Deleterious Dilemma Of Hyperuricemia In Psoriasis And Psoriatic Arthritis - Urate Lowering Drugs Rescue !!

Dr. Balaji Rajagopalan[1*], Dr.T.Rajini Samuel[2]

[1]Professor & HOD, Department of Biochemistry, Shri Sathya Sai Medical College and Research Institute, SBV Chennai Campus, Sri Balaji Vidyapeeth Deemed to be University, Shri Sathya Sai Nagar, Ammapettai, Thiruporur, Chengalpet District, Tamil Nadu, 603108*
[2]Professor, Department of Biochemistry, Shri Sathya Sai Medical College and Research Institute, SBV Chennai Campus, Sri Balaji Vidyapeeth Deemed to be University

***Corresponding Author:** Dr. Balaji Rajagopalan
*Professor & HOD, Department of Biochemistry, Shri Sathya Sai Medical College and Research Institute, SBV Chennai Campus, Sri Balaji Vidyapeeth Deemed to be University, Shri Sathya Sai Nagar, Ammapettai, Thiruporur, Chengalpet District, Tamil Nadu, 603108, Phone number: 9940299545, Email address: dr.balajirajagopalan@gmail.com

KEYWORDS
Psoriasis, Psoriatic Arthritis, uric acid, allopurinol, Febuxostat, Metabolic Syndrome, Cytokines

ABSTRACT
Psoriasis is a chronic auto immune skin disease. Hyperuricemia is frequently associated in patients with Psoriasis and Psoriatic arthritis. Furthermore it can complicate with Cardio vascular Disease and Metabolic Syndrome. Psoriasis is commoner in obese persons that can also result in the development of hyperuricemia. Hyperuricemia can result in gouty arthritis. All Psoriatic patients to be monitored for hyperuricemia and early intervention of the same through therapeutic regimens can avert the development of metabolic syndrome and coronary artery diseases. Psoriatic arthritis (PsA) denotes the articular component of the systemic psoriatic disease and the extra-cutaneous disorder most frequently found in patients with Psoriasis. Apart from the involvement of the joints, PsA is associated with several metabolic disorders like insulin resistance, hypertension, diabetes and hyperuricemia. Hyperuricemia in Psoriasis and PsA is due to the increased cellular turnover characterized typical of this disorder . The hyperproliferation of keratinocytes culminates in the accelerated nucleic acid catabolism and enhanced uric acid synthesis. However, hyperuricemia might also derive from an increased uric acid production in the liver. The overwhelming cytokines synthesis in PsA, in particular IL-17, can affect the liver, leading to hepatic complications such as non-alcoholic fatty liver disease. Psoriatic patients treated with allopurinol showed marked improvement of skin lesions and decreased Serum Uric Acid in most cases. The effects of the febuxostat therapy in patients with Psoriasis, Psoriatic Arthrits and hyperuricemia led to the decreased serum levels of inflammatory markers such as IL-6, IL-17, and TNF-α.

Introduction / Background:

Uric acid an end product of Purine metabolism is associated with various complications when its serum level is enormously increased. The commonest disorder that occurs is Gout with deposition of urate crystals in the joints manifesting as arthritis and also as renal and Ureteric calculi when the same gets deposited in the urinary tract. Hyperuricemia when co exists in the auto immune disorder Psoriasis, can result in serious life threatening complications that are supposedly to be given due care and attention with early diagnosis and treatment. Prevention of the greater risks of Hyperuricemia in the Psoriatic patients is the need of the hour for the better life expectancy of the patients. Hyperuricemia is a usual finding in psoriasis. Adequate treatment will be very useful to avert the drastic complications in the patients. Psoriasis is commonly associated with features of the metabolic syndrome, that may also result in the development of hyperuricemia.[1-3]

Psoriasis is a chronic immune-mediated skin disease that affects about 2% to 4% of the population in Western countries.Multiple types of psoriasis have been described, including pustular, guttate, and erythrodermic psoriasis, in addition to rarer forms such as psoriatic arthritis. In addition, patients with

psoriasis may present itchy or painful lesions that negatively affect their quality of life. The pathogenesis of psoriasis is not completely understood; however, abnormal differentiation of keratinocytes and infiltration of inflammatory cells have been suggested .Inflammatory cytokines that are found in the psoriatic lesions have also been implicated .Patients with psoriasis are at greater risk of cardiovascular disease (CVD),Metabolic syndrome (MetS),Type 2 Diabetes mellitus, dyslipidemia, hypertension, and obesity.[4.5,6]

Hyperuricemia is seen frequently in patients with psoriasis and has also been associated with Cardio vascular Disease and Metabolic Syndrome. The prevalence of CVD has been linked with increased levels of uric acid (UA).[7,8] Hyperuricemia can result in adverse cardiovascular outcomes, specifically sudden cardiac death. Psoriasis patients with extensive involvement of the skin tend to have a higher incidence of hyperuricemia .Psoriasis is commoner in obese persons that may result in the development of hyperuricemia. Hyperuricemia can result in gouty arthritis and is an attributable factor for cardiovascular diseases. Hyperuricemia is a vital marker of Metabolic Syndrome that can ultimately result in the complication of cardio vascular diseases. All Psoriatic patients to be monitored for hyperuricemia and early intervention of the same through therapeutic regimens can avert the development of metabolic syndrome and coronary artery diseases.[7,8]

Psoriasis as a chronic autoimmune disorder results in the Hyperproliferation of Keratinocytes and increased turnover of cells of epidermis are characteristic of this disorder. The various mechanisms involved in psoriasis pathogenesis are activation of dendritic cells and T-lymphocytes, hyperproliferation of epidermis, reduced differentiation of keratinocytes, and oxidative stress damage.[9,10,11] Psoriatic arthritis (PsA) denotes the articular component of the systemic psoriatic disease and the extra-cutaneous disorder most frequently found in patients with psoriasis. Apart from the involvement of the joints, PsA is associated with several metabolic diseases such as insulin resistance, hypertension, diabetes and hyperuricemia. Uric acid is the final product of purine metabolism and the etiological substrate of gout. Increased evidence highlights the pivotal role of hyperuricemia as a major cardiovascular risk factor. The interplay between hyperuricemia and psoriatic disease, suggest that individuals affected by psoriasis or PsA might present higher serum levels of uric acid and that hyperuricemia might affect severity of clinical manifestations and degree of inflammation in PsA patients. The effects of anti-rheumatic drugs on uric acid levels and the benefits of urate-lowering therapies on psoriasis and PsA reduces the morbidity of the disease. [9,10,11]

Serum uric acid possess strong antioxidant effect and metal-chelating properties, acting as a scavenger of plasma nitrogen radicals and reactive oxygen species, thus reducing especially the production of peroxynitrite. Uric acid plays an important role as immune-stimulating agent especially in innate immune responses and type 2 immune responses. Uric acid acts as a damage-associated molecular pattern after transformation in crystals of monosodium urate. In this form it activates dendritic cells and enhances the innate immune system, behaving as an endogenous adjuvant. Urate in its crystalline shape is phagocytized by monocytes or neutrophils causing the generation of pro-inflammatory cytokines such as IL-1. The internalization of uric acid crystals by leukocytes leads to production of free radicals, release of cathepsin B and activation of inflammasome.[12,13,14] Surprisingly higher serum uric acid levels have been hypothesized to play a protective role in the development of some neurological disorders such as dementia, multiple sclerosis, Alzheimer's disease and Parkinson's disease. A significant inverse association between serum uric acid and Alzheimer's disease or Parkinson's disease is an encouraging news.

Hyperuricemia in PsA is due to the increased cellular turnover characterizing this disorder. The hyperproliferation of keratinocytes leads to accelerated nucleic acid catabolism and enhanced UA synthesis. However, hyperuricemia might also derive from an increased uric acid production in the liver. The overwhelming cytokines synthesis in PsA, in particular IL-17, can affect the liver, leading to hepatic complications such as non-alcoholic fatty liver disease. Decreased hepatic ATP production in hepatic steatosis that in turn causes increased production of uric acid from the hepatocytes. [15-18] Additional mechanisms might be related to the reduced renal and extra-renal clearance. Although the kidney represents the main actor of uric acid excretion, also other organs such as the intestine

contribute to its balance. BCRP/ABCG2 is located at the apical membrane of small intestinal epithelial cells and it is involved in the uric acid secretion from blood into the intestinal lumen . A proportion of PsA patients present evidence of clinical or microscopic inflammatory bowel disease, which might reduce the levels of these transporters and consequently impair UA homeostasis.[15-18] Hyperuricemia may also be due to the metabolic comorbidities associated with PsA like obesity, hypertension, insulin resistance or diabetes. In obese individuals, hyperuricemia is the result of both impaired excretion and overproduction of UA. In hyperlipidemia, the major mechanism causing hyperuricemia is the alterations in the lipid metabolism. Indeed, the increased production of triglycerides lessens the expression of OAT1 in the kidney, leading to a reduced excretion of UA.[14-18]

Serum uric acid (SUA) influences the secretion of proinflammatory chemokines, it has also been proposed that serum uric acid acts as a potent antioxidant in psoriasis. Enormous keratinocyte cell production results in the increase of purine metabolism thereby increasing the SUA levels in psoriatic patients. The normal range of serum uric acid is between 3.0 and 7.0 mg/dL. Psoriasis is associated with comorbid conditions like cardiovascular diseases, metabolic syndrome, obesity and chronic obstructive pulmonary disease (COPD).[12,13]

Increased serum uric acid levels have been associated with complications related to metabolic syndrome, such as obesity, cardiovascular diseases, and hypertension .Five common diseases highly associated with high serum uric acid levels are cardiac failure, Hypertension, diabetes mellitus, chronic renal disease, and cardiovascular disease. The potential importance of uric acid, necessitates to upgrade the systematic evaluation of the psoriasis and serum uric acid levels correlation to provide an updated data reference for relevant diagnostic services and clinical interventions. Hyperuricemia is positively associated with metabolic syndrome and obesity. Psoriasis is considered as an independent risk factor for cardiovascular diseases. However, the relationship between serum uric acid levels and cardiovascular events in psoriasis is to be thoroughly studied. Chronic systemic inflammation and dysfunction of the endothelium appear to be the link between hyperuricemia and atherosclerosis. As a result, serum uric acid may be a novel marker of atherosclerosis and cardiovascular diseases in psoriasis patients and high serum uric acid levels are associated with complications related to metabolic syndrome, such as obesity and cardiovascular diseases. Certain studies prove that serum uric acid levels were higher in patients with psoriasis and metabolic syndrome than in those with isolated psoriasis. Obesity is a critical comorbidity of psoriasis. Serum uric acid levels are significantly increased in obese patients than in non-obese patients with psoriasis. Hence the incidence of metabolic syndrome components should be given due attention when Serum uric acid levels are higher in psoriasis patients. Increased Serum uric acid levels play a pivotal role in the progression of metabolic syndrome, cardiovascular disease, and gout in these patients.[15-18]

The prevalence and incidence of psoriasis showed clear ethnic and geographic patterns. Psoriasis is more common in patients from the colder north than in patients from the tropics. The etiology of psoriasis is dependent on both genetic and environmental factors.The genetic component has been demonstrated in epidemiologic studies .Different lifestyles, eating, and social behaviours might also contribute to disease prevalence. Therefore, it is not surprising that the correlation between psoriasis and hyperuricemia displays an ethnicity and/or region-dependent pattern.[16,17] Moreover, additional studies should determine the potential efficacy of systemic therapies for controlling Serum uric acid levels in psoriasis. The psoriasis patients are to be cautioned about being at higher risk of having higher Serum uric acid levels. Moreover, detection of increased Serum uric acid levels in this patient population may enable earlier implementation of preventive measures for metabolic disturbances and awareness of CVD-associated risk of mortality.[16,17]

The Patients with Psoriasis or PsA do have a higher prevalence of hyperuricemia compared with the healthy population but another relevant point to explore is the effect of urate-lowering drugs such as Allopurinol and Febuxostat on alleviating the systemic inflammation. Psoriatic patients treated with allopurinol showed marked improvement of skin lesions in most cases.The effects of urate-lowering drugs on cytokines in patients with other inflammatory diseases such as colitis or gout are more pronounced. The levels of serum CRP, TNF-α and IL-6 and assessment of the mRNA expression of

TNF-α and IL-6 in white blood cells of hyperuricemic patients in comparison with normal serum uric acid levels showed that the former had raised CRP and mRNA expression levels of both IL-6 and TNF-alpha. After advocating 6 months of treatment with allopurinol therapy the mRNA expression of TNF-α and IL-6 are decreased. A significant association was found between variations in serum uric acid levels and changes in serum TNF-alpha.[12,14]

The effects of the febuxostat therapy on serum inflammatory markers such as IL-6, IL-17, and TNF-α in patients with Psoriatic arthritis, gout and hyperuricemia led to the decreased serum levels of IL-6, IL-17, and TNF-α . The reduction in serum concentrations of pro-inflammatory cytokines correlated with the reduction of serum uric acid levels. The effects of febuxostat and allopurinol in reducing serum levels of IL-1, IL-4, IL-6, IL-8, TNF-α, and cyclooxygenase-2 (COX-2) in patients with gout showed that both treatments led to a significantly reduction of inflammatory cytokines, but febuxostat showed a more pronounced effect and also febuxostat led to marked reduction of cyclooxygenase-2 compared to allopurinol .The anti-inflammatory effects of urate-lowering agents were also studied in induced colitis cases and the authors demonstrated that treatment with febuxostat led to a significant reduction of TNF-α, IL-1β, IL-6, and IFN-γ levels. In particular, it was observed a reduced expression of NF-kB in intestinal mucosa after treatment. Allopurinol also used in the treatment of psoriatic uveitis and shown to be more effective than prednisolone in reducing the inflammatory reaction .[12,19,20]

Psoriasis as a chronic autoimmune disorder characterized by the Hyperproliferation of Keratinocytes and increased turnover of cells of epidermis. The various mechanisms involved in psoriasis pathogenesis are activation of dendritic cells and T-lymphocytes, hyperproliferation of epidermis, reduced differentiation of keratinocytes, and oxidative stress damage .Serum uric acid influences the secretion of many proinflammatory chemokines and has also been proposed that serum uric acid is a potent antioxidant in psoriasis. Enormous keratinocyte cell production results in the increase of purine metabolism thereby increasing the serum uric acid levels in psoriatic and psoriatic arthritis patients.

CONCLUSION:

Increased serum uric acid levels have been associated with complications related to metabolic syndrome, such as obesity, cardiovascular diseases, and hypertension .The potential importance of uric acid, necessitates to upgrade the systematic evaluation of the psoriasis and psoriatic arthritis along with the serum uric acid levels correlation to provide an updated data reference for relevant diagnostic services and clinical interventions.

Source(s) of support: NIL
Acknowledgement: NIL

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