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Review Article

Feasibility of Utilizing Transforming Growth Factor Beta as a Biomarker of Depression in Hospitalized Patients

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Abstract
Several mental conditions and depression, have been linked to immune response disorganization. However, it is unclear if particular immune mediators play a part in the etiopathogenesis of depression. Although there are no definite biomarkers to diagnose depression, the current study sought to logically evaluate the possibility and feasibility of checking a biomarker for depression to be utilized for hospitalized patients suspected of depression. In this narrative review, related articles were gathered through a search of PubMed, Scopus, and ScienceDirect databases as well as a manual search of full-text paper references. The reviewed studies demonstrated the potential role of the transforming growth factor beta (TGF-β) in depressive disorders. Previous studies represented a negative role for TGF-β in depression pathophysiology and an increase in TGF-β after depression treatment. Elevated plasma TGF-alpha acted controversial to TGF-β. The level of TGF-β in maternal plasma increased getting close to delivery, and researchers found that it might be associated with postpartum depression. In addition, researchers reported extreme elevations in TGF-β levels in the brain cells of subjects who died by suicide. Although the results of this study revealed a plausible link between TGF-β and depression based on the literature, sensitivity and specificity studies needed before TGF-β as a biomarker may be extensively employed in clinical practice. Depression appears to be down-regulating TGF-β and its signaling or the underlying mechanisms of the pathogenesis of consequent neurological disorders, while further studies are required for the application of the TGF-β assessment in clinical practice.
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Introduction

Patients admitted to different wards of the hospital suffer from short-term emotional distress, and a large number of patients admitted to the ward suffer from depression and anxiety. Depression and anxiety are serious problems of patients admitted to hospital wards and have severe effects on health, improvement of patients' specific and non-specific symptoms, and their quality of life, leading to increased use of health care, premature disability, and imposition. The economic burden is on individuals and the security systems of society (1, 2).

In the field of psychiatry, the gathered evidence suggests that the immune system may be involved in psychiatric disorders, especially major depression. The role of proinflammatory cytokines, including interleukin (IL)-1, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, in the etiology and pathophysiology of major depression has been well established by previous research (3). It is hypothesized that major depression may be associated with significant changes in cell mediation and humoral immunity, and these changes may be related to the pathophysiology or pathogenesis of the disease (4).

Placenta, testis, central nervous system, and adrenal cortex all contain transforming growth factor beta (TGF-β1) (5). Even though TGF-1's key function is well understood, the fact that it is also present in the central nervous system and adrenal cortex implies that this cytokine may have a secondary function in depression, including preserving the equilibrium of T-helper 1 (Th1) and Th2 (6).

Depressive symptoms are linked to an increased risk of hospitalization, a longer length of stay, and a higher chance of re-admission. The existing data indicate that the prevalence is likely to be high enough to warrant screening hospital inpatients for depression and commencing therapy if appropriate (7).

In this study, it was attempted to logically investigate the feasibility and possibility of checking a biomarker for depression to be used for hospitalized patients suspected of depression although there are no definite biomarkers to diagnose depression and many patients being hospitalized for any reason could be experiencing

depression as a coexisting condition.

Methods

This narrative review followed no particular structure for search. Articles were retrieved from PubMed, Scopus, and ScienceDirect databases, along with a manual search of full-text paper references for this narrative review. Studies reporting TGF-β serum or expression levels in human participants in relation to the depression diagnosis were included in the study, and relevant data from the publications were summarized and integrated accordingly.

No exclusion criteria were applied, and the quarry was not limited to any time, language, or study design.

Results

The results of this study were narrated from a definition of depression to its biological causes and the role of the TGF-β in the diagnosis of depression as follows:

What Is Depression?

Depressive disorder is one of the most common psychiatric diagnoses characterized by a depressed mood and a feeling of sadness, low self-esteem, and lack of interest in any kind of daily activities and pleasures; what is known as a "mental cold" (8). Depression is a combination of different mental and emotional states that range from mild boredom to silence and distance from daily activities. Major depression is a term coined by the American Psychiatric Association to describe a set of mood disorders for III-DSM in 1980 and has since become popular. It leads to significant disability in the realms of individual and social life and employment and affects a person's daily functions such as eating and sleeping and health (9).

Causes of Biological Occurrence

Genetics: The prevalence of depression is 65% and 14%-19% in monozygotic and other twins, respectively, which determines the role of genetic factors. Researchers have identified several genes that may be linked to bipolar disorder, and they are looking for genes that are related to the other forms of depression. However, not all people with a family history of depression develop the disorder (10).

Serotonin and other neurotransmitters: Neurotransmitter disturbances at the synaptic level have been observed in depressed patients. In addition to serotonin, norepinephrine and dopamine are impaired in these patients (11).

Medications: Long-term use of some medications such as those used to control blood pressure, sleeping pills, or birth control pills can cause depressive symptoms in some people. Particularly, taking birth control pills has a direct effect on depression in women (12).

Diseases: Having a chronic illness (e.g., heart disease, stroke, diabetes, cancer, and Alzheimer's or migraine) puts a person at greater risk for depression. Studies showed an unproven link between depression and heart disease. It occurs in many people who have had a heart attack. Untreated depression can put an individual at greater risk for death in the first years after a heart attack. Hypothyroidism can cause depression, even if it is mild (13).

Depression and TGF-β

TGF-β is a protein molecule with a molecular weight of 25 kDa. This factor has 3 isoforms 1.2.3 and sends its message into the cell through two membrane receptors TR 1 and TR 2. The intracellular messenger pathway of this factor is facilitated by Smad molecules, and the message eventually reaches the cell nucleus, leading to changes in regulation at the level of DNA transcription. TGF-β also regulates various cellular behaviors, including proliferation, differentiation, migration, and apoptosis (14, 15). The β-TGF signaling pathway inhibits tumor cells and is known to act as a tumor suppressor during the early stages of gynogenesis. TGF-β1 is a cytokine that has an anti-inflammatory role and exerts neuroprotective effects on amyloid-induced nerve damage and plays an important role in memory formation and synaptic flexibility (15, 16).

There is now strong evidence that major depression is associated with significant changes in cellular and humoral immunity. Himmerich et al (17) investigated the relationship between the incidence of depression and the levels of inflammatory and proinflammatory cytokines and found that patients with depression with IL-12 plasma levels are significantly higher than healthy people who are hospitalized in different wards.

The increased levels of IL-12 in depression indicate that IL-12 triggers inflammatory processes and causes depression in hospitalized patients. Other studies have confirmed the overproduction of proinflammatory cytokines such as IFN-γ, IL-1β, TNF-α, and IL-6 in patients with depression. Other studies have also reported an increase in neutrophil and monocyte phagocytosis in depressed patients (15, 16, 18-29).

An annual study by Wang et al (19) demonstrated that treatment with antidepressants leads to a significant increase in TGF-β1 levels in patients with depression. They also noted that the increase in TGF-β1 production is related to the clarity of inflammatory responses, especially in organ-specific autoimmune diseases.

TGF-β1 has several suppressive effects on T cells, B cells, macrophages, and other cells, and increased TGF-β1 production is associated with protection or recovery from autoimmune diseases. TGF-β1 and CTLA-4 are molecules that work together to terminate immune responses (20).

Petralia et al (21) concluded that a significant increase in cytokine Th3 after antidepressant treatment in patients with depression is explained by a decrease in the IL-12/TGF-β1 ratio. Therefore, an increase in cytokine Th3 plays

an essential role in the pathophysiology of depression, and antidepressants have been shown to upset the balance of pro-inflammatory/anti-inflammatory cytokines in hospitalized patients with depression.

The results of Komori (22) represented that the Th1/Th2 cytokine network has a negative effect on the pathophysiology of depression.

Wang et al (14) indicated that IL12 and TGF-β1, which represent the cytokines of Th1 and Th3, play a vital role in major depression. In their study, cytokine levels were measured at the time of admission and after effective antidepressant treatment, and their results showed that TGF-β1 levels significantly increased after antidepressant treatment.

Based on the results of Özkan et al (23), the pro-inflammatory cytokine IL-12 could certainly exert a role in the psychotherapy of depression, and antidepressants have immune-regulating effects by reducing the pro-inflammatory cytokine IL-12 and increasing the anti-inflammatory cytokine TGF-β1.

A vast series of studies have confirmed the neurobiological and psychiatric continuum between depression periods in recent years. During embryogenesis and adult tissue homeostasis, the TGF-superfamily signaling is involved in a number of biological processes. A variety of diseases are caused by the improper regulation of the signaling pathway that transduces TGF-superfamily signals, including cancer, coronary, metabolic, urinary, digestive, skeletal, and immune diseases.

The findings of Caraci et al (24) demonstrated that TGF-β1 plasma levels are lower in major depressive patients, correlate with depression severity, and contribute to major depressive disorder treatment resistance. In their study, they also identified the TGF-β1 signaling pathway as a common drug target in depression and stated that saving this pathway could be an effective way to control depression in hospitalized patients.

The investigations of gene-environment associations in major depressive disorder have been restricted to the hypothesis testing of candidate genes, with polygenic-environmental causation remaining unexplored. In this regard, Zhao et al (25) evaluated the association between TGF-β1 and major depressive disorder and reported that TGF-β1, along with environmental factors, causes and exacerbates depressive disorder in patients.

Various studies have also approved the role of TGF-β1 in causing depression during pregnancy. The results of Qiu et al (26) affirmed the role of the canonical TGF-signaling pathway in children's brain growth in the form of their mother's environment in utero. In fact, they declared that increasing the level of this factor in the babies of depressed mothers would cause depressive symptoms in these babies (26, 29).

As mentioned earlier, depression can be caused by other diseases (27, 28). For example, the results of Bahramabadi et al (29) revealed that depression appears to cause inflammation in patients with chronic hepatitis B virus infection by down-regulating TGF-β. In other words, it was found that the disturbance in the signaling pathway of this factor causes the aggravation of the infection, and the aggravation of leads to depression in hospitalized patients.

In another study, Kashima and Hata (30) examined the role of TGF-β signaling or the underlying mechanisms of the pathogenesis of neurological disorders and indicated the essential role of TGF-β in the pathogenesis of depression.

In depression and anxiety disorders, some researchers demonstrated an imbalance of pro-inflammatory and anti-inflammatory cytokines. Shariat et al (31) found that depression has a strong association with TGF-B levels, with major relationships. In fact, the results of their study represented that the level of TGF-B in maternal plasma increases during hospitalization for delivery. In addition to the increase in TGF-B, an increase in this factor was evident in postpartum breast milk. As a result, more care should be paid to mothers' emotional well-being while breastfeeding (31).

Discussion

Some studies reported the effect of TGF on depression in hospitalized patients. However, some studies indicated that there is a reverse relationship between this factor and depression. In fact, researchers believe that depression upsets the balance of inflammatory and proinflammatory cytokines. Even in people who are otherwise stable, inflammatory responses such as elevated cytokine levels have been linked to major depressive disorder, and some patients with the disorder may have insulin resistance. The results of Al-Hakeim et al (32) confirmed that major depressive disorder is associated with immune system activation, as can be observed by dramatic increases in the levels of four cytokines. These findings point to immune system activation and elevated insulin resistance, as well as resistance regulation by increased cytokine levels in major depressive disorder (27-30).

Chronic stress increases the risk of depression disorder by impairing neurotrophin signalings such as that of the brain-derived neurotrophic factor and TGF-1. In addition to its role in causing and exacerbating depressive disorders in hospitalized patients, TGF-β is effective in the treatment of depressive disorder, which is in line with the findings of several studies. For example, the results of Guerrera et al (33), demonstrated that aerobic exercise reduces the risk of depression and Alzheimer's disease in elderly patients by increasing the levels of TGF-β and brain-derived neurotrophic factors in these patients.

Inflammatory signaling molecules, including cytokines and chemokines, play a significant role in synaptic plasticity, neurogenesis, memory, and learning in the brain. Another study showed that elevated plasma TGF-alpha in hospitalized adolescent girls was a predictor of

their in-hospital depression (34).

Tombácz et al (35) focused on the entire genome of people who had lost their lives to suicide and found an increase in TGF-β levels in the brain cells of these patients, and in their study, all people with a history of depression and hospitalization due to depression . In fact, their results indicated a major defect in TGF-β in causing depression in hospitalized patients.

In another study, Munoz-Pinto et al (36) concluded that TGF-β levels in patients with depression sharply increased, and increased TGF-β in the future could cause Parkinson's disease.

According to Jahangard et al (37), untreated patients have an impaired IL-2 signaling pathway and faulty regulatory T cells (Tregs), and selective serotonin reuptake inhibitor therapy can improve Treg function. Based on their findings, TGF-β levels in hospitalized patients with depression increased compared to before hospitalization.

Depression not only raises the death risk of colorectal cancer patients but also affects their quality of life during recovery. Low levels of systemic inflammation can play a role in depression growth.

Apriansyah et al (38) attempted to find whether there was any connection between TGF-serum levels and depression in colorectal cancer patients, and their results indicated that TGF-β levels in patients with colorectal cancer are increased compared to healthy individuals, and TGF-β is also correlated with the incidence of depression in hospitalized patients.

Conclusion

According to peer-reviewed reports, TGF-β can contribute to depressive disorders. TGF-β has been found to play a detrimental role in depression pathophysiology and improvement following therapy for depression in previous research. TGF-alpha reversely behaved in the presence of elevated plasma TGF-β in depression and an increase in TGF-β after treatment was found. The findings of this study showed a possible relationship between TGF-β and depression based on the literature; nonetheless, the studies of sensitivity and specificity are lacking for the clinical application of TGF-β as a widely used biomarker.

Author Contributions

SASE, ZSG, and LSM designed the study question. SASE, ZSG, and MRS conducted the literature review. SASE, ZSG, LSM, and MRS provided the drafts and contributed to editions.

Conflict of Interests

There are no conflicts of interests.

Ethical Approval

Not applicable.

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