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Diurnal Variation of Uric Acid and its Correlation with Certain Hormones: A Physiological Review

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ABSTRACT

Previous studies showed a diurnal rhythm of uric acid. The mean serum uric acid value between 0800-0900 hours was higher than that observed between 1700-1800 hours. Oxidative stress is traditionally characterized as by imbalance among oxidant and antioxidant factors, occurs commonly in Mets. Antioxidant's system including enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and non-enzymatic substrates like ferritin, transferrin, and uric acid controls oxidative stress. Uric acid is an inactive metabolic result of purine catabolism, has been as of late implicated in various long term illness states, including arterial blood pressure, metabolic condition, diabetes, non-alcoholic fatty liver disorders, and chronic renal disorders. Raised uric acid may end up being one of the more significant remediable problematic factors for metabolic and cardiovascular disorders. A negative correlation is found between the levels of endogenous melatonin and UA. A positive correlation is found between the levels of cortisol and UA. Mets are characterized by hyperactivity of the HPA axis, which leads to "functional hypercortisolism.". Uric acid level is linearly correlated with FT3 and FT4, but not with TSH. In conclusion, catabolic hormones have positive correlation with serum uric acid while hormones which decrease basal metabolism have negative correlation with serum uric acid levels.

Key words: Circadian rhythm, Uric acid, Diurnal variation, Thyroid hormones, Melatonin, Cortisol

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INTRODUCTION

Previous studies showed that all subjects showed a diurnal rhythm. The mean serum urate value between 0800-0900 hours was higher than that observed between 1700-1800 hours. When studying the temporal relation for the medical importance, or when attempting to interpret the serum urate concentration, it is important to consider the diurnal rhythms of this analyte. It was also found that diurnal variation of uric acid is related with certain hormones like melatonin, cortisol and thyroid hormones.

Uric acid and its metabolic relations

Oxidative stress is traditionally characterized as an occasion coming about because of the intensity of imbalance among oxidant and antioxidant factors, created in a setting of oxidation reducing factors [1,2]. Since the age and the activity of these substances rely upon this oxidation-decreasing system, researchers presently utilize the expression "imbalance of oxidation reduction system" to present the oxidative stress [3,4]. Commonly known as free radicals, oxidants include receptive oxygen and nitrogen species, which play role in the oxidation of lipids (lipoxidation) and glucose (glycation), substances found in overabundance in adiposity. Excessive food consumption expands the measure of energy and supplements of blood [5]. Products of lipoxidation incorporate malondialdehyde, glyoxal, acrolein, 4-hydroxy-nonenal (HNE), while the products created from glycation incorporate glyoxal and methyl glyoxal. These substances attach to the amino groups of amino acids, bringing about glycation final products and progressed lipoxidation end products, which are profoundly responsive and partake in the advancement of different segments of MetS [6].

Antioxidant's system including enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and non-enzymatic substrates like as ferritin, transferrin, bilirubin, ceruloplasmin, carrier of albumin low molecular weight, like uric acid and lipoic acid controls oxidative stress [7]. Antioxidants obtained from fruits and vegetables, like vitamin C, flavonoids, vitamin E and carotenoids, are included [8].

Antioxidants can trap free radicals produced by metabolism of cellular products or exogenous sources through the reduction by hydrogen ions of these particles, breaking the continuous reactions, which ceases action on lipids, amino acids in proteins, bonds of the polyunsaturated fats, and DNA bases, preventing lesion formation and loss of cell integrity [9]. Another function of antioxidants is the defense system, which acts in the DNA

repair brought about by free radicals, a cycle identified with the expulsion of the damaged DNA molecule and repair of damaged cell membranes [10].

Uric acid, once seen as an inactive metabolic final result of purine catabolism, has been as of late implicated in various long term illness states, including arterial blood pressure, metabolic condition, diabetes, non-alcoholic fatty liver disorders, and chronic renal disorders. A few trial and clinical research uphold a function for uric acid as a contributory causal factor in these disorders. We have sufficient evidence to suggest association of uric acid to various metabolic associates. Raised uric acid may end up being one of the more significant remediable problematic factors for metabolic and cardiovascular disorders [11].

Relationship between uric acid and melatonin

A negative correlation was found between the levels of endogenous melatonin and UA. Studies have linked elevated UA with endothelial dysfunction and a reduction in nitric oxide levels is a primary determinant of blood vessel tone and thrombogenicity. Khosla et al. demonstrated that UA impairs nitric oxide generation in cultured endothelial cells, inhibits both basal and vascular endothelial growth factor (VEGF)-induced nitric oxide production in bovine aortic endothelial cells, and reduce circulating nitrites in male Sprague-Dawley rats. Gersch et al. showed that UA reacts directly with nitric oxide in a rapid irreversible reaction resulting in the formation of 6-aminouracil and depletion of nitric oxide. In pulmonary arterial endothelial cells uric acid-induced arginase activation reduces nitric oxide production [12-14].

Melatonin, or N-acetyl-5-methoxytryptamine, is an indole mainly produced in the pineal gland during the night. The amount of melatonin and its main urinary metabolite, 6-sulphatoxymelatonin decreases with the advancing age [15,16]. In humans, melatonin production not only diminishes with age, but it is also significantly lower in many age-related diseases such as cardiovascular disease [17,18].

Studies demonstrated that the rhythmicity of melatonin has an important role in a variety of cardiovascular pathophysiology including anti-inflammatory and antioxidant functions. Melatonin stimulates both the gene expression for antioxidative enzymes, such as superoxide dismutase, glutathione peroxidase as well as the levels of glutathione and to increase their activity [19]. Furthermore, melatonin and its metabolites scavenger free radicals such as hydroxyl radicals, superoxide radicals, and hydrogen peroxide which are continuously produced in cells by oxidative phosphorylation in mitochondria and by fatty acid oxidation in peroxisomes and thus terminate the initiation and propagation of lipid peroxidation [20]. High affinity G protein-coupled membrane receptors known as MT1 and MT2 and nuclear receptors called RZR/ROR are responsible for melatonin's effects on cells [21-23]. The relationship between endogenous melatonin and UA levels may be responsible for the pathogenesis of future coronary artery disease. Some studies demonstrated elevated UA and a reduced nitric oxide level [12-14]. Also, elevated UA and reduced melatonin levels may be a reflection as in previous studies. Masue et al. studied the association between the endogenous melatonin level and various established blood biomarkers of risk of cardiovascular disease such as plasma lipids, homocysteine, UA, and high-sensitivity C-reactive protein in 181 Japanese women. They found the urinary 6-sulfatoxymelatonin level was inversely associated with established independent risk factors for cardiovascular disease, including UA, as in our study, and high sensitivity C-reactive protein. If our evidence was extrapolated into clinical situations, the use of exogenous melatonin as a prophylactic agent for cardiovascular disease may offer benefits to decreasing the blood level of UA in men [24]. So, we found that melatonin reduces oxidative stress by stimulating various antioxidant production as well decreasing free radicals production.

In conclusion a significant negative correlation between the levels of endogenous melatonin and UA in healthy young males.

Relationship between uric acid & cortisol

Chronically activated HPA axis was associated with decreased diurnal variability of cortisol levels [25]. It was also proposed that central fat distribution is related to greater psychological vulnerability to stress and greater cortisol reactivity [26]. Animal studies showed a dose-dependent increase in visceral fat during chronic stress [27,28]. In vitro, cortisol appears to increase lipoprotein lipase levels (a fat-storing enzyme) in adipose tissue and particularly in visceral fat [29]. Furthermore, genetics may play a role in the relationship between stress and central fat. Genetics can account for up to 50% of the variance in fat distribution [30]. There are also genetic influences on psychological coping with stress [31]. and on cortisol reactivity [32]. It is therefore possible that stress reactivity and central fat are genetically linked. MetS is a cluster of abnormalities that predispose to the development of diabetes, atherosclerosis, and CVD, although many patients with MetS may already have diabetes and/or vascular disease. Therefore, it is important to always specify whether MetS is or is not accompanied by diabetes. Because MetS shares many characteristics of CS, it was proposed that the pathogenesis of MetS and central obesity involves prolonged and excessive glucocorticoid exposure. Emerging data suggest that patients with MetS are characterized by hyperactivity of the HPA axis, which leads to "functional hypercortisolism." Stress seems to play an important role in this interplay through an increase in the responsiveness of the HPA axis. 11HSD1 is a key enzyme in glucocorticoid metabolism in peripheral tissues (particularly in the adipose tissue and liver). 11HSD1 overexpression in adipocytes is observed in MetS and central obesity and results in increased conversion of cortisone to cortisol and in excessive tissue-specific glucocorticoid activity. Experimental

studies with 11HSD1 inhibitors further support the role of 11HSD1 in the pathogenesis of MetS

and might provide novel therapeutic approaches in patients with MetS or obesity [33].

Elevated serum uric acid (SUA) levels are shared by MetS and CS [34,35]. High SUA levels are regarded as a predictor of cardiac and overall mortality in patients with CHD or stroke [36,37]. Elevated SUA is also associated with higher risk of stroke in patients with or without CHD [38]. We demonstrated that statin (mainly atorvastatin) therapy is associated with a reduction in SUA levels along with an increase in estimated glomerular filtration rate in CHD patients with MetS [39,40]. This effect on renal function is perhaps due to an amelioration of endothelial function and renal blood flow [39]. On the other hand, patients with CS may have higher SUA and urinary uric acid excretion than healthy subjects. This is probably a consequence of the hypercatabolic CS state and is independently correlated with increased body weight [35].

Relationship between uric acid & thyroid hormones

Currently, some studies have pointed out that the correlation between thyroid hormone and uric acid level, but this correlation is still controversial. A recent study suggests that thyroid hormone may regulate uric acid levels in patients with subclinical hypothyroidism by regulating insulin resistance [41-43]. Uric acid is mainly produced by the liver, and it is a water-soluble antioxidant.Uric acid has been shown to directly inhibit the damage which is caused by free radicals and also to protect cell membranes and DNA [44].

The uric acid level increase is believed to be an intermediary factor in adipose tissue that regulates endocrine disorders that promote inflammation and may be an important factor leading to dyslipidemia and atherosclerosis [45]. At present, it can be seen that there are many studies on uric acid, and uric acid is also found to be related to cardiovascular disease, kidney disease, etc., but there are a few studies on the correlation between uric acid and thyroid function, and also, there are some controversies.

A recent study suggests that thyroid hormones and thyroid stimulating hormone (TSH) are associated with the function of each organ system but also affect the body's growth and development, and it was found that the concentration

of the thyroid hormones is owing to different age and sex [46]. Another study has found that thyroid hormones play a central regulatory role in the cardiovascular system and are considered a target for the treatment of heart failure [47]. At present, it is believed that thyroid hormone changes have a certain heritability, but most of the genetic possibilities cannot be explained; also, an analysis has found FT3-related genome-wide variations and new TSH-related loci [48]. It can be seen that studies on thyroid function have gone deep into epigenetics, but the correlation between thyroid function and uric acid is still controversial and cannot be better explained. It was found that there were significant differences in the levels of FT3, FT4, and TSH between different uric acid levels. In the linear correlation analysis, it was confirmed that there was a linear correlation between FT3, FT4, and TSH and uric acid level. In further multivariate linear regression analysis, it was found that FT3 and FT4 were correlated with uric acid, but TSH was not [49].

In conclusion, studies show that under normal thyroid function, there is a close relationship between different uric acid levels and TSH, FT3, and FT4 levels. Further analysis confirmed that the uric acid level was linearly correlated with FT3 and FT4, but not with TSH. In conclusion, the metabolism and production of uric acid mainly pass through the metabolic action of xanthine oxidase and xanthine dehydrogenase. Low oxygen, inflammation, etc can accelerate enzyme metabolism and cause changes in the uric acid level, thereby causing the production of related cytokines.

DISCUSSION AND CONCLUSION

Previous studies showed a diurnal rhythm of uric acid. The mean serum uric acid value between 0800-0900 hours was higher than that observed between 1700-1800 hours. Oxidative stress is traditionally characterized as by imbalance among oxidant and antioxidant factors, occurs commonly in Mets. Antioxidant's system including enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and non-enzymatic substrates like ferritin, transferrin, and uric acid controls oxidative stress. Uric acid is an inactive metabolic result of purine catabolism, has been as of late implicated in various long term illness states, including arterial blood pressure, metabolic condition, diabetes, non-alcoholic fatty liver disorders, and chronic renal disorders. Raised uric acid may end up being one of the more significant remediable problematic factors for metabolic and cardiovascular disorders. A negative correlation is found between the levels of endogenous melatonin and UA. A positive correlation is found between the levels of cortisol and UA. Mets are characterized by hyperactivity of the HPA axis, which leads to functional hypercortisolism. Cortisol is one of important key factors for central obesity and Mets like features. These conditions provide environment of increased cytokines production like IL-1, IL-6 and TNF- alpha. So, oxidative stress increases with higher cortisol level results in increase level of SUA. Uric acid level is linearly correlated with FT3 and FT4, but not with TSH. In conclusion, catabolic hormones have positive correlation with serum uric acid while hormones which decrease basal metabolism have negative correlation with serum uric acid levels. We speculate that thyroid hormones can also change the level of cytokines produced by oxidative stress and inflammation, and the change of thyroid hormones can also cause the production of related cytokines and the change of enzyme level and finally affect the uric acid level. The reason may be that thyroid hormones affect uric acid levels by affecting the

conversion of purine nucleotides and excretion of uric acid.

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