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Review Article

The Link Between Immune Aging and Type 2 Diabetes: A Review of Mechanisms and Implications

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Abstract

Type 2 diabetes (T2D) is a metabolic disorder characterized by insulin resistance (IR), inflammation, and dysregulation in glucose metabolism. The disease is spreading globally, partly due to aging, which can damage the immune system and speed up the progression of the metabolic disorder. This review primarily delves into the triggers for T2D within the framework of the ominous octet, which emphasizes 8 principal factors under the "ominous octet" framework that contribute to high blood glucose and associated metabolic disorders. The article studies the interplay of hyperinsulinemia, mitochondrial dysfunction (MD), and endoplasmic reticulum (ER) stress with immune aging in driving disease progression affecting each component of the octet. MD and ER stress can result in defects in insulin signaling, ultimately leading to β-cell death. Chronic inflammation associated with aging, also known as inflammaging, especially affects older adults by worsening IR and glucose regulation, which creates a continuous sequence of metabolic problems. Thus, the "ominous octet" framework provides fundamental knowledge to develop personalized treatment approaches that target metabolic dysfunction together with ER stress, MD, and immune system imbalances. These strategies show promising potential to improve treatments for T2D and may lead to better health outcomes for older adults dealing with this condition.

Introduction

Demographic shifts and the aging immune system

Demographic projections show a significant rise in the global aging population. According to the World Health Organization (WHO), by 2030, one out of every six people globally is projected to be aged 60 years or above. The number of people in this age bracket is projected to rise from 1 billion in 2020 to 1.4 billion by 2030 and to surpass 2 billion by the year 2050. Moreover, the population aged 80 and above is projected to increase threefold during this period, reaching 426 million by the middle of the century.[1] The demographic shift is calling for immediate attention to the issues of health associated with the aging process, particularly cellular senescence, through which the immune system becomes less effective as people grow older.[2,3] As we age, cellular dysfunctions like telomere shortening and increased oxidative stress activate key signaling pathways, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).[4,5] This, in turn, triggers the senescence-associated secretory phenotype (SASP), a complex pro-inflammatory response marked by secretion of cytokines, chemokines, growth factors, and proteases from senescent cells. SASP is essential in promoting chronic low-grade inflammation, which in turn can interfere with tissue homeostasis and cause the pathogenesis of many age-related diseases, including type 2 diabetes (T2D).[6,7] This phenotype is characterized by excessive production of proinflammatory cytokines, chemokines, growth factors, and lipids. These substances not only impair immune balance but also abrogate inflammation resolution, worsening diseases associated with aging. Immunosenescence accelerates chronic inflammation and disrupts the delicate balance between the innate and adaptive immune systems.[8] The innate immune response, largely driven by innate immune cells like dendritic cells, remains active throughout life.[9] However, aging weakens adaptive immunity, resulting in the hyperactivation of innate immunity. This imbalance substantially reduces vaccine efficacy, increases susceptibility to infections, and heightens the vulnerability of older adults to opportunistic pathogens.[10,11]

Thymic involution: A core driver of immune aging

A key driver of immune dysfunction is thymic involution, the age-associated decline in thymus size and function.[12,13] The thymus is essential for the maturation of hematopoietic stem cells into

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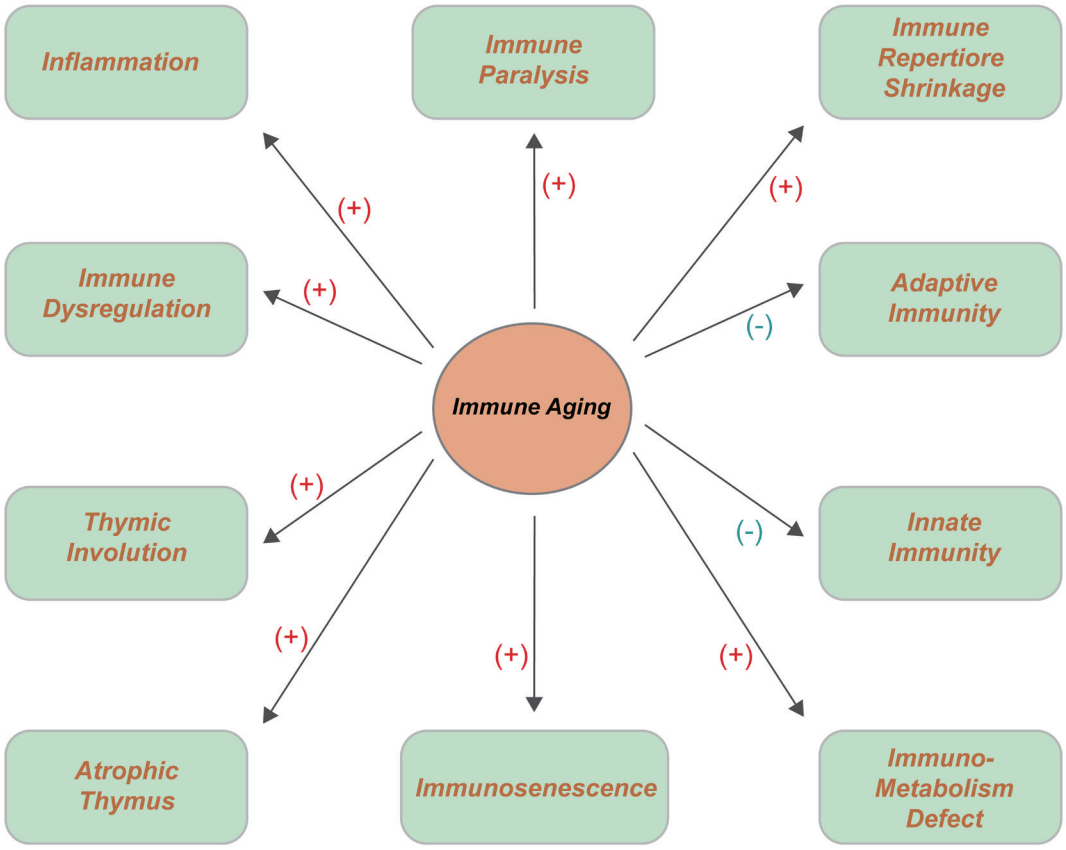

Fig. 1. Summary of the impact of immune aging on immune cell function. Immune function deteriorates progressively with age through a range of mechanisms, including chronic inflammation, immune dysregulation, thymic involution, thymic atrophy, immune paralysis, and a reduction in the diversity of the immune repertoire. Additionally, defects in immunosenescence and immunometabolism contribute to this decline. Immune aging exerts a detrimental effect on both innate and adaptive immunity. The (+) symbol denotes activation, while the (-) symbol indicates inhibition.

functional T cells. As the thymic output of naïve T cells decreases, the diversity of the T-cell repertoire becomes severely limited.[14] This reduction impairs the immune system's ability to mount robust responses to new pathogens. T-cell dysfunction and reduced immune surveillance speed up immunosenescence and raise the risk of chronic diseases in older individuals. Although the thymus naturally shrinks over time, conditions like aging can cause thymic atrophy. Both processes result in a decline in T cell production and function.[15] During thymus involution with aging, the immune repertoire shrinks, reducing the diversity of T cell receptors. This limits the ability to recognize and respond to new pathogens, a key feature of immunosenescence.[16,17] Put another way, immune aging causes the immune cells that have been in the body for a long time to become less effective. In this context, "immune aging" pertains to the general decline of the immune system with increasing age, whereas "immunosenescence" focuses on the specific decline in effectiveness and increased susceptibility to dysfunction of certain immune cells due to aging. Throughout the article, the two terms are used interchangeably, depending on the context. This process is intensified by the decrease in both the number and efficacy of immune cells as people grow older, which ultimately compromises the body's capacity to identify and eliminate pathogens.[16,17] In certain instances, this decline results in a condition referred to as immune paralysis, marked by a substantial reduction in immune system responsiveness, making it unable to effectively ward off pathogens or other immune threats.[3] In essence, immune aging is a multifaceted phenomenon influenced by a variety of interconnected elements that both contribute to and arise from the decline in immune function. As depicted in Figure 1, significant factors leading to immune aging include persistent inflammation, immune system dysregulation, thymic involution, and thymic atrophy. These alterations initiate a cascade of downstream effects such as immune paralysis, a diminished immune repertoire, compromised adaptive and innate immunity, and metabolic dysfunction within immune cells.[14–17] Together, these changes give rise to the concept of immunosenescence. The bidirectional arrows in the figure highlight the cyclical nature of this process, where each factor can worsen or amplify the others, leading to a self-reinforcing cycle of immune decline.

Inflammaging and metabolic disorders

Moreover, chronic systemic inflammation, or "inflammaging", is a key feature of age-related immune dysfunction.[17] It plays a crucial role in the development of metabolic disorders, particularly insulin resistance (IR) and T2D.[18,19] High levels of pro-inflammatory cytokines, like interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), are characteristic of inflammaging.[11,16,17] Interestingly, recent studies have underscored the alterations in metabolism as one of the primary drivers of organism dysfunctions during aging, the deterioration of which with age lowers immune cell function.[20]

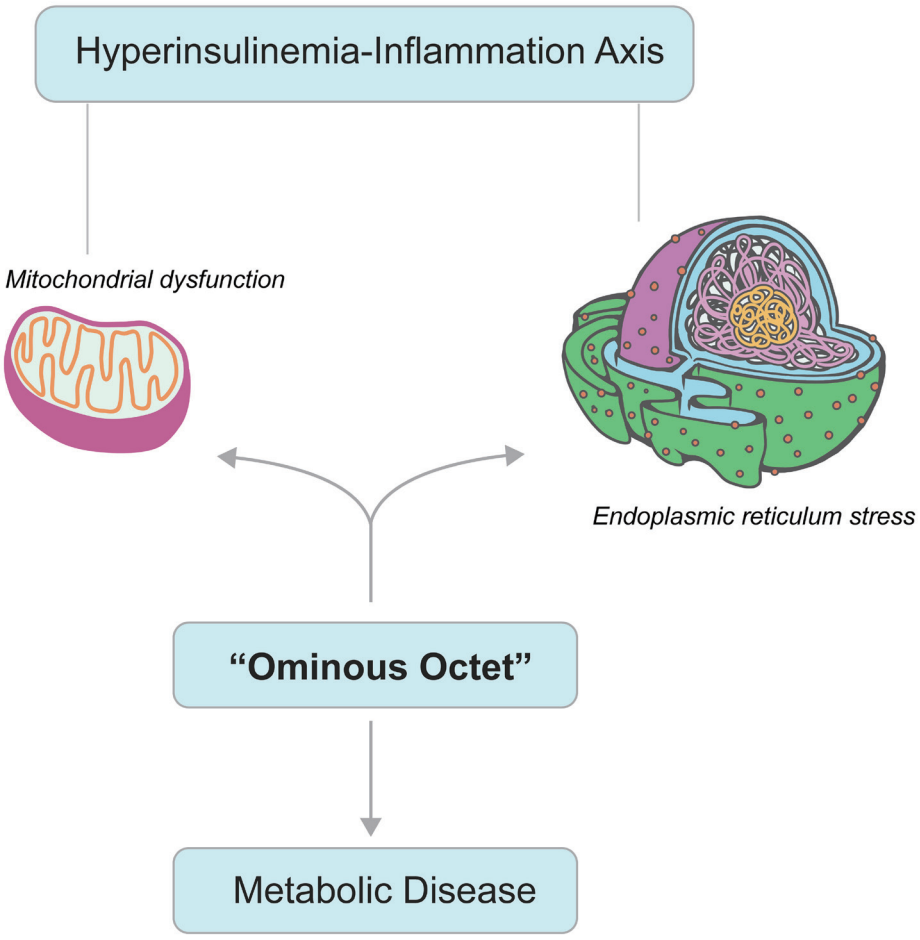

Fig. 2. Organelle dysfunction in insulin resistance (IR) and metabolic disease. This figure captures the core narrative of this review, illustrating how mitochondrial dysfunction (MD) and endoplasmic reticulum (ER) stress act as central drivers of IR and metabolic disease progression. The reciprocal reinforcement between the dysfunction and hyperinsulinemia-inflammation cycle may ignite a self-propagating loop of metabolic disruption. Additionally, the diagram integrates MD and ER stress within the framework of the "Ominous Octet", highlighting their pivotal role in metabolic dysregulation. Targeting both IR and its underlying cellular impairments is imperative for developing effective therapeutic interventions. Mitochondria and ER images were adopted from Pixabay.

Hence, the interplay between metabolism and inflammaging is beginning to receive increasing recognition in the regulation of the development of T2D in recent years. Importantly, hyperinsulinemia, IR, and inflammation establish the cycle, exacerbating the metabolic complications in older adults.[21,22] It starts with elevated glucose levels, leading to hyperinsulinemia, which causes IR and triggers more insulin production and inflammation. At first, pancreatic β-cells can withstand the increased workload, but over time, IR leads to β-cell dysfunction, loss of β-cell mass, and the onset of T2D.[23,24] At the cellular level, the combination of hyperinsulinemia and age-related inflammation plays a key role in causing organelle dysfunction, mainly mitochondrial dysfunction (MD) and endoplasmic reticulum (ER) stress.[25,26] Such impairment at the cellular level further aggravates metabolic dysregulations.

Hyperinsulinemia–inflammation axis and organelle dysfunction in T2D

In light of this, this review provides a detailed analysis of the intricate connections between immune aging, cellular stress mechanisms, and chronic inflammation, particularly in relation to age-associated metabolic issues such as IR and T2D. It seeks to clarify how age-related declines in immune function and ongoing low-grade inflammation, termed "inflammaging", interact with organelle stress-especially MD and ER stress to sustain the detrimental cycle of hyperinsulinemia and inflammation. Distinctively, this review takes a fresh perspective by directly examining how cellular stress responses affect the various elements of the "ominous octet" of T2D, which includes impaired insulin secretion, diminished incretin effect, increased lipolysis, heightened hepatic glucose production (HGP), neurotransmitter dysfunction, augmented renal glucose reabsorption, reduced glucose uptake in muscle, and inflammation-driven IR in adipose tissue (AT).[27–29] By doing this, a mechanistic framework is established that links immune aging, thymic atrophy, and critical signaling pathways—like NF-κB, c-Jun N-terminal Kinase (JNK), and Phosphoinositide 3-Kinase-Protein Kinase B (PI3K-Akt)—to the disruption of glucose homeostasis. What distinguishes this review from current literature is its thorough examination of how immune aging and organelle stress function as significant factors contributing to the pathological mechanisms of T2D, linking all components of the "ominous octet" associated with T2D. To further emphasize this, as illustrated in Figure 2, the hyperinsulinemia–inflammation axis

plays a crucial role in the regulation of metabolic disturbances by compromising the functional integrity of mitochondria and the ER. Dysfunction in mitochondria leads to inefficient energy metabolism, while stress in the ER causes improper protein folding and triggers inflammatory signaling. The dysfunctions occurring in these organelles intersect, amplifying the core pathophysiological mechanisms described in the "Ominous Octet", thereby promoting the onset and worsening of metabolic diseases. This underscores the interconnected relationship between insulin dysregulation, inflammation, and organelle stress in the development of metabolic disorders such as T2D. Furthermore, the article offers fresh insights and highlights essential aspects that require more in-depth exploration through empirical research as it unfolds.

A unified perspective

Together, the article essentially provides a unified and comprehensive perspective that links immunology, cell biology, and metabolic diseases. This holistic examination not only synthesizes current understanding but also delivers a deeper assessment of potential therapeutic targets designed to reverse or mitigate the immunometabolic deterioration associated with aging, exceeding traditional methods that concentrate solely on glycemic management.

Overview of structure

This review is structured into five sections. The first addresses the dual function of inflammation in metabolic control and aging in T2D. The second explores the interaction among hyperinsulinemia, inflammation, and insulin resistance. The third links these systemic factors to organelle impairment. The fourth examines how organelle stress influences the "ominous octet" associated with T2D. The concluding subsection emphasizes the interaction between mitochondria and the ER as an essential modulator of these pathological pathways.

Inflammation in T2D: A double-edged sword in metabolic regulation and aging

The dual role of inflammation in T2D onset

In the early stages of T2D, our body's natural immune system, along with pro-inflammatory cytokines like IL-1β and TNF-α, plays a key role in maintaining metabolic balance.[24] These immune responses help protect us by clearing out cellular waste and enhancing insulin sensitivity in vital metabolic tissues, such as skeletal muscle and the liver.[18,30] Anti-inflammatory macrophages (M2) play a key role by releasing cytokines that improve insulin signaling, boost glucose uptake, and optimize metabolism.[31,32] They also play a role in resolving inflammation, preserving tissue integrity, and ensuring ongoing functional capacity.[33] As a result, the immune response helps control glucose levels and reduces metabolic strain, delaying IR and β-cell dysfunction.[34] The immunometabolic progression of T2D begins with a transient activation of the innate immune system, marked by the release of IL-1β and TNF-α. This early response promotes the recruitment of anti-inflammatory M2 macrophages, which enhance insulin sensitivity and facilitate glucose uptake. In essence, this brings us to the forefront of innovative preventive strategies for mitigating T2D, where pro-inflammatory cytokines, traditionally viewed as harmful, may instead represent therapeutic opportunities when their release is precisely timed and tightly regulated. For example, the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial showed that targeting IL-1β with the monoclonal antibody canakinumab decreased systemic inflammation and improved glycemic control in patients with both cardiovascular diseases (CVDs) and T2D, without raising the risk of infections.[35] Likewise, Anakinra, which functions as an IL-1 receptor antagonist, improved insulin secretion and reduced HbA1c (hemoglobin A1c (glucose-bound hemoglobin)) levels in T2D patients across various randomized controlled trials, reinforcing the potential for modifying inflammation as a therapeutic approach.[36] Hence, understanding the mechanisms that distinguish acute, beneficial inflammation from the chronic inflammation observed in established T2D is critical. Identifying specific cytokines and immune cell subsets involved in these early adaptive responses could guide strategies to fine-tune short-lived inflammation and promote metabolic resilience. Studies on pioglitazone and GLP-1 receptor agonists (GLP-1 RAs) like liraglutide have shown that these medications can indirectly promote M2 macrophage polarization and enhance anti-inflammatory responses, highlighting their dual benefit in enhancing both glycemic management and immunometabolic balance.[37–39]

Modulating immunity to delay T2D onset

Importantly, enhancing or maintaining M2 macrophage polarization, recognized for its ability to improve insulin signaling and reduce inflammation, through lifestyle changes like diet and exercise or through targeted medications may aid in preventing IR.[40,41] Similarly, studying how temporary inflammatory signals make tissues more responsive to insulin, while extended exposure leads to resistance, could uncover biomarkers or signaling pathways essential for the regulation of immune and metabolic functions. Leveraging natural anti-inflammatory processes, such as regulatory T cells (Tregs) and specialized pro-resolving mediators (SPMs), also provides a way to re-establish immune balance and promote metabolic stability.[42] In a pioneering phase 1 clinical trial involving humans, the synthetic Resolvin E1 analog RX-10045 demonstrated safety and good tolerance in both healthy participants and individuals with inflammatory eye conditions (NCT01639846), setting the stage for the exploration of SPM analogs in acute systemic inflammatory diseases such as T2D.[43] Although trials specific to T2D are still in early development, preclinical studies have shown that SPMs like Resolvin D1 and Maresin 1 can improve insulin sensitivity, reduce the infiltration of macrophages into AT, and restore glucose tolerance in obese mice, indicating they could be valuable as metabolic immunomodulators in the future.[44] With clinical-grade analogs approaching readiness, these compounds are set to undergo testing to assess their ability to mitigate chronic inflammation and reestablish immune-metabolic balance in humans. Together, these findings indicate a strategic shift: instead of just suppressing inflammation, therapeutic strategies could aim to modulate it at specific intervals, utilizing the immune system's inherent flexibility to delay or avert the development of full-blown diabetes.

Inflammation's shift from protection to progression in T2D

As T2D advances, the balance between the immune system and metabolism begins to break down. The immune system, which was once protective, starts to contribute to disease progression through chronic inflammation—a characteristic feature of the later stages of T2D.[19,20,24] At first, inflammation helps manage metabolic stress and regulate glucose levels. However, with ongoing activation of pro-inflammatory pathways, this balance is disrupted, resulting in β-cell dysfunction and IR. A transition in macrophage type—from the anti-inflammatory M2 to the pro-inflammatory M1—intensifies tissue damage and boosts the production of inflammatory

cytokines.[31,32,45] These cytokines further hinder insulin signaling, accelerate β-cell death, and interfere with insulin release.[46] Consequently, inflammation transforms from a protective response into a catalyst for metabolic impairment, highlighting its complex role in the progression of the disease. When inflammation becomes persistent or misregulated, it not only harms tissues but also undermines immune regulation, speeding up the deterioration of insulin function and exacerbating the effects of T2D.[47,48] Recognizing this shift in immunometabolism opens up promising avenues for treatment.[19] Employing approaches that focus on inflammation at optimal times, such as modifying macrophage activity or inhibiting specific cytokines, could safeguard β-cell well-being and improve insulin sensitivity.[49,50] Tailored methods that correspond with a person's inflammatory profile could enhance treatment effectiveness and decelerate disease advancement, signifying a significant shift in the management of T2D.[51,52] In the later stages, hyperinsulinemia and aging immune cells propagate chronic inflammation through the SASP, leading to β-cell loss and worsening insulin resistance. Therapeutic strategies that target the SASP, restore M2 macrophages, and enhance β-cell survival may help halt the advancement of the disease.[53,54]

Senescence, inflammation, and β-cell dysfunction in T2D

Moreover, chronic hyperinsulinemia in T2D accelerates the aging process through intricate immune responses.[18,55] During the early stages of T2D, elevated insulin levels, or hyperinsulinemia, attract senescent immune cells, such as aging macrophages, to the pancreatic islets. The sustained inflammatory environment, along with alterations in pro-inflammatory cytokines and reactive oxygen species (ROS) linked to the SASP in these senescent cells, triggers apoptosis of β cells, impairing their function and leading to reduced insulin production in the pancreas.[56,57] As these senescent immune cells accumulate, they worsen inflammatory conditions, creating a self-perpetuating cycle that heightens IR and speeds up the decline of β-cells.[58,59] Ultimately, the reduction in β-cell mass and the dysfunction in insulin signaling contribute to the ongoing persistence and advancement of the disease.[60,61] Strategies for eliminating or diminishing senescent cells, such as senolytics, have demonstrated potential in early-stage studies and may be especially beneficial for managing the chronic inflammation associated with T2D.[62,63] These senolytic drugs could be combined with immunomodulatory therapies that aim to counteract the detrimental immune response to hyperinsulinemia, such as those that affect macrophage polarization, to restore immune equilibrium and safeguard β-cell functionality.[64,65] In the end, a comprehensive approach that simultaneously targets insulin sensitizers, immune-modulating therapies, and senolytics might disrupt the detrimental cycle of inflammation and β-cell impairment. This approach presents a possibility for a treatment strategy to reduce or possibly reverse the advancement of T2D. By addressing the immune-metabolic components of the disease, these findings could lead to an innovative approach in the prevention and treatment of T2D. For instance, a notable clinical trial (NCT02848131) involving the senolytic duo of dasatinib and quercetin in individuals with diabetic kidney disease, a common complication of T2D, led to reductions in senescence markers and inflammatory mediator levels, suggesting potential systemic health advantages of eliminating senescent cells in metabolic conditions.[66] These senolytic treatments may also be paired with immunomodulatory therapies aimed at mitigating the detrimental immune response associated with hyperinsulinemia, including those that focus on altering macrophage polarization to restore immune equilibrium and safeguard β-cell function.

Preserving β-cell function: A key to T2D management

In essence, the interaction between immune cells and β-cell health is essential for comprehending the pathophysiology of T2D. As the mass of β-cells declines, insulin production reduces, exacerbating hyperinsulinemia and disrupting glucose control.[67] This cycle emphasizes the importance of understanding how immune-mediated inflammation impacts β-cell function in the progression of T2D. Strategies that disrupt this cycle could help maintain β-cell health, enhance insulin sensitivity, and slow the progression of the disease, presenting potential therapeutic approaches for better management of T2D.[68]

The interplay of hyperinsulinemia, inflammation, and IR

The rising prevalence of ischemic heart disease during aging is closely linked to the growing incidences of T2D, CVDs, and metabolic syndrome (MS), underscoring the critical role that metabolic dysfunction plays in cardiovascular health.[69,70] A critical factor driving the pathophysiology of IR is the interaction between hyperinsulinemia and systemic inflammation, which has gathered lots of attention in recent years. Ischemic heart disease shows increased incidence with rising prevalence of IR.[71] Generally, this condition develops as a compensatory response to restore the glucose homeostatic effect by increasing the release of insulin when receptor sensitivity is decreased because of associated conditions or the overproduction of insulin by the substrates. This may initially be adaptive, but over time can damage the ability to regulate normal glucose and activate inflammatory pathways of metabolic dysfunction that further complicate IR. These molecules impair the signaling of insulin by promoting serine phosphorylation of insulin receptor substrates (IRS), thereby obstructing glucose uptake in the peripheral tissues.[72] Obesity-induced metabolic disruption further amplifies this effect, as expanded AT releases inflammatory cytokines such as TNF-α and IL-6, along with adipokines like leptin and resistin.[73,74] This leads to hyperglycemia by stimulating liver glucose production through increased gluconeogenesis and glycogenolysis. In the liver, inflammation-driven dysregulation of insulin signaling within hepatocytes results from the increased HGP through the enhancement of gluconeogenesis and glycogenolysis, thus adding to hyperglycemia.[75,76] Similarly, local inflammatory processes in skeletal muscle decrease the activity of insulin receptor signaling, while inflammation in pancreatic islets restricts the secretion of insulin, therefore maintaining hyperglycemia.[77,78] Hyperinsulinemia produces inflammation, which causes conditions that promote hyperinsulinemia, sustaining an evil cycle that leads to an accelerated progression of IR and T2D.[79] This bidirectional feedback mechanism illustrates how hyperinsulinemia intensifies inflammation, which subsequently worsens IR. Increased insulin levels trigger inflammatory pathways such as NF-κB, JNK, and Suppressor of Cytokine Signaling 3, resulting in heightened serine phosphorylation of IRS-1, thereby disrupting insulin signaling and exacerbating IR.[80,81] This feedback mechanism enhances inflammation, boosts HGP, and reduces peripheral glucose uptake, perpetuating a sustained state of hyperglycemia that further raises insulin levels. Moreover, chronic inflammation stimulated by pro-inflammatory cytokines leads to tissue remodeling, enlargement of adipocytes, and infiltration of immune cells, thereby aggravating metabolic dysfunction. Over time, this cycle hastens the development of T2D and MS. Consequently, the interaction between inflammation and hyperinsulinemia underscores the significant role of signaling pathways such as NF-κB, JNK, and PI3K-Akt in the onset of IR and T2D, presenting potential therapeutic avenues to break this cycle and enhance metabolic health.[82] For instance, a double-blind, randomized clinical trial assessed the effects of met-

formin on inflammatory mediators in obese adolescents with IR.[83] After 3 months of metformin treatment, there was a significant reduction in serum levels of TNF-α and stabilization of adiponectin levels, suggesting improved inflammatory activity and potentially cardiovascular implications. Additionally, in a randomized, double-blind, placebo-controlled study, subjects with MS received treatment with galantamine. The findings indicated that galantamine, an acetylcholinesterase inhibitor, significantly lowered plasma levels of proinflammatory mediators (TNF-α and leptin) while increasing anti-inflammatory markers (adiponectin and IL-10). There was also a noted improvement in measurements of IR, including plasma insulin and Homeostatic Model Assessment-IR values. Moreover, a randomized controlled trial assessed the impact of oleoylethanolamide, a naturally occurring lipid (fat-like molecule) produced in the small intestine, especially after eating, supplementation in individuals diagnosed with prediabetes. The findings indicated that oleoylethanolamide intake improved glycemic control, reduced IR, and diminished inflammation by modulating oxidative stress and the release of inflammatory cytokines. Also, in a randomized controlled trial, participants with acute hypertriglyceridemia and IR who received bezafibrate—a medication used to lower lipid levels and activate peroxisome proliferator-activated receptor alpha—experienced significant decreases in inflammatory markers like C-reactive protein (CRP) and interleukin-6, along with enhanced insulin sensitivity.[84] Finally, the Whitehall II study, involving over 7,600 non-diabetic participants, found a positive link between elevated levels of inflammatory biomarkers (high sensitivity CRP and IL-6) and higher fasting insulin and IR over a 5-year follow-up.[85] Conversely, greater levels of adiponectin were correlated with improved glycemic control and enhanced insulin sensitivity.

Importantly, recognizing individuals who are more susceptible to T2D through biomarkers linked to dysregulated signaling pathways like NF-κB, JNK, and PI3K-Akt presents a promising opportunity for early intervention. Instead of solely depending on traditional risk factors such as body mass index and fasting glucose levels, incorporating molecular markers that reflect inflammation and insulin signaling problems leads to a better categorization of patients.[86,87] This approach facilitates a shift from general preventive strategies to specific, mechanism-driven interventions aimed at disrupting established pathogenic processes before significant metabolic damage occurring. For example, elevated levels of CRP, TNF-α, and IL-6 suggest active involvement of the NF-κB pathway and are increasingly recognized as early markers of inflammation related to IR.[88] Similarly, the detection of serine-phosphorylated IRS-1 in muscle tissues and a reduction in Akt phosphorylation in peripheral tissues serve as biological indicators of disrupted insulin signaling via the PI3K-Akt pathway.[89] With this knowledge, current clinical initiatives, such as the Diabetes Prevention Program and extensive studies like the UK Biobank, are beginning to integrate these biomarkers into their risk assessment frameworks to enhance the early identification of T2D risk.[90] This emphasis on pathway-oriented risk profiling signifies a significant transition towards predictive, preventive, and personalized medicine for metabolic disorders, allowing healthcare professionals to respond more swiftly, customize treatments more efficiently, and alleviate the worldwide impact of T2D, especially in the aging demographic.

Connecting hyperinsulinemia, inflammation, and organelle dysfunction in T2D

At the cellular level, organelle dysfunction, particularly in mitochondria and the ER, serves as a significant mechanistic link between metabolic disturbances and inflammation in relation to aging.[91,92] MD, which reduces oxidative phosphorylation (OXOPHOS) and leads to ROS buildup, causes cellular stress that raises inflammation.[93,94] ER stress occurs when the ER, an essential cellular component that ensures proper protein folding and processing, becomes overloaded with an excess of unfolded or incorrectly folded proteins. In response, the cell activates the unfolded protein response (UPR), a sophisticated, adaptive signaling system aimed at reestablishing cellular equilibrium.[95,96] This is achieved by reducing the overall protein load, enhancing protein-folding capacity, and promoting the degradation of misfolded proteins. The UPR operates primarily through three principal ER stress sensors: inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase, and activating transcription factor 6.[97] These sensors initiate signaling pathways that alter gene expression and elicit protective measures to mitigate the stress. However, if ER stress persists or remains unresolved, continuous UPR activation can become harmful. In particular, it can interfere with insulin signaling pathways, potentially leading to IR and disrupting metabolic homeostasis.[98] These organelles play an important role in keeping the cell in homeostasis; therefore, any dysfunction only creates metabolic-inflammation imbalances that spark IR onset. Pro-inflammatory cytokines, adipokines, and immune cells play key roles in driving these dysregulations, creating a harmful feedback loop.[99,100] Investigating the relationships between hyperinsulinemia, chronic low-grade inflammation, and organelle dysfunction opens up promising possibilities for cutting-edge treatments that could prevent or possibly reverse IR before it develops into T2D or causes CVDs. Significantly, this cellular-level dysfunction contributes to a larger systemic context in which metabolic stress, immune reactions, and hormonal imbalances interact in an ongoing cycle.[101] These findings are particularly crucial regarding the ominous octet theory. Organelle dysfunction can act as a unifying factor that exacerbates multiple pathways, either by directly impairing tissue function or by heightening systemic inflammation and IR.

To successfully break this harmful cycle, further investigation is needed to better understand the specific impact of organelle dysfunction in different tissues and how its timing is associated with metabolic issues. This includes examining innovative treatment strategies that focus on the health of mitochondria and the ER, such as promoting mitophagy, enhancing protein-folding capacity, and minimizing ROS build-up.[102,103] Acknowledging the differences in these processes across diverse populations and stages of the disease could aid in developing more personalized methods for managing T2D.

Hence, the following sections offer a concise overview of recent research on organelle dysfunction, particularly in the mitochondria and ER, and its role in driving the development of IR. By examining how dysfunction in these organelles influences the key components of the "ominous octet", we can gain a deeper understanding of the underlying mechanisms of T2D. This knowledge is crucial to furthering the progress of the development of targeted interventions beyond glucose-lowering and addressing the underlying causes of metabolic and cardiovascular complications in T2D. Such strategies have the potential for more effective, disease-modifying therapy.

Organelle dysfunction in T2D: the impact on the ominous octet pathways

The "ominous octet" in T2D highlights how dysfunction in pancreatic β-cells, liver, muscle, AT, GI tract, pancreatic α-cells, kidneys,

and the central nervous system (CNS) contributes to hyperglycemia and metabolic dysregulation.[24,27] To expand on this further, the model details the various factors that contribute to hyperglycemia in T2D. Impaired glucose regulation mainly results from disruptions in the functioning of several interconnected organ systems. Key roles in the "Ominous Octet" concept are played by the liver, pancreatic β-cells, and skeletal muscles, as they lead to IR, reduced insulin secretion, and alterations in glucose utilization. While the primary underlying factors are essential, additional elements such as pancreatic α-cells, AT, the kidneys, the digestive system, and the brain also worsen this metabolic imbalance. These systems engage in a detrimental feedback loop that amplifies hyperglycemia and accelerates the advancement of T2D. In essence, this model highlights the interconnectedness of these organ systems and underscores the importance of a comprehensive strategy for improving T2D management and slowing the advancement of the disease. These pathways are primarily driven by reduced insulin sensitivity and decreased insulin secretion. This section provides a brief overview of the individual elements of the Ominous Octet while adhering to the journal's constraints. The main focus will be on how these factors interact, with a particular emphasis on how MD and ER stress link hyperinsulinemia and inflammation in the context of the ominous octet of T2D.

Decreased insulin secretion

According to the ominous octet of T2D, dysfunctional β-cells reduce insulin secretion.[18,19,22,23] This worsens with lipotoxicity and amyloid deposits, along with the body's resistance to normal blood glucose regulation, leading to hyperglycemia. As we grow older, advanced glycation end products (AGEs) accumulate due to prolonged exposure to high blood sugar levels and oxidative stress.[104] AGEs are created when sugars non-enzymatically attach to proteins, lipids, or nucleic acids and interact with Receptor for Advanced Glycation End Products (RAGE), a receptor found on multiple cell types, including endothelial cells, immune cells, and pancreatic β-cells.[105] The interaction between AGEs and RAGE triggers inflammation and oxidative stress, which significantly disrupts insulin signaling and raises IR in tissues such as the liver, muscle, and AT.[106] In the aging process, this mechanism hastens the deterioration of pancreatic β-cells, resulting in decreased insulin secretion.[107] The activation of RAGE triggers an inflammatory response that leads to vascular damage, disrupts blood flow, and further reduces insulin sensitivity.[108] This creates a persistent cycle of glucolipotoxicity, where high levels of glucose and fatty acids cause additional damage to β-cells, exacerbating the decrease in insulin production and secretion.[109] Over time, the body's capacity to eliminate AGEs declines, worsening the situation and creating a glycotoxic environment.[110] This not only hinders effective glucose regulation but also raises the risk of T2D-related complications such as CVDs and neuropathy, which further diminishes insulin secretion as people age.[111] One of the primary effects of RAGE activation is the stimulation of the NOD-like Receptor Pyrin Domain Containing 3 (NLRP3) inflammasome.[112] This inflammasome is a multi-subunit protein complex that is essential for the innate immune response, as it activates caspase-1 and facilitates the secretion of pro-inflammatory cytokines IL-1β and IL-18.[113] RAGE-induced inflammasome activation contributes to chronic inflammation, which is often observed in aging and several age-associated conditions, like T2D.[114] The increased levels of cytokines lead to IR and damage to pancreatic β-cells, exacerbating metabolic disorders. The activation of inflammasomes through RAGE amplifies the detrimental effects of AGEs, leading to increased inflammation and metabolic issues, especially in older adults.[115] These interrelated factors contribute to the intricate nature of disease mechanisms. Continuous high blood glucose levels and persistent inflammation gradually result in IR and T2D, which, if left untreated, can lead to various complications over time. This underscores the critical need for treatments that address both chronic inflammation and hyperglycemia to manage and prevent disease progression.[116] Additionally, MD impairs adenosine triphosphate (ATP) synthesis, reducing ATP levels and limiting insulin secretion.[117] Excess stress from misfolded proteins like amyloids in the ER causes β-cell apoptosis, reducing insulin production.[60,61] Such deposits further induce the ER stress due to misfolded proteins.[118] An excess of free fatty acids (FFAs), referred to as lipotoxicity, disrupts the functionality of pancreatic β-cells due to the accumulation of FFAs in their mitochondria.[119] This accumulation negatively impacts mitochondrial performance, resulting in increased oxidative stress. The elevated oxidative stress damages β-cell integrity and hinders their ability to efficiently release insulin.[120] Consequently, the buildup of FFAs leads to β-cell dysfunction, which is a significant factor in the development of IR and T2D.[121]

Enhanced gluconeogenesis

Gluconeogenesis mainly affects the liver's ability to generate glucose from non-carbohydrate materials, hence playing an important part in the regulation of metabolism.[122] While this mechanism is essential during fasting or strenuous exercise, an exaggerated form of gluconeogenesis is a serious issue in some metabolic disorders such as T2D, together with IR and hyperinsulinemia. While high insulin is expected to lower blood glucose levels, it counterintuitively enhances gluconeogenesis by stimulating pathways that activate key enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase in the liver, impairing glucose tolerance.[123] This process occurs alongside inflammation, which is commonly observed in obesity and metabolic syndrome, and together these factors hinder the insulin signaling pathway in the liver, worsening gluconeogenesis.[124] These interrelations create a negative feedback loop associated with excess glucose, and blood glucose levels appear to rise even higher, increasing the body's IR. Chronic inflammatory changes will also lead to metabolic derangements of lipids and an increased tendency toward nonalcoholic fatty liver disease (NAFLD).[125] The link between increased gluconeogenesis and inflammation allows one to unravel some of the mechanisms underlying metabolic dysfunction, emphasizing the importance of integrated strategies that combine lifestyle changes with therapies that improve insulin sensitivity and reduce inflammation, breaking harmful cycles and promoting long-term health. Moreover, hepatic gluconeogenesis is curtailed by MD in hepatocytes, and unregulated gluconeogenesis leads to excessive glucose production.[126] In addition, FFAs overload the peroxisomes involved in fatty acid oxidation, causing increased gluconeogenesis and oxidative stress due to their inability to handle the excess.[127] Disruption of mitochondrial OXOPHOS generates increased ROS, thereby worsening IR in the liver and enhancing glucose production.[128]

Importantly, recent research has shifted focus toward how circadian rhythms and neuroendocrine signaling influence the regulation of gluconeogenesis. The liver's gluconeogenic activity is closely governed by the circadian clock, and disruptions, like those caused by poor sleep or shift work, can lead to the desynchronization of metabolic cycles, which exacerbates IR and disrupts glucose regulation.[129] Furthermore, the hypothalamus's regulation through agouti-related peptide (AgRP)/ neuropeptide Y (NPY)

neurons, alongside input from the sympathetic nervous system and vagal signals, plays a crucial role in managing hepatic glucose synthesis.[130] These interconnected systems underscore the importance of communication between the gut, brain, and liver in maintaining bodily balance, suggesting that aligning these regulatory mechanisms may be beneficial in preventing abnormal gluconeogenesis, particularly in the context of T2D.[131]

One major obstacle in targeting gluconeogenesis for the treatment of T2D is the current restrictions of available therapies. Metformin, the primary drug used to suppress HGP, shows inconsistent results across different patients and carries risks of side effects, such as lactic acidosis.[132] Similarly, while sodium-glucose cotransporter 2 (SGLT2) inhibitors boost the elimination of glucose through urine, they also unintentionally trigger the formation of ketone bodies and prompt hepatic gluconeogenesis as a side effect.[133] These challenges highlight the necessity for more comprehensive treatment strategies. The combination of agents that focus on liver metabolism with those that improve peripheral insulin sensitivity and modulate gut hormones, like GLP-1 RAs or gastric inhibitory polypeptide (GIP) co-agonists, may offer a more effective approach to address gluconeogenic abnormalities in T2D.[134,135]

Increased lipolysis

Heightened lipolytic activity results in increased amounts of FFAs, which play a critical role in the development of T2D by disrupting insulin signaling and damaging pancreatic β-cells. Elevated FFA levels impede insulin signaling in muscle and liver cells, resulting in a reduced capacity for glucose uptake from the bloodstream, particularly in cases of obesity.[136] FFAs also cause lipotoxic damage to β-cells, which triggers cell death and reduces insulin secretion. As a result, this creates a situation referred to as glucolipotoxicity, where increased glucose levels further intensify the harmful effects of FFAs, leading to increased oxidative stress and inflammation in β-cells.[137] Research involving both human and animal subjects has identified a robust link between elevated FFA levels and IR, as well as impaired β-cell functionality.[138,139] To further elaborate, animal models have provided valuable insights into the mechanisms by which elevated FFAs contribute to IR, including the roles of inflammation, oxidative stress, and dysregulation in lipid metabolism. These findings illuminate the cellular and molecular processes that contribute to IR in humans. On the other hand, clinical studies in humans have demonstrated similar relationships between increased FFA levels and reduced insulin sensitivity along with β-cell dysfunction, reinforcing the relevance of animal model findings to human physiology.[140,141] Although human studies are crucial for understanding the clinical significance of these results, animal research yields essential mechanistic insights. Collectively, these investigations bridge the gap between fundamental science and clinical applications, highlighting the potential of targeting elevated FFAs as a therapeutic strategy for addressing IR and β-cell dysfunction in humans.[142] A thorough discussion of many of these studies is beyond the scope of this article. Importantly, weight loss interventions aimed at decreasing FFA levels can improve insulin sensitivity and β-cell function, highlighting the crucial role of FFAs in the advancement of T2D. Furthermore, metabolic disorders in AT boost FFA levels, leading to their accumulation in the bloodstream, which can negatively impact other tissues such as muscle and liver.[143] Higher FFA concentrations disrupt mitochondrial functioning in β-cells and muscle cells, contributing to oxidative stress that further aggravates IR and diminishes glucose uptake.[144]

Association between inflammation and lipid metabolism

The connection between lipid metabolism and inflammation plays a vital role in the onset of T2D.[145] Elevated FFAs not only hinder insulin signaling and damage β-cells, but they also function as significant contributors to inflammation.[146] FFAs initiate inflammatory pathways, resulting in a higher release of pro-inflammatory cytokines like TNF-α and IL-6. These cytokines further disrupt insulin signaling, establishing a cycle of ongoing low-grade inflammation that heightens IR and affects glucose metabolism. This inflammatory response exacerbates the metabolic issues triggered by increased lipolysis and is implicated in the development of T2D.[124] Additionally, the interplay between inflammation and altered lipid metabolism leads to MD, ER stress, and further harm to tissues, particularly in muscle and liver cells, thereby worsening the progression of T2D.[147,148]

For example, NAFLD has become a major health concern and is on the rise globally. Once thought to be a benign condition, NAFLD can escalate to non-alcoholic steatohepatitis (NASH), a more serious stage of the disease marked by inflammation, hepatocyte damage, and fibrosis.[149] While NAFLD is largely associated with metabolic disorders, such as IR, obesity, and dyslipidemia, immune system dysfunction becomes particularly important, especially as the disease progresses to NASH.[150] In individuals with T2D, the inflammatory processes that contribute to IR and metabolic disturbances play a key role in the onset of NAFLD.[151] As IR in AT increases, there is a recruitment of macrophages along with the release of cytokines. AT changes into an inflammatory organ, secreting pro-inflammatory cytokines like TNF-α, IL-6, and monocyte chemoattractant protein-1. These cytokines induce inflammation in various tissues, including the liver, leading to fat accumulation (steatosis) and progression to NASH.[152] The rise in FFAs, resulting from enhanced lipolysis in obesity and IR, significantly aids in the development of NAFLD. FFAs activate Toll-like receptors (TLRs) on immune cells, initiating pro-inflammatory signaling pathways such as NF-κB and inflammasomes, which not only exacerbate liver injury but also increase IR, creating a detrimental cycle that exacerbates the disease progression.[153] As NAFLD evolves into NASH, hepatic macrophages (Kupffer cells) become activated and release cytokines that attract more immune cells, resulting in hepatocyte apoptosis, inflammation, and fibrosis.[154] The combination of metabolic issues and persistent inflammation eventually leads to liver cirrhosis and promotes the development of liver cancer, both of which are serious outcomes of NAFLD and T2D.[155] In addition to their role in inflammation, immune cells in AT also have functions related to lipid metabolism that are not solely immune-related. These functions include balancing lipogenesis, which is the production of fatty acids and triglycerides, and lipolysis, the breakdown of stored fats, as well as managing how adipocytes react to changes in nutrient levels and body temperature.[156] For example, immune cells contribute to the adaptive thermogenesis process in brown adipose tissue, where lipid oxidation initiates heat production in response to cold exposure.[157] This highlights the complex interplay between the immune system, lipid metabolism, and energy expenditure. Notably, natural polysaccharides improve lipid and energy metabolism while alleviating inflammation by decreasing MD and ER stress.[158] Given that immunity also impacts lipid and energy metabolism, natural polysaccharides facilitate these processes by modifying host immunity.[159] This strengthens the positive reciprocal relationship between inflammation and lipid metabolism, as they can influence each other and exacerbate conditions, thereby contributing to the onset and advancement of metabolic disorders.

Nevertheless, the relationship between immune and metabolic functions presents a therapeutic challenge, as lowering inflammation might inadvertently disrupt vital metabolic processes. This intricacy necessitates that the immune-metabolic interactions related to pathology and homeostasis are differentiated at the molecular level. For instance, focusing on crucial immunometabolic points—like the states of macrophage polarization, thresholds of TLR signaling, or the function of adipose-resident Tregs—could provide chances to restore metabolic balance without compromising necessary immune responses.[160,161] Such insights could pave the way for more precise and effective treatments for T2D, addressing both the metabolic and inflammatory components of the condition.

Decreased glucose uptake in muscle

Diminished glucose uptake in muscle tissues, in particular, initiates the development of IR.[162] Muscle uptake of glucose from the bloodstream is essential; its derangement raises blood glucose to a degree that causes metabolism to run amok. The IR blocks glucose transporter type 4 (GLUT4) translocation to the plasma membrane, a prerequisite for glucose uptake, disrupting an insulin-mediated signaling pathway. The defect is aggravated in most cases by obesity.[163] This prolonged inflammation due to excess AT further disrupts insulin signaling in a damaging cycle, thereby advancing IR.[164] Excessive FFAs engender lipotoxicity and oxidative stress in muscle tissues, contributing to IR.[165] MD, accompanied by development towards a higher ratio of insulin-resistant fast-twitch muscle fibers, accounts for inadequate glucose transport and consequent metabolic afflictions.[166] MD in muscle cells would impair energy production and would thus, in turn, impede glucose utilization by muscle and promote IR. In addition, increased ER stress would inhibit the translocation of GLUT4 to the plasma membrane for insulin-mediated glucose uptake by muscle, thus further compromising insulin signaling.[167] This information is particularly crucial for understanding the link between T2D and immune aging, as age-associated MD, increased ER stress, and chronic low-grade inflammation significantly enhance IR and hinder glucose metabolism, thereby influencing the pathogenesis and advancement of T2D.

In this regard, one significant challenge in utilizing GLP-1RAs for managing T2D is their potential to aggravate sarcopenia (age-related loss of muscle mass, strength, and function) through negative impacts on muscle functionality and metabolism.[168] Although GLP-1RAs are very effective at improving insulin sensitivity and controlling blood glucose levels, their influence on muscle tissue may lead to unintended adverse consequences, particularly in vulnerable populations. This presents a crucial issue, as the long-term implications of GLP-1RAs on muscle health remain inadequately studied. Specifically, it is essential to elucidate how these medications influence mitochondrial function, ER stress, and muscle fiber structure. Addressing this knowledge deficiency is crucial for developing strategies that prevent or diminish muscle-related side effects. Identifying strategies to mitigate muscle-related side effects while optimizing the metabolic advantages of GLP-1RAs will be critical to ensuring their efficacy in T2D management without compromising muscle integrity.

Increased glucagon secretion

In T2D, pancreatic α-cells produce glucagon improperly, leading to elevated blood glucose levels. Typically, glucagon is secreted when blood glucose falls below a specific threshold, serving to stimulate glucose production in the liver. In T2D, excessive release of glucagon therefore worsens hyperglycemia.[169] IR ameliorates the inhibitory effect of insulin on glucagon production, particularly at high levels of insulin; thus, glucagon levels result in elevated levels despite hyperinsulinemia.[50] Chronic hyperinsulinemia further affects the signaling pathways controlling α- and β-cell function, promoting excessive glucagon secretion.[170] This imbalance causes increased HGP, thereby further worsening hyperglycemia. All of these contribute to complications of T2D, for example, comorbidity with CVDs and neuropathy. ER stress disrupts the normal secretion of glucagon in pancreatic α-cells.[171] The pathways triggered by ER stress led to the activation of the UPR response, which might influence the secretion of certain hormones, including glucagon. MD in α-cells results in inefficient energy production, consequently causing inappropriate glucagon secretion, aggravating IR in the liver, and increasing the production of glucose.[172] These activities are further exacerbated by aging, as age-related declines in mitochondrial function and increased ER stress can impair α-cell function, intensifying the metabolic imbalances that contribute to the onset of T2D.

An innovative approach to improve the treatment for T2D involves investigating the transdifferentiation of alpha (α) cells into beta (β) cells, which could help reduce excessive glucagon secretion and enhance metabolic control.[173] By transforming α-cells into insulin-producing β-cells, it might be feasible to lessen abnormal glucagon levels while boosting insulin production. Nevertheless, this strategy faces considerable challenges, particularly in achieving a proper balance between insulin release and glucagon suppression. Excessive insulin production may lead to hypoglycemia, while improperly functioning transdifferentiated β-cells could contribute to β-cell failure and exacerbate metabolic problems. Moreover, it is essential to tackle the underlying factors of cellular stress, including MD and ER stress, to ensure that the newly created β-cells operate effectively and prevent a resurgence of T2D-related issues. To progress in this field of study, research efforts need to concentrate on the molecular mechanisms that regulate α-cell reprogramming and methods to maintain the functionality of transdifferentiated β-cells over time.[174] By clarifying the intricate relationships between glucagon, insulin, and cellular stress, we can develop more precise and effective methods to manage or potentially reverse the advancement of T2D.

Increased glucose reabsorption in the kidneys

In conditions of hyperinsulinemia and IR, the kidneys increase glucose reabsorption.[175] Insulin causes sodium reabsorption in the proximal tubules, leading to glucose reabsorption through SGLTs and high blood glucose levels even after minor plasma glucose increases.[176] Chronic low-grade inflammation, commonly observed in obesity and metabolic syndrome, worsens this condition as cytokines such as TNF-α and IL-6 disrupt insulin signaling, thereby increasing IR and kidney dysfunction.[177] These processes induce a vicious cycle or feedback loop that elevates the risk for T2D. Thus, exploring the connection between hyperinsulinemia and inflammation is crucial to addressing downstream metabolic disturbances, including organelle dysfunction like MD and ER stress. Moreover, MD and ER stress within renal tubular cells hinder SGLT function, leading to impaired glucose reabsorption and worsening hyperglycemia.[178,179] This emphasizes the importance of addressing organelle dysfunction to avert subsequent metabolic disruptions.

However, SGLT2 inhibitors increase glucose elimination in the urine, leading to fluid loss.[180] This may cause dehydration and low blood pressure, particularly in older adults or those with impaired kidney function. The diuretic effect of SGLT2 inhibitors can exacerbate dehydration, potentially resulting in drops in blood pres-

sure, dizziness, and, in severe cases, fainting. This situation poses a significant challenge for patients on antihypertensive medications, as their combined effects may heighten the risk of dehydration and electrolyte imbalances.[181] To address these issues, certain pharmacological agents that target the UPR might help reduce ER stress by supporting normal protein folding and functionality. Tauroursodeoxycholic acid and 4-phenylbutyrate have demonstrated efficacy in alleviating ER stress and boosting insulin sensitivity.[182] When used alongside SGLT2 inhibitors, these agents could help lessen some undesirable effects of the medication, contributing to a more balanced therapeutic approach.

Decreased incretin effect

Diminished incretin effect hastens the progression of T2D, which results from reduced secretion of GLP-1 and GIP, diminished receptor sensitivity within pancreatic β-cells, and altered dipeptidyl peptidase-4 activity, an enzyme that degrades incretin hormones.[183] This leads to, in turn, insufficient insulin secretion, postprandial hyperglycemia, dysfunctional glucagon secretion, and eventually increased appetite, which typically worsens IR together with increased weight gain.[184] Chronic hyperinsulinemia and inflammation further impair incretin action by blocking insulin signaling and secretion of incretin hormones.[185] Pro-inflammatory cytokines secreted from the AT result in worsening β-cell dysfunction so that the insulinotropic effect fades gradually and converts into a cycle of inflammation, IR, and hyperglycemia.[164] Enteroendocrine, GLP-1, and GIP-producing cells manifest ER stress; the increased production of insulinotropic incretin hormones, together with low glucose control.[186] Chronic inflammation and oxidative stress can cause MD in β-cells, reducing their ability to respond to incretin hormones.[187] This leads to impaired insulin production and hyperglycemia.

Moreover, emerging findings seem to indicate the possibility that IR may play a role in reducing the weight-loss effectiveness of GLP-1 RAs in individuals with T2D.[188] While some individuals with obesity may retain insulin sensitivity, those diagnosed with T2D usually exhibit increased IR, which can disrupt GLP-1 receptor function, particularly within the brain, potentially due to unidentified desensitization mechanisms. Additionally, failures in mitochondrial function, ER stress, and the interplay between hyperinsulinemia and inflammation contribute to β-cell dysfunction and hinder incretin activity. Taken together, these factors may clarify why the weight-loss effects of GLP-1 RAs are diminished in people with diabetes, highlighting the necessity of comprehending the complex interactions between metabolic and inflammatory pathways to enhance treatment outcomes.

Neurotransmitter dysfunction

Neurotransmitter dysfunction is regarded as another essential component of the ominous octet in T2D, dysregulated dopaminergic and serotonergic signaling, and dysregulation of appetite control and reward pathways, leading to unhealthy eating habits and a gross increase in caloric intake.[189] Alteration in dopaminergic function idealizes cravings and promotes the risk of obesity development; on the other hand, imbalance in serotonin reduces satiety and encourages emotional eating.[190] Chronic low-grade inflammation also undermines neurotransmitter action, further aggravating it and metabolic dysregulation.[191] Through increased oxidative stress and inflammation, MD and ER stress interfere with glucose homeostasis and worsen neurotransmitter dysregulation.[192] These systemic interactions may aid in the effective and long-term management of T2D, including hyperglycemia, IR, inflammation, and organelle health. MD interferes with energy metabolism in neurons, affecting neurotransmitter function, especially dopamine and serotonin, which are important for regulating appetite and eating behaviors. With advancing age, MD becomes more common, resulting in compromised neurotransmitter management.[193] Furthermore, ER stress in the brain intensifies this dysregulation, affecting reward pathways and further disrupting appetite regulation.[194] This ongoing cycle exacerbates challenges such as IR and obesity, both prevalent in the cognitive decline associated with aging. Ultimately, these metabolic issues and dysfunctions in organelles may adversely affect cognitive capacities, thus complicating the development of neurodegenerative diseases and age-related disorders.[195,196]

The neuroimmune-metabolic axis in T2D

Building on this foundation, it is evident that an imbalance in neurotransmitters is fundamentally connected to the larger network of immune aging, systemic metabolic dysfunction, and neurological deterioration in T2D. Central to this pathological relationship are mechanisms like neuroinflammation, cellular senescence, glial dysfunction, and the infiltration of peripheral immune cells into the CNS, all of which are influenced by both aging and hyperglycemia. These processes interact to disrupt the equilibrium between neurons and glial cells, leading to a range of cognitive impairments, diminished synaptic plasticity, and heightened susceptibility to neurodegenerative conditions.

Neuronal changes in these conditions are characterized by a decrease in synaptic plasticity, especially the reduction of long-term potentiation in hippocampal neurons, which obstructs memory formation and the capacity to learn.[197] At the same time, neurogenesis is significantly reduced, limiting the brain's flexibility and its ability to reorganize when faced with metabolic stress. AGEs, which are often elevated in T2D and during aging, disrupt neuronal metabolism, hinder axonal transport, and contribute to ongoing neurodegeneration.[198,199] The dysregulation of neuroglial cells is also notably important. In the brains of individuals with diabetes and aging, microglia adopt a pro-inflammatory M1 phenotype, which is marked by the secretion of cytokines such as IL-1β and TNF-α, leading to neuroinflammation and damage.[200] Astrocytes undergo reactive astrogliosis, compromising their ability to regulate the extracellular environment, support synaptic function, and maintain the balance of neurotransmitters.[201] This disturbance in neuroglial cells disrupts essential interactions between neurons and glia, impairs synaptic transmission, weakens the integrity of the blood-brain barrier (BBB), and reduces neurovascular coupling.[202]

The detrimental effects are further aggravated by the active interaction between the CNS and the immune system outside of the brain. Ongoing peripheral inflammation, originating from organs with metabolic imbalances, such as the liver and AT, results in increased levels of systemic cytokines like IL-6 and TNF-α.[203,204] These cytokines can cross a compromised BBB, activating glial cells and initiating neuroinflammatory pathways. Furthermore, the breach of the BBB permits peripheral monocytes to infiltrate the brain, where they become inflammatory macrophages, intensifying neuroimmune responses.[205] The vagus nerve is vital for this interaction, relaying immune signals from the gut and other organs to the brainstem while also regulating microglial function in response to peripheral metabolic signals.[206] Ultimately, the aging of the blood cell-producing system leads to a systemic environment that favors inflammation. Age-related transformations in the properties of immune cells derived from bone marrow, such as monocytes and macrophages, lead to the secretion of inflammatory cytokines

that affect glial activity and the brain's immune landscape.[207,208]

Furthermore, the widespread effects of cellular senescence exacerbate both systemic and central dysfunction.[209] Within the CNS, aging astrocytes and microglia sustain a chronic inflammatory condition, hinder the clearance of neurotoxic proteins, and inadequately support neuronal function.[210] In summary, these systemic and localized senescent processes not only enhance the pathophysiological impact of T2D but also foster an environment that promotes cognitive decline and the advancement of neurodegenerative diseases in older adults.[211] Therefore, the neuroimmune-metabolic axis in T2D and aging becomes an essential framework for comprehending the relationship between immune aging and T2D.[115,212]

Mitochondria-ER crosstalk in regulating the ominous octet of T2D

Mitochondria and the ER are connected at specific contact points known as mitochondria-associated membranes (MAMs), which serve as a platform for interaction and molecular exchange between the two organelles.[213] Their interaction is essential in the regulation of calcium signaling, lipid metabolism, and ROS dynamics. Disruption of the communication between the two organelles can have serious implications, as it is involved in the development of diabetes, impacting the ominous octet of T2D. It is through this interaction between mitochondria and ER that pancreatic β-cells operate, facilitating the flow of calcium between them, which in turn leads to the synthesis of ATP essential for glucose-stimulated insulin secretion.[214,215] When disrupted, this interface causes a calcium imbalance that hampers ATP production, which subsequently affects the glucose-stimulated insulin secretion. Besides, an increase in mitochondrial calcium can bring about apoptosis due to the release of cytochrome c, which is important for the electron transport chain and activation of apoptotic pathways.[216] MD also enhances the production of ROS, which aggravates ER stress and affects β-cell viability and function.[217] Moreover, the disruption of MAM has an impact not only on calcium regulation and mitochondrial function but also results in an imbalance in lipid metabolism, which leads to the accumulation of ceramides. This accumulation, along with elevated levels of ROS and ER stress, triggers the activation of the JNK signaling pathway. The activation of this stress-response pathway interferes with insulin signaling, ultimately resulting in IR and the onset of diabetes. Moreover, in peripheral tissues such as muscle and liver, MAMs are major modulators of insulin sensitivity.[218] These intersectional contacts are at risk for catastrophe in lipid metabolism, allowing toxic intermediates, such as ceramides, to accumulate and interfere effectively with insulin signaling.[219] In parallel, ROS and ER stress can activate inflammatory pathways, such as the JNK pathway, which inhibit critical components of insulin signaling and exacerbate IR.[220,221] To elaborate further, JNK acts as a vital mediator that links cellular stress with inflammation and metabolic dysfunction when it is activated by ER and oxidative stress.[222] Upon activation, JNK migrates to the nucleus and phosphorylates transcription factors such as c-Jun, enhancing the AP-1 (activator protein 1)-driven expression of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, which are involved in the low-grade chronic inflammation seen in aging and metabolic disorders.[223] At the same time, JNK hampers insulin action by attaching phosphate groups to IRS-1 on serine residues (including Ser307 in rodents), which interferes with its tyrosine phosphorylation, thereby impeding the subsequent PI3K-Akt activation necessary for glucose uptake.[224] This alteration not only diminishes insulin sensitivity but also drives cells into a state that is both pro-inflammatory and metabolically inflexible. In tissues such as adipose and muscle, prolonged JNK activation leads to the infiltration of immune cells, changes in adipokine profiles, and a disruption in metabolic homeostasis.[225] In the liver, even minor JNK hyperactivation can result in increased lipid accumulation and IR, which may contribute to the early stages of metabolic dysfunction in this organ.[226] Furthermore, JNK engages with stress-responsive signaling pathways such as NF-κB, IRE1-XBP1 (X-box binding protein 1), and the NLRP3 inflammasome, exacerbating a harmful feedback loop.[227] As a result, the JNK pathway functions as a key element that converts intracellular stress into widespread low-grade inflammation and IR, both of which are crucial to metabolic syndromes associated with aging.[228]

A significant area where ER stress and MD overlap is the activation of inflammatory signaling pathways associated with stress, particularly the NF-κB pathway, which is essential for disturbing metabolic homeostasis.[229,230] The activation of NF-κB, which is often initiated by ROS, the UPR, and lipid-induced ER stress, intensifies inflammation in tissues sensitive to insulin.[231] In AT, NF-κB boosts the generation of chemokines that attract pro-inflammatory M1 macrophages, creating a self-sustaining inflammatory cycle. In both skeletal muscle and liver tissues, cytokines activated by NF-κB disrupt insulin receptor signaling and impede OXOPHOS, further diminishing glucose uptake and utilization.[232,233] Hepatocytes, in particular, experience a mild inflammatory state and cellular stress facilitated by NF-κB, creating a favorable environment for lipid accumulation and the development of hepatic IR.[234] While these alterations might initially remain unnoticed, sustained NF-κB activation accelerates the metabolic decline typically associated with T2D. Additionally, NF-κB indirectly impairs insulin functionality by increasing levels of SOCS proteins and promoting the serine phosphorylation of IRS-1, which together interfere with the insulin signaling pathway and reduce downstream activation of PI3K-Akt.[235] Therefore, given its crucial involvement in inflammation and IR, NF-κB acts as a molecular connection between mitochondrial-ER stress and various aspects of the "ominous octet" that drives the pathophysiology of T2D.

Furthermore, the important molecular elements involved in the anchoring junctions between mitochondria and ER include the mitochondrial calcium uniporter.[236] This would allow entry of calcium into the mitochondria, the subunit essential for ATP formation. Malfunctions of inositol 1,4,5-trisphosphate receptor (IP3R) associated with calcium transport from the ER into mitochondria may cause excessive calcium overload into mitochondria, with increased ROS production.[237] Moreover, proteins such as mitofusin-2 and voltage-dependent anion channel 1 are also critical for the structural integrity of MAM, including maintaining efficient transport of their metabolites, and their malfunction would lead to the onset of diabetes.[238]

The interaction between mitochondria and the ER primarily determines the liver's ability to manage gluconeogenesis.[239] Ineffective calcium signaling can activate enzymatic functions vital to gluconeogenesis, like PEPCK and glucose-6-phosphatase (G6Pase), ultimately resulting in excessive glucose production.[240] Consequently, the liver's ability to reduce glucose production will also decline due to decreased ATP generation from mitochondria, which indirectly elevates blood glucose levels.[241] Incretin hormones such as GLP-1 depend, furthermore, on robust interactions between mitochondrial and ER functions in the body for their impact on insulin release.[242] However, MD disrupts bioenergetics and also hampers the insulin-stimulating effect of GLP-1.[243]

Chronic and excessive strain on the ER leads to a diminished molecular affinity of incretin receptors, thereby severely undermining incretin's role in glucose balance.[244] Importantly, the communication between mitochondria and ERs is essential in AT, where it has an important regulatory role in fat metabolism. If this interaction is disrupted, it could lead to excessive breakdown of AT, resulting in the accumulation of FFAs that damage the β-cells, cause MD, and adversely affect overall IR.[245] Similarly, α-cell metabolism and glucagon secretion are influenced by calcium concentrations at MAMs, where abnormal signaling may trigger excessive glucagon secretion and, as a result, unwarranted glucose production in the liver.[246] As previously stated, disruptions in communication between mitochondria and ER affect renal glucose absorption since renal tubular cell stress has been linked to increased expression of SGLT2, which promotes glucose absorption and poses a burden on rising blood glucose levels.[247] Interestingly, the dysfunction of neurotransmitters, specifically within the hypothalamus, represents yet another aspect that changes the interaction of mitochondria and the ER.[248] The hypothalamus uses this connection to control food intake, maintain energy equilibrium, and support the overall function of insulin.[249] Disruption of calcium transport hinders mitochondrial ATP production and fails to signal the effects of insulin and leptin, with leptin being the hormone that regulates appetite in hypothalamic neurons.[250] Besides, the buildup of ROS intensifies the disruption of neuronal activity, which impacts the central regulation of glucose and lipid metabolism in the body.[251]

In summary, the interaction of mitochondria and the ER is critical given the various obstacles posed by diabetes. Disruption in communication from the mitochondria to the ER may reinforce β-cell failure, IR, hyperglycemia, and lipid mismanagement, creating a vicious cycle of metabolic deterioration by affecting individual components of the "ominous octet" of T2D. Any additional knowledge that may be uncovered about this relationship can serve as a guiding light in the search for new therapeutic tools aimed at restoring cellular homeostasis, as well as forestalling and/or preventing diabetes.

Limitations of the study

This review primarily focuses on the cellular and molecular mechanisms underlying T2D, highlighting essential processes such as metabolic dysfunction, ER stress, ROS, maintenance of calcium levels, and the activation of stress kinases like JNK and NF-κB. These mechanisms offer valuable insights into the pathophysiology of T2D and serve as a foundation for understanding the disease at the cellular level. However, our current knowledge primarily stems from preclinical and mechanistic studies, which do not necessarily accurately capture the clinical diversity found in human populations. Factors such as diet, obesity prevalence, and environmental influences all contribute to this variability, making it difficult for mechanistic research to fully address. While we emphasize the key components of the "ominous octet", a thorough exploration of how these molecular changes translate into clinical outcomes and treatment strategies is not included in this paper. A significant portion of the mechanistic data is derived from *in vitro* studies or animal models, particularly mice, in the context of IR and organelle dysfunctions. However, these models are constrained by their failure to account for metabolic, immune response, and physiological differences between species. Demographic aspects like gender, age, and ethnicity are important but are less emphasized in this review. Variations in mitochondrial and ER functions with age, metabolic differences across genders, and the ethnic disparities in T2D prevalence and prognosis are vital, but they are beyond the focus of this study. Although we talk about well-known therapies such as GLP-1RAs and anti-inflammatory treatments, we do not explore emerging fields of study like the gut microbiome, circadian rhythms, and epigenetic modifications that may affect mitochondrial-endoplasmic reticulum interactions, which could be vital topics for future review articles. These areas hold potential for developing more targeted research into the pathophysiology of T2D. Taken together, many of the study's limitations arise from the inherent difficulty of covering all aspects of T2D in a review that primarily focuses on mechanisms. Essentially, our primary goal is to establish a foundational understanding of mitochondrial-ER interactions in T2D, focusing on the pathological mechanisms that arise across multiple organ systems. This includes exploring the central role of the hyperinsulinemia–inflammation axis in disease progression. This underscores the need for forthcoming research to consider clinical, demographic, and environmental factors. Such studies will be crucial for making T2D treatment more individualized and for devising therapies that are more targeted and efficient.

Future directions

The rising global incidence of T2D in developing countries highlights the urgent necessity for novel and personalized treatment strategies. Predictions indicate that by 2045, around 783 million people are expected to be diagnosed with T2D, making the condition increasingly complicated. The T2D framework, which is based on metabolic imbalances marked by IR and inflammatory mechanisms, termed the hyperinsulinemia-inflammation axis, provides a thorough understanding of the need for customized therapeutic approaches. There are notable gaps in our knowledge regarding which specific factors are most negatively impacted in individuals with T2D, which is critical for implementing targeted treatment options. For instance, when MD becomes a key causal factor, it is essential to prioritize treatment strategies that aim to restore mitochondrial performance. Likewise, intervention methods that concentrate on reducing ER stress or lowering inflammation may yield better results. A comprehensive, multi-dimensional approach that simultaneously targets mitochondrial activity, ER stress, and inflammation is likely to improve the effectiveness of T2D treatment.

An area of research worth exploring is MAMs, which play a role in maintaining cellular balance and are linked to insulin resistance and inflammation in T2D. Treatments aimed at MAMs could restore cellular function and enhance insulin sensitivity by increasing interactions of MAM proteins, such as mitofusin-2, which improves communication between mitochondria and the ER while decreasing oxidative stress. Substances like resveratrol and spermidine promote the generation of new mitochondria, whereas calcium transport proteins at the MAM interface may be leveraged to restore calcium equilibrium, which is crucial for insulin signaling.[252,253] Furthermore, modifying lipid metabolism at MAMs could help to decrease lipid buildup and enhance insulin sensitivity, presenting a new strategy to tackle the metabolic problems central to T2D.

Exploring the oxidative processes that contribute to IR and high blood glucose may create new opportunities for developing treatments that enhance insulin sensitivity, reduce chronic inflammation, and better regulate metabolism. When paired with lifestyle changes, such as physical activity and dietary adjustments, these approaches could present a more integrated strategy for managing T2D. Future studies should also examine drug therapies that im-

pact mitochondrial function or promote insulin secretion. Tailored treatments involving gut hormones like GLP-1RAs, recognized for their anti-inflammatory properties, could enhance glucose management and cognitive functions, especially in older adults.

Ultimately, the role of immune aging in the development of T2D, particularly among older adults, warrants further investigation. Age-related immune changes, such as chronic inflammation and the buildup of senescent cells, can disrupt glucose balance, yet these mechanisms remain inadequately understood. Strategies aimed at mitigating immune aging, like senolytic therapies, immune modulators, and anti-inflammatory agents, show promise but require further refinement and evaluation.[254,255] At the same time, epigenetic clocks that distinguish biological age from chronological age provide a valuable tool for identifying individuals at risk of accelerated immune decline.[256,257] These resources can facilitate early interventions to mitigate immune dysfunction and lower the likelihood of developing T2D. Enhancing mitochondrial function, reducing ER stress, and preserving immune resilience are crucial not only for managing T2D but also for promoting healthy aging. A mechanistic and personalized approach will be essential in shaping future treatments and optimizing long-term care for elderly populations.

Conclusions

The Ominous Octet model offers a comprehensive perspective on the interconnected mechanisms through which T2D develops. The processes that drive T2D include hyperinsulinemia, widespread inflammation, MD, and ER stress, all of which contribute to the gradual decline of glucose metabolism. Compromised insulin signaling, increased gluconeogenesis, and impaired β-cell function led to hyperglycemia and IR. T2D in the elderly should be treated as such, as age-related difficulties complicate the condition due to a generally compromised immune system and, as a result, chronic inflammation, which can emerge from metabolic tissues. Developing personalized and integrated treatment strategies for mitochondrial health, inflammation, and organelle dysfunction is crucial for managing T2D. Key factors include pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) that impair β-cell functionality, along with chemokines such as C-C motif chemokine ligand 2 (CCL2) and C-X-C motif chemokine ligand 10 (CXCL10), which recruit inflammatory monocytes to insulin-sensitive tissues. Adipokines such as leptin and adiponectin play a role in modulating immune responses within adipose tissue, while AGEs activate RAGE receptors, triggering NF-κB signaling and persistent inflammation. Additionally, dysfunction is worsened by senescent cells through the SASP. Future research should prioritize personalized therapies to address T2D in developing nations and improve outcomes for aging populations.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Conceptualization and supervision, formal analysis, original draft preparation, project administration, funding acquisition (SKC), writing—review and editing (SKC, DC). Both authors have approved the final version and publication of the manuscript.

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