

Understanding the Influence of Oxidative Stress and Physical Exercise in the Relationship Between Blood Pressure and Uric Acid

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Received: September 30, 2014 Revised: November 20, 2014

Accepted: November 22, 2014

Published online: December 10, 2014

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Key words: Blood pressure; Uric acid; Oxidative stress; Physical exercise

Jacomini AM, Zago AS. Understanding the Influence of Oxidative Stress and Physical Exercise in the Relationship Between Blood Pressure and Uric Acid. *Journal of Cardiology and Therapy* 2014; 1(9): 221-227 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/943>

ABSTRACT

Due to the high incidence and prevalence of hypertension, especially in the elderly population, several studies have been developed to understand the relationship between etiological factors and blood pressure control. It has been demonstrated that hypertensive patients tend to present a status of hyperuricemia. This result suggested that there is a relationship between blood pressure and uric acid concentrations. However there is still a lack of studies that focus on this relationship, and especially how physical exercise could affect the relationship between both of them. Thus, the purpose of this study is to review and discuss the relationship between hypertension and uric acid concentration pointing the oxidative stress as the main factor of this relationship and discuss the physical exercise as the main preventive factor of high uric acid concentrations and oxidative stress. It has been described an increase in oxidative stress during the uric acid pathway because the high production of anions superoxide. This in turn, increases the activation of renin-angiotensin system and decreases nitric oxide bioavailability which will compromise the vasodilatation mechanism. However physical exercises have been associated with improvements in antioxidant capacity and nitric oxide production and bioavailability which will improve the blood pressure control.

INTRODUCTION

Arterial Hypertension (HT) has been considered one of the main risk factors for cardiovascular diseases and, one of the biggest problems of public health^[1-3]. Studies point for a prevalence above 30% within Brazilian adult population, which values increase even more with aging, reaching 50% between 60 and 69 years old and 75% in individuals above 70 years old^[2]. These data are similar in Latin America countries^[4] and United States^[5].

With the increasing number of elderly population and the problems associated with aging, especially HT, there is a rising demand for health services^[6]. In 2001, around 7.6 millions of deaths in the world were assigned to high blood pressure, which most of them are in Countries with low or medium economic development and most of individuals between 45 and 69 years old^[2].

Because it is considered a chronic degenerative disease, HT has several factors involved in its etiology^[2,7,8], such as genetic and environmental factors, stress, poor diet, and others. However, it has been observed in several studies that, independently of the etiological factor, a large portion of hypertensive individuals present a hyperuricemia profile, which is considered a metabolic disorder marked by the excess of urate in blood. This number can reach about 25%^[9-12] or, according to Heinig *et al*^[12] who found that 89% of teenagers with essential HT presented uric acid (UA) concentrations upper to 5.5 mg/dL, whereas no one of the normotensive teenagers presented high levels of UA. Similar results were found by Assob

*et al.*¹³ who evaluated individuals with high UA concentration and more than 90% were classified as hypertensive or pre-hypertensive. Although UA is more associated with the formation of small crystals, especially in joints, the cited results suggest that there is a relationship between UA and HT.

Turak *et al.*¹⁴ verified in 921 patients with essential hypertension an association between morning blood pressure and UA level and both of them were correlated with major cardiovascular events. In this study the patients classified in the highest quartile (elevated morning blood pressure and UA level) had a 3.55 odds of major cardiovascular events compared with those in the lowest quartile. Tatal *et al.*¹⁵ also found that patients with the highest quadrant for UA levels had higher morning blood pressure compared with the lowest quadrant, and UA levels were also positively correlated with night ambulatory blood pressure. These results suggest that hyperuricemia is closely associated with cardiovascular risk factors such as HT.

Overall, UA is considered as an antioxidant that, theoretically, promotes beneficial effects to the human body decreasing oxidative stress. Waring *et al.*¹⁶ in a study with 20 healthy individuals reported an increase of serum antioxidant capacity and reduced exercise-induced oxidative stress when UA is administered. However, when in high concentrations, several consequences can be observed, such as joints inflammation and accumulation of crystals in the joints and kidneys, which can evolve to renal calculus and increase of blood pressure levels^{9,17,18}.

The high UA levels can be considered as independent cardiovascular risk factor, because the rising of UA serum in patients with cardiovascular disease can be a result of other factors such as the reduced rate of glomerular filtration, hyperinsulinemia, renal vasoconstriction, diuretic, alcohol and tissue ischemia^{11,12,17,18}. However, hyperuricemia is also being considered as a dependent risk factor due to the relationship with HT and oxidative stress. Heining *et al.*¹² increased the UA levels in rats using an uricase inhibitor within 3-5 week periods, and they verified that the animals developed HT and hyalinosis (renal cardiovascular disease).

These data increase the importance about the discussions of mechanisms that are promoting the high incidence of HT, specially, related to UA. The control of blood pressure and all factors that increase the incidence and prevalence of HT may be an important prevention to improvement the life condition. In this way, the purpose

of this study is to discuss the relationship between UA and HT, pointing the hypothesis of oxidative stress as an intermediate factor between them. Even though, it has been pointed that sedentary life style can enhance the incidence of HT². Physical exercise has been considered the main preventive way to the control of HT. Thereby, the purpose is also to discuss the effect of physical exercise in the relationship between UA and HT.

MECHANISM OF URIC ACID FORMATION: NUCLEOTIDE PURINE CYCLE

To understand the relationship between UA and HT initially it is necessary the understanding of the UA formation route. The human body is extremely dependent of “adenosine triphosphate molecule” (ATP), as an energetic source. This metabolism generates the “adenosine diphosphate” molecule (ADP) which in turn can be converted again in ATP or in “adenosine monophosphate” (AMP). These reactions are freely reversible and they are catalyzed by the adenylate cyclase enzyme¹⁹. The AMP molecule can go through three different pathways: (a) suffer a phosphorylation and be transformed in ADP and ATP; (b) suffer a phosphorylation and be transformed in adenosine and then to inosine, or (c) suffer a deamination and be transformed in inosine monophosphate (IMP), which can enter in the nucleotide purine cycle or be converted in inosine^{19,20} (Figure 1).

The nucleotide purine cycle has an important metabolic function in muscle-skeletal which is the maintenance of cell energetic load acting in the ATP resynthesis, especially during physical exercises performance.

The AMP deamination occurs through the AMP deaminase enzyme and it is regulated by ATP, ADP, AMP and inorganic phosphate (Pi) concentrations. However, a resting muscle metabolic condition and the ATP saturation can cause this enzyme inactivation²⁰. This inactivation may result in increased inosine concentrations, which in turn will cause a “biochemical cascade” sequence transforming it in hypoxanthine, xanthine and, finally, UA through the xanthine oxidase enzyme (XO). In contact with a oxygen molecule the XO enzyme produces superoxide anions ($O_2^{\bullet -}$)^{19,20}.

UA is a weak acid distributed in cell liquid as sodium urate, being eliminated from the plasma by glomerular filtration. Approximately

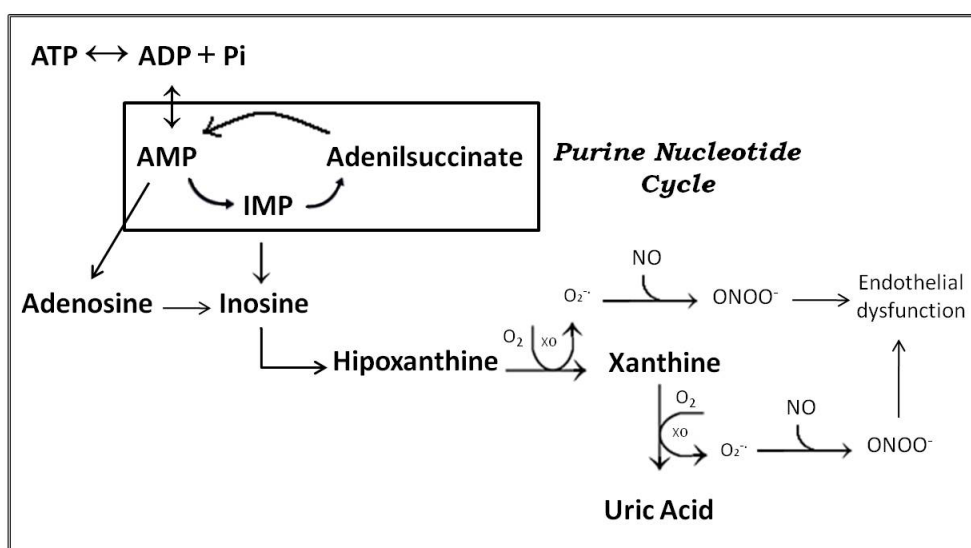


Figure 1 Illustration of uric acid pathways.

90% of UA is reabsorbed by the renal proximal tubule and distal tubule through a mechanism called ATPase-dependent. The metabolic purine can be derived from exogenous via, through diet, or endogenous via, through circulating purine and nucleic acids, or by genetic factors. The urate concentration for an individual is determined by the combination between the purine metabolism rate (exogenous and endogenous) and efficient renal clearance^[19,21].

UA is poorly soluble in aqueous solutions, and as a consequence, the exposition to high serum levels of urate predisposes the deposition of crystals in the soft tissues and the increase of oxidative stress by the increase of $O_2^{\cdot-}$ ^[21].

BLOOD PRESSURE AND URIC ACID: THE EFFECT OF OXIDATIVE STRESS

Although there are studies correlating high UA levels and the increase in cardiovascular risk^[9], there are still some controversies in the relationship between UA and HT levels and kidney diseases in humans^[22]. The hyperuricemia is associated to some risk factors for cardiovascular disease, such as hyperinsulinemia, dyslipidemia and renal failure^[9]. However, it seems to exist an indirect relationship between UA and HT, because the oxidative stress induced by UA formation and the consequent $O_2^{\cdot-}$ production.

It is noteworthy that the superoxide anions, hydrogen peroxide and hydroxyl radical, known as reactive oxygen species (ROS), have continuous production by mitochondria during aerobic metabolism. So, the reduction of mitochondrial activity compromises regular cell activity and contributes to increase oxidative stress^[23]. Both $O_2^{\cdot-}$ and UA are regularly produced by the body and they are necessary in several biological processes, such as cell signaling, muscle contraction and immune system^[24].

However, high levels of $O_2^{\cdot-}$ can damage tissues and produce toxic or harmful compounds resulting in oxidative stress, it means, an unbalance between ROS production and scavenge by organic antioxidant defense systems^[25]. Therefore, the increased level of $O_2^{\cdot-}$ from the high UA concentration, can compromise several functions of cardiovascular control in human body, such as nitric oxide (NO) bioavailability, which plays an important role in vascular homeostasis. A powerful vasodilator, NO is produced by endothelial cells and it has an important role in the relaxation of vascular smooth muscle^[26,27]. However, its bioavailability is reduced when exposed to high concentrations of $O_2^{\cdot-}$, which can promote an increase of blood pressure^[28] (Figure 1).

An important feature in the mechanism of UA formation is that muscle does not have the necessary enzymes to convert hypoxanthine to inosine^[20]. Thus, once formed, hypoxanthine undergoes the action of the XO enzyme, which together with oxygen molecule, is going to produce xanthine molecules and $O_2^{\cdot-}$. Xanthine is also going to suffer an additional action of XO enzyme producing UA and $O_2^{\cdot-}$, as illustrated in figure 1. One of the main cardiovascular sources of ROS is the XO coming from this biochemical pathway^[27].

Physiologically, ROS are produced in low concentrations and work as a molecular indicator to maintain vascular integrity and as a regulator of endothelial function^[28]. However, when in higher concentrations, $O_2^{\cdot-}$ react with NO to form peroxynitrite (ONOO-)^[29,30]. These molecules are largely responsible for the endothelial dysfunction process and for the decreasing of NO bioavailability^[31,32], due to the high affinity of $O_2^{\cdot-}$ with NO, and consequently by the decrease of vasodilatation^[31,32]. The entire process can be associated to an increase of peripheral resistance and, consequently, an increase of blood pressure^[33-37] and the incidence of several cardiovascular

diseases^[28,29].

It is important to highlight that the increase of peripheral resistance also receives influence of the renin-angiotensin system activation (RAS), which is responsible for vasoconstriction and consequent increase in blood pressure and, which also seems to have a relationship with UA high levels. This information was supported by Balda *et al*^[9] that demonstrated a higher UA serum concentration in hypertensive individuals compared to normotensive individuals and that a higher UA serum concentration was related to a higher RAS activation. In study with normotensive and hypertensive individuals, Perlstein *et al*^[22] emphasized the high UA concentration in a hypertensive group. Moreover, the UA concentration presented a correlation with renal plasma flow in response to angiotensin II. According to the authors, the possible explanation to these results is the association between UA and RAS intrarenal. Confirming these results, Zhou *et al*^[38] pointed that high UA concentration is associated to RAS activation, because the increment in justaglomerular renin and, Mazzali *et al*^[39], in experiment with animals, showed that hyperuricemic rats developed HT, had a higher renin expression and had an increase in the angiotensin converter enzyme activity (ACE). This result raises the possibility that UA is considered a nephropathy mediator. However, the RAS activation mechanism by UA is not clear yet.

In an experiment with animals, Choi *et al*^[40] induced rats to a hyperuricemia and after that, they promoted the reduction in UA levels by allopurinol, an UA synthesis selective inhibitor. The reduction in UA levels was able to prevent the increase in blood pressure, which suggests that high levels of UA can be responsible for HT. Also, the authors pointed that even in a physiological concentration, the UA is able to induce an insulin resistance and vascular endothelial dysfunction, which can be involved in phosphorylation of endothelial nitric oxide synthase (eNOS) activity and decrease of NO bioavailability.

Generally, experimental and clinical studies have supported the hypothesis that NO concentrations can be impaired by endothelial dysfunction generated by hyperuricemia which promotes a relevant decrease in NOS and an increase in ROS. Both mechanisms can lead to a decrease in NO bioavailability. Besides, there is still the possibility of increasing RAS activation, considered as one of the main peripheral mechanisms responsible for raising blood pressure.

Moreover, the UA concentration has an association with platelet adhesion which can compromise the vascular control mechanisms^[9]. In a study performed in vitro, the ROS concentration produced during UA pathway can promote an increase in low-density lipoprotein (LDL) oxidation^[41] and Matos *et al*^[42] pointed that individuals with hyperuricemia (urate serum levels higher than 6.0 mg/dL) presented high level of VLDL-cholesterol e triglycerides, highlighting a relationship between UA and atherosclerosis.

In conclusion, it has been suggested that hyperuricemia can promote HT by the increase of ROS. It will compromise the NO bioavailability and increase RAS activity and platelet adhesion.

BLOOD PRESSURE CONTROL: EFFECT OF PHYSICAL EXERCISE

Physical exercises have been pointed as one of the main non pharmacological treatment of several risk factors of cardiovascular diseases, specially the HT^[2,43,44] and it has been approached under two aspects: preventive, involving health promotion and, therapeutic^[45,46].

A comparison between continuous and interval training in an ergometer cycle was performed by Lamina *et al*^[47] that analyzed

the blood pressure and UA concentrations in hypertensive adults and elderly between 50 and 70 years old. Both groups presented a reduction in blood pressure values and UA concentration after a training program (8 weeks, three sections per week and intensity around 60-80% of maximum heart rate), but no difference was found between continuous and interval training. Levya *et al.*^[48] also found positive results in the relationship between physical exercise and UA. In this study it was found a negative correlation between anaerobic threshold and UA, and Levya *et al.*^[49] found the same correlation between functional capacity and UA.

Although the mechanism that modulates the relationship among UA, blood pressure and physical exercise are still unclear, studies have suggested some mechanisms that can perform in order to strengthen such relationship. These mechanisms are:

(a) Increase in the antioxidant capacity:

In order to supply the energetic demand necessary to perform determined activity, physical exercise stimulates the Krebs Cycle and Electrons Transportation Chain to resynthesis of ATP, having as a consequence a great increase of ROS, such as $O_2^{\bullet-}$. Simultaneously, physical exercises promote increase of ADP concentrations and a decrease of ADP concentrations due to energetic demand.

At first, the performance of physical exercises can be considered malefic to the body due to relevant increase in $O_2^{\bullet-}$ and this effect is intimately related to the intensity of exercise. The higher is the intensity, the higher will be the energy coming from the nucleotide purine cycle which will increase accumulation of hypoxanthine, xanthine and UA^[50-52]. It is appropriate to emphasize that although UA is considered an antioxidant, when in high concentrations there are high formations of ROS.

However, physical exercise has an important role in regulation of adenosine monophosphate enzyme kinase (AMPK), modulating the ratio between ATP/ADP, due to muscle contraction^[19,53-56]. This response is dose-dependent to the physical exercise^[57].

The AMPK activation increases the expression of peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1 α) in skeletal muscle^[58-60], which induces an expression of lipid catabolism (β - oxidation), electron transportation chain^[60-62] and genes which are responsible for the formation of antioxidant components that generate a higher body antioxidant capacity due to reactions with $O_2^{\bullet-}$, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX)^[60,61] (Figure 2).

Ookawara *et al.*^[63] verified that after physical exercises SOD levels increased when compared to the baseline moment in healthy male

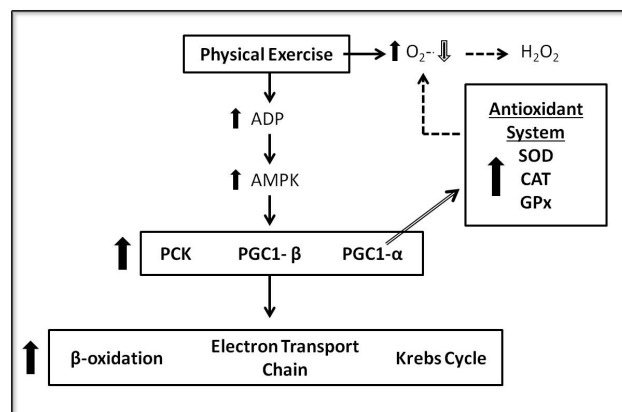


Figure 2 Illustration of the effect of physical exercise in the antioxidant capacity (dotted arrow indicates reduction of anions superoxide).

adults. Fett *et al.*^[64], in overweight women, pointed a relevant decrease in UA levels and oxidative stress after 8-weeks of physical training. In addition, Trape *et al.*^[65] verified that adults and elderly with low level of physical fitness had an increase in the blood pressure values and UA concentration and low values of nitrite, while the inverse results were found in participants with high physical fitness. These studies suggest that the relationship between blood pressure and oxidative stress produced by UA pathway can be modulated by the training state.

These effects were also found in other studies which emphasize the physical exercise as an antioxidant stimulus^[47,66,67], having the capacity to neutralize the $O_2^{\bullet-}$, including those formed by UA pathway.

Thereby, physical exercise not only reduces the ADP in the purina nucleotide cycle, because the ATP resynthesis, but also increases enzymatic activity which confers a protection against antioxidant agents in the body^[61,68].

(b) Increase in NO bioavailability

The high affinity between $O_2^{\bullet-}$ and NO compromise the vasodilatation mechanism and it lead to the failure in the blood pressure control. However, this mechanism can be minimized through regular physical exercise, which promote an increase in blood flow and consequently increase in shear stress^[69,70]. This in turn will stimulate the endothelial superoxide dismutase (ecSOD) promoting a higher antioxidant activity. Briefly, this mechanism occurs due to the high affinity between ecSOD and $O_2^{\bullet-}$ which will neutralize the reaction between NO and $O_2^{\bullet-}$ increasing its bioavailability^[29,31,37,71,72].

(c) Increase in NO concentration

Besides the stimulus for ecSOD, the shear stress also increases the stimulus for eNOS through mechanoreceptors in the artery wall. The eNOS has an important function in activating the pathway for NO production^[46,73], which will promote a vasodilatation and decrease in peripheral resistance.

Graham *et al.*^[74] demonstrated in animal sample, that 6-week of low intensity physical training in treadmill was enough for increasing eNOS levels compared to the control group and Cacicedo *et al.*^[75] verified with exhaustion test in treadmill, not only an increased eNOS levels after exercise, but also a positive correlation between eNOS levels and the distance covered by the animals.

In humans, studies have demonstrated the beneficial effect of physical exercise to increase NO concentrations and reduce blood pressure, especially when there are some associations with genetic factors. This result was observed in older adult women carriers of eNOS genetic polymorphism which performed an aerobic exercise in a treadmill (6 weeks, three section per week, 40 minutes per section and intensity until 70% of VO_{2max})^[37] and also in sedentary elderly women which performed three weeks of aerobic exercise in a treadmill (5 times per week, at 80% of VO_{2max} , 30 minutes per section)^[76] and in healthy and sedentary men that performed an acute exercise until exhaustion^[50].

Figure 3 illustrates a summary of the physical exercise effect in the relationship between UA concentration and blood pressure. Physical exercise induces an increase in the antioxidant system by ATP/ADP balance and increases NO bioavailability and eNOS expression by shear stress. It has a direct effect in blood pressure control. Moreover, there are some evidences that PGC-1 α also has the capacity to increase eNOS expression^[54,55,61], contributing to the increase in NO concentrations and consequently reducing blood pressure.

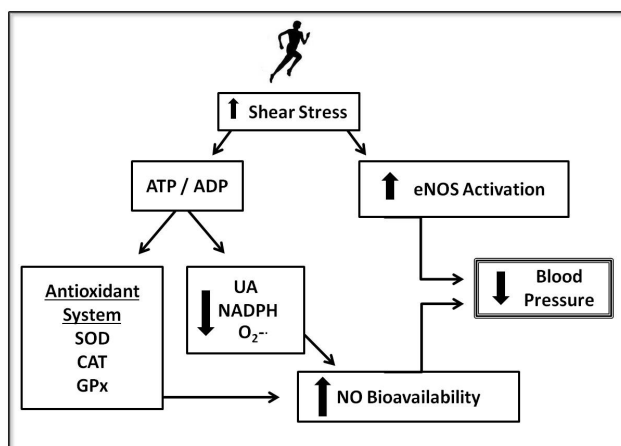


Figure 3 Summary of the effects of physical exercise and decreased blood pressure.

FINAL CONSIDERATIONS

Hypertension has been pointed as one of the main risk factors for cardiovascular diseases and one of the biggest public health problems in the world. Its etiology is multifactorial and one of the factors that can contribute for the high incidence of HT is the oxidative stress from UA pathway.

In the purine metabolism chain, UA formation is associated to a higher ROS generation and consequently reduced NO bioavailability, which has been pointed in the literature as an important factor for development of HT. However, the regular physical exercise and the maintenance of good levels of physical fitness have been associated with reduced UA concentrations and reduced oxidative stress. So, although there is no consensus in the literature, physical exercise has been suggested to be the best non pharmacological treatment against HT and an excellent way to improve the quality of life.

ACKNOWLEDGMENT

FAPESP: São Paulo Research Foundation” (Grant Number -2009/54586-0 and 2013/13146-3).

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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