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Textbook of
Obesity and Diabetes

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2

Obesity and Diabetes Pathophysiology

Key Highlights

- The pathogenesis of obesity and type 2 diabetes mellitus (T2DM) is predominantly driven by the synergistic effects of genetic susceptibility and environmental factors, which intricately interplay to amplify the development of these conditions.
- The metabolic microenvironment undergoes significant remodeling and reshaping in obesity, leading to a marked attenuation of insulin signaling and promoting the progressive elevation of blood glucose.
- These alterations are driven by the detrimental accumulation of specific nutrients and metabolites, persistent low-grade inflammation, impaired autophagy, and disrupted energy balance, all of which stem from dysregulation of the microbiome–gut–brain axis.
- The systemic reprogramming of immunometabolism and the local toxicity inflicted on the pancreas, leading to reduced functional beta cell numbers, primarily result from the extensive ectopic expansion of adipose tissue (AT).
- Disruption of the normal physical interaction between beta and alpha cells in pancreatic islets is alleged to be a contributing factor in dysregulation of glucagon secretion in individuals with diabetes.
- Increased expression of adipocytokines such as resistin, vaspin, apelin, and tumor necrosis factor alpha (TNF-α) has been associated with the development of insulin resistance, which is closely linked to obesity and T2DM.

INTRODUCTION

Obesity is strongly associated with glucose intolerance and type 2 diabetes mellitus (T2DM). Several studies have demonstrated the correlation between increasing body mass index (BMI) and the incidence of impaired fasting glucose and T2DM in both men and women.[1] The Coronary Artery Risk Development in

Young Adults study found that higher BMI was associated with an increased risk of T2DM in women. The study followed a cohort of over 100,000 nurses for 14 years and revealed that women with a BMI of 24.0–24.9 kg/m^2 had five times the risk of T2DM compared to women with a BMI of <22 kg/m^2. The risk of T2DM further increased to 40 times and 93 times in women with a BMI greater than 31 kg/m^2 and 35 kg/m^2, respectively.[2] Similar findings were observed in a study involving male health professionals. Men with a BMI greater than 35 kg/m^2 had 42 times the risk of developing T2DM compared to men with a BMI of <23 kg/m^2. This study also highlighted that BMI at age 21 years and absolute weight gain were independent risk factors for T2DM.[3] Another study conducted by Schienkiewitz et al. revealed that weight gain during early adulthood (between ages 25 and 40 years) was associated with a higher risk of T2DM compared to weight gain during late adulthood (between ages 40 and 55 years). Additionally, individuals who experienced weight gain in both early and late adulthood had a relative risk of T2DM greater than 14 times compared to those who maintained their BMI.[4] These findings emphasize the strong association between obesity, BMI, and the risk of developing T2DM in both men and women.

The consequences of obesity are not limited to simple weight gain but extend to various metabolic disorders, with T2DM being strongly associated with obesity. The development and progression of T2DM are characterized by hyperglycemia caused by reduced insulin sensitivity and a decline in functional beta cell mass. Obesity plays a significant role in driving these processes, contributing to genetic and epigenetic vulnerabilities, microenvironmental changes that impair insulin signaling, compromised beta cell function, and dysregulated microbiome–gut–brain axis **(Fig. 1)**. However, it is important to note that T2DM can also manifest inversely, occurring before the onset of obesity in certain individuals who have inherent insulin resistance. In these cases, increased hepatic glucose production (HGP) and elevated insulin levels are the primary culprits behind obesity development. Therefore, the relationship between obesity and T2DM is complex, involving a bidirectional influence where obesity can contribute to T2DM development, but T2DM can also precede obesity in certain individuals with underlying insulin resistance.[5]

INSULIN SIGNALING, INSULIN RESISTANCE IN OBESITY, AND TYPE 2 DIABETES MELLITUS

Insulin Signaling

Insulin exerts its intracellular functions through the activation of insulin receptor tyrosine kinase (IRTK). Upon binding of insulin to the extracellular domain of IRTK, a conformational change occurs, leading to the autophosphorylation of tyrosine residues within IRTK. This autophosphorylation event triggers the activation of various phosphotyrosine-binding proteins, including insulin receptor substrate (IRS), growth factor receptor-bound protein-2 (GRB-2), GRB-10, SHC-transforming protein (SHC), and SH2B adapter protein-2 (SH2B-2).[6] The effects of insulin on glucose and lipid metabolism primarily rely on the phosphorylation of IRS by IRTK. This phosphorylation event enables IRS to

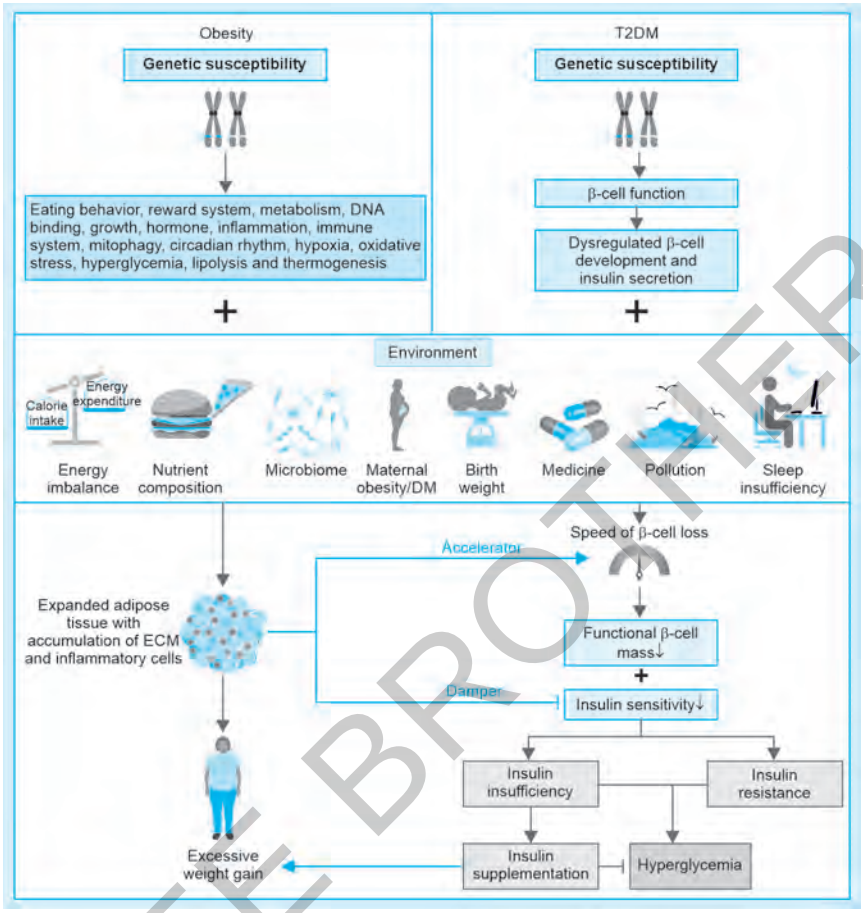


FIG. 1: Genetic and environmental factors affecting islet function and connecting obesity and type 2 diabetes mellitus (T2DM). Genetic and environmental factors play significant roles in the interplay between obesity and T2DM. Genetic factors primarily influence energy balance in obesity and impact the development and function of beta cells in T2DM. Environmental factors further contribute to the progression of obesity and exacerbate beta cell loss while impairing insulin signaling in T2DM. Additionally, the administration of insulin as a treatment for T2DM can potentially lead to weight gain. The colored arrows symbolize the dynamic interactions between obesity and T2DM, highlighting the complex relationship between these two conditions.

(ECM: extracellular matrix)

Source: With permission from Ruze et al. (2023).[5]

recruit phosphatidylinositol 3-kinase (PI3K), which catalyzes the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). Subsequently, PIP3 recruits protein kinase B (Akt) to the plasma membrane, where it is phosphorylated and activated by 3-phosphoinositide-dependent kinase-1 (PDK1) and mechanistic target of rapamycin complex 2 (mTORC2). Akt then phosphorylates various downstream substrates in metabolic tissues, including skeletal muscle, liver, and adipose tissue (AT), leading to insulin-induced nutrient preservation in these tissues.[7]

In skeletal muscle, insulin signaling promotes glucose uptake and glycogen synthesis. Insulin enhances glucose transport activity through the coordinated translocation and fusion of glucose transporter type 4 (GLUT4) storage vesicles (GSVs) with the plasma membrane. Akt, when activated by insulin signaling, inactivates AS160 (TBC1D4), which controls vesicle trafficking by regulating small Rab GTPase protein switches. Additionally, insulin regulates glycogen phosphorylase activity by dephosphorylating phosphorylase kinase.[8,9]

In the liver, insulin activates IRTK, leading to the phosphorylation of IRS1 and IRS2 and subsequent activation of Akt2. This activation decreases HGP, promotes glycogen synthesis, and activates lipogenesis. The primary role of hepatic insulin signaling is to reduce HGP by inhibiting gluconeogenesis through Akt-mediated phosphorylation of forkhead box O1 (FOXO1). This phosphorylation excludes FOXO1 from the nucleus, preventing the transcriptional activation of gluconeogenic genes, such as glucose-6-phosphatase (*G6PC*) and phosphoenolpyruvate carboxykinase (*PEPCK*).[10,11] In addition to suppressing gluconeogenesis, insulin inhibits adipocyte lipolysis, reducing gluconeogenesis substrates in the liver.[12] Furthermore, insulin increases hepatic glycogen synthesis by regulating glycogen synthase (particularly GYS2 in the liver) and glycogen phosphorylase through glycogen synthase kinase 3 (GSK3) and PP1, similar to its actions in skeletal muscle.[13]

In AT, the primary physiological function of insulin is to inhibit lipolysis, thereby suppressing HGP by reducing gluconeogenic substrates **(Fig. 2)**. The

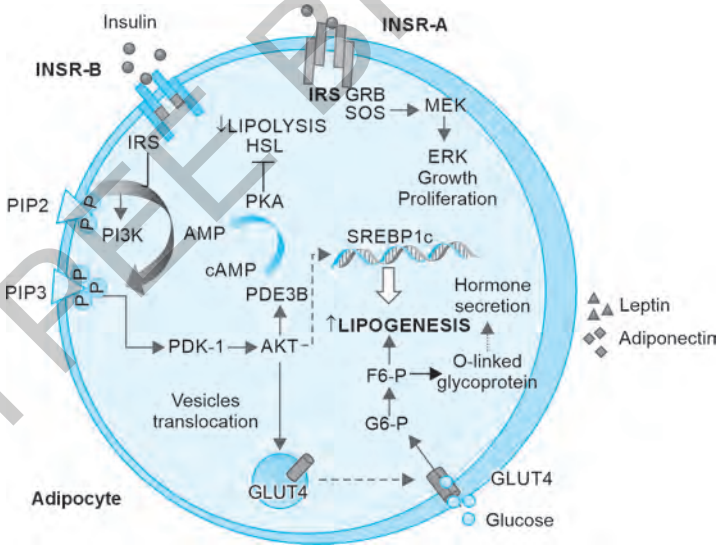


FIG. 2: Insulin action in adipocytes.

(AKT: protein kinase B; AMP: adenosine monophosphate; cAMP: cyclic adenosine monophosphate; ERK: extracellular signal-regulated kinase; F6-P: fructose 6-phosphate; GLUT4: glucose transporter type 4; GRB: growth factor receptor-bound protein; G6-P: glucose 6-phosphate; HSL: hormone-sensitive lipase; INSR-A: insulin receptor isoform A; INSR-B: insulin receptor isoform B; IRS: insulin receptor substrate; MEK: mitogen-activated protein kinase; PDE3B: phosphodiesterase 3B; PDK-1: phosphoinositide-dependent kinase 1; PIP2: phosphatidylinositol 4,5-bisphosphate; PIP3: phosphatidylinositol 3,4,5-triphosphate; PI3K: phosphatidylinositol 3-kinase; PKA: protein kinase A; SOS: son of sevenless protein; SREBP1c: sterol regulatory element-binding protein 1)

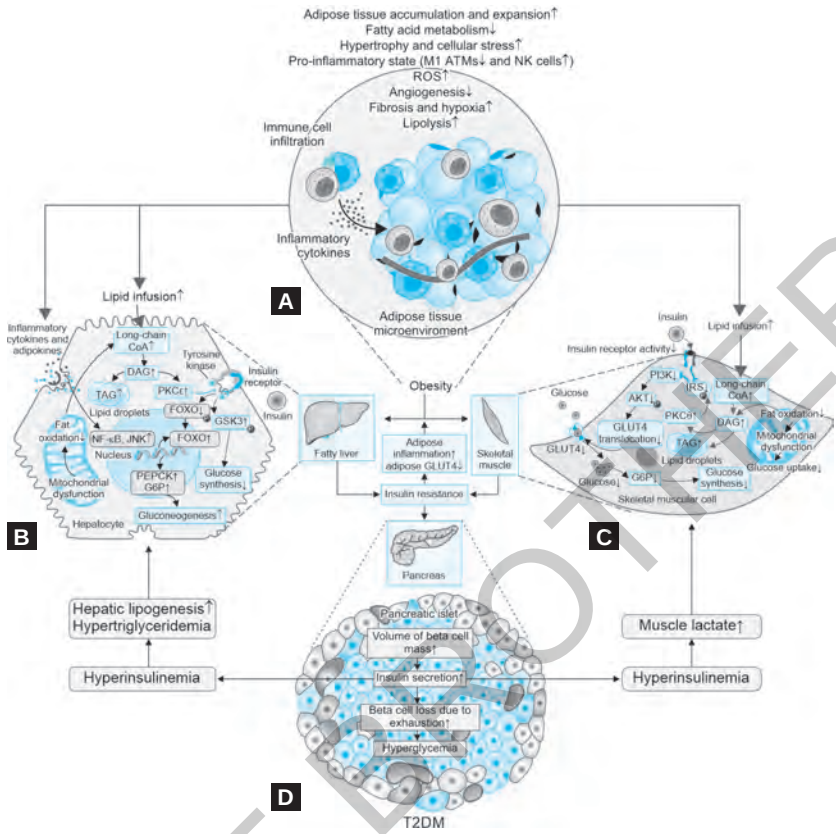
Source: With permission from Cignarelli et al. (2019).[14]

precise mechanism underlying insulin-induced lipolysis suppression is not yet fully elucidated, but it is thought to involve phosphodiesterase 3B (PDE3B) and decreased activity of cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA). Additionally, PP1 and PP2A are believed to mediate the PI3K-dependent insulin-induced suppression of lipolysis through dephosphorylation of lipolytic regulatory proteins.[23,24] While insulin promotes glucose transport by facilitating the phosphorylation of targets involved in vesicle tethering, docking, and fusion, its overall contribution to whole-body glucose disposal is relatively minor. Insulin also plays a role in promoting lipogenesis in white adipose tissue (WAT). It activates the transcription factor called sterol regulatory element-binding protein-1c (SREBP-1c), which leads to the translocation of glucose or fatty acid transport proteins (FATPs), promoting the uptake and esterification of fatty acids. Moreover, insulin stimulates adipogenesis, the process of generating new adipocytes, through the activation of the transcription factor peroxisome proliferator-activated receptor-γ (PPARγ).[14-16]

Obesity and Insulin Resistance

There is a strong association between obesity and insulin resistance, which is characterized by reduced responsiveness to insulin's effects. Obesity encompasses both subcutaneous and visceral adiposity, and the measurement commonly used to assess adiposity is BMI. In obese individuals, increased AT is closely related to elevated insulin levels and insulin resistance. It is proposed that greater lipolytic activity in the abdominal AT of individuals with increased abdominal adiposity leads to higher levels of circulating free fatty acids (FFAs).[17,18] Consequently, the liver increases triglyceride synthesis and becomes less efficient at breaking down insulin, resulting in hyperinsulinemia. Insulin resistance in obesity is also characterized by decreased binding of insulin, which contributes to the development of the condition.[19,20] Despite elevated insulin levels, obese individuals with insulin resistance exhibit hyperinsulinemia during fasting and in response to a glucose stimulus. However, they are unable to fully compensate for insulin resistance in peripheral tissues. Consequently, impaired glucose uptake and inadequate suppression of HGP occur.[21] Both hyperinsulinemia and insulin resistance are strongly associated with glucose intolerance and other metabolic abnormalities. Obesity plays a significant role in worsening the development of T2DM by promoting insulin resistance. Various studies with limited understanding have highlighted the connection between mitochondrial dysfunction, inflammation, hyperinsulinemia, and lipotoxicity in relation to insulin resistance **(Figs. 3A to D)**.[18] Additionally, factors such as endoplasmic reticulum (ER) stress, oxidative stress, genetic background, aging, hypoxia, and lipodystrophy have been implicated in the pathogenesis of T2DM by inducing insulin resistance.

Insulin resistance is characterized by the reduced responsiveness of certain tissues to normal insulin levels, necessitating higher insulin levels to maintain proper insulin function. In insulin-resistant tissues, the beneficial effects of insulin on glucose regulation, such as the inhibition of HGP, suppression of lipolysis, uptake of glucose into cells, and glycogen synthesis, are impaired even with normal levels of insulin in the bloodstream.[15] The balance between insulin and glucagon is crucial in the regulation of various metabolic pathways, as it determines the extent



FIGS. 3A TO D: Obesity-induced insulin resistance contributes to a cascade of metabolic dysregulation. (A) In obesity, the abnormal accumulation and expansion of adipose tissue create a microenvironment characterized by impaired fatty acid metabolism, cellular stress, and inflammation. This leads to increased lipolysis, oxidative stress, and hypoxia due to fibrosis and inadequate blood vessel growth. (B) Within the liver, the excessive influx of fatty acids resulting from enhanced lipolysis in adipose tissue causes a temporary rise in diacylglycerol (DAG) levels. This occurs when DAG synthesis surpasses the capacity of mitochondrial long-chain CoA oxidation due to mitochondrial dysfunction. The elevated DAG is converted into triglycerides (TAG) and stored as lipid droplets. Additionally, DAG activates protein kinase C epsilon (PKCε), impairing insulin receptor signaling and reducing insulin-stimulated glycogen synthesis. It also inhibits glycogen synthase activity and promotes hepatic gluconeogenesis, further contributing to increased glucose production. (C) In skeletal muscle, increased lipid accumulation and reduced fat oxidation, attributed to mitochondrial dysfunction, lead to elevated intracellular long-chain CoA and DAG levels. Similar to the liver, DAG activates protein kinase C theta (PKCθ), which impairs insulin signaling and decreases glucose uptake and glycogen synthesis. These effects hinder the proper transport and utilization of glucose by skeletal muscle. (D) While obesity-induced insulin resistance exacerbates inflammation and impairs glucose transport in adipose tissue, the pancreatic beta cell mass expands to meet the increased demand for insulin secretion. However, the sustained elevation in insulin levels leads to hyperinsulinemia, which further exacerbates lipid accumulation in both the liver and systemic circulation. Hyperinsulinemia also stimulates lactate production in muscles, which is released into the bloodstream and used as a substrate for hepatic lipogenesis. Ultimately, the pancreatic beta cells become overwhelmed, leading to their dysfunction and insufficient insulin secretion, resulting in hyperglycemia.

[AKT: protein kinase B; ATM: adipose tissue macrophage; CoA: acetyl coenzyme A; FOXO: forkhead box subgroup O; G6P: glucose 6-phosphate; GLUT4: glucose transporter type 4; GSK3: glycogen synthase kinase 3; IRS-1: insulin receptor substrate 1; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor kappa B; NK: natural killer (cell); P: phosphorylation; PEPCK: phosphoenolpyruvate carboxykinase; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species]

Source: With permission from Ruze et al. (2023).[5]

of phosphorylation of downstream enzymes involved in signaling pathways. While catecholamines promote lipolysis and glycogenolysis, glucocorticoids stimulate muscle breakdown, gluconeogenesis, and lipolysis. Therefore, excessive secretion of these hormones can contribute to the development of insulin resistance.[22] Insulin resistance or insulin-deficient conditions can be broadly classified into three categories: (1) reduced insulin secretion by pancreatic beta cells, (2) presence of insulin antagonists in the bloodstream, which can be counterregulatory hormones or nonhormonal factors that impair insulin receptors (IRs) or signaling, and (3) impaired insulin responsiveness in target tissues.[23] Among these categories, three key extrapancreatic organs—skeletal muscle, AT, and liver—play significant roles in the aforementioned processes and are highly sensitive to insulin. Defects in insulin action within these tissues often precede systemic insulin resistance and progressively contribute to the development of T2DM.

Insulin resistance in skeletal muscle significantly impacts whole-body metabolism as it is the primary site for insulin-stimulated glucose uptake.[24] Molecular studies have revealed that impaired translocation of GLUT4, a glucose transporter, to the plasma membrane is a key factor in insulin resistance affecting muscle glucose uptake. However, in individuals with T2DM, the translocation of GLUT4 and glucose transport can be stimulated by hypoxia or exercise through AMP-activated protein kinase (AMPK)-mediated regulation of GSV translocation. This suggests that abnormalities in the insulin signaling pathway, rather than the transport system itself, contribute to glucose transport defects in insulin resistance. Moreover, insulin resistance in skeletal muscle can result from defects at the proximal level of insulin signaling, such as impaired activities of IRTK, IRS1, PI3K, and Akt **(Fig. 3C)**.[5,15] Studies have shown reduced IRS1 tyrosine phosphorylation and diminished IRS1-associated PI3K activity in insulin-resistant skeletal muscle.[15]

Adipose tissue, a metabolically active tissue, plays a crucial role in regulating metabolic homeostasis at a systemic level. It participates in various biological processes including immunity, coagulation, angiogenesis, fibrinolysis, reproduction, vascular tone control, appetite regulation, body weight homeostasis, and glucose and lipid metabolism.[25,26] Impaired response to insulin stimulation in AT, known as adipose insulin resistance, leads to impaired suppression of lipolysis, reduced glucose uptake, and increased release of FFAs into the bloodstream, even in the presence of high insulin levels.[5,15] Among the signaling elements affected by adipose-insulin resistance, defective activation of Akt hinders GLUT4 translocation to the membrane and enhances the activity of lipolytic enzymes, further exacerbating hyperglycemia.[27] Adipose–insulin resistance is associated with glucose intolerance and elevated release of FFAs into the bloodstream, which can accumulate in other tissues like muscle or liver. In the case of the liver, increased FFA accumulation impairs insulin signaling, promotes hepatic gluconeogenesis, and disrupts the glucose-stimulated insulin response, ultimately contributing to the development of T2DM.[5,15] **Figure 3A** illustrates the effects of insulin stimulation on hypertrophic AT.

The liver plays a critical role in regulating postprandial carbohydrate levels by suppressing HGP and promoting the storage of glucose as glycogen. During fasting, the liver is the primary source of glucose production.[28] In patients with T2DM, insulin fails to regulate hepatic glycogen synthesis or glucose production, resulting

in increased hepatic gluconeogenesis and fasting hyperglycemia.[29] Defective suppression of hepatic gluconeogenesis in insulin resistance is primarily associated with abnormalities in AT lipolysis and the derepression of the FOXO1 transcription factor in the liver **(Fig. 3B)**. Additionally, insulin resistance is linked to impaired insulin-induced stimulation of glycogen synthesis, as evidenced by lower fasting and postprandial hepatic glycogen content in T2DM patients.[28,30]

ROLE OF ADIPOSE TISSUE AND INFLAMMATION

Molecular Pathways Linking Obesity-induced Inflammation and Insulin Resistance

Systemic inflammation is characterized by elevated levels of inflammatory mediators in the bloodstream and the infiltration of immune cells into insulin-dependent tissues. The initiation of low-grade systemic inflammation primarily occurs in WAT, as discussed earlier in this chapter. In obesity, the accumulation of lipids in AT triggers an inflammatory response, leading to increased secretion of various inflammatory cytokines. These molecules can activate signaling pathways, such as c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB), in the liver and skeletal muscle, thereby inhibiting systemic insulin signaling. The inflammatory cascade initiated by obesity-induced inflammation originates in WAT and spreads to other tissues, causing low-grade systemic inflammation. Both the liver and skeletal muscle exhibit signs of local inflammation in the context of obesity **(Fig. 4)**.[31]

Studies in animals and humans have identified WAT as the main site where chronic inflammation associated with obesity is initiated and aggravated. Remodeling of AT during obesity generates numerous intrinsic and extrinsic signals capable of triggering an inflammatory response. Activation of the JNK and NF-κB signaling pathways enhances the production of pro-inflammatory cytokines, endothelial adhesion molecules, and chemotactic mediators, leading to the infiltration of monocytes into AT and their differentiation into pro-inflammatory M1 macrophages. These infiltrating macrophages secrete various inflammatory mediators that contribute to local and systemic pro-inflammatory conditions and impair insulin signaling **(Flowchart 1)**.[15,32,33]

The effects of these cytokines are mediated through the stimulation of inhibitor of κB (IκB) kinase beta (IKKβ) and *JNK1*, which are expressed in myeloid and insulin-targeted cells.[34-36] JNK has been extensively studied as a signal transducer in models of insulin resistance associated with obesity. It becomes activated in response to various inflammatory stimuli, including cytokines, FFAs, and activation of cellular pathways such as the unfolded protein response (UPR). Once activated, JNK initiates the transcription of pro-inflammatory genes and inhibits the insulin signaling pathway by serine–threonine phosphorylation of IRS-1, thereby reducing PI3K/PKB signaling.[34] Obesity is also linked to the activation of the NF-κB inflammatory pathway. Under normal physiological conditions, NF-κB proteins are retained in the cytoplasm of myeloid and insulin-targeted cells by a family of inhibitors known as inhibitors of κB. Activation of the IKK kinase complex (composed of IKKα and IKKβ subunits) leads to the degradation of IκBα

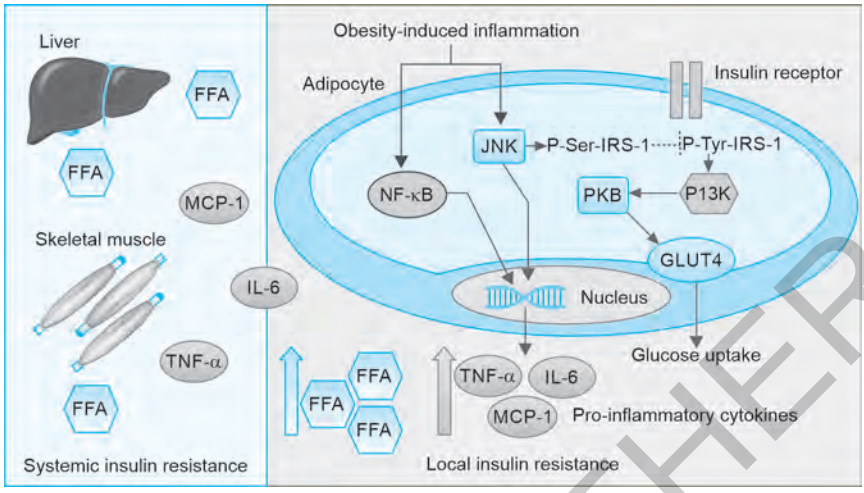


FIG. 4: Pathways linking local obesity-induced inflammation to systemic insulin resistance. The pathways connecting local obesity-induced inflammation to systemic insulin resistance involve the activation of inflammatory signaling pathways mediated by JNK and nuclear factor kappa B (NF-κB). In obesity, these pathways are triggered, leading to the production of pro-inflammatory cytokines in adipocytes, which contribute to insulin resistance and the infiltration of pro-inflammatory macrophages. The activation of the JNK signaling pathway initiates the transcription of pro-inflammatory genes and hinders the insulin signaling pathway by inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby reducing the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling pathway. On the other hand, activation of the NF-κB signaling pathway results in the increased expression of several target genes, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemotactic protein-1 (MCP-1), which leads to serine phosphorylation of IRS-1, ultimately impairing insulin signaling. These inflammatory mediators, such as free fatty acids (FFA), IL-6, TNF-α, and MCP-1, also circulate systemically and activate JNK and NF-κB signaling pathways in the liver and skeletal muscle, thereby inhibiting systemic insulin signaling.

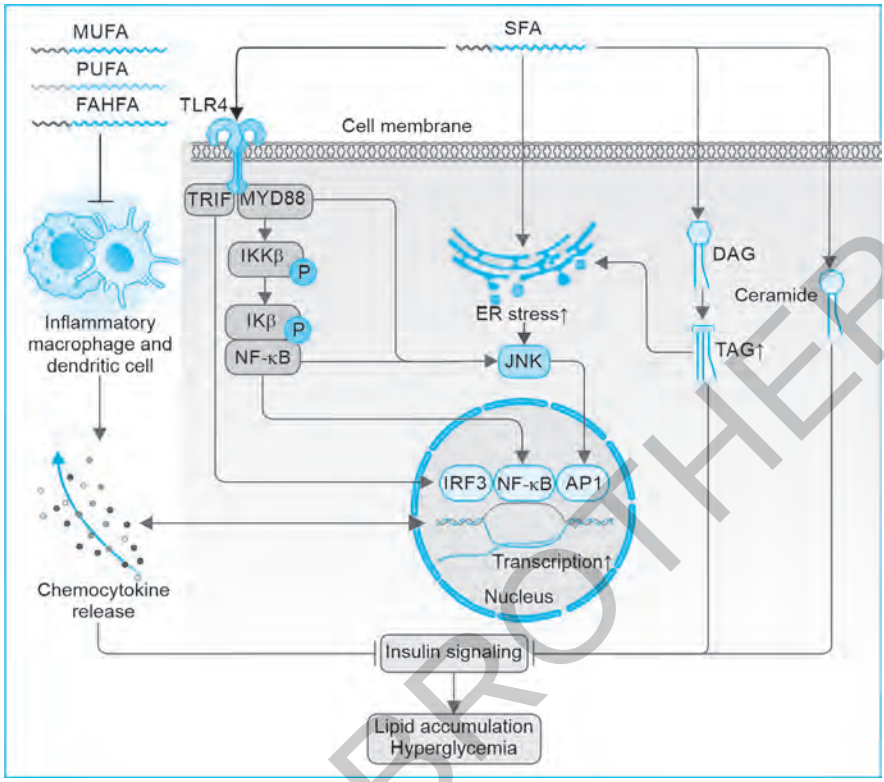
(JNK: c-Jun N-terminal kinase; GLUT4: glucose transporter type 4; P-Tyr: tyrosine phosphorylation)

Source: With permission from Zatterale et al. (2020).[31]

via the proteasome, resulting in the nuclear translocation of NF-κB. This leads to increased expression of several NF-κB target genes, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), transforming growth factor beta (TGF-β), monocyte chemotactic protein 1 (MCP-1), and IL-1β, which further exacerbate the progression of insulin resistance.[35] Macrophages play a significant role in mediating obesity-induced inflammation in AT. During obesity, macrophages infiltrate AT and secrete numerous pro-inflammatory cytokines. These mediators exert local effects on adipocytes and resident immune cells (such as neutrophils, B cells, and T cells) and circulate in the bloodstream, affecting insulin sensitivity in the liver and skeletal muscle.[36]

Obesity Induced at Inflammation Triggers

The precise mechanisms underlying obesity-induced inflammation in AT remain partially understood. However, several potential mechanisms have been identified,



FLOWCHART 1: The mechanisms by which fatty acids affect insulin signaling and contribute to hyperglycemia. Contrary to the anti-inflammatory and insulin-sensitizing effects of PUFAs, MUFAs, and FAHFAs, SFAs hinder insulin sensitivity by promoting pro-inflammatory signaling through TLR4 and its adaptor proteins, such as TRIF and MYD88. This activation of TLR4 and its adaptors enhances the activity of pro-inflammatory pathways and transcription factors like IRF3, NF-κB, and AP1, resulting in increased expression of chemocytokines. Conversely, these pro-inflammatory chemocytokines can activate the same pro-inflammatory transcription factors, establishing a positive feedback loop that perpetuates an inflammatory environment detrimental to insulin signaling. Additionally, the accumulation of TAG, ceramides, and the induction of ER stress, triggered by activated NF-κB signaling and the inflammatory cascade, further exacerbate insulin resistance and contribute to the progression of hyperglycemia.

(AP1: activator protein 1; DAG: diacylglycerol; ER: endoplasmic reticulum; FAHFA: branched fatty acid esters of hydroxy fatty acid; IKKβ: inhibitor of NF-κB kinase subunit beta; Iκβ: inhibitor of NF-κB subunit beta; IRF3: interferon regulatory factor 3; JNK: c-Jun N-terminal kinase; MUFA: monounsaturated fatty acid; MYD88: myeloid differentiation primary response protein 88; NF-κB: nuclear factor kappa B; P: phosphorylation; PUFA: polyunsaturated fatty acid; SFA: saturated fatty acid; TAG: triglyceride; TLR4: toll-like receptor 4; TRIF: TIR-domain-containing adaptor-inducing interferon beta)

Source: With permission from Ruze et al. (2023).[5]

including dysregulation of fatty acid homeostasis, increased adipose cell size and death, local hypoxia, mitochondrial dysfunction, ER stress, and mechanical stress as depicted in **Figure 5**.[15,31] These mechanisms are considered crucial in establishing the connection between chronic caloric excess and inflammation in AT, and they may also contribute to the persistence of chronic tissue inflammation.[33]

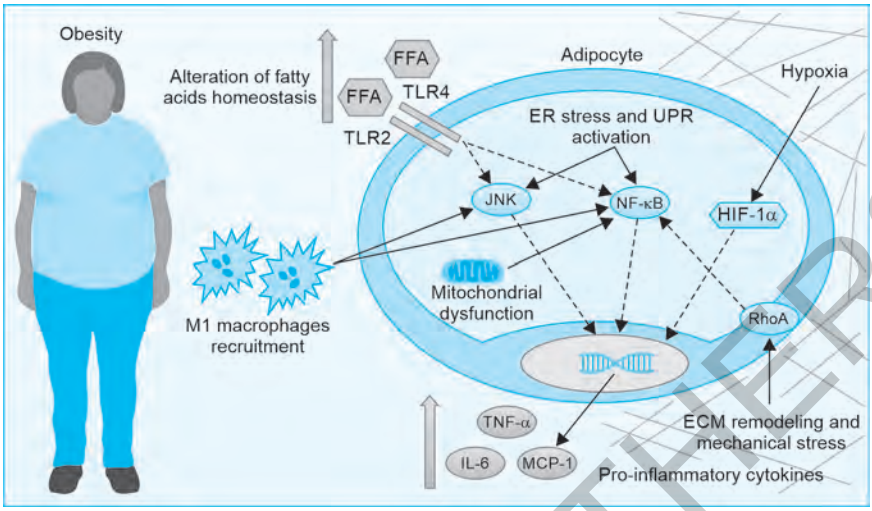


FIG. 5: Obesity triggers inflammation. Obesity gives rise to various intrinsic and extrinsic signals that can initiate an inflammatory response in adipose tissue (AT). These mechanisms serve as the link between prolonged caloric excess and inflammation in AT. Dysregulation of fatty acid homeostasis, increased adipose cell size and death, local hypoxia, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and mechanical stress are some of the mechanisms involved. These triggers converge on the activation of key signaling pathways, namely the c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB) pathways, which are considered central hubs for signaling. Activation of these pathways leads to heightened production of pro-inflammatory cytokines and facilitates the infiltration of pro-inflammatory M1 macrophages.

(ECM: extracellular matrix; FFA: free fatty acids; HIF-1α: hypoxia-inducible factor-1 alpha; MCP-1: monocyte chemotactic protein-1; IL-6: interleukin-6; RhoA: ras homolog gene family, member A; TLR2: toll-like receptor 2; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor alpha; UPR: unfolded protein response)

Source: With permission from Zatterale et al. (2020).[31]

Role of Adaptive and Innate Immunity in Obesity and Type 2 Diabetes Mellitus

In the current understanding, the development of insulin resistance in T2DM is intricately linked to both innate and adaptive immune factors. Epigenetic mechanisms governing the determination, function, and migration of immune cells have emerged as key players in the context of obesity and T2DM. The presence of obesity is associated with a state of chronic low-grade inflammation, triggering activation of the immune system in individuals affected by T2DM. The excessive accumulation of AT in obesity disrupts metabolic homeostasis and sets the stage for dysregulation. Notably, AT inflammation has emerged as a pivotal factor closely intertwined with the development of insulin resistance in the context of obesity. This inflammatory milieu within AT instigates abnormal activation and proliferation of both innate and adaptive immune components, further contributing to the pathogenesis of T2DM.[37-39] For instance, impaired function of natural killer (NK) cells, characterized by reduced expression of the NKG2D receptor, has been

observed, displaying a negative correlation with glycated hemoglobin (HbA1c) levels.[40]

Additionally, there is a pronounced upregulation of pro-inflammatory M1 macrophage polarization and heightened activation of $CD4^+$ T lymphocytes within the visceral AT. These immune alterations signify the intricate interplay between immune dysregulation, AT inflammation, and the development of insulin resistance in T2DM.[31] Role of different immune cells activated after innate and adaptive immunity in AT and further associated with insulin resistance **(Fig. 6 and Box 1)**.[41,42]

Obesity triggers the accumulation of various innate and adaptive immune cell types within AT. Macrophages, constituting a substantial proportion of AT cells in obesity, are considered the primary source of pro-inflammatory cytokines, which contribute to insulin resistance. In obesity, the recruitment of M1-polarized macrophages is prominent, leading to the secretion of pro-inflammatory cytokines like TNF-α and IL-1β. This inflammatory milieu within AT is characterized by an overall increase in macrophage numbers and an elevated ratio of M1 to M2 (anti-inflammatory) macrophages, which coincides with obesity and is associated with the development of insulin resistance.[43,44]

Apart from adipose tissue macrophages (ATMs), other innate immune cell types contribute to the initiation and/or progression of AT inflammation in obesity. Neutrophils, a subset of leukocytes and granulocytes involved in innate immunity, play a role in AT inflammation by producing TNF-α and MCP-1. Moreover, neutrophils release elastase, which impairs glucose uptake in AT and promotes insulin resistance by degrading IRS-1.

Dendritic cells, specialized antigen-presenting cells bridging innate and adaptive immunity, accumulate in AT during high-fat diet feeding and in subcutaneous AT of obese individuals. These cells likely contribute to the pro-inflammatory environment by promoting macrophage recruitment and producing IL-6 which leads to insulin resistance.[44,45]

Mast cells, innate immune cells derived from hematopoietic stem cells, are present in AT and increase in number in both obesity and type 2 diabetes. Mast cells promote low-grade inflammation within AT and mediate macrophage infiltration. Notably, IL-6 and IFN-γ regulate mast cell function, and their dysregulation may contribute to obesity and diabetes. Immature mast cells infiltrating AT during the nonobese stage progress to a mature state and further promote obesity and diabetes progression.[44]

B cells, crucial components of adaptive immunity that produce antibodies, accumulate in AT and potentially contribute to AT inflammation by releasing pro-inflammatory cytokines and immunoglobulin G antibodies. The accumulation of B cells precedes that of T cells during the development of obesity.[46,47]

T cells can be classified into $CD4^+$ and $CD8^+$ subtypes based on surface markers. Obesity is associated with an increase in $CD8^+$ T cells within AT, which promote macrophage differentiation and chemotaxis. $CD4^+$ T cells, recognizing major histocompatibility complex class II on antigen-presenting cells, can be further classified into pro-inflammatory T helper 1 (Th1) and Th17 cells, anti-inflammatory Th2 cells, and regulatory T cells (Tregs). In obesity, the number of $CD3^+$ $CD4^+$ Th1

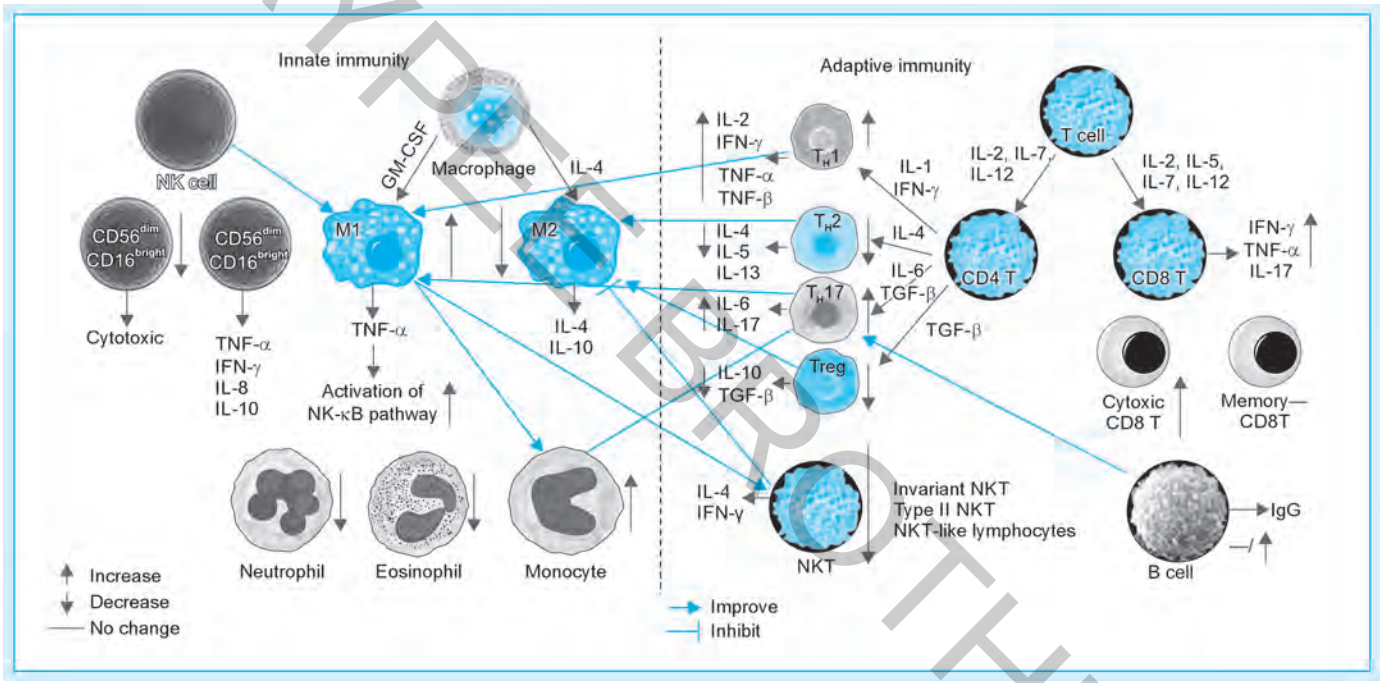


FIG. 6: Change in immune cells during innate and adaptive immunity in the condition of type 2 diabetes mellitus, obesity, or adipose tissue.

(GM-CSF: granulocyte–macrophage colony-stimulating factor; IFN-γ: interferon gamma; IgG: immunoglobulin G; IL-2: interleukin 2; NF-κB: nuclear factor kappa B; NKT: natural killer T; TNF-α: tumor necrosis factor alpha)

Source: With permission from Zhou et al. (2018).[41]

BOX 1: Role of immune cells during innate and adaptive immunity in adipose tissue associated with insulin resistance.

Macrophages:

- Adipocyte death influences macrophage localization and function in adipose tissue and polarization from M2 to M1
- Pro-inflammatory macrophages in adipose tissue are associated with insulin resistance
- Cells cluster around necrotic adipose cells in CLSs

T cells:

- Inflammatory T cell profile in adipose tissue is associated with insulin resistance
- Th2 frequency in visceral adipose tissue inversely correlates with insulin resistance
- Treg frequency in visceral adipose tissue decreases in obese compared to lean mice
- Foxp3 expression increases in obese versus lean humans
- $CD8^+$ T cell frequency increases in visceral adipose tissue compared to subcutaneous adipose tissue

B cells:

- Obesity leads to enhanced infiltration of B cells in visceral adipose tissue
- B cells undergo class switching to IgG^+ in the context of obesity and insulin resistance
- Peripheral B cells in type 2 diabetes mellitus exhibit a pro-inflammatory phenotype
- B cell antigen presentation can promote insulin resistance

Effects of immune intervention:

- Targeted disruption of IKKβ and JNK prevents HFD-induced insulin resistance
- Transfer of IgG from obese diet-induced obese mice to young mice newly on high-fat/caloric diet accelerates onset of inflammation and insulin resistance
- B cell depletion via administration of anti-CD20 antibody results in reduced TNF-α-producing M1 cells in visceral adipose tissue and decreased insulin resistance
- Anti-CD3 antibody therapy results in reversal of insulin resistance

(CLSs: crown-like structures; IgG^+: immunoglobulin G; IKKβ: inhibitor of nuclear factor kappa B kinase subunit beta; JNK: c-Jun N-terminal kinase; Th2: T helper 2; Tregs: regulatory T cells)

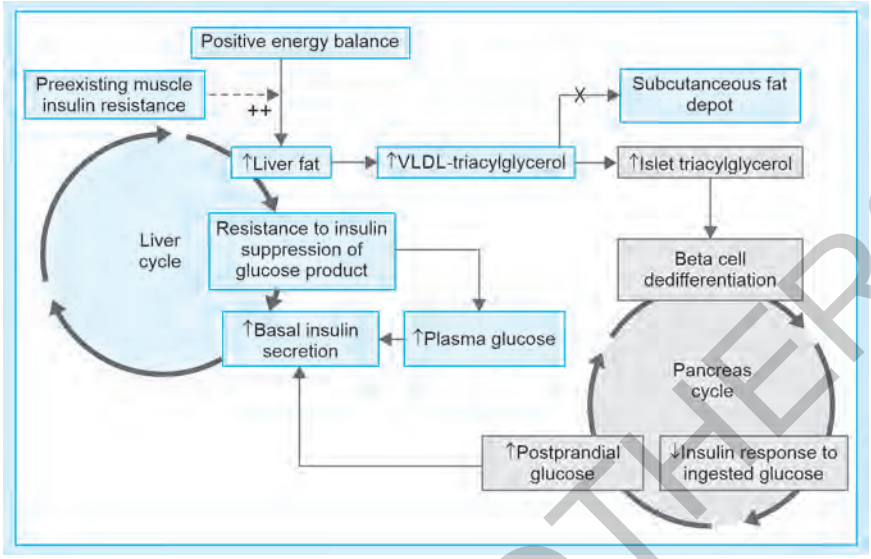
Source: With permission from McLaughlin et al. (2017).[42]

cells increases and contributes to AT inflammation through IFN-γ secretion, while the number of $CD3^+$ $CD4^+$ Th2 cells decreases. Additionally, the reduction of AT Treg cells during obesity further exacerbates AT inflammation.[31,47]

METABOLIC DYSREGULATION AND HORMONAL IMBALANCES

Metabolic Dysregulation

The 2008 twin cycle hypothesis has explained that when an individual consistently consumes more energy than they expend daily, any excess carbohydrates must be converted to fat in the liver for storage of metabolic energy **(Flowchart 2)**.[48] This process is influenced by endogenous insulin levels, and individuals with insulin resistance tend to accumulate liver fat more easily due to higher plasma insulin levels. If the subcutaneous AT reaches its storage capacity, newly synthesized fat, along with excess dietary fat, accumulates in the liver. This accumulation inhibits the liver's response to insulin, resulting in increased glucose production



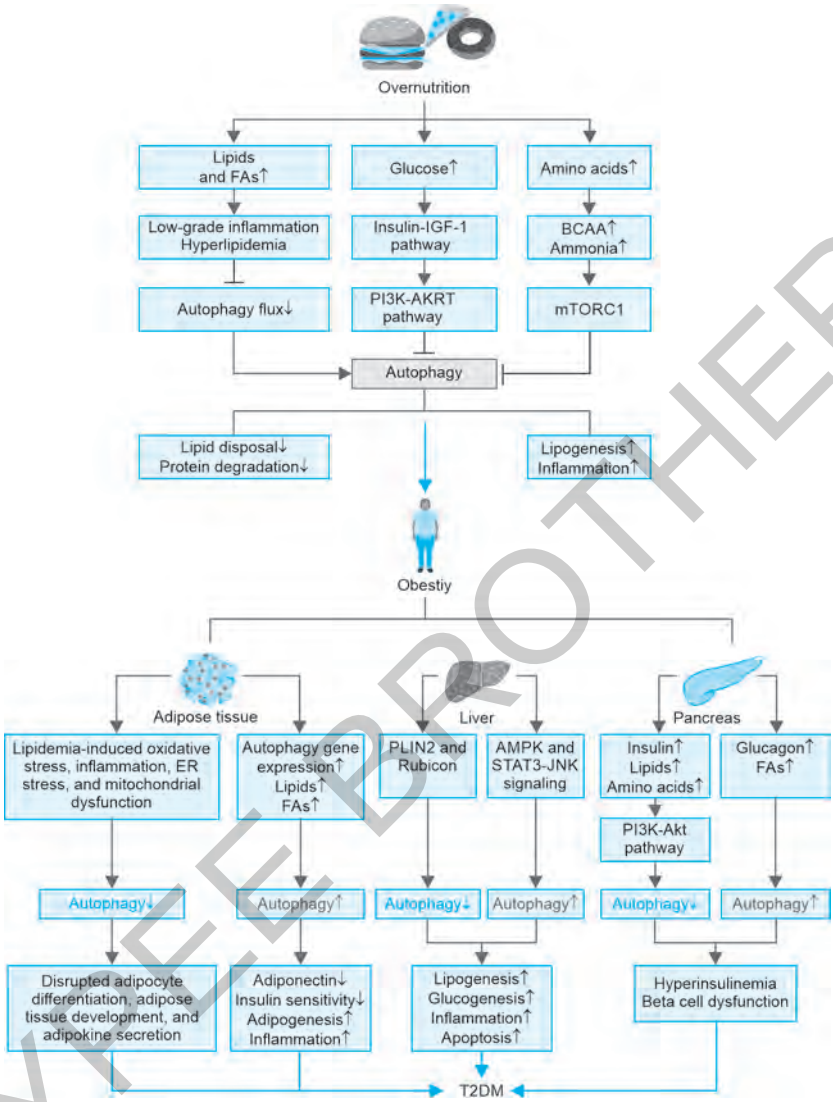
FLOWCHART 2: The 2008 twin cycle hypothesis.

(VLDL: very low-density lipoprotein)

Source: With permission from Taylor R, Barnes AC. Translating aetiological insight into sustainable management of type 2 diabetes. Diabetologia. 2018;61(2):273-83.

and establishing a vicious cycle of hyperinsulinemia and elevated glucose production. Excessive fat in the liver leads to increased export of fat in the form of very low-density lipoprotein (VLDL) triacylglycerol[49] (in **Flowchart 3**, the cyan color indicates the loss of insulin's suppression of liver glucose production). When the storage capacity of subcutaneous fat is exceeded (reaching the personal fat threshold), fat delivery to all tissues, including the pancreatic islets, increases significantly.[50] Postprandial hyperglycemia triggers increased and prolonged insulin secretion, further promoting de novo lipogenesis. This creates a second vicious cycle that enhances de novo lipogenesis and fat delivery to the pancreas. Over many years, the excess fat in the pancreas leads to the loss of specialized function and dedifferentiation of beta cells.[51] Eventually, the inhibitory effects of fatty acids and glucose on the islets reach a critical threshold, resulting in the relatively sudden onset of clinical diabetes. The twin cycle hypothesis suggests that both vicious cycles can be reversed by inducing negative energy balance.

Autophagy: Obesity is associated with various abnormalities in the microenvironment that impair insulin sensitivity. Factors such as lipid accumulation, oxidative stress, inflammation, ER stress, and mitochondrial dysfunction not only affect insulin sensitivity but also have negative consequences for autophagy. Autophagy, the cellular process of self-degradation and recycling, is suppressed in the context of overnutrition. This suppression, coupled with the downregulated secretion of glucagon during nutrient excess, leads to hyperinsulinemia, further inhibiting autophagy. As a result, compromised autophagy compromises insulin signaling, contributing to the development of T2DM **(Flowchart 3)**.[5,52-54] Maintaining metabolic homeostasis relies on the protective role of autophagy in pancreatic beta



FLOWCHART 3: During the transition from overnutrition and obesity to T2DM, alterations in autophagy occur in various metabolic organs. The excessive intake of nutrients, including lipids, glucose, and amino acids, leads to the suppression of autophagy through different signaling pathways. This suppression of autophagy contributes to the development of obesity by increasing lipid and protein accumulation, promoting low-grade systemic inflammation, and exacerbating insulin signaling dysfunction. In obesity, changes in autophagy can differ among various metabolic sites. In adipose tissue, elevated levels of lipids and FAs and upregulated autophagy genes can enhance autophagy. However, cellular stress can have the opposite effect and suppress autophagy. In the liver, autophagy can either be enhanced or blunted by different signaling pathways. These alterations in hepatic autophagy can contribute to increased lipogenesis, gluconeogenesis, inflammation, and apoptosis. Pancreatic autophagy is influenced by insulin as well as metabolites such as lipids, amino acids, glucagon, and FAs. These factors can have a dual impact on pancreatic autophagy, initially promoting hyperinsulinemia as a protective mechanism against hyperglycemia. However, over time, this dysregulation of pancreatic autophagy contributes to the development of insulin resistance and

Continued

Continued

dysfunction of beta cells, ultimately favoring the onset of T2DM. In obesity, elevated levels of FFAs and glucagon can also enhance pancreatic autophagy. Collectively, these disruptions in autophagy in different metabolic organs contribute to the abnormal accumulation of protein aggregates, lipids, and other detrimental components within the cellular microenvironment. This accumulation fuels cellular stress, leading to insulin resistance and the subsequent transition from obesity to T2DM.

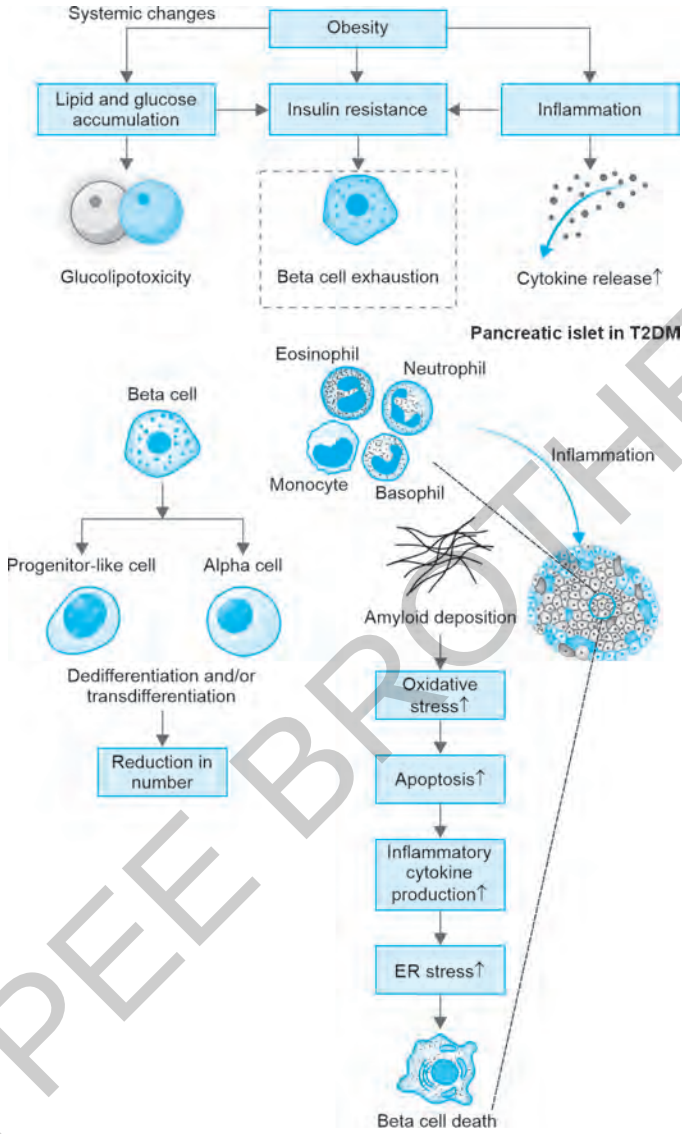
[AMPK: AMP-activated protein kinase; Akt: protein kinase B; BCAA: branched-chain amino acid; DM: diabetes mellitus; ER: endoplasmic reticulum; FAs: fatty acids; FFAs: free fatty acids; IGF-1: insulin-like growth factor 1; JNK: c-Jun N-terminal kinase; mTORC1: mechanistic target of rapamycin (mTOR) complex 1; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; PI3K: phosphatidylinositol 3-kinase; PLIN2: perilipin 2; STAT3: signal transducer and activator of transcription 3; T2DM: type 2 diabetes mellitus]

Source: With permission from Ruze et al. (2023).[5]

cells. However, excessive autophagy, particularly under cellular stress, can lead to beta cell loss and worsen the onset of T2DM. Autophagy also plays a significant role in insulin-sensitive tissues such as AT, skeletal muscles, pancreas, liver, and the brain. The ectopic expansion of AT in these locations disrupts autophagy, leading to the accumulation of dysfunctional organelles, tissue-specific insulin resistance, and impaired pancreatic function. Additionally, the reciprocal relationship between autophagy and pathophysiological changes during insulin resistance further disrupts the autophagic process. As autophagy dysfunction worsens, accompanied by increased accumulation of reactive oxygen species (ROS) and mitochondrial damage, insulin resistance becomes progressively aggravated, ultimately contributing to the development and progression of T2DM.[52,53]

During the slow progression of T2DM, beta cells undergo significant stress and apoptosis **(Flowchart 4)**.[5] Simultaneously, the islets of T2DM show a mild increase in the number of macrophages, and the reduction (~40%) in beta cell mass is attributed to various factors such as glucolipotoxicity and amyloid deposition, which induce apoptosis through oxidative and ER stress. The transition from obesity and insulin resistance to T2DM is initiated by beta cell dysfunction, impaired glucose-stimulated insulin secretion (GSIS), and loss of beta cell function, which occurs independently of cell loss in T2DM. This transition is facilitated by the gradual dedifferentiation of beta cells into endocrine progenitor-like cells or their transdifferentiation into other cell types.[55,56]

Overnutrition: Persistent exposure of pancreatic islets to excessive nutrients and sustained elevation of hormone synthesis and secretion contribute to ER stress, exerting detrimental effects on beta cell function and survival in the context of obesity. In order to compensate for insulin resistance in peripheral tissues, the demand for insulin synthesis is amplified, overwhelming the protein folding capacity of the ER due to the excessive influx of nutrients. This triggers the activation of UPR pathways, including PKR-like ER-associated kinase (PERK), resulting in the inhibition of protein translation and eventual insulin deficiency. Additionally, prolonged hyperglycemia and hyperlipidemia within the islets induce glucolipotoxicity, impairing insulin secretion and promoting beta cell apoptosis. ER stress not only disrupts normal insulin synthesis and secretion but also triggers protein degradation pathways and autophagy. The sustained ER stress ultimately leads to the dedifferentiation and apoptosis of beta cells, further exacerbating the dysfunction of the insulin-producing cells.[57-59]



FLOWCHART 4: Obesity contributes to the accelerated loss of beta cells in the pancreatic islets of individuals with type 2 diabetes mellitus (T2DM). The accumulation of lipids and glucose induces a condition known as glucolipotoxicity, which exacerbates insulin resistance and exhausts beta cells. This process is accompanied by enhanced low-grade inflammation due to the increased secretion of pro-inflammatory cytokines into the microenvironment. In the islets of individuals with T2DM, a microenvironment similar to that found in adipose tissue is established, characterized by inflammation. In this inflammatory milieu, the deposition of amyloid compounds worsens oxidative stress, leading to increased apoptosis of beta cells. Additionally, beta cells may undergo dedifferentiation, transforming into progenitor-like cells or even transdifferentiating into other cell types, such as alpha cells. These changes further compromise the beta cell population. Collectively, the constant proapoptotic and pro-inflammatory signals, coupled with the promotion of ER stress, contribute to the loss of beta cells. This process ultimately contributes to the progression of T2DM.

(ER: endoplasmic reticulum)

Source: With permission from Ruze et al. (2023).[5]

Obesity and high-fat feeding elicit similar effects to the prolonged incubation of islets with FFAs in terms of insulin secretion and distribution of calcium channels. These effects are associated with an elevated accumulation of fat within the islets and the surrounding exocrine pancreas. Furthermore, there exists a negative correlation between pancreatic fat content and GSIS in humans. As pancreatic fat decreases, glucose tolerance and insulin secretion improve concomitantly. This suggests that intrapancreatic or intra-islet fat deposits may serve as a local and persistent source of FFAs, exerting detrimental effects on beta cell function.[58,59]

The microbiome–gut–brain axis, regulated by various factors, plays a pivotal role in regulating overall metabolism, adiposity, energy balance as well as central appetite and food reward signaling in humans. When this axis becomes dysregulated, it becomes closely linked to several metabolic diseases, such as obesity and T2DM. A key factor in this dysregulation is microbiome dysfunction, which is primarily responsible for disrupting energy balance, promoting fat deposition, triggering inflammation, inducing insulin resistance, causing glucolipotoxicity, and disrupting endocrine signaling pathways. These effects can occur through direct interactions or indirect influences on the body's systems. The microbiome's impact on the microbiome–gut–brain axis and its subsequent influence on metabolic health highlights the critical role of microbiome homeostasis in maintaining overall well-being and preventing metabolic diseases.[60] **Figure 7** described the role of the microbiome–gut–brain axis dysfunction in obesity and T2DM.[5] The interaction between the gut microbiota, glucose metabolism, and the immune system involves a complex, three-way relationship. Firstly, the gut microbiota plays a role in influencing the host's glucose metabolism and hormone production by producing various metabolites. Elevated blood glucose levels can increase the permeability of the gut, allowing bacterial components to enter the bloodstream. This bacterial translocation triggers a (pro)inflammatory response from the immune system. Normally, the gut microbiota helps train the immune system through interactions with bacterial components and metabolites. Secondly, the immune system actively shapes and regulates the gut microbiota to maintain a symbiotic relationship between the host and the microbiota. It also works to maintain the integrity of the gut barrier, preventing bacterial translocation. When bacterial translocation occurs, inflammation can arise in various tissues, leading to functional impairments such as beta cell dysfunction, insulin resistance, and fatty liver disease. Lastly, glucose metabolism can stimulate a pro-inflammatory response from the immune system through the interplay of metabolic and inflammatory pathways, known as immunometabolism. In this way, all three factors (gut microbiota, glucose metabolism, and the immune system) interact with and influence each other, potentially contributing to the development of metabolic diseases. Overall, the intricate interplay between the gut microbiota, glucose metabolism, and the immune system demonstrates their interconnectedness and highlights their collective impact on metabolic health.[61] Overall, although the field of microbiota research is still in its early stages, the combination of technical advancements and the dedication of researchers worldwide provides a solid foundation for exploring the complexities of the microbiota and unlocking its vast potential to prevent or treat metabolic diseases like obesity and diabetes.

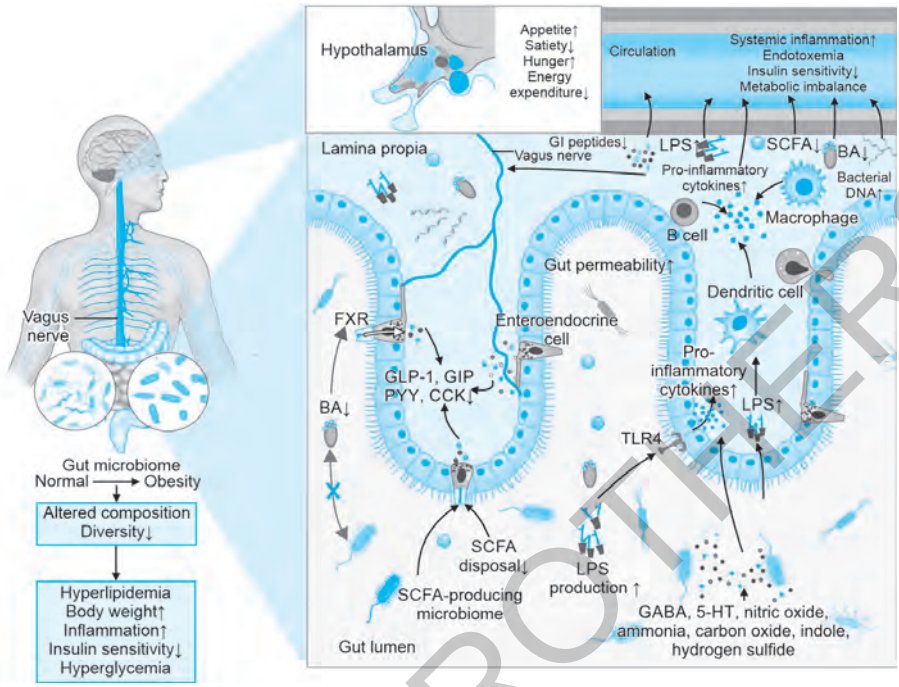


FIG. 7: Dysfunction of the microbiome–gut–brain axis plays a significant role in obesity and type 2 diabetes mellitus (T2DM). In obesity, there are notable changes in the composition and diversity of the gut microbiome. These alterations lead to various metabolic abnormalities and changes in microbial metabolites. For instance, there is a decrease in the production of beneficial compounds like BAs and SCFAs, while there is an increase in LPS levels. These changes compromise the protective function of the gut and contribute to increased gut permeability. Inflammatory stimuli such as nitric oxide, ammonia, carbon oxide, indole, and hydrogen sulfide contribute to this heightened permeability. As a result, there is a significant increase in the flux of LPS, which has multiple effects. LPS can activate TLR4 on enterocytes, leading to the secretion of inflammatory cytokines and the recruitment of inflammatory immune cells like dendritic cells, B cells, and macrophages. Moreover, these immune cells themselves produce inflammatory cytokines upon exposure to LPS. Simultaneously, the reduced production of SCFAs and BAs leads to decreased activation of GPCRs and FXR in enteroendocrine cells. These cells play a crucial role in producing GI hormones essential for energy homeostasis, such as GLP-1, GIP, PYY, and CCK. These hormones have both peripheral and central effects on regulating metabolism and appetite, either directly through the vagus nerve or indirectly via immunoneuroendocrine mechanisms. Centrally, the abnormal hormonal signals transmitted from the gut to the hypothalamus in the brain disrupt eating behavior and metabolic control. Peripherally, the influx of LPS, pro-inflammatory cytokines, and bacterial DNA, coupled with inadequate levels of SCFAs, BAs, and GI peptides in the circulation, further impairs insulin signaling and metabolic balance. These central and peripheral abnormalities in metabolic control ultimately contribute to the development of hyperglycemia in T2DM.

(5-HT: 5-hydroxytryptamine; BA: bile acid; CCK: cholecystokinin; FXR: farnesoid X receptor; GABA: gamma aminobutyric acid; GI: gastrointestinal; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1; GPCR: G-protein coupled receptor; LPS: lipopolysaccharide; PYY: peptide YY; SCFA: short-chain fatty acid; TLR4: toll-like receptor 4)

Source: With permission from Ruze et al. (2023).[5]

Nuclei in the Hypothalamus and Brain Stem Regulating Appetite and Energy Balance

More recently, research into the central nervous system's (CNS) metabolic role has opened doors to the discovery of potential drug targets in metabolic disorders such as T2DM and obesity. Moreover, obesity induces enduring alterations in the brain's cytoarchitecture and synaptic plasticity, particularly within the hypothalamus.[5-7] The hypothalamus and brain stem play pivotal roles in the homeostatic regulation of appetite and energy balance. These critical brain regions encompass distinct neuronal populations and nuclei, each with complementary and contrasting functions, exerting significant control over various aspects of energy balance, encompassing both energy intake and expenditure.[62]

Key hypothalamic nuclei participate in the intricate regulation of appetite and energy balance. The arcuate nucleus (ARC), housing both agouti-related protein (AGRP) and proopiomelanocortin (POMC) neurons, resides adjacent to the median eminence. This region features permeable capillaries that facilitate exposure to circulating signals, thereby enabling the modulation of ARC neuronal populations. These neurons extend extensive projections to the paraventricular nucleus of the hypothalamus (PVH) and other hypothalamic nuclei. The PVH serves as a principal hypothalamic satiety center. POMC neurons activate melanocortin-4 receptor (MC4R) neurons in the PVH to suppress appetite, whereas AGRP neurons inhibit PVH-MC4R neurons, promoting appetite. Additionally, AGRP neurons also inhibit POMC neurons by stimulating inhibitory gamma aminobutyric acid (GABA)-ergic input to POMC neurons. Anorexigenic signals like leptin and glucagon-like peptide 1 (GLP-1) enhance satiety by acting on POMC neurons, whereas orexigenic signals like ghrelin can increase appetite by affecting AGRP neurons. Other hypothalamic neuronal populations maintain extensive connections with neighboring nuclei. For instance, the dorsomedial hypothalamus (DMH) primarily exerts inhibitory projections to the PVH and POMC but also features activating inhibitory GABAergic neurons projecting to the ARC's AGRP neurons. The ventromedial hypothalamus (VMH) primarily sends excitatory projections to POMC neurons, while AGRP neurons send inhibitory projections to the VMH. Furthermore, postprandial satiety signals originating from enteroendocrine cells within the gastrointestinal tract can also influence the dorsal vagal complex (DVC) located in the brain stem to suppress appetite **(Fig. 8)**.[62]

Divergent Functions of AGRP and POMC Neurons in Maintaining Glucose and Lipid Homeostasis

The CNS, encompassing both hypothalamic and brain stem neuronal populations, plays a pivotal role in maintaining the balance of energy intake and expenditure. These neuronal populations respond to circulating signals, orchestrating the adjustment of autonomic nervous system activity toward various metabolic organs and endocrine glands. This intricate communication between the CNS and the periphery is crucial for preserving glucose and lipid homeostasis.[62]

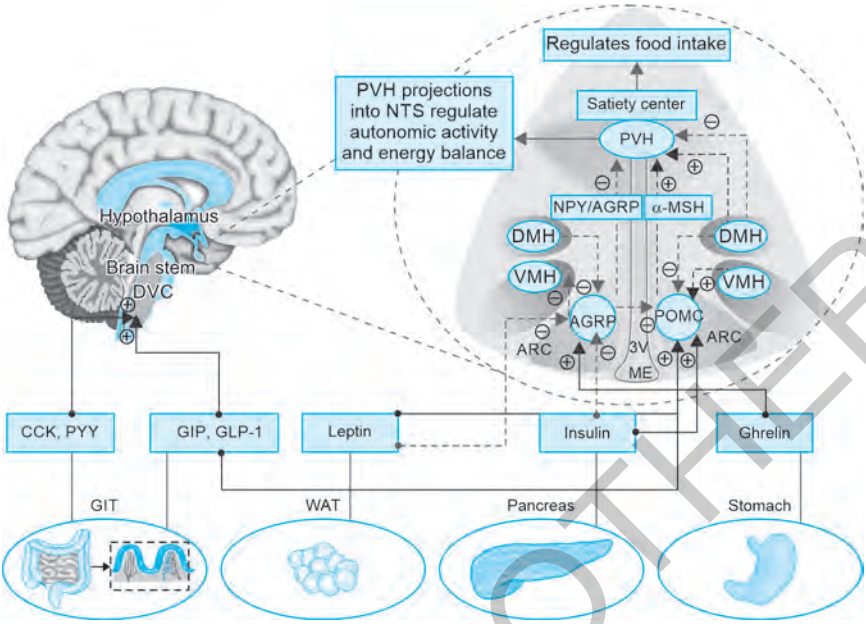


FIG. 8: Key hypothalamic nuclei involved in the regulation of appetite and energy balance.

(AGRP: agouti-related protein; ARC: arcuate nucleus; CCK: cholecystokinin; DMH: dorsomedial hypothalamus; DVC: dorsal vagal complex; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1; GIT: gastrointestinal tract; ME: median eminence; α-MSH: alpha melanocyte-stimulating hormone; NPY: neuropeptide Y; NTS: nucleus tractus solitarius; POMC: proopiomelanocortin; PVH: paraventricular nucleus of the hypothalamus; PYY: peptide YY; VMH: ventromedial hypothalamus; WAT: white adipose tissue; 3V: third ventricle)

Numerous brain regions, including specific hypothalamic and brain stem nuclei, harbor intricate neural networks that govern the function of pancreatic islets through autonomic efferent pathways. These neural circuits have been functionally validated, unveiling the significant roles of several hypothalamic nuclei in regulating pancreatic insulin release. Within these hypothalamic nuclei, a bidirectional control over insulin secretion is evident. Activation of a specific subset of oxytocin neurons in the PVH leads to the suppression of insulin secretion, whereas increased glucokinase activity in the ARC enhances GSIS and improves glucose tolerance. Additionally, neurons projecting to the pancreas within the dorsal motor nucleus of the vagus (DMV) have been observed to be stimulated by GLP-1, suggesting a potential vagal efferent pathway for enhancing insulin release. IRs are widely distributed throughout the brain, enabling circulating insulin to modulate neuronal populations crucial for metabolic regulation. Notably, the hypothalamus stands as a pivotal insulin-responsive brain region dedicated to the maintenance of euglycemia. Intriguingly, the divergent effects of central insulin signaling on glucose and lipid homeostasis may be attributed to the distinct outcomes of IR activation in AGRP neurons versus POMC neurons. Insulin's impact on AGRP neurons contributes to enhanced glucose homeostasis, while its influence on POMC neurons brings about alterations in lipid metabolism.[62]

Hormonal Imbalances

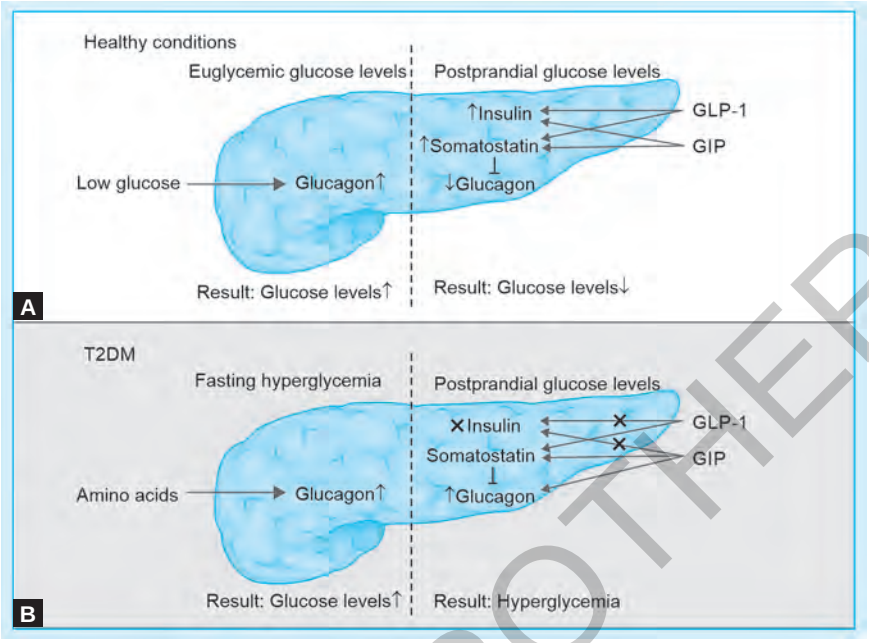
Type 2 diabetes mellitus is a multifaceted, genetically influenced condition characterized by dysregulation or insufficiency in various key hormonal pathways, contributing to its pathogenesis and progression.

Incretin Hormones

The gastrointestinal epithelium secretes incretin hormones, which play a vital role in maintaining normal glucose tolerance. These hormones stimulate insulin secretion in response to glucose, preventing excessive postprandial glucose levels. The incretin effect is dose-dependent, ensuring consistent postprandial glucose control regardless of the carbohydrate content of the meal.[63] The two primary incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are crucial in regulating glucose metabolism. Upon nutrient ingestion, these hormones are secreted by the gastrointestinal tract, and they play a role in modulating the release of insulin and glucagon from pancreatic islet cells. However, their activity is short-lived as they are rapidly degraded into inactive metabolites by dipeptidyl peptidase 4 (DPP-4).[64]

Glucose-dependent insulinotropic polypeptide: This is the first discovered incretin hormone, which contributes to approximately 60% of the total incretin effect. It is released by duodenal K cells in the proximal small intestine in response to the absorption of fats and carbohydrates after a meal. In the pathogenesis of T2DM, there is a genetic component with reduced expression of beta cell GIP receptors, which may be an early event in the development of the disease. This is supported by observations of reduced insulinotropic response to exogenous GIP in patients with T2DM and the decreased GIP effect seen in about 50% of their nondiabetic first-degree relatives. However, other data indicate that rapid desensitization of signaling through GIP receptors occurs in T2DM, which may be associated with GIP hypersecretion, chronic hyperglycemia, or other metabolic abnormalities **(Figs. 9A and B)**.[63,64]

Glucagon-like peptide 1: In patients with T2DM, the loss of the insulinotropic effect of GIP may be either a primary cause of the disease or a consequence of ongoing hyperglycemia, limiting the potential of GIP analogs or mimetics. On the other hand, GLP-1, discovered in 1985, is secreted by L cells in the distal small intestine and colon, alpha cells of the pancreas, and neurons in the hypothalamus. It induces satiety and regulates feeding behavior. Similar to GIP, GLP-1 levels increase after food ingestion, with plasma concentrations rising six- to eightfold following a carbohydrate meal. GLP-1 not only stimulates insulin secretion but also inhibits glucagon secretion, HGP, gastric emptying, and appetite. Additionally, GLP-1 has stimulative and regenerative effects on beta cells. In individuals with T2DM, there appears to be a deficit of GLP-1. Reduced postprandial GLP-1 response has been observed in patients with T2DM, and the degree of reduction correlates with the subject's obesity level **(Fig. 8)**.[62,63] The diminished incretin effect observed in T2DM is primarily attributed to the significant decline in beta cell function and reduced insulinotropic response to GIP. While GLP-1 secretion and activity may remain intact, they are unable to fully compensate for the impaired GIP activity at



FIGS. 9A AND B: Actions of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) in the pancreas. The diagrams show the actions of the incretins under fasting and postprandial glucose levels in (A) healthy individuals and (B) patients with type 2 diabetes mellitus (T2DM).

Source: With permission from Boer et al. (2020).[63]

physiological levels. Recent studies, such as the comprehensive review by Meier et al., have provided detailed insights into the role of reduced insulinotropic response to GIP in T2DM, highlighting its association with decreased beta cell mass and impaired maximum insulin secretory capacity.[65]

Recent research has shed light on the contribution of impaired alpha cell function in the pathophysiology of T2DM. This dysfunction leads to the inadequate suppression of glucagon secretion and HGP, even in the presence of a meal. In the context of insufficient insulin levels and increased insulin resistance, this dysregulated glucagon secretion contributes to the development of hyperglycemia in individuals with T2DM. The incretins, including GLP-1, play a crucial role in mediating insulin release and suppressing glucagon secretion. While GIP activity is impaired in individuals with T2DM, the insulinotropic effects of GLP-1 remain preserved. Therefore, GLP-1 represents a promising therapeutic option for the management of T2DM due to its ability to enhance insulin secretion and suppress glucagon levels.[64]

Glucagon: A Hormone by the Alpha Cells

Glucagon, a peptide hormone consisting of 29 amino acids, is primarily secreted from the pancreatic alpha cells. Its main role is to stimulate HGP, thereby increasing plasma glucose levels. Glucagon is recognized as the counterregulatory hormone

to insulin, and the balance between insulin and glucagon secretion is crucial for maintaining normal glucose homeostasis. Interestingly, in the pathophysiology of T2DM, dysfunction of the pancreatic alpha cells is observed. Individuals with T2DM often exhibit elevated fasting plasma glucagon levels, and their glucagon concentrations fail to decrease appropriately or may even increase paradoxically following meal ingestion.[66]

The theory of bihormonal regulation suggests that diabetes is the result of abnormal secretion of both insulin and glucagon. Insulin deficiency leads to metabolic disorders such as elevated lipolysis, increased proteolysis, and decreased glucose utilization. On the other hand, excess glucagon has various effects including decreased glycogen synthesis, increased ketogenesis, elevated hepatic glycogenolysis, and gluconeogenesis. These effects contribute to severe endogenous hyperglycemia and hyperketonemia in the absence of sufficient insulin. In cases where insulin levels remain relatively stable in patients with diabetes, an increase in glucagon levels can lead to hyperglycemia and glycosuria.[67]

Emerging evidence suggests that targeting glucagon and the glucagon receptor (GCGR) can effectively lower blood glucose levels in both animals and humans, highlighting the significant contributions of glucagon and GCGR in the development of diabetes. The GCGR is a G-protein-coupled receptor primarily found in pancreatic beta cells and liver cells. Upon binding of glucagon to the GCGR, it triggers liver glycogen breakdown and elevates blood glucose levels, which stimulates insulin release. GLP-1, predominantly expressed in intestinal L cells, activates the GLP-1 receptor to regulate metabolism. Both glucagon and GLP-1 are derived from the same precursor molecule, proglucagon, and they play crucial roles in the regulation of lipid and bile acid metabolism, exerting significant influences on glucose metabolism and the development of diabetes.[67]

Adipocytokines: The Adipose Tissue Hormones

Adipose tissue has many important functions other than energy storage that are mediated through hormones or substances synthesized and released by adipocytes. These substances, termed "adipocytokines", act on distant targets in an endocrine fashion or locally in paracrine and autocrine fashions. The adipocyte-derived hormones, such as adiponectin and leptin, have been shown to improve insulin sensitivity, a key factor in the pathogenesis of T2DM. Indeed, obesity induced by eating a high-energy diet is a risk factor for the development of insulin resistance and subsequently, T2DM. AT, in addition to being a fat storage organ, can also secrete several hormones and some proteins (called adipokines), which may act as markers of deteriorating pancreatic islet function. Some of these adipocytokines can increase insulin sensitivity by increasing fatty acid oxidation and reducing the triglyceride levels in skeletal muscle.[68,69]

- *Leptin*: Serum concentrations of leptin increase in proportion to increasing adiposity. In patients with obesity, high leptin levels are associated with low circulating soluble leptin receptors (SLRs) consistent with a state of leptin resistance. Leptin must cross the blood–brain barrier (BBB) to reach the hypothalamus and exert its anorexigenic functions. Decreased transport across the BBB and a decreased ability of leptin to activate hypothalamic signaling in

diet-induced obesity may be crucial in the pathogenesis of leptin resistance. Leptin receptors are also present in peripheral organs, such as the liver, skeletal muscles, pancreatic beta cells, and even adipose cells, indicating endocrine, autocrine, and paracrine roles of leptin in energy regulation. Leptin signaling in these organs is thought to mediate important metabolic effects. For example, leptin has been implicated in glucose and lipid metabolism as an insulin sensitizer.[68,69]

- *Adiponectin*: This is an insulin-sensitizing adipocytokine whose plasma levels were found to be decreased in T2DM, insulin resistance and obesity. It is well known that AMPK is an energy sensor and that it regulates cellular metabolism. AMPK stimulates glucose uptake and lipid oxidation to produce energy during deficient nutrient status. It turns off energy utilization mechanisms through the synthesis of lipid and glucose molecules to reinstate the energy balance.[69]

  Accumulation of excess visceral fat was found to modify the liberation of adipocytokines molecules like resistin, leading to central nervous system-mediated skeletal muscle and hepatic insulin resistance.
- *Resistin*: It is known that resistin increases blood glucose and insulin concentrations in mice and impairs the hypoglycemic response to insulin infusion. Earlier studies reported lower resistin mRNA in AT in various mouse models of obesity, such as diet-induced obesity. Resistin also suppresses insulin-stimulated glucose uptake in cultured 3T3-L1 adipocytes, and antiresistin antibodies reverse this effect. These observations from the above studies clearly suggest that resistin induces insulin resistance and hyperresistinemia that contribute to impaired insulin sensitivity in the obese models studied.[69]

Beyond serving as sites for energy storage, adipocytokines play a pivotal role in governing cellular metabolic pathways in response to the nutritional status. The upregulation of adipocytokines, such as resistin, vaspin, apelin, and TNF-α, has been linked to the development of insulin resistance associated with obesity and T2DM. The evolving understanding of adipocytokines' impact on glucose homeostasis and insulin sensitivity offers valuable insights for shaping therapeutic interventions aimed at mitigating vascular diseases.

Role of Gut Peptide in Obesity

Obesity occurs when energy intake chronically exceeds energy expenditure. By consistently overriding homeostatic signals of energy availability, eating becomes disjointed from energy requirements, resulting in dysregulation of the metabolic mechanisms controlling energy homeostasis, including impaired gut hormone secretion. Abnormal gut hormone responses have been demonstrated in adults and children with obesity. Individuals with obesity have blunted ghrelin reductions post-meal, together with reduced circulating baseline and meal-stimulated levels of the anorectic peptides, peptide YY (PYY), GLP-1, and neurotensin (NT), compared to individuals with normal weight. However, a recent study in rats with diet-induced obesity, akin to a western diet, showed reduced circulating PYY and GLP-1 concentrations and a loss of circadian secretion profiles of PYY, GLP-1, and amylin. In addition, sustained exposure to a high-fat diet in mice has been shown to lead to an increase in ghrelin-producing cells. These findings suggest that high-energy

intake per se may chronically impair gut hormone responsiveness to ingested nutrients. Studies investigating the role of ghrelin in obesity have shown blunted post-meal ghrelin suppression, loss of premeal peaks, along with reduced diurnal variability; these changes are thought to contribute to the lack of regular meals and the frequent snacking behavior often observed in individuals with obesity.[70]

MECHANISM OF ACTION OF GUT MICROBIOTA IN OBESITY

The gut microbiota can achieve this through various means. First, gut microbiota influences host energy balance through sensors of microbial products. Short-chain fatty acids are a subgroup of fatty acids composed of acetate, propionate, and butyrate, which are end products of bacterial fermentation. These metabolites may act as signaling molecules that regulate various transcription factors involved in energy balance. The short-chain fatty acids and conjugated fatty acids can modulate the brain via direct or indirect mechanisms and affect its ability to regulate appetite and food intake.[71] On the other hand, pro-obesity microbiomes have been reported to be involved in various activities that promote body weight gain. Some microbes, such as those belonging to the phylum Firmicutes are involved in promoting adiposity or could enhance host-mediated adaptive response mechanisms that limit energy uptake, such as reducing the capacity to ferment polysaccharides.[72] Firmicutes have been described to possess many carbohydrate metabolism enzymes, which can contribute to the metabolization of carbohydrates allowing a greater energy absorption and contributing to obesity.[73] Furthermore, the pro-obesity gut microbiota is involved in inducing low-grade inflammation by promoting metabolic expression of inflammatory markers in AT and pro-inflammatory cytokines associated with increased risks of weight gain. It was discovered that gut microbiota-associated inflammation is controlled by microbiota lipopolysaccharide (LPS). The LPS from intestinal bacteria may increase the risk of developing obesity and cause insulin resistance via means including inducing obesity–inflammatory markers in AT.[74-76]

ENDOCRINE CAUSE OF OBESITY AND DIABETES

Endocrine Cause of Obesity

Endocrine disorders, such as hypothyroidism and hypercortisolism, are recognized causes of secondary obesity. However, individuals with primary (simple) obesity can also exhibit various hormonal abnormalities. Some of these issues stem from dysfunction in AT, which secretes adipokines influencing endocrine organ function and can often be reversed with weight loss. However, there are cases where these abnormalities indicate a genuine endocrine disorder requiring specific treatment.

The secretion of thyroid hormones (TH) is regulated by the hypothalamic–pituitary–thyroid (HPT) axis. Thyroid-stimulating hormone (TSH or thyrotropin) is released by the anterior pituitary lobe in response to thyrotropin-releasing hormone (TRH) from the hypothalamus. TH, including triiodothyronine (T3) and thyroxine (T4), then regulate both TRH and TSH release in a feedback loop to

maintain overall bodily homeostasis. TH exerts diverse effects, including control of energy expenditure, basal metabolic rate (BMR), adaptive thermogenesis, and appetite regulation. Clinical research has indicated that thyroid status correlates with changes in body weight and adiposity. Even among euthyroid individuals, those with higher TSH levels tend to have a higher BMI than those with TSH levels closer to the lower end of the normal range. Variations in TH levels, even within the normal range, can influence weight gain or impact the effectiveness of weight loss treatments.[77,78]

The secretion of sex hormones is regulated by the hypothalamic–pituitary–gonadal (HPG) axis. In brief, gonadotropin-releasing hormone (GnRH) is produced by the hypothalamus and stimulates the anterior pituitary lobe to release gonadotropins: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins, in turn, stimulate the gonads (ovaries and testes) to secrete estrogen and testosterone and regulate reproductive processes. While testosterone, through negative feedback, inhibits GnRH and gonadotropin secretion, the regulation of female sex steroids is more complex.[79]

Hypogonadism can both cause and result from obesity in both men and women. A recent meta-analysis found that the prevalence of hypogonadism in obese men was 43.8% when measuring total testosterone (TT), but this figure rose to 75.0% in severely obese individuals undergoing bariatric surgery. Several mechanisms contribute to the development of obesity-related hypogonadism in men. Obesity increases aromatase cytochrome P450 activity in AT, leading to enhanced conversion of testosterone to estradiol. Elevated estradiol levels, in turn, downregulate GLUT4 via estrogen receptor beta stimulation, resulting in insulin resistance. This insulin resistance reduces sex hormone-binding globulin (SHBG) synthesis in the liver, increasing the amount of TT available for conversion to estradiol in AT. Elevated estrogen levels then inhibit gonadotropin secretion from the pituitary gland, further contributing to hypogonadism. Consequently, obesity can adversely affect sperm concentration, motility, and morphology in men.[80-82]

ENDOCRINE CAUSE OF DIABETES

The co-occurrence of T2DM alongside various hormonal disorders, such as pituitary, adrenal, and thyroid diseases, is a common observation. For instance, impaired glucose tolerance (IGT) and full-blown diabetes mellitus often accompany conditions like acromegaly and hypercortisolism (Cushing syndrome). The heightened cardiovascular risks and increased mortality associated with acromegaly and Cushing syndrome may, in part, result from the enhanced insulin resistance that typically accompanies excess hormone production.[83]

In acromegalic patients, insulin resistance is apparent both in the liver and the peripheral tissues, leading to elevated insulin levels and increased glucose turnover, especially during the fasting state. The prevalence of diabetes and IGT in acromegaly varies between 16 and 56%. This variation seems to be correlated with circulating growth hormone (GH) levels, patient age, and the duration of the disease. GH has physiological effects on glucose metabolism, including the promotion of gluconeogenesis and lipolysis, resulting in elevated blood glucose and FFA levels. Conversely, insulin-like growth factor 1 (IGF-1) enhances insulin

sensitivity primarily in skeletal muscles. However, in acromegaly, increased IGF-1 levels cannot fully counteract the insulin resistance caused by excess GH.[83]

Hyperproduction of cortisol in hypercortisolism leads to visceral obesity, insulin resistance, and dyslipidemia. These metabolic abnormalities, along with other factors like hypertension, hypercoagulability, and structural and functional changes in the heart ventricles, collectively heighten cardiovascular risk. Even after the resolution of hypercortisolism, these metabolic effects can persist for up to 5 years. Hypercortisolism induces hyperglycemia, reduces glucose tolerance, promotes insulin resistance, and stimulates hepatic gluconeogenesis and glycogenolysis.[83]

In patients with neuroendocrine tumors (NETs), disruptions in glucose tolerance can arise due to decreased insulin secretion, as seen in individuals who have undergone pancreatic surgery or those with pheochromocytoma. Additionally, an imbalance between hormones can contribute to altered glucose metabolism in conditions such as glucagonoma and somatostatinoma. The use of somatostatin analogs (SSAs) for the symptomatic treatment of NETs can also impact glucose metabolism.[83]

In thyroid disorders, abnormal glucose tolerance is primarily encountered in hyperthyroidism. The underlying causes are complex, and there is limited data available on the prevalence and severity of glucose-related issues. Nonetheless, it is crucial to provide appropriate treatment for glucose imbalances in these specific patient populations, aligning with the guidelines set forth by the American Diabetes Association and the European Association for the Study of Diabetes.[83]

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