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The role of inflammation and oxidative stress in the pathophysiology of depressions: time to consider vitamin C deficiency

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Abstract

Depression is on the rise and medication does not always provide satisfactory relief. This raises the question of a treatment gap that has not yet been (sufficiently) addressed. Inflammation and oxidative stress play an important pathophysiological role, which also leads to a deficiency of antioxidants such as vitamin C. This perspective mini-review reflects the results of a PubMed search combining the search terms depression with inflammation, oxidative stress and vitamin C. Vitamin C is an important antioxidant and co-factor for many neuronal metabolic and epigenetic pathways, and a deficiency is associated with depression and cognitive disorders. Inadequate vitamin C blood levels that do not yet result in somatic symptoms may induce neuropsychiatric scurvy, which is associated with increased neuroinflammation and characterized by depression and cognitive impairment. Experimental studies show that vitamin C has multifactorial effects on metabolic pathways relevant to depression. Treatment of vitamin C deficiency, which is more common than appreciated, should be considered in the management of depressed patients. Further studies should investigate whether the pharmacological administration of vitamin C has additional effects beyond the correction of deficiency.

Keywords

Depression, inflammation, oxidative stress, vitamin C, scurvy, ascorbic acid

Depression is on the rise, suggesting a treatment gap

The World Health Organization (WHO) estimates that around 322 million people worldwide suffer from depression. This is more than 4.4% of the world's population and 18% more than a decade ago [1].

Depression often has a greater impact on quality of life and social, physical, and mental functioning than chronic physical illness. The inadequate response to antidepressant treatment in a significant proportion of patients diagnosed with major depressive disorder contributes to the high burden of disability associated with the disease, and inflammation appears to play an important role in the pathophysiology [2]. This raises the question of a treatment gap that has not been (sufficiently) addressed. Since inflammation is closely associated with oxidative stress [3, 4] and vitamin C is one of the most effective physiological antioxidants [5], the following perspective mini-review investigated the data situation in PubMed on the search terms depression in connection with inflammation, oxidative stress, and vitamin C.

Inflammation and oxidative stress—chicken or the egg?

The cytokine and oxidative stress hypothesis of depression was developed more than 15 years ago and suggests that altered peripheral cytokine levels and oxidative stress are involved in the pathophysiology of depressive disorders and in modulating treatment response [3, 4]. The hypothesis states that elevated levels of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, IL-18, and TNF-α and reactive oxygen species (ROS) cause secondary changes such as neurotransmitter depletion, hypothalamic-pituitary-adrenal axis activation and the expression of depressive symptoms [3, 4, 6]. Increased oxidative stress, reduced antioxidant defenses, and anti-inflammatory capacity can lead to increased lipid peroxidation and autoimmune responses to oxidant-specific epitopes, all of which collectively cause increased immune-inflammatory responses and neurotoxicity [7]. According to a recent systematic review, lipid peroxidation seems to be a biomarker in major depression and bipolar disorder [7]. Ex vivo studies on human blood demonstrate that vitamin C can protect against lipid peroxidation [5] and it supports the recycling, formation, and activity of other antioxidants [8].

However, the cytokine hypothesis of depression remains controversial because it has not been conclusively established whether elevated levels of proinflammatory cytokines are the cause of depression or a concomitant phenomenon that perpetuates depressive symptoms regardless of the etiology of depression [9]. This hypothesis is supported by clinical studies that have repeatedly shown that neuroimmune activation due to immune dysregulation and proinflammatory cytokine production caused by medical conditions [e.g., rheumatoid arthritis (RA)], colitis, type 2 diabetes mellitus, autoimmune diseases, and COVID-19) or immunotherapies (e.g., IFN-α) is associated with an increased risk of developing depression [4, 6]. However, this could also be a bidirectional relationship, as RA patients had a 47% higher risk of developing depression compared to controls, while patients with depression had a 34% higher risk of developing RA [10].

A bidirectional association between depression and pro-inflammatory states is also suggested by a meta-analysis showing a positive association of depression with concurrent and future inflammation in children and adolescents [11]. However, the inflammatory hypotheses are supported by meta-analyses showing that epigenome-wide association studies of major depressive disorder implicate inflammation in the neurobiology of depression [12], and observational studies provide evidence of a positive association between a pro-inflammatory diet and an increased risk of depression [13].

Inflammation and oxidative stress as potential therapeutic gap

Depression is associated with alterations in peripheral blood cellular immunophenotype [14] and impaired oxidative stress balance [15]. A meta-analysis supports the fact that serum antioxidant levels are lower and serum levels of oxidative damage products are higher in depressed patients than in controls [16]. Neuroinflammation, peripheral inflammation, and gut dysbiosis are interrelated in depression, leading to disturbances in tryptophan metabolism and neurotransmitter synthesis. Interventions such as exercise, probiotics, and anti-inflammatory vitamins are potential adjuncts to antidepressant therapy [6]. According to a meta-analysis, inflammation also seems to worsen the response rate to antidepressants [2].

Regardless of whether inflammation and oxidative stress are a cause or a consequence of depression, they have a negative impact on the disease process and represent a treatment gap that needs to be addressed.

"Now you C me"

Vitamin C, a potent antioxidant and anti-inflammatory immunomodulator, is inversely associated with the prevalence of depressive symptoms [17]. Vice versa, suboptimal vitamin C status is associated with increased symptoms of depression [18]. Depression is a non-specific symptom of vitamin C deficiency [19], as illustrated by a recent case report entitled "Now you C me: a case of scurvy presenting as depression and anaemia". The diagnosis of scurvy was suspected on the basis of widespread bilateral ecchymoses on the upper limbs and a petechial rash on the lower limbs and was confirmed by a severely low serum vitamin C level [20]. The association between vitamin C deficiency and adverse psychiatric effects has been known for centuries, but it was not known then that scurvy was a clinical vitamin C deficiency. In 1753, the Scottish physician James Lind [21] wrote in his seminal treatise on scurvy that it was associated with "melancholy and despondency of mind".

A systematic review found nine trials in which vitamin C deficiency, including subjects with and without the physical manifestations of scurvy, was associated with depression and cognitive impairment. There was no effect on affective or non-affective psychosis. Comparison between the trials was complicated by different techniques for measuring vitamin C and different definitions of vitamin C deficiency. It was clear that the vitamin C blood levels associated with depression and cognitive impairment were higher than those associated with the clinical manifestations of scurvy. In other words, depressed mood and cognitive impairment occur much earlier than, for example, an increased tendency to bleed. The authors highlight the fact that vitamin C deficiency is more common than generally thought and that vitamin C supplementation is inexpensive and easy to administer [22]. Poor nutrition is common in people with mental disorders, so the risk of vitamin C deficiency is higher in psychiatric patients. In fact, the study authors report from a psychiatric unit in Australia where more than 50% of patients had vitamin C levels below 26 μmol/L, in the hypovitaminosis range [22]. Optimal vitamin C plasma levels should be ≥ 70 μmol/L; an adequate range is given as 50–70 μmol/L, a suboptimal range as 50–23 μmol/L, and hypovitaminosis as 23–11 μmol/L; clinical deficiency/scorbut begins below 11 μmol/L. [23, 24]. According to the latest results of the NHANES study, 6.8% of the population in the USA have a vitamin C level in the scurvy range, i.e. over 20 million people [25]. In Scotland, the rate of subclinical deficiency is 24%, while 20% have blood levels of vitamin C in the scurvy range [26].

Vitamin C: plausibility and study evidence

The influence of vitamin C on psychological state is very plausible because vitamin C plays an important role in the modulation, synthesis, and release of neurotransmitters in the brain [27]. It is a co-factor in the conversion of dopamine to norepinephrine, in dopaminergic and glutamatergic neurotransmission, and in the regulation of catecholamine and acetylcholine release from synaptic vesicles. Vitamin C also has important antioxidant protective functions in the brain, for example in ischemia/reperfusion-induced damage or glutamate excitotoxicity [27]. The latter plays an important role in strokes, Alzheimer's disease, multiple sclerosis, Parkinson's disease, etc., as overstimulation of nerve cells can lead to apoptosis [22]. Neurotransmitters such as dopamine, norepinephrine and serotonin are easily destroyed by ROS. To protect against this, the brain contains by far the highest concentrations of vitamin C in the body [28]. Vitamin C enters the central nervous system by two routes, via the blood-brain barrier [uptake of the oxidized form of vitamin C (dehydroascorbate) by glucose transporter] and blood central spinal fluid barrier [uptake in the reduced form (ascorbate) by sodium-dependent vitamin C transporter]. The highest accumulation is observed in neurons at 10 mmol/L, which is markedly higher than the 1 mmol/L found in cerebrospinal fluid or glial cells, suggesting an important role in the maintenance of neuronal integrity [29].

It is becoming increasingly apparent how important vitamin C is for epigenetics, particularly for neurodevelopment [30]. The vitamin is stored in high concentrations in the brain. RNA analysis of genetically modified rats unable to produce vitamin C shows that even a short-term (3 weeks) mild vitamin C deficiency significantly alters the transcriptome. Vitamin C deficiency affects the expression of genes controlled by the glucocorticoid receptor in the brain. There was an increased secretion of glucocorticoids from the adrenal gland during vitamin C deficiency. Microglia, the immune cells in the brain, changed their transcription pattern in response to the deficiency, and dormant microglia were activated and produced increased levels of pro-inflammatory cytokines such as IL-6 in the hippocampus. In addition, vitamin C deficiency reduced the number of newly formed neurons in the dentate gyrus of the hippocampus, suggesting that vitamin C is required for adult neurogenesis, which plays a crucial role in learning and memory. The authors use the term neuropsychiatric scurvy, which is characterized by depression and cognitive impairment [28].

Experimental studies show that vitamin C has several antidepressant effects, such as anxiolytic effects [31, 32], activation of the opioid system [33], inhibition of glutamate receptors [34] and modulation of GABA receptors [35], activation/modulation of monoaminergic and glutamatergic neurotransmitter systems and inhibition of N-methyl-D-aspartate receptors and nitric oxide synthesis [36, 37], reversal of chronic corticosterone-induced hippocampal synaptic deficits [38], and reduction of oxidative damage [39, 40].

A recent systematic review and random-effects meta-analysis of randomized controlled trials (RCTs) examined the effect of vitamin C supplementation on mood in both depressed and non-depressed populations and included 10 trials with 836 participants up to March 2020. The overall analysis showed no significant improvement in mood status (n = 10, Hedge's g = 0.09; 95% CI: –0.15 to 0.33; P = 0.465). However, subgroup analysis showed beneficial effects of vitamin C supplementation in patients not prescribed antidepressants (subclinically depressed) (n = 5, Hedge's g: –0.18; 95% CI: –0.35, –0.01, P = 0.041; I^2 = 0.00%). These results tentatively suggest that oral vitamin C may have mood-enhancing effects in patients with subclinical depression [41]. Vitamin C was given orally in nine of the ten trials. It is known that oral absorption is limited, and the trials did not monitor compliance by measuring plasma vitamin C levels. It would be important to investigate whether vitamin C could have an effect on major depression when given intravenously at higher doses. The fastest way to correct vitamin deficiencies is by intravenous administration, which also ensures 100% compliance, which is not always guaranteed with oral substitution in patients with depression. As depression is often associated with inflammatory diseases, the need for vitamin C can be so high that it cannot always be met orally. Intravenous vitamin C applications in the gram range can raise blood levels to the mM range (> 2 mM after 7.5 g of vitamin C). Oral substitution is limited to about 0.20 mM even after high-dose gram doses [42].

The data on the benefits of vitamin C for depression is still insufficient and so far only includes studies on oral supplementation. According to these data, there only appears to be a benefit in subgroups such as subclinical depressed patients. Unfortunately, vitamin C plasma levels are hardly ever determined in studies, so there is no certainty regarding compliance. As compliance is problematic in depressed patients anyway, the determination of blood levels is extremely important in the following studies. However, the available data and the importance of vitamin C in many metabolically relevant metabolic processes suggest that a vitamin C deficiency has a significant negative impact on the course of the disease and should be a greater focus of therapy. Furthermore, studies should investigate whether the pharmacological administration of vitamin C has additional effects beyond the correction of deficiency.

Key summary points

1. Despite extensive research efforts, the prevalence of depression continues to increase, indicating a need for closer investigation into potential treatment gaps.

2. Inflammation and oxidative stress appear to damage neuronal metabolism and reduce the response rate to antidepressants.

3. Vitamin C is a potent antioxidant and anti-inflammatory immunomodulator, and sub-optimal vitamin C status is associated with increased symptoms of depression.

4. Vitamin C deficiency occurs more often than generally assumed, and as poor nutrition is common in people with mental disorders, this patient group is likely at higher risk.

5. The current evidence on pharmacological vitamin C supplementation is insufficient, highlighting the need for studies that include monitoring of vitamin C blood levels.

Abbreviations

IL-1β: interleukin-1β

RA: rheumatoid arthritis

Declarations

Author contributions

CV: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation. MW: Investigation, Writing—review & editing, Validation. All authors read and approved the submitted version.

Conflicts of interest

CV is employed part time at Pascoe pharmazeutische Praeparate GmbH (Giessen, Germany). MW states that he has implemented various projects and training courses together with Pascoe pharmazeutische Praeparate GmbH over the last 5 years.

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Not applicable.

Consent to participate

Not applicable.

Consent to publication

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Availability of data and materials

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