Uricaemia as a Cardiovascular Events Risk Factor in Hypertension: The Role of Interval Training Programme in its Downregulation

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Abstract

Objective: Elevated serum uric acid is considered to be positively associated with cardiovascular event risk factor in hypertension. Also, the positive role of exercise in the management of Hypertension has been well and long established. However the relationship between serum uric acid (SUA) level and hypertensive management particularly in non pharmacological technique is ambiguous and unclear. Therefore the purpose of the present study was to determine the effect of interval training programme on serum uric acid level and cardiovascular parameters in male subjects with hypertension.

Methods: Two hundred and forty five male patients with mild to moderate (systolic blood pressure [SBP] between 140-180 and diastolic blood pressure [DBP] between 90-109 mmHg) essential hypertension were age matched and grouped into interval and control groups. The interval (n=140; 58.90 ± 7.35 years) group involved in an 8 weeks interval training (60-79% HR max reserve) programme of between 45minutes to 60 minutes at a work/rest ratio of 1:1of 6 minutes each, while age-matched controls hypertensive (n=105; 58.27± 6.24 years) group remain sedentary during this period. Cardiovascular parameters (SBP, DBP and VO2max) and serum uric acid were assessed. Students’ t and Pearson correlation tests were used in data analysis.

Results: Findings of the study revealed significant effect of interval training programme on VO2 max, SBP, DBP and serum uric acid level at p< 0.05.Also there was significant correlation between changes VO2max and changes in SUA, SBP and DBP

Conclusions: It was concluded that interval training programme is an effective non-pharmacological means of downregulation of SUA.

Introduction

Several epidemiologic studies have shown elevated uric acid levels to predict increased risk of cardiovascular and renal events.1,2,3 It is conceivable that the interpretation of the “independent” role of uric acid is further complicated by the very close correlation of uric acid levels with established cardiovascular risk factors such as hypertension, heart failure, or diabetes.4,5 According to Ward,6 hypertensive patients with serum urate concentration between 5.0 and 6.9mg/dl had a significantly higher relative risk (RR) for both heart attack (RR 1.32) and stroke (RR 1.15). Patients with urate level> 7.0 mg/dl had an RR of stroke and heart attack of 1.5 and 2.2 respectively. This result strongly supports the hypothesis that increased serum urate levels are independent risk factor for hypertension-associated morbidity and mortality.

The pathophysiological mechanism of elevated SUA in hypertension is associated with hypoxia and decrease in uric acid excretion: an imbalance between production and excretion.7 It has been postulated that in hypertension that, SUA under-excretion may be linked to increased tubular sodium reabsorption mediated by insulin. Insulin has a powerful sodium retaining effects and this anti-natriuretic action has been documented. In addition, selective insulin resistance and hyperinsulinaemia are common findings in hypertension. The concept of selective insulin resistance implies the inability of insulin to cause glucose uptake with preservation of the other action of insulin such as renal sodium retaining effect.8 Also, tissue hypoxia determines increased adenosine nucleotide degradation, leading to increased formation of hypoxanthine and xanthine which ends in uric acid overproduction. Furthermore, the oxidation of xanthine can occur in two forms; dehydrogenase (‘D’) or the oxidase (‘O’). Both ‘O’ and ‘D’ lead to the formation of reactive oxygen species(ROS) (superoxide, hydrogen peroxide and hydroxyl radical) all which may play a significant role in tissue damage. However, studies have shown that uric acid could act as marker of oxidative stress,9 antioxidant10 and pro-oxidant particularly at elevated levels.11 Thus, it is unclear whether elevated levels of uric acid in diseases associated with oxidative stress are a protective response or a primary cause.

Another partway mechanism(s) by which SUA may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure.12 In a series of elegant experiments in rats, it was demonstrated that hyperuricemia, induced by an uricase inhibitor, triggers hypertension and impairs nitric oxide (NO) generation in the macula densa, whereas both hypertension and renal injury are reduced by treatment with the NO precursor L-arginine.13,14

Although the relationship between UA and human hypertension has been investigated in several prospective studies,15 until now, the relationship between UA levels and endothelial dysfunction...
has been explored only in a study that combined seemingly healthy individuals and patients with preexisting cardiovascular diseases of various severity or in individuals at increased cardiovascular risk. In this study, SUA was inversely related to flow-mediated vasodilation, but this relationship was much weakened by adjustment for other risk factors and remained significant only in men. Essential hypertension is consistently associated with endothelial dysfunction and hyperuricemia is a strong predictor of hypertension and BP progression. Therefore, individuals with essential hypertension constitute an interesting population in which to investigate the relationship between UA and endothelial dysfunction.

Studies have shown that acute bout of heavy exercise training has been shown to generate reactive oxygen and nitrogen (RONS) species that can cause oxidative damage and stress to the body. Contrarily, several other studies have also shown that regular (repeated) non exhaustive exercise reduces exercise induced oxidation and damage with concomitant hormetic benefit. These contrary reports by various investigators are based on the type of exercise vis-à-vis intensity, frequency and duration. Studies have also linked improved endothelial function to physical activities. However, few studies have actually investigated the effect of exercise on SUA level and concomitant cardiovascular responses in hypertension. Therefore the purpose of the present study was to investigate the effect of interval training programme on blood pressure and SUA level in subjects with hypertension.

Methodology

Research design: In the present study, age matched randomized double blind independent groups design was used to determine the influence of the continuous training program on SUA concentration and cardiovascular parameters. Subjects’ age were arranged in ascending order (50 to 70 years) and then assigned to continuous and control groups in an alternating pattern (age matched). One week wash out period was established and pretest (fasting blood sample collection and stress test) was administered to all subjects on the last day of the wash out period. Following wash out and pretest, all subjects (interval and control) were placed on antihypertensive (aldomet) drug, and the continuous groups involved in continuous training programs for 8 weeks, while the control group remains sedentary during this period,(all subjects were on aldomet during the 8 weeks training and sedentary period) and at the end of the training and sedentary period, Another one week wash out period was establish and post test was administered to all subjects on the last day of the wash out period.

Subjects: population for the study was male essential hypertensive subjects attending the hypertensive clinic of Murtala Mohammed Specialist Hospital Kano Nigeria. Subject were fully informed about the experimental procedures, risk and protocol, after which they gave their informed consent

Inclusion criteria: Only those who volunteered to participate in the study were recruited. Subjects between the age range of 50 and 70 years with chronic mild to moderate and stable (> 1 year duration) hypertension (SBP between 140-180 & DBP between 90-109 mmHg) and SUA level between were selected. Only those who had stopped taking antihypertensive drugs or on a single antihypertensive medication were recruited. They were sedentary and have no history of psychiatry or psychological disorders or abnormalities.

Exclusion criteria: Obese or underweight (BMI below 20 & above 30 kg/m²), smokers, alcoholic, diabetic, other cardiac, renal (particularly nephrosclerosis), respiratory disease patients were excluded. Those involved in vigorous physical activities and above averagely physically fit (VO\textsubscript{max} >27 and >33 ml/kg/min for over 60 and 50 years old respectively) were also excluded.

A total of 323 chronic and stable, essential mild to moderate male hypertensive patients satisfied the necessary study criteria. Subjects were aged matched and randomly grouped into experimental [162] and control [161] groups (figure 1). They were fully informed about the experimental procedures, risk and protocol, after which they gave their informed consent in accordance with the American College of Sports Medicine (ACSM) guidelines, regarding the use of human subjects as recommended by the human subject protocol. Ethical approval was granted by the Ethical Committee of Kano State Hospitals Management Board.

Pretest procedure

Wash out Period: All subjects on antihypertensive drugs were asked to stop all forms of medication and in replaced, were given placebo tablets (consisted of mainly lactose and inert substance) in a single blind method. All subjects including those not on any antihypertensive medications were placed on placebo tablets for one week (7 days); this is known as “Wash out period”. The purpose of the wash out period was to get rid of the effects of previously taken antihypertensive drugs/medications. During the wash out period all subjects were instructed to report to the hypertensive clinic for daily blood pressure monitoring and general observation. The pretest procedure was conducted at the last day of the wash out period, and in the Department of Physiotherapy of Murtala Mohammed Specialist Hospital (MMSH), Kano between 8:00 am and 10:00 am.

Physiological measurement: Subjects resting heart rate (HR), SBP, and DBP were monitored from the right arm as described by Walker et al using an automated digital electronic BP monitor (Omron digital BP monitor, Medel 11 EM 403c; Tokyo Japan). These measurements were monitored between 8:00 am and 10:00 am each test day.

Anthropometric measurement: Subjects’ physical characteristics (weight [kg] and height[m]) and body composition (body mass index [BMI] (kg.m-2)) assessment was done in accordance with standardized anthropometric protocol.

Blood Sample Collection (Venipuncture Method): Both pre and post treatment venous blood samples were obtained between 8:00 am and 10:00 pm after about 12 hour overnight fast (fasting blood sample). Five ml syringe was used for blood sample collection, using the procedure described by Bachorik. About 5ml of blood was drawn from the antecubital vein of each subject under strict antiseptic condition. All samples were stored in a refrigerator at -80°C until analysis.

Stress test: The Young Men Christian Association (YMCA) submaximal cycle ergometry test protocol was used to assess subject’s aerobic power. The YMCA protocol uses two to four 3-minutes stages of continuous exercise, two HR-power output data points will be needed (steady state HR) of between 110 and 150 beat/min. The two steady state HR were plotted against the respective workload on the YMCA graph sheet. A straight line was draw through the two points and extended to the subjects predicted maximum HR (220-Age). The point at which the diagonal line intersects the horizontal predicted HR max line represents the maximal working capacity for the subject. A perpendicular line was dropped from this point to the baseline where the maximal physical workload capacity was read.
in kg.m.min⁻¹, which was used to predict the subject's VO₂ max. This procedure was done for both pre and post test stress test.

Test procedure: The test procedure was also conducted in the Department of Physiotherapy of MMSH, Kano between 8:00 am and 10:00 am.

Training programme: Following stress test and prior to the exercise training, all subjects in both control and interval groups were re-assessed by the physician and were prescribed with aldomet (methyl dopa) as necessary. During the training and sedentary period (8 weeks) all subjects in both continuous and control groups were placed on methyldopa according to their pre recruitment doses and responses at 250mg and 500mg daily. Aldomet was preferred because it does not alter normal hemodynamic responses to exercise. It is a well-tolerated and mostly prescribed antihypertensive drug in Nigeria, particularly Northern Nigeria where the study was conducted and it is also useful in the treatment of mild to moderately severe hypertension. Subjects maintain these prescriptions with regular medical consultation and observation throughout the period of training.

The interval group (group 1): subjects in the interval group exercised on a bicycle ergometer at a moderate intensity of between 60-79% of their HR max reserve that was estimated from 220 minus the age of a subject as recommended by ACSM. The starting workload was 100 kgm (17 watts) which was increased at a pedal speed of 50rpm to obtain a HR max reserve 60% was increased in the first two weeks to and level up at 79% HR max reserve throughout the remaining part of the training period at a work/rest ratio of 1:1 of 6 minutes each. The initial of exercise session was increased from 45 minutes in the first two weeks of training to and leveled up at 60 minutes throughout the remaining part of the training. Exercise session of three times per week was maintained throughout the 8 weeks period of training for interval group.

The control group (group 2): subjects in the control group were instructed not to undertake any vigorous physical activity during the 8 weeks period of study.

Uric acid analysis: Uric acid analysis was determined using commercial enzymatic calorimetry method (PAP-Method) using the Human Kit (Human Gesellschaft Biochemical Diagnostic mbH, Germany) as recommended by the manufacturer.

**Post test procedure**

Wash Out Period: At the end of the 8 weeks training period, all subjects was asked to stop methyldopa (Aldomet) and subjects were prescribed with placebo tablets in a single blinded method.
Results

The subject’s age ranged between 45 and 70 years. Mean age, height, weight and BMI ± SD: Interval group (58.40±6.91years, 167.78±7.81 cm, 70.18±11.37 kg, 24.96±3.88 kg.m⁻²) and Control group (58.27 ±6.24 years, 167.89±5.31 cm, 68.47±17.07 kg, 24.16±4.91 kg.m⁻²). There was no significant difference in age between groups (t=.156, p=.876) (Table 1).

Subject’s pre and post treatment mean± SD BP, SUA level and VO₂ max for the exercise (interval) and control groups are depicted in Table 1. Students’ test results (Table 2) indicated a significant reduction in the exercise groups over control in SBP (t=-6.560, p=0.000), SUA (t =-3.397, p=0.001) and VO₂ max (t =11.955, p=0.000) at p<0.05. There was significant negative correlation between changes in VO₂ max and changes in serum uric acid level (r=-.273, figure 2); DBP(r=-.309); and DBP(r=-.273) at p< 0.01.

Discussion

Findings of the present study indicated significant reduction in SBP, DBP and significant increase in VO₂ max as a result of continuous exercise training; several previous studies have reported similar findings. The present study also demonstrated a significant reduction in exercise group serum uric acid level over control. Filipovsky et al reported similar report by investigating the effect of 5 weeks aerobic physical training course on uricaemia levels of 77 sedentary subjects with hypertension. They reported significant decrease in uric acid level and that the significant change persisted up to between 3 to 7 months after the intervention of exercise training. Langlois etal reported a contrary notion; they investigated whether uric acid (UA) status is related to lower limb function in hypertensive with peripheral arterial disease (PAD). One hundred and forty five non hypertensive subjects with PAD and 166 subjects with hypertension and PAD participated. Subjects involved in aerobic exercise on treadmill. They reported a significant increase in serum uric acid concentration in PAD hypertensive.

The mechanism of down regulation of uric acid by regular non exhaustive exercise training as reported in the present study could be related to the role of regular training in reducing protein carbonyl. A recent study suggests that there is a complex interaction during exercise involving RONS, nuclear factor (NF) leading to the activation of certain signal transmission pathways and up regulation of antioxidant defence system. Another pathway might be through the glutathione ([GSH] (-glutamylycysteiny1glycine). GSH is the most abundant nonproteinthiol source in the cell and serves multiple functions in protecting tissues from oxidative damage and keeping the intracellular environment in the reduced state. GSH reduces hydrogen- and organic-peroxides via a reaction catalyzed by...
GSH peroxidase (GPX); it serves as a scavenger of OH and singlet oxygen (O_2); GSH also reduces tocopherol radicals, either directly or indirectly by reducing semidihydroracorbate thereby preventing free radical chain reaction and lipid peroxidation. Physically trained human subjects and animals generally demonstrate a greater tolerance of exercise-induced disturbance of blood GSH. Furthermore, plasma and erythrocyte GSH contents have been shown to increase significantly after physical training.

Apart from the antioxidant effects of long term exercise training, which are mediated by increased expression of antioxidant enzymes but also by a reduced expression of prooxidant enzymes. It has been reported that exercise training significantly reduced the expression of subunits of the reactive oxygen species (ROS)-producing enzyme NAD (P)H oxidase. Another mechanism may be through the up-regulation of uric acid excretion, a number of previous studies have demonstrated that long-term exercise training improves insulin sensitivity and reduces fasting and glucose-stimulated insulin levels in a wide range of individuals. Thus, increasing glucose uptake with likely decreased renal sodium retention activity.

The present study demonstrated a rationale bases for the role of long term interval exercise training in the down regulation of blood pressure and serum uric acid concentration. However there is a limitation of the study, including failure to distinguish between normoureemic and hyperuricemic subjects with hypertension, this limitation warrants consideration in future studies.

References


