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EXPLORING THE INTERPLAY BETWEEN OBESITY-INDUCED INSULIN RESISTANCE AND TYPE 2 DIABETES- A VICIOUS CYCLE THAT CAN BE BROKEN

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ABSTRACT

Obesity is a growing problem worldwide, with over 650 million obese adults, and has tripled since 1975. It's caused by excessive body fat due to eating too many calories, a sedentary lifestyle, and genetic susceptibility, leading to health issues such as high cholesterol, blood pressure, and risk of secondary diseases. Type 2 diabetes is a complex illness caused by genetic, environmental, and behavioral risk factors, leading to insulin resistance and hyperglycemia. β cells in the islets of Langerhans secrete insulin, which regulates the metabolism of carbohydrates, proteins, and fats by facilitating the uptake of molecules such as glucose from the bloodstream into the liver, fat, and skeletal muscle cells. High glucose stimulates metabolic pathways, generating oxidative stress and insulin resistance, disruptions in insulin signaling due to excess fatty acids and cytokines. Insulin resistance impairs the body's response to insulin, causing hyperinsulinemia and metabolic problems, including type 2 diabetes. Metabolic syndrome and insulin resistance syndrome are clinical indicators of insulin resistance, with specific criteria for diagnosis. It is believed that inflammation plays an important role in regulating metabolism and energy balance, which may lead to new treatments and diagnostic equipment for the treatment of obesity-related insulin resistance. Obesity and insulin resistance research have a promising future, with many exciting developments on the horizon. This may entail utilizing multi-omics methods, such as genomics, transcriptomics, proteomics, and metabolomics, to obtain a more comprehensive understanding of the cellular mechanisms implicated in insulin resistance. In this review, we will discuss the relationship between obesity and the risk of developing insulin resistance, as well as the possible mechanisms underlying this process.

KEYWORDS: Obesity, insulin-dependent diabetes mellitus, Insulin resistance, inflammation, hyperinsulinemia, oxidative stress, Metabolic syndrome.

INTRODUCTION

OBESITY

Worldwide, obesity is a serious problem[1] with over 650 million obese adults, and it has nearly tripled since 1975. Obesity is characterized by an excessive amount of body fat that has a detrimental effect on health and is caused by eating too many calories, not moving around much, and having a genetic susceptibility. High fatty acid levels, insulin resistance, high cholesterol, high blood pressure, metabolic imbalances, exhaustion, gallstones, shortness of breath, and excessive adipose mass production are all indications. Obesity can result in low self-esteem, social isolation, and depression, and it raises the risk of several secondary diseases such as cancer, cardiovascular disease, and insulin resistance. Heart disease, type 2 diabetes, difficulty breathing while sleeping, cancer, and osteoarthritis are just a few of the secondary illnesses associated with pathological obesity.[2]

Modulating factors for obesity

Being overweight or obese as a child increases your chances of becoming obese as an adult. Women have more body fat than men. People with a high socioeconomic status (SES) are more likely to be obese, whereas people with a low SES are more likely to be obese in wealthy countries. Overeating causes you to gain weight and become obese. Dietary fat has been linked to the prevalence of being overweight in ecological research. A low body mass index and RMR (Resting Metabolic Rate) are risk factors for weight gain. Low levels of physical activity (PA) are linked to an increased risk of weight gain. Low GH levels are a risk factor for weight gain. Obese people frequently have high insulin resistance levels. Obese women frequently have elevated androgen levels. Obesity has no effect on skeletal muscle (SM) metabolism, but it does increase SM type IIb fiber type proportion. Smoking

characteristics are associated with lower body weight; cessation increases body weight in most people.[2]

BMI(body mass index)	
18.5-24.9	Normal Body Weight
25.0-29.9	Obesity
30.0-34.9	Class I Obesity
35.0-39.9	Class II Obesity (Severe Obesity)
40- 50	Class III Obesity (Morbid Obesity)

TYPE 2 DM

The earliest known case of diabetes mellitus (DM), which has been around for thousands of years, can be found in an ancient Egyptian manuscript from about three thousand years ago. Type 1 and type 2 diabetes were differentiated from one another in 1936, and type 2 diabetes was recognized as a part of the metabolic syndrome in 1988. Hyperglycemia, insulin resistance, and a relative lack of insulin are the hallmarks of type 2 diabetes, formerly known as noninsulin-dependent diabetes. Genetic, environmental, and behavioral risk factors interact in a complex manner to cause it.[3]

The pathogenesis of type 2 diabetes comprises insulin insensitivity brought on by insulin resistance and a decrease in insulin secretion, which reduces glucose transport into the liver, muscle cells, and fat cells and increases fat breakdown with hyperglycemia. Also contributing to the elevated glucagon and hepatic glucose levels that are not reduced by food is the impaired Alpha-cell function. Adipose tissue is crucial in the development of type 2 DM, which is why the majority of persons with the condition are obese and have central visceral adiposity. The primary theory explaining this connection centers on increased nonesterified fatty acid concentrations and is known as the portal/visceral hypothesis. Research on the role of adipose tissue and mitochondrial dysfunction in the emergence of insulin resistance and type 2 DM is still underway.[3]

The diagnostic standards for type 2 diabetes might differ based on the society or medical organization, however, a typical set of standards includes the following.

1. A fasting plasma glucose (FPG) level of at least 126 mg/dL (7.0 mmol/L), as determined by further testing on a different day, or
2. A repeat test on a different day reveals a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during an oral glucose tolerance test (OGTT), or A patient with hyperglycemia or hyperglycemic crisis symptoms has a random plasma glucose level of 200 mg/dL (11.1 mmol/L) or greater. In addition to these criteria, additional tests, such as glycated hemoglobin (HbA1c) testing and continuous glucose monitoring, may be performed to help in the diagnosis and management of type 2 diabetes.[3]

INSULIN AND ITS BIOSYNTHESIS

Insulin is a hormone made by the β cells in the pancreas that regulates blood sugar levels by assisting with the uptake of glucose into cells, controlling the metabolism of carbohydrates, lipids, and proteins, and encouraging cellular growth and division through mitogenic effects. Insulin is produced in the β cells of the pancreas as proinsulin, which is synthesized in the ribosomes of the rough endoplasmic reticulum from mRNA as pre-proinsulin. This involves the sequential synthesis of a signal peptide, the B chain, the connecting (C) peptide, and the A chain. Proinsulin, which makes up no more than 6% of islet cell secretion, acquires its characteristic 3-dimensional structure in the endoplasmic reticulum before being transferred to the Golgi apparatus by secretory vesicles. In the Golgi, soluble zinc-containing proinsulin hexamers are formed due to the aqueous zinc and calcium-rich environment. Enzymes outside the Golgi then convert proinsulin to insulin and C-peptide as immature storage vesicles form from the Golgi. Insulin forms zinc-containing hexamers that are chemically stable crystals at pH 5.5. When mature granules are released into the bloodstream by exocytosis, insulin, and C-peptide are released in an equimolar ratio. Insulin secretion is pulsatile and reflects the summation of coordinate secretory bursts from millions of islet cells. In response to stimuli such as glucose, insulin secretion is biphasic, with an initial rapid phase of insulin secretion followed by a less intense but more sustained release of the hormone. An ultradian oscillatory pattern of insulin release, as well as post-meal variation, has been reported.[4]

The process by which insulin is secreted

The first phase of insulin secretion in response to increased glucose levels involves the release of insulin from β cell secretory granules. The entry of glucose into β cells is detected by glucokinase, which phosphorylates glucose into G6P and generates ATP, leading to the closure of K+-ATP-dependent channels, membrane depolarization, and activation of voltage-dependent calcium channels. The resulting increase in intracellular calcium levels causes pulsatile insulin secretion. The response can be further enhanced by Ca2+-dependent and Ca2+-independent pathways, as well as through the activation of other mediators such as phospholipases and protein kinase C. The second phase of insulin secretion involves the refilling of secretory granules from reserve pools and is significantly influenced by hormones such as VIP, PACAP, GLP-1, and GIP.[4]

The insulin receptor signaling pathway

Explaining the insulin receptor signaling pathway is crucial when discussing insulin resistance because this process involves numerous proteins and is affected by various other pathways. Glucose transporter 4 (GLUT4) is the primary glucose transporter in insulin-sensitive tissues like skeletal muscle and adipose tissue, and researchers have extensively studied it in connection to insulin resistance. When insulin is present, the cell increases the amount of GLUT4 expressed in the plasma membrane, which leads to greater cellular intake of glucose from the bloodstream. The usual process starts

with insulin connecting to the insulin tyrosine kinase receptor. This prompts the insulin receptor to add phosphate groups to insulin receptor substrate-1 (IRS-1), which then adds phosphate groups to PI3-kinase. PI3-kinase then adds phosphate groups to PIP2, activating Akt, which causes glucose transporter 4 (GLUT4) to move to the plasma membrane of skeletal muscle cells and adipocytes. This allows the cells to take in glucose from outside, which reduces interstitial glucose levels and lowers plasma glucose concentration.[5]

INSULIN RESISTANCE

Insulin resistance is a condition in which the body's ability to respond to the stimulation of certain tissues by insulin, such as the liver, muscle, and adipose tissue, is compromised. As a result of this impairment, glucose is not being eliminated as well, which increases insulin production from beta cells in an effort to overcome the resistance. Hyperinsulinemia, or an excess of insulin in the blood, is the result. Numerous metabolic problems, such as high blood sugar, high blood pressure, abnormal cholesterol, and fat levels, increased fat around organs, high levels of uric acid, elevated inflammatory markers, impaired endothelial function, and a propensity for blood clotting, can be brought on by insulin resistance. Long-term insulin resistance may lead to diseases including metabolic syndrome, nonalcoholic fatty liver disease, and ultimately type 2 diabetes mellitus. Type 2 diabetes, which typically develops 10 to 15 years after insulin resistance starts, is thought to be the most severe consequence of the condition. Insulin resistance worsens as the body creates more insulin to make up for the lost ability to use it, which results in weight gain. This cycle persists until the beta cells in the pancreas are unable to meet the demand for insulin, which results in elevated blood sugar levels and, ultimately, type 2 diabetes.[6]

Potential causes include down-regulation, insufficient tyrosine phosphorylation of the insulin receptor, IRS proteins, PIP-3 kinase, or abnormalities in GLUT 4 function[4]. Muscle, the liver, and adipose tissue are the three body tissues where insulin resistance is most common. It is thought that immune-mediated inflammatory alterations and an excess of free fatty acids, which cause ectopic lipid deposition, are the origins of insulin resistance in muscle tissue. Because insulin is unable to stop lipolysis in adipose tissue, particularly visceral adipose tissue, there is an increase in the amount of free fatty acids in the blood. This has an immediate effect on the metabolism of the liver and muscles, aggravating insulin resistance.[6]

In muscle tissue, after the intake of a caloric load and conversion to glucose, with an excess of calorie intake, glucose uptake by muscle exceeds capacity, and excess glucose returns to the liver, where it triggers de novo lipogenesis. This process increases triglyceride and free fatty acid production, causing ectopic fat deposition in the liver, muscle, and adipose tissue.[6]

In hepatic tissue, Insulin reduces hepatic glucose production via inhibition of glycogenolysis, limiting the postprandial rise in glucose. However, with insulin resistance, this feedback mechanism is impaired, and hepatic glucose production continues to rise, even as postprandial glucose rises. Elevated glucose levels associated with glucotoxicity further contribute to insulin resistance.[6]

- Type-A insulin resistance is a condition that occurs before middle age and is characterized by severe resistance to insulin, resulting in abnormal glucose control, ovarian virilization, and the development of acanthosis nigricans. This condition occurs without the presence of anti-insulin antibodies.[6]
- Type-B insulin resistance is a condition that typically occurs in middle age and is characterized by the development of anti-insulin antibodies. This leads to abnormal glucose control, ovarian hyperandrogenism, and the development of acanthosis nigricans.[6]

HOW OBESITY LEADS TO INSULIN RESISTANCE

Obese adults have a higher risk of developing type 2 diabetes and insulin resistance. In obese individuals, adipose tissue produces an increased amount of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other chemicals. This might result in a failure to control blood glucose levels. Insulin resistance results from this disruption of the channels that carry insulin signals. Elevated blood glucose levels occur from insulin's reduced capacity to promote glucose uptake and utilization, which can cause type 2 diabetes and other metabolic disorders.[7]

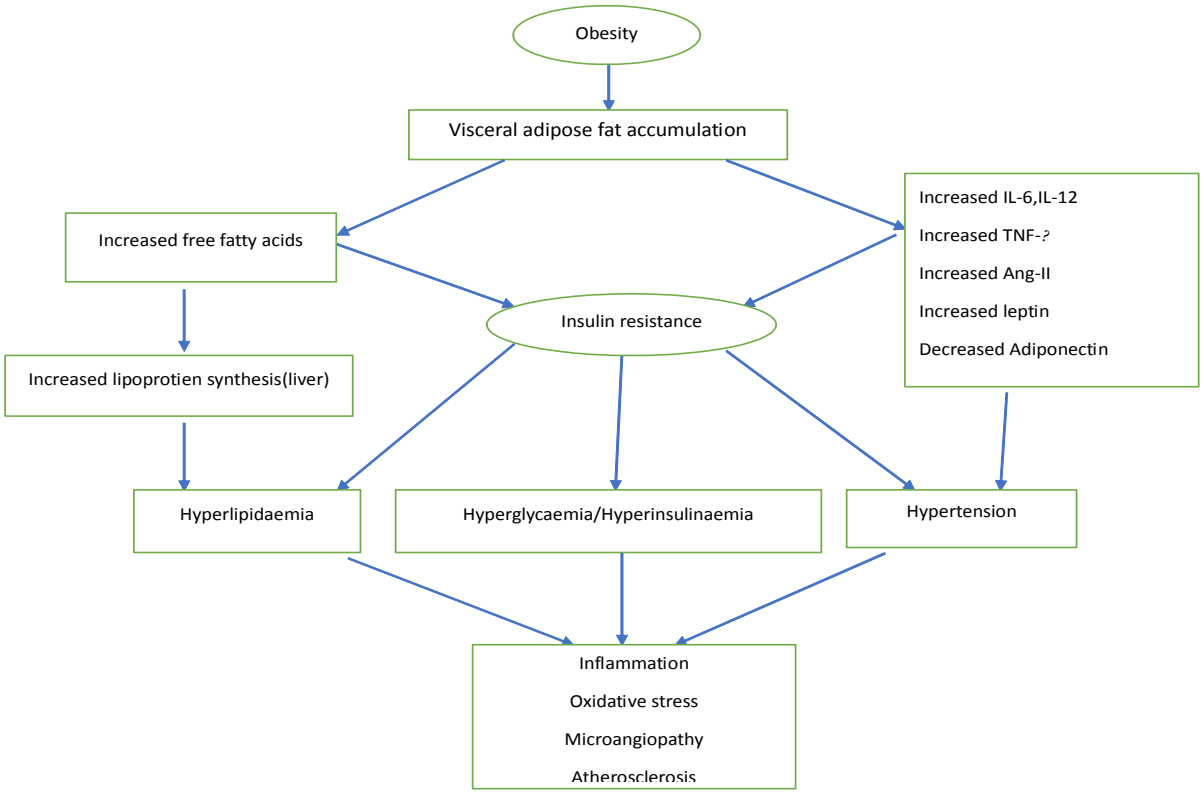

Figure number 1.0 illustration of pathophysiology involved in obesity-induced insulin resistance

THE CELLULAR MECHANISMS OF OBESITY-INDUCED INSULIN RESISTANCE

By promoting glucose uptake in insulin-sensitive tissues such as muscle, fat, and the heart, insulin helps to control blood glucose levels. Moreover, it reduces the amount of glucose that is produced in organs like the liver, kidney, and small intestine. One of the many physiological functions insulin is in charge of is controlling blood glucose levels. Moreover, it stimulates the production of fatty acids and glycogen, raises mitochondrial performance, boosts microcirculation, and stimulates cell division. Insulin resistance develops when the suppression of insulin signaling prevents the absorption of glucose generated by insulin in insulin-sensitive tissues. In an effort to control blood glucose, the pancreas frequently produces higher quantities of insulin as a result, which frequently results in hyperinsulinemia. Type 2 diabetes frequently manifests with both high insulin and glucose levels, in contrast, to type 1 diabetes, which is characterized by low insulin levels and high blood glucose. Type 2 diabetes is primarily caused by insulin resistance, which typically develops years before the beginning of the disease. Many factors, such as obesity, inflammation, mitochondrial dysfunction, elevated insulin levels, lipid imbalances, genetics, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy, and pregnancy, have been proposed to contribute to insulin resistance. Obesity and age are two significant risk factors for insulin resistance in the general population.[8]

What adipose tissue does?

White fat tissue is known to be the primary storage site for excess energy from food intake. White fat cells, which make up the majority of white fat tissue, store this energy as highly concentrated triglycerides in a single large lipid droplet. In times of caloric demand, lipases break down the triglycerides for the rapid release of fatty acids that are used as an energy source in other tissues. Brown fat is specifically designed for non-shivering thermogenesis in animals adapted to cold climates. Brown fat cells contain multiple smaller lipid droplets that can be quickly hydrolyzed and used for energy production in the form of heat.[9]

The impact of adipocyte hypertrophy on insulin signaling

Adipocyte hypertrophy, which refers to the enlargement of fat cells, has a significant impact on insulin signaling. The accumulation of excessive amounts of fat within the adipocytes can interfere with the normal functioning of insulin receptors and disrupt the insulin signaling pathway. This can lead to insulin resistance and decreased sensitivity to insulin, making it difficult for the body to regulate glucose levels effectively, leading to hyperinsulinemia. Adipocyte hypertrophy is commonly associated with obesity and is considered a major contributor to the development of metabolic disorders such as type 2 diabetes.

The effect of lipid accumulation on insulin sensitivity in cells

The strong link between obesity, insulin resistance, and increased concentrations of circulating FFAs supports the concept that free fatty acids (FFAs) contribute to in insulin resistance. Circulating FFA levels that are too high can lead to peripheral insulin resistance. Although fatty acid accumulation in non-adipose fat storage, including muscle, may contribute to insulin resistance in obesity, a spike in muscle triglycerides during exercising is actually associated with good insulin sensitivity. This evidence backs up the concept that FFA mobilization into the circulation and absorption into skeletal muscle increases insulin resistance rather than excess body fat. Adipose tissue is also required for the appropriate production of hormones that improve insulin sensitivity, such as leptin and adiponectin, and a paucity of adipose tissue results in decreased hormone secretion. These findings support the hypothesis that functioning adipose tissue in right proportion to body size is required for adequate insulin sensitivity and glucose management. Adipose tissue performs two crucial functions in this function: it secretes adequate amounts of hormones that influence metabolism and eating patterns, and it sequesters lipids as triglyceride stores to protect against the damage caused by circulating FFAs and aberrant triglyceride storage. When eating, adipocytes can produce and store triglycerides, which are then released as fatty acids and glycerol while starvation. Alteration in adipose tissue impacts the equilibrium between fatty acid generation and utilization, which has been investigated in people and animals with high caloric consumption. Fatty acid levels are low in slim people, and insulin sensitivity is adequate. Adipocytes grow with obesity owing to enhanced triglyceride deposition, yet they may still store more of it and released them upon fasting.[9]

The role of adipokines in insulin resistance and obesity

Adiposity impairs adipocytes' capacity to release a variety of physiologically useful proteins. Adipokines that either directly or indirectly affect triglyceride and fatty acid metabolism in adipocytes. Adipokines that influence inflammatory response in adipose tissue include monocyte chemoattractant protein-1/chemokine (C-C motif) ligand-2MCP-1/CCL2 and TNF. Greater adipocyte hypertrophy results in higher MCP-1 synthesis, which may predispose to a pro-inflammatory environment.[9]

The involvement of inflammatory cytokines in insulin resistance

Inflammation of adipose tissue is linked to insulin resistance in skeletal muscle. Because MCP-1 and other cytokines, such as[9] TNF-, IL-6, resistin, leptin, adiponectin, MCP-1, PAI-1, and angiotensinogen, are proteins produced by adipocytes and macrophages, pinpointing precise sites of production is difficult.[10] As a result, adipocytes experience greater lipolysis and reduced triglyceride synthesis. Excessive circulatory free fatty acids (FFAs) and triglyceride buildup in skeletal muscle, liver, and -cells disturb normal activities. This disruption is caused by an excess of circulating FFAs that are converted to long-chain fatty acyl-CoA esters as well as other fatty acid derivatives. Excessive fatty acid and extremely low-density lipoprotein synthesis in the liver, as well as increased lipoprotein lipase function in skeletal muscle, all contributes to lipid surplus and fatty acid inflow, are also caused by hyperphagia. TNF production by macrophages in the adipose tissue of obese patients involves both the IKK-NF-B and the JNK-MAP4K4-AP1 signalling pathways. JNK1 is required for FFA-induced pro-inflammatory cytokine production in macrophages. These findings, together with evidence showing obese individuals' adipose tissue contains a significant number of macrophages, support the notion that the inflammatory response contributes to metabolic inefficiencies in obesity. Inflammatory response may lead to insulin resistance by directly altering muscle insulin signalling via TNF, which has been demonstrated to reduce insulin signalling and glucose transit in skeletal muscle by boosting the phosphorylation of critical mediator proteins. This impact is dependent on specific protein kinases, JNK1 and MAP4K4, and can be reversed by inhibiting TNF-mediated activation. The inflammatory response in adipose tissue results in an excess of cytokines like TNF, which are primarily produced by macrophages and adipocytes. TNF has a substantial effect on adipocytes, resulting in decreased insulin signaling and adipogenesis suppression. These effects are mediated in part mostly by the downregulation of peroxisome proliferator-activated receptor (PPAR), a primary transcriptional regulator of adipogenesis and necessary for mature adipocyte function, including triglyceride synthesis and storage. TNF seems to influence PPAR transcription, translation, as well as protein recycling. TNF stimulates the NF-B and AP1 transcription factors, which change gene expression to alter cellular responses, with TNF therapy of adipocytes stimulating these transcriptional factors by boosting the IKK (for NF-B) and MAP4K4 (for AP1) cascades. Prior research has discovered that TNF significantly lowers the expression of several adipocyte-specific genes and adipogenic transcription factors, such as C/EBP and PPAR. TNF causes caspase-dependent signalling protein cleavage in cultured adipocytes. Nonetheless, it has to be shown if this caspase-dependent route works in vivo. PPAR regulates genes that encode enzymes involved in fatty acid esterification as well as triglyceride production and storage. Consequently, PPAR disruption lowers adipocyte triglyceride storage, resulting in increased lipid transport into skeletal muscle and liver, culminating with type 2 diabetes and insulin resistance.[9]

TNF stimulates adipocyte lipolysis

Hormones control the balance of lipid storage and mobilization in adipocytes, while insulin reducing and catecholamines boosting cyclic AMP levels. Cyclic AMP controls the stimulation of hormone-sensitive lipase, that

converts triglycerides to fatty acids and glycerol. TNF and adipocyte size are the major variables that contribute to increased lipolysis in obesity, with TNF boosting lipolysis by decreasing insulin signalling, increasing cAMP levels, and inhibiting perilipin activity and expression. This inhibition may enhance overall basal lipolytic rate and raise circulating fatty acid concentrations.[9]

The contribution of mitochondrial dysfunction to insulin resistance in obesity

Mitochondria are important in fuel consumption because they contain the machinery required for the breakdown of fatty acids via -oxidation, as well as the full oxidation of fat and carbohydrate intermediates through the TCA cycle and respiratory chain. Reduced expression of mitochondrial function genes and decreased oxidative phosphorylation have been associated to metabolic disorders, such as prediabetic and age-related insulin resistance. Mitochondrial abnormalities may occur prior to the onset of metabolic illness and may indicate vulnerability.[9] Reduced expression of genes that govern the development of muscle mitochondria, such as PPAR coactivator 1 (PGC-1) and PGC-1, has been related to a decline in the number of mitochondria inside the muscles, resulting in the accumulation of fat in insulin-resistant people' muscles. Because of its function in glucose and lipid metabolism, PGC-1 has been identified as a possible target for diabetes therapy. Recent research, however, have called into question the concept that pharmacological stimulation of PGC-1 is helpful, as overly high levels of PGC-1 have been linked to increased insulin resistance.[11]

The impact of oxidative stress on insulin signaling in obesity

When the quantity of glucose within cells becomes too high, it stimulates the glycolytic cascade and the tricarboxylic acid cycle. This generates an increase in NADH and FADH2 synthesis, resulting in a larger proton gradient across the inner membrane of mitochondria. As a result, electron leakage occurs at complex III, resulting in superoxide generation. This free radical subsequently hinders glyceraldehyde-3-phosphate dehydrogenase and steers upstream metabolites into four different pathways. 1. Glucose is redirected to the polyol pathway, 2.fructose-6-phosphate to the hexosamine pathway, 3. triose phosphates to methylglyoxal - a primary substrate of advanced glycation end products (AGE), and 4. dihydroxyacetone phosphate to diacylglycerol, that triggers the PKC pathway. These mechanisms generate oxidative and nitrosative stress by either increasing free radical generation or decreasing antioxidant defenses. The polyol route depletes NADPH while activating stress genes, whereas the hexosamine pathway decreases thioredoxin activity while inducing oxidative and endoplasmic reticulum stress. Through activating NOX and NF-kB, AGE and PKC promote the formation of ROS/RNS. NOX enzymes, in succession, promote superoxide radical generation (O2).[12]

The increased ROS stimulates casein kinase-2 (CK2), which in turn activates the retromer. The retromer then sends a signal downstream to the trans-Golgi network, and GLUT4 is delivered to lysosomes for destruction rather than the plasma membrane. As a result, in an oxidative environment, intravascular glucose levels stay increased. Mitochondria potentially contribute to cellular oxidation as a result of high nutrition conditions. Because of the increased glucose availability in high-sugar diets, mitochondria have even more substrate available to produce ATP. As a result, the mitochondria become hyperactive, producing more of their natural result, ROS. This elevated ROS damage the cell's architecture and causes stress reactions that the mitochondria are in charge of. ROS directly activate NF-kB, JNK, and p38 MAPK, resulting in mitochondrial stress responses.Increased ROS levels cause mitochondrial fission, which affects the insulin signaling pathway as well as stress proteins. Mitochondrial fission has been related to insulin resistance in muscle tissue.[5]

The role of the insulin receptor and its substrates in insulin resistance

The insulin receptor as well as its subsequent substrates are critical in the progression of insulin resistance. The insulin receptor is indeed a protein that adheres to insulin molecules with in circulation and is present on the surface of cells. The insulin receptor and also its associated signalling pathways do not work correctly in insulin-resistant people.

- Impaired insulin receptor signaling

Insulin resistance develops once the insulin receptor loses its potential to bind to insulin or begin the necessary signaling cascades. When the ligands bind to the insulin and IGF-1 receptors, it triggers a series of phosphorylation events that cause a conformational change and autophosphorylation of the receptors. This, in turn, recruits and phosphorylates receptor substrates like IRS and Shc proteins. Shc activates the Ras-MAPK pathway while IRS proteins recruit and activate PI3K, generating PIP3 as a second messenger. PIP3, in turn, activates PDK-1, which phosphorylates and activates Akt and atypical PKCs. The metabolic effects of insulin, including glucose transport, lipid synthesis, gluconeogenesis, and glycogen synthesis, are primarily mediated by Akt. In addition, Akt also plays a role in cell cycle regulation and survival. The Shc-Grb2-SosRas-Raf-MAPK pathway controls cellular proliferation and gene transcription. Changes in these signaling pathways can contribute to insulin resistance.[13]

- Dysregulation of downstream substrates.

Insulin resistance may happen even if the insulin receptor is working properly when downstream substrates like insulin receptor substrate (IRS) proteins are not regulated correctly. IRS proteins are responsible for relaying signals downstream from the insulin receptor. In cases of insulin resistance, higher levels of

IRS proteins may exist, causing improper signaling and contributing to insulin resistance.

- Lipid accumulation and inflammation

When cells, particularly in the liver and skeletal muscle, accumulate too much fat, it can result in insulin resistance by activating inflammation and oxidative stress. This may lead to the build-up of fat in the liver, which is referred to as nonalcoholic fatty liver disease (NAFLD), and potentially lead to the onset of type 2 diabetes.

The contribution of the akt/mtor pathway to insulin resistance in obesity

The AKT/mTOR pathway is responsible for controlling cell growth and metabolism and can be triggered by both insulin and other growth factors. It's involved in several cellular processes like protein synthesis, glucose uptake, and lipid metabolism. When people become obese, this pathway can become irregular, leading to chronic activation of the pathway, which is caused by an imbalance between energy intake and expenditure. This chronic activation can result in the development of insulin resistance. The AKT/mTOR pathway contributes to insulin resistance in two ways. Firstly, it suppresses insulin signaling, and secondly, it promotes chronic low-grade inflammation, which can lead to the accumulation of fat in cells. This accumulation of fat causes cellular stress and damage, leading to further insulin resistance.

The link between body fat distribution and insulin resistance

Obesity, NIDDM, hyperlipidemia, and cardiovascular disease all seem to be largely influenced by insulin resistance. Contrary to individuals with peripheral (gynecoid) obesity, obese women with abdominal (android) fat distribution are more insulin resistant. NIDDM and a group of atherogenic diseases, including glucose intolerance, dyslipidemia, and hypertension, are both characterized by insulin resistance (Syndrome X). Waist-to-hip ratio (WHR) and subscapular-to-triceps ratio (STR) measurements of central obesity appear to predict hyperinsulinemia, the emergence of NIDDM, and cardiovascular mortality. Regardless of other risk factors for NIDDM, central abdominal fat is a strong and very significant correlate of insulin resistance in both normal and overweight women. High abdominal fat levels were linked to higher lipid use, but variations in circulating lipid levels could not explain the significant correlation between central abdomen fat percentage and insulin sensitivity. Since central obesity in obese women is linked to glucose intolerance, age-related reduction in insulin sensitivity, atherogenic lipoprotein ratios, cardiovascular and noncardiovascular mortality, and a significantly elevated risk of diabetes, it has significant health consequences for women.[14]

THE CONNECTION BETWEEN DIET AND INSULIN RESISTANCE IN OBESITY

A high-fat diet may make someone more likely to become obese. Obesity, particularly abdominal obesity, plays a significant role in determining the likelihood of developing non-insulin-dependent diabetes mellitus and insulin resistance. Independent of obesity and body fat location, it is hypothesized that a high percentage of fat in the diet is linked to reduced insulin sensitivity and an increased risk of developing diabetes and that this risk may be affected by the types of fatty acids consumed. The risk of developing insulin resistance and NIDDM appears to be most strongly correlated with obesity, especially abdominal fat[15].It is believed that inflammation is a major factor contributing to obesity. Inflammation is influenced by diet and particular foods. Greater BMI and fat mass were associated with Western dietary patterns, which also included higher consumption of red meat and sweets. The pro-inflammatory indicators, such as LBP, were also significantly reduced by the healthy pattern's lower intake of SFA and trans fatty acids. Following traditional eating habits full of fruits and vegetables was inversely connected to both DII and IR. All things considered, it appears that eating habits can directly or indirectly impact systemic inflammation.[15]

THE EFFECT OF PHYSICAL ACTIVITY ON INSULIN RESISTANCE AND OBESITY

Regular exercise is beneficial for those with diabetes mellitus, both insulin-dependent, and non-insulin-dependent. It may assist to explain why people with insulin resistance can increase their muscle glucose transport in response to an acute exercise session since exercise and insulin both trigger glucose transport through different signaling pathways. For persons with diabetes, exercise has long been known to have a number of positive effects. In the context of overall glucose homeostasis, a single bout of exercise can considerably increase rates of whole-body glucose clearance and elevate the sensitivity of skeletal muscle glucose absorption to insulin. In addition to the metabolic benefits of a single exercise session (NIDDM), recent epidemiological studies have discovered that regular physical activity can reduce the risk of developing non-insulin-dependent diabetes (NIDDM).[16]

THE ROLE OF GENETICS IN OBESITY AND INSULIN RESISTANCE

Genetics plays a significant role in the development of both obesity and insulin resistance. Studies have shown that genetic factors contribute to approximately 40-70% of the variation in body mass index (BMI), a measure of body weight relative to height.[6] There are various rare genetic disorders that can lead to insulin resistance, such as Down's syndrome, Turner's syndrome, Klinefelter's syndrome, Thalassaemia, Haemochromatosis, Lipodystrophy, Progeria, Huntington's chorea, Myotonic dystrophy, Friedrich's ataxia, Laurence-Moon-Biedel syndrome, Glycogen

storage diseases type I and III, and mitochondrial disorders.[6]

Moreover, type 2 diabetes and insulin resistance risk is influenced by hereditary factors. Some of the main genes linked to type 2 diabetes are listed below.

1. TCF7L2: This gene controls the production of insulin and the metabolism of glucose. The likelihood of acquiring type 2 diabetes has been linked to variations in this gene.[6]
2. KCNJ11: This gene produces a protein that controls the pancreatic hormone insulin secretion. An elevated risk of type 2 diabetes has been linked to variations in this gene.[6]
3. PPARG: This gene controls the metabolism of lipids and glucose. An elevated risk of type 2 diabetes has been linked to variations in this gene.[6]
4. SLC30A8: This gene produces a protein that controls the release of insulin. An elevated risk of type 2 diabetes has been linked to variations in this gene.[6]
5. FTO: This gene has a role in the control of body weight and energy balance. Mutations in this gene have been connected to a higher risk of type 2 diabetes and obesity.[6]

THE DEVELOPMENT OF INSULIN RESISTANCE IN CHILDREN WITH OBESITY

The main cause of insulin resistance in kids is obesity, although diet quality can also influence whether it develops or worsens. In obese children and adolescents, insulin resistance is the most important predictor of poor glucose tolerance and type 2 diabetes. High blood sugar levels are the end outcome of type 2 diabetes, a progressive condition marked by initial increases in insulin resistance and later declines in insulin secretion. Youth type 2 diabetes incidence has considerably grown over the past ten years, primarily as a result of the growth in obesity. Children's high blood pressure is also known to be influenced by insulin resistance, with possible pathways including the sympathetic nervous system and renal sodium reabsorption. Insulin resistance is linked to an aberrant lipid profile that rises in obese children.[17]

CONSEQUENCES OF INSULIN RESISTANCE IN OBESITY: METABOLIC AND CARDIOVASCULAR COMPLICATIONS

Insulin resistance in obesity is strongly linked to the development of various health conditions, including hypertension, dyslipidemia, IGT, hepatic steatosis, and metabolic syndrome. Additionally, it is associated with systemic inflammation, early atherosclerosis, endothelial dysfunction, and disordered fibrinolysis. It's concerning that these metabolic and cardiovascular complications are already evident in obese children and adolescents. This is especially worrying as the influence of puberty, which leads to a natural decrease in insulin sensitivity, may exacerbate insulin resistance and its related complications in prepubertal children.[17]

DIAGNOSIS AND ASSESSMENT OF INSULIN RESISTANCE IN OBESITY

To accurately evaluate insulin resistance, risk factors, and the impact of interventions, it is crucial to use valid and reliable assessment methods. Several methods are available for assessing insulin resistance, including fasting measurements of glucose and insulin, the oral glucose tolerance test (OGTT), insulin tolerance test, hyperinsulinemic-euglycemic clamp, and the frequently sampled intravenous glucose tolerance test (FSIVGTT).

The gold standard technique to measure insulin resistance is the hyperinsulinemic-euglycemic glucose clamp method, where a non-diabetic patient fast and receives a high infusion of insulin to lower glucose production, while glucose is administered to maintain a steady blood glucose level. Insulin resistance is calculated based on the amount of glucose required to maintain this steady state, which reflects glucose disposal due to hyperinsulinemia. However, this method is complex and impractical for clinical use, so alternative markers have been developed, such as HOMA-IR, GIR, QUICKI, Matsuda Index, and ISI, which are based on fasting glucose and insulin levels, or glucose and insulin responses to a glucose challenge test. Other markers include triglyceride levels, which are more likely to indicate insulin resistance in patients with prediabetes, and a triglyceride/HDL ratio, which is correlated with insulin resistance in Caucasian individuals. These surrogate markers are used more frequently than the glucose clamp technique in clinical research due to their limitations.[6]

Generally, a ratio exceeding 3.0 is linked to insulin resistance (IR), with a ratio of 3.5 or higher in men and 2.5 or higher in women indicating insulin resistance more specifically. The Metabolic Syndrome (MetS) and Insulin Resistance Syndrome (IRS) are clinical indicators of insulin resistance6. Insulin resistance syndrome refers to the collection of abnormalities and related physical outcomes that occur more often in people who have insulin resistance. Since different tissues have varying levels of dependence and sensitivity to insulin, the effects of excess insulin and resistance to its actions are likely reflected in the symptoms of the insulin resistance syndrome.[4]

Metabolic syndrome is a clinical diagnosis that identifies people at high risk of (cardiovascular) morbidity linked to insulin resistance.[4]

Several IRS criteria exist to diagnose MetS, and a joint scientific statement was published in 2009 to standardize them.

1. A waist measurement between 32" and 40" dependent on ethnicity and gender.
2. Higher-than-normal triglycerides of at least 150 mg/dL.
3. Reduced HDL below 40 mg/dL in men and below 50 mg/dL in women.

4. High blood pressure with systolic and/or diastolic pressures of at least 130 mmHg and/or at least 85 mmHg.
5. Fasting glucose level of at least 100 mg/dL.[4]

TREATMENT OF OBESITY-INDUCED INSULIN RESISTANCE

- The main treatments for obesity and insulin resistance in kids and teenagers are a balanced diet and more exercise. Research has demonstrated that a reduction in body weight is linked to an increase in insulin sensitivity. In this demographic, little study has been conducted on insulin sensitizers or weight loss drugs.
- Serine phosphorylation blocks insulin signaling as contrasted to tyrosine phosphorylation. As a result, aspirin or salicylate at large doses has been successfully utilized to treat human patients with fat-induced insulin resistance. Salicylates' ability to reduce inflammation is thought to be related to their inhibition of nuclear factor kappa kinase inhibitor (IKK) and NFB, which raises the possibility that NFB inhibition is also responsible for decreasing blood sugar and increasing insulin sensitivity.[17]
- In non-diabetic obese teenagers, metformin has been demonstrated to increase insulin sensitivity and BMI.
- Sibutramine has been shown to be successful in helping people lose weight, however, it can also raise blood pressure and heart rate.
- Orlistat has been linked to weight loss, but it also has negative consequences like digestive problems and vitamin inadequacies, and it hasn't had a big impact on how your body uses glucose. Further research is required to assess the effectiveness and safety of medications used to treat obesity and insulin resistance in children and adolescents, as well as to determine which population subgroups necessitate pharmacological therapies.[17]

PREVENTION OF INSULIN RESISTANCE IN OBESITY THROUGH LIFESTYLE CHANGES

Preventing obesity and insulin resistance requires early intervention, starting during pregnancy and the perinatal period. Encouraging breastfeeding and providing guidance on appropriate food choices, caloric intake, and physical activity for children are important preventive measures that aim to maintain a normal BMI. When obesity has already developed, a secondary prevention program is required to prevent or reverse its progression and reduce the risk of related conditions. During adolescence, controlling body weight is critical, as this period is associated with physiological insulin resistance and hyperinsulinemia. Obesity during puberty can further increase the risk of complications. While medications and other interventions are important, lifestyle changes such as diet and exercise remain critical components of managing and preventing obesity and insulin resistance. Researchers are investigating the most effective personalized diet and exercise plans for prevention and management.[17]

THE FUTURE OF OBESITY AND INSULIN RESISTANCE RESEARCH

Obesity and insulin resistance research have a promising future, with many exciting developments on the horizon. These are some important research areas that could help us better understand and combat these illnesses in the coming years.

1. The goal of personalized medicine is to identify individual risk factors, such as genetics and lifestyle factors, and tailor treatment plans to address these specific factors, potentially leading to more effective and targeted treatments for people with obesity and insulin resistance.
2. It has been discovered that the gut microbiome plays an important role in regulating metabolism and energy balance, which may lead to the development of new therapies targeting the gut microbiome to treat obesity and insulin resistance. Researchers are exploring the neurological pathways and circuits involved in regulating appetite and energy balance in order to develop new treatments for obesity and insulin resistance that target the brain. Current research is concentrated on creating novel treatments that target the hormone leptin, which is involved in controlling hunger, to treat obesity and insulin resistance.
3. Researching the epigenetic modifications brought on by fat, such as DNA methylation and histone modifications, may help create new treatments and diagnostic equipment for insulin resistance.
4. While reducing inflammation has been proven to increase insulin sensitivity, more research is required to better understand the role of inflammation in the emergence of insulin resistance. New anti-inflammatory medications for the treatment of obesity-related insulin resistance may be created as a result of further research in this field.
5. In conclusion, a more thorough and unified methodology is necessary to investigate insulin resistance. This may entail utilizing multi-omics methods, such as genomics, transcriptomics, proteomics, and metabolomics, to obtain a more comprehensive understanding of the cellular mechanisms implicated in insulin resistance.
6. Generally, the prospects for research on obesity and insulin resistance are optimistic, with numerous novel approaches and tactics being devised to gain a better comprehension of and combat these conditions.

CONCLUSION

An inciting determinant for diabetes linked to insulin resistance is obesity. Long known, the link between obesity, insulin resistance, and type 2 diabetes has significant clinical and scientific consequences. Physical inactivity and "convenience" foods reveal underlying genetic predispositions as rapid globalization, urbanization, and industrialization have produced epidemics of obesity, diabetes, and the co-morbidities that go along with them. The biological processes are

complicated, intricate, and not fully known. When we step back, we may need to take into account the significant societal changes that have occurred over the past century regarding physical exercise, diet, employment, socialization, and sleep habits. Increased knowledge of adipocyte function in biology over the past ten years has started to offer mechanistic insights into the causative link between obesity and diabetes. The release of numerous molecules from the adipose tissue, including hormones like leptin, cytokines like TNF-, and substrates like FFAs, enables it to exert significant regulating control over energy balance and glucose homeostasis. Adipose tissue, insulin action, and glucose homeostasis have a complex relationship that likely developed as a result of the need to sustain fuel stores during times of food scarcity. The prevalence of obesity and its associated morbidities has hit epidemic levels in modern Western society, and there has never been a greater need for scientific advancements to identify novel therapeutic modalities. There are significant opportunities to change the trajectory of human disease by tackling the challenge of using the expanding repertoire of adipocyte functions to change the equation of energy intake and utilization towards reduced fat storage.

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