

Effect of Exercise Training for the Chronic Hemodialysis Patients

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The present study was conducted to investigate the effect of exercise training on the glucose level in hemodialysis (HD) patients. Sixteen HD patients aged 60.8±9.5 years old participated in this study. They were asked to engage in 30 minutes of exercise training three times a week on the non-hemodialysis days for three months. Both the physical fitness and the serum creatinine levels increased significantly after the exercise training in comparison to the levels at baseline. The degree of the change in the blood glucose level was negatively associated with the degree of change in the serum BDNF level ($r=-0.59$, $p<0.05$). The results of the present study suggest that home-based exercise training may improve the physical fitness as well as increasing the muscle mass in HD patients. However, further studies are needed to explain the role of BDNF, which was suggested to play a role in glucose metabolism in our study.

Key words: hemodialysis, exercise training, brain-derived neurotrophic factor, glucose metabolism.

INTRODUCTION

Chronic hemodialysis patients (HD patients) show insulin-resistance, which increases their glucose and triglyceride (TG) levels [1]. HD patients sometimes suffer from depression [2-5]. The improvements in HD treatment in Japan have given Japanese HD patients the highest survival rate in the world [6]. However, as the survival rate has

increased, the number of HD patients who receive HD therapy for a long duration of time has increased in Japan. Patients with long-term HD treatment are likely to suffer from cardiovascular and bone diseases [7, 8], which may cause physical inactivity [9, 10].

Prolonged physical inactivity diminishes physical strength and increases the risk of osteoporosis [7, 8], and also decreases the activities of daily living (ADL) and the quality of the life (QOL) in HD patients. Several investigators have reported that exercise may improve physical strength [11, 12], glucose metabolism [12-15] and depression [11] in HD patients.

Many studies have revealed that reduced levels of brain-derived neurotrophic factor (BDNF) in the brain and the blood may be involved in the pathogenesis of mental disorders, including depression [16-19] and Alzheimer's disease [20, 21]. Furthermore, BDNF can cross the blood-brain barrier in both directions [22], and brain tissue is the main contributor to circulating BDNF [23]. Moreover, Karege et al. [24] showed that serum BDNF in rats correlated positively with cortical BDNF levels.

More recent studies have noted that BDNF may also be a mediator of glucose and lipid metabolism [25-29]. Moreover, some studies suggested that acute and regular exercise increased the serum BDNF levels [30, 31]. Although the role of BDNF in the pathogenesis of these mental disorders is still undefined, our previous study revealed that the serum BDNF level was lower in HD patients in the healthy group, thus suggesting that BDNF may play a role in the hyperglycemia and mental disorders in HD patients [32]. However, there have been few studies that have examined the serum BDNF levels

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in HD patients.

The present study was conducted to investigate the changes in glucose, lipids, BDNF levels, physical fitness and mental health after exercise training, and to verify the associations between the serum BDNF level and the glucose changes before and after exercise training, in HD patients.

MATERIALS AND METHODS

Subjects

Chronic HD patients, who were undergoing dialysis in a private dialysis clinic on the outskirts of Fukuoka City in August, 2008 were asked to participate in this study. The patients with psychiatric disorders under treatment, those with infectious diseases, and those with acute complications of HD treatment were excluded. The other exclusion criteria included severe cognitive impairment, depression requiring major tranquilizers, poor activities of daily living (ADL), and who had been undergoing HD for fewer than six months. Twenty-one patients participated in this study. Among them, sixteen patients completed the questionnaires and biochemical tests. This study collected data from the 1st of August to the 31st of December 2009.

All enrolled participants gave their informed consent after receiving enough information about the experimental procedures before giving their written informed consent. This study was approved by the Ethics Committees of St. Mary's College, and was monitored by the Institutional Review Committee.

Measurement of body mass index, blood tests, and serum BDNF levels

The body mass index (BMI) was calculated as the subject's dry weight in kilograms divided by the square of their height in meters. The blood tests included the serum chemistry, blood glucose, and hemoglobin A1C (HbA1c), blood urea nitrogen (BUN) and creatinine (Cr) levels, which were examined in the laboratory of SRL (Tokyo, Japan). The serum samples were frozen and stored below -50°C in a freezer, and the serum BDNF level was measured using the BDNF Emax Immunoassay System kit (Promega, Madison, WI) after three months of exercise training.

Assessments of mental health and physical fitness

The mental health status was assessed by the General Health Questionnaire (GHQ). The GHQ comes in several versions; for this study, the 30-item version of the Japanese GHQ (GHQ-30) was applied, where subjects are asked to compare their perceived state of health with four standard answers to the questionnaire. Scores were obtained according to the GHQ scoring method (0-0-1-1), which allows factor-scoring within the six subscales of the GHQ-30. These factors are identified as Factor A (General Illness), Factor B (Somatic Symptoms), Factor C (Sleep Disturbance), Factor D (Social Dysfunction), Factor E (Anxiety and Dysphoria), and Factor F (Suicidal Depression) [33, 34]. The optimum cutoff point (the best compromise between high sensitivity and a low false-positive rate) was 6/7, based on the receiver operating characteristic curves [33, 34]. If the subject had a total score of 7 or above on the GHQ-30, he or she was included in the psychiatric distress group, whereas subjects with a total score under 7 were included in the non-psychiatric distress group.

Physical fitness was assessed based on the knee extension strength (where the subject was seated, then extended the knee against the resistance provided by the examiner), grip strength (measured using hand dynamometers), the sit and reach test for flexibility (bending forward as far possible.), the chair raise test (ability to stand for one minute), stepping speed to assess agility (using measuring instrument (T. K. K. 5301) for 10 seconds and the one leg stance (measuring how long a subject was able to stand on one leg) [35, 36].

Intervention for the exercise training

The intervention for the physical fitness of the HD patients included 30 minutes of exercise resistance training three times a week on the non-hemodialysis days, and home-based exercise was performed for a three month period from September to December 2008. All parameters were measured before and after the home-based exercise training.

Statistical analyses

The data were expressed as the means \pm SD or

number (%). Spearman's correlation was used for the statistical assessment. The comparisons between the case group on the GHQ were performed using the analysis of variance and chi square test.

The statistical analyses were performed using the SPSS software program (Statistical Package for Social Sciences, version 18.0, SPSS Inc, Chicago, IL, USA), and statistical significance was defined as $p < 0.05$.

RESULTS

The characteristics of the subjects are shown in Table 1. The HD patients included 10 females and six males, with a mean (\pm SD) age of 60.8 (\pm 9.5) years, and the duration of HD was 10.6 (\pm 9.5) years.

Table 2 shows a comparison between the means of the parameters at baseline and those after the exercise training. The mean BUN and Cr levels after the exercise training were significantly higher than those at baseline ($p < 0.001$). The TG,

glucose, and HbA1c levels, as well as the serum BDNF level, were not significantly different before and after the exercise training period. Furthermore, the rate of psychiatric distress among HD patients at baseline did not differ from the rate at the end of the exercise training period. Over the three month period, the HD patients did not develop any alarming symptoms or secondary complication.

Table 1. Characteristics of the subjects

		n=16	
age(years)		60.8 \pm 9.5	
sex			
male		6 (37.5%)
female		10 (62.5%)
HD duration (years)		10.6 \pm 9.1)	
Cause of end-stage renal disease (ESRD)			
Chronic glomerulonephritis		9 (56.3%)
Diabetic nephropathy		1 (6.3%)
Other renal diseases		4 (25.0%)
Others		1 (6.3%)

Values represented the number (%) of subjects or the mean \pm SD.

Table 2. Comparison between the means on the baseline and those on the after 3 months exercise training in the HD patients

				n=16		
		baseline		after 3 months		p value
BMI	(kg/m ³)	20.2 \pm	2.7	20.3 \pm	2.7	0.23
RBC	(10 ⁴ /mm ³)	349.6 \pm	31.3	340.9 \pm	37.4	0.23
Hb	(g/dL)	11.0 \pm	0.7	10.6 \pm	0.9	0.23
Ht		10.6 \pm	2.7	0.9 \pm	2.7	0.23
total cholesterol	(mg/ml)	151.9 \pm	25.7	154.9 \pm	19.2	0.12
HDL-cholesterol	(mg/ml)	59.1 \pm	29.9	54.8 \pm	21.9	0.43
triglyceride	(mg/ml)	122.1 \pm	69.9	111.9 \pm	78.1	0.20
BG	(mg/ml)	122.3 \pm	49.8	105.8 \pm	19.2	0.12
HbA1c	%	4.9 \pm	0.7	4.8 \pm	0.6	0.20
BUN	(mg/ml)	51.7 \pm	9.8	64.6 \pm	9.9	P<0.001
Cr	(mg/ml)	9.4 \pm	1.4	10.4 \pm	1.5	P<0.001
serum BDNF	(ng/ml)	10.0 \pm	2.9	10.4 \pm	2.7	0.23
serum Adiponectin	(ng/ml)	126.9 \pm	80.0	133.5 \pm	68.5	0.40
psychiatric distress		37.5%		25.0%		0.41

Values represented the number (%) of subjects or the mean \pm SD.

The comparisons between the baseline and the after three months were performed using Wilcoxon-test and chi square test.

Definition of abbreviations; BMI =Body Mass Index, RBC =red blood cell count , Hb = hemoglobin, Plat = platelet count, HDL- cholesterol = high-density lipoprotein- cholesterol, BG = blood glucose, BUN = blood urea nitrogen, Cr = creatinine.

Fig. 1 shows a comparison of the physical fitness between the baseline and after the three months of exercise training. The physical fitness improved after the exercise training period. Moreover, knee extension strength, the grip strength, ability to stand for one minute and length of time subjects could stand on one leg were significantly improved after the exercise training period compared to the baseline.

Fig. 2 shows the association between the changes in the glucose level and the changes in the BDNF level. The change in the glucose level from the beginning of the study to the end of the exercise training period was negatively associated with the change in the serum BDNF level after exercise training ($r=-0.59$, $p<0.05$). Moreover, the change in the Cr level was positively associated with the serum BDNF level after exercise training, but the association was not significant ($r=0.43$, $p=0.098$). There was no meaningful correlation between the serum BDNF level and any of the other parameters, including the HbA1c and TG level ($r=-0.40$, $p=0.13$, $r=-0.05$, $p=0.87$).

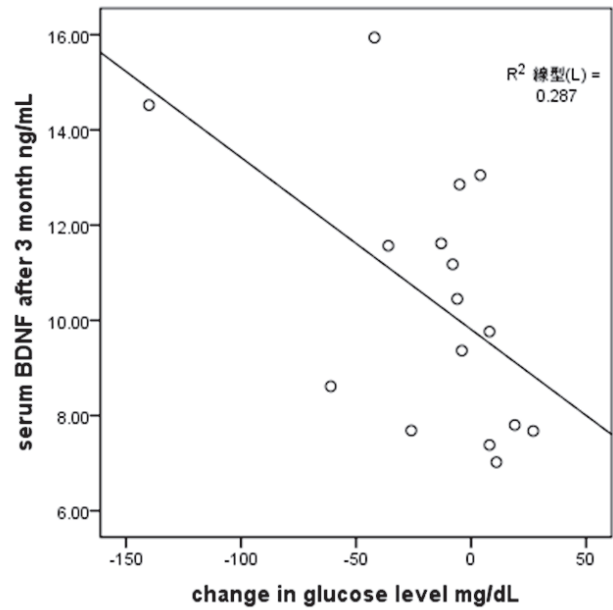


Fig. 2. Correlation serum BDNF after exercise training and change in glucose level

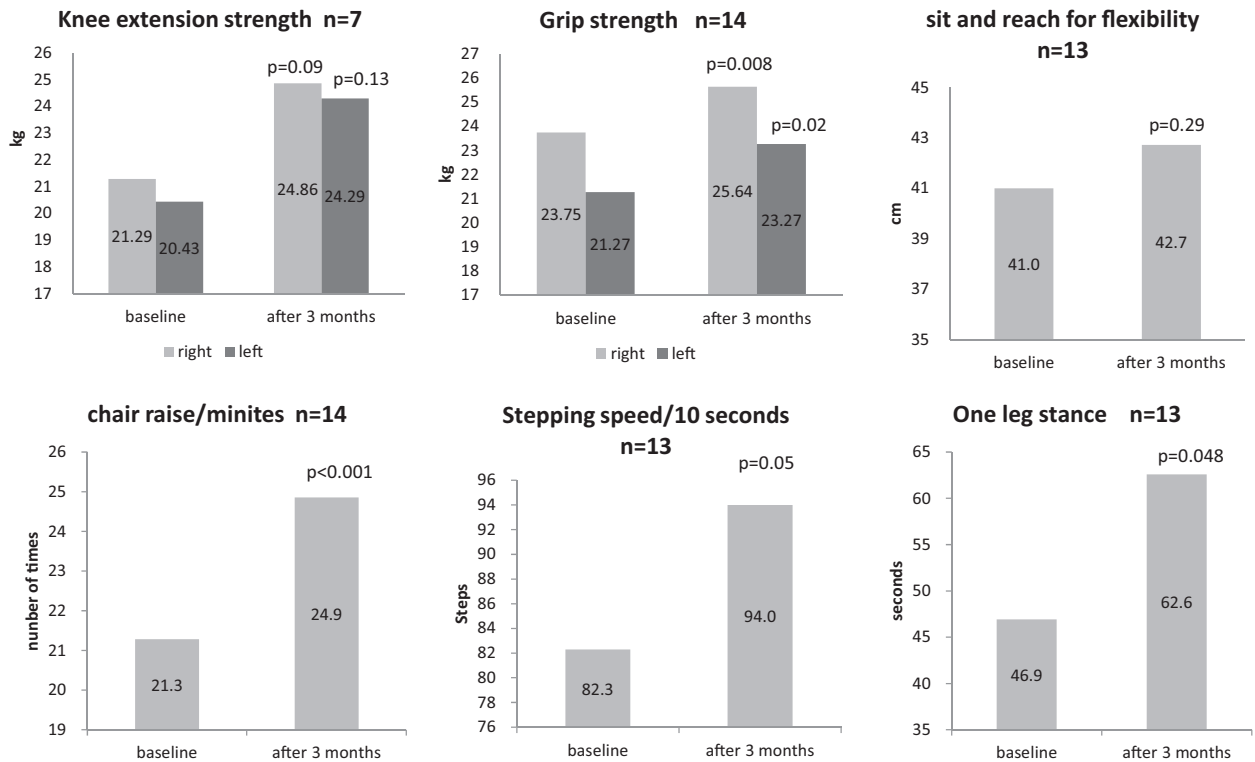


Fig. 1. Comparison between the means of physical strength and fitness on the baseline and those on the after 3 months exercise training

DISCUSSION

BDNF is a member of the neurotrophin family, which is widely distributed throughout the cerebral cortex. More specifically, it is a protein which acts on certain neurons, supporting the survival of existing neurons and encouraging the growth and differentiation of new neurons and synapses [37, 38]. In the brain, it is active in the hippocampus, cortex, and basal forebrain areas vital to memory and learning [39-41].

BDNF is produced by neurons, particularly in the hippocampus and cortex. However, recent studies have demonstrated that BDNF is also produced in inflamed tissues in disease states such as allergic bronchial asthma and multiple sclerosis [42, 43]. Furthermore, several studies have demonstrated that BDNF is released from cells such as T-cells and monocytes [42, 44]. These data suggest that activated macrophages represent a major source of BDNF in inflamed tissues. A more recent study reported that skeletal muscle cells secreted BDNF [45]. Moreover, the serum BDNF level in rats was shown to be positively correlated with the cortical BDNF levels ($r=0.81$, $p<0.01$) [24].

BDNF has been suggested to play a role in the development of mental disorders [16-21]. On the other hand, the serum BDNF level in patients with severe metabolic syndrome was reported to be lower than that in the healthy group [27]. In contrast, another study showed that patients with early diabetes had higher serum BDNF levels than those without diabetes mellitus, and that the serum BDNF level was positively correlated with the body mass index (BMI), the fasting blood glucose (FBG) level, total cholesterol (TC), and insulin resistance [28]. These findings suggest that BDNF may be involved in glucose metabolism, as well as with the insulin level, in patients with diabetes mellitus. In our previous study, there was a negative association between the GHQ-30 score and the serum BDNF level [32]. These findings suggest that there is a negative association between the mental health status and the serum BDNF level, which may be related to the risk factors for atherosclerosis, including insulin resistance.

However, in the present study, exercise failed

to reduce the rate of psychiatric distress among HD patients, although the present study included a small number of participants, which may explain this result. Since exercise is reported to improve the mental health status [11], an additional study with a larger sample size should be performed to fully elucidate the role of BDNF on the improvement of mental disorders as a result of exercise.

In the present study, after three months of exercise training, there were decreases in the TG, glucose, and HbA1c levels, and an increase in the BDNF level, although the changes in these parameters were not statistically different. In addition, the degree of the change in the blood glucose level was negatively associated with the BDNF level after exercise training ($r=-0.59$, $p<0.05$), but the degree of the change in the blood HbA1c and TG levels was not significant.

On the other hand, in our previous study, the serum BDNF level was lower in HD patients in the control group (12.43 ± 5.44 vs. 26.22 ± 5.42 ng/mL, $p<0.001$), thus suggesting that BDNF may play a role in the development of hyperglycemia [25-29]. Krabbe et al.'s [29] study indicated that BDNF plays a role in glucose metabolism and also suggests that neurotrophins such as BDNF may play pathogenetic roles in type 2 diabetes, potentially explaining the clustering of these diagnoses. Moreover, it suggested that the negative correlation between high plasma glucose and the severity of insulin resistance on the one hand and circulating BDNF levels, and that the cerebral output of BDNF which released from the human brain is negatively regulated by high plasma glucose levels [29]. These findings suggest that exercise improves insulin resistance in HD patients, which increases the BDNF level in these patients.

In addition, the results of the present study showed that the Cr levels (a surrogate marker of the muscle mass) significantly increased after the exercise training. Moreover, we observed that the change in the Cr level was positively associated with the serum BDNF level after exercise training, but that the association was not significant ($r=-0.43$, $p=0.098$). The result suggests that exercise may increase the muscle mass but not the overall body weight, suggesting that exercise may decrease the

somatic fat. It is generally assumed that increased muscle strength may contribute to improved physical fitness, and result in increased muscle cells. Cr is synthesized from creatinine phosphate or dehydrated creatine in the muscle and nerve cells, so elevated levels might suggest an increased number of such cells. Alternatively, increased serum Cr levels may result from the deterioration of the renal function. However, increased muscle mass rather than a deterioration of the residual renal function of the subject was considered to be the cause of the elevated serum Cr level in this study. This is because the change in the Cr level tended to be positively associated with the serum BDNF level after exercise training, and all patients had undergone hemodialysis for a long period of time (i. e., 10.6±9.5years), and all of them showed anuria.

It is well known that acute and regular exercise leads to improved glucose metabolism. Insulin and exercise are the two most physiologically relevant stimulators of skeletal muscle glucose transport [46]. Importantly, the insulin-independent mechanisms, including exercise-related mechanisms, of the regulating glucose uptake remain intact in patients with DM. Both insulin and exercise increase the skeletal muscle glucose uptake by translocating the glucose transport from an intracellular location to the plasma membrane and t-tubules [46]. Glucose transport 4 (GLUT4) is the predominant glucose transporter isoform expressed in skeletal muscle [46]. The involvement of AMP-activated Protein Kinase (AMPK) in the AMP-analog, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) or exercise stimulated increases in the GLUT4 protein levels currently remain controversial [46]. The chronic adaptations to exercise training include an increase of mitochondria and thus the oxidative capacity of the skeletal muscle, the transformation of muscle fiber types, and an increase in GLUT4 protein expression [46].

However, Sixt *et al.*'s [47] study of patients with diabetes mellitus type 2 and coronary artery disease (i. e., severe metabolic syndrome) suggested that the plasma insulin levels showed a significant decrease and the mRNA expression of Glut4 was significantly increased after four weeks and six months. In contrast the FBG and HbA1c sig-

nificantly decreased after four weeks, and returned to baseline levels after six months. That study discussed that the home-based exercise training may have decreased in intensity for the subjects over the extended period of time. Moreover, the TG was not significantly changed after either four weeks or six months [47].

By the same token, the results of our present study, which showed a decrease in the glucose and HbA1c levels after three months of exercise training were not statistically significant. Moreover, the exercise training in patients with severe metabolic syndrome could not change the TG level in the blood. Hence, Sixt *et al.*'s [47] study showed that the plasma insulin levels and mRNA expression of Glut4 remained significantly different after six months, thus suggesting that they return to the baseline level for another reason.

Some recent studies have suggested that acute and regular exercise increase the BDNF levels in humans [30, 31]. Furthermore, the study by Matthews *et al.* [45] reported that the BDNF mRNA and protein expression were increased in human skeletal muscle after exercise, but that muscle-derived BDNF did not appear to be released into the circulation. The BDNF mRNA and protein expression were previously shown to be increased in muscle cells that were electrically stimulated [45]. BDNF increases the phosphorylation of AMPK and acetyl coenzyme A carboxylase beta (ACCbeta) and enhances fatty acid oxidation (FAO), both *in vitro and ex vivo* [45]. Therefore, BDNF was suggested to be related to glucose metabolism, which might therefore affect the serum BDNF levels, completing an auto-regulatory cycle [25-29]. Interestingly, a recent study demonstrated that oral creatine supplementation increases the GLUT4 protein content during subsequent rehabilitation training in healthy subjects [48], and this result may be related to the elevated serum Cr level observed in this study.

However, the relationship between BDNF, GLUT4 and AMPK and the mechanisms underlying these relationships are unknown. Even so, we can conclude from the present study that exercise training lead to improvements in the physical fitness of the subjects, elevated the serum Cr level, and im-

proved the glucose metabolism associated with the serum BDNF levels in the HD patients.

A major limitation of our study was that it included a very limited number of subjects, was not randomized controlled trial (RCT), and was performed for only a short period. Future studies should be conducted to examine RCT, more subjects and for a longer period.

In summary, the results of the present study suggested that the increased BDNF levels after exercise training are associated with increased muscular strength and decreased blood glucose levels.

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