Chapter

Metabolic Changes in Obesity

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Abstract

The exact basis for the increase in global obesity rates is complex, so obesity should not be simply viewed as a biochemical problem of energy imbalance. While imbalance in energy metabolism is the main cause of obesity, only 5% of patients return to a normal weight after the incorporation of dietary changes. Eating behavior is enormously complex. It is governed by brain biochemistry influenced by many interdependent peptides or lipids. Excess body fat is the defining characteristic of this disorder, linked to the occurrence of a number of metabolic irregularities, which lead to other health problems. Adipose tissue plays an essential role in the metabolic process of energy balance, essential for understanding the phenomena associated with obesity.

Keywords: metabolism, obesity, food, energy, biochemistry

1. Introduction

1.1 Definition of obesity

Obesity has been defined and categorized by the application of body mass index (BMI), the most used indirect method to define and classify it, which is limited by its low specificity of 36–66% because this method does not allow to distinguish adipose tissue, as well as hydration index or fat mass. However, it continues to be widely used in all age groups because it is simple to apply and economic [1].

Pasca and Montero take a different approach [1]. They did not define obesity as an increase in adipose tissue, but evaluated it as a systemic pathology where various organs are involved, resulting in a deterioration of metabolism, characterized by inflammatory processes, expressed according to the relationship between the genome and the environment, where the phenotypic expression is acquired as a product of this interaction, mainly the increased deposition of adipose tissue [1].

1.2 Ubiquity of adipose tissue

Adipose tissue constitutes 20–28% of the weight in healthy people and 80% in obese people, depending on several factors such as sex, energy status, distribution, and location of adipose tissue that affect its function [2].

Preadipocytes, adipocytes, fibroblasts, macrophages, monocytes, vascular stromal cells, and innervating cells are among the variety of cell types seen in adipose tissue; however, most of these cells do not appear to be adipocytes [3]. Up to 80% of the DNA obtained from adipose tissue is derived from vascular cell, fibroblast, leukocyte,

and macrophage; three varieties of adipose tissue coexist according to function, color, vascularization, and structure [4].

As part of the connective tissue group, adipose tissue provides cohesion to organs or systems, supports structure, and is a key regulator of energy balance [5]. It is a complex endocrine tissue with high metabolic activity, and its function is to maintain energy balance, manage body temperature, regulate lipid and glucose metabolism, control blood pressure, and prevent blood clotting processes [6, 7].

Obese persons produce less elastin and more collagen types I, III, V, and VI, bronectin, and laminin in their adipose tissue than lean people [8]. These changes promote the growth of fibrotic tissue, which is more common in visceral fat than in subcutaneous fat [8]. Fibrosis, which favors lipid storage in the liver, pancreas, heart, skeletal muscle, limits the process of adipose tissue expansion. Collectively, these changes lead to lipotoxicity [8, 9].

Hepatic overload caused by fatty acid accumulation is the origin of increased hepatic gluconeogenesis and lipoprotein metabolism in hepatocytes, which also prevent the breakdown of insulin and apolipoprotein B [8, 9].

2. Types of adipose tissue

2.1 White adipose tissue

In each adipose cell of the target tissue there is a lipid vacuole, where lipids are stored for use when energy demand is required [10]. Triacylglycerols make up 90–99% of the total lipids in the vacuole and provide sufficient energy to meet the daily energy needs of an adult [10, 11].

White adipose tissue produces proteins with a wide range of functions in relation to immunity, proinflammatory cytokines, complement, fibrinolytic system, renin–angiotensin system, lipid mobilization, and steroid enzymes. It also produces large amounts of adipokines and lipokines, which act as metabolic regulatory hormones [2].

Table 1 demonstrates the correlation between adipokines or lipokines produced with anti-inflammatory activity and those with pro-inflammatory and proatherogenic action in metabolic variations in obesity [12].

When there is an excess of energy, the functionality of adipocytes decreases, which is reflected in the imbalance of adipokine production [12]. Adipose tissue can buffer energy profusion through lipid storage is the result of proper expansion of this tissue, which is a sign of proper functionality [13].

Adipose tissue can develop through hyperplasia and hypertrophy and degenerate into malfunction with excess energy. This results in cardiometabolic risk leading to increased lipid deposition and decreased lipid utilization [5, 13].

2.2 Adipocytes

They are considered specialized cells that store lipids, but this is not their primary purpose, as evidenced by beta cells, muscle cells, and neurons [14]. Mature adipocytes develop when markers include the expression and adipocyte-associated hormones, cytokines, and enzymes associated with lipid storage and release into the bloodstream [14].

Adipokine/lipokine	Metabolic effect	Secretory organ or tissue
Leptin	Thermogenesis, lipid oxidation, insulin sensitivity, and anorexigenic impact.	Adipocytes, epithelium of the stomach and intestines, placenta, muscles, mammary gland, and brain.
Adiponectin	Lipid oxidation, reduction of liver gluconeogenesis, reduction of monocyte adhesion, reduction of inflammation and atherosclerotic risk, and anorexigenic effects.	Adipocytes
Omentin	Increased glucose uptake prompted by insulin and peptide release of orexigenic peptides are two aspects of orexigenic impact.	Intestinal cells, vascular stroma, and visceral adipose tissue.
Resistin	Insulin resistance and fatty acid synthesis in the liver have anorectic effects.	Adipocytes
Reintol-4 binding protein	Altered GLUT4 expression leads to reduced retinol transport and insulin resistance.	Adipocytes
Quemerin	If administered persistently, it causes adipogenesis, angiogenesis, proinflammatory, and orexigenic effects.	Adipocytes, hepatocytes, and lung cells
Vistatin	Proinflammatory and proatherogenic factor affecting the development of obesity.	Visceral adipocytes
Palmitoleic acid	Lipogenesis is decreased by insulin.	Adipocytes
Palmitic acid-hydroxyl-stearic acid (PAHSA)	The synthesis of insulin, glucagon-like peptide 1 and other hormones, glucose uptake and anti- inflammatory actions.	Fasting subcutaneous and peri-gonadal adipocytes.

Table 1.
Adipokines/lipokines, metabolic effect, and secretory organ or tissue.

Perhaps the most interesting aspect of adipocyte differentiation is the way in which preadipocytes are added to the adipocyte repertoire, a repertoire of peroxisome-activated receptor family members and protein receptors that bind CCAAT enhancers [14].

Mature adipocytes are highly specialized cells that are central to energy storage and delivery mechanisms and are subject to very tight central and peripheral control, given these characteristics, it is not uncommon to find that adipose tissue is part of several axes, such as the adipose–insulin axis, the adipocyte–vascular–brain axis, and the adipocyte–myocyte axis [14, 15].

On another scale, the metabolic activity of adipocytes changes significantly in the hypoxia state. Indeed, some glycolytic enzyme genes, such as hexokinase 2 (HK2), phosphofructokinase (PFKP), and GLUT1, show increased expression in cultured adipocyte cells under hypoxia conditions. Moreover, while GLUT4 is the predominant isoform in adipocytes, GLUT1 is the most efficient glucose transporter at low oxygen levels. These changes suggest that adipocytes have increased glucose uptake and metabolism, as expected in hypoxic areas, which are supported by their increased secretion of lactate [15].

2.3 Myocytes

Myocytes are affected by obesity, while adipocytes slowly perish from asphyxia [15, 16]. The adipo–hypoglycemic axis plays a key role in obesity and accompanying diseases, such as type 2 diabetes, due to their mutual interaction. Under conditions of overfeeding, adipose tissue does not store excess energy in an adequate manner, resulting in a "spillover" impact on the entire body [15, 16].

2.4 Adiponectin

Adiponectin normalizes glucose metabolism and enables regulation of vascular homeostasis by interfering with key signaling pathways in the endothelial cells and reducing inflammatory activity in the subendothelial region. Adiponectin levels are often low in obese individuals, indicating that obesity, diabetes mellitus type 2 (DM2), and cardiovascular disease (CVD) are examples of insulin-resistant and inflammatory conditions that reduce the amount of insulin produced [17, 18].

Two receptors, AdipoR1 and AdipoR2, were initially cloned in 2003 by Yamauchi et al., modulate the actions of adiponectin [16]. Like the G protein-coupled-receptor (GPCRs) group, being an integral membrane protein with seven transmembrane domains. Adiponectin receptors, unlike GPCRs, have an internal N-terminal and an external C-terminal domain, both receptor subtypes can form homo- and heteromultinomers [18, 19]. In the pancreatic cell, high amounts of fatty acids (FAs) enhance the production of lipoprotein lipase, both receptors have been identified [18, 19].

2.5 Brown or brown adipose tissue (BAT)

This tissue in humans has metabolically active structures, and it consumes energy through thermogenesis to regulate body temperature [12]. It regulates energy balance by regulating metabolism. This is done by stimulating uncoupling proteins, and it uses proton flux from oxidative phosphorylation to produce heat, by activating beta-adrenergic receptors in this tissue [20].

The brown adipocyte is a biological heat-producing powerhouse due to its unique ability to uncouple the process of oxidative phosphorylation and respiratory chain in its mitochondria [21]. As of the uncoupling protein UCP1, which renders the inner membrane of mitochondria proton permeable and causes brown adipocyte mitochondria to act as a metabolic substrate oxidation machine to produce heat rather than AT, this tissue is active in adults and abnormally inactive in obese people [21].

Differentiation in certain brown adipose tissue areas of white adipose cells, and increased activation of adrenaline and some cytokines promote trans-adaptive thermogenesis. This increases the expression of UCP1, the presence of brown and beige adipose tissue markers, enhances energy consumption, and promotes glucose tolerance [22]. The ability of brown and beige adipocytes to convert chemical energy into heat contributes to adaptive thermogenesis, a metabolic process whose metabolic function is correlated with a person's overall metabolic profile [22].

2.6 Beige adipose tissue

When experimental animals were exposed to prolonged cold to induce thermogenesis, beige adipose tissue (BAT) activation occurred with the development of brown adipose tissue at sites typical of white adipose tissue [23, 24].

Beige adipocytes that develop at the level of white adipose tissue have a completely different cell lineage than "traditional" brown adipocytes, according to several studies [25, 26].

Investigation of the browning process as a means of promoting BAT activity in the organism is of interest given this, along with the inducibility in the development of beige adipocytes in response to environmental variables [23, 24].

Following transdifferentiation, UCP1-expressing beige adipocytes can manifest in response to hormones, exercise, or cold exposure. These cells show a pattern of thermal gene expression that elevates energy and oxygen consumption [27]. Adipose tissue depots wait for environmental cues to become active, activating hormones such as leptin, FGF 21, and U2P (UF2) [3].

3. Vasocrine regulation in pathological conditions

Consistent with the plasticity of adipocytes observed in their preadipocyte differentiation into macrophages and hypertrophy/hyperplasia of differentiated adipocytes, the epicardial adipocyte also undergoes several changes [25]. Elevated synthesis of saturated free FAs, which bind toll-like receptor-4 (TLR-4) in macrophages and activate NF-kB, as well as increased TNF-α, are two modifications observed in larger adipocytes [25, 26]. However, macrophages may also develop from monocytes that spread through the subendothelial region via CAM-1 and MCP-1, rather than solely from differentiated preadipocytes [25, 26].

Most of the adipokines generated from adipose tissues have receptors expressed on blood arteries, which is crucial for cardiovascular pathology [28]. Proinflammatory adipokines are transported from epicardial fat to the vascular wall much more easily and efficiently due to the proximity of the epicardial adipose tissue (EAT) and coronary arteries. TNF from EAT readily diffuses into the blood arteries during RV by blocking the PI3K pathway in the endothelial cells [28].

In situations of insulin resistance, it has been confirmed that increased TNF-α locally induces a vasoconstriction related to ET-1 synthesis in coronary artery endothelium [25]. Together with the maintenance of chronic inflammation and insulin resistance in endothelial cells, this also plays a role. The extracellular signal-regulated kinase, which moves from the cytosol to the nucleus and triggers ET-1 production, is phosphorylated in this TNF-activated pathway [26, 28].

4. Energy metabolism of obesity

Imbalances in energy metabolism can lead to obesity [29]. In general, molecules that cause hunger tend to reduce energy expenditure, and compounds that cause satiety tend to increase the body's energy expenditure. This is because the basic mechanism of biochemical control of energy behavior is highly redundant and pleiotropic. This is congruent with the energy saving or energy expenditure tactics that the body uses depending on physiological and dietary circumstances [29].

According to Rial-Pensado et al. [30], the AMP-activated kinase enzyme plays a crucial role in this process by regulating brain-derived signals that regulate energy balance from the hypothalamus [30].

The malfunctioning of both cell typologies is due to an increase in white fat cells and a reduction in brown fat cells as a result of excessive energy intake [31]. The

intervention of the immune system in adipocytes is crucial to maintain the balance in both tissues and favors the oxidation of FAs, which prevail in brown and beige cells [31].

It is important to understand these connections and the sequence of events that occur throughout the development of obesity [32].

4.1 Obesity and energy balance

The energy balance is neutral when these two variables are equal, i.e. balance between intake and expenditure; when there is an imbalance if the energy intake is greater than that expended, as with obesity, body weight slowly increases [33].

At the biochemical and physiological level, the many components of the energy balance equation are intrinsically related, so that alterations in one component of the equation may have a reverse effect on another; conversely, when food is restricted, as in the case of fasting, energy is conserved, and appetite is increased [33]. Despite these homeostatic reactions to preserve homeostasis, sedentary habits and/or chronic caloric excess can affect the efficacy of these regulatory mechanisms [33].

4.2 Hypothalamic regulation of energy balance

The hypothalamus is divided into nuclei or clusters of anatomically distinct neurons, which are linked by axonal projections to form neural circuits. The neuropeptides orexigenic, feeding promoter, agouti-related protein (AgRP), and neuropeptide Y are expressed by a cluster of neurons [34]. A second population of neurons expresses the anorexigenic products propiomelanocortin, which is the precursor of melanocyte alpha-stimulating hormone; these neurons project to other second-order neurons present in other hypothalamic nuclei [33].

The dorsomedial, lateral, and paraventricular nuclei are some of the secondary hypothalamic nuclei served by this group of first-order neurons, which send their axons widely to the central nervous system (CNS) [34]. The ventromedial nucleus of the hypothalamus, which is dorsal to the arcuate nucleus (ARC), receives mainly projections from AgRP/NPY and CART/POMC neurons. Axons from ventromedial nucleus (VMH) neurons also travel to the ARC, secondary hypothalamic nuclei, and brainstem areas [34].

4.3 AMPK

In eukaryotes, an enzyme known as an AMP-driven protein kinase functions as an energy sensor [35]. AMP-activated protein kinase (AMPK) is a heterotrimeric complex that exists at the molecular level. It consists of two regulatory and catalytic subunits that include serine/threonine protein kinase domains that are phosphorylated at threonine. The AMPK complex can exist in 12 different configurations in mammals because several genes are involved in the expression of each component [36].

4.4 Hypothalamic AMPK as a regulator of ingestion

ARC, paraventricular nucleus (PVN), VMH, and lateral hypothalamic area (LHA) are some of the hypothalamic areas where AMPK is expressed. The fact that AMPK modification is associated with insulin resistance, obesity, hormonal problems, metabolic changes, and cardiovascular disease serves as evidence of its physiological value [36].

Accordingly, fasting elevates hypothalamic AMPK activity, while refeeding inhibits it, acting as an energy sensor [37]. There is evidence linking hypothalamic

AMPK in the regulation of food intake. The orexigenic function of ghrelin is related to several findings on the hypothalamic role of AMPK in the management of energy balance [36].

4.5 Hypothalamic AMPK as a regulator of thermogenesis

Hypothalamic AMPK is involved in the control of brown adipose tissue thermogenesis by the CNS. Pharmacological and genetic studies demonstrate that VMH causes a decrease in weight and increase in the thermogenic program in the BAT in depletion of AMPK, the deduction of its activity, in response to thyroid hormones increases thermogenesis [34, 37].

4.6 A regulator of glucose homeostasis: Hypothalamic AMPK

These neurons are found in specific regions of the brain, including certain hypothalamic nuclei. Excess glucose inhibits the ability of the hypothalamus to activate AMPK, resulting in prolonged hypoglycemia. The ARC and VMH primarily control this impact. By fusing nutritional and hormonal information in the hypothalamus, AMPK functions as a crucial sensor in energy balance [36].

By accumulating altered lipid species that are "toxic," lipotoxicity affects cellular functioning as well as organs and tissues. Most of these lipid species have critical structural, signaling, or bioenergetic substrate functions that support the equilibrium state of the cell. However, harmful lipid derivatives can be produced by lipid species that are created as a direct result of chemical agents of reactive oxygen or nitrogen agents [36].

4.7 Pathophysiological and metabolic changes in obesity

Lipid reserve, prolonged inflammation, tissue hypoxia, endoplasmic reticulum (ER) stress **(Figure 1)**, and the emergence of insulin resistance constitute the physiological process of the development of overweight to obesity [38].

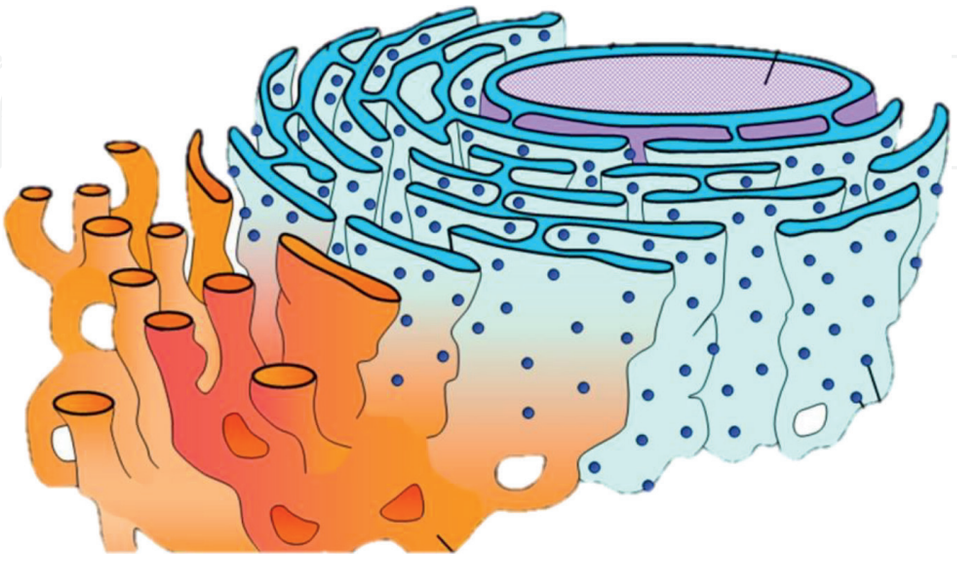

Figure 1.
The endoplasmic reticulum (ER) is a central cell organelle in which transmembrane and secretory proteins are synthesized, folded and matured.

The ER is a central cell organelle in which transmembrane and secretory proteins are synthesized, folded, and matured.

4.8 Lipid accumulation

Increased visceral and intra-abdominal fat is a sign of systemic fat deposition which triggers the production of cytokines that favor the onset of insulin resistance, inflammation, and development of cardiovascular pathology [31, 39].

5. Lipoinflammation in obesity

Adipose tissue has a significant impact on the inflammatory, antifibrinolytic, and vasoactive cascades, indicating that it has an immediate effect on the inflammatory process [38, 40]. Adipocytokines, which are elevated by hyperplasia, proliferation, and differentiation of preadipocytes, are the cytokines responsible for controlling the physiological response of adipose tissues [40].

The visceral fat depot expands with decreasing lipogenic capacity and by the process of hypertrophy, when the subcutaneous adipose tissue does not adequately store surplus energy exceeding the storage level [41].

The release of proinflammatory adipocytokines causes the macrophage scrolling inhibitor, IL-6 metalloproteinases, PAI-1, the vascular endothelial growth factor leptin [42]. Oxygen triggers cell death in the more peripheral fat cells, which transcribe into increased inflammation [42]. Hypoxia of adipose tissue is generated with death of peripheral adipocytes, transformation of M2 to M1 macrophages, angiogenesis, and increased production of inflammatory and anti-inflammatory proadipocytokines as shown in **(Figure 2)** [43].

This dysregulation is the result of adiponectin's disabling of NF-kB activation [43]. Macrophages located in obese adipose tissue alter and remodel with marked

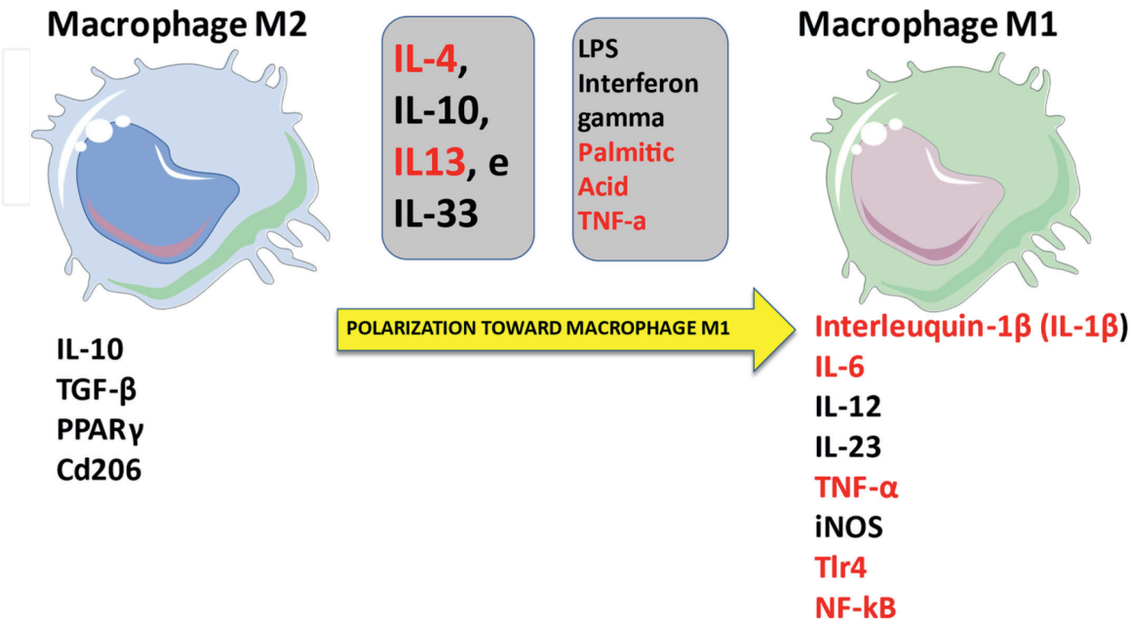

Figure 2.
Source: Valmore Bermúdez.

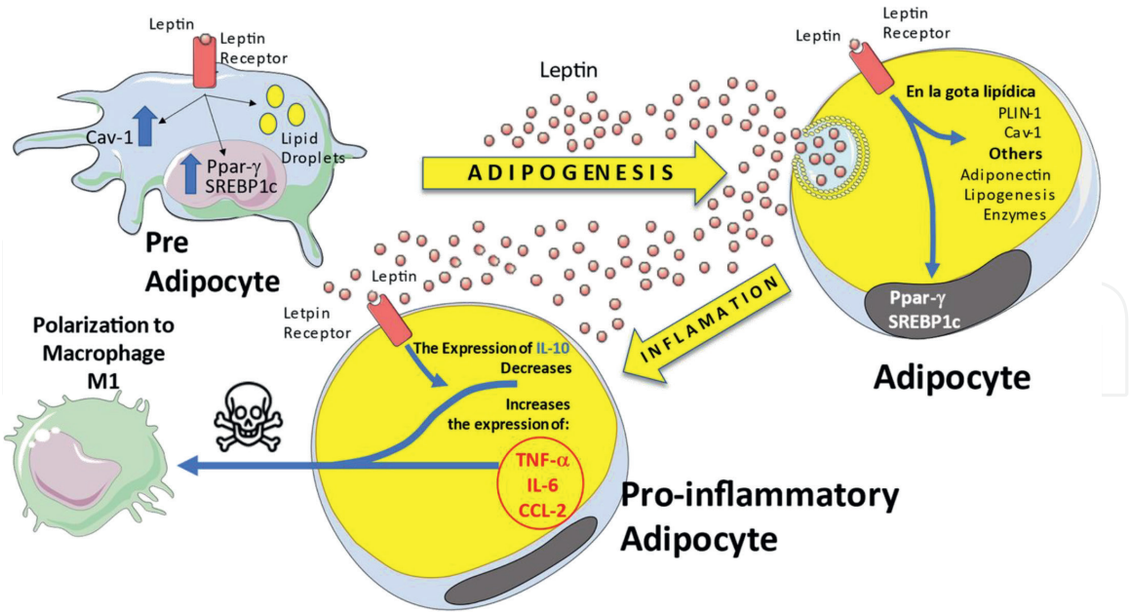

Figure 3.
Source: Valmore Bermúdez.

heterogeneity in activity and function due to complex metabolic and immunological changes that vary according to the expression of specific antigens [43].

The phenomenon of a transient "phenotypic shift" from the primarily anti-inflammatory M2 state of macrophage polarization to the more pro-inflammatory M1 form takes place during negative energy equilibrium [44].

The percentage of macrophages increased from 10–40% in the cells responsible for the release of proinflammatory chemicals, particularly TNF, in more than 50% of adipose tissue as shown in **(Figure 3)** [44, 45].

Metabolic and inflammatory processes are strongly connected and influence the progression of obesity, despite the fact that the mechanism of macrophage incorporation and adipose tissue filtration operate independently [45].

One of the most important indicators of subclinical inflammation is C-reactive protein (CRP) [46]. Regarding the regulation of macrophages, CRP has been related to M1 polarization, which is created in stimulating endothelial cells to produce M-CSF and activates NF-B [47]. Finally, since adiponectin is a hormone that promotes M2 polarization through AMPK, PPAR-, and PPAR-, low levels of adiponectin, as observed in the presence of visceral obesity, also favor M1 polarization [47, 48].

M2 polarization requires the attenuation of several mediators that promote M1 [49]. In this regard, the p50 subunit of NF-B has been found to inhibit NF-B-induced M1 polarization. Similarly, the complement protein C1q has been found to inhibit NF-B activation of macrophages during endocytosis and processing of lipoproteins, reducing the release of inflammatory cytokines [47, 49, 50].

As can be seen, macrophage polarization in each situation is a power play, the outcome of which is determined by the most common type of microenvironmental stimuli as can be seen in **(Figure 4)** [47, 50].

5.1 Consequences of lipoinflammation

Lipoinflammation involves a number of interconnected pathways that support and maintain obesity [53]. Chronic acceleration of proinflammatory pathways is one of the

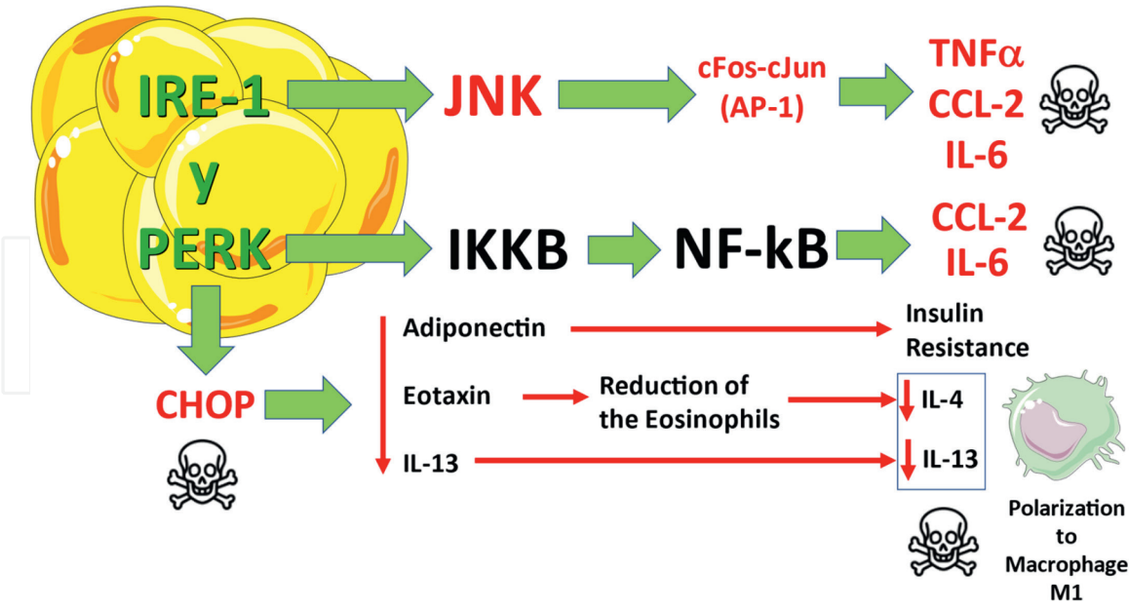

Figure 4.
Source: Valmore Bermúdez.

key processes underlying the relationship between a chronic low-grade lipoinflammatory state, the emergence of insulin resistance, and development of comorbidities [51, 52].

According to the study, comorbidities, persistent low-grade lipoinflammation, and the occurrence of insulin resistance are related [52]. The maintenance of plasma insulin levels is known as hyperinsulinemia [52].

At the level of the CNS, insulin inhibits the action of leptin, promoting satiety and energy expenditure [52, 53]. The catalytic portion of the receptor is activated by binding to its transmembrane receptor heterotetrameric [52, 53].

To bind to more intracellular substrates and maintain signaling, the receptor undergoes autophosphorylation [55]. Phosphorylated tyrosine residues bind and phosphorylate various substrate proteins of the insulin receptor, allowing phosphoinosidase to bind and become active, thus connecting insulin signaling with neuronal firing rate regulation [53].

The signal transducer and transcription generator (STAT), which links insulin signaling to gene transcription of neurotransmitters responsible for appetite control and thermogenesis, is phosphorylated following phosphorylation of JAK-2 [53].

The hormone leptin is a part of the class I cytokine receptors lacking intrinsic catalytic activity. The JAK-2 enzyme binds to the leptin receptor forming a dimeric structure when bound to it, favoring the uptake of a second adjacent receptor unit [54].

A protein called STAT-3 is also recruited and phosphorylated, and it is this protein that is ultimately responsible for sending the leptin signal to the nucleus, controlling neurotransmitter transcription [54]. The signaling molecule involved in the anorexigenic effects of leptin is STAT-3, which regulates the transcriptional activity of numerous different genes [54, 55].

When SOCS3 is increased, it interacts with the leptin-JAK-2 receptor and disables leptin signaling [56]. The JAK-2/STAT-3 pathway is predominantly regulated by leptin in the hypothalamus, and insulin modulates this pathway [55]. There is a crosstalk in the insulin and leptin signaling pathways in the regulation of the satiety mechanism [54].

5.2 Lipotoxicity due to lipid modification

Some lipids play substantial roles in revising the catalytic activity of enzymes and their cellular localization, in addition to their structural and cell signaling functions, for example, by allowing translocation to the plasma membrane or the nucleus [31]. In describing the lipid modifications that determine lipotoxicity, we can also include modifications caused by the products of lipid peroxidation. In particular, we can focus on 4-hydroxynonenal, malondialdehyde and acrolein, which can mediate lipid elimination and, at the same time, have effects other than toxicity, such as the formation of amino acid side-chain conduits [31].

5.3 Hypoxia and ER stress

Obesity generates an increase in tissue irrigation, as the amount of adipose tissue directly affects blood flow [38]. In this situation, the aforementioned pro-inflammatory systems are activated, which is considered an aggression, favoring the reduction of blood flow and thus restricting the inflow of nutrients and unregulated tissue growth [38].

Nitric oxide is an important vasodilator of adipose tissue and is produced more frequently in hypoxic environments [57]. Anaerobic glycolysis is initiated, which releases energy in the form of ATP and changes the redox state of the cell, leading to a decrease in oxygen level, maintaining tissue hypoxia, and inducing acidification [57].

It generates dysfunction of mitochondria and ER, affects the insulin signaling pathway, and favors the secretion of proinflammatory cytokines in tissue [57].

The malfunction of protein production is called ER stress, also known as ER dysfunction. Due to a deposit of defective unfolded or misfolded proteins into the lumen of the ER or excessive protein production [58]. This response is triggered by any physiological or pathological circumstance that obstructs the ability of the ER to fold proteins. Inflammation and insulin resistance associated with obesity are closely related to UPR activation [58].

Adipocyte lipolysis is mediated by ER stress, by producing more IL-6 and less leptin and adiponectin, contributes to dysregulation of adipokine secretion [57, 58].

6. Insulin resistance

The increased blood glucose level causes the pancreatic islets of Langerhans to secrete insulin, which causes these tissues to take up more glucose. In addition, hepatic and muscle glycogen generation is enhanced by the process of dephosphorylation and activation of glycogen synthase [59].

Through activation of SREBP-1c, insulin exerts a hypogenic influence on lipid metabolism, promoting lipid synthesis and reducing lipid degradation. Insulin directly affects the expression, phosphorylation, and dephosphorylation of enzymes involved in gluconeogenesis and hepatic glycogenolysis [59].

Insulin resistance inhibits the body's ability to regulate blood glucose by reducing the cellular responsiveness to normal amounts of circulating insulin [60].

The insulin-signaling pathway is regulated by the insulin receptor, a tyrosine kinase that phosphorylates receptor substrates upon binding and activation. The expression, substrate binding, phosphorylation, and kinase activity of the insulin receptor can be modified [53].

Such phosphorylation can lead to the activation of the two major protein kinase signaling pathways, the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) and serine–threonine Akt pathways, responsible for the arrangement of cell growth, gene expression, and protein synthesis and glucose uptake [53].

Excessive increase of lipids, triacylglycerol, saturated FAs in myocytes, promotes the synthesis of harmful lipid intermediates such as ceramides and diacylglycerols which have an adverse effect on insulin signaling, persistent inflammation, influences insulin signaling, where invading macrophages, release more TNF, thereby activating c-Jun-terminal kinase (JNK) and kappa-B kinase (IKK) signaling kinases promoting serine phosphorylation at IRS-1, favoring the onset of insulin resistance and type 2 diabetes [61].

7. Metabolic stages of obesity

In obesity, there are three metabolic stages involved in its development.

7.1 Insulin control: gradual weight gain

Insulin stimulates the production of glycogen, an energy store, and glucose oxidation at the hepatic level during the postprandial phase, producing ATP as an energy source and maintaining stable glucose levels between meals and during sleep. The liver uses a process called lipogenesis to convert the extra glucose into FAs [62, 63].

High-density lipoprotein transports the excess cholesterol to the hepatic level, where it interacts with nascent LDLV once in the blood (reverse cholesterol transport) [62, 63].

7.2 Liver and adipose tissue metabolism under insulin control

Adipose tissue: lipoprotein lipase (LPL) breaks down TGs into FAs and glycerol when mature VLDLs transport TGs into adipose tissue (the activity of this enzyme is insulin-dependent). As soon as the FAs enter the adipocytes, they are esterified with the help of glycerol phosphate, which is produced there by the glucose that was introduced by Glut-4 under the effect of insulin, then the liver receives the glycerol again [49, 53].

Adipocytes fill with TGs from the liver as they gain weight, even though the person is initially normoinsulinemic, normo-glycemic, and has normal lipid readings [49]. Depending on the level of adipose tissue storage, the duration of the "honeymoon" can vary adipogenesis, lipogenesis, apoptosis, and angiogenesis. This time span is short in people with low-lipid storage capacity; it is prolonged in those with high capacity. This process depends to a large extent on the anatomical compartment where the adipose tissue accumulates [62].

7.3 Adipose tissue storage

Adipocyte hyperplasia and adipocyte hypertrophy are inherited processes that affect the storage capacity of adipocytes [49].

7.4 Molecular factors influencing body fat distribution

Body fat distribution and total adiposity have an impact on systemic metabolism, and changes in either can increase the risk of metabolic pathology [63].

According to the amount of TG present, each anatomical depot has between 10 and 100 billion white adipocytes ranging in size from 10 to 200 microns [49]. The ability of the adipocytes in each depot to undergo hyperplasia and hypertrophy determines the amount of growth that each depot can support [49].

When the size of an adipocyte reaches a "critical" point where it can no longer expand, recruitment of preadipocytes occurs; the extent of this recruitment will depend on the pool of available adipocyte precursor cells. Adipocytes tend to evolve in both size and number over the course of growth [52, 63].

Subcutaneous adipocytes have a half-life of up to 10 years [52]. In addition to the recruitment of APCs and preadipocytes, the adipocyte undergoes continuous remodeling or turnover in which senescent and dysfunctional adipocytes are replaced by new differentiated adipocytes [52]. This continuous replacement is necessary because older adipocytes deteriorate, lose sensitivity to insulin action, and develop a proinflammatory phenotype [63].

It is believed that there are several interacting variables, which differ depending on the growth and age of the individual, resulting in epigenetic modifications that can be passed on from generation to generation, restricting the ability of adipocytes to grow and perform healthy remodeling [64].

Therefore, it can be assumed that a "metabolically ill" patient will have lower levels of APC, restricted adipocyte remodeling, less hyperplasia, and greater adipocyte hypertrophy, all leading to metabolic dysfunction [63]. On the other hand, regardless of the degree of obesity, a "metabolically healthy" obese person has more adipocyte hyperplasia in the abdominal subcutaneous depot, which is associated with metabolic health [63, 64].

8. B. Insulin control vs. counterinsulin control

When a person approaches the limit of storage capacity, they generate insulin resistance. Insulin levels are higher than physiological levels in maintaining blood glucose below 100 mg/dl, as defined by IR [63].

Adipose tissue develops insulin resistance (stage D) through upregulation of insulin receptors and increased sensitivity to hormones that act as counterinsulins (CI), including glucagon, cortisol, and adrenaline. These hormones trigger hormone sensitive lipase (HSL), an enzyme that controls the lipolytic process of TG breakdown [63].

Now that the partially filled adipocyte has room to store TG once more, insulin can activate LPL, causing it to fill with TG once more [63]. When the storage capacity of an adipocyte is exceeded, an inflammatory response is generated and the adipocyte releases cytokines that attract macrophages to the adipose tissue (stage F) [62, 63].

The TG overloaded adipocyte (stage A) undergoes morphological and functional changes and secretes resistin, infiltrating macrophages that produce TNF and other proinflammatory cytokines that permanently maintain the IR state, permanently slowing cell metabolism (stage C) [38].

Compensatory hyperinsulinemia is necessary to reverse the disabling of insulin action caused by -TNF and resistin, allowing the adipocyte to refill with TG (phase D). Plasma TG levels at this time may be normal, above the upper limit, or even only slightly above the upper limit [63].

8.1 Perpetuation of insulin resistance in adipose tissue

FAs created by lipolysis act on pancreatic beta cells, initially increasing insulin secretion. However, over time, they cause lipotoxicity by producing ceramides, which

lead to cell deterioration processes by releasing cytochrome C from the mitochondria. As a result, pancreatic beta cells undergo apoptosis, which reduces insulin release. Reduced insulin secretion potentiates the influence of anti-insulin hormone, raising blood GA levels and increasing lipolysis, which affects skeletal muscle [62, 65].

GAs from hydrolysis of TGs exceed glucose from muscle glycogen storage because of palmitic acid, the fatty acid that accumulates most frequently [63, 65]. This limits the absorption of blood glucose from food and excess glycogen. Skeletal muscle glycogen stores remain full or partially full, making it difficult for the muscle to continue to absorb blood glucose from food, increasing postprandial glucose levels [66].

9. C. Contrainsulin control

TI impaired gluconeogenesis results in uncontrolled creation of glucose at the hepatic level from the amino acids created by the breakdown of protein [66]. Glucotoxicity and lipotoxicity in pancreatic β-cells culminate in β-cell apoptosis, which further reinforces the control of metabolism by insulin resistance. FAs are converted to acetyl-CoA through the process of beta-oxidation, in diabetic patients, and excessive and uncontrolled hepatic glucose synthesis elevates blood sugar levels [63].

This state indicates that the body is under the control of insulin-resistant hormones and uses FAs to provide energy to the liver in the absence of absolute or relative insulin [66]. FAs that are not β-oxidized by the liver is esterified by glycerol, coupled to apoB100 and transported into the blood. The reason for elevated plasma TGs in obese individuals with insulin-controlled reverse metabolism is that these large VLDL accumulate in the blood without their TGs being digested, and low levels of HDL cholesterol are another characteristic of obese people under insulin control [63, 67].

10. Conclusions

Obesity is defined as generalized increase in adipose tissue. It is a systemic illness which affects various body organs, resulting in metabolic deterioration, characterized by inflammatory processes, expressed according to the interactions between the genome and the environment, and manifest phenotypically as increased deposition of adipose tissue. Adipose tissue has the ability to buffer the surplus of energy through lipid storage through the expansion of this tissue, which is a sign of proper functionality.

Increased adipocytokines resulting from hyperplasia, proliferation, and differentiation of preadipocytes are responsible for controlling the physiological response of adipose tissue. When the subcutaneous adipose tissue does not adequately store the energy surplus due to exceeding storage capacity, the visceral fat depot expands with decrease in lipogenesis and increased adipocyte hypertrophy.

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Conflict of interest

The authors declare no conflict of interest.

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