

## Review Article

# Psychosomatic Health and Serum BDNF, Brain-Derived Neurotrophic Factor, in Elderly People

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### Abstract

Developed countries including Japan are higher senior citizen's country and the population of elderly people of over 65 years old occupied almost close to 1/3 of the whole population in the country. To prolong the healthy life expectancy which elderly people can make a life vigorously by themselves without caregiver's help is important for the individual's happiness and reduction of social security costs. We have reported that individuals having thick quadriceps muscle and/or higher BMI show higher serum BDNF levels in a paper of "Relationships between brain-derived neurotrophic factor concentration and parameters for health scores in community-dwelling older adults". Geriatr Gerontol Int 2017 BDNF has properties to enhance neurogenesis and inhibition of neuronal apoptosis in the brain and reported lower serum levels in the Alzheimer's disease and depression. Therefore, to keep higher serum BDNF values protects from Alzheimer's disease and the depression etc. We have reviewed and discussed how can aged people to keep higher serum BDNF levels doing exercise, consuming a nutrient meal and supplements with the evidence.

**Keywords:** Body mass index; Brain-derived neurotrophic factor; Elderly people; % of fat mass; Quadriceps muscle

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### Introduction

Population of elderly people of 65-years and over in Japan is figure of 34,590, 000 at September 2016, and stand up to 27.3% of Japanese total population (Just for reference, 75-years and over is 13.3%), top class aging country among the developed countries [1]. The work force of 65-years and over is 20.1% in total worker in Japan and this rate is top in the world, then it is 17.7% in USA >12.5% in Canada. The average life expectancy of Japanese at 2015 is 86.6 (87.14 in 2016) years old and 80.21 (80.98 in 2016) years old in women and men, respectively. The healthy life expectancy which means a span with health and independently making a life without caregiver's help is 74.21 years old and 71.19 years old in women and men at 2015, respectively. The difference between the average life expectancy and the healthy life expectancy is 12.4 and 9.02 years in women and men, respectively [2]. To expand the healthy life expectancy and to shorten the period receiving caregiver's help links to one's happiness and reduce a cost of social security. To expand of health life expectancy may be kept with a good lifestyle including healthy meal, exercise and positive thinking with reducing stress. In case of meal, vegetables with much of vitamins and high dietary fiber, and meat and fish with high protein content should take much and carbohydrate and fat intake should lessen. Taking foods with much anti-oxidative activity is necessary activating longevity-related genes. Moreover, exercise is important to produce neurotrophic factors and development of skeletal muscles, cardiovascular and respiratory systems as well as energy consume and fat metabolizing. For the vivid daily living, a person had better to make a life with positive thinking and reduced stress. We would like a review concerning to healthy life of elderly people based on our paper of "relationships between serum BDNF values and various health parameters" [3].

### Biology and the role of BDNF

Neurotrophins having activities to promote neuro-survival, maintenance and to protect apoptosis of neurons etc., and is produced by neurons. Among the neurotrophins, BDNF is present most abundantly and various regions in the brain [4]. BDNF has various activities, i.e. neurogenesis, neuro-survival, growth of axons and dendrite and synaptogenesis. BDNF is processed from precursor-BDNF (pro-BDNF) synthesized by activation of CREB through various neurotransmitter signals [5]. The BDNF is processed from pro-BDNF intracellularly and extracellularly [6,7]. The pro-BDNF has opposing action of BDNF i.e., induce neuronal apoptosis [7] and hippocampal long-term depression [8]. The BDNF paths through blood brain barrier from both sides [9,10]. It is known that the serum BDNF contents are low at depressed patients and Alzheimer's disease when compared with healthy people and are restored by the medication [11-13]. The BDNF contents elevated in the brain of rats housed in enriched environment which provide tunnels, platforms, balls, ladders and toys, and housing with several rats for social stimulation [14]. The gender difference of serum BDNF levels is controversial. Komulainen et al., reported [15] higher serum BDNF level in women among 57-79 year-old elderly people, while Murawska-Cialowicz et al., [16] that is higher in men

at 20-30 young adults. We observed no difference between the sex i.e.,  $9.52 \pm 4.38$  ng/ml ( $n=304$ ) in male and  $9.33 \pm 3.80$  ng/ml ( $n=501$ ) in female, respectively [3]. BDNF is considered to be expressed in the central nervous system at initial period of discovery, while it is also found the expression in the muscle, especially in satellite cells [17]. Expression of BDNF is enhanced by the exercise and excreted to extracellularly. Especially, satellite cells located around the skeletal muscle express BDNF and regenerate skeletal muscle by differentiating the satellite cells itself [17]. Moreover, BDNF enhance glucose uptake into skeletal muscles and contributes energy metabolism [18]. Therefore, BDNF takes a role to promote mental health and physical health through central nervous systems and peripheral muscles activity, respectively.

BDNF level is usually measured By Enzyme-Linked Immunosorbent Assay (ELISA) kit and the BDNF antibody is cross-reactive with pro-BDNF [19]. So, the most reports measured BDNF levels possibly express the levels of both BDNF and pro-BDNF. Conversely, pro-BDNF ELISA kit does not cross reacts with BDNF [19].

### Exercise and BDNF

We found positive relationship between thickness of quadriceps muscle and serum BDNF contents in elderly people of 898 community-dwellings [3]. However, there was no enough survey about exercise type or strength influencing quadriceps size, just asking frequency of walking or physical exercise in a week. So, we will review exercise types enhancing circulating BDNF and the origin of serum BDNF increasing after the exercise. There are various types of exercise influencing quadriceps size, i.e., aerobic exercise like jogging, cycling or stationary bicycling and resistance exercise like squat, leg extension or leg curl etc. In both aerobic and resistance exercises, the circulating BDNF contents are increased after chronic exercise for 3 to 6 months. Aerobic exercise preferably increased BDNF contents in healthy people [20,21] and in various disease of people such as type II diabetes, hypertension and Alzheimer's disease [22-24]. Resistance training also increases circulating BDNF [25-27] in healthy young and elderly people and Alzheimer's disease, while the increment of BDNF is more pronounced in the aerobic exercise than the resistance training [25,26]. Even at the same resistance training, there is a difference in the increment of peripheral serum BDNF levels between strength exercise and hypertrophy exercise (The strength exercise is lift up two or three reps of maximum power and the hypertrophied exercise is 8 to 12 reps for one set and repeats more than 3 sets). The fatigue hypertrophy based resistance exercise more pronouncedly increased BDNF than strength resistance exercise [25]. Based on this report [25], we describe our data again that an elderly people who have thick quadriceps muscle provide higher serum BDNF levels. This means that people who have thick quadriceps muscle are living a life to be hypertrophied the quadriceps. So, the people who have larger quadriceps show higher serum BDNF levels. As the elderly people decreasing vitality, they decrease number of stand up from sitting position and/or time for standing or walking at their daily life. Therefore, the degenerate of the lower part of the body, hips and legs, is outstanding than the decline of upper part of body. It is reported that the thigh muscle lineally decreases 1% at each year after passing the age of 30 years old, due to aging mechanism and a decrease of activity of daily living [28]. We recommend to do aerobic exercise of jogging or resistance exercise of slow squat to keep a larger quadriceps and higher serum BDNF levels. Doing aerobic exercise like jogging is

seems hard for the latter-stage elderly people (>75 years old), because of pulmonary and cardiovascular risk. So, we recommend doing hypertrophied resistance exercise such as slow squat and stretch legs and hips (muscles and tendons around pelvis).

We have mentioned that measured BDNF with BDNF-ELISA kit is possibly including certain amount of pro-BDNF due to cross-reaction between them. There are few reports separately to measure BDNF and pro-BDNF at simultaneously. By the chronic exercise, increase of serum BDNF and decrease of serum pro-BDNF levels are reported [29]. Therefore, the report of BDNF change by the exercise and by the supplement measured with BDNF-ELISA kit is considered not over estimated.

### BMI and BDNF

We have also obtained positive relationships between serum BDNF levels and Body Mass Index (BMI) /% body fat mass [3]. Suwa et al., [30] and Jung et al., [31] reported similar positive relationships between serum BDNF levels and BMI or % body fat mass in a type-2 diabetes mellitus and healthy subjects, respectively. Our paper shows just positive relationship between the serum BDNF levels and BMI by Spearman's correlation. When the variables of the serum BDNF levels of our cohort of 65 to 84 years old living in Tokyo area is observed by the category of BMI classification of Japan Society for the Study of Obesity, JASSO [32], the normal BMI value from 18.5 to 24.9 is 548 individuals (68.1%), underweight (BMI<18.4) is 67 individuals (8.3%), pre-obese (BMI 25.0-29.9) is 165 individuals (20.5%), obese class I (BMI 30.0-34.9) is 19 individuals (2.4%) and obese class II (BMI 35.1-40) is 5 individuals (0.6%). There was no obese class III (BMI>40). About 70% of elderly people in this cohort are within a normal range of BMI. This means elderly people living in Tokyo area make a life with healthy diet and exercise habit at their daily living. Serum BDNF levels in underweight (BMI<18.4) people are significantly lower than that of people in normal (BMI 18.5-24.9), pre-obese (BMI 25.0-29.9) and obese class (BMI 30.0-34.9) and the mean value of serum BDNF levels linearly increased from underweight to obese class I. While the serum BDNF levels in the obese class II lowered. Tamakoshi et al., [33] reported a relationship between BMI and mortality among Japanese older people that BMI from 20 to 30 is lowest the mortality risk and the underweight of BMI at <16.0 increased the mortality risk 1.78 times in men and 2.55 times in women, respectively than that of BMI from 20 to 30. She is warning about osteoporosis and Protein-Energy Malnutrition (PEM) in case of underweight at older people. As shown in our data and in the report of Tamakoshi et al., [33], in case of older adults, a little bit higher BMI seems better for their health than the normal BMI which recommend JASSO in young adults. Because, when they getting older, they reduce the daily living activity and appetites, so they become PEM. So, control of living environment and consumption of enough nutrition are important for older adults not to be malnutrition. There is a possibility to increase a morbidity risk of cancer and pneumonia in underweight group. The groups in obese I and II were a little bit higher the mortality hazard ratio than the group of BMI 20-30 [33]. In case of older adults, a little bit higher BMI groups of obese I and II is better than underweight group in mortality. As we know the BMI is numerical value of [bodyweight (kg)/height<sup>2</sup> (m)], this includes not only body fat mass but also muscle mass. Although the higher BMI group is expressed as obese I, II, III and IV, this is included proportional value of muscle mass. So, sometimes the higher

BMI groups mean that the individuals might take a healthy nutrition including higher protein and vegetables diet rather than fat and carbohydrate.

### Diet and BDNF

We described a little bit higher BMI is better for higher serum BDNF levels and leading to longevity when getting older. When getting older, they reduce the daily living activity and appetites being PEM and become underweight. So, it is important to take a balanced meal i.e., carbohydrate and lipids for energy, proteins for body composition and minerals, vitamins and dietary fibers (vegetables) for body conditioning. For the elderly people over 70 years old, intake of energy is required 2200 kcal and 1750 kcal and proteins are required 91g and 72g in men and women, respectively, and vegetables are required over 350g in a day [34].

After taking enough volume of balanced meal, take a supplement to increase BDNF is recommended. As the many supplements are reported to enhance BDNF, we will introduce them with verifying the possibility. Among the many supplements, omega-3 fatty acid such as DHA, EPA and alpha-linolenic acid [35,36], and sulforaphane [37] an isothiocyanate present in cruciferous vegetables, curcumin [38,39] and resveratrol [40,41], kinds of polyphenol are highly probable to enhance the production of BDNF. Possible mode of action of omega-3 fatty acid is activation of Nuclear Factor Kappa B (NF- $\kappa$ B) levels and Cyclic AMP Response Element Binding protein (CREB), then enhancement the expression of BDNF mRNA and protein. Another pathway is to inhibit microglia release of pro-inflammatory cytokines such as Interleukin-1 Beta (IL-1 $\beta$ ), Interleukin-6 (IL-6), Tumor Necrosis Factor (TNF), reactive oxygen species ROS and inducible form of Nitric Oxide (iNOS) through bind to peroxisome proliferator activated receptors gamma and alpha (PPAR $\gamma$  and PPAR $\alpha$ ) [35]. Production of BDNF by omega-3 fatty acid implies the enhancement of neurogenesis, and the neurogenesis and production of BDNF is inhibited by the inflammation. Omega-6 fatty acid is also important for the neurogenesis, though it does not enhance BDNF production. Arachidonic acid, omega-6 fatty acid has role of maintenance of neural stem/progenitor cells pool which is differentiated and proliferated by the BDNF [42]. Therefore, it is important to consume the ratio of omega-6 and omega-3 fatty acids as 2:1.

Curcumin, ingredient of turmeric and resveratrol, containing in grape skin and well known presents in a red wine are bioactive polyphenols and have anti-inflammatory and antioxidant properties. Both curcumin [43] and resveratrol [44] decrease expression of pro-inflammatory cytokines, such as interleukins and Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ) and increase expression of BDNF levels. An expression of anti-inflammatory cytokine of interleukin 10 is enhanced by the curcumin [45] and resveratrol [46]. Another polyphenol, quercetin [47], catechin [48,49], anthocyanin [50] etc., have antioxidant properties and enhance production of BDNF or BDNF signaling pathway. Carnosine and anserine are dipeptides composed with beta-alanine and histidine or methylhistidine, respectively and they present much in the avian breast having antioxidant activity [51]. The beta-alanine dipeptides also increase secretion of BDNF acting glial cells penetrating into the brain [52]. Supplementation of beta-alanine also increases expression of BDNF in rat [53] and mice [54] in the brain increasing carnosine production of the brain.

Sulforaphane, organosulfur compounds, widely distributed in cruciferous vegetables such as broccoli sprout and cabbages increases BDNF expression in the diabetic rats [55] and social defeat stress mice [56]. Sulforaphane is well known as Nrf2 activator expressing anti-oxidant gene and simultaneously inhibit pro-inflammatory gene expression [57], therefore having anti-inflammatory profiles. Reduction of expression of BDNF by inflammatory cytokines is reversed by the anti-inflammatory profiles of sulforaphane. Moreover, sulforaphane is well known to have anti-carcinogenic activity in animals and humans, generating Reactivating Oxygen Species (ROS) for promoting apoptosis [58] and Inhibiting Histone Deacetylase (HDAC) for inhibiting telomerase activity etc., [59].

### Conclusion

The developed countries including Japan become higher senior citizen's country and the population of elderly people of over 65 years old occupy about the 1/3 of the whole population in the country. To prolong the healthy life expectancy which elderly people can make a life vigorously by themselves without caregiver's help is relation to individual's happiness and reduction of social security costs. We reported that "Individuals having higher serum BDNF levels have thick quadriceps muscle and is in normal and higher BMI levels, respectively". While the BMI value of 30 and higher (Obese III) lowered the serum BDNF levels. The BDNF has properties to enhance neurogenesis and inhibition of neuronal apoptosis in the brain. It is reported that the serum contents of BDNF levels are decreased in the Alzheimer's disease and depression. We have reviewed how can aged people to keep higher serum BDNF levels doing the exercise, taking a healthy dieting and supplements with the evidence. Although any exercise enhances the expression of BDNF in the muscle, the aerobic exercise seems more pronounced to increase BDNF than resistance exercise. In case of elderly people, higher BMI shows higher serum BDNF levels and considering the prevention of locomotive syndrome, muscle hypertrophied resistance exercise might be better among to do various exercise.

On the other hand, there is a report that BDNF controls appetite activating TrkB receptor on the dopamine 1 neuron in the ventral tegmental area projecting to hypothalamus [60]. Furthermore, caloric restriction, 20 to 40% below the amount of calories that would be consumed ad libitum enhances expression of sirtuin gene [61]. The caloric restriction of 20 to 40% of normal daily calorie intake is not a level to be malnutrition in usual case. The sirtuin has histone deacetylase activity, and modifies DNA stability epigenetically by enhancing histone de-acetylation. Therefore, sirtuin is so called anti-ageing gene inhibiting gene aging and inferiority by the inhibiting gene transcription. Although the caloric restriction and normal and a little bit higher BMI provides higher serum BDNF levels are contradictory, a level not to be under normal BMI (<18.4) value is required for expressing sirtuin gene and keep a considering higher serum BDNF level. Consequently, individuals are necessary higher lean body mass doing with hypertrophied resistance exercise and take a food with higher protein, vitamins with dieting fibers and appropriate supplements to enhance BDNF expression. The higher BDNF levels are good for cognition and depression, and also good for prevention of locomotor syndrome and for frailty.



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