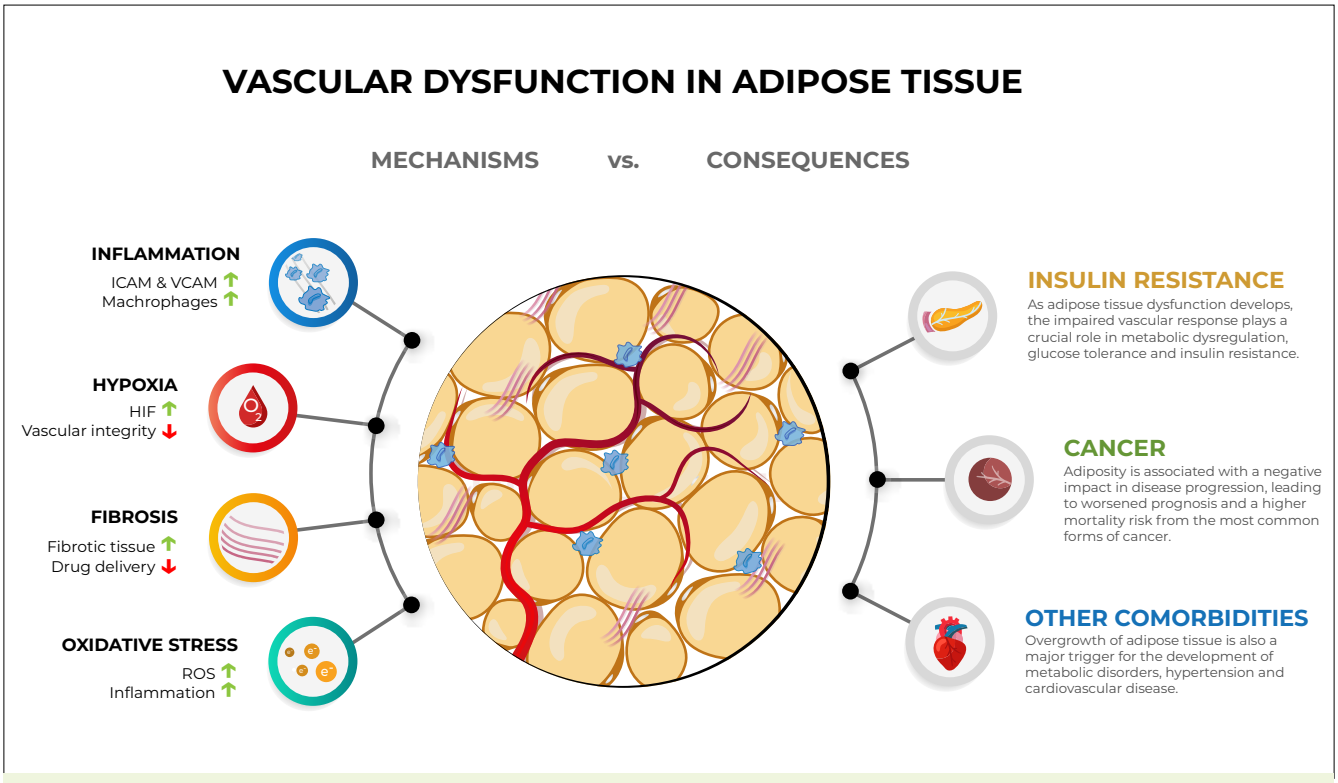

Figure 1 - Schematic overview illustrating the mechanisms behind vascular dysfunction in adipose tissue, and their consequence in development of metabolic disorders.

vasoconstrictors. Uncoupling of endothelial nitric oxide synthase (eNOS) leads to endothelial activation, increase in inflammatory cytokines and oxidized LDL and VLDL lipoproteins (Theofilis et al., 2021). NFkB activity plays an important role in these endothelial cell changes, resulting in the overexpression of intercellular (ICAM-1) and vascular cell (VCAM-1) adhesion molecules, which promote leukocyte adhesion, their rolling and extravasation, enhancing atherosclerotic and prothrombotic events. Moreover, damaged endothelial cells enhance the release of pro-inflammatory mediators, including interleukins and TNF-alpha, further aggravating the inflammatory process.

> HYPOXIA, A TRIGGER TO THE VASCULAR DYSFUNCTION

Acute hypoxia is a natural consequence of lipid accumulation in the adipose tissue. However, along the weight gain process, continuous tissue enlargement and dysmetabolism, unknown mechanisms hinder the coupling between immune cells, vasculature, and extracellular matrix, resulting in adipose tissue dysfunction and chronic and unresolved hypoxia. Indeed, high-fat/caloric diet consumption for 3 months induced upregulation of hypoxia, inflammation, and vasculature-related genes in adipose tissue, accompanied by a marked impairment in glucose metabolism in the C57BL/6J mice (Ye et al., 2007). Recently, a study conducted by our group reinforced this hypothesis, by unveiling that impairment in vasculature remodelling was one of the earliest molecular alterations in the visceral adipose tissue function in subjects with obesity and insulin resistance (Rosendo-Silva et al., 2024), suggesting impaired angiogenesis as the central piece of adipose tissue dysfunction.

Angiogenesis plays a fundamental role in obesity, since the accumulation of fat requires the expansion of adipose tissue and, concomitantly, alterations and remodelling of the vascular network (Corvera et al., 2022). As such, adipocytes are key factors in this process, as they are responsible for its strict regulation (Herold & Kalucka, 2021). Angiogenesis is also fundamental to tumour progression as it enables oxygen and nutrients delivery but also facilitates tumour cell dissemination (Al-Ostoot et al., 2021). Adipocyte-secreted angiogenic factors triggers angiogenesis in tumours early on, independently of hypoxia, even before the tumour reaches a significant dimension (Aguilar-Cazares et al., 2019). Overweight

and obese individuals are, therefore, more prone to develop tumours with accelerated growth and metastases (Pellegata et al., 2022).

> THE FIBROTIC MODULATION IN THE VASCULAR DYSFUNCTION

Another key player in the obesity-T2D cross talk is fibrosis, which is caused by a complex interaction between the metabolic, inflammatory, and immunological processes (DeBari & Abbott, 2020). Fibrosis is attributed to several mechanisms, including the obesity-associated chronic low-grade inflammatory status (DeBari & Abbott, 2020; Khanna et al., 2022); The increased oxidative stress characteristic of the adipose tissue in obese individuals, which can damage cells and tissues, leading to the activation of fibrogenic pathways and the collagen deposition (Cheresh et al., 2013); changes in immune system function, including increased activation of pro-fibrotic immune cells, such as macrophages and T-cells, and decreased anti-inflammatory immune cells activity (Huang et al., 2020); The presence of metabolic disorders, such as insulin resistance and dyslipidaemia, further contribute to fibrosis (Nogueira & Cusi, 2024). Excessive deposition of fibrotic tissue affects angiogenesis in adipose tissue, interfering with the blood vessels normal functioning, causing their narrowing or partial obstruction, reduced blood flow and increased vascular stiffness (Harvey et al., 2016; Crewe et al., 2017).
In cancer, fibrosis also impacts drug delivery (Gu et al., 2022), since it constitutes a physical, irregular, and disorganised barrier that prevents the uniform drug release from blood vessels to tumours (Qiu et al., 2024). Obesity is not only associated with the onset of cancer but has also a negative impact in the disease progression leading to a worsened prognosis and a higher mortality risk from the most common forms of cancer in overweight patients.

> OXIDATIVE STRESS IN THE VASCULAR DYSFUNCTION

The impaired function of the endothelium found in diabetes, involves decreased nitric oxide (NO) availability and increased oxidative stress which hinders vasodilation (Deanfield et al., 2007). Insulin resistance is thought to be a major driver of endothelial dysfunction since NO synthesis is dependent on insulin-stimulated eNOS activation (Muniyappa & Sowers, 2013). Indeed, mice lacking endothelial insulin receptors, displayed reduced eNOS mRNA levels, resulting in decreased NO synthesis (Vicent et al., 2003; Wheatcroft et al., 2004). In patients with T2D, acetylcholine-induced vasodilation was impaired in isolated arteries, and eNOS activity was reduced (Okon et al., 2005). Dyslipidemia, another common metabolic feature of obesity and T2D, characterized by altered levels of cholesterol and triglycerides, is also implicated in endothelial dysfunction. Oxidized low-density lipoprotein cholesterol (LDL-C) was shown to decrease eNOS activation and to increase the expression of adherence mediators, such as ICAM-1 and VCAM-1, that facilitate immune cells' recruitment and the formation of plaques (Gliozzi et al., 2019; Higashi, 2023).
Oxidative stress is also a cancer hallmark. In fact, one characteristic of the tumor microenvironment (TME) is the presence of high amounts of reactive oxygen and nitrogen species (ROS and RNS), including NO and peroxynitrite (ONOO-), which result from the local exacerbated inflammatory cells and cytokines. Cancer cells rapidly adapt to the highly oxidative environment that characterizes tumors by increasing anti-oxidant pathways. NADPH levels are thus increased in cancer cells, ultimately shifting major metabolic pathways, namely pentose phosphate pathway, AMPK signaling activity, folate metabolism or glutathione. Oxidative stress results in cell damage and cancer progression, by playing major roles in cancer cell proliferation, migration, invasiveness, stiffness, as well as in angiogenesis and metastization, (Iqbal et al., 2024). Therefore, reducing oxidative stress is mandatory to control cancer progression.

> CONCLUSION TO THE IMPACT OF VASCULAR DYSFUNCTION IN DIABETES AND CANCER

As illustrated in Figure 1, inflammation, hypoxia, fibrosis, and oxidative stress underlying vascular dysfunction in adipose tissue, display a huge impact on a wide variety of metabolic conditions, including insulin resistance, T2D, cardiovascular disease and cancer. Therapeutic strategies that modulate adipose tissue vasculature function are paradoxically associated with improvement in health, probably depending on the timing of the therapeutic window being in early stages of obesity and metabolic disease or later stages. A comprehensive understanding of the mechanisms addressing adipose tissue vascular dysfunction is therefore of paramount importance.
Endothelial dysfunction impairs the function of several organs in the body, since the vasculature has a crucial role in providing oxygen and nutrients to cells, allowing waste removal, and adapting blood flow according to metabolic needs (Deanfield et al., 2007). Impaired vas-

cular function of the adipose tissue is a major hallmark of adipose tissue dysfunction, and thus, a crucial driver for the development of metabolic disease and T2D in both rodents and humans (Hu et al., 2018; Rodrigues et al., 2017).

Our group has been studying obesity influence in breast cancer. We showed recently that obese subjects are more susceptible to develop poorly differentiated breast carcinomas. Nevertheless, this association is rather complex depending on a wide variety of other factors, including histological type, presence of hormone receptors and systemic and tumor metabolic markers (Luís, et al., 2023). Studying breast cancer in an obese mouse model, it was recently observed that obesity induced neutrophils release of reactive oxygen species, which impaired vascular integrity, and hence facilitated tumour cell dissemination (McDowell et al., 2021). Interestingly enough, the expression of rate-limiting enzymes implicated in glycolysis and gluconeogenesis in tumour cells depend not only on the BMI, but also on the presence of T2D and its comorbidities (dyslipidemia and hypertension) (Luís, et al., 2023), rendering the influence of obesity in breast cancer even more complex. Nevertheless, most findings reveal that obesity enhances breast cancer aggressiveness being endothelial dysfunction a major player in this cross talk.

Counterintuitively, adiposity appears to be protective and associated with favorable outcomes in other types of cancer, holding the "obesity paradox" hypothesis. For melanoma, numerous reports support fat-rich diets role as melanoma growth promoters. Actually, calorie-restriction is known to inhibit B16F10 melanoma cell tumorigenesis and slower melanoma growth while concomitantly enhancing pulmonary colonization *in vivo*. Our data point towards the inverse relationship, where HFD acts as a two-edged sword in melanoma: supporting primary tumor growth and vascularity, but at the same time decreasing melanoma metastatic spread. Despite the strong association between adiposity and cancer and their relevance in vascular impairment, their role depends on many factors, including the type of cancer, or presence of other metabolic comorbidities such as T2D. Further studies are needed to highlight the influence of obesity-driven vascular dysfunction in metabolic diseases.

Altogether, these data demonstrate the pivotal role of impaired vascular response in the development of adipose tissue dysfunction in obesity, T2D and cancer. However, therapeutic options that rely on the modulation of the vascular function of the adipose tissue are still not consensual. For instance, direct overstimulation of VEGF/VEGFR2 specifically in the subcutaneous adipose tissue led to a reduction in adipocyte size and improved glucose tolerance in diet-induced obese rodents (Sun et al., 2012). On the other hand, in the ob/ob model, the metabolic profile is improved upon VEGFR2 blockade instead. Thus, therapeutic strategies that stimulate or inhibit adipose tissue vasculature function are paradoxically associated with health improvement, probably depending on the timing of the therapeutic window being in early stages of obesity and metabolic disease (as in diet models), or in later stages (simulated by the genetic ob/ob model). In summary, a comprehensive overview of the vascular dysfunction is essential, and may pave the way to identify novel therapeutic approaches against these prevalent diseases displaying such huge morbidity and mortality rates worldwide. <

Conflicts of interests/*Conflitos de interesses*:
The authors declare that they have no conflicts of interests./*Os autores declaram a inexistência de conflitos de interesses.*

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