endocrines

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Review

The Bidirectional Link between Major Depressive Disorder and Type 2 Diabetes: The Role of Inflammation

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Abstract: Background/Objectives: There is a bidirectional relationship between major depressive disorder (MDD) and type 2 diabetes (T2D), as MDD increases the risk of T2D by 38% to 67%, and T2D increases the risk of MDD by 15% to 33%. Many factors contribute to the occurrence of comorbid MDD and T2D, including converging pathophysiological pathways like inflammation. The objective of this review was to comprehensively summarize available evidence on the relationship between MDD, T2D, and inflammation. **Results**: Although the precise mechanisms linking T2D and MDD are still not fully understood, shared inflammatory mechanisms likely contributes to the heightened risk of developing this comorbidity. To date, the evidence supports that chronic low-grade inflammation is a feature of both MDD and T2D and has been shown to interact with pathways that are relevant to the development of both chronic disorders, including the hypothalamic–pituitary–adrenal (HPA) axis, neuroplastic processes, gut microbiome, insulin resistance, and adipose tissue dysfunction. Through their impact on inflammation, dietary and physical activity interventions can play a role in the risk and management of MDD and T2D. **Conclusions**: Deepening our understanding of the mechanisms underlying the augmented inflammatory responses observed in individuals with the MDD and T2D comorbidity is essential for tailoring appropriate therapeutic strategies.

Keywords: depression; type 2 diabetes; obesity; comorbidity; inflammation; diet; physical activity

Citation: Bodnaruc, A.M.; Roberge, M.; Giroux, I.; Aguer, C. The Bidirectional Link between Major Depressive Disorder and Type 2 Diabetes: The Role of Inflammation. *Endocrines* **2024**, *5*, 478–500. https://doi.org/10.3390/endocrines5040035

Academic Editor: Maria Mirabelli

Received: 23 April 2024
Revised: 6 September 2024
Accepted: 27 September 2024
Published: 9 October 2024

1. Introduction

Major depressive disorder (MDD) and type 2 diabetes (T2D) are heterogeneous and complex disorders that are responsible for considerable proportions of disability and mortality worldwide [1,2]. Affecting over 250 million individuals globally and with a prevalence that is still on the rise, MDD ranks among the most common and burdensome mental health disorders [1]. Similarly, with global prevalence having nearly quadrupled over the past three decades, T2D affects approximately 537 million adults, making it one of the most widespread cardiometabolic disorders and one of the biggest public health challenges of the century [2].

Over the past three decades, the prevalence of comorbid mental health and cardiometabolic disorders has drastically increased, reaching epidemic proportions in numerous countries [3]. Meta-analyses of prospective cohort studies have reported a 38% to 67% higher risk of developing T2D in individuals with MDD, and a 15% to 33% higher risk of developing MDD among individuals with T2D [4–6]. Comorbid MDD and T2D have been associated with poorer health outcomes [7–9], lower quality of life [10,11], higher mortality [12,13], as well as increased healthcare-related costs [14,15].

Many factors can contribute to the occurrence of comorbid MDD and T2D, such as shared genetic susceptibility, converging pathophysiological pathways, as well as psychosocial and environmental factors [3]. In this regard, the involvement of inflammation in the pathophysiology of both MDD and T2D has gained increased attention over the past two decades [16]. The objective of this review was to comprehensively summarize available evidence on the relationship between MDD, T2D, and inflammation.

2. MDD

According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), the core symptoms of MDD are persistent low mood and anhedonia, which are accompanied by alterations in emotion regulation (e.g., excessive feelings of guilt, unworthiness), cognitive abilities (e.g., decreased concentration, memory), and physiological functions (e.g., dysregulated sleeping patterns and appetite, hypo- or hyperlocomotion) [17]. One meets the diagnostic criteria for MDD when there is evidence supporting (1) the manifestation of five or more depressive symptoms, of which at least one is a core symptom, and that these symptoms (2) are present for at least two consecutive weeks and (3) are associated with clinically significant psychological distress and/or disabilities in essential areas of functioning, including activities of daily living, professional activities, and social interactions [17].

Despite significant advances in the understanding of MDD, there are currently no established mechanisms that can explain all facets of the disease. The etiology of MDD involves genetic predispositions, which explain 30–40% of MDD risk [18] and interact with a wide range of psychological (e.g., negative self-concept, sensitivity to rejection, negative emotionality) and environmental factors (e.g., adverse life events, social isolation, low socioeconomic status, poor lifestyle) [19]. These etiological factors are at the origin of pathophysiological alterations affecting, among others, the immune system [20–34], monoamine neurotransmitters' metabolism [35–38], the hypothalamic-pituitary-adrenal (HPA) axis [39–41], neuroplasticity [42–45], and the gut microbiome [46–48].

MDD is associated with a significant increase in morbidity and mortality, often resulting in higher levels of disability and impairment than most physical conditions [49]. MDD increases the risk of several physical disorders, including obesity [50] and T2D [51]. MDD also increases the risk of other mental disorders, such as anxiety [52]. MDD is associated with premature mortality, with a significant proportion attributable to elevated rates of comorbid conditions [49]. Suicide also plays a crucial role in increasing mortality rates, with MDD elevating the risk of suicide death nearly 20-fold [53].

3. T2D

T2D accounts for 90% of all cases of diabetes and is characterized by a chronic state of hyperglycemia resulting from insulin resistance and/or impaired insulin secretion [54]. According to Diabetes Canada, T2D occurs when one has a fasting blood glucose $\geq$ 7.0 mmol/L, a 2 h post-prandial or random blood glucose $\geq$ 11.1 mmol/L, or glycated hemoglobin (A1c) $\geq$ 6.5% [55].

Following a meal, the hormone insulin is secreted into the bloodstream by the pancreatic β-cells, allowing for glucose uptake into the cells [56]. Early in T2D development, the target tissues of insulin, mainly the liver, adipose tissues, and skeletal muscles, become less sensitive to its action, ultimately leading to decreased glucose uptake [56]. This decreased ability of target tissues to respond to insulin is called insulin resistance [56]. The proposed contributors to β-cell dysfunction and insulin resistance include oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas, ectopic lipid deposition, as well as lipotoxicity and glucotoxicity [57]. Although pinpointing the most significant T2D pathophysiological mechanism has proven to be challenging, each of these cellular stressors is believed to either trigger an inflammatory response or be worsened by inflammation. As such, emerging evidence suggests that dysregulation of inflammatory markers and abnormalities in immune function play significant roles in T2D pathogenesis [58].

T2D is closely linked with a plethora of comorbidities, including cardiovascular diseases, chronic kidney disease, osteoporosis, vision impairment, as well as mental health comorbidities such as depression [59]. Estimates indicate that adults with T2D tend to have a life expectancy of around six years shorter than those without the condition [59].

4. Inflammation

4.1. Acute vs. Chronic Inflammation

The term inflammation encompasses a broad range of immune-related processes occurring within the body. Acute inflammation is a protective reaction typically triggered by the recognition of extracellular stimuli by nearby immune-responsive cells and regulated by cytokines, chemokines, and various other signaling molecules [60]. These stimuli can involve damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), activating receptors on or within cells present in the affected tissues [60]. In response, these cells induce and regulate varying degrees of inflammation, chemotaxis, cell growth, and tissue repair locally and throughout the body [60].

After the threat or damage has been addressed, the resolution of acute inflammation is crucial for restoring homeostasis [60,61]. If the inflammatory response is not resolved properly, it can transition into chronic inflammation [60,61]. The feedback loops required for a robust acute inflammatory response may instead exacerbate inflammation, sustaining immune responses and causing tissue damage, leading to tissue fibrosis and destruction [60,61]. While acute inflammation is a normal and essential step in healing, chronic inflammation is detrimental and contributes to the development of several pathologies [60,61].

As shown in Table 1, acute and chronic inflammation differ based on their onset, duration, cause, cells and mediators involved, tissue damage, and outcomes [60,61]. Acute inflammation has an immediate onset in response to pathogens and tissue damage and lasts from days to weeks [60,61]. In contrast, chronic inflammation is due to persistent foreign bodies, persistent acute inflammation, and autoimmune reactions, has a delayed onset and lasts from months to years [60,61]. Acute inflammation promotes tissue repair and primarily involves neutrophils, vasoactive amines, and eicosanoids [60,61]. Conversely, chronic inflammation promotes tissue damage and primarily involves monocytes, macrophages, lymphocytes, fibroblasts, as well as cytokines, growth factors, hydrolytic enzymes, and reactive oxygen species [60,61].

4.2. Central Inflammation

Central inflammation, also called neuroinflammation, refers to inflammatory processes occurring within the central nervous system (CNS), namely in the brain and the spinal cord [62,63]. Central inflammation involves inflammatory mediators that are commonly used by the immune system for inflammatory processes occurring in the periphery, such as cytokines and chemokines [62,63]. Exchanges between the periphery and the CNS are tightly regulated by the blood–brain barrier (BBB), a semi-permeable membrane situated at the interface between the circulatory system and the brain [62,63]. There are several pathways through which peripheral inflammatory mediators can access the CNS, such as (1) passage through leaky regions of the BBB at circumventricular organs, (2) active transport via mediator-specific saturable transporters, (3) neural afferent fiber activation transducing signals to the brain, (4) activation of endothelial cells and perivascular macrophages in the cerebral vasculature to produce local inflammatory mediators such as cytokines, chemokines, prostaglandins, and nitric oxide, and (5) attraction of activated peripheral immune cell including monocytes and T cells to the meninges and the brain parenchyma by chemokines released by activated microglia and adhesion molecules expressed in the CNS [62,63]. Chronic peripheral inflammation also has the potential to disrupt the integrity of the BBB, namely by increasing solute permeability and leukocyte traffic as well as by inducing signaling changes and structural damages [64]. Disruption of the BBB integrity can further facilitate the entry of inflammatory molecules [64]. Inflammatory molecules are

also synthesized within the CNS, mainly by microglia, which are the resident macrophages of the brain [65]. Although peripheral inflammatory mediators that migrate or relay information to the brain contribute to the central inflammatory response, the primary features of neuroinflammation include the abnormal activation of resident immune cells, namely microglia, and subsequent involvement of astrocytes [62,63].

Table 1. Characteristics of acute versus chronic inflammation.

	Acute Inflammation	**Chronic Inflammation**
Onset	Immediate	Delayed
Duration	Days to weeks	Months to years
Cause	- Pathogens - Tissue damage	- Persistent foreign bodies - Persistent acute inflammation - Autoimmune reactions
Primary cells	- Neutrophils	- Monocytes - Macrophages - Lymphocytes - Fibroblasts
Primary meditators	- Vasoactive amines - Eicosanoids	- Cytokines - Growth factors - Hydrolytic enzymes - Reactive oxygen species
Tissue damage	Minimal (promotes tissue repair)	Prolonged (promotes tissue damage)
Outcomes	- Resolution - Accesses formation - Chronic inflammation	- Tissue fibrosis and destruction

4.3. Inflammation and MDD

Extensive evidence stemming from both observational and experimental studies supports the involvement of inflammation in the pathophysiology of MDD. As evidenced by multiple meta-analyses of observational studies, individuals with MDD exhibit key features of an inflammatory response, including increased peripheral levels of proinflammatory cytokines (e.g., interleukin-1 receptor antagonist (IL-1RA), IL-6, IL-12, IL-13, IL-18, tumor necrosis factor alpha (TNF-α) [20]), proinflammatory cytokines receptors (e.g., soluble interleukin-2 receptor (sIL2R), soluble tumor necrosis factor receptor 2 (sTNFR2) [20]), acute phase reactants (e.g., C-reactive protein (CRP), albumin), and chemokines (e.g., C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 4 (CXCL4), CXCL7 [21]). Elevated inflammatory markers, including IL-6 and TNF-α, have also been observed in the cerebrospinal fluid and post-mortem brains of individuals with MDD [22]. Similarly, translocator protein, a positron emission tomography marker of central inflammation, has also been shown to be elevated in the anterior cingulate cortex and temporal cortex of individuals with MDD [22]. These brain areas are involved in processing sensory input, memory functions and complex cognitive functions such as emotionality, empathy, impulse control, and decision-making [24]. While inconsistent, some studies have also reported increased markers of microglial activation and decreased expression of astrocyte-specific markers [22]. Adding to these findings, observational studies have shown that both prior severe infections and autoimmune diseases increase the risk of subsequently developing MDD [25].

The implication of the immune system in the development of depressive symptoms and MDD has also been confirmed by numerous experimental and drug vigilance studies. In animal models, studies have shown that the administration of immune challenges

(e.g., lipopolysaccharide (LPS)) can lead to depressive-like behavior and that stress-induced depression is partly mediated by inflammatory changes [27]. Conversely, the administration of antidepressants to animals with inflammation or stress-induced depression decreases depressive-like behaviors partly through a reduction in inflammation [29]. In humans, it has been shown that individuals who receive cytokine treatments (i.e., IL-2 or interferon-alpha (INF-α)) as part of their treatment for hepatitis or cancer often develop depressive symptoms [30]. Several meta-analyses also support that cytokine treatment-induced depression can be prevented with the prophylactic administration of antidepressants [31]. Further supporting the involvement of the immune system in the development of MDD, meta-analyses of randomized controlled trials have shown that treatment with antidepressants reduces inflammation and that treatment with anti-cytokine drugs is effective in diminishing depressive symptoms in individuals with MDD. More specifically, treatment with antidepressants has been shown to decrease circulating levels of IL-4, IL-6, and IL-10 [32]. A decrease in peripheral levels of IL-1β was also observed, but only among individuals treated with SSRI antidepressants [32]. A meta-analysis of 16 clinical trials assessing the antidepressant activity of anti-cytokine drugs reported small-to-moderate beneficial effects for all agents, which targeted TNF-α (i.e., Etanercept, Adalimumab, Infliximab, Eisenberg), IL-6 receptor (i.e., Toclizumab), IL-4 receptor-α (e.g., Dupilumab), and IL-12/23 (i.e., Ustekinumab) [33]. Similarly, in a meta-analysis, the use of the non-steroidal anti-inflammatory drug Celebrex as an adjunctive treatment was found to be associated with significantly higher mean changes in depression scores as well as significantly higher remission rates than placebo in individuals with MDD [34]. As described in the sections below, inflammation plays a role in several pathophysiological alterations associated with MDD, namely alterations within monoamine neurotransmitter systems, the HPA axis, neuroplasticity, and the gut microbiome.

4.3.1. Inflammation and Monoamine Neurotransmitters in MDD

The decreased availability of monoamine neurotransmitters (i.e., serotonin (5-HT), noradrenaline (NA), and dopamine (DA)) is one of the most widely known pathophysiological features of MDD. While results remain somehow inconsistent, studies have reported that individuals with MDD have decreased cerebrospinal fluid levels of monoamine neurotransmitter metabolites (e.g., 5-hydroxyindoleacetic acid, homovanillic acid) and monoamine-degrading enzymes (e.g., monoamine oxidase A (MAO-A)) [37,38]. Furthermore, acute depletion of the 5-HT precursor tryptophan, leading to temporarily lowered 5-HT levels in the CNS, has been shown to influence emotional regulation and contribute to lowering mood, particularly in individuals with a family history of MDD [35,36]. Nonetheless, the most robust proof of the implication of monoamine neurotransmitters in the pathophysiology of MDD stems from the effectiveness of monoamine-targeting antidepressants (e.g., tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SSNRIs)) in diminishing depressive symptoms among individuals with MDD [66,67].

There are several pathways through which inflammatory cytokines can lead to reduced synaptic availability of monoamines, including by increasing their reuptake into pre-synaptic neurons and by decreasing their synthesis. In this context, IL-1β and TNF induction of p38 mitogen-activated protein kinase (p38MAPK) has been shown to increase the expression and activity of 5-HT reuptake pumps, leading to decreased synaptic availability of 5-HT and depressive-like behavior in laboratory animals [68]. Inflammatory cytokine administration and chronic low-grade inflammation have also been shown to increase indoleamine 2,3-dioxygenase (IDO) activity, the latter decreasing the conversion of tryptophan into the 5-HT precursor 5-hydroxytryptophan (5-HTP) and increasing the conversion of tryptophan into kynurenine (KYN), which can be further converted into the neurotoxic metabolite quinolinic acid (QUIN) by activated microglia [69,70]. In this regard, correlations between INF-α-induced MDD, decreased plasma tryptophan, and increased KYN have been reported [69,70]. Similarly, INF-α-induced MDD has been associated with

increased cerebrospinal concentration of KYN and QUIN [71]. Inflammatory cytokines have also been shown to reduce the synthesis of monoamine neurotransmitters by decreasing the availability of tetrahydrobiopterin (BH4), a key enzyme co-factor in the synthesis of all monoamines [72].

4.3.2. Inflammation and the HPA Axis in MDD

Another widely confirmed biological feature of MDD is the abnormal activity of the HPA axis, which is the principal regulator of physiological processes in response to physical and psychological stress [73]. A recent meta-analysis indicates that cortisol levels, measured in saliva, cerebrospinal fluid, urine, or hair, are slightly higher in individuals with MDD than in healthy controls [39]. More specifically, one meta-analysis has shown that higher morning cortisol levels specifically are associated with a higher prospective risk of MDD in adult populations [40]. Recent findings from a meta-analysis also suggest that high cortisol levels in individuals with MDD are resistant to feedback inhibition by the HPA axis [41]. Further supporting the involvement of the HPA axis in the pathophysiology of MDD, almost all currently available anti-depressants are known to influence cortisol levels [74].

There is a bidirectional relationship between inflammation and the HPA axis whereby, in normal physiological conditions, inflammation activates the HPA axis, and glucocorticoids decrease inflammation [73]. In individuals with MDD, however, evidence suggests that elevated levels of glucocorticoids may co-exist with high levels of inflammatory cytokines [75]. Several inflammation-related mechanisms have been proposed to account for this phenomenon, such as disruption of negative feedback via glucocorticoid receptors (GRs) [41], variations in GR expression and function [76,77], and changes in glucocorticoid bioavailability [78,79]. Studies conducted in individuals with MDD have found positive associations between cytokine production and glucocorticoid resistance, as assessed by the dexamethasone suppression test [41]. Proinflammatory cytokines have also been shown to impact the relative expression of the α and β isoforms of GRs, with a shift towards the inactive β isoform in individuals with MDD [76]. Along the same lines, proinflammatory cytokines affect GR function by inhibiting their translocation from the cytoplasm to the nucleus as well as by altering their interactions with nuclear proteins, including Nuclear Factor kappa B (NF-κB) [77]. Additional potential impacts of cytokines on glucocorticoid homeostasis encompass the activation of 11 beta-hydroxysteroid dehydrogenase 2 (11β-HSD-2), leading to cortisol inactivation [78], as well as the augmentation of activity and expression of the multidrug resistance P-glycoprotein pump, prompting the expulsion of glucocorticoids from the cell [79]. These mechanisms collectively result in reduced bioavailability of glucocorticoids at the cellular level [78,79].

4.3.3. Inflammation and Neuroplasticity in MDD

Several indicators of reduced neuroplasticity, which denotes the ability of the CNS to reorganize its connections (i.e., synaptic plasticity), structure (i.e., structural plasticity), and function (i.e., functional plasticity) in response to various stimuli, have been associated with MDD [80]. Numerous studies indicate that individuals experiencing MDD may exhibit reduced neurogenesis, as evidenced by decreased volumes in several areas of the brain, including the basal ganglia and frontal regions [45]. Interestingly, antidepressants have demonstrated the ability to enhance hippocampal neurogenesis [42]. Along the same lines, brain-derived neurotrophic factor (BDNF), a neurotrophin promoting nerve cell survival, differentiation, and maintenance, has been observed to be diminished in individuals with MDD, with partial restoration observed following antidepressant administration [43,44].

Inflammation can impact neuroplastic processes through several mechanisms. Elevated levels of inflammatory cytokines, along with their signaling pathways, such as NF-κB, have the potential to diminish the expression and efficacy of the excitatory amino acid transporter 2 (EAAT2) present on astrocytes, leading to the reversal of glutamate efflux [81,82]. Conversion of KYN to QUIN by microglia further contributes to excessive

glutamate signaling, notably through N-Methyl-D-Aspartate (NMDA) receptors, by decreasing astrocytic glutamate reuptake and stimulating glutamate release [82,83]. The overflow of glutamate into the extrasynaptic space triggers an activation of extrasynaptic NMDA receptors, which can result in decreased levels of neurotrophic factors, including BDNF [82,84]. When combined with excessive synaptic NMDA receptor signaling, which creates a swift influx of calcium ions that accumulate in the mitochondria, triggering apoptotic cascades, including caspase activation and heightened production of reactive oxygen species, this process ultimately leads to excitotoxicity and synaptic damage [82].

4.3.4. Inflammation and the Gut Microbiome in MDD

Systematic review and meta-analyses have shown that the gut microbiota of individuals with MDD differ from those of healthy individuals [46,47]. Differences in the representation of up to 50 bacterial taxa have been reported, with individuals with MDD having a higher abundance of pro-inflammatory bacterial species (e.g., *Enterobacteriaceae* and *Desulfovibrio*) and a lower abundance of short-chain fatty acid (SCFA)-producing bacterial species (e.g., *Faecalibacterium*) [46,47]. While results have been inconsistent, there is also some evidence of disparities in the α-diversity (differences in the types of species living in a given gut area) and β-diversity (differences in the types of species living in multiple gut areas) of the microbiota of individuals with MDD compared to healthy controls [46,47]. Supporting a more causal relationship between the gut microbiome and MDD, fecal transplantation from adults with MDD to germ-free mice has been shown to increase depressive-like behavior in recipients [48].

Several gut microbiota alterations observed in individuals with MDD have been linked with inflammation. For example, a higher abundance of pro-inflammatory bacterial species has been associated with "leaky gut", promoting macrophage infiltration and active LPS translocation into the systemic circulation [85]. Macrophage infiltration produces and activates pro-inflammatory cytokines, leading to local inflammation, while LPS binds to Toll-Like Receptor 4 (TLR-4) expressed on immune cells, thereby activating pro-inflammatory cascades both locally and systemically [85]. The lower abundance of SCFA-producing bacteria can also directly influence inflammation, as SCFAs have been shown to reduce the secretion of pro-inflammatory cytokines, increase the secretion of the anti-inflammatory cytokine IL-10, and induce the development of regulatory T (Treg) cells [86]. Gut microbiome α and β-diversity have also been linked with the severity of systemic and local gut inflammation following trauma exposure [87].

4.4. Inflammation and T2D

T2D is increasingly recognized as an inflammatory disorder, with substantial evidence linking inflammation directly to insulin resistance. In states of overnutrition, such as obesity, hyperglycemia and hyperlipemia occur, promoting insulin resistance and persistent inflammation. In this context, pancreatic β-cells are exposed to various forms of stress, including inflammation, endoplasmic reticulum stress, oxidative stress, and amyloid stress, which can ultimately compromise their integrity [88]. Activation of pro-inflammatory macrophages and their accumulation in metabolic tissues play a pivotal role in sustaining the inflammatory state. While macrophages are the primary effector cells involved in this chronic state of low-grade inflammation, various other immune cell types are also at play [89].

4.4.1. Obesity and Adipose Tissue Inflammation in T2D

It is estimated that 80 to 90% of individuals who develop T2D are either overweight or have obesity [90]. Excessive body fat accumulation after the onset of T2D also further promotes hyperglycemia, which contributes to increasing the risks for T2D comorbidities and overall mortality rates [90]. The association between obesity and chronic low-grade inflammation is pivotal in the onset and progression of obesity-related metabolic disorders, notably insulin resistance, in the context of T2D [91]. Indeed, inflammation within adipose

tissue is deemed a critical precipitating metabolic dysfunction. Studies have consistently demonstrated the accumulation of macrophages in both murine and human adipose tissue during obesity, with adipose tissue macrophages significantly contributing to the insulin-resistant state [92,93]. Consistent with the aforementioned findings, preventing the accumulation of adipose tissue macrophages has been shown to protect obese mice from glucose intolerance and insulin resistance [94]. Various other immune cell types contribute to the inflammatory state in adipose tissue during obesity, such as specific T and B cell subsets that play regulatory roles. Nevertheless, macrophages are generally considered the principal effector cells responsible for reduced insulin signaling [95].

In lean individuals, adipose tissue macrophages constitute a minority of stromal-vascular cells and typically exhibit an M2-like polarization state [92,93]. However, in obesity, adipose tissue macrophages increase substantially, comprising a significant proportion of adipose tissue cells, primarily exhibiting a pro-inflammatory (M1-like) phenotype [96]. Importantly, visceral adiposity, primarily located around abdominal viscera, exhibits distinct metabolic characteristics compared to subcutaneous adipose tissue. Visceral obesity is more strongly associated with heightened lipotoxicity and impaired insulin sensitivity [97]. Furthermore, higher levels of inflammatory cells are found in visceral compared to subcutaneous fats [98]. Consequently, the intricate association between T2D and obesity is more dependent on the role of visceral adipose tissue on metabolic dysregulation.

Macrophages undergo notable changes during obesity, with an increased number of M1-polarized macrophages characterized by heightened pro-inflammatory phenotype and secretion of cytokines such as TNF-α. This increase in macrophage number and altered M1 to M2 ratio typifies adipose tissue inflammation in obesity and is associated with T2D development [99]. Additionally, upregulation of other pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), in enlarged adipose tissue sites of individuals with obesity and those with T2D, further exacerbates inflammation and insulin resistance. It is important to note that, independent of body weight, a small number of studies have also shown a positive relationship between inflammation and T2D, with an increase in genes related to the recruitment of macrophages, including cluster of differentiation 68 (CD68), MCP-1, IL-6, and IL-8 [100].

Various lipid species elevated due to diet or obesity may also contribute to inflammation by promoting endoplasmic reticulum stress and activating intracellular inflammatory pathways [101]. For instance, nutrient overload (i.e., excess glucose and free fatty acids) can activate the inflammasome complex, which in turn triggers downstream inflammatory pathways, including IL-1β production [102].

In addition, hypoxia, particularly prevalent in obesogenic conditions due to impaired angiogenesis and reduced oxygen perfusion, serves as another initiator of inflammation within adipose tissue [103]. Hypoxia-inducible factor 1 alpha (HIF-α) induction, primarily driven by intra-adipocyte hypoxia, initiates an inflammatory response by upregulating chemokines, thereby recruiting and differentiating monocytes into pro-inflammatory M1-like adipose tissue macrophages [103]. Genetic deletion of adipocyte HIF-α has been shown to prevent obesity-induced inflammation and insulin resistance, further supporting the role of hypoxia in adipocyte tissue inflammation during obesity [103]. Furthermore, it has been evidenced that hypoxia can alter the secretome of murine 3T3-L1 adipocytes, leading to increased expression of prothymosin-alpha (ProT-α), an immunomodulatory protein [104]. Elevated levels of circulating ProT-α are associated with obesity and can be detected prior to the onset of cardiometabolic diseases. As such, ProT-α may serve as a biomarker for inflammation and insulin resistance in T2D [104].

4.4.2. Neuroinflammation and Insulin Resistance in T2D

In addition to peripheral metabolic dysfunction, obesity and associated inflammation have been implicated in brain function alterations, particularly in regions governing energy homeostasis and metabolism. The hypothalamus, crucial in regulating body weight through energy intake and expenditure, exhibits increased glial cells and/or astrocytes

presence during obesity [105]. Studies have shown that elevated expression of inflammatory cytokines mediated by PRRs in obesogenic conditions is correlated with hypothalamic insulin resistance. Resistin emerges as a significant hormone linking obesity-induced hypothalamic inflammation and insulin resistance via TLR4 signaling pathways [106].

Furthermore, chronic exposure to glucocorticoids in humans is recognized to induce whole-body insulin resistance and obesity. Subtle forms of glucocorticoid excess are observed in chronic stress scenarios due to activation of the HPA axis, resulting in heightened adrenal cortisol production [107]. Moreover, obesity is intricately linked with abnormalities in the HPA axis, encompassing increased local production of glucocorticoids in adipose tissue, alterations in cortisol circadian rhythm, and heightened susceptibility to HPA axis activation. These factors collectively lead to prolonged exposure to glucocorticoids over time [108]. Glucocorticoids can induce insulin resistance by suppressing the transcription of IRS1 while enhancing the transcription of proteins which oppose insulin action, including protein tyrosine phosphatase type 1 B (PTP1B) and p38MAPK [109]. Moreover, glucocorticoids directly stimulate hepatic gluconeogenesis, which contributes to hyperglycemia and thus increases the risk of T2D [110]. This means that chronic exposure to glucocorticoids, whether through stress-induced activation of the HPA axis or exogenous administration, further exacerbates insulin resistance and obesity, highlighting the intricate interplay between neuroinflammation and metabolic dysregulation in the development of T2D.

4.4.3. Inflammation and the Gut Microbiome in T2D

Similarly to MDD, the gut microbiome composition also influences the inflammatory pathways involved in metabolic disorders. In mice with diet-induced obesity, alterations in intestinal immune cell populations, including decreased Treg cells and eosinophils and increased macrophages in the lamina propria, are observed [111]. These alterations, termed dysbiosis, affect body fat distribution, systemic inflammation, and insulin resistance [112]. Dysbiosis is implicated in systemic low-grade inflammation, facilitated by increased permeability of the gastrointestinal tract leading to leakage of bacterial products like LPS, as well as localized inflammation in the small bowel and colon [113,114]. Supporting this, microbiota transplantation from individuals with obesity into lean hosts exacerbates systemic insulin resistance [115].

5. Role of Inflammation in the Bidirectional Relationship between MDD and T2D

5.1. MDD Leading to T2D

5.1.1. Inflammation, Monoamine Neurotransmitters, and T2D in Individuals with MDD

MDD-associated alterations in monoamine metabolism (particularly 5-HT and DA), which, as discussed above, are partly related to inflammation, may play a role in the development of T2D via their involvement in appetite and food reward regulation [116,117]. More specifically, alterations in monoamine metabolism could stimulate greater consumption of energy-dense foods, potentially contributing to weight gain and excessive fat accumulation, thus increasing the risk of T2D [116,117]. In this regard, 5-HT depletion in the CNS has been shown to promote hyperphagia, whereas the administration of drugs enhancing 5-HT neurotransmission, 5-HT receptors agonists, and 5-HT itself all appear to reduce food and energy intake [116,118]. Similarly, DA antagonists are known to increase appetite, food intake, and body weight, while DA agonists reduce energy intake and lead to weight loss [117,119]. Decreased DA signaling in regions involved in food reward regulation has been shown to increase anticipatory food reward (the anticipated rewarding effect of food), while concomitantly decreasing consummatory food reward (the actual rewarding effect of food), thereby promoting cravings for highly palatable foods as well as increased consumption of high-fat, high-sugar, energy-dense foods [117,119].

5.1.2. Inflammation, the HPA Axis, and T2D in Individuals with MDD

MDD-associated alterations in the regulation of the HPA axis, which are partly related to inflammation, may play a role in the development of T2D via their impact on glucose homeostasis [120], food intake [121], and patterns of fat storage and distribution [122]. High cortisol levels and their resistance to feedback inhibition by the HPA axis enhance hepatic glucose release and disrupt insulin function by inhibiting its secretion from pancreatic β-cells and impairing insulin-mediated glucose absorption via the GLUT4 transporter, collectively leading to increased blood glucose levels [122]. Higher cortisol levels, as well as high cortisol reactivity, have been shown to influence food intake, particularly in individuals with obesity. A study conducted in women with obesity showed that cortisol excretion rate was positively correlated with weekly starchy food consumption as well as daily carbohydrate and lipid intakes [123]. Similarly, individuals with obesity displaying high cortisol reactivity had significantly higher food intakes following stress induction via a Trier Social Stress Test, which appeared to be partly mediated by decreased cognitive reappraisal [121]. Cortisol is also well-known to impact fat storage and distribution patterns, with hypercortisolemia promoting central adiposity, especially visceral fat depots, which are strongly associated with insulin resistance and other cardiometabolic disturbances, such as dyslipidemia [122]. In this regard, several studies have also shown that individuals with MDD having hypercortisolemia also had higher abdominal and visceral fat deposits than healthy controls as well as individuals with MDD without hypercortisolemia [124,125].

5.1.3. Inflammation, Neuroplasticity, and T2D in Individuals with MDD

While evidence is somewhat limited, MDD-associated alterations in neuroplasticity, which are partly related to inflammation, may play a role in the development of T2D via their impact on insulin resistance [126,127], blood glucose regulation [128], and food intake [129,130]. A study conducted in a mice model of high-fat diet-induced insulin resistance showed that insulin resistance was dependent on amygdalar neuroadaptation [126]. Along the same lines, high-fat diet-induced metabolic disturbances and depressive phenotypes in mice were underlined by an astrocyte-mediated disturbance in glutamatergic neurotransmission [131]. In humans, a study reported increased insulin resitance in normal weight individuals with lower serum BDNF levels [127]. Similarly, a meta-analysis of observational studies found that individuals with T2D had lower BDNF plasma/serum levels than healthy controls [132]. Along the same lines, in mice models of T2D, systemic and intracerebroventricular BDNF administration was shown to reduce blood glucose levels, possibly by increasing insulin secretion and inhibiting glucagon secretion by the pancreas [128,133]. BDNF also appears to play a role in the regulation of food intake, with central BDNF administration reducing appetite, food consumption, and body weight in rodents [129,130].

5.1.4. Inflammation, the Gut Microbiome, and T2D in Individuals with MDD

MDD-associated alterations in the composition of the gut microbiome may play a role in the development of T2D, partly via their involvement in the regulation of inflammatory processes and their potential subsequent impact on glycemic parameters [85–87,134–136]. Similar to what has been observed in individuals with MDD, individuals with T2D have a lower abundance of SCFA-producing bacterial species [137], particularly butyrate-producing species, as well as lower α and β-diversity [138]. Lower abundance of butyrate-producing bacteria has been associated with poorer glycemic parameters, including higher A1c levels, higher fasting blood glucose levels, higher insulin resistance, as well as lower levels of insulin and C-peptide, an indicator of insulin synthesis [137]. As previously described, these alterations in glycemic parameters could be partly mediated by the effects of SCFAs on circulating levels of pro-inflammatory and anti-inflammatory cytokines [86], as well as by the pro-inflammatory effects of macrophage infiltration and active LPS translocation into the systemic circulation due to increased intestinal permeability or "leaky gut" [85,134,135]. Similarly, lower α and β-diversity were both associated with higher

insulin resistance [137], which could be mediated by the impact of bacterial diversity on the severity of systemic inflammation [87].

5.2. T2D Leading to MDD

5.2.1. Inflammation and MDD in Individuals with T2D

The precise pathophysiological mechanisms leading to MDD in individuals with T2D remain incompletely understood. However, a prominent mechanism implicated in comorbidity is the inflammation hypothesis. This theory suggests that the elevation of pro-inflammatory markers seen in obesity-induced T2D fosters a systemic pro-inflammatory milieu across various tissues, potentially contributing to the onset of MDD [139]. Notably, studies have shown that adults and elderly individuals with the MDD and T2D comorbidity exhibit higher levels of CRP and IL-6 in their plasma than those with only T2D [140]. Furthermore, hyperglycemia and hyperinsulinemia in T2D may further exacerbate this pro-inflammatory state, potentially facilitating access of pro-inflammatory mediators to the CNS and thereby activating pathways associated with depressive symptoms. In diabetic animal models, both central and peripheral anti-inflammatory responses are compromised, correlating with an increase in depressive-like behaviors [141]. Another study found that combinatorial treatment with Metformin and Telmisartan (hypertension medication) alleviated depressive behaviors in rats while reducing levels of inflammatory mediators, including nitric oxide, IL-6, and IL-1β [142].

Furthermore, dysfunction of the BBB emerges as a hallmark linking T2D to neuropathology [143]. Studies in diabetic mice have shown a significant increase in BBB permeability, a phenomenon also observed in MDD [144]. However, the specific role of BBB dysfunction in precipitating depressive symptoms in T2D requires further investigation. Nonetheless, the downstream consequences of BBB disruption, including inflammation, oxidative stress, and glial activation, have been extensively associated with MDD and may thus represent a shared mechanism underlying the comorbidity [145,146].

Additionally, elevated inflammatory cytokines downregulate BNDF expression, crucial for neurogenesis, in the hippocampus and prefrontal cortex, thus inducing depressive phenotypes in individuals with T2D [147]. Studies on insulin resistance-induced mice corroborate this, demonstrating increased immobility time, anhedonia, and anxiety-like behaviors alongside diminished plasmatic and amygdalar BDNF levels [148]. This suggests that insulin resistance may influence this behavioral phenotype in the modulation of neurotrophic factor expression.

5.2.2. Inflammation, Oxidative Stress, and MDD in Individuals with T2D

Another proposed mechanism involves oxidative stress stemming from T2D. In individuals with T2D, hyperglycemia hampers the activity of antioxidant enzymes in the brain, leading to an accumulation of reactive oxygen species, which instigates apoptotic and necrotic cell death, culminating in cerebral injury and inhibition of neurogenesis [149]. Reactive oxygen species trigger the activation of NF-κB (regulator of brain inflammation), thereby upregulating the expression of pro-inflammatory cytokines like TNF-α and IL-1β [150], further contributing to MDD pathogenesis. Although oxidative stress may have independent effects on the comorbidity, it is still relevant to the context of this review as there is a bidirectional relationship between oxidative stress and inflammation, whereby oxidative stress can lead to chronic inflammation, while chronic inflammation increases oxidative stress by promoting reactive oxygen species production and decreasing antioxidant reserves [151]. This suggests that oxidative stress may exacerbate the negative effects of inflammation, which may, in turn, exacerbate the detrimental effects of oxidative stress, ultimately increasing the risk of developing MDD in individuals with T2D.

5.2.3. Inflammation, the HPA Axis, and MDD in Individuals with T2D

Emerging evidence suggests that disturbances in the HPA axis link stress exposure to mood disorders [152]. Diabetic conditions hyperactivate the brain renin-angiotensin

system, a system involved in brain homeostasis, by acting on angiotensin receptor subtypes, including the angiotensin II receptor type 1. The activation of this receptor promotes inflammation and oxidative stress [153]. Further, this subsequently hyperactivates the HPA axis and elevates cortisol and proinflammatory cytokine levels, fostering an environment favorable to MDD onset. Notably, hyperinsulinemia exacerbates HPA axis hyperactivation, leading to elevated plasma cortisol levels and subsequent hippocampal atrophy, which, in turn, disrupts HPA axis feedback modulation [154]. Furthermore, neuroinflammation attributed to microglial and astrocytic activation, alongside increased hippocampal microglial and astrocyte numbers, was observed in hyperglycemic animal models of metabolic syndrome [155]. In diabetic rats, impaired adaptation of the HPA response to various stress forms was noted, partially due to defects in glucocorticoid receptors [156]. Nonetheless, neuroinflammation appears linked to MDD in T2D, suggesting immunomodulatory strategies targeting inflammatory mediators to mitigate neuroinflammation and disturbed redox homeostasis may hold promise.

5.2.4. Inflammation, Neuroplasticity, and MDD in Individuals with T2D

The activation of innate immunity and increased cytokine levels seen in T2D can lead to microglial activation and subsequent reductions in neurogenesis [157]. Studies in T2D rodent models have revealed decreased dendritic branching and plasticity of neurons, along with cognitive deficits and depression-like behaviors correlated with reduced hippocampal neurogenesis [157,158]. It is worth noting that hyperglycemia and hyperinsulinemia, other characteristics of T2D, may also lead to decreased neurogenesis [159]. Thus, further investigations must be performed to pinpoint the independent impact of T2D-associated inflammation on neurogenesis and the associated increased vulnerability to MDD.

6. Targeting Inflammation through Lifestyle Interventions in the Management of MDD and T2D

6.1. Diet Interventions

Diet plays a fundamental role in the management of T2D and is increasingly recognized for its potential role in the management of depressive symptoms in individuals with MDD. Healthy dietary patterns and dietary improvements have the potential to elicit a variety of biological changes, including changes in inflammation, which might be relevant for the prevention and management of MDD and T2D.

Numerous systematic reviews and meta-analyses of observational studies have shown that healthy dietary patterns, characterized by high intakes of fruit, vegetables, nuts, whole grain, legumes, low-fat dairy products, fish, and lean cuts of meat, decrease the risk of developing MDD in generally healthy adults [160–162]. Similarly, interventions promoting the adherence to healthy dietary patterns, such as the Mediterranean diet, have the potential to significantly decrease depressive symptoms among adults with MDD or high depressive symptoms [163,164]. Along the same lines, consumption of healthy dietary patterns has been associated with a lower risk of T2D in observational studies [165–167] and improvements in glycemic control in intervention studies conducted in adults with T2D [168,169].

In line with this review's topic, diet is known to play a pivotal role in influencing the body's inflammatory response, with certain dietary patterns, foods, and food components capable of either promoting or alleviating inflammation. Healthy dietary patterns, such as the Mediterranean diet, the Dietary Approach to Stop Hypertensions (DASH) diet, and vegetarian diets, have been demonstrated to reduce inflammation in both healthy individuals and individuals with chronic diseases such as T2D [170]. Similarly, specific foods, beverages, nutrients, and other food components, including tea, omega-3 fatty acids, and flavonoids, have been found to have beneficial impacts on inflammation [171–173]. Conversely, unhealthy dietary patterns [174] as well as high intakes of some nutrients, such as saturated fatty acids [175], can lead to increased inflammation. Particularly, saturated fatty acids have been shown to promote a pro-inflammatory response predominantly

through the activation of TLR4 signaling [176]. TLR4 binding to diet-derived saturated fatty acids also contributes to adipose tissue inflammation and dysfunction [177].

Diet has also been associated with other pathways linking inflammation to the development of MDD and T2D, including HPA axis dysregulation, neuroplasticity, and gut microbiome modulations. For example, in a sample of healthy men, fish oil supplementation over a period of 3 weeks has been shown to reduce basal cortisol levels and to prevent adrenal activation elicited by mental stress [178]. Similarly, high doses of vitamin C as well as flavonoid-rich foods (e.g., dark chocolate, pomegranate juice) were shown to decrease cortisol levels in healthy individuals as well as individuals with overweight or obesity [179,180]. In contrast, high glycemic index diets, even when consumed over short periods of time (e.g., $\leq$3 weeks), were shown to increase cortisol levels in healthy adults [181,182]. In rodents, diets high in fats and refined sugars have been shown to decrease neurogenesis, potentially through a decrease in hippocampal BDNF [183]. Conversely, dietary compounds such as omega-3 fatty acids, fiber, vitamins, and flavonoids appear to have a beneficial impact on hippocampal neurogenesis [184,185]. The diversity, composition, and metabolic function of the gut microbiota are also well recognized to be influenced by both short-term nutrient intake and long-term dietary patterns [186,187]. Notably, the abundance of SCFA-producing bacterial species as well as bacterial species involved in nutrient metabolisms has been positively correlated with the consumption of plant-based and Mediterranean-like diets, while the abundance of pro-inflammatory bacterial species has been positively associated with the consumption of processed and animal-derived foods [188,189].

While dietary improvements have beneficial effects on the risk and management of both MDD and T2D, a limited number of studies have assessed the role of diet in the prevention and management of the MDD and T2D comorbidity. It would be relevant to study the association between diet and inflammation in individuals with this comorbidity.

6.2. Physical Activity Interventions

Physical activity has been demonstrated to have beneficial effects on both MDD and T2D management. The extensive array of biological changes observed in exercise studies highlights its potential to elicit beneficial effects through various pathways. Regarding MDD, it is widely acknowledged that exercise effectively treats mild to moderate MDD, with response rates comparable to pharmacotherapies and cognitive behavioral therapy. Evidence suggests that physical activity may alleviate depressive phenotypes through several biological mechanisms. For example, exercise is linked with an increase in BDNF, which is known to play a role in alleviating symptoms by promoting neuron health and synaptic plasticity [190]. Moreover, as reviewed in this article, MDD is also associated with an upregulation of inflammatory pathways in the brain. At the same time, physical activity is linked with a reduction in systemic inflammatory signaling, suggesting a potential for mitigating these pathways [191]. More specifically, a study conducted on rodents found that the number and activation of hippocampal microglia, along with neuroinflammation in the hippocampus, may contribute to the pathogenesis of MDD [192]. A running exercise regimen was shown to reverse these changes, suggesting that the antidepressant effects of exercise may be, in part, due to alternations in hippocampal microglia and neuroinflammation [192]. Additionally, endurance exercise training has been shown to increase the release of transcriptional factors that enhance the expression of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) gene. The PGC1α gene is heavily involved in preserving and protecting against neuronal loss [193] and is associated with a reduction in inflammatory markers, notably IL-6 and TNF-α [193,194].

In the context of T2D, both aerobic and resistance exercises have been established to enhance glycemic control, thereby aiding in the management of T2D [195]. Evidence has also linked exercise to lower BMI, with a reduction in pro-inflammatory cytokine secretion and an increase in anti-inflammatory cytokines [196]. Reducing the body's inflammatory state through physical activity holds significant importance in mitigating the development

of T2D. Although findings in the literature are mixed, long-term exercise has demonstrated a capacity to decrease the levels of inflammatory markers such as CRP, TNF-a, and IL-6, potentially alleviating chronic low-grade inflammation [197]. Hyperglycemia in individuals with T2D upregulates the expression of inflammation markers, and exercise has been shown to diminish their expression, thereby improving insulin sensitivity and reducing blood glucose levels [198]. Furthermore, physical inactivity is strongly correlated with obesity, particularly the accumulation of visceral fat, which exacerbates systemic inflammation [199]. Conversely, long-term physical exercise serves as a protective mechanism against abdominal fat accumulation and subsequent chronic inflammation [200]. This is partly mediated by myokines, in particular IL-15, which is implicated in the control of visceral adiposity. Indeed, a study demonstrated that elevated IL-15 levels protected mice from obesity, particularly by limiting visceral fat deposition. Interestingly, a 12-week endurance training study conducted in men has shown an increase in the expression of muscular IL-15 following endurance training [201], potentially contributing to decreasing visceral fats and subsequent inflammation. Additionally, exercise has been demonstrated in both men and women following a 12-week training program to lessen oxidative stress by enhancing the expression of antioxidant enzyme genes, increasing nitrogen oxide availability, and decreasing the production of reactive oxygen species [202]. In turn, this indirectly reduces the levels of inflammatory markers.

In the context of T2D, both aerobic and resistance exercises have been established to enhance glycemic control, thereby aiding in the management of T2D [195,203]. Various studies have also linked exercise to lower BMI, with a reduction in pro-inflammatory cytokine secretion and an increase in anti-inflammatory cytokines [196,204]. Reducing the body's inflammatory state through physical activity holds significant importance in mitigating the development of T2D. Although findings in the literature are mixed, long-term exercise has demonstrated a capacity to decrease the levels of inflammatory markers such as CRP, TNF-a, and IL-6, potentially alleviating chronic low-grade inflammation [197]. Hyperglycemia in individuals with T2D upregulates the expression of inflammation markers, and exercise has been shown to diminish their expression, thereby improving insulin sensitivity and reducing blood glucose levels [198]. Furthermore, physical inactivity is strongly correlated with obesity, particularly the accumulation of visceral fat, which exacerbates systemic inflammation [199]. Conversely, long-term physical exercise serves as a protective mechanism against abdominal fat accumulation and subsequent chronic inflammation [200]. This is partly mediated by myokines, particularly IL-15, which is implicated in the control of visceral adiposity. Indeed, a study demonstrated that elevated IL-15 levels protected mice from obesity, particularly by limiting visceral fat deposition. Interestingly, a 12-week endurance training study conducted in men has shown an increase in the expression of muscular IL-15 following endurance training [201], potentially contributing to decreasing visceral fats and subsequent inflammation. Additionally, exercise has been demonstrated in both men and women following a 12-week training program to lessen oxidative stress by enhancing the expression of antioxidant enzyme genes, increasing nitrogen oxide availability, and decreasing the production of reactive oxygen species [202]. In turn, this indirectly reduces the levels of inflammatory markers.

7. Conclusions

There is a bidirectional relationship between the risk of MDD and the risk of T2D. Additionally, MDD exacerbates the complications of T2D by promoting unhealthy behaviors, inadequate self-care, and difficulties in adhering to T2D management strategies, making it a crucial comorbidity to further investigate. Although the precise mechanisms linking T2D and MDD are still not fully understood, shared inflammatory mechanisms likely contribute to the heightened risk of developing this comorbidity. As described in this review, inflammation serves as a common denominator exacerbating the adverse impacts of both MDD and T2D, complicating the management of the comorbidity. Indeed, chronic low-grade inflammation characterizes both conditions, exerting profound effects on the

HPA axis, neuroplastic processes, gut microbiome, insulin resistance, and adipose tissue dysfunction. Deepening our understanding of the mechanisms underlying the augmented inflammatory responses observed in individuals with this comorbidity is essential for tailoring appropriate therapeutic strategies. Interventions targeting inflammation through dietary modifications and physical activity hold significant promise as adjunctive strategies in the management of the MDD and T2D comorbidity. However, it is important to note that most studies included in this review involved Caucasian North American populations, which may limit the generalizability of these findings. To better understand the relationship between MDD and T2D across different demographic groups and to ascertain whether inflammatory pathways vary among these populations, it is crucial to broaden the scope of research to include more diverse populations.

Lastly, policymakers should prioritize recommendations for preventing both disorders, recognizing their significance as public health concerns. The effective management of MDD leads to improved glycemic control, thereby enhancing overall health outcomes. A collaborative interprofessional approach involving the individual with MDD and T2D, mental health professionals, primary care providers, and other care partners is therefore essential to mitigate the impact of this comorbid psychopathology.

Author Contributions: Conceptualization, A.M.B. and M.R.; writing—original draft preparation, A.M.B. and M.R.; writing—review and editing, A.M.B., M.R., I.G. and C.A.; visualization, A.M.B. and M.R.; supervision, I.G. and C.A.; project administration, I.G. and C.A.; funding acquisition, I.G. and C.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by an Interstrategic Direction Grant (2016) from the Institut du Savoir Montfort (https://savoirmontfort.ca (accessed on 22 April 2024)) to I.G. and C.A. The Institut du Savoir Montfort is an organization dedicated to education, research and community engagement, and often collaborates with Universities. A.B. was funded by a Nutrition and Mental Health Doctoral Scholarship from the School of Nutrition Sciences of the University of Ottawa. M.R. was funded by a Canadian Institutes of Health Research (CIHR) Master's Scholarship.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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