# Effect of interval training program on white blood cell count in the management of hypertension: A randomized controlled study

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#### **ABSTRACT**

Objective: Elevated white blood cell (WBC) count is considered to be prospectively and positively associated with cardiovascular diseases, particularly hypertension. Also, the positive role of exercise in the management of hypertension has been well and long established. However the relationship between WBC count and hypertensive management particularly in the nonpharmacological technique is ambiguous and unclear. Therefore the purpose of the present study was to determine the effect of interval training program on WBC count and cardiovascular parameters in male hypertensive patients. Materials and Methods: A total of 245 male patients with mild to moderate (systolic blood pressure (SBP) between 140 mmHg and 179 mmHg and diastolic blood pressure (DBP) between 90 mmHg and 109 mmHg) essential hypertension were age matched and grouped into experimental and control groups. The experimental (n=140; 58.90±7.35 years) group involved in an 8-week interval training (60-79% HR max reserve) program of between 45 minutes to 60 minutes, while the age-matched controls hypertensive (n=105; 58.27±6.24 years) group remain sedentary during this period. Cardiovascular parameters (SBP, DBP, and VO max) and WBC count were assessed. Student's t and Pearson correlation tests were used in data analysis. Results: Findings of the study revealed a significant effect of the interval training program on VO2max, SBP, and DBP and WBC count at P < 0.05 and VO2max is negatively related to the WBC count (r=-0.339) at P<0.01. **Conclusions:** It was concluded that the interval training program is an effective adjunct nonpharmacological management of hypertension and the therapeutic effect of exercise programs may be mediated through suppression of inflammatory (WBC count) reaction.

Key words: Exercise, hypertension, inflammation, white blood cell

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#### INTRODUCTION

Several prospective studies have shown a positive and independent association between white blood cell (WBC) count and coronary heart disease, hypertension, and ischemic stroke incidence and mortality. <sup>1-6</sup> According to Lee and Associates, <sup>3</sup> the relationship is irrespective of sex, ethnic, and smoking status. Chronic low-grade inflammation is believed to be the mechanism behind this association whereby WBC-derived macrophages and other phagocytes contribute to vascular injury, endothelial

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dysfunction, and atherosclerotic disease progression.<sup>7-9</sup> However, inflammation may also contribute to increasing microvascular capillary resistance, initiation of platelet aggregation, increased cathecolamine levels, and there is considerable evidence of a link between inflammation and hypertension.<sup>2, 9-12</sup>

Another possibility for the relationship between WBC and hypertension might be the close relationship between leucocytes count and activity of corticosteroids in hypertension and other vascular diseases. This has been reported previously in both animal models and humans. <sup>13,14</sup> The total leucocytes count and blood pressure are increased by cortisol administration in normal human subjects. <sup>15</sup> Previous studies have shown that elevated WBC count is associated with a small, but significant increase in the risk of hypertension among white men. <sup>10,16</sup> Nakanishi and co-workers <sup>17</sup> also found this association to be true among Japanese men irrespective of their smoking status.

Previous reports<sup>18-21</sup> show that moderate to high levels of cardiorespiratory fitness are protective against Cardiovascular disease (CVD) and all-cause mortality, even in individuals with CVD risk factors. Regular exercise induces anti-inflammatory actions. Geffken  $et\ al.^{22}$  found WBC to be inversely related to physical activity in a large sample (n=5201) composed of men and women from diverse racial backgrounds. Nieto  $et\ al.^{23}$  reported sport activity index to be inversely related to WBC in whites but not in blacks.

Studies that investigated the association between WBC count and hypertension management particularly the nonpharmacological are few and the exact nature of this relationship is ambiguous and unclear.<sup>24</sup> Therefore, the purpose of the present study was to investigate the relationship between interval training program and WBC in the noninvasive management of chronic essential hypertension

# **MATERIALS AND METHODS**

## Research design

In the present study, age-matched randomized independent pretest-posttest-control group design was used to determine the influence of the interval training program on WBC count.

## **Subjects**

The population for the study was male essential hypertensive subjects attending the hypertensive clinic of Murtala Muhammed Specialist Hospital Kano Nigeria. Subjects 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 45-70 years with chronic mild to moderate and stable (>1 year duration) hypertension (systolic blood pressure (SBP) between 140 mmHg and 179 mmHg and diastolic blood pressure (DBP) between 90 mmHg and 109 mmHg) were selected. Only those who had stopped taking antihypertensive drugs or on a single-antihypertensive medication (monotherapy) were recruited.<sup>25</sup> They were sedentary and have no history of psychiatry or psychological disorders or abnormalities.

#### Exclusion criteria

Obese or underweight (body mass index (BMI) between 20 and 30 kg/m²), smokers, alcoholic, diabetic, other cardiac, renal, respiratory disease patients were excluded. Those involved in vigorous physical activities and above averagely physically fit ( $VO_2$ 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. 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<sup>26</sup> as recommended by the human subject protocol. Ethical approval was granted by the Ethical Committee/Board 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 1 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 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.*,<sup>29</sup> and Musa *et al.*<sup>30</sup> using an automated digital electronic BP monitor (Omron digital BP monitor, Medel 11 EM 403c; Tokyo, Japan). These measurements were monitored between 8:00 and 10:00 am each test day.

## Anthropometric measurement

Subjects' physical characteristics (%body fat, weight [kg] and height [m]) and body composition (body mass index [BMI] (kg/m $^{-2}$ )) assessment were done in accordance with the standardized anthropometric protocol.  $^{31,32}$ 

#### Blood sample collection (venipuncture method)

Both pre- and post-treatment venous blood samples were obtained between 8: 00 and 10:00 pm after about 12-hour overnight fast (fasting blood sample). A 5 ml syringe was used for blood sample collection, using the procedure described by Bachorik.<sup>33</sup> One milliliter of blood sample was immediately transferred into a special container containing anticoagulant (heparin, 75 U/ml) for WBC count. All samples were stored in a refrigerator at -80°C until analysis.<sup>34</sup>

#### Stress test

The Young Men Christian Association (YMCA) submaximal cycle ergometry test protocol was used to assess subject's

aerobic power. $^{35,36}$  The YMCA protocol uses two to four 3-minute 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 drawn 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 which was used to predict the subjects VO<sub>2</sub>max. This procedure was done for both pre- and post-test stress test.

## **Test procedures**

The test procedures were conducted in the Department of Physiotherapy of MMSH, Kano between 8:00 and 10:00 am.

# Training program

Following the stress test and prior to the exercise training, all subjects in both control and interval groups were reassessed by the physicians and were prescribed with methyldopa (500 mg-1 g daily in divided doses of 2 to 4 times) based on the subject's responses and tolerance to therapy. Methyldopa was preferred because it does not alter normal hemodynamic responses to exercise,<sup>37</sup> and it is a well-tolerated antihypertensive drug in Africa.<sup>38-40</sup> In addition, it is the drug prescribed the most in Kano, where the study was conducted and had proved useful in the treatment of mild to moderately severe hypertension either as monontherapy or combination therapy.<sup>39-41</sup> Subjects maintained these prescriptions with regular medical consultation and observation throughout the period of exercise training.

# The interval group (group 1)

Subjects in the interval group exercised on a bicycle ergometer at a low 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.<sup>42</sup> The starting workload was 100 kg (17 watts) which was increased at a pedal speed of 50 rpm to obtain a HR max reserve 60% was increased in the first 2 weeks to and level up at 79% HR max reserve throughout the remaining part of the training period at a work/rest ratio of 1:10f 6 minutes each. The initial of exercise session was increased from 45 minutes in the first 2 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 the 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 the study.

## White blood cell count

The WBC count was analyzed using the Turks method as described by Dacie and Lewis.<sup>43</sup>

# Posttest procedure

# Wash out period

At the end of the 8-week training period, all subjects was asked to stop methyldopa (Aldomet) and subjects were prescribed with placebo tablets in a single-blinded method for 1 week in order to get rid the effect of the methyldopa taken during the training period.

# Blood sample collection

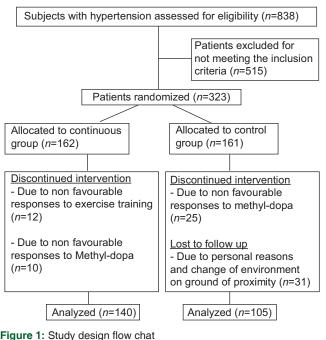
Immediately after the post-training wash out period, fasting blood samples were collected as earlier described.

Post-training SBP, DBP, WBC count 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. A total of 257 subjects (140 from the interval, and 105 from the control groups) completed the 8 weeks training program. Seventy-eight subjects (22 from interval, and 56 from the control groups) had dropped out because of noncompliance, unfavorable responses to methyldopa, and exercise training or had incomplete data; therefore, the data of 245 subjects were used in the statistical analysis [Figure 1].

## **Statistical analysis**

Following data collection, the measured and derived variables were statistically analyzed. The descriptive



statistics (means and standard deviations) of the subject's physical characteristics, estimated VO<sub>2</sub>max, WBC count, and cardiovascular parameters were determined. Analysis of covariance (ANCOVA) was used to assess the outcome variables; in the ANCOVA, the post-test values were the outcome variables and the cocovariates were the pretest values, age, baseline BMI, and % body fat. The Pearson product moment correlation test was also computed for the variables of interest; in the correlation test, the difference between subjects posttraining and pretraining measurements (changed score) were used as dependent measures. 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.

## **RESULTS**

The subject's age ranged between 45 and 70 years. The mean age, height, weight, BMI, and % body fat±SD were as follows, respectively: the interval group ( $58.40\pm6.91$  years,  $167.78\pm7.81$  cm,  $70.18\pm11.37$  kg,  $24.96\pm3.88$  kg/m<sup>-2</sup>, and  $17.69\pm6.50$ %) and the control group ( $58.27\pm6.24$  years,  $167.89\pm5.31$  cm,  $68.47\pm17.07$  kg,  $24.16\pm4.91$  kg/m<sup>-2</sup>, and  $22.27\pm9.82$ %). There was no significant difference in age between the groups (t=0.156, P=0.876).

Table 1 shows pre- versus (vs.), post-treatment mean BP±SD mmHg, WBC (cells/ml³) count and VO $_2$ max (ml/kg/min) for the exercise (SBP166.05±14.10; DBP, 96.80±3.38; WBC count 7.61±1.17, and VO $_2$ max 23.62±9.15 vs. SBP, 150.00±16.67; DBP, 94.98±5.40; WBC count 7.57±1.26, and VO $_2$ max 37.46±7.42) group and the control (SBP160.87±13.23; DBP, 97.17±1.43; WBC count 7.13±1.30, and VO $_2$ max 21.23±5.76 vs. SBP, 163.47±14.88; DBP, 96.10±2.67; WBC count 8.21±1.60, and VO $_2$ max 22.82±7.44) group.

The Table 2 ANCOVA test results indicated a significant reduction in the exercise groups over control in SBP (P=0.000), DBP (P=0.000), WBC (P=0.001), and VO $_2$ max (P=0.000) at P<0.05.

The results also showed significant negative correlation Figures 2 and 3 between changes in VO<sub>2</sub>max and changes

in other parameters such as WBC count (r=-0.339); SBP (r=-0.304); and DBP (r=-0.289) at P<0.01. Changes in the WBC count positively and significantly correlated with both SBP (r=0.200) and DBP (r=0.263) [Figure 4].

#### **DISCUSSION**

Findings from the present study revealed a significant decrease in SBP, DBP, and increase in  $\rm VO_2max$  in the experimental group over the control group. The favorable changes resulting from aerobic training on both SBP and DBP demonstrated in the present study is consistent with previous studies. Also, the result of the present study indicated a significant reduction in the WBC count in the

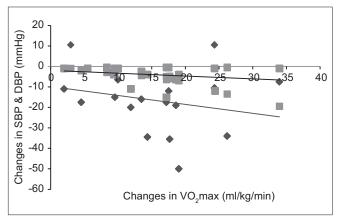


Figure 2: Correlation between training changes in VO<sub>2</sub>max and BP

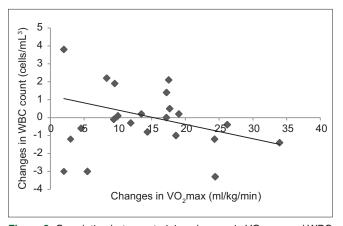


Figure 3: Correlation between training changes in  $\mathrm{VO}_2\mathrm{max}$  and WBC count

Table 1: Groups me	an and standar	deviation for nre-	and nost-test values

Variables	Interval group X±SD		Control group X±SD	
	Pretest	Post-test	Pretest	Post-test
SBP (mmHg)	166.05±14.10	150.00±16.67	160.87±13.23	163.47±14.88
DBP (mmHg)	96.80±3.38	94.98±5.04	97.17±1.43	96.10±2.67
VO <sub>3</sub> max (ml/kg/min)	23.62±9.15	37.46±7.42	21.23±5.76	22.82±7.44
WBC count (cells/ml3)	7.61±1.17	7.57± 1.26	7.13± 1.30	8.21± 1.60

 $X-Groups\ mean; SD-Standard\ deviatioN; SBP-Systolic\ blood\ pressure; DBP-Diastolic\ blood\ pressure; WBC-White\ blood\ cell; (N=357)$ 

Table 2: Analysis of the covariance test between the interval and control groups

8 1							
Source of variables	SS	df	MS	F	Р		
SBP	17,393.958	1	17,393.958	132.211	0.000*		
DBP	184.572	1	184.572	16.268	0.000*		
WBC count	23.889	1	23.889	11.535	0.001*		
VO_max	10,831.877	1	10,831.877	253.234	0.000*		

 $SBP-Systolic \ blood\ pressure;\ DBP-Diastolic\ blood\ pressure;\ WBC-White\ blood\ cell;\ *P<0.05;\ (N=245)$ 

experimental group over control. There was a negative significant correlation between changes in VO<sub>2</sub>max and WBC count. This finding is in agreement with the report of Kullo et al., 52 they investigated the association between WBC count and VO<sub>2</sub>max in men without CHD. In their study, 172 asymptomatic men (age, 51±9.3 years) engaged in a symptomless graded treadmill aerobic exercise. They reported an inverse association between WBC count and  $VO_2$ max (r=-0.22, P=0.004). Another study in support of the present study was conducted by Church et al.,1 in their study, they investigated 4057 men, after age-adjusted resting levels and risk of having a clinically significant elevation of the WBC count across nine fitness body fatness combinations. They reported that fitness as measured by VO<sub>2</sub>max was inversely related to the age-adjusted values of WBC count (P for trend P<0.0001).

A contradictory finding was reported by Shankar et al.<sup>24</sup> they studied the relationship between WBC count and physical activity in the development of hypertension. They studied 2459 hypertension-free women and men participated after adjusting and stratifying by smoking and several other potential confounding factors. They reported a nonsignificant effect of moderate physical activity of twice per week on the WBC count (P=0.06).

Kim et al.53 investigated the relationship between WBC count and cardiorespiratory fitness (VO2max) after adjusting for several well-known cardiovascular risk factors. Subjects who visited the health promotion center for a medical checkup and treadmill test (n=8241; age: median, 48 years; range, 16-79 years) were classified into three groups based on their WBC counts (group 1, 2200–5300 µl, n=2823; group 2, 5301–6500 µl, n=2709; group 3, 6501–10,000  $\mu$ l, n=2709). After adjusting for age, body mass index, body fat percentage, smoking history, systolic blood pressure, diastolic blood pressure, serum lipid profile, and fasting plasma glucose, VO2max still showed a significant association with WBC count (partial r=-0.11, P<0.001). They concluded that the WBC count in the normal concentration range is independently related to cardiorespiratory fitness in Korean men.

In cross-sectional analyses, Volpatoe *et al.*<sup>54</sup> found IL-6 levels to be inversely related to exercise tolerance in disabled older women, while Taaffe *et al.*<sup>55</sup> reported an

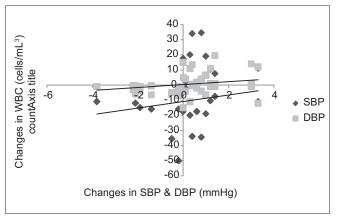


Figure 4: Correlation between training changes in WBC count and BP

inverse relationship between accumulated moderate and strenuous activity with IL-6 in 880 adults aged 70-79 years. Smith *et al.*<sup>44</sup> found that a 6-month-exercise program reduced Tissue necrosis factor (TNF)- (*n*=43, average age=49.0 years). Tsukui *et al.*<sup>56</sup> reported exercise training in 29 obese women (average age=56 years) reduced TNF with only modest weight loss.

It is generally at large accepted that the physiological mediator of low-grade chronic inflammation and raised WBC count is the TNF-alpha, which has been proven to be downregulated by regular physical activities. Another mechanism is that the postexercise hypotension which is accompanied by a decrease in serum cathecolamines, norepinephrine, dopamine, cortisol, sympathetic nervous system, plasma rennin activity, 57-60 thus, suppressing inflammatory reaction and finally downregulating WBC count.

Reasons for diversities in findings between the present study and several others might not be unconnected to types of exercise, plasma IL-6 during exercise increase with the intensity and duration of exercise, 61 interracial differences that might exist in exercise responses to WBC count. 62,63 The effect of subjects' condition cannot be ruled out, previous studies utilized normotensive subjects compared to hypertensive patients in the present study.

## **CONCLUSION**

Based on the results of the present study, it was concluded that interval training program is an effective adjunct nonpharmacological management of hypertension. The therapeutic effect of interval training program on blood pressure and VO<sub>2</sub>max (aerobic fitness) may be mediated through suppression of inflammatory (WBC count) reaction.

#### **LIMITATIONS**

The present study demonstrated a rationale bases for the role of interval exercise training in the down regulation

of the blood pressure and WBC count. However, there are limitations of the study, including failure to investigate the effect of severity of hypertension and other markers of inflammation on the outcome variables. It is however unlikely that a single biomarker reflects all health risk.<sup>64</sup> These limitations warrant attention in future studies.

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