ORIGINAL ARTICLE

Effect of low intensity continuous training programme on serum uric acid in the non pharmacological management of hypertension: A randomized controlled trial

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Abstract

Background: *Elevated serum uric acid (SUA) 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 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 continuous low intensity training programme on SUA level and cardiovascular parameters in male subjects with hypertension.*

Method: *Two hundred and seventeen male patients with mild to moderate (systolic blood pressure [SBP] between 140-180 & diastolic blood pressure [DBP] between 90-109 mmHg) essential hypertension were age matched and grouped into continuous and control groups. The continuous (n=112; 58.63 ± 7.22years) group involved in an 8 weeks interval training (35-9% HR max reserve) programme of between 45minutes to 60 minutes, while age-matched controls hypertensive (n=105; 58.27± 6.24 years) group remain sedentary during this period. Cardiovascular parameters (SBP, DBP & VO2max) and SUA 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, and DBP and SUA concentration at p< 0.05 and changes in VO2max negatively correlated with SUA (r= -.266) at p<0.05.*

Conclusion: *it was concluded that low intensity continuous training programme is an effective non-pharmacological management and may prevent cardiovascular event through the down regulation of SUA in hypertension.*

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Introduction

Hypertension is a major global health problem and public-health challenge, demanding a vast proportion of health care resources directly and indirectly because of its high and increasing prevalence and the concomitant risks of cardiovascular events such as stroke, kidney disease, decreased disability adjusted and mortality. It is a well established fact that sedentary lifestyle contributes to increased risk of cardiovascular disease especially hypertension. Indeed hypertension is a major independent risk factor for cardiovascular and renal disease, increasing the risk of myocardial infarction, stroke and heart failure. Hypertension and its complications are largely responsible for morbidity and mortality of all age groups.[1,2] It has been reported that elevated serum uric acid (SUA) is an independent risk factor for hypertension.[3,4]

Extensive epidemiologic and experimental evidence now suggests that SUA is a relevant and independent risk factor for cardiovascular and renal disease, particularly in patients with hypertension, heart failure, or diabetes. Hyperuricemia predicts mortality in patients with heart failure,[5] or coronary heart disease,[6], cerebrovascular events in individuals with diabetes,[7] and cardiac ischemia in hypertension.[8] Campion, Glynn, Delabry[9] reported that patients with essential hypertension also showed an increased risk of gout, and that, gout incidence was 3-fold higher in hypertensive patients compared with normotensive subjects. However, two epidemiological studies[10,11] reported a

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contrary report that uricaemia could not be recognized as an independent cardiovascular risk factor. 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> 7.0mg/dl had an RR of stroke and heart attack of 1.5 and 2.2 respectively. [12] These results strongly support 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.[13] It has been postulated that in hypertension, 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[14]. 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[14]. However, studies have shown that uric acid could act as marker of oxidative stress[15], antioxidant[16] and pro-oxidant particularly at elevated levels.[17] Thus, it is unclear whether elevated levels of uric acid in diseases associated with oxidative stress are a protective response or a primary cause.

Studies[18,19] 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[20,21] 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. Exercise scientists and other health related professionals have used various training methods to evaluate many of the physiological changes in healthy and various conditions. 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 continuous low intensity 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 (continuous & control) were placed on antihypertensive (aldomet) drug, the and 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 posttest 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.

Inclusion criteria: Only those who volunteered to participate in the study were recruited. Subjects between the age range of 45 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 [22]. 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 (VO2max >27 & >33 ml/kg.min for over 60 & 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 ACSM guidelines, regarding the use of human subjects [23] 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[24,25]. 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.[26] using an automated digital electronic BP monitor (Omron digital BP monitor, Medel11 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] & height[m]) and body composition (body mass index [BMI] (kg.m-2)) assessment was done in accordance with standardized anthropometric protocol.[27]

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[28]. About 5ml of blood was draw from the antecubital vein of each subject under strict antiseptic condition. All samples were stored in a refrigerator at -800C until analysis.[29]

Stress test: The Young Men Christian Association (YMCA) submaximal cycle ergometry test protocol was used to assess subject's aerobic power as described by ACSM.[30,31] 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 subjects VO2 max. This procedure was done for both pre and posttest stress test.

Test procedure: The test procedure was also conducted in the Department of Physiotherapy of Murtala Mohammed Specialist Hospital (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. [32]It is a well-tolerated and mostly prescribed antihypertensive drug in Nigeria,[33] particularly Northern Nigeria where the study was conducted and it is also useful in the treatment of mild to moderately severe hypertension.[34] Subjects maintain these prescriptions with regular medical consultation and observation through-out the period of training.

The continuous group (group 1): subjects in the continuous group exercised on a bicycle ergometer at a low intensity of between 35-59% of their HR max that was estimated from 220 minus the age of a subject as recommended by ACSM[23,30]. The starting workload was 100 kgm (17 watts) which was increased at a pedal speed of 50rpm to obtain a HR max 35% was increased in the first two weeks to and level up at 59% HR max throughout the remaining part of the training period. 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 training period for continuous 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.

Posttest 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 for one week in order to get rid the effect of the methyldopa taken during the training period.

Blood Sample Collection: Immediately after the post training wash out period, fasting blood samples were collected as earlier described.

Post training SBP, DBP, VO2max, SUA assessment and stress test were conducted as earlier described in the pretest procedures using standardized protocols, techniques and methods.

All pre and post test measurements were recorded on a data sheet. Two hundred and seventeen subjects (112 from continuous, and 105 from control group) completed the eight weeks training program. One hundred and six subjects (50 from continuous, and 56 from control group) had dropped out because of non-compliance, unfavorable responses to methyldopa and exercise training or had incomplete data; therefore, the data of 217 subjects were used in the statistical analysis (figure 1: flow chart).

Statistical analysis: Following data collection, the measured and derived variables were statistically analyzed. The descriptive statistics (Means, standard deviations and % change) of the subject's physical characteristics, estimated VO2max, SUA, cardiovascular parameters were determined. Student's t test and Pearson product moment correlation tests were computed for the variables of interest. In the t and correlation tests, the difference between subjects post-training and pre-training measurements (changed score) were used as dependent measures.

The score changed was the difference between the posttest and pretest values. All statistical analysis was performed on a Toshiba compatible microcomputer using the statistical package for the social science (SPSS), (Windows Version 16.0 Chicago IL, USA). The probability level for all the above tests was set at 0.05 to indicate significance.

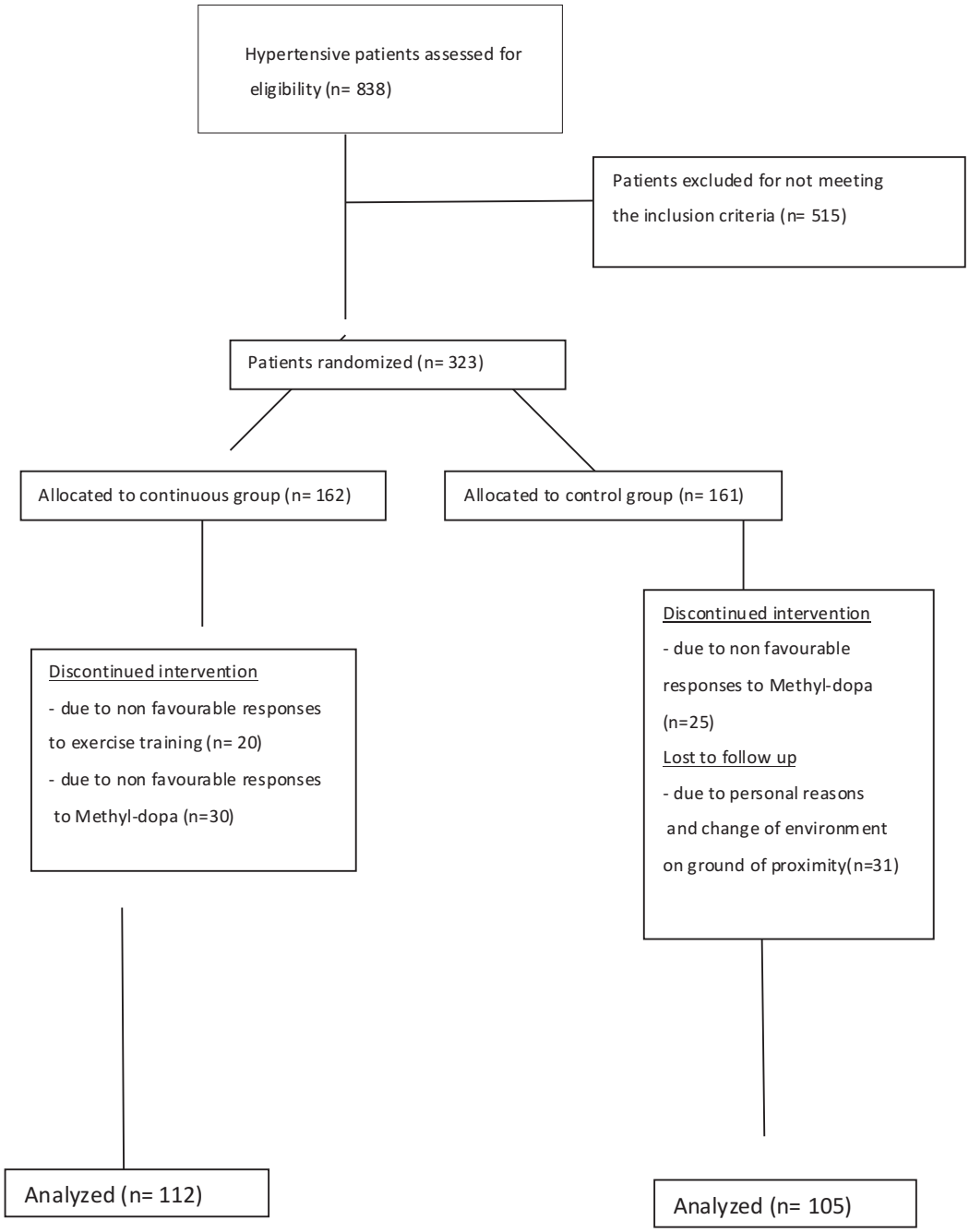

Figure 1: Study design flow chat

Results

The subjects' ages ranged between 50 and 70years. Subjects' mean± SD age, height, weight and BMI: continuous group (58.63±7.22years, 173.16±6.97cm, 67.49±10.16kg, 22.48±2.89 kg.m-2) and Control group (58.27 ±6.24years, 167.89±5.31cm, 68.47±17.07kg, 24.16±4.91 kg.m-2). There was no significant age difference between groups (t= .390, p= .697).

Subject's pre and post treatment mean± SD BP, SUA level and VO2max for the exercise and control groups are depicted in table I. Students' test results (table II) indicated a significant reduction in the exercise groups over control in SBP (t=-16.465, p=0.000), DBP (t= -10.018, p=0.000), SUA (t =-5.131, p=0.000) and VO2 max (t= 8.797, p=0.000) at p<0.05. There was significant negative correlation between changes in VO2max and changes serum uric acid level (r = -0.266) at p< 0.01(figure 2).

Table I: Groups pre and posttest mean(X) ± standard deviation (SD) (N = 217)

	Continuous group X±SD (n=112)		Control group X±SD (n= 105)	
Variables	Pretest	Posttest	Pretest	Posttest
SBP(mmHg)	168.31±12.73	154.37±12.63	160.87±23.91	163.47±14.88
DBP(mmHg)	101.85±7.01	94.44±8.77	97.17±7.20	96.10±2.67
VO_2max(ml/kg/min)	20.69±12.49	28.68±13.60	21.23±5.76	22.82±7.44
Serum uric acid(mg/dl)	4.69±1.56	2.73±1.56	4.68±1.29	3.97±1.75

Table II: Groups changed scores mean(X) ± standard deviation (SD) and t-test values (N = 217)

	Changed score values X±SD			
Variables	Continuous group n= 112	Control group n= 105	t-values	p-values
SBP(mmHg)	-13.94± 6.95	2.61± 7.85	-16.465	.000*
DBP(mmHg)	-7.41± 6.26	-1.07±1.76	-10.018	.000*
VO_2max(ml/kg/min)	7.99± 6.62	1.59± 3.52	8.797	.000*
Serum uric acid(mg/dl)	-1.96± 1.09	-0.71±2.32	-5.131	.000*

df = 215, * Significant, p< 0.05

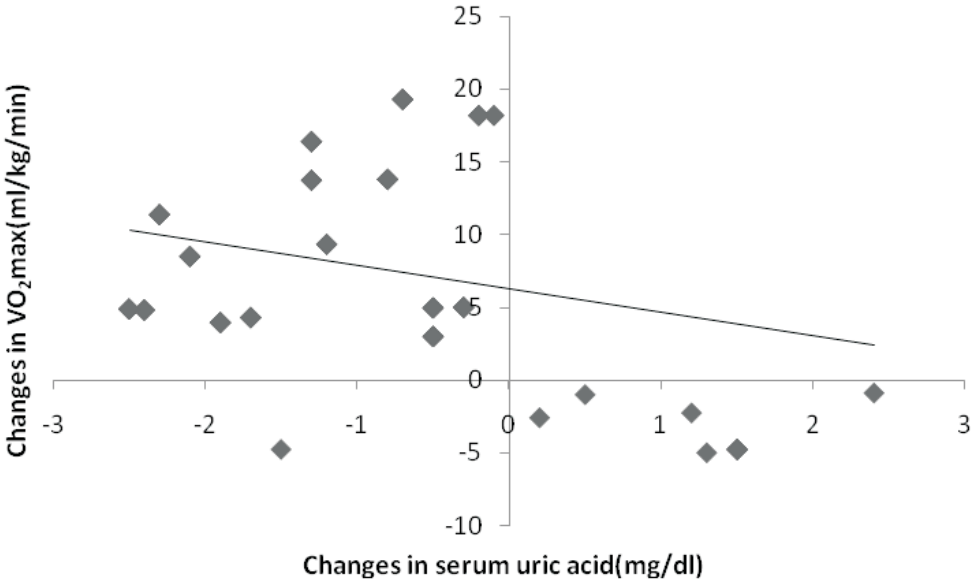

Fig 2: correlation between training changes in VO_2max and serum uric acid concentration.

Discussion

Findings of the present study indicated significant reduction in SBP, DBP and significant increase in VO2max 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. This finding is in line with the report of Filipovsky et al[35] who investigated 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 at p< 0.001. This significant change persisted up to between 3 to 7 months after the intervention of exercise training. They concluded that 5-week intensive physical training had a favorable on both short and long -term effect on uricaemia levels in hypertension.

Langlois et al[36] 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 increased in serum uric acid concentration in PAD hypertensive (404± 101 versus 347± 80 µmol/L, p<0.001).

Leyver et al.[37] investigated the relationship between SUA concentrations and the measures of functional capacity. Fifty nine patients with a diagnosis of chronic heart failure due to coronary heart disease (n=34) or idiopathic dilated cardiomyopathy (n=25) and 20 healthy controls underwent assessment of functional capacity. Maximal oxygen uptake (VO2max) and SUA were measured during a maximal treadmill exercise test. They reported an inverse relationship between SUA concentrations and measures of functional capacity in patients with cardiac failure. They concluded that the strong correlation between SUA and VO2max suggests that in chronic heart failure increased SUA concentrations reflect an impairment of oxidative metabolism.

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.[38] Another pathway might be through the glutathione ([GSH] (-glutamylcysteinylglycine), GSH is the most abundant nonprotein thiol source

in the cell and serves multiple functions in protecting tissues from oxidative damage and keeping the intracellular environment in the reduced state.[39] GSH reduces hydrogen- and organic-peroxides via a reaction catalyzed by GSH peroxidase (GPX); it serves as a scavenger of .OH and singlet oxygen (1O2); GSH also reduces tocopherol radicals, either directly, or indirectly by reducing semidihydroascorbate thereby preventing free radical chain reaction and lipid peroxidation.[40] Physically trained human subjects and animals generally demonstrate a greater tolerance of exercise-induced disturbance of blood GSH.[41,42,43] Furthermore, plasma and erythrocyte GSH contents have been shown to increase significantly after physical training.[42,44,45]

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.[46] 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[47,48,49]. The present study demonstrated a rationale bases for the role of long term low intensity continuous 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 normouremic and hyperuremic subjects with hypertension, this limitation warrants consideration in future studies.

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