*International Journal of Research and Review*
*Vol. 10; Issue: 9; September 2023*
*Website: www.ijrrjournal.com*
*Review Article* *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

# Obesity and Diabetes Mellitus 2: Interrelated Relative Relationship

**Maitham Abdallah Albajy[1,2], Dan Florin Mihailescu[1,3]**

[1]Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania
[2]National Center for Occupational Health and Safety, Dhi Qar City, Iraq
[3]Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Psychiatric Hospital, 10 Şoseaua Berceni Str., 041914 Bucharest, Romania

Corresponding Author: Maitham Abdallah Albajy

**DOI: https://doi.org/10.52403/ijrr.20230933**

## ABSTRACT

Obesity, defined as the excessive accumulation of body fat, is determined using body mass index (BMI) classifications. This condition is a primary contributor to several severe health issues, encompassing heart diseases, diabetes, hypertension, and specific cancers. Predominantly, environmental influences and lifestyle choices, such as inactive behaviors and unhealthy diets, are the culprits behind obesity. Common therapeutic interventions for obesity include dietary modifications, physical activity, and in some cases, medications or surgical procedures.

A heightened BMI can signal the potential onset of Type 2 diabetes, given that an increased fat percentage elevates the risk of this disease. Globally, obesity rates have surged, positioning it as a top health concern and a notable medical condition. This rise is largely attributed to the widespread adoption of poor dietary practices and inactive lifestyles. Consequently, there's a parallel increase in Type 2 diabetes cases, especially among those labeled as "extremely obese."

The relationship between obesity and Type 2 diabetes is intricate, stemming from complex cellular and physiological interactions. These interactions influence beta cell functions, modify the biology of fat tissues, and amplify insulin resistance. Given the multifaceted link between obesity and Type 2 diabetes, it's imperative to consider this when formulating efficient prevention and treatment methodologies. Notably, due to shifts in the functionality of pancreatic beta cells, the nature of adipose tissue, and insulin resistance, adults with significant weight gains are predisposed to Type 2 diabetes. Addressing this escalating health challenge necessitates strategies focusing on both weight management and metabolic health optimization.

***Keywords:*** *Obesity, Type 2 Diabetes, Insulin resistance, Adipose tissue, Free fatty acid*

## INTRODUCTION

Adipose tissues, commonly known as fat tissues, serve as the primary energy reservoir in the human body, distributing energy to all organs. They play a crucial role in sustaining life during periods of food scarcity or prolonged fasting. Typically, cells store glycogen in a gel-like form, with every gram of glycogen being associated with two grams of water. When oxidized, this glycogen yields about 4.1 calories per gram. Conversely, triglycerides stored within fat cells, which are compacted similarly to oil, generate roughly 9.3 kilocalories for each gram when oxidized.[1]

A person's resilience to starvation is inversely related to their percentage of body fat. A loss of around 35% of one's body weight can be lethal within two months.[2] Remarkably, obese individuals can survive extended periods without food. The longest recorded fast for an obese individual lasted

382 days, during which they only consumed fluids, minerals, and vitamins. This individual lost 60% of their initial body weight but experienced no severe adverse effects.[3] Additionally, adipose tissue releases "exosomes and adipokines," playing a pivotal role in regulating vital physiological functions, notably appetite and insulin response.[4]

Excessive fat accumulation can trigger a range of metabolic disorders, including "insulin resistance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and alterations in cholesterol and triglyceride levels." These issues often coincide with an elevated body mass index (BMI), a primary indicator of obesity.[5] A balanced distribution of body fat and triglycerides can mitigate the metabolic disruptions associated with obesity.[6] Notably, individuals with extreme obesity, characterized by significant fat accumulation, especially in central regions like the abdomen, are at a heightened risk for Type 2 diabetes. In contrast, this condition is rare among lean individuals.[7] Insulin resistance is a precursor to Type 2 diabetes, and a diminished capacity of pancreatic beta cells to produce insulin is a warning sign of this disease's onset. When insulin resistance and reduced insulin production coexist, the body struggles to manage glucose levels effectively, leading to elevated blood sugar. If Type 2 diabetes is not adequately managed, it can result in severe complications such as heart diseases, kidney failure, and nerve damage.[8]

Individuals who are overweight often struggle with producing adequate amounts of insulin, which sheds light on the global prevalence of Type 2 diabetes and obesity. In this article, we aim to elucidate the physiological link between obesity and Type 2 diabetes.

## THE LINK BETWEEN BETA CELL FUNCTION AND INSULIN DYNAMICS

Beta cells produce insulin, which is then channelled to the liver through the portal vein. The balance of insulin in the bloodstream hinges on a fine equilibrium between its secretion and the liver's ability to clear it. Once released by the beta cells, the liver disposes of more than half of this insulin. The body's elimination mechanism sees about 30% taking place in the kidneys and skeletal muscles, with the remaining 70% being processed through other pathways.[9] Factors such as heightened insulin secretion in the pancreas, reduced partial extraction, and the filtration of insulin as it enters cells, collectively lead to elevated insulin levels in the basal plasma of obese individuals post-meal.[10,11,12] The role of pancreatic beta cells is pivotal in understanding the health of obese individuals with Type 2 diabetes. Notably, obese individuals without Type II diabetes have higher insulin levels in their plasma compared to their normal-weight counterparts.[13] The ability to process oral glucose and sustain regular fasting blood sugar levels, coupled with managing insulin resistance, is realized by boosting insulin secretion and increasing its concentration. A steady decline in the performance of pancreatic beta cells causes a consistent weakening of blood sugar control, paving the way for prediabetes and eventually, the onset of Type 2 diabetes. [14,15].

## IMPACT OF PANCREATIC BETA CELLS ON INSULIN SECRETION

The total count of pancreatic beta cells significantly influences insulin secretion during and post meals. In obese individuals, the pancreatic beta cell mass is over 50% larger compared to those of average weight, a phenomenon termed as "relative size" or "pancreatic beta cell mass". However, for those exhibiting signs of IFG (impaired fasting glucose) or DM2, this relative size is about 50% smaller than in lean individuals, attributed to the programmed death of B cells.[16] In mice on a high-fat diet, obesity developed before insulin resistance, with subsequent increases in both B and T cell masses. This suggests a potential link between the proliferation of B cells in

obesity and the onset of insulin resistance.[17] When both obese and lean groups are at their peak insulin sensitivity, insulin production rates, both primary and postprandial, are higher in the obese group.[18] The exact mechanism behind the expansion of pancreatic beta cells in obese individuals remains elusive, but high-calorie nutrient types might stimulate it.[19] A rise in "free fatty acids" in the plasma is observed to potentially associate with the onset of Type 2 diabetes and obesity. This increase has shown to adversely affect the basal state of pancreatic beta cells. Thus, free fatty acids appear to be pivotal in metabolic regulation. Glucose accounts for nearly 30% of the total insulin production rate in humans. Adipose tissue releases free fatty acids, which help maintain insulin sensitivity and regulate glucose balance. Given the potential link between high free fatty acid levels and insulin resistance, it's vital to understand their impact on insulin production.[20].

## INSULIN RESISTANCE IN RELATION TO FAT TISSUE

Balancing energy during fasting or breastfeeding periods requires managing significant and swift physiological shifts. Adipose tissue must exhibit considerable metabolic adaptability throughout the day to accommodate long-term energy balance changes, leading to the growth or reduction of fat tissue. The buildup of triglycerides and their elevated levels in fat cells play a pivotal role in altering cell size. This fat accumulation prompts an energy equilibrium, causing a sustained growth in adipose tissue mass and subsequently restructuring the supporting "framework" of these cells. [21,22,23]

Research on various mouse groups has revealed intricate biological processes related to obesity. Notably, the interplay of fat tissue significantly influences the onset of insulin resistance. This includes: (A) Oxygen shortages within fat cells due to inadequate oxygen supply [24,25], leading to fibrous tissue formation and connective tissue chemotaxis [26,27]. This can also elevate plasma levels of branched-chain amino acids by suppressing their breakdown in fat tissue. [28,29]. (B) An observed increase in inflammatory cell proliferation within fat tissue (like macrophages and T-cells) and the expression patterns of inflammation-related proteins.[30]. (C) A decline in insulin secretion and fat tissue formation.[31]. (D) Enhanced lipolysis in fat tissue and increased release of free fatty acids into the bloodstream.[32].

Researchers identified that these combined factors are primary contributors to insulin resistance in the studied RAT model. However, further studies and rigorous clinical trials are essential to validate these findings for human applicability. The overarching understanding of these factors in insulin resistance development remains fragmented, urging researchers to intensify their investigative efforts.

In obese mouse groups, several irregularities in adipose tissue were observed [33]. There was also a noted rise in macrophages that induce inflammation, T-cell content, and processes that translate coding for inflammatory proteins [34]. While there are nuanced differences in various markers among individuals with insulin sensitivity, insulin resistance, and those who are obese, these distinctions hold statistical relevance. Despite the data pointing towards a strong link between many of these markers and the onset of severe obesity, they predominantly contribute to the development of insulin resistance (IR) [35].

Research on mice has demonstrated that an uptick in cytokine production, which promotes inflammation, can also trigger insulin resistance [36]. Additionally, the accumulation of connective cells in adipose tissue has been linked to human obesity. This finding shed light on the complex relationship between adipose tissue and weight gain, prompting further investigations into the root causes and potential solutions to the escalating obesity epidemic [37]. This has given rise to the theory that adipose tissue inflammation is a

primary driver of insulin resistance in the obese. Studies on mouse models indicate that insulin resistance can lead to "metabolically unhealthy obesity" by amplifying the count of inflammatory macrophages and inducing mutations in genes responsible for coding inflammatory proteins located subcutaneously [34]. Such studies are pivotal as they explore the potential role of immune cells in adipose tissue. Notably, inflammation in this tissue might precipitate insulin resistance in individuals experiencing rapid weight gain [38]. To fully grasp this intricate relationship, more extensive research, including longitudinal studies, factor analyses, and studies across diverse populations and settings, is imperative.

Based on our discussion, it's evident that adipose tissue plays a pivotal role in regulating metabolism within the body. This necessitates a mechanism for these tissues to communicate and interface with other organs. One widely suggested method is for the adipose tissue to discharge its byproducts into the bloodstream, allowing them to be transported to the requisite organ or tissue. These byproducts encompass free fatty acids, adiponectin, and inflammatory proteins, which we will delve into subsequently.

Recent research has assessed plasma cytokines over a continuous 24-hour span in individuals with pronounced obesity rates, comparing those with insulin sensitivity to those with insulin resistance. The findings revealed no discernible difference in plasma concentration levels throughout the 24-hour duration, with the exception of the plasminogen activator inhibitor 1 (PAI-1) curve.[44]. Notably, the plasma PAI-1 concentration was markedly higher in overweight individuals with insulin resistance than in their hyper-obese, insulin-sensitive counterparts. Additionally, an inverse correlation was observed between plasma PAI-1 and insulin sensitivity metrics in the muscular, skeletal, and hepatic systems. Further studies on individuals with insulin resistance indicated that those with elevated plasma PAI-1 levels exhibited diminished insulin sensitivity in muscle cells. This reduction hampers the glucose absorption process, elevating the risk of type 2 diabetes. It was also revealed that such individuals.

experienced a decline in insulin sensitivity across various bodily organs, especially the liver and muscles, leading to metabolic disruptions and ensuing challenges [39]. The outcomes suggest that, with the exception of PAI-1, the production of most cytokines by adipose tissue primarily exerts local paracrine effects on pancreatic beta cells without directly influencing metabolism.

Plasma adiponectin levels typically have an inverse relationship with body fat percentage, often linked to insulin sensitivity. Yet, there are instances where individuals with a higher body fat percentage maintain elevated plasma adiponectin levels. This anomaly might be attributed to genetic predispositions or other metabolic irregularities that affect adiponectin's production and secretion, even in the face of insulin resistance. [40,41] Such markers can serve as indicators of the health status of adipose tissue [42,43]. In mouse studies, adiponectin has demonstrated anti-inflammatory properties and acts as an insulin-enhancing agent, promoting the longevity and rejuvenation of pancreatic cells [42,44,45]. The beneficial impacts of adiponectin are believed to be mediated through various mechanisms, notably by amplifying ceramidase activity and diminishing its intracellular concentrations. This is a consequence of the binding of adiponectin to its receptors 1 and 2 on cellular surfaces. [46].

Elevated free fatty acid levels in the blood plasma of obese individuals are often linked to insulin resistance in their muscles and liver. This resistance results in reduced glucose absorption and metabolism, leading to potential metabolic imbalances.[47]. However, the credibility of this theory has been questioned due to inconsistent research findings and ambiguous evidence regarding

the direct link between obesity and insulin resistance. Physiologically, those categorized as "highly obese" often show reduced free fatty acid release into the bloodstream compared to their leaner counterparts. This is because obese individuals typically have a higher proportion of non-fat adipose tissue due to their excess fat [47]. The breakdown of adipose tissue triglycerides, or lipolysis, is heavily influenced by insulin. [13,48]. After eating, the suppression of free fatty acid levels in the bloodstream and the corresponding lipolysis rates are consistent across individuals, regardless of their weight. In obese individuals, any significant post-meal increase in these levels is often offset by their increased body fat mass. [13,49]. Treatments like fat emulsions and heparin can mitigate the rise in plasma fatty acids, while acipimox, a derivative of nicotinic acid that inhibits the hormone-sensitive lipase in adipose tissue, can reverse this trend. This drug enhances glucose disposal induced by insulin, thereby reducing insulin resistance. [50,51]. However, some studies have noted that changes in free fatty acid levels during fasting are more pronounced than those observed in both normal-weight and obese individuals, irrespective of their insulin sensitivity status. [48,52,53,54]. The metabolism of free fatty acids within cells can produce by-products (e.g., reactive oxygen species, diacylglycerol, ceramides) that influence the amount of free fatty acids distributed to body tissues and cells.

The common understanding is that an increase in visceral fat mass plays a significant role in the onset of insulin resistance, largely due to the rise in free fatty acid levels within cells. There's also a noted association between visceral fat mass, insulin resistance, and type 2 diabetes mellitus.[55]. Yet, in obese individuals, only about 20% of free fatty acids (FFA) that reach the liver result from visceral lipolysis, with the majority, around 80%, coming from the breakdown of subcutaneous fat [56]. These figures can vary among individuals, with some showing up to 50% of available fatty acids being directed to the liver from visceral adipose tissue lipolysis. This suggests that the insulin resistance might be linked to an increase in visceral fat mass. Generally, of the vital fatty acids found in systemic circulation, only about 14% are sourced from the "visceral" region, with the rest primarily emanating from subcutaneous and visceral fat. Moreover, when about a third of visceral fat is surgically removed from individuals with Type II diabetes, there isn't a significant improvement in their insulin sensitivity. This observation further strengthens the idea that factors other than visceral fat might have a more profound impact on insulin sensitivity in those with Type 2 diabetes. To better manage diabetes, it's essential to explore other interventions or lifestyle changes that directly address these factors and improve insulin sensitivity [57]. While free fatty acids from visceral fat can influence insulin sensitivity, they aren't the sole contributors to insulin resistance in other body tissues.

## METABOLIC DISTURBANCES IN OBESITY LINKED TO ADIPOSE TISSUE CHANGES

Obesity is closely linked to a range of health issues, including insulin resistance, cardiovascular diseases, type 2 diabetes, and hypertension. Central to these complications is the role of adipose tissue, the body's fat storage, in regulating metabolism and overall health. An excess of this tissue can lead to metabolic dysfunction. Consuming excessive fat can be detrimental, often resulting in insulin resistance and a heightened risk of chronic diseases like heart and vascular diseases, and type 2 diabetes. Thus, maintaining an optimal level of adipose tissue is vital for health.[58] The metabolic issues in obese individuals are deeply rooted in the alterations in the biology of their adipose tissue. Key changes that contribute to this dysfunction include:[59]

• Adipocyte Enlargement: Overconsumption of calories, leading to triglyceride accumulation, results in the expansion of adipocytes (fat cells). This enlargement is a defining feature of obesity and is associated with inflammation, insulin resistance, and cell dysfunction.[60]

• Inflammation in Adipose Tissue: In obese individuals, immune cells like macrophages and T lymphocytes infiltrate the adipose tissue, triggering inflammation. This infiltration initiates a series of events causing chronic, low-grade inflammation. The inflammatory cytokines these cells release further exacerbate insulin resistance and systemic inflammation.[61]

• Adipokine Imbalance: Adipocytes produce bioactive compounds called adipokines, including hormones like adiponectin, leptin, and resistin. In obesity, there's an upsurge in pro-inflammatory adipokines and a decline in anti-inflammatory ones, contributing to insulin resistance and metabolic inefficiency.[62]

• Lipid Storage and Release Issues: In obese individuals, the capacity of adipose tissue to store triglycerides can be overwhelmed, leading to lipid spillover to surrounding tissues, aggravating lipotoxicity and insulin resistance.[63]

• Mitochondrial Dysfunction: Mitochondria are the cell's powerhouses. Dysfunction in adipose tissue mitochondria can lead to reduced energy expenditure and increased fat storage. This dysfunction is also linked to insulin resistance and metabolic anomalies.[64]

• Hypoxia and Tissue Scarring: As obesity progresses, adipose tissue can surpass its blood supply, resulting in oxygen shortage (hypoxia) and tissue scarring (fibrosis). These conditions further impair adipose tissue function and induce inflammation.[65]

• Disrupted Fat Metabolism: The balance between lipolysis (fat breakdown) and lipogenesis (fat formation) is disturbed in obese individuals, leading to excessive fat storage and insulin resistance.[66]

• Ectopic Fat Deposition: Besides the usual subcutaneous storage, fat can also accumulate in places like the liver, muscles, and other organs, known as ectopic fat sites. This accumulation can lead to insulin resistance and disrupt the normal functioning of these organs.[67]

The alterations in adipose tissue biology culminate in an environment characterized by inflammation, insulin resistance, and metabolic anomalies.[68] Addressing these issues is paramount to mitigate the health hazards associated with obesity and metabolic dysfunction. Interventions such as weight reduction, dietary modifications, physical activity, and in certain cases, medical treatments, can help alleviate these adverse impacts and enhance metabolic health.[69]

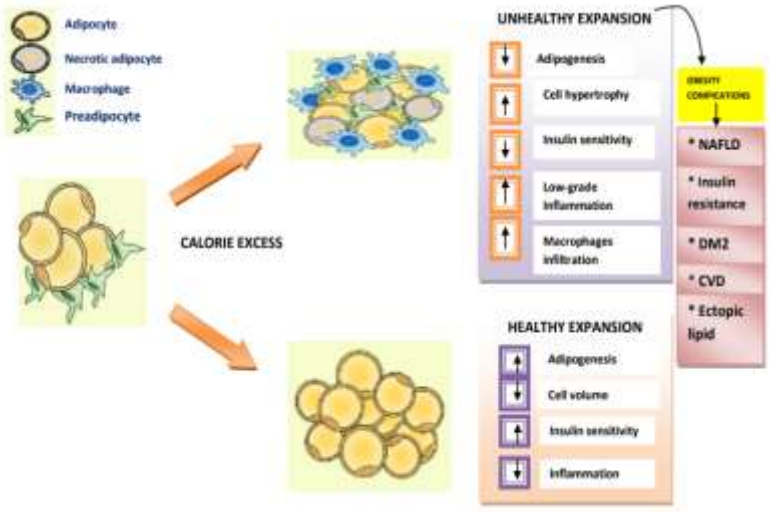


**Figure 1: The role of adipose tissue in the progression of metabolic disorders linked to obesity**

## THE LINK AMONG TYPE 2 DIABETES, OBESITY, AND INSULIN RESISTANCE

Obesity amplifies several health risks, notably Type 2 diabetes and insulin resistance, stemming from disruptions in the body's essential processes. Consequently, obesity is a significant and elevated risk factor for the onset of Type 2 diabetes.[70]. A relationship is evident between insulin resistance, where the body's response to insulin diminishes, and both obesity and DM2.

Obesity amplifies the risk of several health complications, notably Type 2 diabetes (DM2) and insulin resistance (IR). Insulin resistance hinders the hormone's ability to regulate blood glucose effectively, elevating the chances of DM2 onset and subsequent high blood sugar levels. Obesity's detrimental effects on metabolic-related physiological processes further intensify insulin resistance issues.[71]. Elevated insulin levels, known as hyperinsulinemia, are associated with insulin resistance and potential disruptions in glucose metabolism. [72,73]. A hallmark of DM2 is the disruption in insulin production in response to glucose, coupled with alterations in pancreatic beta cell functionality. This imbalance is frequently observed in individuals with obesity.[73]. These metabolic challenges often overlap and manifest at different stages of disease progression.[74]. The intricate relationship between obesity, DM2, and IR involves numerous molecular interactions, including the release of pro-inflammatory cytokines, shifts in lipid and glucose metabolism, and changes within adipose tissue.[75]. Gaining a deeper understanding of these interconnections is pivotal for crafting effective interventions for DM2 and obesity-induced IR.

## METABOLIC DISORDERS AND INSULIN SENSITIVITY

While insulin resistance is a key factor in the onset of metabolic syndrome, it's important to note that not everyone diagnosed with metabolic syndrome exhibits signs of insulin resistance.[76]. Conditions like hyperglycemia and dyslipidemia can both stem from and aggravate insulin resistance.[77]. Even though obesity is a common feature in those with metabolic syndrome, it isn't a mandatory criterion for its diagnosis. The emergence of metabolic syndrome is linked to heightened risks of cardiovascular ailments, heart and brain strokes, and is often accompanied by obesity and diabetes. Other contributing factors include hypertension, dyslipidemia, and of course, insulin resistance, all of which play a role in the manifestation of metabolic syndrome.[78].

Metabolic syndrome encompasses a range of conditions, including glucose intolerance, obesity, dyslipidemia, and hypertension. This syndrome significantly elevates the risk of cardiovascular diseases, a leading global cause of mortality. An individual with metabolic syndrome faces a heightened risk of Type 2 diabetes due to glucose intolerance. Concurrently, they might also exhibit dyslipidemia, characterized by elevated cholesterol and triglyceride levels, amplifying their susceptibility to atherosclerosis and cardiovascular incidents like heart attacks and strokes.[79]. Metabolic syndrome, often denoted as MetS, is typically characterized by the coexistence of obesity and insulin resistance.[80].

## EPIGENETIC INFLUENCES ON OBESITY

Obesity is largely influenced by epigenetic factors, which involve modulating gene activity without altering the underlying DNA sequence. Several epigenetic pathways, such as DNA methylation, histone modifications, and the generation of noncoding RNAs, play pivotal roles in transcription regulation and phenotype adaptability. Factors like diet, stress, and exposure to chemicals are just a few environmental elements that can impact these epigenetic pathways. A more profound grasp of how these elements shape

epigenetic regulation can offer insights into the complex interplay between genetics and environmental factors in obesity's evolution. [81,82].

While genetics play a role in obesity, they don't entirely account for its hereditary nature, suggesting that epigenetic modifications also come into play.[83]. The epigenetic shaping of obesity and metabolic well-being is crucial throughout embryonic, fetal, and postnatal stages. During these phases, elements such as maternal nutrition, stress, and pollutant exposure can significantly sway the risk of obesity and associated ailments.[84]. Environmental aspects, including dietary influences, can modify epigenetic events and the expression of genes pivotal to weight regulation and the onset of obesity.[85].

Environmental exposures during vital developmental windows can induce epigenetic changes that predispose individuals to obesity. Delving into the epigenetic foundations of obesity can pave the way for preventive measures centered on lifestyle modifications. Recognizing individuals with altered methylation patterns in obesity-linked genes can be instrumental in gauging their risk and crafting personalized treatment strategies.

## MUSCLE GLUCOSE METABOLISM AND STRUCTURE

At rest, skeletal muscles primarily utilize free fatty acids from the bloodstream as their primary energy source.[86] post-meal, elevated insulin levels in the plasma inhibit the breakdown of triglycerides in adipose tissue, reducing free fatty acid concentrations in the plasma. This promotes glucose uptake by the body's core muscles, converting fatty acids to glucose. Within muscle cells, insulin triggers a cascade of events, culminating in the movement of the glucose transporter 4 to the cell membrane, enhancing glucose transport. This process allows glucose to enter muscle cells, where it serves as fuel for various metabolic activities. Insulin also encourages the formation of glycogen, a glucose storage form, within these cells.[87] This stored glucose can either be used for energy via glycolysis or be stored as glycogen. Approximately 30% of ingested glucose is consumed by skeletal muscles, other tissues utilize about 50%, and 35% is stored as glycogen. Anaerobic glucose breakdown transforms roughly 15% of this glucose into amino acids like alanine, pyruvate, and lactate. [88,89]

In individuals with Type II diabetes and obesity, there's a noted decline in the functionality and quantity of insulin receptors, coupled with disruptions in post-receptor insulin signaling.[25,90] This results in hindered insulin-stimulated glucose oxidation and glycogen synthesis in muscles. The onset of insulin resistance, often linked with obesity and type 2 diabetes, can be influenced by changes in lipid distribution and metabolism within muscles. Research indicates that an accumulation of lipids within muscle cells can disrupt insulin signaling pathways and glucose balance. Additionally, it's been found that intramuscular fat releases pro-inflammatory cytokines, exacerbating insulin resistance and hastening the progression of metabolic disorders. [91,92].

## EFFECTS OF FAT REDUCTION THROUGH WEIGHT LOSS

Weight loss can lead to a myriad of physiological changes. Prolonged, significant weight reduction, even if followed by weight regain, has been associated with positive impacts on visceral fat mass, inflammation levels, lipid processing, and markers of cardiovascular health. However, it's essential to note that individual factors like genetics, overall well-being, and lifestyle can influence how weight loss affects different individuals. Achieving sustained weight loss through a balanced diet and consistent exercise has been correlated with improvements in mental well-being, energy, and overall life quality.[93]. Consuming fats rich in omega-3 fatty acids during weight loss can optimize fat metabolism, ensure adequate

energy, and enhance various health metrics.[94]. Rapid weight loss followed by immediate weight recovery can lead to improved body composition and energy utilization due to increased fat burning and decreased carbohydrate burning. This might also enhance the body's metabolic adaptability, facilitating a seamless switch between using fats and carbohydrates as energy sources, benefiting intentional weight maintenance and overall physical performance.[95]. Regardless of their specific makeup, weight loss diets can decrease serum urate levels and ameliorate cardiometabolic risk factors, likely driven by reductions in body fat and improved insulin sensitivity.[96]. Purposeful weight reduction through lifestyle modifications can positively influence heart health, blood pressure, cholesterol levels, insulin sensitivity, and diabetes management.[97].

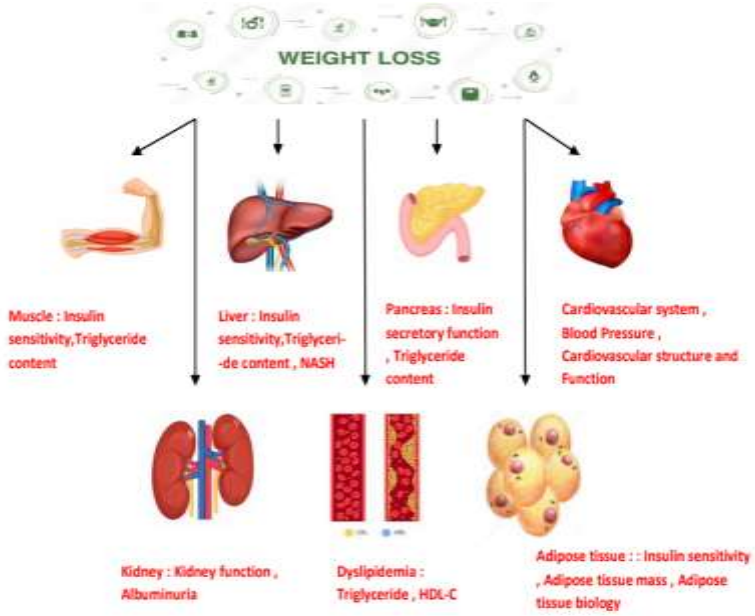


**Figure 2: The therapeutic impacts of weight loss on various bodily organs.**

## SURGICAL REMOVAL OF FAT VERSUS METABOLIC IMPROVEMENTS

Surgical removal of adipose tissue doesn't necessarily equate to metabolic enhancements, especially when compared to weight loss achieved through dietary or pharmacological means. Numerous studies have shown that in overweight women with type 2 diabetes, liposuction fails to enhance insulin sensitivity in adipose tissue, liver, skeletal muscles, or blood lipid levels.[98]. Even when surgery targeted a 30% reduction in abdominal fat, there were no noticeable improvements in insulin sensitivity across these areas. These findings suggest that alternative treatments might be necessary to enhance insulin responsiveness in obese women diagnosed with type 2 diabetes.

## TACKLING INSULIN RESISTANCE THROUGH WEIGHT MANAGEMENT

Further research is imperative to identify alternative treatments that effectively address insulin resistance. The findings underscore the importance of achieving a negative energy balance for metabolic benefits associated with fat reduction.[99] A moderate weight reduction of just 5% can significantly enhance insulin sensitivity across various organs, including the liver, fat tissues, and skeletal muscles. [100,101]. However, given the variations in the severity and duration of metabolic disorders among individuals, the exact amount of weight loss required to achieve optimal metabolic benefits across different organs remains uncertain. Fat reduction facilitates the efficient transportation of glucose from the bloodstream to cells and tissues by

insulin. This not only helps regulate blood sugar levels but also diminishes the chances of insulin resistance and the onset of type 2 diabetes. Beyond this, shedding excess fat offers other advantages such as improved metabolic health and better cardiovascular function. [101,102]. For optimal enhancement in insulin sensitivity, particularly given insulin's role in moderating glucose production in the liver and fat breakdown in adipose tissue, a weight reduction of 5-8% is likely ideal.

## THE MOLECULAR UNDERPINNINGS OF WEIGHT LOSS AND METABOLIC IMPROVEMENTS

The precise molecular pathways by which weight reduction enhances metabolic health remain elusive. Weight loss has been associated with heightened insulin sensitivity and metabolic enhancement, largely attributed to reduced inflammation. Weight loss might also induce alterations in gene expression and hormone production, further influencing metabolic processes. As the body undergoes caloric deficit and weight is shed, adipose tissue is among the first to respond. Dietary-induced weight loss primarily diminishes the volume of adipose tissue, both subcutaneous and visceral, largely due to adipocyte shrinkage.

Several elements, such as modifications in lipogenesis, extracellular matrix restructuring, PAI-1 production, and shifts in oxidative stress and collagen synthesis gene expression, are intertwined with steady weight reduction. Dietary weight loss has been linked to enhanced insulin sensitivity and diminished inflammatory markers, culminating in better metabolic health and a decreased propensity for ailments like diabetes and heart disease.[101]

A weight reduction of 5-10% has been observed to bolster insulin efficiency, enhancing blood sugar control, plasma triglyceride levels, HDL cholesterol, and blood pressure regulation. As weight diminishes over time, the liver's histological characteristics of NAFLD improve, and intrahepatic triglyceride content declines. Remarkably, intrahepatic triglycerides are especially responsive to caloric restriction.[103] A mere two-day stint on a calorie-restricted diet led to a notable plunge in intrahepatic triglyceride levels.[104]

Even slight weight loss can activate beneficial systemic pathways, such as adiponectin, PAI-1, and exosome release, reshaping liver and adipose tissue physiology and endorsing weight loss interventions. These enhancements in liver and adipose tissue can elevate insulin sensitivity and fat metabolism, subsequently slashing the risk of chronic conditions like Type 2 diabetes, cardiovascular ailments, and hypertension. Key players in this metabolic enhancement include adiponectin, PAI-1, and exosome release, all pivotal in fostering metabolic health and curbing inflammation.

## CONCLUSION

The body's primary fuel reservoir resides within adipose tissue, rendering it an invaluable asset during periods of food scarcity.

The prevalence of Type 2 diabetes has surged in tandem with the global upsurge in obesity rates.

Excessive fat accumulation can give rise to a multitude of metabolic irregularities and ailments, including but not limited to insulin resistance, atherogenic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), beta cell dysfunction, pre-diabetes, and Type 2 diabetes.

Obesity, a significant risk factor, substantially contributes to the development of prediabetes and Type 2 diabetes. This association stems from its correlation with insulin resistance and impaired pancreatic beta cell function. Consequently, the worldwide increase in obesity prevalence has correspondingly driven up the incidence of Type 2 diabetes.

A more profound comprehension of the fundamental mechanisms that underlie the detrimental impact of excessive body fat on the various components involved in the onset of Type 2 diabetes could potentially

facilitate the discovery of innovative therapeutic approaches for both prevention and treatment of this debilitating ailment. Multiple studies conducted on both murine models and human subjects have revealed changes in adipose tissue biology that establish a link between obesity, insulin resistance, and beta cell dysfunction. These alterations encompass heightened fibrogenesis and upregulated expression of extracellular matrix-associated genes, indicative of adipose tissue fibrosis. Additionally, escalated inflammation is marked by an increased presence of proinflammatory macrophages and T cells, along with heightened production of PAI-1. Moreover, the generation of insulin resistance-inducing exosomes is also discernible. Nevertheless, the influence of these factors on systemic metabolic function hinges on a mechanism that facilitates communication between adipose tissue and other organs.

Several secretory products from adipose tissue, such as PAI-1, adiponectin, FFAs, and exosomes, have the potential to significantly impact intercellular communication upon their release into the bloodstream. For instance, PAI-1 not only fosters inflammation but also impedes the responsiveness of distant tissues like the liver and skeletal muscle to insulin. Conversely, adiponectin demonstrates insulin-sensitizing properties and the ability to regulate glucose metabolism in various organs. Furthermore, the liberation of free fatty acids (FFAs) from adipose tissue can serve as an energy source for multiple tissues or participate in lipid accumulation.

When contrasting individuals with varying body compositions, those who are overweight possess approximately 50% more bulk pancreatic B cells. Obese individuals with diabetes might find benefit in achieving a negative energy balance to reduce body fat, as opposed to surgical fat removal, as a means to restore B-cell functionality.

Further research and investigations are imperative to comprehensively evaluate the clinical significance of disorders such as insulin sensitivity and immunity in adipose tissue, infections in people with obesity, and non-alcoholic fatty liver diseases. It remains somewhat unclear whether these disorders actively contribute to the instigation of insulin resistance.

### *Declaration by Authors*

**Ethical Approval:** Not Required
**Acknowledgement:** None
**Source of Funding:** None
**Conflict of Interest:** The authors declare no conflict of interest.

### REFERENCES

1. Arrese, E. L., & Soulages, J. L. (2010). Insect fat body: energy, metabolism, and regulation. Annual review of entomology, 55, 207-225.
2. Vadivel, V., Kunyanga, C. N., & Biesalski, H. K. (2012). Health benefits of nut consumption with special reference to body weight control. Nutrition, 28(11-12), 1089-1097.
3. Stewart, W. K., & Fleming, L. W. (1973). Features of a successful therapeutic fast of 382 days' duration. Postgraduate medical journal, 49(569), 203-209.
4. Funcke, J. B., & Scherer, P. E. (2019). Beyond adiponectin and leptin: adipose tissue-derived mediators of inter-organ communication. Journal of lipid research, 60(10), 1648-1697.
5. Weiss, R., Bremer, A. A., & Lustig, R. H. (2013). What is metabolic syndrome, and why are children getting it?. Annals of the New York Academy of Sciences, 1281(1), 123-140.
6. Jung, U. J., & Choi, M. S. (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. International journal of molecular sciences, 15(4), 6184-6223.
7. Terranova, F. (2015). The nodule of discord: the unresolved diatribe on the pathogenesis of cellulite in the light of the ad-ipocyte pathophysiology. Union of Aesthetic Medicine–UIME, 77.
8. Arslanian, S., Bacha, F., Grey, M., Marcus, M. D., White, N. H., & Zeitler, P. (2018).

Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes care, 41(12), 2648.
9. Rorsman, P., & Ashcroft, F. M. (2018). Pancreatic β-cell electrical activity and insulin secretion: of mice and men. Physiological reviews, 98(1), 117-214.
10. Gastaldelli, A., Abdul Ghani, M., & DeFronzo, R. A. (2021). Adaptation of insulin clearance to metabolic demand is a key determinant of glucose tolerance. Diabetes, 70(2), 377-385.
11. Kotronen, A., Vehkavaara, S., Seppala-Lindroos, A., Bergholm, R., & Yki-Jarvinen, H. (2007). Effect of liver fat on insulin clearance. American Journal of Physiology-Endocrinology and Metabolism, 293(6), E1709-E1715.
12. Smith, G. I., Polidori, D. C., Yoshino, M., Kearney, M. L., Patterson, B. W., Mittendorfer, B., & Klein, S. (2020). Influence of adiposity, insulin resistance, and intrahepatic triglyceride content on insulin kinetics. The Journal of clinical investigation, 130(6), 3305-3314.
13. van Vliet, S., Koh, H. C. E., Patterson, B. W., Yoshino, M., LaForest, R., Gropler, R. J., ... & Mittendorfer, B. (2020). Obesity is associated with increased basal and postprandial β-cell insulin secretion even in the absence of insulin resistance. Diabetes, 69(10), 2112-2119.
14. Pamidi, S., Wroblewski, K., Broussard, J., Day, A., Hanlon, E. C., Abraham, V., & Tasali, E. (2012). Obstructive sleep apnea in young lean men: impact on insulin sensitivity and secretion. Diabetes care, 35(11), 2384-2389.
15. Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet, 383(9922), 1068-1083.
16. Marrif, H. I., & Al-Sunousi, S. I. (2016). Pancreatic β cell mass death. Frontiers in pharmacology, 7, 83.
17. Mosser, R. E., Maulis, M. F., Moullé, V. S., Dunn, J. C., Carboneau, B. A., Arasi, K., ... & Gannon, M. (2015). High-fat diet-induced β-cell proliferation occurs prior to insulin resistance in C57Bl/6J male mice. American Journal of Physiology-Endocrinology and Metabolism, 308(7), E573-E582.
18. Tan, V. M. H., Lee, Y. S., Venkataraman, K., Khoo, E. Y. H., Tai, E. S., Chong, Y. S., ... & Khoo, C. M. (2015). Ethnic differences in insulin sensitivity and beta-cell function among Asian men. Nutrition & diabetes, 5(7), e173-e173.
19. Linnemann, A. K., Baan, M., & Davis, D. B. (2014). Pancreatic β-cell proliferation in obesity. Adv. Nutr. 5: 278–288.
20. IS Sobczak, A., A. Blindauer, C., & J. Stewart, A. (2019). Changes in plasma free fatty acids associated with type-2 diabetes. Nutrients, 11(9), 2022.
21. Crewe, C., An, Y. A., & Scherer, P. E. (2017). The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. The Journal of clinical investigation, 127(1), 74-82.
22. Scherer, P. E. (2016). The multifaceted roles of adipose tissue—therapeutic targets for diabetes and beyond: The 2015 Banting Lecture. Diabetes, 65(6), 1452-1461.
23. Smith, G. I., Mittendorfer, B., & Klein, S. (2019). Metabolically healthy obesity: facts and fantasies. The Journal of clinical investigation, 129(10), 3978-3989.
24. Seo, J. B., Riopel, M., Cabrales, P., Huh, J. Y., Bandyopadhyay, G. K., Andreyev, A. Y., ... & Olefsky, J. M. (2019). Knockdown of Ant2 reduces adipocyte hypoxia and improves insulin resistance in obesity. Nature metabolism, 1(1), 86-97.
25. Sun, K., Asterholm, I. W., Kusminski, C. M., Bueno, A. C., Wang, Z. V., Pollard, J. W., ... & Scherer, P. E. (2012). Dichotomous effects of VEGF-A on adipose tissue dysfunction. Proceedings of the national academy of sciences, 109(15), 5874-5879.
26. Sun, K., Li, X., & Scherer, P. E. (2023). Extracellular matrix (ECM) and fibrosis in adipose tissue: overview and perspectives. Comprehensive Physiology, 13(1), 4387.
27. Heinz, A. (2020). Elastases and elastokines: elastin degradation and its significance in health and disease. Critical reviews in biochemistry and molecular biology, 55(3), 252-273.
28. Blanchard, P. G., Moreira, R. J., Castro, É., Caron, A., Côté, M., Andrade, M. L., ... & Festuccia, W. T. (2018). PPARγ is a major regulator of branched-chain amino acid blood levels and catabolism in white and brown adipose tissues. Metabolism, 89, 27-38.

29. Lo, K. A., Labadorf, A., Kennedy, N. J., Han, M. S., Yap, Y. S., Matthews, B., ... & Fraenkel, E. (2013). Analysis of in vitro insulin-resistance models and their physiological relevance to in vivo diet-induced adipose insulin resistance. Cell reports, 5(1), 259-270.
30. Crewe, C., An, Y. A., & Scherer, P. E. (2017). The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. The Journal of clinical investigation, 127(1), 74-82.
31. Straub, L. G., & Scherer, P. E. (2019). Metabolic messengers: adiponectin. Nature Metabolism, 1(3), 334-339.
32. Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. Physiological reviews.
33. Cifarelli, V., Beeman, S. C., Smith, G. I., Yoshino, J., Morozov, D., Beals, J. W., ... & Klein, S. (2020). Decreased adipose tissue oxygenation associates with insulin resistance in individuals with obesity. The Journal of Clinical Investigation, 130(12), 6688-6699.
34. Fuchs, A., Samovski, D., Smith, G. I., Cifarelli, V., Farabi, S. S., Yoshino, J., ... & Klein, S. (2021). Associations among adipose tissue immunology, inflammation, exosomes and insulin sensitivity in people with obesity and nonalcoholic fatty liver disease. Gastroenterology, 161(3), 968-981.
35. World Health Organization. (2011). Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December 2008.
36. Hotamisligil, G. S., Shargill, N. S., & Spiegelman, B. M. (1993). Adipose expression of tumor necrosis factor-α: direct role in obesity-linked insulin resistance. Science, 259(5091), 87-91.
37. Burhans, M. S., Hagman, D. K., Kuzma, J. N., Schmidt, K. A., & Kratz, M. (2018). Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus. Comprehensive Physiology, 9(1), 1.
38. Zhu, Q., An, Y. A., Kim, M., Zhang, Z., Zhao, S., Zhu, Y., ... & Scherer, P. E. (2020). Suppressing adipocyte inflammation promotes insulin resistance in mice. Molecular metabolism, 39, 101010.
39. Alessi, M. C., Poggi, M., & Juhan-Vague, I. (2007). Plasminogen activator inhibitor-1, adipose tissue and insulin resistance. Current opinion in lipidology, 18(3), 240-245.
40. Straub, L. G., & Scherer, P. E. (2019). Metabolic messengers: adiponectin. Nature Metabolism, 1(3), 334-339.
41. Basu, S., Laffineuse, L., Presley, L., Minium, J., Catalano, P. M., & Mouzon, S. H. D. (2009). In utero gender dimorphism of adiponectin reflects insulin sensitivity and adiposity of the fetus. Obesity, 17(6), 1144-1149.
42. Li, N., Zhao, S., Zhang, Z., Zhu, Y., Gliniak, C. M., Vishvanath, L., ... & Scherer, P. E. (2021). Adiponectin preserves metabolic fitness during aging. Elife, 10, e65108.
43. Scherer, P. E. (2019). The many secret lives of adipocytes: implications for diabetes. Diabetologia, 62(2), 223-232.
44. Rutkowski, J. M., Wang, Z. V., Park, A. S. D., Zhang, J., Zhang, D., Hu, M. C., ... & Scherer, P. E. (2013). Adiponectin promotes functional recovery after podocyte ablation. Journal of the American Society of Nephrology: JASN, 24(2), 268.
45. Ye, R., Wang, M., Wang, Q. A., & Scherer, P. E. (2015). Adiponectin-mediated antilipotoxic effects in regenerating pancreatic islets. Endocrinology, 156(6), 2019-2028.
46. Holland, W. L., Miller, R. A., Wang, Z. V., Sun, K., Barth, B. M., Bui, H. H., ... & Scherer, P. E. (2011). Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nature medicine, 17(1), 55-63.
47. Yazıcı, D., & Sezer, H. (2017). Insulin resistance, obesity and lipotoxicity. Obesity and lipotoxicity, 277-304.
48. Conte, C., Fabbrini, E., Kars, M., Mittendorfer, B., Patterson, B. W., & Klein, S. (2012). Multiorgan insulin sensitivity in lean and obese subjects. Diabetes care, 35(6), 1316-1321.
49. McQuaid, S. E., Hodson, L., Neville, M. J., Dennis, A. L., Cheeseman, J., Humphreys, S. M., ... & Karpe, F. (2011). Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition? Diabetes, 60(1), 47-55.
50. Boden, G., Chen, X. I. N. H. U. A., Ruiz, J., White, J. V., & Rossetti, L. (1994). Mechanisms of fatty acid-induced inhibition of glucose uptake. The Journal of clinical investigation, 93(6), 2438-2446.

51. Santomauro, A. T., Boden, G., Silva, M. E., Rocha, D. M., Santos, R. F., Ursich, M. J., ... & Wajchenberg, B. L. (1999). Overnight lowering of free fatty acids with Acipimox improves insulin resistance and glucose tolerance in obese diabetic and nondiabetic subjects. Diabetes, 48(9), 1836-1841.
52. Fabbrini, E., Magkos, F., Mohammed, B. S., Pietka, T., Abumrad, N. A., Patterson, B. W., ... & Klein, S. (2009). Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. Proceedings of the National Academy of Sciences, 106(36), 15430-15435.
53. Arner, P., & Rydén, M. (2015). Fatty acids, obesity and insulin resistance. Obesity facts, 8(2), 147-155.
54. Gastaldelli, A., Gaggini, M., & DeFronzo, R. A. (2017). Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio Metabolism Study. Diabetes, 66(4), 815-822.
55. Kissebah, A. H., Vydelingum, N., Murray, R., Evans, D. J., Kalkhoff, R. K., & Adams, P. W. (1982). Relation of body fat distribution to metabolic complications of obesity. The Journal of Clinical Endocrinology & Metabolism, 54(2), 254-260.
56. Nielsen, S., Guo, Z., Johnson, C. M., Hensrud, D. D., & Jensen, M. D. (2004). Splanchnic lipolysis in human obesity. The Journal of clinical investigation, 113(11), 1582-1588.
57. Fabbrini, E., Tamboli, R. A., Magkos, F., Marks–Shulman, P. A., Eckhauser, A. W., Richards, W. O., ... & Abumrad, N. N. (2010). Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. Gastroenterology, 139(2), 448-455.
58. Packer, M. (2018). Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. Journal of the American College of Cardiology, 71(20), 2360-2372.
59. Choe, S. S., Huh, J. Y., Hwang, I. J., Kim, J. I., & Kim, J. B. (2016). Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. Frontiers in endocrinology, 7, 30.
60. Hammarstedt, A., Gogg, S., Hedjazifar, S., Nerstedt, A., & Smith, U. (2018). Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity. Physiological reviews, 98(4), 1911-1941.
61. Stolarczyk, E. (2017). Adipose tissue inflammation in obesity: a metabolic or immune response? Current opinion in pharmacology, 37, 35-40.
62. Taylor, E. B. (2021). The complex role of adipokines in obesity, inflammation, and autoimmunity. Clinical Science, 135(6), 731-752.
63. Jersin, R. Å., Sri Priyanka Tallapragada, D., Skartveit, L., Bjune, M. S., Muniandy, M., Lee-Ødegård, S., ... & Dankel, S. N. (2023). Impaired adipocyte SLC7A10 promotes lipid storage in association with insulin resistance and altered BCAA metabolism. The Journal of Clinical Endocrinology & Metabolism, dgad148.
64. Lowell, B. B., & Shulman, G. I. (2005). Mitochondrial dysfunction and type 2 diabetes. Science, 307(5708), 384-387.
65. Engin, A. (2017). Adipose tissue hypoxia in obesity and its impact on preadipocytes and macrophages: hypoxia hypothesis. Obesity and Lipotoxicity, 305-326.
66. Saponaro, C., Gaggini, M., Carli, F., & Gastaldelli, A. (2015). The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. Nutrients, 7(11), 9453-9474.
67. Smith, U. (2015). Abdominal obesity: a marker of ectopic fat accumulation. The Journal of clinical investigation, 125(5), 1790-1792.
68. Chait, A., & Den Hartigh, L. J. (2020). Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Frontiers in cardiovascular medicine, 7, 22.
69. Garber, A. J. (2012). Obesity and type 2 diabetes: which patients are at risk? Diabetes, Obesity and Metabolism, 14(5), 399-408.
70. James, D., Johnson. (2021). On the causal relationships between hyperinsulinaemia, insulin resistance, obesity and dysglycaemia in type 2 diabetes. Diabetologia, 64(10):2138-2146. doi: 10.1007/S00125-021-05505-4
71. Habib, Yaribeygi., Mina, Maleki., Thozhukat, Sathyapalan., Tannaz, Jamialahmadi., Amirhossein, Sahebkar. (2021). Obesity and Insulin Resistance: A Review of Molecular Interactions. Current

Molecular Medicine, 21(3):182-193. doi: 10.2174/1566524020666200812221527
72. Saira, Sattar., Muhammad, Faisal, Nisar., Onyeka, Kingsley, Nwosu. (2021). Insulin Resistance: A Link Between Obesity and Cancer. 81-93. doi: 10.1007/978-3-030-72999-8_5
73. Yohannes, Tsegyie, Wondmkun. (2020). Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 13:3611-3616. doi: 10.2147/DMSO.S275898
74. Tiffany, Scully., Abora, Ettela., Derek, LeRoith., Emily, J., Gallagher. (2021). Obesity, Type 2 Diabetes, and Cancer Risk. Frontiers in Oncology, 10:615375-. doi: 10.3389/FONC.2020.615375
75. Cruz, N. G., Sousa, L. P., Sousa, M. O., Pietrani, N. T., Fernandes, A. P., & Gomes, K. B. (2013). The linkage between inflammation and Type 2 diabetes mellitus. Diabetes research and clinical practice, 99(2), 85-92.
76. Nasser, Mikhail. (2009). The metabolic syndrome: insulin resistance. Current Hypertension Reports, 11(2):156-158. doi: 10.1007/S11906-009-0027-4
77. Mary, Ann, Banerji., Mary, Ann, Banerji., Rochelle, L, Chaiken., Rochelle, L, Chaiken. (2010). Insulin Resistance and the Metabolic Syndrome. 531-555. doi: 10.1007/978-0-387-09841-8_34
78. Ko, Kotani., Kouhei, Kaku. (2005). The metabolic syndrome and insulin resistance. Nihon rinsho. Japanese journal of clinical medicine, 63(8):1485-1491.
79. Alvaro, L., Ronco., Eduardo, De, Stefani. (2012). Insulin Resistance and Metabolic Syndrome. 99-108. doi: 10.1007/978-94-007-2397-9_9
80. Beverley, Balkau. (2006). The metabolic syndrome — a risk factor for diabetes and cardiovascular diseases. European Diabetes Nursing, 3(3):126-130. doi: 10.1002/EDN.58
81. A, Lopomo., E, Burgio., Lucia, Migliore. (2016). Epigenetics of Obesity. Progress in Molecular Biology and Translational Science, 140:151-184. doi: 10.1016/BS.PMBTS.2016.02.002
82. O., V., Kochetova., T., V., Viktorova. (2015). Genetics and epigenetics of obesity. Biology Bulletin Reviews, 5(6):538-547. doi: 10.1134/S2079086415060043.
83. Simonetta, Friso., Sang-Woon, Choi. (2014). Epigenetics of Obesity. 187-198. doi: 10.1007/978-1-62703-770-9_13
84. O., M., Drapkina., O., T., Kim. (2020). Epigenetics of obesity. Cardiovascular Therapy and Prevention, 19(6):2632-. doi: 10.15829/1728-8800-2020-2632
85. Javier, Campión., Fermín, I., Milagro., José, Alfredo, Martínez. (2009). Individuality and epigenetics in obesity. Obesity Reviews, 10(4):383-392. doi: 10.1111/J.1467-789X.2009. 00595.X
86. Frayn, K. N. (2010). Fat as a fuel: emerging understanding of the adipose tissue–skeletal muscle axis. Acta physiologica, 199(4), 509-518.
87. Rorsman, P., & Renström, E. (2003). Insulin granule dynamics in pancreatic beta cells. Diabetologia, 46, 1029-1045.
88. Kelley, D., Mitrakou, A., Marsh, H., Schwenk, F., Benn, J., Sonnenberg, G., ... & Berger, M. (1988). Skeletal muscle glycolysis, oxidation, and storage of an oral glucose load. The Journal of clinical investigation, 81(5), 1563-1571.
89. Woerle, H. J., Meyer, C., Dostou, J. M., Gosmanov, N. R., Islam, N., Popa, E., ... & Gerich, J. E. (2003). Pathways for glucose disposal after meal ingestion in humans. American Journal of Physiology-Endocrinology and Metabolism, 284(4), E716-E725.
90. Mitrakou, A., Kelley, D., Veneman, T., Jenssen, T., Pangburn, T., Reilly, J., & Gerich, J. (1990). Contribution of abnormal muscle and liver glucose metabolism to postprandial hyperglycemia in NIDDM. Diabetes, 39(11), 1381-1390.
91. Kiefer, L. S., Fabian, J., Rospleszcz, S., Lorbeer, R., Machann, J., Kraus, M. S., ... & Bamberg, F. (2021). Distribution patterns of intramyocellular and extramyocellular fat by magnetic resonance imaging in subjects with diabetes, prediabetes and normoglycaemic controls. Diabetes, Obesity and Metabolism, 23(8), 1868-1878.
92. Sangwung, P., Petersen, K. F., Shulman, G. I., & Knowles, J. W. (2020). Mitochondrial dysfunction, insulin resistance, and potential genetic implications: potential role of alterations in mitochondrial function in the pathogenesis of insulin resistance and type 2 diabetes. Endocrinology, 161(4), bqaa017.

93. Heikki, V., Sarin., Heikki, V., Sarin., Joseph, H., Lee., Matti, Jauhiainen., Matti, Jauhiainen., Anni, Joensuu., Anni, Joensuu., Katja, Borodulin., Satu, Männistö., Z., Jin., Joseph, D., Terwilliger., Joseph, D., Terwilliger., Ville, Isola., Juha, P., Ahtiainen., Keijo, Häkkinen., Kati, Kristiansson., Kati, Kristiansson., Juha, J., Hulmi., Juha, J., Hulmi., Markus, Perola., Markus, Perola. (2019). Substantial fat mass loss reduces low-grade inflammation and induces positive alteration in cardiometabolic factors in normal-weight individuals. Scientific Reports, 9(1):3450-3450. doi: 10.1038/S41598-019-40107-6
94. Zhu, Yixin., Wang, Yun., Zhang, Nana., Wang, Yunxiang. (2016). Weight-loss fat and use method thereof.
95. Hiroyuki, Sagayama., Eiichi, Yoshimura., Yosuke, Yamada., Hiroaki, Tanaka. (2019). The effects of rapid weight loss and 3-h recovery on energy expenditure, carbohydrate, and fat oxidation in boxing athletes. Journal of Sports Medicine and Physical Fitness, 59(6):1018-1025. doi: 10.23736/S0022-4707.18.08677-2
96. Chio, Yokose., Natalie, McCormick., Sharan, K, Rai., Na, Lu., Gary, C., Curhan., Dan, Schwarzfuchs., Iris, Shai., Hyon, K., Choi. (2020). Effects of Low-Fat, Mediterranean, or Low-Carbohydrate Weight Loss Diets on Serum Urate and Cardiometabolic Risk Factors: A Secondary Analysis of the Dietary Intervention Randomized Controlled Trial (DIRECT). Diabetes Care, 43(11):2812-2820. DOI: 10.2337/DC20-1002
97. Keon, E., Menzies., Patrick, D., Savage., Philip, A., Ades. (2012). Cardiovascular Effects of Weight Loss. Current Cardiovascular Risk Reports, 6(1):91-101. DOI: 10.1007/S12170-011-0211-3
98. Klein, S., Fontana, L., Young, V. L., Coggan, A. R., Kilo, C., Patterson, B. W., & Mohammed, B. S. (2004). Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. New England Journal of Medicine, 350(25), 2549-2557.
99. Frayn, K. N., & Karpe, F. (2014). Regulation of human subcutaneous adipose tissue blood flow. International journal of obesity, 38(8), 1019-1026.
100. Lim, E. L., Hollingsworth, K. G., Aribisala, B. S., Chen, M. J., Mathers, J. C., & Taylor, R. (2011). Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia, 54(10), 2506-2514.
101. Magkos, F., Fraterrigo, G., Yoshino, J., Luecking, C., Kirbach, K., Kelly, S. C., ... & Klein, S. (2016). Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell metabolism, 23(4), 591-601.
102. Petersen, K. F., Dufour, S., Befroy, D., Lehrke, M., Hendler, R. E., & Shulman, G. I. (2005). Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes, 54(3), 603-608.
103. Wing, R. R., Lang, W., Wadden, T. A., Safford, M., Knowler, W. C., Bertoni, A. G., ... & Look AHEAD Research Group. (2011). Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes care, 34(7), 1481-1486.
104. Kirk, E., Reeds, D. N., Finck, B. N., Mayurranjan, M. S., Patterson, B. W., & Klein, S. (2009). Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology, 136(5), 1552-1560.

How to cite this article: Maitham Abdallah Albajy, Dan Florin Mihailescu. Obesity and diabetes mellitus 2: interrelated relative relationship. *International Journal of Research and Review*. 2023; 10(9): 320-335. DOI: *https://doi.org/10.52403/ijrr.20230933*

******