RELATIONSHIP BETWEEN SERUM BDNF AND BMI IN COMMUNITY-DWELLING ELDERLY: POSSIBLY PRESENCE PRODROMAL FRAILTY IN HEALTHY INDIVIDUALS

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Running title: Relationships Between Serum BDNF and BMI

**Abstract**

**Introduction**: We previously reported positive linear relationships between serum brain-derived neurotrophic factor (BDNF) concentrations and both body mass index (BMI) and quadriceps muscle thickness in elderly individuals aged 65–84 years using Spearman’s regression analysis. In this paper, we re-analyzed how serum BDNF levels are distributed across BMI (kg/m2) classifications of the Japan Society for the Study of Obesity. We discussed the importance of the mean serum BDNF levels in each BMI category, as the elderly psychosomatic health is dependent on the levels in BDNF and/or BMI. **Methods**: We measured serum BDNF concentrations as well as BMI and various health parameters in 805 elderly people aged 65–84 years who participated in the regional health examination in the Tokyo area. The serum BDNF concentrations were divided according to BMI classification. **Results**: The mean serum BDNF levels increased linearly according to BMI categorization from thin (<18.4 kg/m2) to obese2 (30–34.9 kg/m2) and decreased in the obese3 group (35–39.9 kg/m2), peaking in the obese2 group. The mean serum BDNF level in the thin group was significantly lower than that of the normal group (p=0.0006). The BDNF levels in the obese1 and obese2 groups did not differ significantly from that in the normal group. Mean hand grip strength (kg) was also similarly distributed to the mean BDNF level distribution. **Conclusions**: Elderly people in the thin BMI group had significantly lower serum BDNF levels and weaker hand grip strength than those in the normal or slightly obese groups.

**Keywords:** Frailty, body mass index, brain-derived neurotrophic factor, elderly cohort, health examination, hand grip strength

**Introduction**

We previously reported positive relationships between serum brain-derived neurotrophic factor (BDNF) levels and both body mass index (BMI) and quadriceps thickness in elderly people aged 65–84 years[1]. When we re-analyzed serum BDNF concentration according to the BMI classifications of the Japan Society for the Study of Obesity, we observed significantly lower BDNF levels in the thin BMI group (<18.4 kg/m2) than that in the normal (18.5–24.9 kg/m2), obese1 (25–29.9 kg/m2) and obese2 (30–34.9 kg/m2) BMI groups. Significant correlations between BMI and serum BDNF levels analyzed by single regression analysis were considered to be a consequence of the coarse categorizations; i.e. the significantly lower BDNF levels in the thin BMI group and non-significant differences in BDNF levels in the obese1, obese2, and obese3 BMI groups compared to that in the normal BMI group. Low BMI typically means low body fat mass and/or low muscle mass as the BMI value is computed as body weight (kg)/height (m2). Several decades ago, individuals with low BMI were considered slender and beautiful; however, the normal BMI range (18.5–24.9 kg/m2) is optimal for health. With aging, individuals experience reduced appetite and decreased bioavailability of absorbed proteins. This phenomenon reduces BMI and decreases health. Fried et al. [2] defined five criteria of frailty in a study including more than 5,000 elderly individuals aged ≥65 individuals in the US; namely, 1) shrinking and weight loss; 2) weakness, evidenced by reduced hand grip strength; 3) poor endurance and energy; 4) slowness, evidenced by slow gait speed and performance; and 5) low physical activity level. Individuals meeting at least three of these criteria are defined as frail.

Decreased BMI is a symptom of frailty and occurs due to reduced daily activity or exercise from poor endurance or energy and low protein bioavailability and appetite. The group of participants with low BMI and low BDNF levels in our cohort may have presented prodromal symptoms of frailty.

BDNF is expressed in the brain and plays roles in neuronal survival, phenotyping differentiation, maintenance of various neurons, and neurogenesis [3]. BDNF is also found in the plasma and serum and can pass through the blood-brain barrier (BBB); hence, blood BDNF concentrations reflect changes in BDNF expression in the brain [4]. The low serum BDNF concentrations reported in depressed and Alzheimer’s patients are restored by treatment [5-7]. Serum BDNF expression was recently reported to be enhanced after acute and chronic exercise [8-10]. Moreover, the increased levels of circulating BDNF following exercise may penetrate the brain and affect neurons [11]. Therefore, increased serum BDNF levels may play a role in mental wellbeing and physical daily living.

This paper discusses the significance of the correlations between serum BDNF levels and BMI on frailty according to physical and psychiatric health in elderly people.

**Methods**

**Participants**

Participants undergoing medical health examinations were recruited by the Tokyo Metropolitan Institute of Gerontology as previously described1. Briefly, we sent a letter to 7,162 community-dwelling elderly individuals aged 65–84 years to invite them to participate in a medical health examination in the Tokyo area; of these 805 participants were willing to receive the examination. Subjects with low basic activities of daily living (ADL) based on Katz Index under 3 points, severe visual and auditory disorders, severe post-stroke symptoms, and cognitive impairment with MMSE (Mini-mental state examination) scores under 24 were excluded [1].

**Measurement of serum BDNF concentrations**

Blood samples were collected and serum BDNF concentrations were measured as described previously1. Serum BDNF levels were measured using the BDNF Emax immunoassay system (Promega Corp., Madison, WI, U.S.A.) according to the supplier protocol. All samples were assayed in duplicate.

**Measurements of BMI, BFM, and hand grip strength**

Total body fat mass was measured using a Well-scan multi-frequency bioelectrical impedance analyzer (Elk Corporation, Japan) and expressed as %BFM. BMI was calculated as body weight (kg)/height (m2). Handgrip strength was measured using a Smedley grip dynamometer (As One, Osaka, Japan).

**Statistical analysis**

We used Student’s t-tests to compare two groups and analysis of variance (ANOVA) to compare three or more groups. The associations of BMI, %BFM, hand grip strength (kg), prescribed medicines and/or serum BDNF levels were examined using Spearman’s correlation coefficients and multiple regression analysis. We used PASW Statistics for Windows, version 18.0 to perform all statistical analyses (SPSS Inc., Chicago, IL, USA).

**Results**

The demographic data and their relation to serum BDNF levels are presented in a previous report1. Briefly, the mean participant age was 73.2 (SD: 4.9) years and the mean serum BDNF level was 9.40 (SD: 4.06) ng/mL (n=805) among those 65–84 years of age with distributing normally and was no sex difference. Individuals with cardiovascular disease represented 16.4% of the cohort and their BDNF levels were significantly lower than that of people without cardiovascular disease (p=0.021). Hypertension, hyperlipidemia, and diabetes mellitus was reported in 45.5%, 30.7%, and 11.8%, of the cohort, respectively. The serum BDNF levels of these participants did not differ from that in healthy people. The use of medicines such as anti-hypertensive and anti-inflammatory drugs, hypnotics, anxiolytics, and osteoporosis drugs was reported in 43.6%, 9.2%, 14.0%, 7.7%, and 12.0% of participants, respectively. The serum BDNF levels in subjects taking hypnotics for less than 1 year were significantly (p=0.0191) lower and significantly higher in subjects taking hypnotics for more than 1 year (p=0.0184) than in subjects not taking hypnotics.

**Serum BDNF levels according to BMI classification**

We re-analyzed the distribution of mean serum BDNF levels according to BMI classification. BMI was classified as thin (<18.4 kg/m2), normal (18.5–24.9 kg/m2), obese1 (25.0–29.9 kg/m2), obese2 (30.0–34.9 kg/m2), obese3 (35–39.9 kg/m2) or obese4 (over 40 kg/m2). Assessment of the distribution of subjects by BMI classification showed that 68.1% were in the normal group and 20.5% were in the obese1 group. The thin and obese2 groups comprised 8.3% and 2.5% of subjects, respectively. The obese3 was very small, at 0.6% of the cohort, or only five of the total of 805 people, and no participants were categorized as obese4. The mean serum BDNF levels increased linearly from thin to obese2, then decreased in the obese3 group. The mean serum BDNF level in the thin group was significantly lower than in the normal group (p=0.0006). However, the BDNF levels in the obese1and obese2 groups did not differ significantly compared to in the normal BMI group (Figure 1).

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**Serum BDNF levels according to %BFM**

We re-analyzed the distribution of serum BDNF concentrations depending on %BFM classified according to 5% steps from below 14.9% to over 40%, similar to the classification for BMI. The distributions of %BFM in our cohort were 3.0% under 14.9%BFM, 8.8% with 15.0–19.9 %BFM (standard lower [-] class), 21.4% with 20–24.9 %BFM (standard higher [+] class), 31.1% with 25.0–29.9%BFM (pre-obese), 24.2% with 30–34.9％BFM (obese1), 9.9% with 35.0–39.9 %BFM (obese2), and 1.6% with over 40%BFM (obese3). The mean %BFM values did not differ between men and women in our elderly cohort (27.7 ± 7.4% [n=304] and 27.2 ± 6.2 % [n=501], respectively). The mean serum BDNF levels increased linearly from under 14.9%BFM to over 40%BFM, with no ceiling. The mean serum BDNF concentration in the under 14.9 %BFM group was 7.6 ± 3.0 ng/mL and no significant difference was observed when compared to the 15.0–19.9%BFM (standard lower [-]), or to the 20–24.9% BFM (standard higher [+]) groups, respectively (Data not shown).

**Hand grip strength according to BMI classification**

The mean hand grip strength in our cohort was 25.5 ± 7.84 kg, exhibiting a significant difference (p=0.0000) between males (32.1±6.99 kg) and females (21.21±4.75 kg). A significant positive correlation was observed between hand grip strength and BMI (p=0.0000). The distributions of hand grip strengths in the BMI classifications from thin to obese3 are shown in Figure 2. The mean hand grip strength in the thin BMI group (21.4 ± 6.4 kg) was significantly lower than in the normal BMI (25.4 ± 5.4 kg, p=0.0004), obese1 (p=0.0000) and obese2 (p=0.0027) groups. The mean hand grip strength in the obese1 group was significantly higher than that in the normal BMI group (p=0.0104). Hence, the hand grip strength was lowest in the thin BMI group (Figure 2.).

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**Discussion**

**Relationships between prescribed medicines or diseases and serum BDNF**

As BMI or %BFM were positively correlated with serum BDNF concentrations, we assessed how diseases and prescribed medicines influenced serum BDNF concentrations. In our study, individuals with cardiovascular disease alone showed significantly lowered serum BDNF concentrations across various diseases. Other diseases, even hyperlipidemia and diabetes mellitus, did not significantly influence serum BDNF concentrations. In the case of diabetes mellitus, low serum BDNF concentrations [12] have been reported in diabetic patients with retinopathy progression; however, a lack of change has also been reported [13, 14]. The HEARTY randomized controlled trials[13] reported reductions in diabetic risk factors associated with increased BDNF levels with exercise training.

Regarding prescribed medicines, the use of hypnotics alone influenced serum BDNF concentrations; other prescribed medicines studied included antihypertensive drugs, anti-inflammatory drugs, anxiolytics, and anti-osteoporosis drugs. Individuals who had taken hypnotics taken for less than 1 year showed lower serum BDNF concentrations while those taking hypnotics for more than 1 year showed higher levels of BDNF than individuals who had not taken hypnotics. Hence, it appears that the lower serum BDNF concentrations in those who had taken hypnotics for less than 1 year reflected an anxiety disorder halfway to cure [15, 16] while the higher BDNF concentrations in those taking hypnotics for more than 1 year may indicate hypnotic dependence in spite of cured anxiety [17]. Individuals able to stand without holding onto something may indicate physically vitality. Therefore, BDNF levels appeared to be related to physical vitality.

**BMI or %BFM classifications and serum BDNF levels**

The mean BMI in this cohort of community-dwelling individuals in the Tokyo area was 22.8 ± 3.4 kg/m2 (23.1 ± 3.1 kg/m2 in male and 22.6 ± 3.2 kg/m2 in female participants). The reported BMIs among community-dwelling individuals aged 60 years and over in rural and urban areas of Indonesia have previously reported to be 22.7 ± 2.2 and 24.9 ± 3.4 kg/m2, respectively [18]. In the Programa Municipal da Terceira Idade (PMTI) program in Vicosa, Minas Gerais, Brazil, the mean BMI was 27.4 kg/m2 among those aged 60 years and over (average 72 years), and about half were overweight [19]. The BMI in the current cohort of community-dwelling individuals in the Tokyo area was close to that in the rural area of Indonesia and lower than that in Brazil. Assessment of the distributions of the participants by BMI classification showed that 68.1% and 8.3% were the normal and thin groups, respectively, among those aged 65–84 years in the Tokyo area.

The mean (± SD) %BFM in our cohort was 27.4 ± 6.3 %, with no significant difference between males and females (male 27.7 ± 6.4 % and female 27.2 ± 6.2%). This cohort is unique as the %BFM in females is generally higher than that in males [19, 20]. The %BFM is increased with age in males and remained steady in females; therefore, the values were comparable between sexes [21].

In this study, the mean serum BDNF levels increased linearly from the thin to obese2 BMI groups and decreased in the obese3 group, peaking in the obese2 group. Unexpectedly, the mean serum BDNF levels in the thin group were significantly lower than in the normal BMI group (p=0.0004). Regarding %BFM, categorized at 5% intervals from under 14.9% to >40%, the mean BDNF levels increased lineally with no upper limit. This phenomenon was unexpected. The serum BDNF levels in the under 14.9%BFM group did not differ significantly from that in the 15.0–19.9%BFM (normal lower [-]) and the 20.0–25.9%BFM (normal higher [+]) groups, respectively. The mean serum BDNF levels in the slightly obese (BMI 25–29.9% kg/m2) and obese1 (BMI 30–34.9% kg/m2) groups were significantly higher than in the under 14.9% BFM group (p<0.05). Since Keys [22] reported that there is a strong correlation between BMI and BFM, BMI is currently used as an index of obesity. Indeed, BMI was also well correlated with %BFM (r=0.9912, p=0.01) in our cohort, while something different in the relationships between BDNF levels distribution and in the BMI or %BFM classification as shown at results.

Tamakoshi et al. [23] reported similar findings regarding BMI and mortality risk in a longitudinal observation lasting 11.2 years among Japanese aged 65–79 years. In this study, the mortality risk was lowest for individuals with BMIs of 20–29.9 kg/m2 (normal to obese1) and the risk increased with decreasing BMI. Grabowski and Ellis [24] also reported that obesity (BMI >28.5 kg/m2) had a protective effect against mortality compared to thinness (BMI <19.4 kg/m2) and normal BMI in older Americans. Thus, a BMI slightly above the normal range seems better for health and longevity in older people. Furthermore, older adults with higher muscle mass showed a low mortality risk in a 10–16-year longitudinal follow-up study in the US [25].

Low BMI or BFM indicates thinness while low BMI indicates not only low BFM but also low muscle mass, as BMI is calculated as body weight (kg)/height (m2). Low muscle mass may cause sarcopenia and frailty. We observed significantly lower serum BDNF levels in the thin BMI group than in the normal BMI group (p=0.0004). Frailty is a condition characterized by weakness, low body weight and low activity that is sometimes also reported to include reduced mood and cognition. Ingles et al. [26] reported lower plasma BDNF levels in frail individuals than in non-frail individuals, which was associated with lower cognition.

**Hand grip strength according to BMI classification**

We observed significantly lower hand grip strength in the thin BMI group than in the normal, obese1, and obese2 BMI groups. This pattern was similar to the distribution observed for serum BDNF levels according to BMI classification. The five frailty criteria proposed by Fried et al include “weakness: reduced hand grip strength” [2]. The thin BMI group showed low serum BDNF levels and weak hand grip strength. Moreover, individuals with frailty reportedly show low levels of circulating BDNF[25]. Therefore, individuals in the thin BMI group with low BDNF levels and weak hand grip strength in our cohort likely had prodromal frailty (not pre-frailty).

We previously reported higher serum BDNF concentrations in individuals with thick quadriceps muscles [1]. These individuals may receive adequate physical exercise in their daily lives. Physical exercise reportedly increases serum BDNF levels in both pre-frail and non-frail women [27]. Moreover, the authors suggested that BDNF levels may be a key pathophysiological mediator in frailty. Therefore, we first showed the presence of prodromal frailty in a healthy cohort of community-dwelling individuals with low BDNF levels, weak handgrip strength, and low BMI. To prevent frailty, individuals in the thin group with low BDNF level should start exercising and ingest proper nutrition with high protein. Resistance training, especially hypertrophied resistance training, is recommended to increase muscle mass[28-30] at 8 to 12 reps per set for more than three sets [28]. Leg exercises; i.e., squats, are recommended for hypertrophied thigh muscles, one of the largest muscles in the body, for the prevention of falls and slowed gait speed associated with frailty. Consumption of high protein and/or amino acid diets can reverse frailty and increase strength and muscle mass with elevated levels of circulating BDNF [31].

There were some limitations to this study. The cohort in this study comprised individuals who were interested in and paying attention to their health, who presented to the institute at their own volition and mostly by themselves. Therefore, the cohort may be representative of vital elderly people rather than average community-dwelling elderly individuals aged 65–84 years in the Tokyo area. Moreover, the observations were made on a single day rather than as part of a longitudinal study; therefore, BMI or %BFM changes in individual cannot be used to explain changes in BDNF concentration.

**Conclusions**: Elderly people in the thin BMI group had significantly lower serum BDNF levels and weaker hand grip strength than those in the normal or slightly obese groups.

**Declarations**

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**Conflicts of Interest**: The authors declare no conflict of interest.

**Ethical approval and informed consent:** We assert that all procedures contributing to this study complied with the ethical standards of the relevant national committees on human experimentation. The study was conducted in accordance with the Declaration of Helsinki (as revised in Brazil 2013), and the protocol was approved by the Ethics committee of the Showa University School of Pharmacy (Approval No. 160, August 4, 2012). We obtained informed consent to perform the medical health examination, including blood collection, following oral explanations provided before the examination.

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