Effects of Exercise on Metabolic Markers and Biomarkers of Inflammation in Hypertensive cases: A Randomized Controlled Trial

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Abstract

Background: Hypertension has been hypothesized to be a part of inflammatory disorder and elevated low density lipoproteins or total cholesterol, and reduced high density lipoproteins, increase the risk of coronary events in these patients.

Objectives: To determine the effects of exercise (interval training program) on metabolic markers and biomarkers of inflammation in black African men with essential hypertension.

Subjects and Methods: A total of 245 male patients having mild to moderate essential hypertension (systolic BP between 140-179 & diastolic BP between 90-109 mmHg) were age and gender matched into experimental and control groups. The experimental group was put to exercise for 8 weeks using interval training (60-79% HR max reserve) program ranging between 45minutes to 60 minutes, while control group remained sedentary. Cardiovascular parameters (systolic blood pressure, diastolic blood pressure) and VO₂max, biomarkers of inflammation (C-reactive protein, white blood cell) and metabolic makers (fasting blood sugar), total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein and artherogenic index) were assessed. Analysis of co-variance (ANCOVA) and Pearson correlation tests were used in data analysis.

Results: Of 254 subjects, the experimental group had 140 cases whose ages ranged from 58.9±7.3 years) while 114 were controls of similar age. There was significant effect of interval training program on VO₂max, systolic blood pressure, diastolic blood pressure, C-reactive protein, white blood cell, fasting blood sugar, total cholesterol, triglyceride, high density lipoprotein, low density lipoprotein and artherogenic index (p<0.05). Changes in VO₂max significantly correlated with all other variables (p<0.05).

Conclusions: Therapeutic role of interval training program in the reduction of blood pressure could be through the suppression of systemic inflammation and abnormal metabolic markers.

Key words: Hypertension, biomarkers of inflammation, metabolic markers, lipid profile, artherogenic, exercise.

Introduction

Research into the etiology of hypertension has yielded an important array of lifestyle, dietary, psychosocial factors and biochemical markers of inflammation. It has been hypothesized and confirmed that hypertension may be a part of chronic inflammatory disorder where white blood cell (WBC) derived macrophages and other phagocytes contribute to vascular injury, endothelial dysfunction, and atherosclerotic disease progression. About 40% of hypertensive patients also have high blood cholesterol levels. Factors that increase the risk for coronary events in hypertensive cases include; elevated low density lipoprotein cholesterol (LDL) or total cholesterol (TC), smoking, impaired glucose tolerance and reduced high density lipoprotein (HDL).

Ability of exercise to alter inflammatory markers has provided mixed results where as in general population there is an inverse association between WBC, C-reactive protein (CRP) levels and self-reported physical activity or physical fitness. These studies suggested that regular physical exercise might lower CRP levels by an anti-inflammatory action. On the contrary, non beneficial effect of exercise on CRP has also been reported.

Most previous studies were done on older population using white, caucasian and other mixed black subjects. However, the role of genes, heredity, race, ethnicity, environmental factors and gene-environmental interaction in the aetiology and biomarkers of
inflammation in hypertension has also been stressed\(^7\).
Bouchard et al\(^8\) reported genetics plays a major role in a
person’s \(\text{VO}_2\text{max}\) and heredity can account for up to 25-
50% of the variance between individuals. This
interpersonal and interracial difference clearly indicates
the needs for study on pure black African population.

For this study, 3 hypotheses were formulated
and tested:

(1) There would be significant correlation between
baseline \(\text{VO}_2\text{max}\) and other variables of interest such as:
Blood Pressure (BP), systolic blood pressure (SBP) &
diastolic blood pressure (DBP), biomarkers of
inflammation (CRP & WBC), metabolic markers
[(fasting blood sugar (FBS), total cholesterol (TC),
triglyceride (TG), high density lipoproteins (HDL), low
density lipoproteins (LDL)] & artherogenic index (AI).

(2) There would be significant difference between
experimental and control groups in blood pressure,
biomarkers of inflammation, metabolic markers, lipid
profile and \(\text{VO}_2\text{max}\).

(3) Changes in \(\text{VO}_2\text{max}\) would significantly correlate
with changes in BP, biomarkers of inflammation and
metabolic markers.

**Subjects and Methods**

Study population were males with essential
hypertension who were attending the hypertensive clinic
of Murtala Muhammed Specialist Hospital Kano Nigeria.
Subject were informed about the experimental
procedures, risk and protocol. Only those who consented
to participate in the study were recruited. Subjects
between the age range of 45 and 70 years having chronic
mild to moderate stable hypertension for 1 year duration
were selected. Hypertension was defined as systolic
blood pressure between 140-179 & diastolic blood
pressure between 90-109 mmHg.

Only those cases who volunteered to stop taking antihypertensive
drugs were selected. Hypertension who were attending the hypertensive clinic
at Murtala Muhammed Specialist Hospital (MMSH), Kano between
8:00 - 10:00 am.

Subjects’ resting systolic and diastolic blood
pressures were measured daily in the right arm as
described by Musa et al\(^9\) using an automated digital
BP monitor (Omron digital BP monitor, Medel
11 EM 403c; Tokyo Japan). Venous blood samples were
also taken between 8-10:00 am after 12 hour overnight
fast (fasting blood sample). Five ml blood was taken
where 1 ml was transferred into a heprinised container
(heparin, 75U/ml) for WBC count while remaining 4ml
was allowed to coagulate (clot) at room temperature for
one hour and later centrifuged to separate serum which
was stored at -80ºC until analysis.

Serum C-reactive protein was determined
qualitatively and semi-quantitatively using commercial
latex agglutination method (by Dialab Producnd und
Vertrieb Von Chemisch, Gesellschatt M.B.H), WBC
count was analyzed using Turks method\(^11\), blood sugar
and serum lipids by commercial enzymatic method
(Randox kits and manuals by Randox Laboratory,
Antrim, United Kingdom), LDL was estimated indirectly
using Friedwald et al formula\(^12\) ([LDL = TC- (TG/5)-
HDL]). Artherogenic index was estimated from the ratio
of TC and HDL (TC/HDL).\(^10\)

The Young Men Christian Association (YMCA)
submaximal cycle ergometry test protocol was used to
assess subject’s aerobic power\(^9\). The protocol uses two
for four 3-minutes stages of continuous exercise. Two steady
heart rates of between 110 and 150 beat/min were marked
and these two rates 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 heart rate (220 minus age).
The point at which the diagonal line intersects the
horizontal line predicts the heart rate and 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 \(\text{VO}_2\) max. This procedure was done for both pre
and posttest stress test.
Test procedures
The test procedures were conducted in the department of physiotherapy of Murtala Mohammed Specialist Hospital (MMSH), Kano. Following stress test and prior to the exercise training, all subjects in control and experimental groups were assessed by the physician and were prescribed with methyldopa (500mg-1g daily in divided doses of 2 to 4 times) based on individual’s response and tolerance to therapy. Methyldopa was preferred because it does not alter normal haemodynamic responses to exercise and is a well-tolerated and most prescribed antihypertensive drug in Africa. Subjects used this drug with regular medical consultation and observation throughout the period of exercise training.

Subjects in the experimental group exercised on a bicycle ergometer at a low intensity of between 60-79% of their heart rate 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 50 rpm to obtain a heart rate max reserve 60% in the first two weeks to and level up at 79% heart rate 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
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Table 2: Changed score values and ANOVA test. (N = 245)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Interval group</th>
<th>Control group</th>
<th>F-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>-16.40±13.16</td>
<td>2.61±7.85</td>
<td>137.220</td>
<td>0.000*</td>
</tr>
<tr>
<td>DBP</td>
<td>-4.01±6.34</td>
<td>1.07±1.17</td>
<td>42.059</td>
<td>0.000*</td>
</tr>
<tr>
<td>VO\textsubscript{2}max</td>
<td>13.85±9.94</td>
<td>1.59±3.54</td>
<td>199.262</td>
<td>0.000*</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.03±0.05</td>
<td>0.01±0.03</td>
<td>22.261</td>
<td>0.000*</td>
</tr>
<tr>
<td>WBC</td>
<td>0.02±1.67</td>
<td>1.09±1.89</td>
<td>34.289</td>
<td>0.000*</td>
</tr>
<tr>
<td>FBS</td>
<td>-30.08±18.72</td>
<td>0.14±0.40</td>
<td>511.463</td>
<td>0.000*</td>
</tr>
<tr>
<td>TC</td>
<td>-22.71±28.59</td>
<td>6.20±7.94</td>
<td>160.104</td>
<td>0.000*</td>
</tr>
<tr>
<td>TG</td>
<td>11.69±7.58</td>
<td>0.07±8.72</td>
<td>532.172</td>
<td>0.000*</td>
</tr>
<tr>
<td>HDL</td>
<td>8.70±12.15</td>
<td>0.01±0.33</td>
<td>28.181</td>
<td>0.000*</td>
</tr>
<tr>
<td>LDL</td>
<td>-19.80±12.15</td>
<td>3.67±3.42</td>
<td>171.679</td>
<td>0.000*</td>
</tr>
<tr>
<td>AI</td>
<td>-3.11±3.61</td>
<td>0.22±0.30</td>
<td>58.065</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

*significant p<0.05

was increased from 45 minutes in the first two weeks and leveled up at 60 minutes throughout the remaining part of the training. Exercise session was three times per week for 8 weeks in the experimental or interval group. Subjects in the control group were instructed not to undertake any vigorous physical activity during the 8 weeks period of study.

Posttest procedure

At the end of the 8 weeks, all subjects were asked to stop methyldopa and were prescribed placebo tablets in a single blinded method for a week to wash out the effect of the methyldopa. Immediately after the post training wash out period, fasting blood samples were collected again. All pre and post test measurements were recorded on a data sheet.

Following data collection, the variables were statistically analyzed. The descriptive statistics (Means and standard deviations) of the subjects’ physical characteristics, estimated VO\textsubscript{2}max, BP, CRP, WBC, FBS and lipid profile were determined. Analysis of co-variance (ANCOVA) was used to assess the outcome variables; in the ANCOVA, the posttest values were the outcome variables and the co-covariates were the age and pretest (baseline) values. Pearson product moment correlation tests were computed for the variables of interest. In the 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.

Results

Two hundred and fifty seven subjects (140 experimental, and 105 controls) completed the 8 weeks training program while data of 78 subjects (22 experimental and 56 controls) was not used because they either dropped or were non-compliant, unfavorable responses to methyldopa and exercise training or due to incomplete data. The final analysis was done on the data of 245 subjects (Figure-1).

The ages of the subjects ranged between 45 and 70 years. In the experimental or interval group the mean age was 58.40±6.91 years, height 167.78±7.81 cm, weight 70.18±11.37 kg, BMI 24.96±3.88 kg.m\textsuperscript{-2} and % BF±SD of 17.69±17.69± 6.50%. In the control group these were 58.27±6.24 years, 167.89±5.31 cm, 68.47±17.07 kg, 24.16±4.91 kg.m\textsuperscript{-2} & 22.27± 9.82% respectively. There was no significant difference in the age between the two groups (t=.156, p=.876).

Table-1 shows pretest versus and posttest mean BP, CRP, WBC, FBS, HDL and VO\textsubscript{2}max for the exercise group and controls.

Figure 2: Correlation between baseline VO\textsubscript{2}max and other variables (BP, CRP, WBC, FBS, Lipid Profile). N=245
Table-2 shows a significant reduction in both systolic and diastolic blood pressure, CRP, WBC, FBS; TC, TG, HDL, LDL, AI and VO\textsubscript{max} in the exercise groups over control group ($p<0.05$).

![Graph showing changes in SBP and DBP](image)

*significant $p<0.05$, **significant $p<0.01$

SBP $r = -0.304^{**}$, DBP $r = -0.289^{**}$

Figure 3: Correlation between training changes in VO\textsubscript{max} and BP (SBP & DBP). N=140

![Graph showing changes in CRP and WBC](image)

*significant $p<0.05$, **significant $p<0.01$

CRP $r = -0.444^{**}$, WBC $r = -0.378^{**}$

Figure 4: Correlation between training changes in VO\textsubscript{max} and Biomarkers of inflammation (CRP & WBC). N=140

Significant positive correlation was seen in the baseline VO\textsubscript{max} and other variables (SBP, DBP, CRP, WBC) (Figure-2). Training or exercise significantly changed ($p<0.01$)VO\textsubscript{max} negatively and positively and it correlated with training changes in other parameters too like systolic blood pressure ($r=-.304$); diastolic blood pressure ($r=-.379$); C reactive protein ($r=-.444$); WBC ($r=-.225$); Total cholesterol ($r=-.232$); TG ($r=-.190$); LDL ($r=-.197$); AI ($r=-.283$) and HDL ($r=.232$) (Figure-3, 4 & 5).

**Discussion**

To our knowledge, this is the first randomized, controlled trial examining the simultaneous impact of interval, moderate intensity, aerobic training on blood pressure, biomarkers of inflammation and metabolic markers in pure black African hypertensives. The study showed a significant correlation between baseline VO\textsubscript{max} and other variables like BP (SBP & DBP), biomarkers of inflammation (CRP & WBC), metabolic markers (FBS, TC, TG, HDL, LDL& AI). It also showed a significant difference between experimental and control groups in BP(SBP & DBP), biomarkers of inflammation (CRP & WBC), metabolic markers (FBS, TC, TG, HDL, LDL& AI) and VO\textsubscript{max}. The changes in VO\textsubscript{max} significantly correlated with changes in BP (SBP & DBP), biomarkers of inflammation (CRP & WBC), metabolic markers (FBS, TC, TG, HDL, LDL& AI) but there was no significant correlation between baseline VO\textsubscript{max} and FBS.

**VO\textsubscript{max}**

Our findings are similar to the report of Mughal et al\textsuperscript{16}, who studied the effect of aerobic exercise in patients with essential hypertension. Dengel and associates\textsuperscript{17} also conducted a study on the effect of physical training on maximum aerobic capacity and reported a significant increase in maximal aerobic capacity (VO\textsubscript{max}:18.3±3.8 versus output of 20.7±4.2ml/kg/min, at $p<0.017$). Both these studies showed outstanding results with exercise but had limitation of lacking control group.

The present study showed a significant decrease in blood pressure in the experimental groups over placebo group. These favorable from aerobic training on blood pressure were also reported by others\textsuperscript{18,19}.

Figure 5: Correlation between training changes in VO\textsubscript{max} and Metabolic markers (TC, TG, HDL, LDL & AI). N=140
A significant reduction in CRP and WBC was seen in the present study in the interval group over control. Kullo et al. also reported similar findings and showed inverse correlation with VO\textsubscript{2max} (r=-0.40, p=0.001) and IL-6 (r=-0.38, p=0.001). Effects of long-term exercise intervention on two biomarkers of inflammation (C-reactive protein [CRP] interleukin-6 [IL-6]) and WBC were studied by workers who reported no significant differences in CRP and WBC\textsuperscript{21}. The effect of exercise and weight loss on FBS in hypertensives reported a significant reduction in FBS exercise cases as compared to controls\textsuperscript{22}. Effect of mild exercise reported a significant reduction in FBS and insulin levels\textsuperscript{23}. The changes in the lipid profile seen in the present study are in agreement with other study\textsuperscript{24} who used a treadmill exercise program. They reported significant reductions in clinic and ambulatory BP, plasma TC, LDL and triglyceride along with elevation of HDL. However, others have reported contrary findings\textsuperscript{25}. The differences in findings could be attributed to the differences in exercise intensities, subjects’ health status and pre (baseline) lipid profile status. 

It was concluded from the present study that physical activity and fitness are related to lower levels of the inflammatory marker and various metabolic markers. Interval training program is an effective adjunct non-pharmacological multipurpose management of hypertension; and that the therapeutic role of interval training program in the reduction of blood pressure may be through the suppression of systemic inflammation and abnormal metabolic markers.

References