Effect of six weeks of endurance exercise and following detraining on serum BDNF and memory performance in middle aged males with metabolic syndrome

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ABSTRACT

Aim. Brain derived neurotrophic factor (BDNF) and physical inactivity contribute to the development of metabolic syndrome (MetS). Aerobic training has been reported to improve MetS, however less attention has been directed toward the role of training and detraining on cognitive function in MetS.

Methods. Forty middle-aged male were randomized to four groups: MetS exercise (ME), MetS control (MC), Healthy exercise (HE) and healthy control (HC) and followed a 6-week aerobic training program (3 sessions/week). Digit Span memory test and blood sampling were conducted pre training, post training as well as following a six weeks detraining. Data were analyzed using spearman, pearson and repeated measure ANOVA tests.

Results. Baseline serum BDNF level was positively correlated with waist circumference (r=0.383, P=0.012) and showed significant elevation in MetS compared with healthy subjects (1101.66±281.1 vs 903.72±213.42 pg.ml⁻¹, P=0.014). After aerobic exercise BDNF level significantly increased in HE, but decreased in ME group (P=0.001). Both short and mid term memory significantly increased (P<0.05) only in HE group.

Conclusions. This study suggest that BDNF might mediate exercise-induced cognitive improvement in healthy people.

Key words: Metabolic Syndrome, Cognitive Function, Exercise Training

It is well known that metabolic syndrome predisposes individuals to cardiovascular diseases and diabetes. There are discrepancies in the existing literatures regarding to MetS and cognitive function including: decline 1-5, better cognitive performance 6 and no effect 7. The association between some indices of MetS and cognitive decline has been reported before 2,3. For example midlife obesity 8, hypertension 8,9 and elevated total cholesterol 8,10 are associated with reduced cognitive function in later life. Exercise as a costless, therapeutic tool could positively affect on cognitive function 11,12, mostly due to the release of neurotrophic factors 13. Brain derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family, plays a key role in learning and memory 14. In human, a growing number of studies reported an elevation in peripheral BDNF following acute but not chronic exercise 15. Moreover, to the best of our knowledge far less attention has been directed to the effects of detraining on serum BDNF and cognitive function in human. There is interesting study indicates that both 8 weeks of aerobic training and detraining did not influence on short and mid-term memory tests 16. In another report, BDNF increased after 8-weeks of exercise training in the hippocampus of rat, and decreased after detraining period, to a lower level compared with control group 17. Most of the studies focused on the benefits of acute exercise in young adult populations. Here we
studied the effect of chronic aerobic exercise training and following detraining on cognitive function and serum BDNF level in middle aged participants with MetS and healthy males.

**Materials and methods**

Participants: At the beginning of the experiment 76 male volunteers underwent a clinical and physical examination, then 52 subjects (28 patient with MetS and 24 healthy) included in this study. Subjects characteristics is shown in table 1. None of the subjects were physically active for more than one hour per week or during the past 2 years. Sedentary midlife males (57.13±5.87 yrs) were divided into two groups of MetS and healthy, based on the National Cholesterol Education Program Adult Treatment Panel III.

According to this program MetS is defined as the presence of three or more of the following five criteria: increased waist circumference (≥102 cm), hypertriglyceridemia (≥150 mg/dl), low (≤40 mg/dl) high-density lipoprotein, hypertension (≥130/85 mm Hg), and high (≥110 mg/dl) fasting glucose. Exclusion criteria were smoking, alcohol drinking, coronary heart disease, pulmonary disease, uncontrolled hypertension, poorly controlled diabetes mellitus, musculoskeletal complaints, depression and sleep disorder. Some of the MetS participants were taking a range of medications, including beta blockers (n=2), statins (n=3) and metformin (n=4).

The study was approved by the local ethics committee of the Guilan University of Medical Sciences and performed according to the principles of the Declaration of Helsinki. Initially, Then participants were distributed into four groups: MetS-exercise (ME), MetS-control (MC), Healthy-exercise (HE) and Healthy-control (HC). The study was started after taking the written informed consent from all subjects.

**Study protocol**

Subjects were tested on 3 occasions during the 12 weeks of experiment: at baseline, after 6 and 12 weeks. At each time point, a blood sample (fasting state) was taken and memory performance was tested, then the subjects performed a graded exercise test (GXT) to exhaustion in order to determine their VO2 peak. The GXT was performed on a cycle ergometer, at 50W and resistance was increased by 25W every 3 min to exhaustion. Heart rate was measured every three min and also at the VO2 peak point. Training guidelines for ME and HE groups were based on the results of the GXT. They followed a 6-week aerobic training program (3 sessions/week; 20–40 min walking, running by 50 to 60% of VO2 peak adjusted by heart rate). There were 20 min for warm up and calisthenics at beginning of each session and also a 10 min cool down period at the end. Following the 6-week training period, subjects were asked to return to their sedentary activity level. The control groups were asked not to change their sedentary activity level during 12 weeks. 10 subjects (six in the third week, two in the week sixth and two in the week 12th) left the study for personal reasons.

**Blood pressure**

Blood pressure was measured using a mercury sphygmomanometer after taking a 15 min rest.

**Metabolic factors**

Fasting blood samples were divided into three distinct falcon tubes, one pre-cooled for BDNF (BD Vacutainer® SST II Advance), and two others for insulin and lipids profile analysis. Blood were left to clot at room temperature and were centrifuged (12 min, 3000 rpm), then serum was stored at −80 °C until analysis. Serum BDNF was assayed in duplicate according to the manufacturer’s instructions (R&D BDNF ELISA kit, USA). The BDNF ELISA kit has a detection range from 7.8 to 500 pg/mL. The intra-assay and inter-assay variations were ±4.66% and ±9%, respectively.

**MetS z Score**

A modified z score for MetS was calculated for each variable following equation:

\(<z-score>=[(40–HDL)/6.2]+[(TG–150)/66.2]+\)
BDNF & COGNITIVE FUNCTION IN METABOLIC SYNDROME

Cognitive function

To study the cognitive function, both short and mid-term memory were assessed using Digit Span memory test. Subjects were presented a series of numbers, each for 1 s with interval of 0.5 s. The task was to recall the numbers in the right order immediately after the latest presented number. To assess mid-term memory, Subjects were shown 12 pictures, each for 10 s, then they were asked 30 min later to write down remembered pictures.

Nutrition data

Participants received a kitchen scale and recorded their diet in details for two weekdays and a weekend day in three phases (three weeks before the beginning of the study and also in the weeks of 3, 5, 9 and 11 of study). The logs were analyzed by a Nutrition analyzer software N4.

Statistical analysis

Normality of data was checked using a Kolmogorov–Smirnov Goodness of Fit test. Baseline data was compared by means of independent sample t test between healthy and MetS subjects. Pearson correlation was used to assess correlations between BDNF and memory function and other metabolic risk factors. Stepwise multiple regression analysis was used to identify the variable with the strongest correlation with risk factors. By using repeated measure ANOVA we tested the effects of training and detraining over the time between each of two health status groups (MetS vs healthy, referred as p value “Health status×time”) and between the two trial groups (Exercise vs control). Post hoc analysis for time effect was applied by using the Bonferroni test. ANCOVA was also used by considering carbohydrate, protein and lipid intake as covariate factor. All statistical analyses were conducted at the 95% level of significance.

Results

Correlation between BDNF and risk factors at baseline: Waist circumference and baseline serum BDNF were significantly higher in MetS compared with healthy (97.71±10.13 vs 90.05±8.47 cm, P=0.011), (1101.66±281.1 vs 903.72±213.42 pg.ml⁻¹, P=0.014) respectively. Baseline BDNF level was positively correlated with waist circumference (r=0.383, P=0.012). There was no significant correlation between BDNF and plasma FBS, TG and HDL, overall Z score in MetS (P>0.05).

The effect of aerobic exercise training and detraining on Z score, BDNF and memory

\[
\frac{(\text{fasting blood glucose} - 100)}{10.4} + \frac{(\text{waist circumference} - 102)}{9.3} + \frac{(\text{mean arterial pressure} - 100)}{8.7}
\]\n
19.

\(\text{TABLE I—Values are presented as mean ± SD. BMI: Body-Mass Index; BDNF: Brain derived neurotropic factor. *: between group difference (P<0.05).}\)

<table>
<thead>
<tr>
<th>factor</th>
<th>HC (n=10)</th>
<th>MC (n=10)</th>
<th>HE (n=11)</th>
<th>ME (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59±6.5</td>
<td>58.57±4.23</td>
<td>57.25±7.90</td>
<td>54.12±3.31</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.97±4.42</td>
<td>27.04±5.53</td>
<td>25.39±4.47</td>
<td>29.8±4.48</td>
</tr>
<tr>
<td>Education</td>
<td>12±2.56</td>
<td>11±3.07</td>
<td>12±4.65</td>
<td>12±2.87</td>
</tr>
<tr>
<td>HR (b/min)</td>
<td>67.57±6.35</td>
<td>71±3.82</td>
<td>68.12±4.7</td>
<td>72.5±2.77</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>86±12.23</td>
<td>96.57±11.47</td>
<td>91.25±6.55</td>
<td>98.75±13.3</td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td>9.5±0.63</td>
<td>9.8±0.97</td>
<td>8.7±0.66</td>
<td>9.8±0.88</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>94.28±7.72</td>
<td>121.57±15.41</td>
<td>119±7.13</td>
<td>130.87±27.12</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>147.42±2.99</td>
<td>203.14±35.31</td>
<td>168.87±24.07</td>
<td>252.5±178.73</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>44.71±1.16</td>
<td>37.28±1.79</td>
<td>46.5±5.63</td>
<td>37.5±3.33</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>115.28±25.11</td>
<td>163.28±10.43</td>
<td>119.25±33.8</td>
<td>133.25±46.53</td>
</tr>
<tr>
<td>Overall MetS Z Score</td>
<td>3.47±1.29</td>
<td>2.83±1.84</td>
<td>-0.73±4.34</td>
<td>4.22±1.84</td>
</tr>
</tbody>
</table>

| No. of Total Risk Factors | 8 | 38 | 17 | 38 |
| Waist Circumference>102cm | 1 | 3 | 0 | 3 |
| TG>150 mg/dl | 3 | 9 | 8 | 10 |
| HDL<40 mg/dl | 2 | 10 | 1 | 6 |
| BP>130/85 mmHg | 2 | 8 | 3 | 9 |
| FBS>110 mg/dl | 0 | 8 | 5 | 10 |
function: Overall MetS z Score was significantly higher in MetS patients compared to healthy counterparts (3.56±1.93 vs. −2.03±3.48, P=0.001). Exercise training significantly decreased total MetS z score in both ME (F2=25.81, P=0.001) and HE (F2=6.37, P=0.007) groups; however, there was a trend to return to the basal levels during the detraining period (Fig 1). BDNF levels (Fig 2) also significantly changed in both training groups during the study (P=0.001).

In HE group, memory function significantly increased after exercise training and slightly decreased after 6 weeks of detraining (Fig 3, 4; F3, 38=11.831, P=0.001 F3, 38=8.25, P=0.002 respectively for both short and midterm memory), however the reduction in midterm memory was not significant. Short and midterm memory didn’t show significant changes in ME group after training and also detraining (P>0.05).

Energy intake: No significant change in total energy intake was observed during the study within each group (P>0.05), however, significant interaction between time and trial was observed in the micronutrients components of the diet within groups (P=0.02, P=0.105, P=0.051) respectively for carbohydrate, lipid and protein). The results of ANCOVA showed that none of these micronutrients (or as a whole) could remarkably affect the results of repeated measure ANOVA for BDNF and memory function.

Figure 1. Shows MetS z Score during study. *, †: significant differences compared to baseline and after training respectively (p<0.05).

Fig. 2. Shows Serum BDNF levels during study. *, †: significant differences compared to baseline and after training respectively (p<0.05).

Fig. 3. Short-term memory function during study *: significant differences compared to baseline (p<0.05). In HE group, both short and mid term memory significantly increased (P<0.05) and after 6 weeks of detraining showed slightly reduction.

Fig. 4. Mid-term memory function during study. *: significant differences compared to baseline (p<0.05). In HE group, mid term memory significantly increased (P<0.05) and after 6 weeks of detraining showed slightly reduction.
Discussion

Our exercise protocol improved MetS z score in both ME and HE groups as a comprehensive indices, indicating cardio metabolic health benefits of exercise, which is consistent with other studies\textsuperscript{19,21,22}. A surprising finding in the present study was that the endurance training decreased basal serum BDNF level in subjects with MetS, while increased it in healthy subjects. Increased serum BDNF concentration has been previously reported following endurance\textsuperscript{23,24} and strength training\textsuperscript{25}. In our study, parallel with BDNF elevation, both short term and midterm memory increased in healthy subjects which is in agreement with the concept of BDNF neurotrophic effect\textsuperscript{26}. Therefore chronic physical activity might facilitate the availability of neurotrophins in the brain, and consequently induces synaptic plasticity or even neurogenesis to support the brain. However, we cannot exclude other possible mechanisms at the systemic, molecular and cellular levels\textsuperscript{27}. Increased short and mid-term memory and attention in our study might be related to increase in temporo - parietal and frontal lobes activity in response to serum BDNF elevation\textsuperscript{28,29}. An interesting study showed that injection of antibody against BDNF in the hippocampus blocked the benefit of exercise on special memory\textsuperscript{30}. Therefore, BDNF could be a potential mediator of exercise effects on cognition performance in healthy participants. Higher baseline serum BDNF levels in subjects with MetS is in agreement with some studies\textsuperscript{20,31,32}, however it is in contrary with two reports in patients with type 2 diabetes mellitus (T2DM)\textsuperscript{36,37}. This finding supports the idea that BDNF might be a biomarker of metabolic syndrome\textsuperscript{33,34} and T2DM\textsuperscript{20} progress. According to previous literatures, the elevated plasma BDNF might represent a compensatory response in the early stage of the MetS\textsuperscript{32,35}. Based on insulin concentration (unpublished data), it seems that our MetS participants with high level of BDNF had not yet developed overt disease\textsuperscript{20,32}. These subjects with high level of serum BDNF, didn’t show better memory function compared to healthy counterparts, and after chronic exercise they demonstrated significant reduction in BDNF level with no change in cognitive function. Therefore we cannot attribute the reduction in serum BDNF to more uptakes by CNS, representing the idea that peripheral BDNF doesn’t always reflect brain BDNF levels. It seems in MetS the serum BDNF is likely acts as an inflammatory factor\textsuperscript{36,37} rather than a marker of health as typically assumed. Lack of improvement in memory performance even after 6 weeks of aerobic training in MetS subjects indicating possible involvement of other MetS-related markers in the development of cognitive impairment\textsuperscript{38,39}. For example β-Amyloid production has recently been found to be up-regulated in obese individuals\textsuperscript{40}. It seems the situation in which an individual faces with metabolic syndrome risk factors is strong enough to overrides exercise benefits on cognition during 6 months.

Our results showed that any changes in serum BDNF and also memory function induced by exercise training in middle aged men could slightly decline in the following detraining period in healthy people. This may emphasize on continuous exercise training to prevent cognitive decline in healthy middle aged. To the best of our knowledge this is the first study which considered the effect of detraining on BDNF and memory function in MetS patients. For future studies it is suggested to design a more comprehensive study with large sample size and prolonged exercise training. All together these data suggest that in healthy subjects chronic exercise improves cognitive function concomitant with increased serum BDNF concentration.

Conclusions

Our exercise protocol was sufficiently effective to induce positive adaptations in both MetS and healthy middle aged males, but in the opposite direction. This implies that BDNF might mediate exercise -induced memory improvement in healthy people, but not in metabolic syndrome. From clinical point of view these findings gain our understanding about the importance of physical fitness as a preventive tool for future dementia in middle-aged healthy subjects.
References


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