Genotype-dependent Response to a Low-energy, Moderate Fiber Diet on Brain-Derived Neurotrophic Factor in Patients who are Obese and Overweight with Type 2 Diabetes

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Research note

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Abstract

Objective

Brain-Derived Neurotrophic Factor (BDNF) plays a key role in the pathway of the hypothalamus by reducing appetite, controlling body weight and maintaining energy balance. The aim of this study was to investigate the effects of a low-energy, moderate fiber diet on BDNF in obese and overweight type 2 diabetic patients with the APOA-II polymorphism.

Results

Serum BDNF levels increased significantly in the total participants following the low-energy, moderate fiber diet intervention (from 177.54 ± 141.54 pg/ml to 253.79 ± 206.34 pg/ml, p value = 0.025). However, the increase of serum BDNF levels did not signifcanty differ between gentyipc sub-types.

Introduction

Obesity has been regarded as major public health issue, globally, and may be described as an accrual of excess body fat [1]. Obesity is accepted to be a multifactorial condition, encompassing physiological, genetic, behavioral, and cultural contributions [2]. Obesity is characterized as a chronic disease and strongly associated with several non-communicable diseases, including; diabetes, osteoarthritis, hypertension, Non-alcoholic Fatty Liver Disease (NFLD), sleep apnoea, cardiovascular disease, certain cancers and mental disorders [3–5]. Moreover, obesity and its comorbidities escalate societies health expenditure with increasing medical costs for the treatment of obesity-related complications [6, 7].

In recent decades, diet has been introduced as one of the most efficacious environmental factors in the prevention, amelioration, and treatment of obesity. Various diets, such as low-fat diet, low-carbohydrate diet, low energy, Mediterranean diet, etc. have been empirically studied for their obesity-combating ability [8–10]. However, markedly different idiosyncratic responses to similar environmental changes highlight that some of these differences are rooted within the genome and the genetic structure of individuals, which has been coined " Nutrigenetics " [11]. Among the genes involved in the development of obesity, APOA-II, LEPR and APO A5 are routinely purported [12]. One of the polymorphisms of APOA-II, polymorphism T < C-265, there is a T replacement with C at position 265; empirical studies on T < C-265 have shown that this polymorphism is related to the risk of obesity, highlighting that homozygous CC individuals have a greater BMI, body fat percentage, waist circumference, visceral fat and higher food intake than carriers T allele [13–15].

Neurotrophins are a family of growth factors that are identified, principally, by their ability to protect neuronal survival [16, 17]. Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, plays a pivotal role in preserving the survival, growth and maintenance of the nervous system [18]. It has also been shown that BDNF plays a key role through the pathway of the hypothalamus by reducing appetite, controlling body weight and maintaining energy balance [19]. Studies related to the level of

BDNF and obesity are contradictory [20, 21]. Moreover, some studies have shown that an energy-restricted diet can increase the serum levels of BDNF [22, 23], whilst an equitable number of studies have shown the opposite [24, 25]. Considering the relationship between APOA-II and BDNF in controlling weight and obesity [13, 19, 26] and the possible effect of this polymorphism and serum factor in receiving food and feeding behaviors, the aim of present study was to determine the effect of a low-energy, moderate fiber diet on BDNF in patients who are obese and overweight, with type 2 diabetic patients and different genotypes of APOA-II T < C-265.

Materials And Methods

Study design and diet intervention

The current study was performed on 44 overweight and obese type 2 diabetic patients with mean age of 56.68 ± 5.9 years. Participants were selected from 697 patients specified before in the study [27]. The APOA-II groups had an equal number of patients (22 individuals in TT/TC group and 22 individuals in CC group) matched for gender, BMI, age, and use of lipid-lowering medications at the beginning of the study. The exclusion criteria were: smoking, alcohol consumption, pregnancy, having concurrent diseases; such as liver and thyroid disease, kidney failure, cancer, and use of some medications, including; insulin injection, nutrient supplements, and anti-inflammatory agents. This study and associated protocol was approved by the Tehran University of Medical Sciences (IR.TUMS.VCER.REC.1397.168), and adhered to the Declaration of Helsinki. Informed consent was obtained prior to participation (IRCT20180715040479N1).

Height and body weight were measured by using a standard wall-mounted stadiometer (Seca, Germany) and digital scale (Seca 808, Germany) respectively. BMI was obtained by dividing weight in kilograms by the height in meters squared. Waist circumference was measured with a tape measure between the iliac crest and the lowest rib after expiration. Basal energy expenditure (BEE) was calculated for each participant using the Mifflin St-Jeor formula then activity thermogenesis (AT) and the thermic effect of food (TEF) were summed to BEE to calculate total energy expenditure (TEE) [28].

In the current study, all patients were given an individualized diet plan of 750 kcal/d less than their estimated energy intake. The diet plan compositions were planned by a trained dietician, and comprised; fiber intake (30 gr/d) [29] with 55–65% carbohydrate, 20–25% Fat, and 15–20% protein [30]. The daily meal plan was determined for each person for six weeks.

The compliance for each subject was confirmed using weekly-based telephone call, and every second week, participants were asked to the clinic with the intention of measuring anthropometric indices and estimation of dietary consumption. Participants were instructed by trained dietitians on how to complete the 7-day diary, if patients exchanged their planned diet, they had to report this in their food diaries. The international physical activity questionnaire (IPAQ) was used to evaluate patients' physical activity. In addition, the patients were instructed to maintain ad libitum physical activity during the intervention.

Sample collection and measurement of serum BDNF

Overnight fasting blood samples (15–20 ml) of all subjects were taken at the besline of the study and after six weeks. Following this, samples were decanted into separate tubes with and without anticoagulant Ethylenediaminetetraacetic acid (EDTA). Subsequent centrifugations were conducted at 3000 rpm and 4 C, for 10 minutes and and stored at − 80 °C until the analysis. The serum BDNF consentertion was measured using a commercial ELISA kit (ELISA kit, R & D Systems, Minneapolis, MN, USA) and performed according to manufacturer guidelines.

Statistical analysis

Statistical analysis of data was performed using SPSS software (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA). The normality of distribution was evaluated, and subsequently confirmed, using the Kolmogorov-Smirnov test. In this study, the Paired sample T-test was used to compare mean and standard deviation before and after low-energy diet intervention in each group. An independent t-test and chi-square test were applied to compare the mean of serum of BDNF between the two groups. An analysis of covariance test was also performed to adjust the confounders. Significance was accepted at $\alpha \leq 0.05$.

Results

The characteristics of the study population at study entry are presented in Table 1. The variables did not differ significantly between the two genotypic sub-types. This study demonstrated that a six week intervention of low-energy, moderate fiber diet decreased BMI (from 31.07 $kg.m^2$ to 29.76 $kg.m^2$), weight (from 81.68 kg to 78.41 kg) and waist circumference (from 106.47 cm to 100.70). The effect of the six week intervention on serum BDNF are provided in Table 2, and demonstrates a significant increase in serum BDNF from 177.54 ± 141.54 pg/ml to 253.79 ± 206.34 pg/ml (p = 0.025). However, the increase of serum BDNF levels in each group of TT / TC and CC genotypes was not statistically significant after the intervention. The mean difference of variables between the TT / TC and CC genotypes before and after adjusting for baseline values is detailed in Table 3.

Discussion

The current study showed that adherence to a low-energy, moderate fiber diet significantly increases serum BDNF levels. However, serum BDNF levels did not show any significant difference between the TT / TC and CC genotypes. These results were consistent with similar studies conducted on overweight and obese individuals. For example, Aryana et al. reported that a reduction of 7 kg over a three-month period, in 70 obese adults with insulin resistance, lead to a significant increase in serum BDNF. In Aryana et al, the distribution of macronutrients in the diet was similar to the present study, and was reported as 55% carbohydrate, 20% protein and 25% fat [22]. In addition, in another study by Kuo et al. (37), serum BDNF levels reportedly increased significantly over the course of a three month, which only included

recommendations for modification lifestyle included increased consumption of vegetables and reduced consumption of simple sugars and saturated fats, albeit in a population of patients with Schizophrenia [23]. Moreover, comparable results, to the present study, were also observed in a study by Lee et al., whom implemented a diet of 1,200 kilocalories, lifestyle changes and increased physical activity [31]. However, whilst the positive effects of dietary restriction or adaptation have been well reported, the responses have been notably different, depending upon the population of inquiry. Lee et al reported that, in 36 obese patients with metabolic syndrome and 25 healthy individuals, serum BDNF levels were higher in obese subjects than in normal subjects. It has been asserted that increasing serum BDNF levels after glucose intake was associated with obesity, in the same way as with weight loss, serum BDNF levels decreased with glucose consumption compared with baseline values [24]. In fact, the increase in BDNF levels after glucose consumption is associated with body weight [32]. However, serum BDNF concentrations were not significantly related to body fat mass in some studies [20, 33].

Such contradictory results were also found in another study on children, in which, after one year of lifestyle changes in individuals, the serum BDNF concentration in obese children was higher than normal weight counterparts. Problematically, it was not specified what type of lifestyle changes had a greater effect on its increase [25].

The difference between the results of the studies mentioned above and the present study may be due to differences in the type of intervention, age of subjects, differences in lifestyle characteristics, BMI of the participants, different methods of serum BDNF detection, and adjustment for different confounding factors. The present study showed that there was no significant difference in serum level of BDNF in TT / TC and CC genotypes. Several studies have suggested that one of the APOA-II polymorphisms known as T < C-265 polymorphism is associated with an increase in inflammation in various diseases [34]. In addition, a recent study by Moradi et al. found that gene expression and serum levels of VCAM1 in the CC group had a significant reduction following a low-energy diet [35]. On the other hand, it has been shown that inflammation is one of the most important reasons for lowering the serum levels of BDNF, which has been well documented in diabetics and heart patients due to elevated inflammatory factors such as VCAM-1. As in the study by Lee et al., where high levels of VCAM-1 were significantly associated with low serum BDNF levels in cardiac patients [36]. Therefore, it appears that an energy-restricted dietary intervention in diabetic and obese patients with APOA-II T < C-265 polymorphisms may be effective, justifiable and tolerable. However, our results did not support this hypothesis, and conceivably because the present study allocated participants to two genotypic groups, this limited the number of participants, thereby confounding our ability to discern significant differences between the TT / TC and CC genotypic groups.

In general, BDNF and its receptor TrkB are widely expressed in the brain of growing and mature mammals. Intracellular signaling stimulated by BDNF / TrkB is essential for neuronal survival, cellular differentiation, cell migration, synaptic synthesis and synaptic flexibility or 'plasticity' [16, 17, 37]. Minor changes in BDNF levels or repeated expression of uncertain single nucleotide polymorphism(SNPs) in the BDNF gene are related to behavioral changes including abnormal nutritional behaviors, episodic memory

changes (events), and sensitivity to psychiatric disorders of anxiety and depression in humans and animal models [38, 39]. In recent years, numerous studies have been conducted on the association of BDNF and various mental illnesses such as stress and anxiety [40], autism [41], bipolar disorder [42, 43], depression [44, 45], and eating disorders [46, 47]. Furthermore, it has been shown that serum levels of BDNF are associated with levels of nutrient peptides such as leptin and cholecystokinin (CCK) [48, 49]. Although there is tentative evidence for the mechanistic action of BDNF, it is far from elucidatory or confirmatory, and, as such, it is strongly recommended that the relationship between BDNF levels and hormones involved in appetite and fat mass, and mechanism of action be further investigated.

Conclusion

The present study revealed that adherence to a low-energy, moderate fiber diet significantly increases serum BDNF concentrations. However, serum BDNF levels did not significantly differ between the TT / TC and CC genotypes.

Study limitation

The main limitation of the present study was the relatively small sample size with different APOAII-265 polymorphism genotypes, which hindered the achievement of meaningful results in relation to genotypes, although the sample size was sufficiently estimated by the proposed formula. Furthermore, the present study utilized a matched-pairs design, opposed to randomization, which may have conceivably affected the results.

Abbreviations

BDNF: Brain-derived neurotrophic factor LEPR:Leptin receptor, NAFLD:Non-alcoholic fatty liver disease, BMI:Body mass index, BEE:Basal energy expenditure, AT:Activity thermogenesis, TEF:Thermic effect of food, TEE:Total energy expenditure, IPAQ:International physical activity questionnaire, EDTA:Ethylenediaminetetraacetic acid, VCAM1:Vascular cell adhesion molecule1, SNPs:Single nucleotide polymorphism, CCK:Cholecystokinin

Declarations

Ethics approval and consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of The Tehran University of Medical Sciences (IR.TUMS.VCER.REC.1397.168) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (IR.TUMS.VCER.REC.1397.168). written consent was obtained from all individual participants included in the study.

Consent for publication

Not Applicable.

Availability of data and materials: The data are not publicly available due to containing information that could compromise the privacy of research participants.

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Conflict of Interest

All of authors declared that they have no competing interests.

Author Contribution: "FK designed research; MM and ANV conducted research; ANV and MSY analyzed data; ANV wrote the paper; FK had primary responsibility for final content. CC helped us in the process of revises and improve grammar. All authors read and approved the final manuscript."

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we ensure our manuscript reporting adheres to CONSORT guidelines (http://www.consort-statement.org/) for reporting clinical trials.

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