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HOW OBESITY AFFECTS INSULIN RESISTANCE AND THE CONSEQUENCES OF THIS PROCESS

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Abstract: Introduction. Obesity is a medical condition characterized by the excessive accumulation of body fat, which has become a global concern due to its impact on public health. One of the main problems associated with obesity is insulin resistance, a condition in which the body's cells are less sensitive to the hormone insulin, which is essential for glucose metabolism. People with obesity and type 2 diabetes (T2D) often have lower postprandial insulin levels than individuals without T2DM, and the relative insufficiency of insulin contributes to the hyperglycemia characteristic of these patients. In addition, obesity is related to cardiovascular diseases, which represent significant public health risks, especially in today's Western societies. **Objective.** The aim of this study was to conduct a literature review to identify new data exploring the relationship between increased adipose tissue and insulin resistance, highlighting the metabolic processes involved in this mechanism. **Material and Methods.** This review analyzed published studies that address the relationship between obesity, insulin resistance and associated metabolic processes. The search was conducted in the main academic databases, such as PUBMED, SCIELO and LILACS, initially identifying 60 papers using the terms: Inflammation in obesity, Adipokines and resistance, Lipotoxicity and mitochondria, Microbiota and obesity, Hormones and appetite control, Diets and insulin resistance, Pharmacological therapies, Lifestyle and inflammation, Adipose tissue modulation, Oxidative stress. These terms were combined using Boolean operators: "and", "or" and "not". After analysis, 36 studies were selected for the review, based on relevance, methodological quality and timeliness. **Discussion.** The relationship between obesity and insulin resistance is multifactorial and involves various metabolic, inflammatory and hormonal mechanisms. The increase in adipose tissue, especially in the

visceral region, alters the profile of adipokines and inflammatory mediators, such as TNF-α, IL-6 and leptin, which activate intracellular pathways such as NF-κB and JNK, leading to inhibitory phosphorylation of the IRS-1 receptor and insulin resistance (AHMED *et al.,* 2021). In addition, the lipotoxicity caused by excess free fatty acids promotes oxidative stress and mitochondrial dysfunction, aggravating the metabolic condition (YOON *et al.,* 2021). Adipose tissue, in addition to storing fat, functions as an endocrine organ**,** secreting adipokines that modulate insulin sensitivity and the inflammatory state, factors that favor the development of complications such as cardiovascular diseases (FONSECA- ALANIZ *et al.,* 2006; PALAY & JOHNSON, 2018). Lifestyle interventions, balanced diets and pharmacological strategies have shown potential in reducing inflammation and improving insulin sensitivity, reinforcing the importance of integrated approaches in the treatment of obesity (TRACHTENBERG *et al.,* 2021). However, a thorough understanding of metabolic mechanisms is still essential for the development of more effective therapies**.**

Keywords: obesity, insulin resistance,

INTRODUCTION

Obesity is a complex, multifactorial disease in which excess accumulated body fat has negative effects on health. Obesity is a pandemic that does not show significant figures that indicate a decrease in the population. In this context, evaluating BMI gives us clues about the progress of obesity in the population. BMI is used to define and diagnose obesity according to the guidelines of the World Health Organization (WHO, 2000). In adults, the WHO defines "overweight" as a BMI of 25.0 to 29.9 and "obesity" as a BMI ≥ 30.0. Obesity is further classified into three levels of severity: class I (BMI 30.0-34.9), class II (BMI 35.0-39.9) and class III (BMI ≥ 40.0) (POIRIER et al., 2006). However, there are large individual differences in the percentage of body fat for the given BMI value, which can be attributed to gender, ethnicity and age (KOK *et al.,* 2004). Excess fat deposition in the abdominal region is termed 'abdominal obesity' and is associated with greater health risks (LØVSLETTEN, *et al.,* 2020). Obesity has differed from the WHO, IDF (International Diabetes Federation) and AHA (*American Heart Association*). However, there is no international standard suitable for all countries or regions (PALEY and JOHNSON, 2018).

Increased body mass index (BMI) is a risk factor for non-communicable diseases. Individuals over 30 kg/m^{2}can develop problems such as diabetes, cardiovascular diseases and musculoskeletal disorders, resulting in a dramatic decrease in quality of life and life expectancy. Over the last three decades, the worldwide prevalence of obesity has increased by 27.5% for adults and 47.1% for children (LIN and LI, 2016; APOVIAN, 2016).

Obesity is the result of complex relationships that include genetic, socio-economic and cultural influences. Consumption patterns, urban development and lifestyle habits influence the prevalence of obesity. Obesity can also be the result of disease or pharmacological treatment. Obese people have lower school attendance, lower earning potential and higher health costs, which can result in a serious social problem (LIN and LI, 2016).

Compared to healthy lean people, people with obesity have increased basal and postprandial plasma insulin concentrations (FERRANINI, 2021; DEFRONZO, 2009; MITTENDORFER *et. al.,* 2009). People with obesity and type 2 diabetes (T2D) have lower postprandial insulin than those without T2DM, and relative insulin insufficiency is responsible for the marked hyperglycemia in people with T2DM (FERRANINI, 2021; DEFRONZO, 2009; MITTENDORFER *et. al.,* 2009). The prevailing

thought is that the increase in plasma insulin in people with obesity is a compensatory response to the insulin resistance associated with obesity. Presumably, pancreatic β-cells and insulin--secreting tissues feel the need to secrete more and eliminate less insulin to prevent hyperglycemia when there is insulin resistance, and this compensatory mechanism is impaired in people with DM2 (ESSER *et al.,* BERGMAN *et al.,* 2002; NATURE MEDICINE, 2017; Piccinini *et al.,* 2020; GASTALDELLI *et al.,* 2021).

OBJECTIVES

This study aims to investigate how the inflammatory and hormonal mechanisms associated with the expansion of visceral adipose tissue contribute to insulin resistance in obesity, identifying possible targets for therapeutic interventions. The aim is to understand the role of pro-inflammatory adipokines, chronic inflammation and oxidative stress in mitochondrial and hormonal dysfunction, as well as to assess the impact of dietary interventions and lifestyle changes on improving insulin sensitivity and metabolic balance.

MATERIAL AND METHODS

The aim of this study was to analyze and synthesize the available data on the relationship between obesity, insulin resistance and the metabolic processes involved. To this end, a systematic search was carried out on academic databases , selecting relevant studies published in the scientific literature. Initially, approximately 60 studies related to the topic were identified, of which 36 were selected for detailed analysis based on the relevance, methodological quality and timeliness of the data presented.

The selection of articles took into account inclusion criteria, such as studies that addressed the molecular mechanisms involved in obesity and insulin resistance, including inflammatory aspects, adipokines, lipotoxicity and mitochondrial dysfunction. Priority was given to studies that presented experimental evidence, systematic reviews and clinical trials relevant to the topic.

To organize the analysis of the mechanisms of action, we used a table describing the main mechanisms involved in the relationship between obesity and insulin resistance, including examples of search terms used in search engines, using Boolean operators (Table 01). This table helped to understand and systematize the metabolic and inflammatory processes discussed in the literature.

Subject	Combination of Boolean terms and keywords
Inflammation in obesity	"Chronic inflammation" AND "obesity" OR "low-grade inflammation" AND "metabolic syndrome"
Adipokines and resistance	"adipokines" AND "insulin resistance" OR "adipose tissue cytokines"
Lipotoxicity and mitochondria	"lipotoxicity" AND "mitochondrial dysfunction" OR "fatty acids" AND "oxidative stress"
Microbiota and obesity	"gut microbiota" AND "obesity" OR "microbiome" AND "metabolic health"
Hormones and appetite control	"leptin resistance" OR "ghrelin" AND "obesity" OR "appetite regulation" AND "hormones"
Diets and insulin resistance	"low carbohydrate diet" AND "insulin sensitivity" OR "Mediterranean diet" AND "glucose metabolism"
Pharmacological therapies	"anti-inflammatory therapy" AND "obesity" OR "metformin" AND "insulin resistance"
Lifestyle and inflammation	"lifestyle intervention" AND "metabolic inflammation" OR "exercise" AND "obesity"
Adipose tissue modulation	"adipose tissue modulation" AND "inflammation" OR "hypoxia" AND "adipose tissue"
Oxidative stress	"oxidative stress" AND "metabolic disease" OR "antioxidants" AND "insulin resistance"

Table 01. Search Strategies with Boolean Operators

Source: Own elaboration.

THE ROLE OF ADIPOSE TISSUE

Adipose tissue, previously seen only as an energy storage compartment, is now recognized as an active endocrine organ that plays a central role in metabolic homeostasis. It secretes a series of bioactive substances called adipokines, which regulate both metabolism and inflammatory processes (CLÉMENT; DELAUNAY, 2021).

In obesity, there is an expansion of adipose tissue, especially in the visceral region, which is associated with a chronic low-grade inflammatory state. This state is characterized by the infiltration of immune system cells, such as macrophages and T lymphocytes, which promote changes in the secretory profile of adipokines. As a result, there is an increase in the production of pro-inflammatory adipokines, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and resistin, while adipokines with anti-inflammatory and insulin-sensitizing properties, such as adiponectin, have their secretion reduced (CLÉMENT; DELAUNAY, 2021).

These alterations contribute directly to the development of insulin resistance, mainly through the activation of inflammatory intracellular signaling pathways such as JNK and IKKβ/NF-κB. These pathways induce inhibitory phosphorylation of the insulin receptor substrate (IRS), impairing the action of insulin in target tissues such as the liver, muscle and adipose tissue itself (CLÉMENT; DELAUNAY, 2021). In addition, obesity is associated with increased lipolysis, which raises the levels of free fatty acids in the circulation. These fatty acids contribute to mitochondrial dysfunction, oxidative stress and inflammation, factors that also impair insulin sensitivity (CLÉMENT; DELAUNAY, 2021).

Other authors have also highlighted the multifaceted role of adipose tissue in insulin resistance, influencing it both directly, through the secretion of adipokines and free fatty acids, and indirectly, through the modulation of inflammation (FONSECA-ALANIZ *et. al.,* 2006). Commonly known as body fat, adipose tissue is highly active, secreting hormones that regulate metabolism, such as leptin and adiponectin (GUIMARÃES *et al.,* 2007).

In addition, this tissue produces pro-inflammatory substances that interfere with insulin signaling. Excessive consumption of high-fat foods activates inflammatory proteins such as c-jun N-terminal kinase (JNK), IκB kinase (IKK) and the transcription factor nuclear factor kappa B (NF-κB), impairing the response to insulin (AHMED; SULTANA; GREENE, 2021). The release of TNF-α and free fatty acids by adipose tissue promotes an inflammatory environment that contributes to insulin resistance.

As fat accumulates, immune cells, mainly macrophages, infiltrate the adipose tissue. These, together with hypertrophied adipocytes, secrete inflammatory cytokines such as TNF-α, IL-6 and IL-1, which affect the insulin receptor and compromise its signaling in tissues such as the hypothalamus, skeletal muscle and liver (FONSECA-ALANIZ *et. al.,* 2006). In the hypothalamus, this resistance impairs the anorexigenic action of insulin, promoting hyperphagia (AHMED; SULTANA; GREENE, 2021). This contributes to increased food consumption, both because of the difficulty in controlling appetite associated with ultra-processed foods and because of the hormonal dysfunction related to obesity.

In skeletal muscle, insulin resistance interferes with glucose uptake by GLUT-4 transporters. As this is the main tissue responsible for glucose absorption in the postprandial period, its dysfunction contributes significantly to hyperglycemia. In the liver, insulin normally inhibits gluconeogenesis; however, when its action is compromised, there is an increase in hepatic glucose production, further aggravating glycemic levels.

Hormones also play an essential role in regulating appetite, fat storage and energy balance. Hormonal alterations, such as leptin resistance, make it difficult to control body weight (GUIMARÃES *et. al.,* 2007). Leptin, produced by adipocytes, acts to regulate satiety, but in obese individuals resistance to the hormone can occur, leading to increased food intake, reduced energy expenditure and weight gain (FONSECA-ALANIZ *et. al.,* 2006).

On the other hand, ghrelin, an orexigenic hormone that stimulates hunger, can be elevated in obese individuals, contributing to hyperphagia and consequent weight gain (AHMED; SULTANA; GREENE, 2021).

Therefore, adipose tissue plays a central role in the pathophysiology of insulin resistance. Its role goes beyond energy storage, being fundamental in the connection between metabolic and immunological processes, and directly influencing the risk of developing diseases such as type 2 diabetes and metabolic syndrome.

PRODUCTION AND TISSUE ACTION OF INSULIN

Insulin is an anabolic hormone produced by the β cells of the islets of Langerhans in the pancreas. Its synthesis begins in the form of pre-pre-insulin, which undergoes successive cleavages giving rise to biologically active insulin and C-peptide, both of which are secreted into the bloodstream in equimolar proportions. Insulin secretion is mainly regulated by blood glucose: when blood glucose rises, glucose enters the pancreatic β-cells via the GLUT2 transporter and is metabolized via the glycolytic and mitochondrial pathways, generating ATP. The increase in the ATP/ADP ratio causes ATP-sensitive potassium channels (K_ATP) to close, depolarizing the cell membrane and opening voltage-dependent calcium channels. The influx of calcium, in turn, stimulates the exocytosis of insulin-containing granules (DIMITRIADIS *et. al.,* 2021).

In addition to glucose, other stimuli contribute to insulin release, such as amino acids (especially arginine and leucine), fatty acids and incretin gut hormones - such as GLP-1 and GIP - which amplify insulin secretion after food intake, characterizing the so-called incretin effect (DIMITRIADIS *et. al.,* 2021).

Once released, insulin acts on different target tissues, regulating the metabolism of glucose, lipids and proteins. Its action begins with binding to the insulin receptor (IR), which has tyrosine kinase activity. Activation of the receptor triggers phosphorylation of IRS (*Insulin Receptor Substrates*) proteins and subsequent activation of PI3K (phosphatidylinositol 3-kinase), which converts PIP2 into PIP3, leading to activation of the PDK1 and Akt (PKB) enzymes. Akt acts on various cellular targets and is responsible for translocating the GLUT4 transporter to the plasma membrane, which allows glucose to enter peripheral tissues (DIMITRIADIS *et. al.,* 2021).

In the liver, insulin plays a role in suppressing gluconeogenesis and glycogenolysis, while stimulating glycogenolysis and lipogenesis. An essential mechanism for this regulation is the inactivation of the FoxO1 transcription factor through Akt-mediated phosphorylation. The inactivation of FoxO1 results in a reduction in the expression of genes such as PEPCK (phosphoenolpyruvate carboxykinase) and G6Pase (glucose-6-phosphatase), which leads to a decrease in hepatic glucose production (TEANEY; CYR, 2023).

In skeletal muscle, insulin promotes glucose uptake via GLUT4, stimulates glycogen synthesis and also increases protein synthesis by promoting amino acid uptake. In addition, insulin has a vasodilating effect on muscle capillaries, which further facilitates the delivery of glucose and insulin to muscle cells (DIMITRIADIS *et al.,* 2021).

In adipose tissue, insulin inhibits lipolysis by suppressing hormone-sensitive lipase, increasing glucose uptake and triacylglycerol synthesis. It also increases the activity of lipoprotein lipase (LPL), favoring lipid storage. The reduction in the release of free fatty acids into the circulation contributes to improved insulin sensitivity in tissues such as liver and muscle (DIMITRIADIS *et al.,* 2021).

In the central nervous system, particularly in the hypothalamus, insulin acts by regulating food intake and hepatic metabolism through autonomic pathways. The presence of FoxO1 in the hypothalamus is also related to the regulation of satiety and central sensitivity to insulin (TEANEY; CYR, 2023).

In insulin resistance, present in conditions such as obesity and type 2 diabetes, there is a reduction in the response of target tissues to insulin. This results in hyperglycemia and compensatory hyperinsulinemia. In the liver, insulin resistance keeps gluconeogenesis active even with high insulin levels. In muscle, there is a reduction in glucose uptake, and in adipose tissue, there is an increase in lipolysis, which raises circulating levels of free fatty acids and perpetuates insulin resistance (TEANEY; CYR, 2023).

A key molecular factor in this process is FoxO1, whose activity increases in states of insulin resistance. This transcription factor favors hepatic glucose production and reduces GLUT4 expression in peripheral tissues. Studies in animal models show that selective deletion or inhibition of FoxO1 can improve glycemic control, although its effects are dependent on the tissue in which it acts (TEANEY; CYR, 2023).

Finally, recent studies highlight the role of GDF15 (*Growth Differentiation Factor 15*) as a modulator of insulin sensitivity. As demonstrated by Sjøberg *et. al.* (2023), GDF15 improves glucose metabolism in liver, white adipose tissue (WAT) and brown adipose tissue (BAT), independently of weight loss. Its action is mediated by the GFRAL receptor in the brainstem, promoting β1/β2 adrenergic activation, which reduces hepatic glucose production and improves peripheral uptake. These findings indicate a possible therapeutic use of GDF15 in metabolic disorders such as obesity and type 2 diabetes (SJØBERG *et. al.,* 2023).

HOW INSULIN IS REMOVED FROM PLASMA

The elimination of insulin from the plasma, also known as clearance, is an essential process in regulating its bioavailability and maintaining tissue sensitivity to the hormone. After its secretion by pancreatic β-cells, insulin enters the circulation and is first taken to the liver, which is responsible for approximately 50 to 80% of its removal during the first hepatic passage (KOH, CAO & MITTENDORFER, 2022). In this organ, insulin binds to specific receptors on the hepatocyte membrane, is internalized by endocytosis and is subsequently degraded in lysosomal compartments by enzymes such as *insulin-degrading enzyme* (IDE).

The liver's ability to remove insulin can vary according to the physiological or pathological state. In individuals with obesity or type 2 diabetes, there is a significant reduction in the efficiency of this hepatic uptake and degradation, leading to an increase in circulating levels of the hormone. This decrease in hepatic clearance contributes to compensatory hyperinsulinemia, a factor that aggravates insulin resistance and perpetuates a vicious cycle of metabolic dysfunction (KOH, CAO & MITTENDORFER, 2022).

After passing through the liver, the insulin that remains in the circulation is filtered by the kidneys, which are responsible for approximately 30 to 40% of its clearance under normal conditions. In the proximal tubules, insulin is reabsorbed and degraded by mechanisms similar to those in the liver. Changes in kidney function, such as chronic renal failure, can prolong the half-life of the hormone, increasing its systemic exposure and contributing to worsening insulin resistance (GUBENSEK, 2023).

In addition to the liver and kidneys, peripheral tissues such as skeletal muscle and adipose tissue also take part in the insulin remo-

val process. The hormone's binding to specific receptors on the cell membrane promotes its internalization by endocytosis, followed by degradation or recycling, processes which regulate the duration and intensity of insulin signalling (RONNETT *et al.,* 1983).

Thus, insulin *clearance* is a complex mechanism regulated by multiple factors. Dysfunctions in this process, such as reduced hepatic clearance capacity, are associated with visceral obesity, systemic inflammation and metabolic dysfunction, contributing to worsening insulin resistance and increasing the risk of developing type 2 diabetes (KOH, CAO & MITTENDORFER, 2022).

Thus, the removal of insulin from plasma is a complex, multifactorial and finely regulated process, primarily involving the liver and kidneys, but with the participation of peripheral tissues. Alterations in any of these pathways can have significant implications for glycemic homeostasis and cardiometabolic risk, highlighting the relevance of the subject to both physiology and clinical practice.

EFFECTS OF OBESITY AND TYPE 2 DIABETES ON INSULIN CLEARANCE

Insulin is a fundamental hormone for controlling blood glucose, and its regulation in the body depends not only on its secretion, but also on its clearance, i.e. the removal of insulin from the circulation. This process takes place predominantly in the liver, which is responsible for removing between 50% and 80% of the endogenous insulin released by the pancreas. However, both obesity and type 2 diabetes significantly alter this mechanism, impairing glucose homeostasis and contributing to the onset and progression of insulin resistance (TRICÒ *et. al.,* 2021).

In obesity, reduced hepatic clearance of insulin is a striking feature. Excess adipose tissue, often accompanied by hepatic steatosis, directly interferes with the liver's ability to capture and degrade insulin. The presence of fat in the liver impairs insulin receptor signaling and reduces the expression of the *enzyme* IDE (*Insulin-Degrading Enzyme*), which is responsible for the degradation of intracellular insulin. In addition, the state of chronic low-grade inflammation common in obese people leads to the production of inflammatory cytokines such as TNF-α and IL-6, which negatively affect insulin receptor signalling and hinder its internalization and subsequent degradation. Insulin resistance in the liver, associated with high levels of free fatty acids and mitochondrial dysfunction, further compromises the removal of insulin from the circulation. As a result, compensatory hyperinsulinemia occurs, a response by the body to try to overcome peripheral insulin resistance, but which at the same time contributes to aggravating it (KOLB; MARTIN; KEMPF, 2021).

In type 2 diabetes, these mechanisms are even more compromised. Initially, the reduction in insulin clearance may represent an attempt by the body to prolong the action of the hormone in the face of resistance to its action. However, as the disease progresses, there is progressive failure of the pancreatic beta cells, leading to a drop in insulin production and deterioration in glycemic control. Liver dysfunction is aggravated by the presence of glycotoxicity and lipotoxicity, which affect the function of the liver's mitochondria and reduce the ability to metabolize insulin. As a result, the liver loses its efficiency both in signaling and in clearing the hormone (TAYLOR; BLAU; ROTHER, 2015).

The IDE enzyme, which is essential in this process, has its activity negatively regulated by inflammation and excess lipids, which makes it less efficient in states of obesity and diabetes. Studies show that reduced activity of this enzyme is associated with an increased risk of developing type 2 diabetes, precisely because it favors the maintenance of hyperinsulinemia

and insulin resistance. Hepatic insulin resistance compromises not only the uptake of the hormone by hepatocytes, but also the regulation of FDI itself, aggravating the metabolic imbalance (TRICÒ *et. al.,* 2021).

Therefore, in both obesity and type 2 diabetes, insulin clearance is profoundly altered. The combination of liver dysfunction, systemic inflammation, reduced FDI and changes in energy metabolism contributes to insulin remaining in the circulation for a long time, albeit ineffectively. This perpetuates the cycle of insulin resistance, contributing to the worsening of the metabolic condition. Understanding the mechanisms that affect insulin clearance is essential for developing therapeutic strategies aimed at restoring insulin sensitivity, improving liver function and more effectively controlling the metabolic alterations associated with obesity and type 2 diabetes.

CHRONIC LOW-GRADE INFLAMMATION

Chronic low-grade inflammation is a persistent condition characterized by a continuous but subtle activation of the immune system. Unlike acute inflammation, which is a beneficial and temporary response to infection or injury, this type of inflammation is silent, has no obvious symptoms and is strongly associated with several modern chronic diseases, such as obesity, type 2 diabetes, cardiovascular disease, neurodegeneration and even cancer (FAHED *et. al.,* 2022).

One of the main triggers of this inflammatory process is obesity, especially the accumulation of visceral fat. As adipose tissue expands excessively, it becomes metabolically active, secreting various pro-inflammatory cytokines such as TNF-α, IL-6 and MCP-1. These mediators not only perpetuate local inflammation, but also contribute to low-grade systemic inflammation. This process is sustained by the activation of inflammatory molecular pathways in cells, such as NF-κB and JNK, which are directly involved in insulin resistance, endothelial dysfunction, hepatic steatosis and other metabolic complications (FAHED *et al.,* 2022).

Moreover, inflammation is not limited to peripheral tissue. Recent evidence shows that it also affects the brain, particularly the hypothalamus, a critical region for controlling appetite, energy expenditure and metabolism. The activation of microglia - immune cells of the central nervous system - in the hypothalamus induces a local inflammatory response that impairs the signaling of hormones such as insulin and leptin. This phenomenon contributes to a vicious cycle: hypothalamic inflammation worsens appetite control and leads to weight gain, which in turn further intensifies inflammation (ORISAKA *et al.,* 2023).

Another fundamental component in this scenario is the role of the intestinal microbiota. An imbalance in the composition of intestinal bacteria - known as dysbiosis - can increase the permeability of the intestinal barrier, allowing endotoxins to enter the bloodstream and stimulating a systemic inflammatory response. This link between the gut and chronic inflammation is strongly influenced by diet (FAHED *et. al.,* 2022).

The modern diet, based on ultra-processed foods, rich in refined sugars, saturated fats and additives, has a pro-inflammatory effect. On the other hand, dietary patterns such as the Mediterranean diet, rich in fruit, vegetables, olive oil, whole grains, fish and nuts, have been shown to have a protective effect, with the ability to reduce inflammatory markers such as C-reactive protein (CRP), IL-6 and TNF-α. Bioactive compounds present in these foods - such as polyphenols, flavonoids, carotenoids, fibers and omega-3 fatty acids - play an important role in modulating the immune system and maintaining inflammatory homeostasis (TRISTAN ASENSI *et al.,* 2023).

Against this backdrop, chronic low-grade inflammation stands out as a key factor in the development and maintenance of various pathological conditions. Strategies to combat it involve lifestyle changes, including an anti-inflammatory diet, regular physical activity, stress management, improved sleep and, in some cases, the use of pharmacological therapies or supplements with anti-inflammatory action.

ADIPOKINE DYSFUNCTION

Adipose tissue, for a long time considered just an energy storage site, is now recognized as an important endocrine organ, responsible for the secretion of various adipokines - bioactive proteins that play critical roles in regulating metabolism, inflammation, energy homeostasis and immunity. Among the main adipokines are leptin, adiponectin, resistin, TNF-α and IL-6. In eutrophic individuals, these substances act in a coordinated manner to maintain metabolic homeostasis. However, in the context of obesity, there is a significant change in both the quantity and quality of these secretions, characterizing a picture of adipokine dysfunction (UNAMUNO *et al.,* 2018).

With the expansion of adipose tissue during the development of obesity, there is a disproportion between the growth of adipocytes and local vascularization. This leads to hypoxia, i.e. low oxygen supply to adipose tissue. This hypoxic condition triggers a series of cellular responses mediated by the transcription factor HIF-1α (Hypoxia-Inducible Factor 1-alpha), which regulates the expression of genes related to inflammation, fibrosis and remodeling of the extracellular matrix. As a result, there is an increase in the production of pro-inflammatory adipokines such as TNF-α, IL-6 and leptin, while adiponectin - which has an anti-inflammatory profile - has its expression reduced (TRAYHURN, 2013).

Hypoxia also favors the infiltration of immune cells into adipose tissue, mainly macrophages, which transform from an anti-inflammatory phenotype (M2) to a pro-inflammatory phenotype (M1). These M1 macrophages secrete high amounts of inflammatory cytokines, perpetuating a state of chronic low-grade inflammation characteristic of obesity. This inflammation impairs insulin signaling, contributing significantly to insulin resistance (UNAMUNO *et al.,* 2018; TRAYHURN, 2013).

Leptin, whose main function is to signal satiety and energy balance to the central nervous system, is increased in obesity (hyperleptinemia). However, the body develops resistance to leptin, making it ineffective in regulating appetite and energy expenditure. In addition, leptin has immunomodulatory functions, promoting the activation of T cells and macrophages and contributing to the inflammatory environment (TAYLOR, 2021).

On the other hand, adiponectin, which has anti-inflammatory, anti-atherogenic and insulin-sensitizing properties, is reduced in obese individuals. This reduction aggravates insulin resistance, favors atherosclerosis and compromises lipid and glucose metabolism. Adiponectin acts directly to inhibit TNF-α and the NF-κB pathway, two important mediators of inflammation. It also promotes the oxidation of fatty acids in the liver and muscles, which contributes to better energy utilization (TAYLOR, 2021; UNAMUNO *et. al.,* 2018).

Resistin, whose expression is also increased in obesity, has been associated with insulin resistance and increased systemic inflammation. This adipokine induces the production of IL-6 and TNF-α by immune cells, strengthening the inflammatory cycle in adipose tissue and other organs (TAYLOR, 2021).

Inflammatory and metabolic changes in adipose tissue lead to its remodeling, with collagen accumulation and the development of fibrosis. This fibrosis makes the tissue stiffer and functionally compromised. Apoptosis (programmed death) of adipocytes further increases the recruitment of immune cells, perpetuating inflammation. In addition, dysfunctional adipose tissue loses its ability to store lipids properly, which results in ectopic fat deposition in organs such as the liver and muscles, exacerbating insulin resistance and contributing to the development of hepatic steatosis (TRAYHURN, 2013; UNAMUNO *et al.,* 2018).

Adipokine dysfunction plays a central role in the genesis and progression of several obesity-associated comorbidities, including type 2 diabetes, dyslipidemia, hypertension, non-alcoholic fatty liver disease and cardiovascular disease. Low-grade systemic inflammation, resulting from the imbalance between pro- and anti-inflammatory adipokines, is one of the main pathophysiological mechanisms of these conditions (TAYLOR, 2021; UNAMUNO *et al.,* 2018).

Therefore, a thorough understanding of the mechanisms involved in adipokine dysfunction is essential for developing more effective therapeutic strategies. Interventions such as weight loss, regular physical activity and the use of drugs that modulate insulin sensitivity (such as thiazolidinediones) can help restore the functional profile of adipokines, contributing to metabolic improvement and reducing cardiovascular risk in obese individuals.

LIPID ACCUMULATION AND LIPOTOXICITY

The accumulation of lipids in tissues that are not specialized for fat storage, such as the liver, pancreas, skeletal muscle and heart, is a key factor in the development of various chronic metabolic diseases. This process occurs when there is an imbalance between lipid intake and the cells' ability to metabolize or store them safely, resulting in the abnormal deposition of free fatty acids and their derivatives (YOON *et al.,* 2021). Under physiological conditions, lipids can be oxidized in the mitochondria for energy production, converted into triglycerides for storage in lipid droplets or used in the formation of cell membranes. However, when these pathways are saturated or dysfunctional, cells begin to accumulate intermediate lipid species such as ceramides and diacylglycerols, which have toxic effects on cell function - a phenomenon known as lipotoxicity.

This process can originate from exacerbated uptake of fatty acids from the circulation, increased de novo lipogenesis from glucose or even uncontrolled mobilization of intracellular triglycerides. In pancreatic β-cells, studies show that overexpression of the FATP1 protein, responsible for fatty acid uptake, increases intracellular lipid content, leading to mitochondrial dysfunction, reduced insulin secretion and ceramide accumulation (CHEN *et al.,* 2012). This lipotoxic environment compromises cell viability and contributes directly to the development and progression of type 2 diabetes, since these cells are essential for regulating blood glucose.

In the liver, the accumulation of lipids observed in animal models fed a high-fat diet causes inflammation, oxidative stress and mitochondrial dysfunction, as well as activating endoplasmic reticulum stress pathways. These mechanisms lead to hepatocellular degeneration and the development of non-alcoholic steatohepatitis (NASH), a severe inflammatory condition that can progress to liver fibrosis, cirrhosis and even hepatocellular carcinoma (YOON *et al.,* 2021). Lipotoxicity in the liver, as in other tissues, is associated with the activation of inflammatory intracellular pathways such as the NF-κB pathway, increased production of reactive oxygen species (ROS), and the induction of apoptosis, or programmed cell death.

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Mitochondrial dysfunction is a critical component in this process, as failure to properly oxidize fatty acids results in the accumulation of toxic lipid substrates and a decrease in the cell's energy capacity (CHEN *et al.,* 2012). This situation further aggravates cellular stress and favors tissue damage. Lipotoxicity, therefore, is not just a secondary effect of excess lipids, but an active mechanism of cellular dysfunction, capable of profoundly compromising metabolic homeostasis.

In general, lipotoxicity emerges as a fundamental link between deregulated lipid metabolism and cellular dysfunction in multiple tissues. Its consequences include insulin resistance, pancreatic beta cell failure, liver inflammation, impaired cardiac function and reduced insulin sensitivity in skeletal muscle. Therapeutic strategies aimed at reducing the intake of saturated fatty acids, increasing the oxidative capacity of mitochondria and modulating safe lipid storage pathways are essential to prevent and treat the deleterious effects of lipotoxicity in modern metabolic diseases (YOON *et. al.,* 2021; CHEN *et al.,* 2012).

METABOLIC IMPACT

Metabolism plays a central role in the pathophysiology of obesity, directly influencing the energy balance and the way the body stores and uses energy. Obesity is the result of a persistent imbalance between calorie intake and total energy expenditure, which is made up of three main components: resting metabolic rate (RMR), the thermic effect of food (TEE) and energy expenditure from physical activity.

The RMT, which accounts for 60% to 70% of daily energy expenditure, corresponds to the energy needed to maintain vital functions at rest, such as breathing, circulation and cell function. WTP represents approximately 10% of total expenditure and is related to the digestion, absorption and metabolization of ingested nutrients. The most variable component is physical activity expenditure, which can reach up to 50% of daily energy expenditure in active individuals. In people with obesity, these mechanisms are significantly altered and a relatively low BMR for body weight is common, which hinders the weight loss process and favors the accumulation of body fat.

Another crucial factor is the function of adipose tissue, which goes beyond a mere energy reservoir. White adipose tissue (WAT) acts as an active endocrine organ, releasing inflammatory cytokines such as TNF-α and IL-6, which contribute to a chronic low-grade inflammatory state. This process impairs insulin signaling, promoting insulin resistance and facilitating the onset of metabolic disorders such as type 2 diabetes and non-alcoholic fatty liver disease. On the other hand, brown adipose tissue (BAT), whose main function is thermogenesis - that is, the dissipation of energy in the form of heat - shows reduced activity in obese individuals, compromising the body's ability to oxidize energy substrates. Recent research also highlights the potential of "browning", the process of converting white cells into cells with BAT characteristics, as a possible therapeutic approach to increasing calorie expenditure (FERNANDO *et. al.,* 2022).

Hormonal and genetic factors also have a significant influence on metabolism and the development of obesity. Hormones such as leptin, insulin, ghrelin and cortisol are essential regulators of appetite, satiety and energy metabolism. In obesity, resistance to leptin and insulin is common, which impairs satiety signaling and glycemic control, respectively. Ghrelin, in turn, stimulates appetite and tends to increase with low-calorie diets, making it difficult to adhere to treatment. In addition, genetic variants can affect both basal energy expenditure and the propensity to store fat, modulating the individual response to diet and exercise.

One of the biggest challenges in maintaining weight loss is adaptive thermogenesis, a compensatory mechanism by which the body reduces its basal metabolism in response to calorie restriction and weight loss. This process makes it difficult to maintain weight loss in the long term and favors regaining body weight.

Thus, metabolism not only influences the onset of obesity, but also largely determines the effectiveness of therapeutic interventions. Strategies aimed at increasing energy expenditure, improving insulin sensitivity, reducing metabolic inflammation and modulating the activity of different types of adipose tissue represent promising approaches for the sustainable treatment of obesity (FERNANDO *et al.,* 2022).

DISCUSSION

The understanding of obesity as a multifactorial condition, especially in the context of insulin resistance, has evolved considerably, revealing an intricate interaction between adipocyte components, chronic low-grade inflammation and hormonal dysfunctions. Recent studies highlight that adipose tissue, especially in its visceral fraction, is an active endocrine organ that regulates essential metabolic processes through the distribution of adipokines and bioactive mediators (FONSECA--ALANIZ *et al.,* 2006; LEWIS & BRUBAKER, 2021). Its expansion in obesity promotes changes in the cartilage profile of adipokines, such as an increase in leptin and a decrease in adiponectin, as well as increasing the infiltration of immune cells, especially M1-type macrophages, which are responsible for releasing pro-inflammatory cytokines (UNAMUNO *et al.,* 2018; TRAYHURN, 2013).

These cytokines, such as TNF-α, IL-6 and IL-1β, activate intracellular pathways, including NF-κB and JNK, which inhibitively phosphorylate the IRS-1 receptor, compromising insulin signal transduction and promoting insulin resistance (AHMED *et al.,* 2021; DEFRONZO, 2009). In addition, lipotoxicity resulting from increased lipolysis of free fatty acids, specific to obesity, contributes to oxidative stress and mitochondrial dysfunction, further aggravating insulin resistance and facilitating the development of type 2 diabetes (YOON *et al.,* 2021; FERRANNINI, 2021).

Pancreatic β-cell dysfunction also plays a central role in this process, with evidence showing that insulin resistance initially compensates through hyperinsulinemia, but progressively leads to insulin periodicity supervision, worsening the clinical picture (BERGMAN *et al.,* 2002; ESSER & KAHN, 2020). In addition, leptin resistance and changes in ghrelin levels make it difficult to control appetite and regulate body weight, perpetuating the vicious cycle of weight gain and inflammation (APOVIAN, 2016; TRISTAN *et al.,* 2023).

Additional factors, such as resistance to insulin action in the liver, muscle and adipose tissue, reinforce the complexity of the condition, showing that insulin resistance is not an isolated condition, but a consequence of multiple interconnected dysfunctions (GASTALDELLI & DEFRONZO, 2021; KOH *et al.,* 2022). Therapeutic interventions aimed at reducing inflammation, improving insulin sensitivity and restoring mitochondrial function show promise, especially those that modulate the distribution of adipokines or involve dietary strategies such as low-carbohydrate or Mediterranean diets (TRACHTENBERG *et al.,* 2021; TRACHTENBERG *et al.,* 2021).

On the other hand, environmental and behavioral factors, including ultra-processed food and a sedentary lifestyle, are indicated for the maintenance of chronic inflammation, reinforcing the need for multidisciplinary approaches involving lifestyle changes, nutritional control and possible pharmacological interventions (TRAYHURN, 2013; TRISTAN *et al.,* 2023). It also highlights the importance

of strategies that promote modulation of the adipocyte microenvironment, changes to reduce hypoxia and oxidative stress, factors that perpetuate inflammatory dysfunction and insulin resistance (TRAYHURN, 2013; FONSECA-ALANIZ et al., 2006).

In short, insulin resistance in obesity results from a complex interaction between immuno metabolic factors, adipocyte dysfunction and hormonal alterations, reinforcing which practices require a holistic approach. An in-depth understanding of these mechanisms offers significant potential for the development of more targeted therapies, capable of interrupting this vicious cycle and preventing complications such as type 2 diabetes and cardiovascular disease.

CONCLUSION

From the article submitted, we can conclude that obesity, especially abdominal obesity, is a multifaceted risk factor that promotes a complex interaction between adipose tissue, interactive processes and hormonal dysfunctions, culminating in insulin resistance. Adipose tissue, currently recognized as an active endocrine organ, plays a central role in maintaining metabolic homeostasis through the dysfunction of adipokines and other bioactive mediators. In obesity, the expansion of visceral adipose tissue causes an infiltration of immune cells, such as macrophages, and alters the secretory profile of adipokines, favoring a low-grade inflammatory environment.

This chronic inflammation activates intracellular pathways such as JNK and NF-κB, which inhibitively phosphorylate the IRS receptor, impairing insulin signaling. In addition, the increase in lipolysis and the consequent excess of free fatty acids strains oxidative stress, mitochondrial dysfunction and insulin resistance in the main target tissues - muscular liver, skeletal and adipose tissue. Hormonal changes, such as leptin resistance and high ghrelin levels, also play a role in appetite deregulation and fat storage, aggravating the clinical picture.

Therefore, insulin resistance in obesity does not arise from a single factor, but from a complex interaction between inflammatory factors, adipocyte dysfunction, hormonal signals and metabolic alterations. Understanding these mechanisms offers a broader perspective for developing targeted therapeutic strategies that can act to reduce the inflammatory state, improve insulin sensitivity and prevent complications such as type 2 diabetes and cardiovascular disease.

Thus, adipose tissue emerges as a crucial target in the clinical and research approach to tackling obesity and its metabolic consequences, highlighting the need for multidisciplinary interventions that promote the modulation of the inflammatory environment and the re-establishment of endocrine-metabolic homeostasis

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