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URIC ACID IS A SIGNIFICANT ANTIOXIDANT

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ABSTRACT

Uric acid (UA) is the end product of purine metabolism in humans due to the loss of uricase activity by various mutations of its gene during the Miocene epoch, which led to humans having higher UA levels than other mammals. Furthermore, 90% of UA filtered by the kidneys is reabsorbed, instead of being excreted. These facts suggest that evolution and physiology have not treated UA as a harmful waste product, but as something beneficial that has to be kept. This has led various researchers to think about the possible evolutionary advantages of the loss of uricase and the subsequent increase in UA levels. It has been argued that due to the powerful antioxidant activity of UA, the evolutionary benefit could be the increased life expectancy of hominids. For other authors, the loss of uricase and the increase in UA could be a mechanism to maintain blood pressure in times of very low salt ingestion. The oldest hypothesis associates the increase in UA with higher intelligence in humans. Finally, UA has protective effects against several neurodegenerative diseases, suggesting it could have interesting actions on neuronal development and function. These hypotheses are discussed from an evolutionary perspective and their clinical significance. UA has some obvious harmful effects, and some, not so well-known, beneficial effects as an antioxidant and neuroprotector. High plasma uric acid (UA) is a precipitating factor for gout and renal calculi as well as a strong risk factor for Metabolic Syndrome and cardiovascular disease. The main causes for higher plasma UA are either lower excretion, higher synthesis or both. Higher waist circumference and the BMI are associated with higher insulin resistance and leptin production, and both reduce uric acid excretion. The synthesis of fatty acids (tryglicerides) in the liver is associated with the de novo synthesis of purine, accelerating UA production. The role played by diet on hyperuricemia has not yet been fully clarified, but high intake of fructose-rich industrialized food and high alcohol intake (particularly beer) seem to influence uricemia. It is not known whether UA would be a causal factor or an antioxidant protective response. Most authors do not consider the UA as a risk factor, but presenting antioxidant function. UA contributes to > 50% of the antioxidant capacity of the blood. There is still no consensus if UA is a protective or a risk factor, however, it seems that acute elevation is a protective factor, whereas chronic elevation a risk for disease.

KEYWORDS: Uric acid Diet Protection Risk Metabolic syndrome.

INTRODUCTION

High plasma uric acid (UA) is a prerequisite for gout and is also associated with the Metabolic Syndrome and risk factors for cardiovascular diseases.[1] Hyperuricemia increase in 16% all causes of mortality and 39% of total cardiovascular disease. The hyperuricemia is defined as ≥7 mg/dL for men and ≥6.0 mg/dL for women, and is found mainly in postmenopausal women, Furthermore, many factors can influence the concentrations of UA, eg. Diet, obesity, and Metabolic Syndrome.[8] However, we still don't know if UA is a protective factor for the moderate oxidative stress in these situations or if it's a risk factor. Uric acid (2, 6, 8 trioxypurine-C5H4N4O3) is an organic compound that is endogenously produced by animals as a purine metabolite. It is formed by the liver and mainly excreted by the kidneys (65-75%) andintestines (25-35%). UA is the end product of purine metabolism in humans due to the loss of uricase activity, which led to humans having higher UA levels than other mammals. Due to its double bonds, uric acid has excellent antioxidant capacity, and it can be responsible for 2/3 of total plasma antioxidant capacity. Because it is a weak acid that have a high dissociation constant, uric acid circulates in plasma (pH 7.4) predominantly (98%) in the form of a monovalent sodium salt (urate). It shows low solubility in water (as well as in plasma), and it would theoretically reach plasma saturation in the concentration of 6.4 mg/dL, which may not occur because solubility increase is provided by its binding to proteins, namely albumin, which is its main transporter. Protein-bound uric acid shows plasma solubility that is70% higher than in its free state. Uric acid pathogenesis is usually associated with gouty arthritis or nephrolithiasis.[9] High uricemia pathogenicity is

associated with its low solubility in the extracellular environment leading to crystal formation, low affinity (and deposition) to certain tissues and antigenicity (after crystal phagocytosis). This mixture of quantitative andqualitative etiological hyperuricemia factors is confounding because normouricemic individuals may show symptoms while others with hyperuricemia may not. In the clinical context, hyperuricemia is seen as a prognostic indicator of renal disease, diabetes mellitus, cardiovascular disease and inflammation. Thus being a (modest) risk factor for mortality.[2]
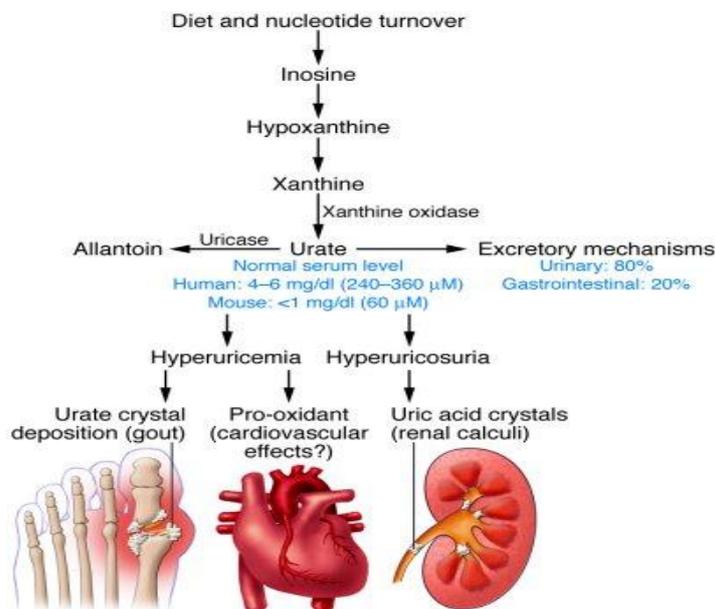
Physiologically, uric acid plasma concentrations increases with age; they are smaller in women of childbearing age and, in post menopause women, it increase to similar values to those found in males. The balance between uric acid production and excretion in males shows a turnover of 600- 700 mg/day for a pool with a maximum of 1,000 mg, as shown by isotopic studies. Uric acid entry into the pool is controlled by hepatic production, which receives endogenous (nucleoproteins) and exogenous (dietary) precursor proteins. Uric acid exit from the pool in males is mainly controlled by the kidneys and by urine-forming factors, renal plasma flow, glomerular filtration and tubular exchange .In the kidney, uric acid and urate are initially filtered and additionally secreted. However, the largest part (90%) is usually reabsorbed and returns to blood[3]
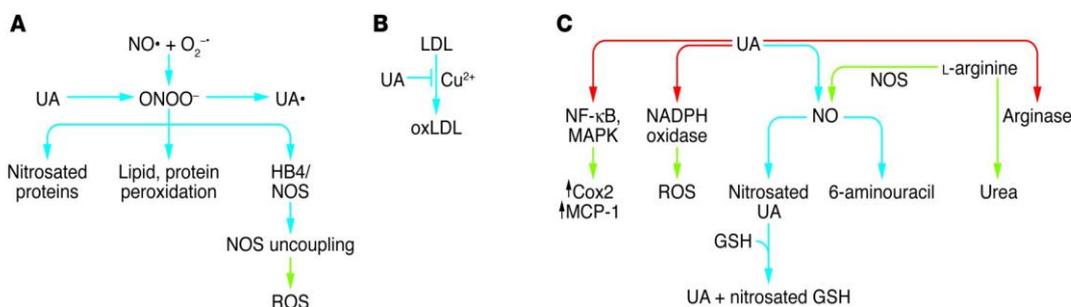

REVIEW
The factors that can influence the uptake of urate by the kidney are: plasma concentrations, volemia and renal plasma flow modulators.[6] At this point, renal excretion of urate follows the same extra-renal limiting factors as those of glomerular filtration. Kidney participation is associated with glomerular filtration (90%filtrate), proximal reabsorption (by an active process) and post-secretory resorption in the distal tubule, ascending loop and collecting duct. In this phase, the renal excretion of urate follows the limiting factors that accompany renal diseases (glomerular and medullary). The urate renal excretion phase is that of post-secretory resorption.

Proximal tubular reabsorption of uric acid is competitive with monocarboxylic organic acids, and it can be inhibited by oxalic acid, lactic acid and ketone bodies (acetoacetic and beta-hydroxybutyric acids). Metabolic situations with higher production and circulation of such acids are accompanied by the hypoexcretion of uric acid in urine. Lactic acid is a product of anaerobic glycolysis (NADH-dependent) in alcoholics, resulting from the metabolism of ethanol (due to higher NADH production), and in inflammation/infection (due to PDH inhibition by pro-inflammatory cytokines) .Ketone bodies are produced in the liver by partial oxidation of acetyl coenzyme A due to excessive peripheral lipolysis.

Ketonuria occurs in decompensated diabetic individuals and in acute fasting (weight loss by carbohydrate-restricted diets). Factors that increase uric acid urinary excretion: extracellular volume expansion and tubular resorption inhibition. Acute renal failure can also rise UA by decreased of renal excretion.[11] Furthermore, the consumption of some drugs are associated with the raise of serum UA (ciclosporin, ethambutol, pyrazinamide, cytotoxic chemotherapy). Purine bases and their nucleotides are rapidly captured by the liver and converted into xanthines, metabolized by uric acid or recycled by salvage pathways or *de novo* synthesis, and the latter requires a higher energetic cost (ATP consumption). Uric acid formation by xanthine occurs via hypoxanthine by the action of xanthine oxidase. In most mammals, uric acid is converted into allantoin by uricase and later into urea, which are excreted. For this reason, uricemia in these animals corresponds to 10% of human values .Diseases accompanied by great cell depletion, such as leukemia, leukocytosis and dystrophies can increase the provision of nucleic acids to the liver and result in a larger production of uric acid[12] Hence, diseases resulting from innate purine metabolic errors may also result in hyperuricemia. As far as diet is concerned The relation between diet and UA has not yet been fully clarified since most studies have not estimated basal urate concentrations, have not excluded confounding factors or have not even correctly evaluated ingested nutrients. The human diet is very poor in urate, which is produced mainly in the liver and to a less extent in the small intestine. The production of UA depends of purine ingestion [.however, a purine-rich diet would be responsible for an increasing only in 1 to 2 mg/dL of UA .It is recommended that individuals with hyperuricemia should not ingest a large amount of purine-rich food (for instance, veal, bacon, kid meat, mutton, turkey, pork, duck, goose, etc.) and it is suggested that a high intake of meat and seafood are related to increase UA, but the same relation is not valid for total protein intake.(12)
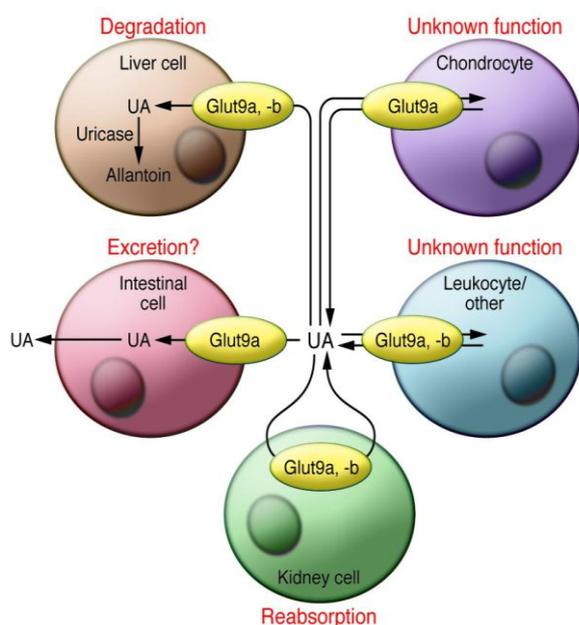

During fructose metabolism, the phosphorylation of such monosaccharide into fructose 1-phosphate occurs by means of enzyme fructokinase. Next, enzyme aldolase B breaks fructose 1-phosphate into dihydroxyacetone phosphate (DHAP) and D-glyceraldehyde. When high fructose intake occurs, fructose phosphorylation into fructose 1-phosphate is fast, but the reaction with aldolase is slow.[5] Hence, fructose 1-phosphate accumulates, and inorganic concentrations of intracellular phosphate also decrease. The low availability of phosphate limits ATP formation (ADP + Pi), and ADP or AMP resulting from such metabolism is catabolized, thus leading to hyperuricemia.[3]

There are other ways to increase urate concentrations, such as the intake of sorbitol, sucrose, lactate and methylxanthines. After absorption, Sorbitol is converted into fructose by the liver, and thus, it can increase UA production. Fruit and vegetables, in addition to flavonoids, can contain other nutrients that can affect the plasma total antioxidant capacity (TAC). Lotito & Frei (2006). Reported that the TAC increase observed after the intake of these flavonoids-rich food types is not specifically caused by flavonoids because such nutrients are probably highly metabolized after ingestion. Possibly, what would increase TAC would be the UA elevation resulting from fructose metabolism. The mechanism for such elevation would be the degradation of purine nucleotides or UA excretion reduction. High vitamin-C intake shows an inverse relation with UA as such vitamin has a uricosuric effect due to competition of UA renal resorption through a change in the anion transportation system in the proximal tubule .Beer intake is an independent factor from UA increase. Both due to its alcoholic content and high-quality purine. Beer intake has a stronger power to increase UA than liqueur, but moderate wine intake does not increase UA. Alcohol intake increases UA concentrations by reducing excretion and increasing urate production. Dairy product intake has an inverse relation with UA. Probably, the mechanism for such association is due to milk-forming proteins (lactalbumin and casein), which have a uricosuric effect. There is an inverse relation between coffee intake and UA concentrations , but such association seems to be due to other substances, as it does not seem to result from caffeine. Decreased UA concentrations would result from the improved insulin resistance observed with increased coffee intake, which occurs mainly due to chlorogenic acid, an antioxidant found in that drink .Renal calculi are formed by calcium salts deposited on an organic matrix of oxalate or urate.[4] Their formation occurs in the glomerular filtrate in acid (oxalate or urate) or alkaline (carbonates and phosphates) pH in the presence of high calciuria (hyperparathyroidism or bone demineralization). They are usually formed and then dissolved, but under abnormal pH variation or filtrate concentration conditions, they may remain until excretion.[5] The contribution of UA to renal stone formation has an important role in progressive renal failure. Meta-analysis

has recently shown that UA elevation is related to an increase in (coronary artery disease) infarction and mortality events, and epidemiological studies showed that UA is an independent risk factor for cardiovascular diseases, particularly in hypertensive and diabetic individuals.[6] It is also speculated that UA is one of the determinants of the metabolic syndrome. Individuals with high UA levels have an odds ratio of 1.6-fold higher for developing MS .UA is associated with Metabolic Syndrome and its components , obesity, dyslipidemia, hypertension, insulin resistance (metabolic syndrome), increased C-reactive protein (PCR) concentration, and endothelial dysfunction, or even, to risk factors for cardiovascular diseases.[7] UA increase is observed in individuals with insulin resistance, probably because hyperisulinemia would cause lower renal UA excretion. Additionally, insulin could indirectly act on UA, since there is an association between hyperinsulinemia and hypertriglyceridemia. Some studies show that high concentrations of plasma triglycerides are related to hyperuricemia, There are some explanations for such relation, and one of them is that during triglycerides (TG) synthesis there would be a greater need for NADPH, The synthesis of fatty acids in the liver is associated with the *de novo* synthesis of purine, thus accelerating UA production .Chen *et al.* (2007), observed negative correlation between HDL-c and UA. The likely mechanism is the relationship between decreased HDL-C and insulin resistance. Confirming this hypothesis, our research group showed that when adjusted for the other

MS components, the relation between UA and HDL-c is lost, In the adipose tissue, there is adipokine production, including that of leptin. One possible explanation for the association between higher waist circumference and hyperuricemia were suggested by Bedir et al. (2003) and Fruehwald-Schultes et al. (1999) which studies found that UA serum concentrations are independently related to leptin concentration, thus suggesting that would be a pathogenic factor responsible for UA increase in obese patients.[8] Some authors report UA to be responsible for blood pressure increase, and others show arterial hypertension (AH) to be a risk factor for hyperuricemia. UA inhibits the bioavailability of nitric oxide, which is a vasodilator, and, on the other hand, AH would lead to vascular disease and increase renal vascular resistance. Both of these processes reduce renal flow, thus increasing urate resorption. A recent study showed an inverse relation between muscle mass (MM) and UA in healthy individuals older than 40 years. Chronic elevation of UA concentrations would be a causal factor for sarcopenia, especially through increased inflammation and oxidative stress.[9] The activation of the xanthine oxidase metabolic pathway, which increases UA production and the superoxide radical, could elevate the reactive oxygen species (ROS) and it could be the main mechanism for the reduction of MM. Furthermore, UA exerts a pro-inflammatory effect, thus stimulating the production of interleukin-1, interleukin-6 the tumor necrosis factor which also can influence the muscle mass.
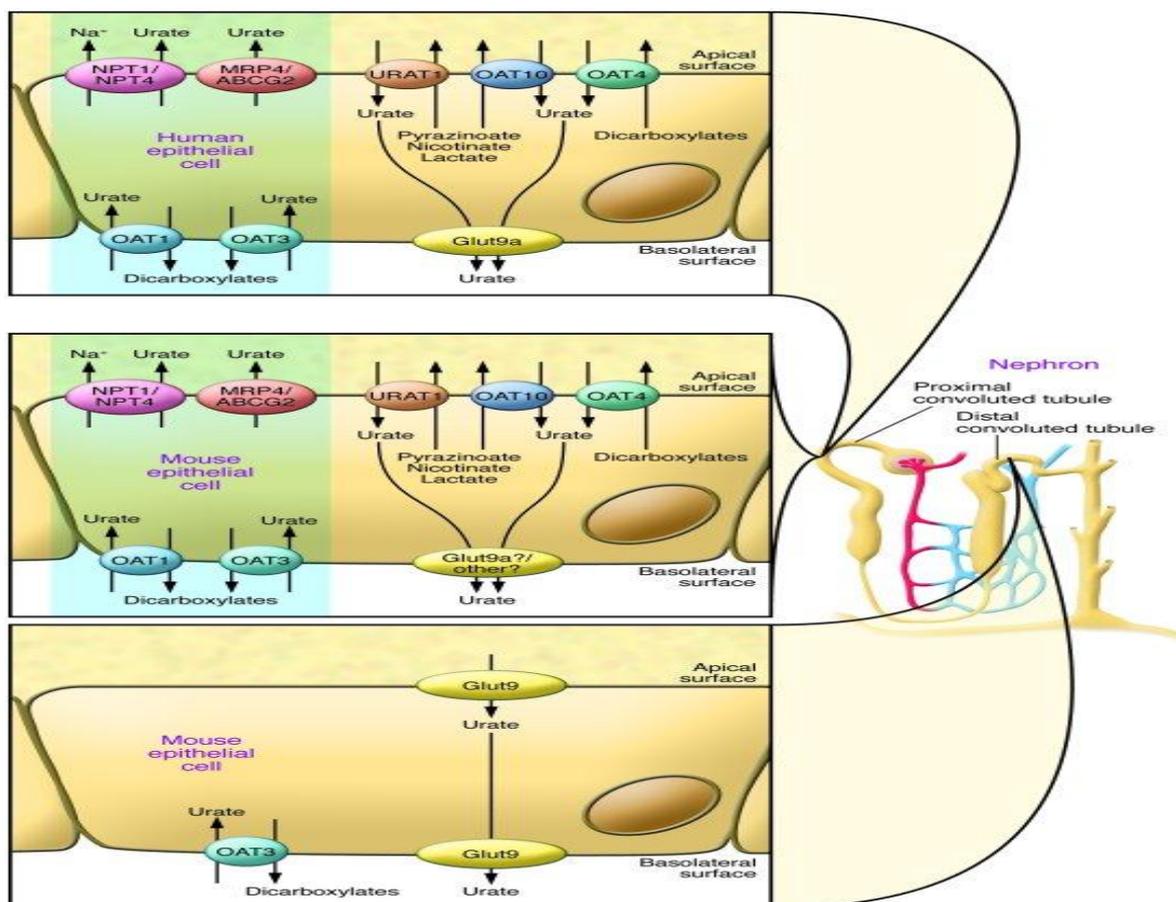
Observation

Uricemia as a protective factor. It is not known whether UA would be a causal factor or an antioxidant protective response against oxidative stress. While chronic high UA concentrations are associated to increased risk for CAD, acute elevations seem to provide antioxidant protection. UA contributes to > 50% of the antioxidant capacity of the blood.[17] Furthermore, the UA has a protective action in vitamins C and E[10] with the stabilizing activities in these vitamins and the presence of ascorbic acid in plasma is required for the antioxidant effect of UA . Also, it has a direct effect on the inhibition of free radicals such as peroxyl radical and peroxynitrite, protecting the cell membrane and DNA .Most authors do not consider UA as a detrimental factor to the body health, because of its antioxidant function .The antioxidant activity of UA also occurs in the brain, being a protector for several disease such as multiple sclerosis and neurodegenerative disease. Higher concentration of UA is associated with lower risk of development of Parkinson's disease and a favorable effect at the disease progression mainly. The results are consistent with the possibility that uric acid may protect against IPD. Since uric acid is a known antioxidant, proponents of the free radical theory of Parkinson's disease etiology had previously hypothesized such a protective effect.

DISCUSSION

In this study, rates of incident IPD were lower in men with serum uric acid concentrations above the population median at two points in time separated by an approximate6-year interval. These results could support either an etiologic role for uric acid or a role in delay ingdisease progression. However, these findings must be interpreted with caution, as the associations between median dichotomized uric acid values and IPD were only marginally significant. When uric acid was categorized into quartiles or modeled as a continuous variable, the associations were not statistically significant.[11] The pattern using quartiles, however, did support a threshold effect, with rates increasing above the median. A potential explanation of the apparent "high threshold effect" on protection from IPD is that of "selective mortality".[8-10] Mortality also becomes an issue because IPD is difficult to diagnose: Early symptoms, such as confusion or slow gait, can be mistaken for aging or attributed to other diseases. As a consequence, it has been argued that IPD may be under-diagnosed among subjects who die of other diseases, especially if they die "early." (We believe it equally likely; however, that IPD is more frequently diagnosed in persons with potentially fatal chronic diseases because of the "medical detection/surveillance biases" associated with frequent physician visits and hospitalizations)(12). Among Honolulu Heart Program cohort subjects, men in the highest quartile of serum uric acid not only had a reduced rate of IPD, but also had a 30 percent higher mortality rate than did men in the lowest quartile. This is in the direction that would be expected if selective mortality were operative. Some men with high uric acid

levels and IPD may have died before their disease was diagnosed. The type of selective mortality often discussed is an increased mortality among smokers who develop Parkinson's disease.[17] If a selective mortality bias exists, however its magnitude might increase with age, since mortality increases with age and the combination of smoking and Parkinson's disease is hypothesized to accelerate death. Before IPD could be diagnosed, increasing proportions of cases might die from other smoking-related causes. However, when we restricted analyses to cases diagnosed before age 75 years (61 percent of all cases), the association between uric acid and IPD was as strong for the younger men as for the older men. There are several other plausible explanations for the results. Previous analyses in the Honolulu Heart Program documented that uric acid is associated with a complex array of physiologic and lifestyle variables, including age and smoking, which are independent predictors of IPD occurrence.[13] When age and smoking were adjusted for, however, the association between uric acid and IPD "protection" persisted. The association was also most pronounced in "never smokers."This finding is intriguing in that smoking has been associated with an approximate halving of IPD risk. Conceivably, unknown beneficial effects of both smoking and uric acid might operate in only a subset of susceptible persons. Other variables associated with uric acid within the Honolulu Heart Program cohort include weight, alcohol intake, serum triglycerides, and glycosuria. When included in multivariate models, none of these variables were associated with substantial alteration of the rate ratio for uric acid. A further possible bias is a diagnostic bias if men with high uric acid levels were selectively under diagnosed. In the Honolulu Heart Program, however, uric acid is positively associated with education and management or skilled occupation. As a consequence, men with high uric acid levels may be more likely to be diagnosed with early disease. Another potential bias is "reverse causation bias.[14] To examine this possibility, we excluded cases diagnosed within 5 years of the uric acid measurements. Such case subjects might have had early IPD symptoms or a presymptomatic state that led to an altered diet or physiologic state. However, the association between uric acid and IPD persisted even with this exclusion (table 2). Our attempts to explain the association between uric acid and IPD by study bias did not lead to an obvious explanation. Consequently, an alternative explanation— that uric acid may protect against IPD—also deserves consideration. The plausibility of this explanation is supported by circumstantial evidence that oxidative damage plays an etiologic role in IPD[18] Among several observations supporting this possibility are evidence in IPD patients of increased lipid peroxidation, increased levels of non heme iron, which can accelerate oxidative reactions, and reduced levels of glutathione and glutathione Peroxidase which can limit the intracellular generation of free radicals.[15] These observations suggest that patients with Parkinson's disease may be under sustained oxidative stress. The evidence for oxidative

damage was considered sufficiently persuasive that vitamin E antioxidant therapy has been under investigation in clinical trials, although it has been shown not to slow IPD progression. Support for the hypothesis that uric acid may protect against IPD is limited. Since uric acid is a water-soluble antioxidant that inactivates free radicals of oxygen and binds the main electron-transfer medium for free radical generation (iron), there is a theoretical basis for its involvement in decreasing oxidative damage through one or more mechanisms. In one study, uric acid was significantly lower in postmortem extracts of the parkinsonian versus normal substantia nigra. In a second study, serum uric acid concentrations were lower in Parkinson's disease patients than in control subjects. Our results now add prospective evidence consistent with an association between uric acid

and reduced IPD occurrence, suggesting a need for further study.

CONCLUSIONS
Several factors are associated as cause and consequences of high UA concentration. Higher waist circumference and BMI are associated with higher insulin resistance and leptin production, and both reduce renal uric acid excretion, thus increasing its concentration. HDL-c concentration is negatively associated to insulin resistance, what can influence its negative correlation to uric acid. Obese individuals usually have Metabolic Syndrome diagnostic, which can also increase uric acid serum concentrations due to synthesis increase (triglycerides - TG concentration) and lower excretion (arterial hypertension - AH).
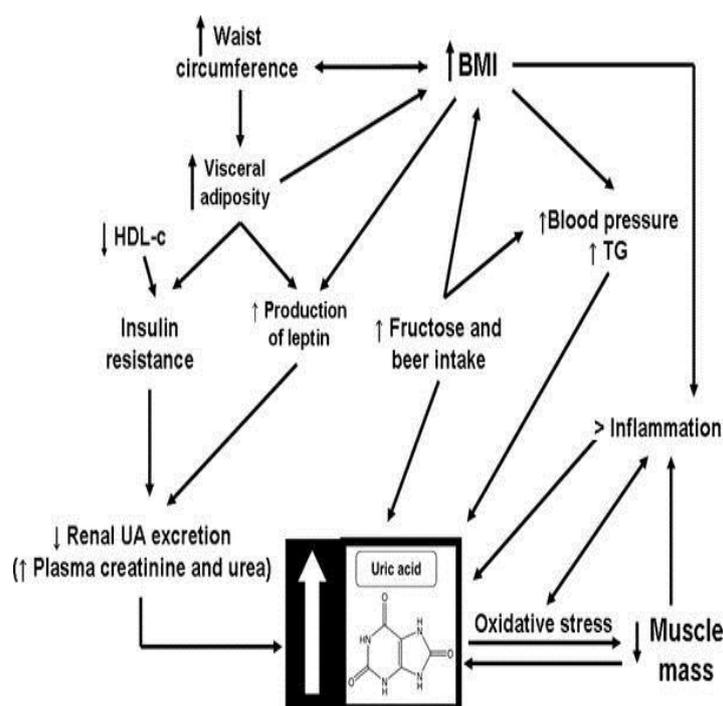

Figure 1

Determinants of hyperuricemia
UA = Uric Acid, BMI = Body Mass Index, TG = triglycerides.

Additionally, obesity and muscle mass (MM) reduction are associated with low-intensity chronic inflammation, and uric acid levels can increase in order to protect the organism against the moderate oxidative stress resulting from this situation. Low muscle mass (sarcopenia) is negatively associated with uric acid, However, it has not yet been clarified what the cause or effect is. Probably, oxidative stress produced by excessive uric acid can influence muscle mass reduction. The role played by diet on hyperuricemia has not yet been fully clarified, but high intake of fructose-rich industrialized food and high alcohol intake (particularly beer) seem to influence uricemia. The main mechanism of excretion of urate concentrations occurs by means of renal excretion;

hence, glomerular function markers (urea and creatinine) are positively associated with uric acid .Furthermore, there is still no consensus if UA is a protective or a risk factor; however, it seems that the quantity and the duration of the concentration of the uric acid in the blood is essential for this answer. Acute elevation seems to be a protective factor, whereas chronic elevation a risk factor.[16]

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