J. Phys. Ther. Sci.
26: 1199–1204, 2014

Original Article

The Effects of 12 Weeks Regular Aerobic Exercise on Brain-derived Neurotrophic Factor and Inflammatory Factors in Juvenile Obesity and Type 2 Diabetes Mellitus

Sung Soo Lee[1)], Jae Ho Yoo[2)], Sung Hwun Kang[5)], Jin Hee Woo[1)], Ki Ok Shin[1)], Kwi Beak Kim[3)], Su Youn Cho[4)], Hee Tae Roh[4)], Young Il Kim, PhD[3)*]

[1)] *Department of Physical Education, College of Sports Science, Dong-A University, Republic of Korea*
[2)] *Department of Pediatrics, College of Medicine, Dong-A University Medical Center, Republic of Korea*
[3)] *Department of Sport and Health Management, College of Sports Science, Young-san University: 288 Junam-ro, Yangsan, Gyeongnam 626-790, Republic of Korea*
[4)] *Department of Physical Education, Yon-sei University, Republic of Korea*
[5)] *Department of Aero Physical Education, Republic of Korea Airforce Academy, Republic of Korea*

Abstract. [Purpose] The purpose of this study was to investigate the effects of 12 weeks regular aerobic exercise on brain-derived neurotrophic factor (BDNF) and inflammatory factors in juvenile obesity and type 2 diabetes mellitus (T2DM). Obesity and T2DM, typically common among adults, have recently become more prevalent in the Korean juvenile population, affecting not only their lipid profiles and oxidant stress levels, but also their BDNF and inflammatory factor levels. [Subjects] This study enrolled 26 juveniles (boys = 15, girls = 9) who were assigned to a control group (CG, n = 11), obesity group (OG, n = 8), or T2DM group (TG, n = 7). [Methods] The outcome of a 40–60-minute aerobic exercise session that took place three times per week for 12 weeks at a maximum oxygen intake (VO_{2max}) of 50~60% was investigated. [Results] The exercise resulted in a significant reduction in the resting serum BDNF and TrkB levels (baseline) among juveniles in the OG and TG as compared to those in the CG. Additionally, the 12 weeks of regular aerobic exercise led to significant reductions in body weight, body fat percentage, and body mass index in the OG and a significant increase of VO_{2max} in the OG and TG. However, no significant differences in serum NGF or inflammatory factors were found among the three groups. There was a significant increase in resting serum BDNF levels following the 12 weeks regular exercise only in the OG. [Conclusion] While 12 weeks of regular aerobic exercise had a positive effect on body composition, and increased BDNF levels of juveniles in the OG, it did not affect the inflammatory factor levels and had no effect on the TG.
Key words: Obesity, T2DM, BDNF

(This article was submitted Jan. 10, 2014, and was accepted Feb. 16, 2014)

INTRODUCTION

Obesity and diabetes are common metabolic diseases. The prevalence rate of juvenile obesity has broad and serious health implications, since obesity can increase the risks of type 2 diabetic mellitus (T2DM), hypertension, cardiovascular disease (CVD), sleep apnea, and cancer[1)]. Abnormal glucose tolerance, disturbed glucose tolerance, and T2DM have been identified as increasing the risk of cognitive impairment, and are been known to induce cognitive damage, both of which are early-stage symptoms of Alzheimer's disease and dementia[2)]. Diabetes mellitus is also known to have adverse effects on the peripheral nervous system leading to detrimental changes in brain structure and other neurophysiological traits[3)].

Brain-derived neurotrophic factor (BDNF) is generated and distributed from platelets in the peripheral and central nervous systems, endotheliocytes, smooth muscle, immunocytes, and skeletal muscle. It is a nerve growth and positively contributes to neurogenesis, neurodegeneration, and hippocampal neural plasticity, and enhances memory and learning[4)]. A lower than normal BDNF level has been observed among individuals with obesity and T2DM[5)], and this has been reported to bring about neuropsychosis, severe depression, and Alzheimer's disease[6)], and has also recently been found to affect metabolism in the skeletal muscles[6)].

Inflammatory factors are highly prevalent among individuals with obesity, T2DM, and metabolic syndrome, and such inflammatory factors are associated with obesity and inactivity. High levels of inflammatory factors have also been identified as an independent factor in the progress of

*Corresponding author. Young Il Kim (E-mail: kyi0234@ysu.ac.kr)
©2014 The Society of Physical Therapy Science. Published by IPEC Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives (by-nc-nd) License <http://creativecommons.org/licenses/by-nc-nd/3.0/>.

T2DM and CVD[7].

Research on regular exercise and related neurotrophic factors has determined that exercise can be divided between that which greatly increases the resting BDNF level[8–10] and that which does not[11–13], but the findings are not conclusive due to variations in exercise mode and duration.

Oberbach et al. studied the effects of regular exercise on inflammatory factors by observing middle-aged men and women over the course of 12 months during which they performed 60 minutes of exercise once a week. There results show that as body mass index (BMI) decreased with progression of the exercise training, serum IL-6 and C-reactive protein (CRP) levels at rest decreased correspondingly. Christiansen et al.[7] observed men and women over 12 weeks while they performed 60–75 minutes of endurance training 3 times a week, accompanied by diet control. They also reported a decrease in resting levels of IL-6 and monocyte chemoattractant protein-1 (MCP-1) after training. In addition, CRP levels increased after one intense bout of exercise[15], and a regular exercise training group had lower levels of CRP than a control group[16].

Although, the relationship between neurotrophic and inflammatory factors and regular exercise has been investigated in recent research, the debate on whether regular exercise can alter the resting BDNF level and inflammatory factor levels continues, and existing research on the subject mainly concerns adults and the elderly. Insufficient research has been conducted on juvenile obesity and T2DM, which are rapidly increasing. As adolescence marks an important period of learning and development, the investigation of the effects of regular exercise on juvenile obesity and T2DM is indispensable.

In this study, we examined the effects of exercise by measuring the resting levels of neurotrophic factors (BDNF, NGF, and tropomyosin receptor kinase B [TrkB]), and inflammatory factors (IL-6, tumor necrosis factor α [TNF-α], and CRP) of juveniles assigned to an obesity group (OG, n = 8), T2DM group (TG, n = 7), and control group (CG, n = 11) following 12 weeks of aerobic exercise 3 times a week.

We hypothesized that juveniles with obesity and T2DM would have lower resting BDNF levels, and that 12 weeks of regular exercise would result in increased levels of resting neurotrophic factors and decreased levels of inflammatory factors.

SUBJECTS AND METHODS

This experiment initially recruited originally began with 45 teenagers who were assigned to the OG (n = 15), TG (n = 15), and CG (n = 15). However, due to withdrawals, only 26 teenagers in the OG (n = 8, boys = 4, girls = 4, age; 16.3 ±0.91), TG (n = 7, boys = 2, girls = 5, age; 15.5 ±2.14), and CG (n = 11, boys = 11, age; 16.4 ±1.36) completed the 12 weeks program. All participants were between the ages of 13 and 19 years, and there were 17 boys and 9 girls. The OG teenagers were selected based on the 1998 standards for children and juvenile growth of the Korean Pediatrics Society: BMI > 95th percentile, or obesity index >120%. The TG teenagers were selected from among D University Hospital out-patients whose 2-hour glucose tolerance test was 140 mg/dL ≤ blood sugar ≥ 200 mg/dL, and who had no other complicating diseases. The CG was created by age-matching with the TG and OG juveniles. The study subjects were recruited via poster advertisements or the internet. The study was approved by the D University Hospital Institutional Review Board (IRB) and the subjects were included after medical examination and diagnosis by medical specialists. Additionally, signed consent forms were obtained from the guardians of all participants prior to the commencement of the study.

Height, weight, and BMI were measured as the physical characteristics, and body fat percentage was measured using an impedance analyzer (Venus 5.5, Jawon Medical, Gyeongsan, Korea). The subjects physical characteristics are summarized in Table 1. A submaximal oxygen consumption exercise test (85% VO_2submax test) was conducted before the start of the exercise training. All participants were tested on a Quinton Q65 treadmill (Quinton Co., USA) in a laboratory with 50–55% humidity and a temperature 24–25 °C. The subjects wore a Polar system (Polar Electro, Kempele, Finland), and were measured using a breath-by-breath test. Each respiration was automatically measured for ventilatory volume, oxygen consumption, carbon dioxide emission, respiratory exchange ratio (RER), and heart rate (HR).

The exercise test was conducted using a treadmill exercise test and the Bruce protocol[17]. This method involves steadily increasing the exercise level until the target heart rate (THR) reaches 85% of the maximum oxygen consumption (VO_2max). No subjects exhibited cardiac abnormalities or high blood pressure before reaching the THR. To prevent accidents, participants were asked to subjectively identify the intensity of exercise on the Borg scale of rate of perceived exertion[18].

Aerobic exercise was conducted for a total of 40–60 minutes per session, 3 sessions a week, for 12 weeks. Participants attained 50% of their oxygen consumption as measured by the VO_{2max} test. Between week 1 and week 4, they engaged in 30–40 minutes walking/running aerobic exercise on a school field under the instruction of a professional trainer while wearing a Polar system at a calculated heart rate recovery (HRR) of 50% VO_{2max}. Between week 5 and week 12, the participants exercised in a similar manner but for 40–50 minutes at a HRR equivalent to 60% of VO_{2max}. Each session was preceded and followed by a 5-minute warm up and cool down, respectively.

Blood samples were drawn from the forearm vein after a 12-hour fast. Samples were centrifuged at 3,000 rpm for 10 minutes, stored at −80 °C, and directly analyzed.

The biochemical analyses of serum IL-6, TNF-α, and NGF were performed using enzyme-linked immunosorbent assays for quantitative detection of human IL-6, TNF-α (eBioscience, Vienna, Austria) and NGF (Abcam, MA, USA). All factors were quantified using polyclonal antibodies that recognized native human IL-6, TNF-α, or NGF and a series of plates containing wells coated with predetermined amounts of recombinant human IL-6, TNF-α, or NGF.

Table 1. Changes in baseline characteristics following 12 weeks of aerobic exercise training

Variable	Group	Baseline	12 weeks
Age (yrs)	CG	16.45±1.36	
	OG	16.37±0.91	
	TG	15.57±2.14	
Height (cm)	CG	171.11 ±5.17	171.34* ±5.07
	OG	171.22 ±6.31	172.25 ±5.93
	TG	161.15[b,c] ±7.70	161.27[b,c] ±7.86
Weight (kg)	CG	65.92 ±14.58	66.10 ±14.84
	OG	80.20 ±7.50	73.06* ±10.91
	TG	61.84[b] ±13.68	62.61 ±14.23
BMI (kg/m^2)	CG	22.35 ±3.94	22.37 ±4.07
	OG	27.47[a] ±2.51	24.70* ±3.24
	TG	23.72 ±4.47	24.07 ±4.52
Body fat (%)	CG	16.56 ±6.96	16.84 ±7.18
	OG	31.77[a] ±5.19	25.52*,[a] ±5.52
	TG	28.20[c] ±4.77	27.18[c] ±7.73
VO_{2max} ($mL\ kg^{-1}\ min^{-1}$)	CG	33.28 ±3.76	33.97 ±3.44
	OG	29.20 ±5.45	33.91* ±4.60
	TG	28.60 ±4.88	32.86* ±4.56

Means ±SD. CG, Control group; OG, Obesity group; TG, T2DM group
*, Significant difference ($p<0.05$) between baseline and 12 weeks
a, Significant difference ($p<0.05$) CG vs. OG; b, Significant difference OG vs. TG; c, Significant difference CG vs. TG

Serum BDNF levels were analyzed with an R & D system (Minneapolis, Minn., USA) kit and serum TrkB levels were analyzed with a Sino Biological kit (Sino Biological Inc, Beijing, China). First, the antibody was incubated overnight and washed 3 times. Next, the samples and the standard were reacted with the detection antibody. Then, substrate solution and streptavidin-HRP were added, the reaction was terminated with a stop solution, and the results obtained by measuring the optical density at 450 nm.

Serum CRP was analyzed with an automatic analyzer (AdipoGen, Seoul, Korea) using latex cohesion turbidimetry with a CRP(II) X2 latex reagent.

For all data, the mean and standard deviation were calculated using SPSS for Windows ver. 14.0 (SPSS, Chicago, IL, USA). Repeated measures two-way ANOVA was used to control for differences between groups, test periods, physical characteristics, and biochemical blood component changes caused by exercise, using Scheffe's method for the post hoc test. Statistical significance was accepted for value of $\alpha \leq 0.05$.

RESULTS

Subjects' physical characteristics were recorded at baseline and after the 12 weeks of regular aerobic exercise. The results are presented in Table 1. There were no significant differences in weight among the groups, but there was a difference between the test periods. There was an interaction effect between group and time ($F = 12.779$, $p<0.05$), and further analysis of the interaction effect revealed a significant weight reduction ($p<0.05$) in the OG after the 12 weeks of regular exercise.

There were no significant differences in BMI among the groups, but there was a significant difference between the test periods ($F = 8.011$, $p<0.05$). There was an interaction effect between group and time ($F = 12.685$, $p<0.05$), and further analysis of the interaction effect revealed a significant BMI reduction ($p<0.05$) in the OG after the 12 weeks of regular exercise.

There were significant differences in body fat percentage among the groups ($F = 10.726$, $p<0.05$) and test periods ($F = 16.820$, $p<0.05$). There was an interaction effect between group and time ($F = 12.898$, $p<0.05$), and further analysis of the interaction effect revealed a significant body fat percentage reduction ($p<0.05$) in the OG after the 12 weeks of regular exercise.

There were no significant differences in the VO_{2max} among groups, but the VO_{2max} between the test periods differed significantly ($F = 19.348$, $p<0.05$). There was an interaction effect between group and time ($F = 3.441$, $p<0.05$), and further analysis revealed a significant VO_{2max} increase ($p<0.05$) in the OG and TG after the 12 weeks of regular exercise.

The serum BDNF, NGF, and TrkB levels were recorded at baseline and after the 12 weeks of regular aerobic exercise. The results are presented in Table 2. There was a significant difference in BDNF levels among the groups ($F = 13.673$, $p<0.05$) and test periods ($F = 6.338$, $p<0.05$). There was an interaction effect between group and test period, and further analysis of the interaction effect revealed a significant BDNF increase ($p<0.05$) in the OG after the 12 weeks of regular exercise.

There were no significant difference in NGF levels among the groups or test periods, and there was no interaction effect between group and test period.

There was a significant difference in TrkB levels among the groups ($F = 6.400$, $p<0.05$), but there was no interaction effect between group and test period.

The 12 weeks regular aerobic exercise resulted in little changes in the inflammatory factors (serum IL-6, TNF-α, CRP). The results are presented in Table 2. There were no significant differences or interaction effects of IL-6, TNF-α, and CRP among groups, or between test periods, or

Table 2. Changes of the serum neurotrophic factors and inflammatory factors following 12 weeks of aerobic exercise training.

Variable	Group	Baseline	12-week
BDNF (pg/ml)	CG	21,178.33 ±4,306.14	20,670.40 ±5,021.47
	OG	8,003.79[a] ±6,559.10	19,617.53* ±8,098.60
	TG	25,136.14[b] ±3,814.16	25,104.58 ±5,389.95
NGF (pg/ml)	CG	5.14 ±2.35	6.21 ±1.78
	OG	8.83 ±8.66	30.55 ±44.04
	TG	5.58 ±3.33	7.80 ±8.86
TrkB (pg/ml)	CG	182.71 ±32.07	187.11 ±65.44
	OG	123.20[a] ±50.80	146.77 ±29.98
	TG	112.02[c] ±40.30	143.85 ±56.52
IL-6 (pg/ml)	CG	1.42 ±2.85	1.47 ±2.84
	OG	0.90 ±0.42	1.52 ±1.42
	TG	0.92 ±0.72	0.61 ±0.40
TNF-α (pg/ml)	CG	3.35 ±1.74	8.12 ±13.33
	OG	4.27 ±1.73	3.71 ±1.89
	TG	3.18 ±1.77	2.93 ±0.84
CRP (mg/dl)	CG	0.10 ±0.06	0.22 ±0.45
	OG	0.15 ±0.13	0.13 ±0.19
	TG	0.06 ±0.05	0.08 ±0.09

Means ±SD. CG, Control group; OG, Obesity group; TG, T2DM group
*, Significant difference ($p<0.05$) between baseline and 12 weeks
a, Significant difference ($p<0.05$) CG vs. OG; b, Significant difference OG vs. TG; c, Significant difference CG vs. TG

group and test period.

DISCUSSION

We aimed to test whether 12 weeks of regular aerobic exercise would have a positive effect on neurotrophic and inflammatory factors.

As described earlier, BDNF is mainly responsible for nerve survival, growth, maintenance, learning, and memory. Patients with Alzheimer's disease exhibit low levels of BDNF expression in the hippocampus[19] and low serum BDNF[20]. Similarly, patients with Parkinson's disease and Huntington's disease have low levels of hippocampal BDNF[21], and patients with depression have low levels of serum BDNF[22]. This experiment revealed that the resting BDNF level at baseline before the 12 weeks of aerobic exercise was significantly lower ($p<0.05$) in the OG than in the CG. This result is in agreement with previous research[5], which has reported low levels of BDNF among people with obesity and T2DM. It also agrees with the findings of previous research conducted on adults, which revealed that BDNF plays a very important role in controlling energy homeostasis and weight[23, 24], and has an inverse relation with weight and age[25].

It is also was interesting to note that the TG and CG had similar resting BDNF levels, i.e., the resting BDNF levels of the TG teenagers of normal weight were not greatly depressed. This raises the question as to whether the resting BDNF levels of juveniles with T2DM have a greater effect on body composition, such as weight, than the disease itself.

Another interesting point is that after 12 weeks of regular aerobic exercise, the resting BDNF level of the OG increased to 19,617 pg/mL, a level close to the adult normal range of 22,600 pg/mL[25]. This was a significant increase ($p<0.05$) and it was only observed in the OG (Table 2). We suggest that there was no significant increase in the resting BDNF level after the 12 weeks of exercise in the TG, because the exercise did not result in significant changes in body composition (weight, BMI, body fat percentage).

TrkB is a BDNF receptor that is expressed abundantly and widely in the brain[26], and NGF plays an important role in the sustenance of sympathetic and sensory neurons as well as biological activities, including cell growth[27]. Schulz et al.[13] studied the effects of 8 weeks of aerobic ergometry exercise on patients with multiple sclerosis (MS), and reported no significant difference in the NGF level of the exercise group. Bansi et al.[28] conducted 3 weeks of regular exercise (aquatic vs. overland) for middle-aged patients with multiple sclerosis and also failed to significantly alter resting NGF levels. While our present findings did not reveal a significant difference in resting NGF levels in the OG, compared to the CG and TG, we did note an increase. A previous study of 146 adults[29], also reported the NGF levels of obese subjects were higher than those of normal weight subjects. Although TrkB levels increased in the OG and TG following the 12 weeks of aerobic exercise, there was no significant difference between the two groups. However, comparison of the resting TrkB levels of the CG with OG and TG at baseline revealed that OG and TG had significantly lower resting TrkB levels than CG, and we consider this proof of them having decreased BDNF receptor levels, as TrkB is a BDNF receptor (Table 2).

One of the limitations of this experiment was that while there have been many studies of neurotrophic factor BDNF, few human studies of NGF and TrkB have been conducted. This renders comparative analysis difficult, and much more research concerning NGF and TrkB levels will need to be conducted in the future.

High levels of inflammatory cytokines are observed in

patients with obesity, T2DM, and MS, and such high levels of inflammatory factors are an independent factor in the development of CVD[7]. Additionally, arteriosclerosis and coronary artery disease are associated with increased levels of IL-6, CRP, and TNF-α[30, 31], and higher IL-6 and CRP have been observed in metabolic disabilities such as T2DM, MS, and obesity[31, 32].

IL-6, a typical inflammatory factor, is a multifunctional cytokine responsible for pleiotropism in immunomodulation[33], and was recently reported to be a myokine, involved in energy metabolism in skeletal muscle[34]. CRP also serves as an indicator of systemic inflammatory response. An increased CRP level in obese patients is explained by IL-6 originating from adipose tissue, and CRP levels are significantly decreased by aerobic exercise and diet[35]. Christiansen et al.[7] conducted a study of men and women engaged in aerobic exercise lasting 60–75 minutes per session, 3 sessions a week for 12 weeks. They noted that there were no significant reductions in IL-6, IL-15, IL-18, or MCP-1 without dieting or significant reductions in weight. Kohut et al.[36] studied patients with metabolic disease who showed no reduction in weight over the course of 10 months by comparing a group that did aerobic exercise for 45 minutes per session, 3 sessions a week, with a resistance/flexibility training group. They found that the aerobic exercise group showed significant reductions in CRP, L-6, and IL-18. Additionally, a study of middle-aged men and women performing endurance exercise, consisting of one 60-minute training session per week for 12 months, reported a significant decrease in serum CRP levels following a reduction in BMI[14].

To date, reducing circulating inflammatory factors has been proposed to be associated with weight reduction[37] and adipose tissue reduction[36, 38, 39], but our 12 weeks of exercise failed to result in a significant reduction in inflammatory factors (especially IL-6) in the OG, despite a significant reduction in weight, body fat percentage, and BMI. We believe that, compared to the 10–12-month study periods of other experiments[14, 36] that saw reductions in IL-6 through regular training, the exercise period of this study was too short to reduce resting IL-6 levels. Another interesting point is that this study recorded very low levels of IL-6 (0.9–1.4 pg/mL) compared to the average resting IL-6 level (3.4–5.0 pg/mL) reported by previous studies of adults (healthy people in their 30s and middle-aged patients with T2DM) and the elderly over 64 years of age[7, 14, 36, 40]. As the immune and inflammatory systems progressively change with age[41], perhaps the subjects' youth may have been a factor influencing their lower IL-6 levels, despite their obesity and T2DM. The resting IL-6 levels of the teenagers were also close to the 1.1–1.6 pg/mL of young adults aged between 20 and 30 years with simple obesity[42].

Previous research related to exercise has reported significant reductions in inflammatory factors (IL-6, TNF-α, hs-CRP) following long-term training lasting 10–12 months[14, 36] rather than a 12-week period[42, 43]. The only exception was an 8-week aerobic training and diet restriction study of a group of children with obesity. That study reported a significant reduction in inflammatory markers (IL-6, TNF-α, hs-CRP), and it argued that the significant changes in body composition (body weight, BMI, body fat percentage), induced by exercise and diet restriction, had a strong effect on the inflammatory factors[44].

We also observed slight changes in TNF-α and CRP levels after the 12 weeks of aerobic exercise, but did not find significant differences, in agreement with previous studies[40, 42, 43]. Taken together, our present results and those of other studies[40, 45] indicate that exercise has limited or no effect on inflammatory markers.

While many studies of exercise effects have been conducted using adults and the elderly, comparisons with our results were limited by the lack of researches involving juveniles between the ages of 13 and 17 years, and differences in training period, exercise intensity, exercise frequency, and sample size used in the other studies of BDNF and inflammatory markers.

The juveniles with obesity and T2DM exhibited reduced levels of resting neurotrophic factors (BDNF, TrkB) at baseline, but after the 12 weeks aerobic exercise, there was a significant increase in the BDNF level of the OG. However, these findings are limited, and the effects of regular exercise on neurotrophic factors and inflammatory factors in juvenile obesity and T2DM were not conclusively proven. Future research will need to focus on related areas of research.

ACKNOWLEDGEMENT

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (NRF-2011-332-1-G00080).

REFERENCES

1) Reilly JJ, Methven E, McDowell ZC, et al.: Health consequences of obesity. Arch Dis Child, 2003, 88: 748–752. [Medline] [CrossRef]
2) Luchsinger JA: Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention? J Alzheimers Dis, 2010, 20: 723–736. [Medline]
3) Manschot SM, Biessels GJ, de Valk H, et al. Utrecht Diabetic Encephalopathy Study Group: Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. Diabetologia, 2007, 50: 2388–2397. [Medline] [CrossRef]
4) Tapia-Arancibia L, Aliaga E, Silhol M, et al.: New insights into brain BDNF function in normal aging and Alzheimer disease. Brain Res Brain Res Rev, 2008, 59: 201–220. [Medline] [CrossRef]
5) Krabbe KS, Nielsen AR, Krogh-Madsen R, et al.: Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. Diabetologia, 2007, 50: 431–438. [Medline] [CrossRef]
6) Matthews VB, Aström MB, Chan MH, et al.: Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia, 2009, 52: 1409–1418. [Medline] [CrossRef]
7) Christiansen T, Paulsen SK, Bruun JM, et al.: Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. Am J Physiol Endocrinol Metab, 2010, 298: E824–E831. [Medline] [CrossRef]
8) Baker LD, Frank LL, Foster-Schubert K, et al.: Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol, 2010, 67: 71–79. [Medline] [CrossRef]
9) Seifert T, Brassard P, Wissenberg M, et al.: Endurance training enhances BDNF release from the human brain. Am J Physiol Regul Integr Comp Physiol, 2010, 298: R372–R377. [Medline] [CrossRef]
10) Zoladz JA, Pilc A, Majerczak J, et al.: Endurance training increases plasma brain-derived neurotrophic factor concentration in young healthy men. J Physiol Pharmacol, 2008, 59: 119–132. [Medline]

11) Schiffer T, Schulte S, Hollmann W, et al.: Effects of strength and endurance training on brain-derived neurotrophic factor and insulin-like growth factor 1 in humans. Horm Metab Res, 2009, 41: 250–254. [Medline] [CrossRef]
12) Castellano V, White LJ: Serum brain-derived neurotrophic factor response to aerobic exercise in multiple sclerosis. J Neurol Sci, 2008, 269: 85–91. [Medline] [CrossRef]
13) Schulz KH, Gold SM, Witte J, et al.: Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. J Neurol Sci, 2004, 225: 11–18. [Medline] [CrossRef]
14) Oberbach A, Lehmann S, Kirsch K, et al.: Long-term exercise training decreases interleukin-6 (IL-6) serum levels in subjects with impaired glucose tolerance: effect of the -174G/C variant in IL-6 gene. Eur J Endocrinol, 2008, 159: 129–136. [Medline] [CrossRef]
15) Kasapis C, Thompson PD: The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol, 2005, 45: 1563–1569. [Medline] [CrossRef]
16) Kim JK, Shin YH, Moon HW, et al.: Effect of combined aerobic and resistance exercise on plasma C-reactive protein, interleukin-6, lipids and insulin resistance in obese adolescent. Kor J Spo Sci, 2007, 18: 1–9.
17) Bruce RA, Kusumi F, Hosmer D: Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J, 1973, 85: 546–562. [Medline] [CrossRef]
18) Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc, 1982, 14: 377–381. [Medline] [CrossRef]
19) Connor B, Young D, Yan Q, et al.: Brain-derived neurotrophic factor is reduced in Alzheimer's disease. Brain Res Mol Brain Res, 1997, 49: 71–81. [Medline] [CrossRef]
20) Laske C, Stransky E, Leyhe T, et al.: Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm, 2006, 113: 1217–1224. [Medline] [CrossRef]
21) Zuccato C, Cattaneo E: Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol, 2009, 5: 311–322. [Medline] [CrossRef]
22) Karege F, Perret G, Bondolfi G, et al.: Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res, 2002, 109: 143–148. [Medline] [CrossRef]
23) Rosas-Vargas H, Martínez-Ezquerro JD, Bienvenu T: Brain-derived neurotrophic factor, food intake regulation, and obesity. Arch Med Res, 2011, 42: 482–494. [Medline] [CrossRef]
24) Zhang XY, Tan YL, Zhou DF, et al.: Serum BDNF levels and weight gain in schizophrenic patients on long-term treatment with antipsychotics. J Psychiatr Res, 2007, 41: 997–1004. [Medline] [CrossRef]
25) Lommatzsch M, Zingler D, Schuhbaeck K, et al.: The impact of age, weight and gender on BDNF levels in human platelets and plasma. Neurobiol Aging, 2005, 26: 115–123. [Medline] [CrossRef]
26) Huang EJ, Reichardt LF: Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci, 2001, 24: 677–736. [Medline] [CrossRef]
27) Steers WD, Tuttle JB: Mechanisms of disease: the role of nerve growth factor in the pathophysiology of bladder disorders. Nat Clin Pract Urol, 2006, 3: 101–110. [Medline] [CrossRef]
28) Bansi J, Bloch W, Gamper U, et al.: Training in MS: influence of two different endurance training protocols (aquatic versus overland) on cytokine and neurotrophin concentrations during three week randomized controlled trial. Mult Scler, 2013, 19: 613–621. [Medline] [CrossRef]
29) Bulló M, Peeraully MR, Trayhurn P, et al.: Circulating nerve growth factor levels in relation to obesity and the metabolic syndrome in women. Eur J Endocrinol, 2007, 157: 303–310. [Medline] [CrossRef]
30) Larsson PT, Hallerstam S, Rosfors S, et al.: Circulating markers of inflammation are related to carotid artery atherosclerosis. Int Angiol, 2005, 24: 43–51. [Medline]
31) Ridker PM, Buring JE, Cook NR, et al.: C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation, 2003, 107: 391–397. [Medline] [CrossRef]
32) Pradhan AD, Manson JE, Rifai N, et al.: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA, 2001, 286: 327–334. [Medline] [CrossRef]
33) Starkweather AR: The effects of exercise on perceived stress and IL-6 levels among older adults. Biol Res Nurs, 2007, 8: 186–194. [Medline] [CrossRef]
34) Pedersen BK, Febbraio M: Muscle-derived interleukin-6—a possible link between skeletal muscle, adipose tissue, liver, and brain. Brain Behav Immun, 2005, 19: 371–376. [Medline] [CrossRef]
35) Jae SY, Fernhall B, Heffernan KS, et al.: Effects of lifestyle modifications on C-reactive protein: contribution of weight loss and improved aerobic capacity. Metabolism, 2006, 55: 825–831. [Medline] [CrossRef]
36) Kohut ML, McCann DA, Russell DW, et al.: Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. Brain Behav Immun, 2006, 20: 201–209. [Medline] [CrossRef]
37) Goldhammer E, Tanchilevitch A, Maor I, et al.: Exercise training modulates cytokines activity in coronary heart disease patients. Int J Cardiol, 2005, 100: 93–99. [Medline] [CrossRef]
38) Cancello R, Henegar C, Viguerie N, et al.: Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. Diabetes, 2005, 54: 2277–2286. [Medline] [CrossRef]
39) Clément K, Viguerie N, Poitou C, et al.: Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. FASEB J, 2004, 18: 1657–1669. [Medline] [CrossRef]
40) Byrkjeland R, Nilsson BB, Westheim AS, et al.: Inflammatory markers as related to disease severity in patients with chronic heart failure: limited effects of exercise training. Scand J Clin Lab Invest, 2011, 71: 598–605. [Medline] [CrossRef]
41) Aw D, Silva AB, Palmer DB: Immunosenescence: emerging challenges for an ageing population. Immunology, 2007, 120: 435–446. [Medline] [CrossRef]
42) Carrillo AE, Flynn MG, Pinkston C, et al.: Vitamin D supplementation during exercise training does not alter inflammatory biomarkers in overweight and obese subjects. Eur J Appl Physiol, 2012, 112: 3045–3052. [Medline] [CrossRef]
43) Stensvold D, Slørdahl SA, Wisløff U: Effect of exercise training on inflammation status among people with metabolic syndrome. Metab Syndr Relat Disord, 2012, 10: 267–272. [Medline] [CrossRef]
44) Ben Ounis O, Elloumi M, Zouhal H, et al.: Effect of individualized exercise training combined with diet restriction on inflammatory markers and IGF-1/IGFBP-3 in obese children. Ann Nutr Metab, 2010, 56: 260–266. [Medline] [CrossRef]
45) Pedersen BK, Febbraio MA: Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev, 2008, 88: 1379–1406. [Medline] [CrossRef]