Universitat de Barcelona

Facultat de Farmàcia i Ciències de l'Alimentació

Departament de Nutrició, Ciències de l'Alimentació i Gastronomia

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Laura Bayod Jaime

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Laura Bayod Jaime

REVIEWED BY
Laura Bayod Jaime

*CORRESPONDENCE
Laura Bayod,
bayod99@gmail.com

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Molecular mechanisms of hyperinsulinemia in obesity

Laura Bayod Jaime*

[1]Facultat de Farmàcia i Ciències de l'Alimentació, Campus de l'Alimentació de Torribera, Universitat de Barcelona.

Abstract: Obesity-associated insulin resistance and hyperinsulinemia are two interrelated health conditions that have become increasingly prevalent in recent years. For many years, it has been thought that hyperinsulinemia comes after insulin resistance. The truth is that recent data suggests that insulin resistance can follow hyperinsulinemia and vice versa. Obesity is commonly associated with insulin resistance and hyperinsulinemia, but although some molecular mechanisms have been proposed, there is no clear evidence as to which condition occur before in humans. Despite much controversy over the timing of the onset of hyperinsulinemia in obesity, it is well established that the presence of insulin is necessary for obesity to occur and that chronically elevated insulin levels enhance diet-induced obesity. Therefore, the aim of this review is to provide a comprehensive up-to-date on the molecular mechanisms underlying hyperinsulinemia and the relationship between hyperinsulinemia and insulin resistance in obesity. In addition, we will examine the role hyperinsulinemia plays in cellular senescence, cancer and in dysregulating the insulin/IGF-1/GH axis. Finally, we will discuss possible current therapeutic strategies targeting hyperinsulinemia that are being used to treat obesity-associated insulin resistance, including current pharmacological therapies, the effects of multiple dietary interventions, physical exercise, and surgery. We conclude that hyperinsulinemia is a prevalent condition in obesity, but its time of occurrence and relationship with obesity are still under investigation. Dietary interventions, particularly low glycemic load diets and low carbohydrate diets, as well as regular exercise have shown promise in reducing hyperinsulinemia, while the long-term efficacy and potential side effects of pharmacological interventions require further study.

KEYWORDS

Hyperinsulinemia, Obesity, Insulin, Obese, Insulin clearance, Insulin signaling.

Resum: L'obesitat associada a la resistència a la insulina i la hiperinsulinemia són dues condicions de salut interrelacionades que han esdevingut cada vegada més prevalents en els últims anys. Durant molts anys, s'ha pensat que la hiperinsulinèmia ve després de la resistència a la insulina. La veritat és que les dades recents suggereixen que la resistència a la insulina pot seguir la hiperinsulinèmia i viceversa. L'obesitat s'associa comunament amb la resistència a la insulina i la hiperinsulinèmia, però tot i que s'han proposat alguns mecanismes moleculars, no hi ha evidència clara de quina condició ocorre abans en els éssers humans. Malgrat molta controvèrsia sobre el moment de l'aparició de la hiperinsulinèmia en l'obesitat, està ben establert que la presència d'insulina és necessària perquè es produeixi l'obesitat i que els nivells d'insulina crònicament elevats promouen l'obesitat induïda per la dieta. Per tant, l'objectiu d'aquesta revisió és proporcionar una actualització completa dels mecanismes moleculars subjacents a la hiperinsulinèmia i la relació entre la hiperinsulinèmia i la resistència a la insulina en l'obesitat. A més a més, examinarem el paper de la hiperinsulinèmia en la senescència cel·lular, el càncer i en la desregulació de l'eix insulina/IGF-1/GH. Finalment, es discutiran possibles estratègies terapèutiques actuals dirigides a la hiperinsulinemia que s'estan utilitzant per tractar l'obesitat associada a la resistència a la insulina, incloent les teràpies farmacològiques actuals, els efectes de múltiples intervencions dietètiques, l'exercici físic i la cirurgia. Concloem que la hiperinsulinèmia és una condició prevalent en l'obesitat, però el seu inici i relació amb l'obesitat encara estan en investigació. Les intervencions dietètiques, en particular les dietes de baixa càrrega glucèmica i dietes baixes en carbohidrats, a més de l'exercici regular, han demostrat ser prometedores per reduir la hiperinsulinèmia, mentre que l'eficàcia a llarg termini i els possibles efectes secundaris de les intervencions farmacològiques requereixen un estudi addicional.

PARAULES CLAU

Hiperinsulinèmia, Obesitat, Insulina, Obès, Depuració d'insulina, Senyalització de la insulina.

Sustainable Development Goals (SDG): The first of the SDG regarding the person field is Goal 3: Good health and well-being, especially the target 3.4, which focuses on reducing premature mortality from non-communicable diseases. Hyperinsulinemia, a condition prevalent in obesity, is strongly associated with the development of chronic diseases like type 2 diabetes, cardiovascular diseases, and certain cancers. Understanding the molecular mechanisms underlying hyperinsulinemia can contribute to the identification of new therapeutic targets and interventions primarily by reducing premature mortality and promoting good health and well-being, directly in line with indicator 3.4.1. Secondly, and also within the personal field, we find Goal 4: Quality education. This review is in line with objective 4.7, which focuses on the promotion of health and well-being through education, including disease prevention. The study of the molecular mechanisms of hyperinsulinemia helps to identify key factors involved in the pathophysiology of obesity-related metabolic disorders, thus linking to indicator 4.7.1. By integrating this review into educational programs, quality evidence is provided, thus providing effective educational initiatives and interventions aimed at reducing the burden of obesity-related diseases and promoting healthier populations. Finally, the next SDG is included in the prosperity field, which is Goal 8: Decent work and economic growth. Particularly, this work is based on the target 8.1 and more specifically with the indicator 8.1.1 based on the importance of promoting decent work and economic growth. Obesity-related conditions, including hyperinsulinemia, can have significant economic burdens due to healthcare costs, reduced productivity, and increased absenteeism. Moreover, obesity is a major risk factor for various chronic health conditions that require ongoing medical management, including medications, bariatric surgeries, regular check-ups, and hospitalization among other issues, leading to an increased in health costs. Furthermore, obesity is associated with an increased risk of mental health such as depression and anxiety, which can further increase healthcare expenses and therefore have a negative impact on overall economic productivity. Hence, the work it provides an overview of evidence-based approached which promotes sustained, inclusive, and sustainable economic growth, full and productive employment, and decent work for all.

1. Introduction

Insulin is a hormone secreted by β cells of Langerhans islets located in the endocrine pancreas. It is responsible for regulating glucose metabolism as well as promoting actions such as lipogenesis, increase the transport of amino acids into the cell or decrease lipolysis. Also, it participates in multiple signaling transduction pathways (Rahman et al. 2021). Hyperinsulinemia is a condition characterized by abnormally high levels of insulin in the bloodstream. At the meantime, there is no universally defined range for hyperinsulinemia, although many studies have reported a wide range of values, typically falling between 5-13 µU/ml, ≤ 30 µU/ml and 18 a 173 pmol/l (3-28 µU/ ml). It is important to note that these values serve as general guidelines, and specific reference ranges may vary depending on the laboratory test used to conduct the analysis as well as the specific population being studied (Janssen, 2021; Tsujimoto et al., 2017).

Hyperinsulinemia is associated with higher comorbidities and mortality from cardiovascular complications in patients with obesity (D. D. Thomas et al., 2019), but it also has a multiple role in a variety of disorders such as metabolic syndrome, type 2 diabetes, and cancer (Huang et al., 2021). Hyperinsulinemia rarely shows symptomatology unless hypoglycemia is present. This may cause mental confusion, fatigue, temporary muscle weakness, visual problems, headache, tremors and/or thirst (Parker, 2020).

Obesity is a chronic condition that has increased substantially worldwide and will continue to expand in the future (Lustig et al. 2022). Typically, the development of obesity is described as a condition caused by an imbalance between energy intake and energy expenditure (Huang et al., 2021). Nevertheless, obesity is a multifactorial condition that can result from genetic, environmental, and behavioral factors (Kawai et al., 2021). Obesity is characterized by an excessive accumulation of body fat, which depending on its localization and extent is associated with a major health risk limiting the lifespan and life expectancy of the subject and is defined by World Health Organization (WHO) as a Body Mass Index (BMI) of ≥ 30kg/m².

To undertake this bibliographic review, it was conducted a systematic search to identify the most relevant studies on this subject, mainly in online databases such as PubMed and Cercabib, although they were also used SciELO and Scopus. The articles were selected based on the level of evidence, year of publication and reference authors proposed by the author's tutor and others found during the bibliographic search. The keywords used for the search were: "hyperinsulinemia", "obesity", "obese", "insulin", "insulin clearance" and "insulin signaling". Regarding the inclusion criteria, it has been mainly looked for reviews but also for journals, meta-analyses, and randomized controlled clinical trials among others. In general, it has been tried to exclude very old articles in order to take into account the most current evidence, with the majority being between 2017-2023.

2. Functional role of insulin

2.1. Insulin synthesis

Insulin is a polypeptide hormone composed of 51 amino acids. In humans, the family of insulin-like genes comprises a group of genes that share structural similarities with insulin and have important roles in various biological processes. This family includes insulin, two insulin-like growth factors (IGF-1 and IGF-2), and relaxins (RLN1, RLN2, and RLN3) (Patil et al., 2017). Insulin is synthesized from the insulin gene (INS gene) as a prohormone in the β cells of Langerhans islets. The human pancreas contains 1 to 2 million of pancreatic islets (Rahman et al., 2021). Contrary to humans, mice and rats have two insulin genes, INS1 and INS2. It has been discovered that there is a strong similarity between the rodent INS2 gene and the human INS gene.

Insulin mRNA is translated as a single-chain polypeptide precursor named preproinsulin of 110 amino acids, which is converted to proinsulin when the signal peptide is cleaved off in the cisternae of the endoplasmic reticulum resulting in proinsulin. Proinsulin consists sequentially of 3 domains: the N-terminal B-chain, the connecting C-peptide and the C-terminal A-chain. Furthermore, it has 3 disulphide bonds, two of them between A-chain and B-chain and another disulphide bond within A-chain. The proteases that cleave proinsulin (proprotein convertases) are packaged with proinsulin inside secretory vesicles. Through proteolytic cleavage, the C-peptide is cut, and the mature hormone is formed. The mature insulin consists of two chains, an α-chain and a β-chain, which are connected by disulphide bonds. Insulin is then stored as hexameric insulin/Zn^{2+} crystals within mature secretory granules. Upon stimulation, the secretory granules undergo exocytosis, leading to the release of the granule contents into the extracellular space (Koeppen & Staton, 2017).

2.2. Regulation of insulin secretion

The major stimulus for insulin to be released by β cells is glucose through a process referred to as glucose-stimulated insulin secretion (GSIS) (Rahman et al., 2021). Once glucose is in the bloodstream is distributed to all the tissues of the body including the pancreas, which means the concentration of glucose is high in the blood compared to the concentration of glucose in tissues. This leads to the transport of glucose through facilitated diffusion mediated by glucose transporter 2 (GLUT2) (Rorsman & Ashcroft, 2018). Once glucose is inside the cell, glucokinase (GCK) will turn glucose into glucose-6-phosphate (G6P). GCK is an enzyme that is directly related with insulin secretion. Thus, it has been seen that an aberration or dysfunction of the GCK gene leads to a decrease in insulin release that can trigger diabetes. In contrast, an activating mutation of this gene is clinically manifested as congenital hyperinsulinism (Sternisha & Miller, 2019). G6P is then converted to pyruvate. Pyruvate dehydrogenase complex (PDHc) oxidates pyruvate into acetyl-CoA, which is oxidated in the TCA cycle. The resulting NADH and $FADH^2$ are oxidated via the oxidative phosphorylation machinery resulting in an increase of ATP/ADP ratio, which causes an inhibition of ATP sensitive K^+ channel, leading to depolarization of the cell with the opening of voltage-dependent Ca^{2+} channels and the entrance of calcium into the β-cell, followed by migration of insulin-containing vesicles into the plasma membrane releasing insulin into the blood (Koeppen & Staton, 2017), Figure 1. It is important to note that glucose is not the only nutrient capable of stimulating insulin secretion, other molecules such as amino acids, free fatty acid (FFA), ketone bodies and even different hormones are known to promote insulin release (Fu et al., 2013). A variety of incretins can modulate and enhance insulin secretion, being the gastrointestinal polypeptide (GIP), pancreatic glucagon and glucagon-like peptides (GLP) the ones that have a major role. Whilst these hormones and nutrients may themselves stimulate insulin secretion, in the presence of glucose this mechanism is reinforced by a synergistic relationship (Pettinato et al., 2022).

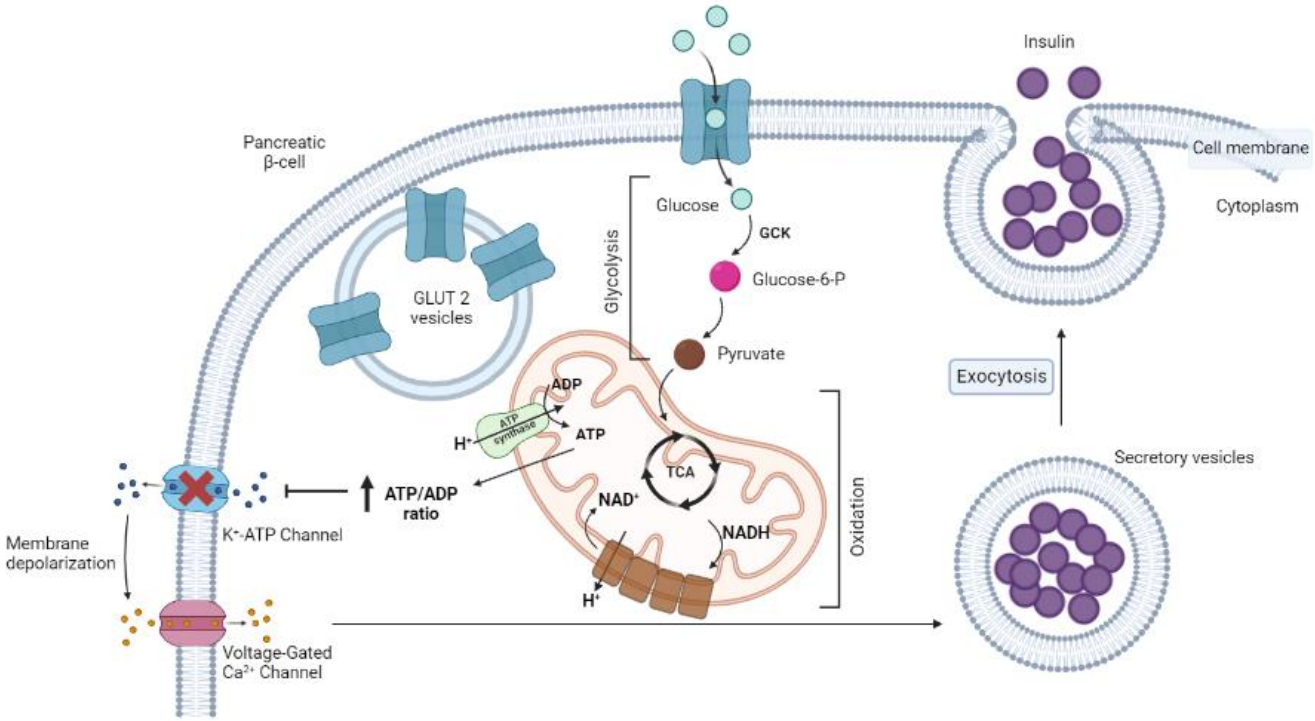

FIGURE 1
Mechanism of glucose-stimulated insulin secretion (GSIS). *Created with BioRender by the author.

2.3. Insulin receptor

The insulin receptor (InsR) is a tetrameric glycoprotein composed of two extracellular α-subunits and two β-subunits that have extracellular transmembrane and intracellular domains (Meyts, 2016). It belongs to the family of membrane receptors with intrinsic tyrosine kinase activity. The cytosolic region of β-subunit possesses several tyrosine residues. When insulin binds to the InsR, the α subunits will drive a conformational change of β-subunits that causes auto phosphorylation of various tyrosine residues in the β subunit, which serves as a signal for downstream signaling molecules to bind to the receptor and initiate further cellular responses. The α and β subunits are both derived from the INSR gene. It has two possible isoforms: IR-A and IR-B. The second is mainly involved in insulin-regulated metabolic processes in adults. IR-A, on the other hand, is relevant in prenatal growth and development. The two isoforms (IR-A, IR-B) are able to make hybrid complexes with insulin-like growth factor 1 receptor (IGF1R). In addition, IR-A is also capable of binding IGF-2. Insulin is therefore able to execute all its biological activities, either as a hormone or as a growth factor, by binding to its cell-surface receptor (Koeppen & Staton, 2017).

2.4. Insulin signaling pathways

When insulin binds to its receptor, this results in autophosphorylation of tyrosine residues in the catalytic domains of the β-subunits (Koeppen & Staton, 2017). This leads to the activation and initiation of two main signaling pathways: the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway and the mitogen-activated protein kinase (MAPK) pathway. These two pathways modulate multiple actions of insulin associated with the regulation of gene expression, energy metabolism and mitogenic effects (Rahman et al., 2021).

2.4.1. PI3K/AKT cell signaling pathway

It is the major mechanism by which insulin exerts its effects on glucose and lipid metabolism. Hormone-bound InsR will drive phosphorylation of insulin receptor substrate (IRS) on tyrosine residues, which act as SH2-domain docking sites for the recruitment of PI3K. The PI3K converts the phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 is a signaling lipid which attracts proteins to the membrane. In this pathway, phosphoinositide dependent protein kinase-1 (PDK-1) will bind to PIP3 and get activated. PDK-1 will then draw in the PKB/Akt and phosphorylate it (Rahman et al., 2021). Furthermore, PKB/Akt is also activated by the phosphorylation of mTORC2 (Titchenell et al., 2017). PKB/Akt then is the responsible for regulating multiple metabolic actions of insulin in hepatocytes, skeletal muscle and adipocytes including protein synthesis (via mTORC1), gene transcription (via FOXO, SREBP1 among others), etc. (Fazakerley et al., 2019; Koeppen & Staton, 2017).

2.4.2. MAPK cell signaling pathway

Insulin has its effects on the regulation of protein synthesis mainly through this pathway. The phosphorylation of IRS promotes the recruitment of the SH2 domain of Grb2 (adapter protein), which binds to phosphorylated tyrosine residues on IRS1, and this will eventually activate the MAPK pathway. Then, SOS protein binds to Grb2, leading

to the recruitment of monomeric G protein (RAS). Once RAS is activated the Rapidly Accelerated Fibrosarcoma (RAF-1) will be recruited to the cellular membrane and activated. Activated RAF will phosphorylate another protein named Map Kinase Kinase (MEK), which in turn will phosphorylate and concomitantly activate Extracellular Regulated Kinase (ERK). ERK enters to the nucleus and phosphorylates nuclear transcription factors such as Elk1 or SRF, which induce a transcriptional program able to induce mitosis and thus promote cell division, protein synthesis and cell growth (Rahman et al., 2021).

2.5. Insulin journey through the body

It is crucial to understand the pathway of insulin since it allows us to appreciate how insulin production, release and elimination are tightly regulated to maintain a proper balance in the body. Any disruption in any of these processes can have significant consequences for metabolic homeostasis. When blood glucose level rises after a meal, β cells of the pancreas release insulin into the bloodstream. The release of insulin is tightly regulated and occurs in a pulsatile manner (Laurenti et al., 2021). At this point, the insulin travels through the portal circulation to the liver and 50% of its content is filtered by the hepatocytes during the first pass. The resulting insulin travels via venous circulation to the heart. Subsequently, insulin is distributed via arterial circulation throughout the body. Remaining circulating insulin is degraded by the kidney and excreted by urine (Tokarz et al., 2018), Figure 2.

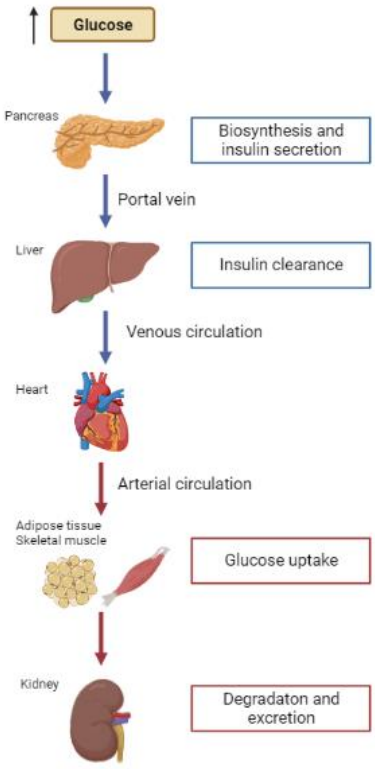

FIGURE 2
Simplification of the main organs and tissues through which insulin circulates and acts. *Created with BioRender by the author.

2.6. Metabolic effects of insulin

Insulin is the main anabolic hormone that dominates the regulation of the metabolism during the digestive phase. It is also important to mention that glucagon is another relevant hormone which likewise plays a critical role in maintaining metabolic homeostasis and acts antagonistically to insulin. Therefore, glucagon acts mainly in the fasting state while insulin acts in the fed state. Hence, the primary actions of insulin are glucose utilization (glycolysis), storage of glucose as glycogen (glycogenesis), lipid synthesis (lipogenesis) and protein synthesis, as well as promoting the uptake of glucose into tissues (Templeman et al., 2017). Even though insulin acts on multiple tissues, there are three particular targets, which are the liver, skeletal muscle and adipose tissue (Koeppen & Staton, 2017; Titchenell et al., 2017).

It has been suggested that insulin exerts its effects on the liver through direct and indirect mechanisms. It primarily acts indirectly by inhibiting lipolysis, promoting glucose uptake by peripheral tissues such as skeletal muscle and adipose tissue in addition to lowering glucagon secretion and increasing glycogen synthesis as well as influencing neural signals that affect liver metabolism. On the other hand, the direct mechanisms of insulin action in the liver involve its binding to InsR located on the surface of hepatocytes which subsequently activates insulin signaling pathways in the liver. Both intrahepatic and extrahepatic pathways control insulin regulation of glucose and lipid metabolism (Rahman et al., 2021), Figure 3.

2.6.1. Metabolic effects on the liver

The liver is the principal organ for insulin action. Glucose can enter the liver via GLUT2 transporters, which are independent of insulin. Nonetheless, insulin increases hepatic glucose utilization and retention by increasing the expression of GCK in the liver through activation of the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c). In addition, insulin is able to inhibit the expression of the G6Pase enzyme gene via FOX01, resulting in the inhibition of gluconeogenesis. Alternatively, insulin represses the expression of genes for the gluconeogenic enzymes pyruvate carboxylase (PC) and phosphoenolpyruvate carboxylase (PEPCK). Insulin inactivates hepatic phosphorylase, an enzyme responsible for degrading hepatic glycogen to glucose, thereby inhibiting glycogenolysis. Insulin increases the expression of GCK, which converts glucose to G6P, thus preventing the degradation of stored glycogen, since G6P is the main substrate used by glycogen synthase (GS) for glycogen synthesis in the liver. Furthermore, GS can be activated by insulin through the phosphorylation and inhibition of glycogen synthase kinase 3 (GSK3). Moreover, with the action of specific protein phosphatases, such as protein phosphatase 1 (PP1), GS can be dephosphorylated and activated, leading to increased glycogen synthesis in the liver (Vargas et al., 2022). Insulin via Akt activates protein phosphatases which can stimulate glycolysis, gluconeogenesis, and de novo lipogenesis (DNL). In glycolysis, insulin-mediated activation of protein phosphatases promotes the dephosphorylation and activation of enzymes such as phosphofructokinase-1 (PFK1) and pyruvate kinase (PK), leading to increased glycolytic flux and glucose utilization. In DNL, insulin promotes the activation of protein phosphatases that dephosphorylate and activate key enzymes involved in fatty acid synthesis, such as

acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). This leads to an increase in the production of fatty acids from glucose, contributing to lipid synthesis and storage. Furthermore, Akt activates mTORC1 (mammalian target of rapamycin complex 1) stimulating protein synthesis and inhibiting protein degradation and autophagy. Additionally, FOX01, is also responsible for inducing the expression of proteins implicated in the assembly and export of VLDL. Moreover, by activating mTORC1 and inhibiting FOX01, Akt also regulates genetic expression through the activation of SREBP-1c, which regulates glycolysis and DNL to produce phospholipids, triglycerides, and fatty acids in situations of excess glucose and fructose (Koeppen & Staton, 2017).

2.6.2. Metabolic effects on the skeletal muscle

In the skeletal muscle the activation of Akt/PKB increases the translocation of glucose transporter type 4 (GLUT4) to the cell membrane in order to promote the entrance of glucose (Vargas et al., 2022). Akt is responsible for inhibiting GSK3 thereby removing its inhibitory effect on GS, thus promoting glycogen synthesis for energy storage (Rahman et al., 2021). Another fraction will be used for ATP production in glycolysis. Akt also stimulates protein synthesis by activating the mTORC1 pathway, leading to muscle protein synthesis. Moreover, it also inhibits protein breakdown (proteolysis) since it decreases the activity of proteolytic systems such as the ubiquitin-proteasome and autophagy-lysosome pathways (Cohen et al., 2014; Sylow et al., 2021). Lastly, insulin is capable of inhibiting lipolysis in muscle cells by suppressing the activity of hormone-sensitive lipase (HSL) and it also promotes lipogenesis via the Akt pathway, stimulating the ACC, which converts acetyl-CoA into malonyl-CoA, the latter being a key precursor for fatty acid synthesis (Sylow et al., 2021).

2.6.3. Metabolic effects on the adipose tissue

Insulin signaling in adipocytes, as in skeletal muscle, leads to the translocation of GLUT4, leading to increased glucose influx into the cell. In addition to increasing glucose transport, it also suppresses lipolysis by Akt (Fazakerley et al., 2019), which phosphorylates and inactivates HSL, an enzyme responsible for the breakdown of stored triglycerides into FFA during lipolysis, thus preventing the release of fatty acids (Lan et al., 2019). Another important downstream target of insulin signaling in adipose tissue is the transcription factor SREBP-1c, which activates the transcription of genes involved in fatty acid and triglyceride synthesis, promoting DNL (Song et al., 2018). Glycolysis in adipose tissue has a dual function: it provides energy in the form of ATP and generates glycerol-3-phosphate (G3P) necessary for the esterification of fatty acids to triglycerides. These metabolic processes are essential for the storage of energy in the form of fat in adipose tissue (Czech et al., 2013).

3. Possible molecular mechanisms implicated on the development of hyperinsulinemia in obesity

3.1. Insulin resistance

Insulin resistance is defined as a condition in which cells throughout the body become less responsive to the effects of insulin (Sarwar et al., 2022). Nevertheless, other investigators go beyond the classical definition of insulin resistance by saying that is a phenomenon where there is reduced insulin signaling at the cellular level but also

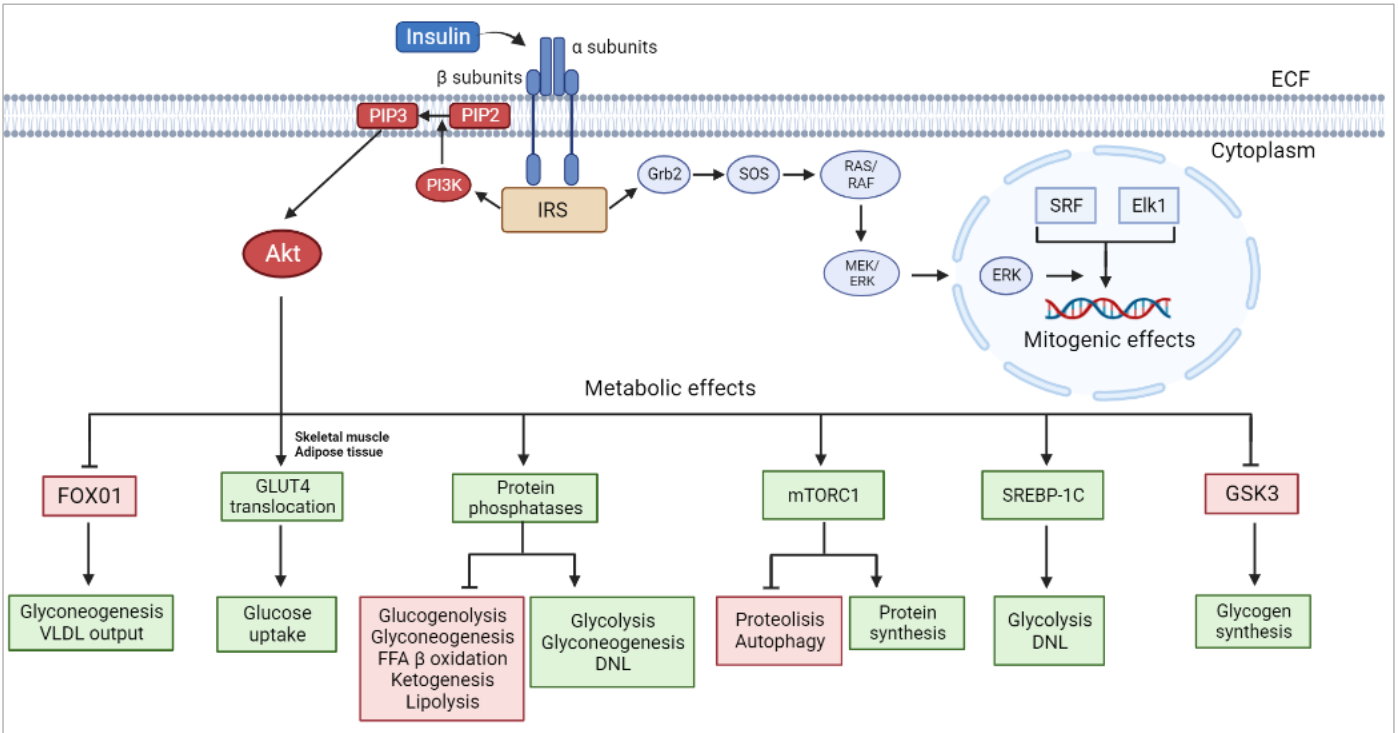

FIGURE 3
Simplification of the main insulin-dependent signaling pathways (PI3K/AKT and MAPK) and the metabolic effects induced by the activation of Akt/PKB.
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hyperinsulinemia, arguing that hyperinsulinemia always accompanies insulin resistance and often even precedes it (Janssen, 2021; Shanik et al., 2008; Fryk et al., 2021; Kahn & Flier, 2000; Kobayashi & Olefsky, 1978; Marín-Juez et al., 2014; Martin et al., 2011; Rizza et al., 1985) saying that both conditions tend to coexist as one condition leads to the other and vice versa. For a long time, it was firmly believed that insulin resistance was the initial event and preceded hyperinsulinemia. From this perspective, hyperinsulinemia was considered to be a compensatory response to counteract insulin resistance in the body and insulin resistance the main factor in the development of obesity, type 2 diabetes, cardiovascular disease and cancer. Nowadays, this has been much debated and it appears that hyperinsulinemia may precede insulin resistance in obesity in some cases (Abdul-Ghani & DeFronzo, 2023; M. K. Kim et al., 2017; Sarwar et al., 2022; van Vliet et al., 2020). It is even shown to be a causal factor in that insulin hypersecretion from beta cells is the major deficiency and will subsequently lead to insulin resistance. Additionally, research indicates that hyperinsulinemia leads to a decrease in receptor affinity and number, favoring the development of insulin resistance (van Vliet et al., 2020). However, there is still much contradiction between the timing of the onset of these two events (Araújo et al., 2013; Chen et al., 1994; Najjar et al., 2022; RAO, 2001; Sbraccia et al., 2021; Shinozaki et al., 1996). The possible sequences of events regarding the onset of hyperinsulinemia and insulin resistance will be discussed in more depth below along with the two theories of origin of hyperinsulinemia in people with obesity in section 4.2.

3.2. Adipose tissue inflammation

Insulin is known to regulate white adipose tissue (WAT) accumulation through inhibition of lipolysis and stimulation of both fatty acid uptake and triglyceride synthesis (lipogenesis). It also increases the expression of genes involved in fatty acid uptake and storage. In the long term, it has been observed that insulin signaling drives adipogenesis in adipose tissue. In experimental studies in mice, hyperinsulinemia promotes inflammation of adipose tissue leading to disruption of various metabolic processes. Additionally, a deletion of InsR in WAT was shown to protect rats from obesity. This shows the indispensability of insulin for adipocyte differentiation and/or hypertrophy and/or hyperplasia (Templeman et al., 2015, 2017). High-calorie diets and overfeeding were seen to cause an inflammatory state (De Vries et al., 2014; Herieka & Erridge, 2014). In obesity, the chronic accumulation of excess energy in adipose tissue initiates pathological changes that elicit an immune response characterized by inflammation. This inflammatory response hinders the normal tissue remodeling processes, including angiogenesis and tissue repair, which are essential for healthy expansion of adipose tissue. Consequently, adipocytes undergo hypertrophy and exhibit heightened expression and secretion of proinflammatory cytokines, which then promote serine phosphorylation of IRS-1 through signaling pathways involving nuclear factor kappa β (NF-kβ) and Jun N-terminal kinase (JNK), ultimately leading to the development of insulin resistance (Choe et al., 2016; Hirosumi et al., 2002; Yung & Giacca, 2020). When cells do not respond adequately to insulin, they cause a rise in blood glucose, which increases insulin production and secretion by pancreatic beta cells in an attempt to compensate normal glucose levels in the blood (Ahmed et al., 2021). What is known for sure is that hyperinsulinemia plays an important role in adipose tissue inflammation and insulin sensitivity, as a reduction in hyperinsulinemia shows a significant improvement in both functions (Abdul-Ghani & DeFronzo, 2023; Pedersen et al., 2015).

3.3. Loss of pulsatile insulin secretion

Insulin is a pulsatile hormone; this means that its release into the bloodstream occurs in the form of intermittent pulses rather than a continuous and steady secretion over time. The pulsatile pattern of insulin is essential for accurate regulation of blood glucose levels and serve as an indicator of β-cell health (Laurenti et al., 2021). When glucose levels rise after a meal, there is a sharp increase in insulin secretion in the form of a pulse. This insulin pulse helps to facilitate glucose uptake by peripheral tissues, such as muscle and adipose tissue, but in addition to glycemic control it is important for preserving normal hepatic insulin signaling function and preserving insulin sensitivity (Laurenti et al., 2021; Matveyenko et al., 2012; Žarković et al., 2000). Loss of pulsatile insulin secretion is one of the first defects detected in individuals at risk for T2DM (O'Rahilly et al., 1988; Wahren & Kallas, 2012). It is known that the way the pancreas releases insulin dictates hepatic insulin clearance as the liver primarily removes insulin administered in pulses (Meier et al., 2005). While a short-term rise in insulin levels activates the InsR, prolonged and continuous elevation of insulin leads to the desensitization of the InsR. This desensitization process involves a decrease in the number of InsR on the cell surface due to increased internalization and degradation, thus contributing to insulin resistance (Janssen, 2021).

3.4. Decreased insulin clearance

Insulin has a short half-life of about 5 minutes and is rapidly degraded in the liver, kidney and other tissues by the insulin-degrading enzyme (IDE) although there are other minority insulin degradation systems such as protein disulphide isomerase and lysosomal cathepsin D. The primary event in the degradation of insulin is the binding to InsR, which then makes it a substrate for the IDE, located in the endosomes. The liver is the main place for insulin clearance where approximately a 50% is eliminated before arriving at peripheric circulation (Najjar et al., 2022; Valera Mora et al., 2013). As determinants of insulin clearance, we find both the expression of the basal InsR and the supply of insulin to insulin-clearing tissues (Najjar et al., 2022). Insulin resistance has been identified in some clinical trials as a causal factor for the reduced insulin clearance rate (Gastaldelli et al., 2021; M. K. Kim et al., 2015). Other studies even propose the reduction of hepatic insulin clearance as the primary cause of peripheral hyperinsulinemia (Bojsen-Møller et al., 2018). It has been seen that people with obesity have a reduction in the number of cell surface InsR on the major tissues of insulin clearance (Kolterman et al., 1979; Wondmkun, 2020) which can result in a reduction of insulin clearance. This places hyperinsulinemia at least partly responsible for the reduction of InsR expression in cell membrane in subjects with obesity (Najjar et al., 2022). For example, Kim et al. found that individuals with obesity, regardless of the degree of insulin resistance, tend to have elevated insulin levels in the bloodstream and increased insulin secretion and that reduced insulin clearance is observed specifically in those individuals with insulin resistance (M. K. Kim et al., 2017). In addition, they previously demonstrated that obese individuals, regardless of their insulin sensitivity or resistance, exhibit fasting hyperinsulinemia, but those with obesity and insulin resistance had the greatest increase in hyperinsulinemia (M. K. Kim et al., 2015). Moreover, Bergman et al. propose that impaired liver insulin clearance contributes to sustained elevation of insulin levels in the bloodstream,

leading to insulin resistance and eventually the inability of beta cells to adequately compensate for the insulin resistance through increased secretion. This progressive dysfunction of beta cells ultimately results in persistent hyperglycemia over time (Bergman et al., 2019, 2022).

Obesity is also associated with a reduction of the Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) expression in the liver, a transmembrane protein of the InsR in liver that promotes insulin clearance (Deangelis et al., 2008; Fosam et al., 2020; Poy et al., 2002) and negatively regulates insulin effects on hepatic de novo lipogenesis through fatty acid synthase (Heinrich et al., 2017). Therefore, a significant decrease or a mutation of CEACAM1 in the liver leads to a reduction of insulin clearance, resulting in hyperinsulinemia with subsequent insulin resistance. This results in increased hepatic lipogenesis, which in turn promotes the deposition of visceral adiposity leading to hyperleptinemia, which will then stimulate food intake and energy imbalance, two factors that play a highly significant role in obesity (Heinrich et al., 2017). Although it has been shown that insulin clearance is often impaired in obese subjects with hyperinsulinemia there are some conflicting studies as to the specific mechanisms involved, which does not provide us with a clear result as to the relationship between insulin clearance and hyperinsulinemia (Consortium et al., 2018; Faber et al., 1981; Flier et al., 1982; Meistas et al., 1983; Polonsky et al., 1988; Robertson et al., 1992). It is therefore essential to determine why a reduction in insulin clearance is observed in individuals with obesity and hyperinsulinemia, and the role that insulin resistance plays in this equation.

3.5. Influence of different molecules on insulin secretion

Insulin secretion is a process that can be influenced by various nutrients and other circulating factors. The combined sensing of nutrients and the metabolic products resulting from the metabolism of glucose, amino acids and fatty acids triggers several metabolic factors involved in signaling insulin release. These metabolic factors (e.g. ATP, NADPH, glutamate, long-chain acyl-CoA and diacylglycerol) are involved in the process of insulin exocytosis. Carbohydrates, especially glucose, is the major secretagogue, although fructose is also capable of stimulating insulin secretion (Newsholme & Krause, 2012). However, arginine is a potent insulin secretagogue and it has been proposed that it may act directly and indirectly on the beta cell. Indirectly, since it can increase nitric oxide production, which acts as a signaling molecule that enhances insulin release. But also, directly by entering to the beta cells through cationic amino acid transporters and undergoing metabolism. In both animal models and patients with obesity, it has also been shown to lower blood glucose levels, reduce adiposity and improve insulin sensitivity (Forzano et al., 2023; Halperin et al., 2022; Leiss et al., 2014). Others amino acids such as leucine, alanine and glutamine can also be potent insulin secretagogues through various molecular mechanisms (Newsholme et al., 2015). On the other hand, it is thought that FFA acutely stimulate insulin secretion (Cen et al., 2016; Ježek et al., 2018; Staaf et al., 2016). The mechanisms proposed through which fatty acids can stimulate insulin secretion are either through the generation of LC acyl-CoA or by the stimulation of signal transduction events (Newsholme & Krause, 2012). Yet, others suggest that FFA only stimulate insulin secretion via GSIS (Losada-Barragán, 2021; Rahman et al., 2021; Salehi et al., 2005). It is important to note that both fatty and amino acids can stimulate insulin secretion individually or in conjunction with elevated glucose levels, although there will always be a greater increase in insulin secretion when glucose is present. (Losada-Barragán, 2021; Templeman et al., 2017). Apart from that, neurohormonal signals also can regulate insulin secretion. One important group of signals are the incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) in addition to autonomic innervation. These hormones are released from the gut in response to nutrient ingestion, particularly carbohydrates. When these incretin hormones bind to their receptors on pancreatic beta cells, they stimulate insulin secretion in a glucose-dependent manner. This ensure an increase in insulin release through modulation of signal transduction and/or ion channel activity when blood glucose levels are elevated, promoting glucose uptake and utilization by peripheral tissues (Newsholme et al., 2015).

3.6. Adiponectin and leptin: two critical hormones in adipose tissue

The WAT secretes various molecules including adiponectin, TNF-alpha, resistin, interleukins, leptin, among others. Leptin is a hormone that transmits signals to the hypothalamus participating in the suppression of appetite and energy expenditure. In obesity, there is a disruption in the response to leptin. This condition is known as leptin resistance. As fat accumulation increases, leptin levels in the blood also rise, but the brain becomes less responsive to its signals, leading to an excessive appetite and reduced energy expenditure. Interestingly, insulin and leptin interact with each other since leptin has the ability to inhibit insulin, while insulin promotes the synthesis and release of leptin. Leptin also enhances insulin sensitivity by reducing adiposity (fat accumulation) and the lipotoxicity caused by excessive fat as well as exerting insulin-independent effects both in the central nervous system and in peripheral tissues, further enhancing insulin sensitivity (Paz-Filho et al., 2012). Leptin may also interact with insulin signaling and affect the function of insulin-producing pancreatic beta cells (Cochrane & Shyng, 2019). Adiponectin is a hormone that plays an important role in regulating insulin sensitivity and glucose and lipid metabolism. Under normal conditions, adiponectin levels are elevated and help to improve insulin sensitivity and reduce inflammation (Nguyen, 2020). Leptin resistance and decreased adiponectin were associated with the risk of insulin resistance and obesity (Agostinis-Sobrinho et al., 2022; Cochrane & Shyng, 2019; Shih et al., 2022; Yadav et al., 2013; Funcke & Scherer, 2019; Stern et al., 2016). Hyperinsulinemia may also be part of this equation, since it was found that, in young non-obese men, hyperinsulinemia was shown to increase leptin levels (Boden et al., 1997) and is even proposed as the first event before insulin resistance and obesity (Denroche et al., 2012). Still, there is little evidence to support this hypothesis and there is a lack of human studies demonstrating the mechanisms by which hormones such as leptin and adiponectin may contribute to hyperinsulinemia and obesity.

3.7. Influence of physiological, genetic, dietary and environmental factors

The influence of racial and ethnic differences between people in insulin sensitivity, beta cell function and insulin clearance has been observed in many studies (Goodarzi et al., 2014; Guo et al., 2012; Harris et al., 2002; Hasson et al., 2015). Furthermore, genetic factors are associated with insulin secretion and clearance (Bergman et al.,

2019). For instance, black children and adolescents were found to have significantly higher insulin responses than whites, suggesting that they are more susceptible to hyperinsulinemia (D. Thomas et al., 2019). In addition, the occurrence of insulin resistance and hyperinsulinemia is higher in black African women when compared to white women (Goedecke et al., 2009) . Moreover, there are genetic variants such as FTO gene that may contribute to develop obesity since it has been associated with insulin resistance, insulin sensitivity and adiposity. However, the mechanisms by which FTO influences obesity is still not fully understood and requires further research (Do et al., 2008; Iskandar et al., 2018; Jacobsson et al., 2008).

In terms of physiological factors, sex and age have been shown to influence the distribution of adipose tissue. For instance, central adiposity tends to increase with age and men tend to have more visceral tissue than women (Nauli & Matin, 2019). It also has been suggested that the prenatal and adolescent period are determinants of the metabolic characteristics of adipose tissue in the future and that with poor habits they will be more susceptible to obesity in the future (Templeman et al., 2017).

Furthermore, environmental factors such as air pollution can influence adipose tissue inflammation, insulin resistance and it has also been linked to obesity (Dendup et al., 2018). Also poor dietary choices, especially a diet high in refined carbohydrates, sugar and saturated fat can contribute to hyperinsulinemia by decreasing insulin pulses (Janssen, 2021; D. D. Thomas et al., 2019) as well as lack of physical activity and a sedentary lifestyle (Park et al., 2020).

Research has uncovered interesting insights into the relationship between gut microbiota and obesity, who exhibit an imbalance in their gut microbiota composition, characterized by a reduction in beneficial bacteria and an increase in harmful bacteria, known as dysbiosis. Specific bacteria in the gut can ferment dietary fibers, giving rise to the production of short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate (C. H. Kim et al., 2014). These SCFAs have been found to impact insulin signaling and glucose metabolism. In mice it was found that gut microbes regulate insulin clearance during diet-induced obesity (K. P. Foley et al., 2020). Additionally, SCFAs can stimulate the release of gut hormones, such as GLP-1 and GIP, which play a crucial role in regulating insulin secretion (B.-N. Liu et al., 2021). Lastly, a dysbiosis leads to an increase in pro-inflammatory bacteria, which can secrete endotoxins such as lipopolysaccharides (LPS). These molecules can translocate from the gut lumen into the bloodstream, initiating an immune response, affecting the gut barrier function and increase intestinal permeability (often referred to as leaky gut) and finally triggering a state of low-grade chronic inflammation. This inflammation disrupts insulin signaling pathways, leading to insulin resistance and impaired gut hormone secretion, indirectly influencing insulin secretion (Aoun et al., 2020; Boulangé et al., 2016; Sarmiento-Andrade et al., 2022; Scheithauer et al., 2020; Vetrani et al., 2022; Xu et al., 2021), Figure 4.

4. Role of hyperinsulinemia in obesity

4.1. Proposed theories for the pathogenesis of obesity

Currently, there are two paradigms regarding the pathogenesis of obesity, the carbohydrate-insulin model (CIM) and the energy balance model (EBM), which are two theoretical frameworks that provide different perspectives on the factors influencing weight regulation and the development of obesity (Ludwig et al., 2022). Despite the fact that there is some level of contradiction between these models, it's important to note that they are not necessarily mutually exclusive, and both have contributed to our better understanding of the onset/development of obesity. While CIM emphasizes the role of hormonal responses to carbohydrate consumption, the EBM is focused on the overall energy balance between energy intake and energy expenditure as the primary determinant of body weight. The EBM is based on the brain controlling food intake to regulate body weight through complex metabolic, endocrine, and nervous system signals as well as environmental influences. In this model obesity is caused by the total calories consumed through energy-dense, ultra-processed foods high in portion size, fat, sugar and low in protein and fiber, resulting in overeating, and ultimately excess energy being deposited in body fat. However, the CIM proposes that high-glycemic load and high-sugar diets, particularly in the form of refined carbohydrates and added sugars, leads to a rapid and excessive rise in blood glucose levels. This results

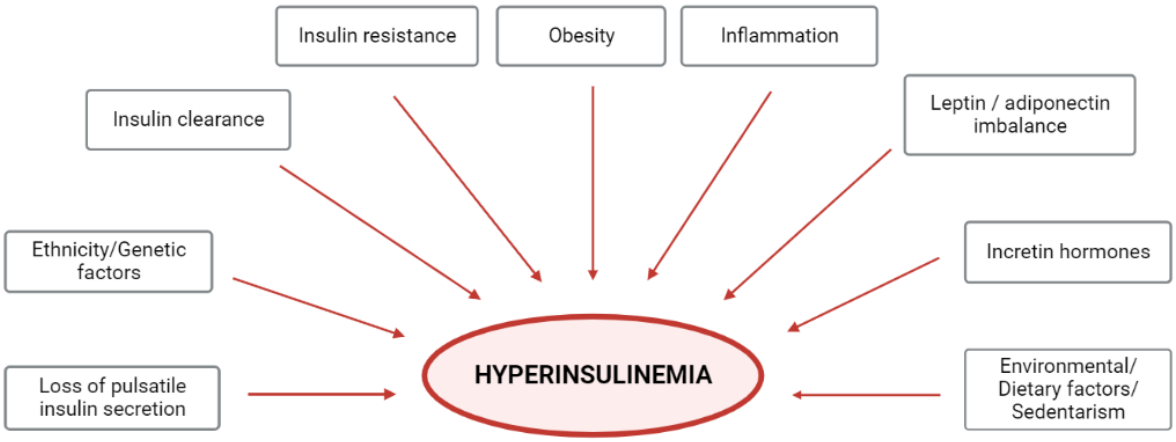

FIGURE 4
Possible etiologies of hyperinsulinemia in the context of obesity. *Created with BioRender by the author.

in a large increase in insulin and GIP secretion, a highly anabolic profile that leads to fat deposition. By shifting substrate partitioning towards deposition, less energy is left available for metabolically active tissue. In response to this, the brain activates pathways to promote energy intake (Holsen et al., 2021), and when we restrict ourselves to the impulse of eating, it leads to a conservation of metabolic fuels through a reduction in energy expenditure. This manifests itself as fatigue, decreased thermogenesis, an increase in muscle efficiency, among others contributing to positive energy balance and thus weight gain. Concerning hyperinsulinemia, the CIM proposes a diet-phenotype interaction, where people with high endogenous insulin secretion would be more susceptible to the adverse metabolic effects of a high glycemic index diet. Accordingly, this model proposes a stronger link between hyperinsulinemia and obesity, as it focuses on excessive consumption of carbohydrates, the nutrient that stimulates insulin the most (Henquin, 2000; Losada-Barragán, 2021). In contrast, EBM has some limitations such as not considering the effects of different macronutrients and ignores the influence of hormones in the regulation of metabolism. Therefore, on the basis of the CIM, chronically elevated insulin levels, caused by repeated spikes in blood glucose due to high carbohydrate intake, could lead to the inhibition of fat mobilization (lipolysis) and the promotion of fat deposition in adipose tissue resulting in obesity (Ludwig et al., 2022; Soto-Mota et al., 2023).

4.2. Contrasting recent evidence: two main hypotheses of the effect of obesity on hyperinsulinemia

There are two main theories that may explain how hyperinsulinemia occurs in obesity. Both suggested theories emphasize the complex interaction between obesity, hyperinsulinemia, and insulin resistance. In one theory, chronic inflammation may play a key role in the development of insulin resistance, while in the other, excessive stimulation of beta cells due to dietary intake may contribute to hyperinsulinemia.

4.2.1. Proinflammatory state and insulin resistance

Concerning the first theory and the one that was formerly thought to be the only possible one, obesity causes an inflammatory state in the adipose tissue called low-grade chronic inflammation (LGCI). In obesity, the excessive accumulation of fat in WAT results in a phenotypic change characterized by hypertrophy of adipose cells, leading to inflamed and dysfunctional adipocytes along with infiltration of immune cells into the vascular fraction of stroma. There is a more complex and intense inflammatory reaction in visceral adipose tissue compared to subcutaneous adipose tissue due to the higher accumulation of immune cells, the increased release of pro-inflammatory adipokines and the greater capacity to produce FFA (Ibrahim, 2010; Kawai et al., 2021). In order to compensate this proinflammatory state, adipose tissue starts to recruit monocytes, which become differentiated into proinflammatory macrophages M1 (Lumeng et al., 2007). With the tissue enlargement, the adipocytes and macrophages release FFA together with reactive oxygen species (ROS) and pro-inflammatory cytokines and adipokines. Cytokines act both locally and systemically, some of them are tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). Additionally, the excess of FFA into circulation results in their incorporation into the cells of non-adipose tissues, thereby producing lipotoxicity, which will begin to deregulate multiple cellular organelles that will subsequently release pro-inflammatory cytokines and ROS. Consequently, the systemic pro-inflammatory state is generated (Khan et al., 2020), where many molecules are altered, including the hormones adiponectin, leptin and resistin (Choe et al., 2016; G. R. Kim et al., 2020). Chronic inflammation in adipose tissue can result in increased release of FFA into the circulation. In some studies, FFA are positioned as the main cause of insulin resistance, rather than glucose, since it has been observed that there is a disconnection between hyperinsulinemia and hyperglycemia in some obese individuals, as they may have hyperinsulinemia but still maintain normal glucose tolerance. This finding has prompted a reassessment of the conventional understanding that elevated levels of FFA are the primary metabolic disturbance responsible for the presence of fasting hyperinsulinemia in individuals with obesity but normal glycemic control, which later can induce insulin resistance (Fryk et al., 2021). Nevertheless, further research is needed to prove this hypothesis. What is clear, however, is that FFA may contribute to insulin resistance (Boden, 2001; Chueire & Muscelli, 2020; Jiang et al., 2020; Sears & Perry, 2015; Stefanovski et al., 2021; Xin et al., 2019).

This inflammatory state also activates specific signaling pathways involving the JNK, IκB kinase (IKK) and RNA-activated protein kinase (PKR), which may cause insulin resistance in the context of obesity and a high-fat diet (Feng et al., 2020; Nakamura et al., 2010; Nandipati et al., 2017). In obesity, conditions such as increased pro-inflammatory cytokines (TNF-α and some interleukins), FFA, ROS or endoplasmic reticulum stress (ERS) exacerbate the activity of these three kinases, inhibiting InsR signaling via serine phosphorylation of IRS-1. Consequently, this phosphorylation event triggers ubiquitination and subsequent degradation of IRS-1, effectively preventing the downstream effects of insulin following receptor activation and finally inducing insulin resistance in obesity. Furthermore, these kinases have the ability to trigger inflammatory reaction through the activation of key transcription factors such as AP-1, NF-κB and IRF (Gal-Ben-Ari et al., 2019; Gregor & Hotamisligil, 2011; Khalid et al., 2021), Figure 5.

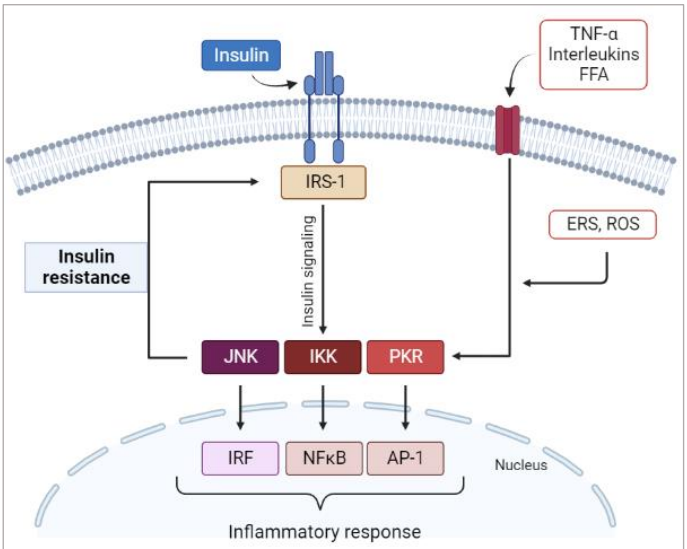

FIGURE 5
The mechanisms through which obesity-induced kinase activation leads to insulin resistance. *Created with BioRender by the author.

In short then, depending on the individual, this resistance may be caused by some of these factors or even by a combination of all of them: impaired insulin signaling, disrupted glucose homeostasis, systemic dysregulation and elevated FFA (Ahmed et al., 2021; Kolb, 2022; Wu & Ballantyne, 2020). As insulin resistance develops, pancreatic beta cells attempt to compensate for this resistance by producing and releasing more insulin in an attempt to maintain blood glucose levels within a normal range. However, chronic inflammation and other factors such as lipotoxicity and oxidative stress can affect beta cell function and survival, resulting in a reduced ability to respond adequately to increased insulin demand. This leads to insufficient beta-cell compensation and an increase in blood insulin levels, which we define as compensatory hyperinsulinemia (Bergman et al., 2019; Czech, 2017), Figure 6A.

4.2.2. High-glycemic load diets

Regarding the second and more recent theory, is being closely linked to the CIM. This theory is based on the fact that high-glycemic load diets (HGLD) are a major driver to obesity (Astley et al., 2018; Ss, 2022). This type of diet is characterized by foods rich in refined carbohydrates and simple sugars, such as white bread, pasta, white rice, baked goods, sugary drinks, etc. These foods are absorbed more quickly into the bloodstream, causing hyperglycemia during the early postprandial stage (0-2 hours) due to their rapid digestion and absorption (Chiu & Taylor, 2011; Onna Lo, 2018). This causes the pancreas to release an excessive amount of insulin to compensate for the elevated glucose levels, resulting in an overstimulation of pancreatic beta cells causing hyperinsulinemia. The main purpose of this hypersecretion of insulin is to lower blood glucose levels, allowing glucose to enter the cells for use as an energy source, storage as glycogen in the liver and muscles, and conversion to fat for storage in adipose tissue. Additionally, this glucose spikes lead to reactive hypoglycemia during the late postprandial phase (3-6 hours), resulting in an activation of lipolysis as a compensatory mechanism to release fatty acids and provide an alternative source of energy in the absence of sufficient glucose (Bernroider et al., 2005; Brun et al., 2019; Stuart et al., 2013). However, in obese individuals, adipose tissue is already saturated with fatty acids due to excess fat storage. Therefore, this can lead to an increased release of FFA into the bloodstream, which can interfere with insulin action in peripheral tissues such as muscle and liver, known as insulin resistance. The counter-regulatory hormonal response following hypoglycemia (glucagon, cortisol and growth hormone) with sustained hyperinsulinemia and constant glucose availability was found to induce resistance by stimulating lipolysis (Fanelli et al., 1992). Also, it has been demonstrated that, during hypoglycemia, the PKA pathway is activated in adipose tissue, leading to activation of the HSL enzyme and the release of fatty acids from adipose tissue into the blood via lipolysis (Voss et al., 2017). In the face of insulin resistance, the pancreas attempts to compensate by secreting even more insulin to overcome this lack of response from peripheral tissues. Continued abuse of these dietary habits results in chronic hypersecretion of insulin to overcome the unresponsiveness of peripheral tissues to the hormone. Both the existence of hyperinsulinemia and insulin resistance ultimately cause stress on pancreatic beta cells, which in the long term can lead to beta cell dysfunction and T2DM (Esser et al., 2020; Furth-Lavi et al., 2022; Willett et al., 2002), Figure 6B.

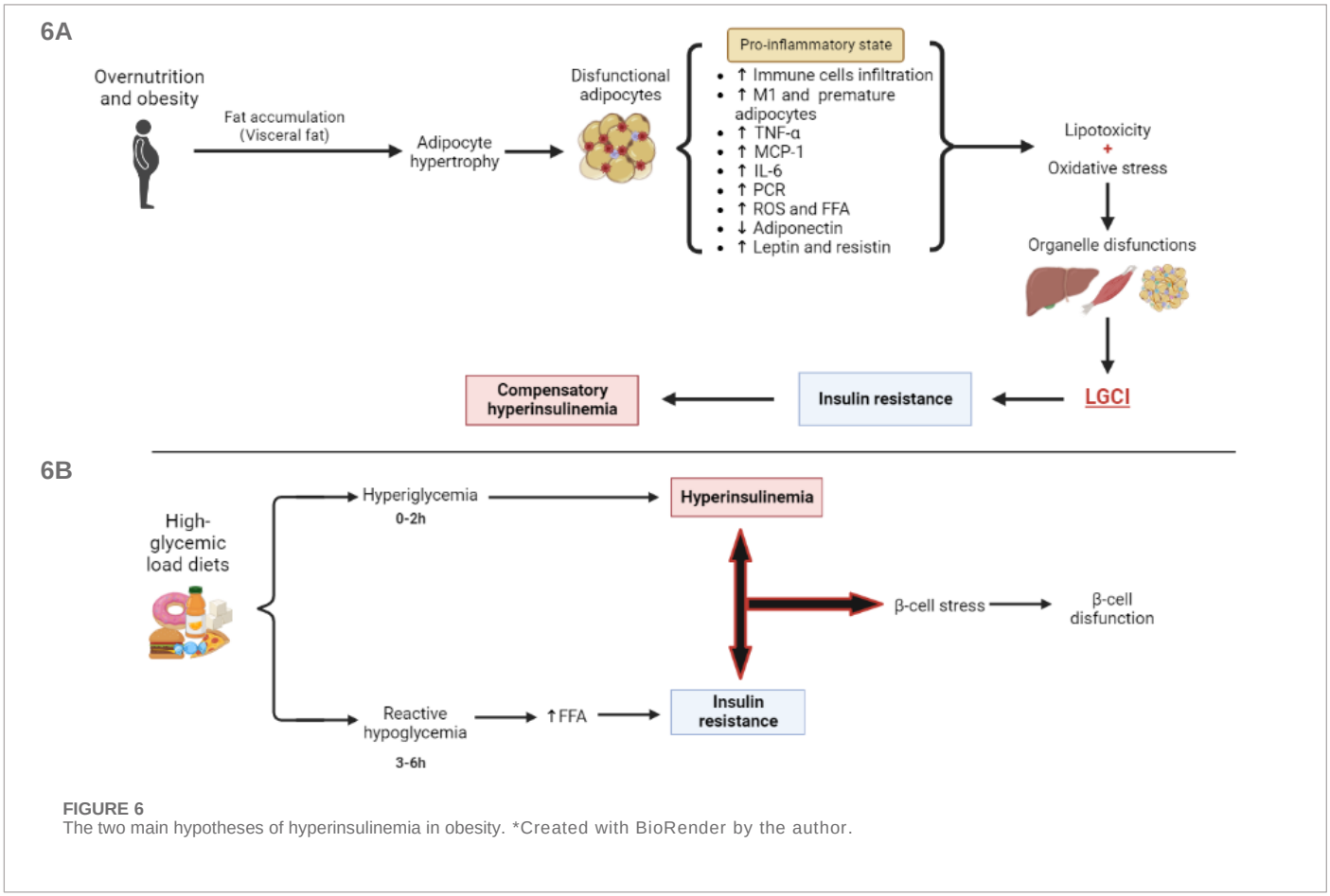

FIGURE 6
The two main hypotheses of hyperinsulinemia in obesity. *Created with BioRender by the author.

4.3. Insulin/IGF-1/GH axis

The insulin-GH-IGF axis is a complex hormonal system that regulates various physiological processes, including growth, metabolism, and nutrient utilization. Growth hormone (GH) is known to enhance lipolysis and increase the metabolic rate, leading to greater energy expenditure. IGF-1 is produced mostly in the liver in response to GH stimulation and acts as a key mediator of GH effects in peripheral tissues. In healthy people there is a state of balance in the insulin-GH-IGF-I axis, functioning in a coordinated and harmonious way where insulin and GH stimulate IGF-1 production in the liver, and once secreted it feeds back negatively to suppress both insulin and GH secretion (Huang et al., 2021). Hyperinsulinemia increases IGF-1 secretion (Brugts et al., 2010), which inhibits GH secretion, and within a few days of overeating insulin is able to suppress GH synthesis and release from the pituitary gland (Cornford et al., 2011). Additionally, hyperinsulinemia induces loss of pulsatile insulin secretion, contributing to insulin resistance, which intensifies lipolysis in adipocytes by increasing FFA release, further inhibiting GH (Kreitschmann-Andermahr et al., 2010). Consequently, the insulin-GH ratio becomes skewed towards insulin dominance. This promotes energy storage and lipid synthesis and inhibits lipid breakdown, leading to a reduced energy expenditure, coupled with increased energy storage, favoring weight gain and obesity (Huang et al., 2020; Janssen, 2021; Sbraccia et al., 2021), Figure 7.

4.4. Other roles (senescence and cancer)

In normal conditions, insulin exerts autocrine effects by promoting beta-cell growth to ensure a sufficient mass of beta-cells to produce and secrete insulin. Moreover, it supports the survival and prevents the apoptosis of beta-cell as well as influencing its own production and secretion when beta-cells are exposed to elevated glucose levels (Mehran et al., 2012; Templeman et al., 2017). In people with obesity, however, this has been found to be altered. In situations of chronic hyperinsulinemia, even in nonproliferating cells, this prolonged mitogenic signal can trigger the reentry of the cell cycle. This, when combined with cellular stress, leads to the induction of senescence in mature adipocytes (Li et al., 2021). Basically, as we accumulate fat and obesity increases, leading to hypertrophy of adipocytes (Choe et al., 2016). Hyperinsulinemia has been shown to cause a phenomenon called endo-reduplication (duplication of genomic DNA without chromosome segregation during mitosis) in these hypertrophied adipocytes, which results in cellular senescence. “Endo reduplicated” adipocytes start to secrete increased amounts of pro-inflammatory cytokines which promote a state of chronic inflammation in adipose tissue and finally throughout the body. This can trigger systemic inflammatory responses and contribute to the development of several metabolic diseases and neurodegenerative disorders (Baboota et al., 2022; Chow et al., 2019; Meijnikman et al., 2022; Narasimhan et al., 2022; Rodriguez-Cuenca & Vidal-Puig, 2021), Figure 8A.

Obesity is associated with an increased risk of developing certain types of cancer (Lauby-Secretan et al., 2016; Leitner et al., 2022), including breast, colorectal, liver, esophageal, gallbladder, kidney, uterine and pancreatic cancer (Gunter et al., 2009; Pati et al., 2023; Zhang et al., 2022). Hyperinsulinemia is thought to be one of the key mechanisms linking obesity and cancer (Gallagher & LeRoith, 2020; Vigneri et al., 2020). Numerous systemic factors that experience dysregulation in conditions like obesity have been identified as potential contributors to the development and progression of cancer. These factors encompass insulin, IGF-1, glucose, lipids, inflammatory cytokines, immune cells, steroids, the autonomic nervous system, adipokines, and the microbiome (Avgerinos et al., 2019; Gleeson, 2019). The mechanism by which insulin is able to contribute to tumor formation/progression is through the activation of PI3K, initiating downstream Akt/mTOR network signaling as well as MAPK pathway. Is demonstrated that PI3K/Akt pathway activates NF-kβ, which is responsible for increasing the production of inflammatory cytokines (e.g. TNF-α, IL-1, IL-6 and chemokines) finally resulting in a low-grade inflammation. MAPK is mainly responsible for activating several transcription factors that induce elevated expression of c-fos and its binding to the activator protein-1 (AP-1) (De Marco et al., 2015), which can lead to altered of cellular dynamics characterized by an acceleration of the cell cycle, decreased apoptosis and increased angiogenesis and

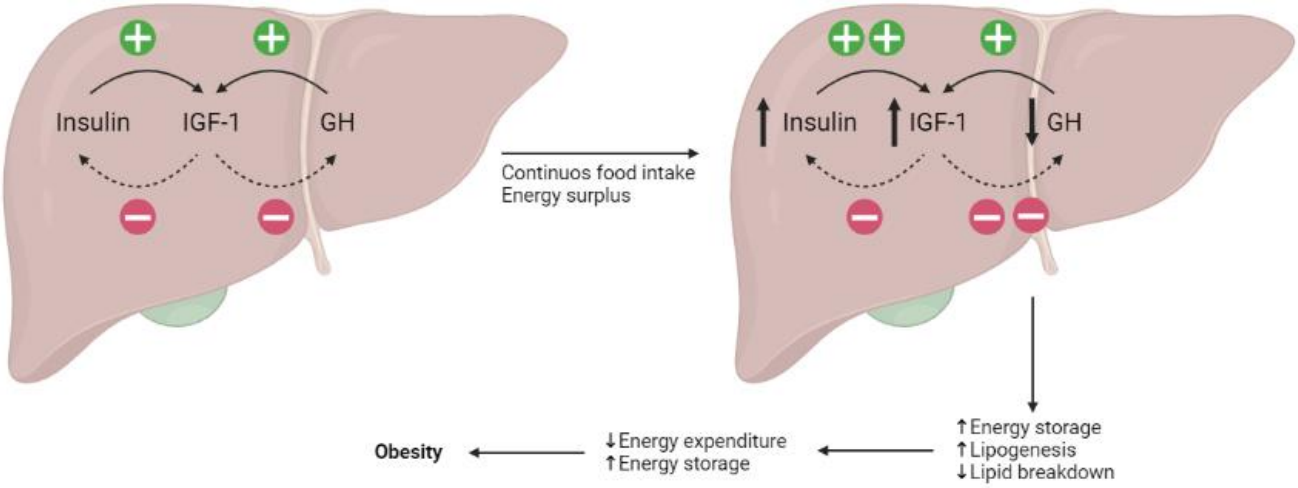

FIGURE 7
Simplification of hormonal imbalance (high insulin and IGF-1 and low GH) caused by hyperinsulinemia and its effect on obesity. *Created with BioRender by the author.

metastasis (Yee et al., 2020). Importantly, IGF-1 shares common signaling pathways with insulin so it can also promote cancer progression by binding to the InsR and activating both signaling pathways (Cai et al., 2017), Figure 8B.

5. Current strategies and emerging approaches to reduce hyperinsulinemia in obesity

It has been demonstrated that hyperinsulinemia is required for weight gain and that lower insulin levels increase energy expenditure, therefore it could be assumed that a reduction in circulating insulin will help to control/reduce obesity (Kolb et al., 2018; Page & Johnson, 2018; Templeman et al., 2015, 2017; Velasquez-Mieyer et al., 2003).

5.1. Pharmacological options

In individuals with obesity but without diabetes, the addition of liraglutide (GLP-1 analogue) to diet and exercise resulted in decreased body weight, reduced fasting insulin levels, and a lower incidence of prediabetes (Astrup et al., 2011; Pi-Sunyer et al., 2015; Wadden et al., 2013). However, it has been associated with many side effects such as acute pancreatitis, gallbladder, liver disease and some cancers (Seo, 2021). For this reason, we need more conclusive trials to demonstrate a causal effect. Another drug used is fenofibrate, a PPARα agonist. Studies in mice have shown that fenofibrate has the ability to increase fat oxidation and reduce both insulin clearance and insulin secretion when administered in conjunction with a high-fat diet (Ramakrishnan et al., 2016). Also it is worth noting that the use of rosiglitazone, a PPARγ receptor agonist, in individuals with type 2 diabetes showed a significantly increase insulin clearance, even in the absence of significant weight loss (Tiikkainen et al., 2004). Other widely used drug is diazoxide, which activates ATP-sensitive potassium channels and exerts inhibitory effects on insulin secretion in pancreatic cells. In experimental studies, it has demonstrated an improvement in insulin secretion and insulin sensitivity, and a preventive effect on obesity with a significant weight loss (Alemzadeh et al., 1998, 2008; Sato et al., 1995) and they have proposed the use of diazoxide could potentially normalize GH secretion and enhance the metabolism of substrates and energy (Huang et al., 2021). Its use has also been studied in humans, clearly reducing body weight and improving insulin resistance, but there is still much contraindication to its treatment of hyperinsulinemia in obesity (Brar et al., 2020; Lustig et al., 2006). Moreover, tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has also been suggested for use in the treatment of obesity, resulting in a decrease in body weight which improves fasting insulin levels (Jastreboff et al., 2022). Finally, metformin is a drug typically used for the treatment of type 2 diabetes although it has also been investigated for use in obese people with hyperinsulinemia. It acts mainly by reducing hepatic glucose production and improving insulin sensitivity in peripheral tissues, such as muscle and adipose tissue. Metformin may help control elevated insulin levels by reducing insulin resistance and decreasing excessive insulin production by the pancreas (Atabek & Pirgon, 2008; Herman et al., 2022; Hundal et al., 2000; Patanè et al., 2000; Velazquez et al., 1994). However, there are conflicting studies that say that although metformin contributes to weight loss in obesity, there is no improvement in insulin resistance, fasting insulin, and insulin sensitivity in obesity (Pau et al., 2014; Sun et al., 2019). In brief, while pharmacological therapies exist, their efficacy in the long term may be limited compared to sustained lifestyle changes. Furthermore, the vast majority of these drugs aim to increase insulin levels to lower blood glucose, thus further worsening hyperinsulinemia. Therefore, only drugs that reduce insulin secretion should be used in conjunction with lifestyle modifications and not as stand-alone treatments, as this will have a much more significant effect (Aaseth et al., 2021; Gadde & Allison, 2009).

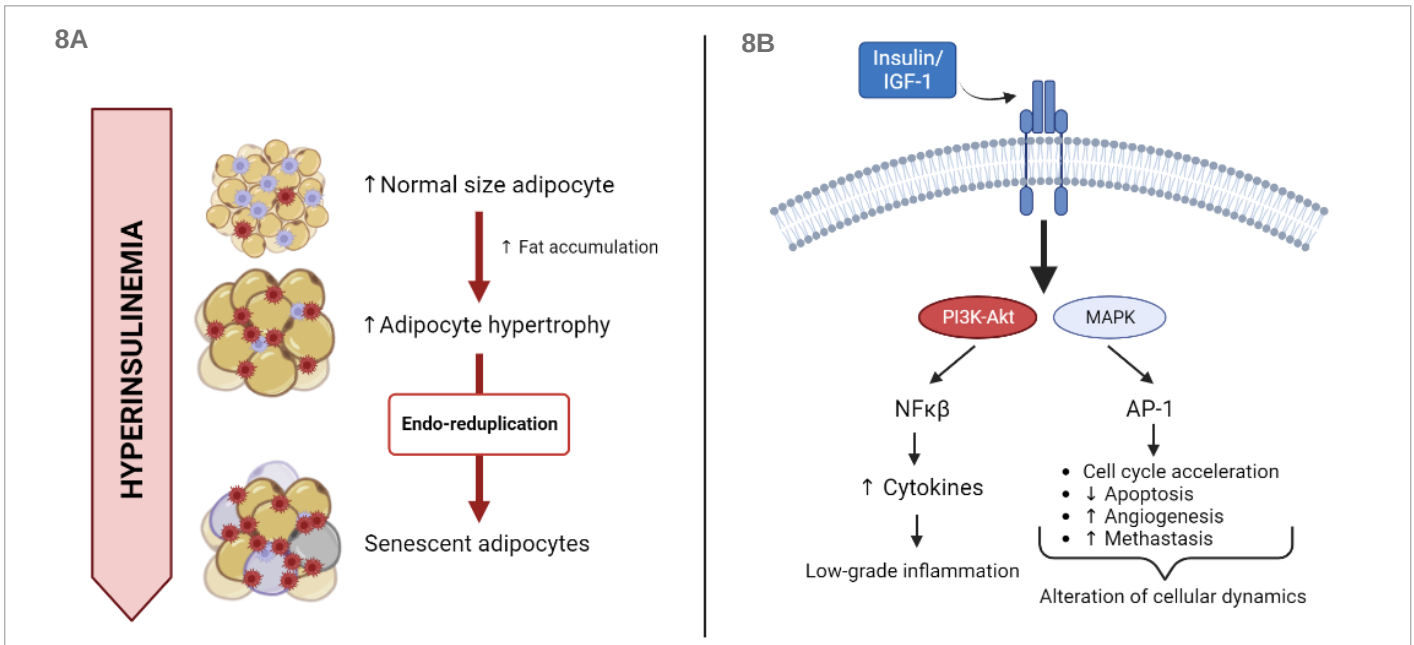

FIGURE 9
9A: Simplified explanation of how hyperinsulinemia activates premature adipocyte senescence and inflammation in obesity. 9B: Key pathways through which insulin and InsR signaling may promote cancer progression. *Created with BioRender by the author.

5.2. Dietetic interventions

A wide range of dietary interventions have been proposed to reduce hyperinsulinemia in obesity, the most studied being the low-carbohydrate diet (LCD), low-fat diet (LFD), ketogenic diet (KD) and low-glycemic load diet (LGLD).

Regarding the LCD, it is generally accepted that it should contain less than 130g/day of carbohydrates or <20 % of total energy intake, although there is no clearly defined limit. Reducing carbohydrate intake seems to be a safe dietary approach to improve hyperinsulinemia among other conditions associated with obesity (Berger & Thorn, 2022; P. J. Foley, 2021; Hron et al., 2015). KD often contain less than 50g of carbohydrate/day and it is also associated with a greater long-term weight loss, an improvement in fasting insulin and lipid profile (Bueno et al., 2013; Michalczyk et al., 2020). LCD has been shown to contribute to reduced hepatic glucose production and increased insulin clearance among other benefits on lipid profile (Lundsgaard et al., 2019; Suzuki et al., 2019).

In terms of a LGLD, it has been found that produces a more significant increase in weight loss compared to a low-fat diet (Chaput et al., 2008) as well reducing the risk of several complications associated with hyperinsulinemia (Ebbeling et al., 2007; Ludwig et al., 2000; Perin et al., 2022). It has been shown that reducing glycemic load can be particularly important in achieving weight loss among individuals with high insulin secretion (Ebbeling et al., 2007; Pittas et al., 2005; Rasaei et al., 2023; Sipe et al., 2022; D. E. Thomas et al., 2007). However, other studies support that there is probably no causal relationship between high-glycemic diets and obesity associated with hyperinsulinemia (Aston et al., 2008; Gaesser et al., 2021; Milton et al., 2007; Vega-López et al., 2018). One possible explanation for this contradiction is confounding factors such as the use of food frequency questionnaires in self-reported observational studies or the fiber content of low GI diets as well as physical activity among others. On the contrary, there are no relevant studies showing that a LGLD does not have beneficial effects such as weight loss or enhanced insulin levels.

On the other hand, there is the LFD, which is one of the most widely analyzed dietary interventions. Despite a reduction in insulin levels and body weight (among other parameters), this reduction is not as clear-cut as in the case of LCD (Mancini et al., 2016). Other dietary interventions used in obesity management include calorie restriction (CR) and time-restricted eating, the latter being a type of intermittent fasting (Soliman, 2022). CR has shown a significant weight loss and an improvement in hyperinsulinemia and insulin sensitivity (Michalczyk et al., 2020; Siklova-Vitkova et al., 2009), but it is important to consider their negative impact on muscle mass, bone density, and overall health (Ard et al., 2018; Dorling et al., 2021; Most et al., 2017). In contrast, the long-term weight loss effects of time-restricted eating are still unknown, and its other demonstrated beneficial effects do not outweigh those of calorie restriction since it has inconsistent effects concerning insulin levels and sensitivity to insulin in obese people (Andriessen et al., 2022; D. Liu et al., 2022).

In a nutshell, the first result in all the diets mentioned is the loss of body weight. Even so, the LFD can be seen to have a lack of long-term efficacy compared to other interventions such as LCD and KD. Even knowing that carbohydrates (specially glucose) are the nutrient that most stimulates insulin secretion at first sight we could assume that the implementation of diets that reduce both the amount of carbohydrates and the glycemic index will have better results on hyperinsulinemia in obesity (Ebbeling et al., 2007). However, it is necessary to take into account that various nutrients and other compounds may stimulate insulin secretion differently in each individual, this could mean that a LCD will not be sufficient for all people. Therefore, the origin of the onset of obesity in each individual should be analyzed, in order to make a more complex and individualized approach for better optimization and bear in mind that there is no universally healthy diet which can be uniformly prescribed to treat hyperinsulinemia in obesity.

TABLE 1

Simple comparison of the effects of current dietary interventions in obesity. Created by the author.

	LCD/KD	LFD	LGLD	CR
Weight loss	↑↑	↑	↑↑	↑↑
Fasting insulin	↓↓	↓	↓↓	↓
Insulin sensitivity	↑	---	↑	↑
Lipid profile	↑ HDL	---	↑ HDL	↑ HDL
	↑ LDL	↓ LDL	---	↓ LDL
	↓ TG	---	↓ TG	↓ TG
Total fat content	↓	↓	↓	↓

5.3. Physical activity

Physical activity is considered to be a determinant factor of hyperinsulinemia for many years (Feskens et al., 1994). It can significantly lower insulin levels and improve insulin sensitivity (Lin et al., 2022; Vetrivel Venkatasamy et al., 2013). Physical activity has an effect on insulin sensitivity by enhancing glucose transport in skeletal muscle via pathways dependent on both the GLUT4 transporter protein and the response to hypoxia, as well as increasing skeletal muscle vascularization and tissue mass, distributing intracellular fat more efficiently and contributing to fat mass loss (Balkau et al., 2008). In some experimental studies with rats, they found that strength exercise effectively protected against hyperinsulinemia, insulin resistance, and inflammation, regardless of any changes in body weight (Botezelli et al., 2016; Muñoz et al., 2022). Moreover, in a randomized controlled trial of African women, they saw also an increase in insulin sensitivity, while there were no concurrent changes in insulin secretion/clearance or central and ectopic fat deposits (Fortuin-De Smidt et al., 2020).

TABLE 2

The effects of physical activity in obesity. Created by the author.

Physical activity
↓ Body weight
↓ Fasting insulin
↑ Insulin sensitivity
Improves lipid profile and total fat content
↑ **Muscular mass** (strength exercise)
…

5.4. Bariatric surgery

Bariatric surgery has been shown to improve insulin sensitivity and pancreatic beta-cell function in obese non-diabetic subjects when they lost weight. The curious thing is that it seems to be that losing weight is the main trigger for these improvements, independently of the type of surgery. It has also been observed that both insulin and fasting glucose levels improved after the intervention (Bradley et al., 2012; Lima et al., 2010; Y. Liu et al., 2022; Malik et al., 2016). Bariatric surgery has also been associated with a decrease in systemic inflammation markers, such as C-reactive protein (CRP), TNF-α and IL-6, indicating a potential anti-inflammatory effect (Biobaku et al., 2020; Hafida et al., 2016; Rao, 2012; Villarreal-Calderon et al., 2021). Overall, bariatric surgery has demonstrated significant benefits in reducing hyperinsulinemia, improving insulin sensitivity, increasing insulin clearance and promoting metabolic health in individuals with obesity (Bojsen-Møller et al., 2014; Erion & Corkey, 2017; D. D. Thomas et al., 2019). Some research also suggests that changes in gut microbiota composition after bariatric surgery may play a role in improving insulin sensitivity and reducing hyperinsulinemia among other benefits (Ulker & Yildiran, 2019).

6. Insulin measurement methods

In the clinical practice, despite methodological advances over the last half century, the measurement of insulin in blood still poses numerous analytical and clinical challenges. Accurate insulin measurements are crucial for both clinical and research purposes. However, there is currently no standardized reference method to compare insulin assays from different manufacturers and laboratories (Taylor et al., 2016). Insulin secretion occurs in pulses, causing fluctuations in blood insulin concentrations every 5-15 minutes (Pørksen et al., 2002). To obtain a reliable fasting insulin level, it is recommended to calculate the mean of three blood samples taken at 5-minute intervals (Crofts et al., 2015). Unfortunately, this practice is rarely followed in clinical settings and epidemiological studies (De León & Stanley, 2013; Janssen, 2021). Hence, two proposed markers for diagnosing hyperinsulinemia in obese patients are C-peptide and fasting insulin. While the liver does not remove C-peptide to any significant extent during its first passage, the kidney is primarily responsible for removing it from the bloodstream. This unique clearance pattern makes peripheral C-peptide concentrations a more accurate measure of insulin secretion from the pancreas via the portal vein than peripheral plasma insulin concentrations. For this reason, peripheral C-peptide levels are often used as a measure of beta-cell secretory activity in a wide range of clinical situations. However, because C-peptide has a longer half-life (approximately 35 minutes) than insulin (3-8 minutes), this can dampen oscillations and decrease pulsatility, making insulin the preferred choice when studying insulin secretory dynamics (Venugopal et al., 2022).

It should also be understood that obesity is a disease that, if left untreated, can lead to a pre-diabetic state (Miao et al., 2020). A common medical error regarding the identification of prediabetes is that blood glucose levels are looked at instead of fasting insulin or C-peptide, the latter being of greater validity for diagnosing prediabetes (Gedebjerg et al., 2023; Leighton et al., 2017; Ohkura et al., 2013). But it should be noted that in this specific context, when blood glucose levels are normal it may be because insulin is acting compensatory to reduce hyperglycemia, thus producing hyperinsulinemia. For this reason, when some health professionals see a decent glucose range, they will probably assume that there is no metabolic problem. Therefore, it would be much better to look at the hormone insulin in the blood and C-peptide, as elevated glucose levels are simply a manifestation of poor insulin action (Saisho, 2016).

7. Conclusions

Hyperinsulinemia is a condition normally found in people with obesity. Having reviewed and compared multiple reviews and clinical trials and so forth, there is a lot of contradiction regarding the timing of the onset of hyperinsulinemia in obesity and it turns to be a topic of ongoing research and debate. Therefore, it is required further interventional studies to establish a causal or non-causal relationship of hyperinsulinemia in obesity. To accomplish this, it is also essential to determine the causal mechanisms of insulin resistance and hyperinsulinemia in obesity, in order to be clear about the precise moment of occurrence for each one. A possible underlying explanation for this controversy over the results may be due to differences in the metabolic status of the participants and the large variability in the methods used for assessing hyperinsulinemia among other causes. Nevertheless, it is known that hyperinsulinemia is capable of inducing insulin resistance, it has been proposed that it may do so by reducing the affinity and number of insulin receptors. Moreover, overnutrition can directly stimulate insulin hypersecretion leading to reduced peripheral insulin sensitivity. In addition, high insulin levels have been linked to a range of pathological conditions, including cancer and diabetes, highlighting the importance of addressing elevated insulin levels in obesity. However, regarding the strategies to reduce hyperinsulinemia in patients with obesity, there is still a lack of knowledge about its long-term effectiveness. Diet is placed as one of the most powerful variables, with LGLD and LCD appearing to have the greatest effect, both of which have shown promising results in improving obesity, hyperinsulinemia, and diabetes risk. Additionally, incorporating regular exercise alongside dietary changes has been found to have the greatest impact on reducing insulin levels. In terms of the wide range of pharmacological interventions available, it is noteworthy that a considerable proportion operate on the premise of increasing insulin levels as a means of improving blood glucose concentrations. Paradoxically, this approach tends to exacerbate the existing scenario, culminating in the development of chronic hyperinsulinemia and insulin resistance, along with a multitude of associated adverse effects. It is therefore far more effective to employ pharmacotherapeutic agents that attenuate excessive insulin secretion. Nevertheless, it is worth noting that long-term efficacy and potential side effects of the majority of these drugs warrant further investigation. In brief, it is necessary to understand that both hyperinsulinemia and obesity are complex conditions with multifactorial origins, which contribute to the challenges of studying their molecular mechanisms. Understanding the interplay between various factors involved in the development of these two conditions is crucial for developing effective treatment strategies.

Conflict of interest

The author declares that this review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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