The cardiovascular metabolic syndrome
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Increased Level of Cardio-Respiratory Fitness Blunts the Inflammatory Response in Metabolic Syndrome
Abstract

Objective:
The presence of metabolic syndrome is associated with a higher degree of inflammation. We sought to assess whether the higher levels of cardiorespiratory fitness attenuates the levels of inflammation in people with metabolic syndrome.

Methods:
We studied 449 consecutive asymptomatic men (47±7 yrs) who underwent a maximal treadmill exercise test according to the Bruce protocol. Cardiorespiratory fitness was divided into tertiles based on metabolic equivalents (METs). White blood cells (WBC) (x10^9 cells/L) count was used as marker of inflammation.

Results:
In our study population, 23% of the participants had the metabolic syndrome. The WBC count increased (p <0.0001 for trend) with increasing number of risk factors for metabolic syndrome; however there was an inverse relationship (p <0.0001 for trend) with increasing tertiles of fitness (6.47 cells x10^9 cells/L for lowest tertile and 5.7 x10^9 cells/L for highest tertile). Multiple linear regression analyses demonstrated that as compared to individuals with no MS risk factor, the WBC count remained significantly higher in men with metabolic syndrome in first tertile (regression coefficient: 1.2 95% CI 0.4-2.0, p=0.003) and second tertile (regression coefficient: 0.61 95% CI 0.4-2.0, p=0.02) of cardiorespiratory fitness, respectively. However, in the highest tertile of fitness no increase in level of WBC count observed with increasing metabolic syndrome risk factors.

Conclusion:
Our findings suggest that in people with metabolic syndrome an increased level of physical fitness might exert its beneficial effect via attenuating inflammation.
Introduction

The diagnosis and treatment of metabolic syndrome has become increasingly important in recent years. In one study, patients with metabolic syndrome but without diabetes had a considerably higher prevalence of coronary heart disease (CHD) than patients with diabetes and no metabolic syndrome; the combination of diabetes and the metabolic syndrome had the worst prognosis (1). Others have shown that the risk of prevalence of cardiovascular disease is nearly two fold higher in subjects with metabolic syndrome than in those without (2).

The white blood cell (WBC) count is an inexpensive, reliable, easy to interpret, and routinely ordered indicator of cellular response to inflammation (3). Recent systematic analyses have highlighted an increasing number of prospective studies conducted in populations free of CHD, that have demonstrated a strong and independent association between WBC count and risk of CHD. These studies support the concept that cardiovascular risk categorization by inflammatory markers, including the WBC count, may identify high-risk individuals who are not currently identified by traditional risk factors (4,5).

Studies have also shown an association between the metabolic syndrome and chronic subclinical inflammation (6). Such a state of inflammation in metabolic syndrome may be a contributory factor towards increased risk of cardiovascular events among individuals with metabolic syndrome. A higher WBC count has been shown to be associated with worsening of insulin action, and the development of type 2 diabetes (7). Recently it has been shown that subjects in the highest quartile of WBC counts demonstrated a three-fold increase, in the odds ratio for metabolic syndrome compared to subjects in the lowest quartile of WBC counts (8). Another study showed that means of WBC count were significantly higher in metabolic syndrome subjects, compared to subjects without metabolic syndrome (9).

The prevalence of the metabolic syndrome has been shown to be markedly lower across progressively higher levels of cardiorespiratory fitness (10). Cardiorespiratory fitness appears to provide a strong protective effect against all-cause and CVD mortality in men with the metabolic syndrome (11). Exercise has been shown to decrease levels
of inflammation and the anti-inflammatory effect of exercise is being recognized as one of its physiological benefits (12). Lowering levels of inflammation has recently been shown to be useful in reduction in cardiovascular events (13). The clinical effect of lowering of inflammation in people with metabolic syndrome remains to be explored. In this study we sought to assess the impact of higher levels of cardiorespiratory fitness (CRF) in reduction in inflammation or WBC levels, in asymptomatic men with increasing risk factors for metabolic syndrome as well as in those without metabolic syndrome.

Methods

Study population
This is a cross-sectional study on a consecutive sample of 559 white previously non-diabetic, asymptomatic individuals free of known coronary heart disease who presented for a cardiac risk assessment consisting of a clinical consultation between July 1999 and June 2003 at the Preventive Medicine Center of the Albert Einstein Hospital (Sao Paulo, Brazil). None of the study participants were on any hypoglycemic agents at the time of examination. Overall 110 men with missing variables of interest were excluded from the analyses. This study was approved by the local institutional review board and received a waiver of patient consent.

Risk factor assessment
All individuals provided details of their demographics, medical history and medication usage at a clinical consultation. A history of cigarette smoking was considered present if a subject was a current smoker. Weight, height, and waist circumference and blood pressure were determined for each subject. Weight (kilograms) and height (meters) were measured with a standard physician's scale and a stadiometer. Waist circumference (centimeters) was measured at the narrowest diameter between the costal margin and the iliac crest using a plastic anthropometric tape. Blood pressure (mm Hg) was obtained with a mercury sphygmomanometer (in a sitting position after approximately 5 minutes) using auscultatory
methods following the American Heart Association protocol (14). Body mass index (BMI) (kg/m$^2$) was calculated using the following formula: Weight/Height$^2$.

Blood specimens were collected after an overnight fast. Total cholesterol and triglycerides were estimated by enzymatic methods (cholesterol oxidase/peroxidase-aminophenazone for cholesterol, glycerol phosphate oxidase/peroxidase-aminophenazone for triglycerides) on an automated system using standard kits (Johnson and Johnson Clinical Diagnostics, Rochester, NY). High-density lipoprotein cholesterol was estimated using a precipitation method and LDL cholesterol was calculated (total cholesterol-HDL cholesterol-triglycerides/5) for triglyceride levels up to 400 mg/dL. Fasting blood glucose was measured with a glucose oxidase method using a colorimetric assay on the Vitros automated platform (Johnson and Johnson Clinical Diagnostics, Rochester, NY). Leukocyte count ($10^9$/L) was measured automatically in a Sysmex XE 2100 equipment (Roche Diagnostics, Kobe, Japan) (normal range 6-10 x $10^9$/L).

Metabolic syndrome was defined (15) by the presence of at least three of the following criteria: 1) waist circumference ≥102 cm; 2) serum triglycerides ≥150 mg/dl; 3) HDL cholesterol levels of <40 mg/dl; 4) fasting glucose ≥110 mg/dl; or 5) blood pressure of at least 130/85 mm Hg or treated hypertension.

The asymptomatic participants underwent a maximal treadmill exercise test according to the Bruce protocol. Cardiorespiratory fitness ("fitness") was quantified as the maximal metabolic equivalents -METs attained (1 MET=3.5 ml O$_2$/kg$^1$ min$^{-1}$) determined from the final speed and grade of a physician supervised maximal treadmill exercise test (16). Individuals were then divided into tertiles of cardiorespiratory fitness with first tertile (<9 METs), second tertile (9-12 METs) and highest tertile (≥13 METs), respectively.

**Statistical Analysis**

The distribution of values was assessed by the Kolmogorov-Smirnov test for normality of distribution. Continuous variables are presented as mean ± SD. Significance in differences across metabolic syndrome risk factors as well across tertiles of CRF were determined with the chi-square testing for categorical variables and analysis of variance for continuous variables. Multiple linear regressions were used to determine the independent association of increasing metabolic syndrome risk category with WBC.
count across levels of CRF. The additional variables adjusted for in the model were age, smoking, total cholesterol and cholesterol lowering medication. Two-sided probability values <0.05 were considered statistically significant. All analyses were performed using STATA version 8 (Austin, TX).

Results

The final study population consisted of 449 men (mean age 47±7 years, range=39-65 years). Overall, 23% (n=109) of these participants had the metabolic syndrome. The clinical characteristics of the study participants, according to CRF and MS risk factors are presented in table 1A and 1B. Subjects in higher fitness tertiles were younger, less likely to be current smokers, and had a better metabolic profile with a lower fasting glucose, lesser waist circumference, better lipid profile and lower systolic blood pressure. As expected with increasing numbers of risk factors for the metabolic syndrome subjects manifested higher fasting glucose, increased waist circumference, more dyslipidemia and higher systolic blood pressure.

The proportion of participants with MS (≥3 risk factors) was highest (33%) in the lowest tertile for cardiorespiratory fitness. Conversely the prevalence of MS decreased to 6% in the highest tertile for fitness (figure 1). The WBC (x10^9 cells/L) levels increased

![Figure 1: Percentage (%) of metabolic syndrome risk factors (RF) across increasing tertiles of METs.](image-url)
Table 1. Characteristics of Study Participants (n=449) A) According to tertiles of Cardio Respiratory Fitness (METs).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fitness (METs) Tertiles</th>
<th>P value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 9(n=172)</td>
<td>9-12(n=196)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48±8</td>
<td>46±8</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>93±25</td>
<td>90±18</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>101±11</td>
<td>96±9</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>29±5</td>
<td>27±3</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>215±42</td>
<td>202±37</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>136±41</td>
<td>126±32</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45±15</td>
<td>44±12</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>184±117</td>
<td>173±154</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128±14</td>
<td>128±14</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>56</td>
<td>53</td>
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</table>

B) According to Risk Factors for Metabolic Syndrome.

<table>
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<th>Variables</th>
<th>Metabolic Syndrome Risk Factors</th>
<th>P value for trend</th>
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<tr>
<td></td>
<td>0 RF(n=129)</td>
<td>1-2 RF (n=216)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±7</td>
<td>48±7</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>85±6</td>
<td>91±23</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>90±7</td>
<td>97±10</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25±3</td>
<td>27±4</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>206±41</td>
<td>207±38</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>135±40</td>
<td>130±33</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>52±11</td>
<td>48±14</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>97±28</td>
<td>152±79</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>118±7</td>
<td>128±13</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>37</td>
<td>55</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SD and percentage. ≥3 Risk factors (RF) is considered Metabolic Syndrome. METs= metabolic equivalents; TC= Total cholesterol; BP= blood pressure; HDL= high-density lipoprotein; LDL= low-density lipoprotein; TG= Triglycerides; BMI=Body Mass Index (p <0.001 for trend) with increasing number of risk factors for metabolic syndrome (figure 2A). Conversely, the WBC count demonstrated an inverse relationship (p <0.001 for trend) with increasing CRF levels (figure 2B).

Figure 3 displays the mean WBC count with increasing MS risk factors across tertiles for fitness (figure 3). Mean WBC levels increased with increasing risk factors for metabolic syndrome in the lowest tertile (p=0.002 for trend) and second tertile (p=0.02).
Figure 2 A: Mean WBC ($x10^9$ cells/L) levels across increasing metabolic syndrome risk factors (RF).

Figure 2 B: Mean WBC ($x10^9$ cells/L) levels across increasing tertiles of METs

Figure 3: Mean WBC ($x10^9$ cells/L) levels across increasing metabolic syndrome risk factors (RF) across tertiles of METs

Subjects with metabolic syndrome who were in the highest tertile for fitness had a markedly lower WBC ($x10^3$/mm3) levels as compared with subjects in the lowest fitness tertile. However, within the highest tertile for fitness, the difference in the extent of inflammation across increasing risk factors for metabolic syndrome was not significantly higher (p=0.8).
Figure 4: Mean WBC changes calculated by linear regression analyses adjusting for age, smoking, cholesterol lowering medication and total cholesterol with increasing metabolic syndrome risk factors across tertiles of METs.

Figure 4 demonstrates the adjusted mean difference in the WBC(x10^3/mm3) count calculated by linear regression analyses adjusting for age, smoking, cholesterol lowering medication and total cholesterol, in the WBC (x10^3/mm3) count with individuals with no MS risk as reference group. There was a strong trend toward a significant interaction between the fitness level and number of components of the metabolic syndrome in the adjusted model (p = 0.08). As compared to individuals with no MS risk factor, the WBC count remained significantly higher in subjects with metabolic syndrome in first tertile (regression coefficient: 1.2, 95% CI 0.4-2.0, p=0.003) and second tertile (regression coefficient: 0.61 95% CI 0.4-2.0, p=0.02) of CRF, respectively. However in the highest tertile of fitness the level of WBC was blunted irrespective of number of increasing risk factors for metabolic syndrome (figure 4).

Conclusions

Our findings demonstrated that increasing cardiorespiratory fitness levels appear to modulate the effect of the metabolic syndrome on white blood cell levels. Although MS was associated with significantly higher WBC counts, its effect seemed to be...
attenuated among asymptomatic men who achieved the highest CRF levels. This finding emphasizes the potential beneficial effects of achieving higher CRF especially in subjects with clinical evidence of insulin resistance.

Our study findings are consistent with previous reports that have shown that men with high level of cardio-respiratory fitness are less likely to have metabolic syndrome (17). Moreover Franks et al. (18) in their study demonstrated a strong inverse association between physical activity and metabolic syndrome, an association that was much steeper in unfit individuals. Thus prevention of metabolic disease may be most effective in the subset of unfit inactive people (18).

We also demonstrate that higher levels of fitness were associated with decreased amount of inflammation as shown by lower levels of WBC levels. Troseid et al. (19), previously showed that a 12 week exercise program reduced plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. Aronson et al. (20) showed that a strong inverse trend toward decreasing C-reactive protein (CRP) levels with increasing fitness levels was present in subjects in both with and without metabolic syndrome. They also showed that subjects with the metabolic syndrome who maintained a high fitness level had markedly lower CRP concentrations, as compared with those with a low fitness level. We also found that the level of inflammation as shown by WBC levels still remained significantly high in subjects with metabolic syndrome in low-intermediate levels of CRF; the effect of MS on inflammation seemed to be blunted only among men with the highest CRF levels (third tertile). In a recently published follow-up study of 19,173 men (average 43 ± 9 years), CRF greatly attenuated the effect of MS on all-cause and CVD mortality (21). Our finding that high levels of CRF blunts the inflammatory response of MS, may explain, at least in part, the effect modification of CRF levels in the relationship between metabolic status and mortality. There are several mechanisms through which cardio-respiratory fitness may mediate its beneficial effects in patients with metabolic syndrome and its associated components. Exercise has shown to improve insulin resistance and its associated metabolic abnormalities, including dyslipidemia, hypertension, platelet function, fibrinolysis, and endothelial dysfunction (22).

The protective effect of exercise might in part be due to suppression of the inflammatory process (11,12). Albert et al. (23) demonstrated that more strenuous
Increased Level of Cardio-Respiratory Fitness Blunts the Inflammatory aerobic activity was associated with lower CRP levels among men; they suggested that one of the major mechanisms for this was reducing body mass index. However another study demonstrated that nearly 40% reductions in CRP after exercise training program appeared to be independent of statin use and weight loss (12). Even those patients who gained weight during cardiac rehabilitation had 40% reductions in CRP. Within levels of obesity, risk for significant elevations in fibrinogen, white blood cells, uric acid and metabolic syndrome score is lower for the higher fitness groups (24). Thus, the inverse relationship between physical fitness and WBC may reflect a fitness-induced decrease in inflammation in patients with metabolic syndrome since such participants in low level of fitness still had significantly higher adjusted levels of inflammation.

This study should be interpreted in light of some limitations. The study population consisted exclusively of middle-aged Brazilian men; as a result, it is uncertain whether these findings can be extrapolated to females, older individuals or in other ethnic groups. Also, the cross sectional nature of the study permits only associations, rather than causality.

In summary, in men with the metabolic syndrome, inflammation as manifested by WBC levels is attenuated by a high cardio-respiratory fitness. Therefore, higher level of cardiorespiratory fitness should be recommended for patients with the metabolic syndrome, not only for weight reduction, but also to reduce the high levels of inflammation associated with this syndrome.

References


