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REVIEW article

Serum uric acid as an adjunct in the assessment of psychiatric disorders: an overview

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Abstract: Oxidative stress is due to altered levels of prooxidants and anti-oxidants in the body. This can lead to tissue damage especially, the central nervous system. Oxidative damage has been implicated in several disorders including some psychiatric disorders such as schizophrenia and major depressive disorder. Uric acid is an anti-oxidant that prevents tissue damage caused by oxidative stress. In this review, the reduced levels of serum uric acid in schizophrenia and depression are discussed. The effect of treatment in these disorders leading to increased serum uric acid levels is also reviewed.

Introduction

Oxidative stress occurs due to an imbalance of prooxidants and anti- oxidants [1]. It results due to the inability of the antioxidant defense mechanism by the cells to overcome the reactive oxygen species (ROS) which are normally produced during cellular oxidative metabolism [2]. This can result in extensive damage to cellular components such as lipids, proteins, carbohydrates and DNA [1]. The central nervous system (CNS) is rendered more vulnerable to oxidative damage in comparison to the rest of the body. The oxidative metabolism in the cells of the CNS is very high resulting in a high consumption of oxygen (more than 20.0% of the body's oxygen consumption) [2]. In addition, the CNS has lower levels of protective antioxidant enzymes and a high concentration of metallic substances such as iron, zinc, copper and manganese which can result in excessive formation of the ROS [1, 2]. The amount of polyunsaturated fatty acids and neurotransmitters such as dopamine, epinephrine and norepinephrine which are easily oxidizable are high in the brain rendering it vulnerable to oxidative stress induced damage. These neurotransmitters are metabolised with the production of large amounts of hydrogen peroxide which can cause oxidative damage. Basal ganglia contain large amount of iron making it more susceptible to damage by ROS [1]. Oxidative damage is implicated in several disorders. It is associated with schizophrenia and results in poor prognosis and a decline in the condition of the patient [1]. In schizophrenia, a membrane dysfunction secondary to the oxidative damage by free radicals could result in some of the symptoms the treatment complications.

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Negative symptoms such as tardive dyskinesia, neurological 'soft' signs and Parkinsonian symptoms could be due to oxidative stress mediated neurotoxicity. An imbalance between free radical production and antioxidant activity results in the neurotoxicity in schizophrenia [3]. Oxidative stress due to lipid peroxidation and lower levels of antioxidant enzymes has been implicated in major depression. It causes neurotoxicity and a reduction in the hippocampus volume in major depression. Enzymatic and non-enzymatic antioxidants are responsible for the anti-oxidative defence function. In major depression, enzymatic antioxidants like superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSHPx) etc. and non-enzymatic antioxidants such as albumin, bilirubin, uric acid and ascorbic acid have lowered levels [4]. It has also been suggested that oxidative stress could be partially responsible in the pathogenesis of Alzheimer's disease. This could be due to the accumulation of ROS with the ageing process causing damage to the CNS [5].

In plasma, more than 85.0% of the antioxidant capacity is due to uric acid, albumin and ascorbic acid. Metabolism of adenine and guanine-based purines results in the production of uric acid. Since uricase, a urate oxidase is absent in humans, the end product of the purine pathway is uric acid. Several decades back, the physiological importance of uric acid was unknown and it was considered to be a metabolically inert waste product. Research has established uric acid to be an antioxidant which can specifically react with hydroxyl radicals, nitrogen peroxide, hypochlorous acid, superoxide and singlet oxygen [6-8]. In addition, uric acid stabilizes another antioxidant, ascorbic acid which is present in the CNS [9]. Since uric acid is found in almost all tissues, measuring its level in the plasma is useful, as lower values indicate oxidative stress [6]. The antioxidant effect of uric acid is particularly in the CNS resulting in appropriate inflammatory response and prevention of tissue damage [10]. The levels of uric acid are lower in conditions such as Parkinson's disease, Alzheimer's disease, multiple sclerosis and major depressive disorder. Some studies have also reported lower levels of uric acid in schizophrenia [7, 11]. Higher levels of uric acid are associated with lesser incidence and better prognosis of Parkinson's disease [8]. The rate of decline is slower in cognitive impairment if the levels of uric acid are high. Since oxidative stress is implicated in depression and anxiety disorders, the antioxidant potential of uric acid could be beneficial to improve the prognosis of these disorders. These neuroprotective effects of uric acid are due to its antioxidant properties [9, 11].

Uric acid in schizophrenia

Oxidative stress in schizophrenia: Several clinical and preclinical studies have indicated an association of oxidative stress with the incidence and progression of schizophrenia [2]. Reduced levels of antioxidants have been implicated in the early stages of schizophrenia. Studies have shown a significant reduction in the total plasma antioxidant activity in patients with schizophrenia as compared to normal controls. A reduced level of antioxidants is associated with poor prognosis of psychopathological conditions in patients with schizophrenia [12]. Aberration in the antioxidant levels could be associated with cognitive impairment and biochemical changes seen in schizophrenia [2]. Cabungcal and others [13] have conducted experimental studies in which oxidative stress was induced in the rats that resulted in glutathione deficiency leading to behavioural alterations. The findings of their study implicated the association of oxidative stress with schizophrenia. A study reported by Steullet et al. [14] revealed that oxidative stress is associated with abnormal cerebral integration, cognitive function and behaviour in patients with schizophrenia. Gonzalez-Liencres and others [15] studied the role of oxidative stress on schizophrenia and concluded that since the levels of pro-oxidants such as nitric oxide and malondialdehyde were elevated and that of anti-oxidants such as glutathione, superoxide dismutase and neurotrophin 4/5 was reduced in schizophrenia as compared to healthy controls, oxidative stress is involved in schizophrenia.

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Uric acid in schizophrenia: Uric acid, bilirubin and albumin are the non-enzymatic anti-oxidants present in plasma. Several studies have reported that levels of these anti-oxidants are significantly lower in schizophrenic patients compared to normal controls, particularly in the first episode schizophrenia [12, 16]. This suggests that there is an early association of reduced anti-oxidant levels in the pathogenesis of schizophrenia [12]. Reddy et al. [17] reported that uric acid levels in the first episode schizophrenia are significantly low with a value of 4.92±1.38 mg/dl as compared to 5.76±1.25 mg/dl in normal controls. In this study, neuroleptic naive participants were included and therefore the reduced uric acid levels were not related to the treatment. The anti-oxidant potential of uric acid is due to the urate radical that reacts with and inactivates peroxynitrite intermediates, nitric oxide and peroxyl radicals. These results in lowered levels of uric acid in oxidative stress which is implicated in schizophrenia [18]. Flatow and his group [19] showed that uric acid levels are significantly low in first episode psychosis in schizophrenic patients. Also, Yao et al. [20] have reported that the levels of uric acid are lowered in chronic schizophrenia. In the early stages of schizophrenia, the formation of uric acid from purine catabolism is altered [20]. The activity of xanthine oxidase in the occipital cortex and thalamus in schizophrenic patients is lower compared to healthy controls, resulting in a lesser metabolism of adenosine to uric acid [7].

Uric acid in prognosis of schizophrenia: Uric acid levels in schizophrenia have important clinical implications [7]. The levels of serum uric acid are significantly low in first episode schizophrenia thereby implicating lowered anti-oxidant effect in the early stages of the disease [21]. Li and his associates [22] studied the levels of oxidants and antioxidants in the blood samples from schizophrenic patients and postulated that an imbalance in the oxidative and anti-oxidative processes is associated with the pathogenesis of schizophrenia. Therefore, they suggested that anti-oxidants can be beneficial to improve the outcome and prognosis of schizophrenia. A reduction in oxidative stress is recommended as early as in the course of schizophrenia [23].

Uric acid in major depressive disorder

Oxidative stress in major depressive disorder: Excessive production of ROS can cause damage to the macromolecules such as DNA, protein, fatty acids etc. The CNS is particularly vulnerable to the oxidative damage resulting in neuropsychiatric disorders. Therefore, it has been suggested that ROS is associated with the pathogenesis of depressive disorder by causing tissue damage, inflammation, neurodegeneration, autoimmune mechanisms generated by tissue damage, and apoptosis [24]. There is nerve cell destruction and reduction in hippocampus volume in patients with major depressive disorder (MDD) [4]. In MDD, the levels of oxidative stress markers in the plasma and/or urine such as F2-isoprostanes or 8-hydroxyde-oxyguanosine (8-OHdG) are found to be elevated whereas the levels of anti-oxidants such as vitamins C and E are reduced. It has also been reported that the severity and chronicity of depression increase with an elevation in the peripheral oxidative stress markers. Some reports have suggested the use of antioxidant compounds as antidepressants for the management of major depression [25]. Lindqvist and others [26] studied the correlation between the oxidative stress markers and antidepressant response in patients with MDD. It was found that the levels of F2-isoprostanes and 8-OHdG are significantly higher in the MDD patients compared to healthy controls. It was also shown that there is a significantly poor response to antidepressant selective serotonin reuptake inhibitor (SSRIs) in patients with high baseline levels of F2-isoprostanes. The levels of F2-isoprostanes and 8-OHdG remained significantly high in non-responders to SSRI treatment.

Uric acid in major depressive disorder: Several studies have indicated a lower level of serum uric acid in patients with MDD [4, 9, 10, 27]. Wen et al. [28] conducted a study to establish the association between levels of uric acid and depression. They concluded that the levels of uric acid are significantly lower in patients with depression (271.97±77.50 μmol/l) compared to healthy controls (315.76±87.50 μmol/l, p=0.012) Chaudhari

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et al. [4] observed that the plasma uric acid levels are markedly significantly reduced in newly diagnosed patients with MDD compared to healthy controls. The levels of uric acid were found to significantly lower in patients with recurrent depressive episode, major depressive disorder, depression with anxiety compared to healthy controls in a study done by Meng et al. [29]. This could be due to excessive consumption of uric acid in oxidative stress in depression [29]. Black et al. [11] suggested that lower uric acid levels are associated with severe symptoms and longer symptom duration in patients with MDD which could be due to a dose-response relationship. The study also reported that lower levels of serum uric acid in patients with depression compared to healthy controls are independent of antidepressant use [11].

Uric acid in prognosis of major depressive disorder: Uric acid can be used as a biomarker for depression [29]. The incidence of hospitalization for depression and the use of antidepressants is lower in patients with high plasma uric acid levels [27]. Uric acid causes suppression of inflammation, decreases permeability of the blood brain barrier and prevents CNS damage and neuronal death, thereby improving the prognosis in patients with MDD. It is suggested that uric acid levels may respond to treatment for depression and thereby could prove to be useful to detect the disease activity as a marker [28]. Liu et al. [30] conducted a meta-analysis study and reported that the levels of serum uric acid increases after antidepressant treatment. Thereby, it was proposed that serum uric acid can be used as a biomarker in MDD since it is easily detectable.

Uric acid in treatment for psychiatric disorders

Numerous studies have reported that treatment with antidepressants can increase uric acid level [11, 22, 31]. Thus, following treatment with antidepressants for five weeks, the uric acid levels of depressive patients showed normal values [28]. Chaudhari et al. [4] found an increase in plasma uric acid levels and improvement in Hamilton rating scale for depression score after a 12-week treatment of depression with SSRIs like citalopram and fluoxetine. They concluded that after 12 weeks of treatment with antidepressants, there is a strong significant and negative correlation between Hamilton rating scale for depression score and serum uric acid level (r=-0.864). Peela and his group [32] studied the levels of serum uric acid in patients treated with tranquilizers for manic depressive psychosis and schizophrenia. They concluded that in patients treated with tranquilizers, the serum uric acid levels are significantly elevated compared to controls. Thus, there is a positive correlation between the effect of treatment and serum uric acid levels in certain psychiatric disorders [32]. Wen et al. [28] reported that serum uric acid levels are significantly higher in patients treated for MDD for a period of five weeks compared to the values before treatment initiation. The mode of action of antidepressant treatment could be due to improved antioxidant function [10]. A meta-analysis study conducted by Bartoli et al. [10] reported that there is significant increase in uric acid levels after anti-depressant treatment (MD=0.71 mg/dl) The pre-treatment pooled mean uric acid levels are 3.89 (3.44 - 4.34) mg/dl which increased to 4.60 (4.17-5.04) mg/dl after anti-depressant treatment [10]. It has also been reported that haloperidol withdrawal in schizophrenic patients resulted in a decrease in the serum uric acid level. Thus, it is concluded that there could be a correlation between haloperidol treatment and an increase in uric acid [12]. Yao et al. [6] conducted a study to evaluate the effect of antipsychotic treatment on plasma uric acid levels in schizophrenia. It was found that the patients treated with haloperidol have significantly higher serum uric acid levels (4.62± 0.99 mg/dl, n=35) compared to haloperidol withdrawal in the same subjects (4.29±0.95 mg/dl, n=35). It was reported that schizophrenic patients responding to risperidone treatment had an increase in serum uric acid levels. Therefore, serum uric acid can be used for monitoring or predicting treatment outcome in schizophrenia [19, 33].

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Conclusion: Oxidative stress is implicated in psychiatric disorders such as schizophrenia and MDD. The level of oxidative stress may be significantly related to the severity of depression. Reduction in the volume of the hippocampus due to tissue damage by oxidative stress is associated with depression. Oxidative stress results in cell death by apoptosis particularly in the CNS, due to oxidation of macromolecules as DNA, proteins and fatty acids by ROS [34]. There is a positive correlation between serum uric acid and disease prognosis in schizophrenia and MDD. Therefore, antioxidants and antioxidant enzymes are increasingly seen as novel targets for treatment of these disorders. Treatment that could increase uric acid is being considered since it could result in neuroprotection by preventing oxidative injury and CNS damage [28]. Serum uric acid can indicate the state of oxidative stress in the body [7]. Thus, serum uric acid has the potential to serve as a biological marker during the treatment of schizophrenia and MDD.

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