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Mini Review

MAJOR DEPRESSIVE DISORDER, TYPE 2 DIABETES MELLITUS AND INFLAMMATION

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ABSTRACT

Inflammation may play a key role in the pathogenesis of both depression and type 2 diabetes. However, elevated levels of circulating IL-6 are an independent predictor of type 2 diabetes and are thought to occur with the development of insulin resistance and β-cell dysfunction. There is no evidence linking IL-6 to β-cell dysfunction and eventual β-cell apoptosis. Elevated levels of IL-6 are always associated with increased hypothalamic-pituitary-adrenal (HPA) activity in depression. This increases cortisol, which then triggers TDO and reduces the availability of tryptophan for the production of melatonin, NAS and serotonin. Therefore, IL-6 contributes to the regulation of important biological pathways that underlie stress and the subsequent depression that results from stress.

Key words: Inflammation, depression, diabetes

TYPE 2 DIABETES MELLITUS AND INFLAMMATION

The multifunctional cytokine interleukin 6 (IL-6) is associated with the pathophysiology of type 2 diabetes (T2D). Increased levels of circulating IL-6 are an independent predictor of type 2 diabetes and are thought to contribute to the development of inflammation, insulin resistance, and β-cell dysfunction. (1) The IL-1 family comprises two pro-inflammatory cytokines, IL-1α and IL-1β, as well as the naturally occurring anti-inflammatory agent IL-1 receptor antagonist (IL-1Ra or IL-1RN). (2) The inflammatory stress response pathways in men and women with T2D differ, with women exhibiting higher increases in IL-6. (3) Serum levels of interleukin-6 (IL-6) are higher in people with type 2 diabetes (T2D). Reduced omentin-1 serum levels, elevated IL-6 and insulin serum levels, and occasionally elevated HOMA-IR indicate that inflammation and insulin resistance are important factors in the development of diabetic nephropathy in people with type 2 diabetes (4). It is not yet known if high blood levels of IL-6 play a part in causing type 2 diabetes, despite evidence showing these levels exist years before the disease manifests. There's no proof that IL-6 has a special role in β-cell malfunction and ultimately β-cell death. (5) The IL-6 α-receptor (IL-6R) is responsible for the pleiotropic effects of IL-6. It can be found in both membrane-bound and soluble (sIL-6R) forms and activates cells through the glycoprotein 130 (gp130) β-receptor. T2D is associated with the nonsynonymous single nucleotide polymorphism (SNP) rs2228145 (Asp358Ala) at the IL6R locus. (6). Hepatocytes, skeletal muscle cells, and adipocytes are the primary cell types that regulate peripheral insulin sensitivity and glucose homeostasis. They react differently to IL-6. Hepatocytes seem to be more responsive than other cell types, which could be explained by the presence of IL-6R that is membrane-bound. (7)

TNF-α and IL-6 can cause peripheral neuropathy in patients with impaired glucose regulation; additionally, TNF-α may function as a stand-alone risk factor for peripheral neuropathy in these patients. (8) Improvements in pancreatic insulin secretory function and

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decreases in markers of systemic inflammation were brought about by some IL-1-blocking drugs, and these effects lasted for 39 weeks following the conclusion of treatment. (9) Adiponectin levels are lower in elderly diabetic patients with MCI, but leptin and IL-1β levels are higher. (10)

Nedeva I et al. (11) report that carbohydrate tolerance deteriorates with rising IL-18 levels. Moreover, IL-18 demonstrated strong positive correlations with a variety of anthropometric parameters, liver enzymes, fasting, post-load glucose, insulin, uric acid, and triglycerides, but it was negatively correlated with HDL. Serum levels of IL-18 and its receptor, IL-18R, are significantly higher in patients with newly diagnosed type 2 diabetes. (12) Increased levels of real-time biomarkers suggest that intensive insulin treatment does not produce the anticipated decrease in oxidative processes involving ROS and NO, most likely because of "metabolic memory." (13)

There is a connection between neuropathy and IL-6 levels in younger people. A higher level of IL-6 in the control group than in the diabetic groups suggested a greater inflammatory response in younger, healthy subjects compared to diabetic patients. (14) TNF-alpha, IL-1 beta, and VEGF levels in the serum have an impact on the development and progression of DR. They are connected to the disease's presence and severity. (15)

The glomerulus is one of the primary sites of diabetic damage, and podocyte damage is a hallmark of diabetic glomerular lesions. (16) The onset and progression of diabetic nephropathy and diabetes mellitus are linked to the release of proinflammatory cytokines and low-grade inflammation both locally and systemically. (17). IL-6 and an increased risk of DKD progression are independently correlated. (18) When exposed to interleukin-6, renal mesangial cells multiply (IL-6). Though it is possible that IL-6 plays a major role in such mesangial proliferation, little research has been done on the relationship between IL-6 and diabetic nephropathy because it is difficult to measure IL-6 levels in serum and urine. Urinary IL-6 levels seem to be a helpful indicator of diabetic nephropathy, and serum IL-6 levels are linked to atherosclerotic alterations, per a study by Shikano M et al. (19). As a result, serum IL-6 may be helpful in assessing atherosclerosis, which includes nephropathy. Diabetes accompanied by clinical proteinuria was linked to higher levels of IL-6 and IL-18 as well as lower levels of TTP in the serum and urine, according to research by Liu F et al. (20). It's possible that TTP expression declines before IL-6 and IL-18 levels rise, and that TTP declines before IL-6 and IL-18 do as an early warning sign of glomerular dysfunction. According to Yaribeygi H et al. (21), IL-18 is expressed in renal tissue and is stimulated by a number of factors, including high blood sugar. Urinary albumin excretion rate and diabetic nephropathy progression both showed a positive correlation with urinary IL-18 expression/level.

Urinary IL-18 levels seem to be linked to higher carotid-femoral pulse wave velocity, suggesting that urinary IL-18 levels and arterial stiffness may be related in T2D patients. (22) Given their strong correlation with both hypertrophy and left ventricular systolic dysfunction, proinflammatory cytokines may serve as early non-invasive markers to identify left ventricular remodelling and systolic dysfunction in patients with type 2 diabetes. (23) In patients with type 2 diabetes who were at high risk for cardiovascular disease, Koshino A, et al. (24) discovered a relationship between baseline IL-6 and its 1-year change and renal and cardiovascular outcomes. A strong positive correlation was observed between the levels of TNF-α, IL-6, and HbA1C ($P > 0.05$). TNF-α and IL-6 levels can be used as markers for the onset of atherosclerosis. When compared to non-diabetic atherosclerosis, TNF-α and IL-6 have a stronger prognostic value in the development of diabetic atherosclerosis. (25) Diabetic patients frequently have severe coronary artery disease (CAD) that is symptomless. In people with type 2 diabetes, higher levels of OPG, leptin, and IL-6 are linked to the incidence and severity of SMI (silent myocardial ischemia). (26) Disruption of IL-6 through genetic engineering of IL6 or IL6R is linked to comparable risk reduction for several cardiometabolic diseases, suggesting that both IL-6 and IL-6R are potential therapeutic targets to lower CVD. (27) Interleukin-1 (IL-1) is a proinflammatory cytokine that mediates processes linked to obesity and dyslipidemia. IL-1β is linked to type 2 diabetes and the cardiovascular complications that come with it. (28) In addition to primary dyslipidemia, oxidative damage and irreversible chemical lipoprotein modifications resulting in the

production of oxidized low-density lipoproteins contribute to the accelerated rate of atherosclerosis in type 2 diabetes (T2DM). (29, 30)

In proliferative diabetic retinopathy, there is evidence to support local inflammation over systemic inflammation due to increased levels of IL-6 and IL-8 in the vitreous but not in the plasma. In addition, the vitreous contains an unbalanced combination of pro- and anti-inflammatory cytokines. (31) Diabetic retinopathy was not associated with CD4+CD25+ T cells or T regulatory cells, but was associated with age, sex, and duration of diabetes. There was an inverse relationship between diabetic retinopathy and serum levels of IL-6 and IL-17. (32).

RECURRENT DEPRESSIVE DISORDER AND INFLAMMATION

In addition to exhibiting anti-inflammatory qualities, each omega-3 formulation promoted the maintenance of neuronal stability and normal neurotransmitter function, including dopamine and serotonin (33). One meta-analysis suggests that taking omega-3 PUFA with EPA ≥ 60% at a dose ≤1 g/day may help with depression (34). Both DHA and EPA prevented interferon-alpha (IFN-α), IL6, and interleukin 1beta (IL1β) from inducing apoptosis and decreasing neurogenesis. The metabolites of EPA/DHA, 5-hydroxyeicosapentaenoic acid (HEPE), 4-hydroxydocosahexaenoic acid (HDHA), 18-HEPE, 20-HDHA, 17(18)-epoxyeicosatetraenoic acid (EpETE) and 19(20)-epoxyecosapentaenoic acid (EpDPA))), were found in human hippocampal neurons by mass spectrometric lipidomics of the supernatant to be mediating agents for these effects. Indeed, co-treatment with these metabolites, such as EPA/DHA, reverses cytokine-induced reductions in neurogenesis and apoptosis. (35)

Interleukins 6 and 8 are among the proinflammatory cytokines that are activated by NF-kB. The levels of ROS and glutamic acid regulate this transcription factor's activity. But the transcription factor itself raises oxidative stress levels, which sets off an inflammatory reaction. It was discovered that MDD patients had higher NF-kB levels. (36) Interleukin-1beta (IL1B), a critical mediator of inflammation, is highly expressed in the brain, particularly in the hippocampus, which is critical for memory and mood regulation. In the brain, IL1B mediates a variety of processes, such as neuronal proliferation, differentiation, apoptosis, and long-term potentiation. (37).

Elevated levels of IL-6 are typically linked to increased activity of the hypothalamic-pituitary-adrenal (HPA) axis in depression. This raises cortisol, which then triggers TDO and decreases tryptophan availability for the production of melatonin, NAS, and serotonin. As a result, IL-6 is involved in the coordination of key biological pathways that are responsible for stress and depression brought on by stress. (38) An analysis of the quantitative relationship between depression and major inflammatory markers to date reveals a positive relationship between depression and IL-6, IL-1, CRP, and IL-1 (and its surrogate, IL-1ra). (39) Increased IL-6 activity may exacerbate depression by influencing neurotransmitter metabolism or activating the hypothalamic-pituitary-adrenal axis. (40) According to Jin K et al. (41), IL-1β, IL-6, and Hypocretin-1 may be involved in the pathophysiology of MDD. Hypocretin-1 may be a potential biological mechanism for the reduction of anxiety. According to a study by Mao L et al. (42), serum levels of IL-6 and IL-17 directly affect the course of HAMD, and patients with FDD have an overactive immune system.

Higher autoimmune status activation and HAMD scores were linked to more negative life events; SSRI treatment can lower serum levels of IL-6 and IL-17. Another study that compared normal controls to depressed patients with atypical depression found that IL-6 levels were higher in the former group but not in the latter (43). Serum levels of TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10, and TNF-α appeared to be significantly lower in patients who experienced depressive episodes more quickly than in those who did not. Furthermore, compared to patients whose episode lasted between six and twenty-four months, patients whose current depressive episode lasted less than six months had lower serum levels of cytokines, such as IL-2, IL-8, IL-10, and IFN-γ. (44) Evidence that IL6 methylation in the elderly may be a sign of depression in older people was presented by Ryan J et al. (45). TNF-α and IL-6 concentrations were found to be significantly positively correlated with Hamilton Depression Scale-17 scores in depressed patients, but IL-18 was lowered in comparison to controls. (46) A study by showed that older depressed patients had higher IL-6 than controls. (47) IL-6 levels were found to be higher in patients with major depressive disorder and suicidal thoughts by

Guo Y et al. (48). Serum CRP levels in patients with bipolar disorder and major depressive disorder (MDD) did not differ from one another in a different study examining the role of inflammatory factors. However, serum levels of IL-6 and IL-8 were higher in BD patients but not in MDD patients. (49) Genetically predicted IL-6 was linked to major depression, but no meaningful associations were found with bipolar disorder. (50)

In a population-based study, IL-10 levels were found to be lower in stroke patients who developed depressive illness and in individuals with symptoms of anxiety, depression, and an increased risk of suicide. (51) The IL18 haplotype, which includes both risk-associated alleles, was found to increase threat-related reactivity of the left centromedial amygdala in women but not in men. Moreover, women only exhibited increased threat-related reactivity of the left centromedial amygdala, which predicted increased symptoms of anxiety and depression, among those who also reported higher levels of life stress. (52) The IL-18/IL-18BP ratio changed as a result of cortisol and depression symptoms. Our findings support the activation of inflammatory pathways in adolescent psychosis and point to connections between stress, inflammation, and depressive symptoms in EOP. (53) Increased soluble TNF receptor 2 and KLOTHO protein are the primary immunoregulatory mechanisms in BD, whereas increased IL-10 is the primary immunoregulatory mechanism in MDD. (54)

Compared to controls, MDD patients exhibited significantly higher levels of TNF-α and interleukin-6 (IL-6). The brain-derived neurotrophic factor (BDNF) and proBDNF levels were negatively correlated with the HAMD-17 total score in female MDD patients, while the two variables were positively correlated in male MDD patients. IL-18, or interleukin 18. (55) It is appropriate to evaluate the effects of the immune response during a depressive episode because depression is known to impair cognitive abilities. In patients with MDD, working memory was negatively correlated with eotaxin, IL-1β, IL-4, MCP-1, G-CSF, and PGF-BB. (56) IL18 levels were significantly lower in healthy female subjects than in male subjects, and higher in depressed patients, than in controls. Additionally, standardized IL18 and standardized Tau as well as the standardized Aβ42/Aβ40 ratio correlated with depressed patients. (57)

IL-10 mediated by the glucocorticoid receptor decreased in proportion to a higher decline in the MADRS score in depressed patients. Patients with remitted MDD had higher TNF-α values at baseline and follow-up than those with active MDD. (58) Treatment with fluoxetine exacerbates depressive symptomatology by upregulating pro-inflammatory processes like TNF-α, IL-6, and IL-1β. (59) Compared to nonresponders, women with depression who respond to ECT have reduced IL-8 levels. (60) Serum levels of cortisol, C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were significantly higher in patients with TRD who did not have treatment-resistant depression. Furthermore, the TRD group's serum levels of cortisol, CRP, TNF-α, and IL-6 were significantly lower than those of patients without treatment-resistant depression. (61) In a different study, patients with depression had significantly higher levels of IL-6 and 8 iso-prostaglandin F 2 alpha. (62) Compared to healthy individuals, MDD patients exhibit significantly higher serum levels of β-endorphins, mu-opioid receptors, IL-6, and IL-10. The levels of IL-10 and MOR are highly correlated. There was no discernible relationship between endogenous opioids and IL-6 or IL-10. (63) TNF-alpha and IL-6 levels are higher in depressed patients than in healthy subjects.

Leptin levels are significantly lower in depressed patients. Significant differences were also seen in leptin levels, with healthy women having higher levels than healthy men and female patients having higher levels than male patients. (64) It is believed that atypical depression (AD) is a unique subtype of depression with biological and psychological differences. It's possible that AD and melancholic depression (MD) have different effects on cytokine activity. Atypical depression patients had lower levels of TNF-α and higher levels of IL-2, but no difference in IL-6 or IL-4 levels was observed. (65) Compared to those who are not depressed, those who are depressed have lower IL-6 levels. Atypical depression is linked to triglyceride levels. There is no conclusive evidence linking immunometabolic functioning to antidepressant use. In older people with depression, immunometabolic downregulation was seen overall, especially in those with milder symptoms and later onset. Individuals with atypical depression exhibit metabolic

dysregulation, in contrast to other depressed people. (66) Principal component analyses revealed clusters of CSF inflammatory markers (IL-1beta, TNF, and interleukin (IL)-6) that were linked to elevated plasma CRP (> 3 mg/L) and correlated with the severity of depressive symptoms. CRP seems to be a peripheral biomarker for both peripheral and central inflammation in MDD patients, which makes it a viable target for immunotherapies that target IL-6 and TNF. (67)

Variations in the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) and in tryptophan-kynurenine metabolism may be a major contributing factor to major depression (MD). These variations may lead to increased tryptophan and serotonin breakdown, glutamate imbalance, agonism of N-methyl-D-aspartate, and most likely increased quinolinic acid production. The immune imbalance leads to increased prostaglandin E_2 production and potentially COX-2 expression. (68)

Reactive oxygen species (ROS), transient receptor potential ankyrin A1, and calcitonin gene-related peptide signalling modulate cortical susceptibility to cortical spreading depression. The prevention of stress-induced migraine may be achieved therapeutically through the use of calcitonin gene-related peptide, which inhibits reactive oxygen species (ROS) and inactivates transient receptor potential ankyrin A1 channels. (69) According to Malkov A et al. (70), ROS accumulation may also be the main cause of cortical spreading depression. Indeed, they found that Tempol significantly reduced the incidence of cortical spreading depression in vivo, indicating that ROS accumulation may be a crucial mechanism for the onset of cortical spreading depression. Research shows a link between impaired mitophagy and the activation of microglia, which leads to neuroinflammation. (71) The polysaccharide *Polygonatum sibiricum* prevents depression-like behaviours and synaptic and neuronal damage possibly by reducing ROS/HPA axis hyperfunction and the inflammatory response. (72) TNF-α and soluble interleukin-2 receptor (sIL-2R) are two interleukins that are more prevalent in depressed patients. (73) HG was observed to stimulate acute and prolonged production of IL-1β during the differentiation process of macrophages. (74) In type 2 diabetes (T2DM), but not in type 1 diabetes, there was a positive correlation found between the ratio of high molecular weight (HMW) to total adiponectin and serum high-sensitivity C-reactive protein (hsCRP) and the degree of depression. (75) Tempol has shown effectiveness in reducing the negative consequences of inflammation and oxidative stress, which are the primary causes of radiation damage and numerous age-related illnesses. (76)

In conclusion, a number of interleukins, including IL-1, IL-6, and IL-18, seem to have a role in the etiology of type 2 diabetes mellitus and major depressive disorder. Additional research is required to validate these results.

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