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Epidemiology

Boron-rich diet may regulate blood lipid profile and prevent obesity: A non-drug and self-controlled clinical trial

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ABSTRACT

Background: Boron is an element commonly found in nature. The main boron source for organisms is through food and drinking water. In recent years, it is suggested that the "boron-rich diet" can affect human health positively. However, more detailed studies are needed.

Objective: The aim of this study was to examine the effect of increased dietary boron intake on some biochemical parameters in humans.

Material and methods: Thirteen healthy women consumed diets containing 10 mg more boron than their routine diet for one month. This boron intake was provided with the increase of boron-rich foods such as dried fruits, avocado, and nuts in the diet. Some biochemical and hematologic parameters were determined in blood, urine and saliva samples taken before and after a boron-rich diet.

Results: Serum, salivary, and urine boron concentrations increased 1.3, 1.7, 6.0 fold, respectively. The most significant clinically change was found in the lipid profile. Serum total, LDL, VLDL cholesterol, and triglyceride levels decreased significantly. Body weight, body fat weight, and Body Mass Index also decreased. Significant changes in serum TSH and salivary buffering capacity were also found.

Conclusion: Increasing the intake of boron through dietary means might contribute to beneficial effects on lipid metabolism, obesity, and thyroid metabolism; salivary boron may reflect serum boron; and boron may be used as a cariostatic agent in dentistry. An increased intake of other dietary factors such as fiber, potassium, iron, vitamin A, and vitamin E in the boron-rich foods might have been responsible of the effects described. To our knowledge, this study is the first clinical study in which dietary boron intake is increased via foods.

1. Introduction

Boron is present as compounds in nature with sodium, calcium, and oxygen elements [1]. It has been known that it is an essential micronutrient for plants since 1923 [2]. However, the biological roles of boron in animal and the human body have not been fully explained. Therefore, boron is considered as a potentially essential element [3].

Plant-derived foods such as dried nuts, legumes, fruits, and vegetables are rich in boron while meat and meat products from animal-derived foods, milk and dairy products, and grains are poor in boron [4,5]. According to the World Health Organization (WHO), approximately 0.2-0.6 mg of boron enters the human body through drinking water and 1.2 mg through nutrition [6]. It is known that boron level in nutrients and drinking water directly reflects the exposure of boron for humans [7]. The Recommended Daily Intake (RDA), Estimated Average Requirement (EAR), and Adequate Intake (AI) values for boron have not yet been determined. Tolerable upper intake level for boron has been established, which is 20 mg boron/day for adults [8].

Recent studies have indicated that boron has positive effects on human health and it is emphasized that boron has very beneficial roles in bone development, antioxidant defense system, mineral and hormone metabolism, wound healing, energy metabolism, and immune

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system [9–15]. In various studies, the effects of boron supplementation on some biochemical and hematological parameters have been investigated [16–20]. In recent years, it has been suggested that the "boron-rich diet" can affect human health positively [4,7,21]. However, comprehensive studies on the effects of a boron-rich diet on human health are not sufficient. There are studies that were conducted on boron supplements. This study is the first clinical study in which dietary boron intake is increased via foods and aims to examine the effect of dietary boron intake on some biochemical parameters in humans. Our study is a non-drug and self-controlled clinical trial.

2. Materials and methods

2.1. Subjects

Thirteen healthy adult subjects who applied for general control purposes to the Endocrinology and Metabolism Clinic of Sisli Hamidiye Etfal Training and Research Hospital of the University of Health Sciences participated in this study. After medical and nutritional evaluation was established, an informed consent was taken from all the participants who were healthy. Marmara University Faculty of Medicine Clinical Research Ethics Committee approved this study (09.2016.647). The average age of the participants was 36.85 ± 11.89 years. Patients with the following conditions were not included in the study: patients who had diabetes or any systematic disease, patients who received medical nutrition treatment for any reason; patients who were allergic to any kind of food; patients whose average daily dietary boron intake was more than 5 mg; patients who used any vitamins and/or minerals, and smokers.

2.2. Experimental protocol

Basal nutrients status was detected at the beginning of our study [22]. In the calculation of the daily food boron intake of each participant from the seven-days food consumption records, food boron content obtained from the studies conducted in Turkey were used. All participants were given a diet containing 10 mg more boron than their daily boron intake for 1 month. An example of these diets is given in Table 1. Diets were prepared according to the food boron data from our previous study [5]. The amounts of energy and macronutrient in diets were kept approximately the same as the average amounts calculated from the 7-days food records. Participants were weighed before consuming the boron-rich food and allowed to do shopping from the same market. The amounts of energy, macronutrients, and micronutrients in all diets were calculated by BeBiS program (for Windows, Turkish version). The previously calculated average water consumption was also maintained for one month. Participants were not permitted to do extra physical activity other than their daily routine activities.

Table 1
An example of a diet applied during one month.

Meals	Food Items	Boron (mg)
Breakfast	Egg (50 g)	0.021
	White cottage cheese (60 g)	0.010
	Whole wheat bread (30 g)	0.021
	Black Olive (35 g)	0.249
	Tomato (150 g), Cucumber (150 g), Green pointed pepper (15 g), Parsley (15 g)	0.347
	Dry plum (40 g)	0.968
Lunch	Meat or Chicken (80 g)	0.208
	Yoghurt (full fat) (200 g)	0.024
	Avocado (130 g)	3.796
	1 Cucumber (100 g)	0.094
Dinner	Vegetable Meal	0.300
	Bulgur or Pasta (60 g)	0.038
	Yoghurt (full fat) (100 g)	0.012
	1 Cucumber (100 g)	0.094
Snacks	Dry Apricot (40 g)	1.485
	Nut (20 g)	0.372
	Raisin (50 g)	1.050
	Almond (25 g)	0.820
	Green plum (150 g)	0.880
	Drinking Water (2.5 L)	0.225
	Total Daily Dietary Boron Intake (mg boron/day):	11.014

This table is an example planned to be a daily boron uptake of 11.01 mg per month for a person whose boron level is about 1.01 mg according to the 7-day nutritional record.

2.3. Samples

After 10-h fasting period, blood, urine, and saliva samples were taken from all participants at the beginning and at the end of the boron-rich diet application. Fresh urine samples were taken for complete urinalysis and 24-h urine samples were taken to measure daily urine boron excretion. Some parameters were studied immediately in whole blood. For the others, the blood sample was centrifuged, and the serum was separated, and stored until the day of the analysis first at −80 °C in deep freeze (Arctico-ULTF80, Denmark). 24-hour urine specimens were collected in 5 L clean urine bottles without added preservatives. Except for the first urine, participants accumulated all their urine during the day in the collection bottles and they added the next day's first urine to the collection bottle. Urine samples were stored in small volumes in deep freeze until the experimental day. To take unstimulated saliva samples, the mouth was first rinsed with distilled water. The saliva accumulated in the oral cavity was taken into falcon tubes with a plastic funnel. The volume and collection time of saliva samples were recorded. The saliva samples were also stored in deep freeze until the day of analysis. Oral examination of each participant was done by the same dentist.

2.4. Reagents

The chemical substances used in the study are of analytical purity and were from Merck (Germany), Sigma-Aldrich (UK), and ChemLab (Belgium). Adiponectin, Sodium-Coupled Borate CoTransporter 1 (NaBC1), Sterol Regulatory Element Binding Protein (SREBP), and Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) kits used in this study were obtained from Thermo Fisher (BMS2032-2), SunRed (201-12-5997), Elabscience (E-EL-H1162), and Elabscience (E-EL-H1361), respectively.

2.5. Analyses

In the blood samples of each participant, fasting blood glucose (FBG), fasting insulin, thyroid-stimulating hormone (TSH), urea, uric acid, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C), alkaline phosphatase (ALP), calcium, magnesium, vitamin D_3, total bilirubin, direct bilirubin, indirect bilirubin, C-reactive protein (CRP), creatinine, complete blood count parameters, while in the urine samples, complete urine analysis and 24-hour creatinine levels were directly measured by routine laboratory techniques using by Roche Cobas c(501,602,701), Sysmex XE2100, and FUS 200/H 800 devices. The saliva pH was measured with a pH-meter (Thermo Scientific Orion 3 Star Benchtop). The salivary flow rate was calculated. Saliva buffering capacity was determined using the Ericson method [23]. PPAR-γ, SREBP, NaBC1, and adiponectin levels were assayed via Elisa kits in serum and saliva samples. In the serum, urine and saliva samples, the boron levels were determined by Inductively Coupled Plasma-Mass Spectrometer (ICP-MS) (Thermo Scientific X Series 2 ICP-MS; power, 1051 W; nebulizer gas, 1.2 / min; cooling gas, 13 / min; auxiliary gas, 0.9 / min). All of the above analyses were done at the beginning and at the end of the one-month boron-rich diet application.

2.5.1. Boron analyses

Serum sample (0.5 mL) was diluted to 10 mL with serum dilution solution. The 24-h urine sample (0.5 mL) was diluted to 13 mL of 2% nitric acid solution (Merck, Darmstadt, Germany). One mL of each saliva sample was diluted to 10 mL of 2% nitric acid solution. They were filtered using a syringe filter (0.2 µm) and were then placed in the autosampler unit of the ICP-MS. All analyses were repeated at least four times. Calibration solutions were prepared at eight different boron concentrations between 0.002–20000 ppb using boric acid solution (1000 µg boron/mL, Chem Lab, Zedelgem, Belgium).

Serum dilution solution: Five mL of 25% ammonia solution (Merck, Darmstadt, Germany) was mixed with 3.72 mg of ethylenediaminetetraacetic acid (EDTA) (Merck, Darmstadt, Germany) dissolved in distilled water. Triton X-100 (0.8 mL)(Sigma, St. Louis, MO, USA), 15 mL of butane-1-ol (Sigma, St. Louis, MO, USA) were then added to this solution, stirred and the volume was completed to 1 L with distilled water.

2.6. Anthropometric measurements

The height measurements (cm) of the participants were made with a stadiometer (Seca), in position without shoes, in the Frankfort plane, and with feet side by side. Weights (kg), body fat mass (kg) and body mass index (BMI) were obtained using the Inbody-230 (Korea) body composition analyzer device before and after the one-month's boron-rich diet. The necessary conditions for this analysis were not to eat anything for at least 2 h before measurement, not to drink a lot of water before analysis, not to have any metal accessories on, and not to do heavy physical activity 1–2 days before the measurement.

2.7. Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Version 24.0 for Windows, Chicago, Illinois) Software and $p < 0.05$ was considered statistically significant. Normal distribution of continuous variables was checked using the Shapiro-Wilk test. Normally distributed variables were compared using the Student *t*-test for two independent groups and paired *t*-test for dependent groups. These variables were given as mean ± standard deviation. Non-normally distributed variables were compared using the Mann-Whitney U test for two independent groups and Wilcoxon test for the dependent groups. Median values of these variables were also given. Pearson correlation was used for normally distributed variables and Spearman correlation was used for non-normally distributed variables.

3. Results

The amount of energy, macro, and micronutrient contents calculated from the 7-days food records and from one-month diets were about the same. Dietary boron, fiber, magnesium, potassium, iron, folic acid, pyridoxine, vitamin A, C, E contents in the one-month diets were higher than those calculated from the 7-days food records (Table 2).

Serum, saliva, and 24-hour urine boron concentrations of the participants increased significantly after the one-month boron-rich diet (Fig. 1).

BMI, body weight, and body fat mass decreased significantly after the one-month boron rich diet (Table 3).

Serum boron, creatinine level, urine density, 24-h urine boron level, salivary boron concentration, and saliva buffering capacity increased significantly after the one-month boron-rich diet; FBG, TC, LDL-C VLDL-C, TG, ALP, TSH, urea, insulin level, white blood cell counts, eosinophil ratios, and mean corpuscular hemoglobin values decreased significantly (Table 4). Glucose, protein, nitrite, and ketone were not detected before and after the one-month boron-rich diet in urine specimens of participants and the urine urobilinogen level was normal.

There was a significant negative correlation between serum boron concentration with serum TC, urea, blood erythrocyte count, but positive correlation with urine boron concentration. The urine boron concentration correlated positively with saliva boron concentration, serum boron concentration, and urine density (Table 5).

Table 2
Energy, macro, and micronutrient contents of diets.

	Calculated from 7-days food records	Calculated from one-month diets
Boron (mg/day)	1.4 ± 0.50	11.4 ± 0.50
Energy (kcal/day)	1740 ± 216	1746 ± 216
Carbohydrate (g/day)	172 ± 41	172 ± 40
Protein (g/day)	77.8 ± 7.70	78.5 ± 7.10
Fat (g/day)	82.0 ± 9.30	82.6 ± 9.60
Fiber (g/day)	14.4 ± 7.50	38.1 ± 5.10
Magnesium (mg/day)	256 ± 47	305 ± 56
Calcium (mg/day)	947 ± 74	1019 ± 86
Potassium (mg/day)	2253 ± 350	4043 ± 519
Sodium (mg/day)	2064 ± 283	2051 ± 208
Folic Acid (µg/day)	119 ± 15	354 ± 21
Vitamin C (mg/day)	49 ± 18	152 ± 24
Iron (mg/day)	6.09 ± 1.61	11.82 ± 1.91
Phosphorus (mg/day)	1124 ± 81	1368 ± 87
Vitamin A (µg/day)	590 ± 125	1696 ± 188
Vitamin E (mg/day)	5.87 ± 0.81	15.91 ± 1.38
Zinc (mg/day)	8.1 ± 0.93	9.9 ± 1.12
Tiamin (mg/day)	0.82 ± 0.14	1.06 ± 0.18
Riboflavin (mg/day)	1.72 ± 0.11	1.89 ± 0.12
Pridoxin (mg/day)	1.29 ± 0.10	2.08 ± 0.09

4. Discussion

4.1. Diet

In the literature, there are studies that investigate the effects of boron intake as dietary supplement on human health [16–20]. However, few specific biochemical parameters have been examined. To our knowledge, our study is the first clinical study in the literature that increases the boron intake via diet. Furthermore, the effect of dietary boron on biochemical and hematological parameters was investigated in detail in this study.

At the beginning of the study, the mean daily dietary boron intake was 1.4 ± 0.5 mg/day; however, it became 11.4 ± 0.5 mg/day after the one-month boron-rich diet. These values were not higher than the boron toxic dose of 500 mg/day and the boron tolerable safe uptake level of 20 mg/day. Nielsen determined the lowest limit of daily dietary boron intake as 0.25 mg for boron deprivation in humans [24]. Accordingly, there was no boron deprivation for the participants in our study. However, Nielsen suggested that intake of boron near 1.0 mg/day might be a beneficial intake for boron [4]. At the beginning of this study, the variation in average intake (1.4 ± 0.5 mg/day) suggests some of the participants had intakes less than this amount.

In this study while preparing the boron-rich diet, care was taken to ensure that the macronutrients and calorific values were the same as the previous diet. This was extremely important for the standardization of the study. Because changes in dietary calorific values and macronutrients amounts may affect the biochemical and hematological parameters, body weight, and the body composition of participants. It is known that boron rich foods are rich in fiber, vitamins and minerals. Therefore, we found increased content of dietary fiber, magnesium, calcium, potassium, sodium, zinc, iron, phosphorus, folic acid, thiamine, riboflavin pyridoxine, vitamins C, A, and E vitamins in our experiment. Clinically significant changes were boron, fiber, potassium, iron, magnesium, and vitamins C,A,E. This was an expected result, since we used a boron rich diet. However, the increased values of vitamins, minerals, and fiber did not exceed tolerable intake levels [25]. Similar to our study, Naghii et al. also examined seven-days food consumption

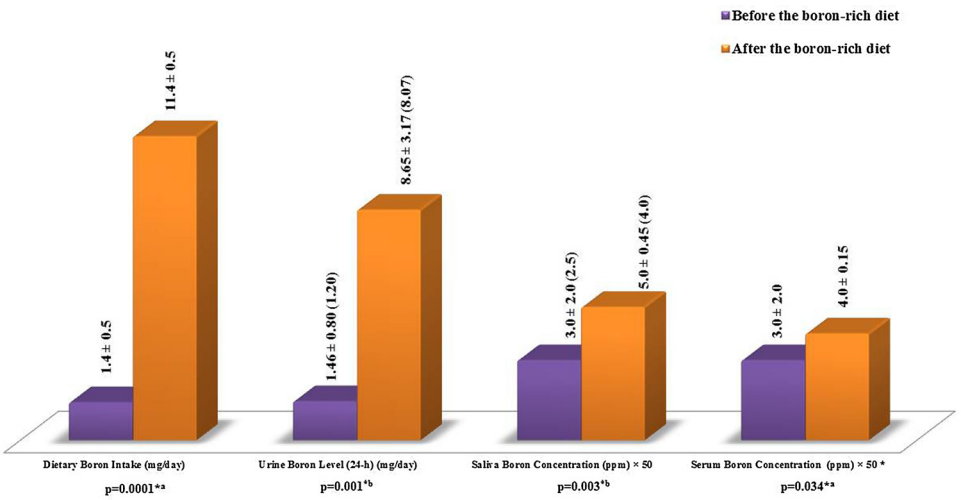

Fig. 1. Dietary boron intake, urine, saliva, and serum boron concentrations before and after the boron-rich diet.
Values are given as mean ± standard deviation. Median values are given in parentheses for non-parametric variables. Serum and salivary boron values are multiplied by 50.* $p < 0.05$. a: Paired t-Test, b: Willcoxon Test.

Table 3
Comparison of Body Mass Index, body weight, and body fat levels before and after the boron-rich diet.

	Before boron-rich diet (n = 13)	After boron-rich diet (n = 13)
Body Mass Index (kg/m^2)	27.74 ± 6.02	27.40 ± 5.93 *,a
Body Weight (kg)	70.50 ± 15.93	69.72 ± 15.51*,a
Body Fat Mass (kg)	28.12 ± 11.84	27.37 ± 11.46 *,a

Values are given as mean ± standard deviation.
* $p < 0.05$.
[a] paired t-Test.

records of 32 people and calculated their mean daily dietary boron intake as 2.2 ± 1.2 mg/day and found a positive correlation between dietary fiber and boron intake [26].

4.2. BMI and body fat

One-month boron-rich diet caused a decrease in the body weight of the participants by 800 g (1.1%) and almost all of this amount was body fat mass. Furthermore, the BMI of participants decreased by 0.35 kg/m^2. It is known that the amount of daily calorie should be reduced by 200 kcal for a person who wants to lose weight by 800 g per month [27]. In this study, a weight loss of 800 g was achieved without reducing calories. The effect of dietary vitamins and minerals on body weight is not well known yet. The results of the other studies were also contradictory [28,29]. Furthermore, there is no clinical study showing the effects of boron supplementation on body weight. Therefore, more detailed clinical studies should be carried out. Boron perhaps will be a promising agent in the treatment of obesity and in the prevention of future obesity-related diseases.

There are, other studies showing that boron reduces the body weight of experimental animals [30–33]. A negative correlation was found between BMI and daily boron uptake in our previous

Table 4
The significant differences of serum, urine, and saliva parameters before and after the boron-rich diet.

	Before boron-rich diet (n = 13)	After boron-rich diet (n = 13)	p
Serum Parameters			
Boron (ppm)	0.06 ± 0.02	0.08 ± 0.03	0.034*,a
Fasting Blood Sugar (mg/dL)	90.85 ± 10.16 (90)	86.46 ± 11.3 (85)	0.013*,b
Serum Urea (mg/dL)	25.54 ± 4.55 (25)	21.15 ± 5.61 (20)	0.008*,b
Serum Creatinine (mg/dL)	0.67 ± 0.09	0.71 ± 0.11	0.026*,a
Total Cholesterol(mg/dL)	184.47 ± 42.5	168.39 ± 32.9	0.014*,a
Triglyceride (mg/dL)	120.99 ± 104.67 (81)	89.92 ± 58.96 (70)	0.039*,b
VLDL-Cholesterol (mg/dL)	24.2 ± 20.93 (16)	17.99 ± 11.79 (14)	0.039*,b
LDL-Cholesterol (mg/dL)	104.18 ± 32.19	90.48 ± 25.1	0.011*,a
Alkaline Phosphatase (U/L)	61.31 ± 15.83 (59)	57.85 ± 15.05 (56)	0.041*,b
Thyroid-Stimulated Hormone (mIU/mL)	2.96 ± 2.15 (2.66)	2.21 ± 1.42 (1.79)	0.023*,b
Fasting Insulin (μU/mL)	10.74 ± 6.52 (8.42)	8.24 ± 6.19 (7.30)	0.039*,b
Hematologic Parameters			
White Blood Cells (WBC) (10^9/L)	8.29 ± 1.73	7.49 ± 1.66	0.017*,a
Eosinophil Ratio (%)	3.23 ± 2.53 (3.20)	2.68 ± 1.77 (2.00)	0.037*,b
Mean Corpuscular Hemoglobin (MCH) (pg)	27.86 ± 2.15	27.59 ± 2.22	0.018*,a
Urine Parameters			
24-h boron level (mg/day)	1.46 ± 0.8 (1.20)	8.65 ± 3.17 (8.07)	0.001*,b
Density	1006.85 ± 5.98 (1005.00)	1018.15 ± 6.62 (1018.00)	0.002*,b
Saliva Parameters			
Boron Concentration (ppm)	0.06 ± 0.04 (0.05)	0.10 ± 0.09 (0.08)	0.003*,b
Buffering Capacity	4.42 ± 0.69	5.21 ± 0.78	0.0001*,a

Values are given as mean ± standard deviation. Median values are given in parentheses for non-parametric variables.
* $p < 0.05$.
[a] Paired t-Test.
[b] Willcoxon Test.

Table 5
The significant correlations between serum, saliva, and urine boron concentration and other parameters.

	Parameters	Correlation Coefficient
Serum Boron Concentration (ppm)	Serum Urea	−0.539**
	Serum Total Cholesterol	−0.404*
	Blood Erythrocyte Count	−0.452*
	Urine Boron Concentration	0.425*
Urine Boron Concentration (mg)	Urine Density	0.596**
	Serum Boron Concentration	0.425*
	Saliva Boron Concentration	0.600**
Saliva Boron Concentration (ppm)	Urine Boron Concentration	0.600**

* $p < 0.05$.
** $p < 0.01$.

retrospective study [34]; the inhibition of adipogenesis by boron affecting the Wnt/β-catenin pathway in progenitor cells [35]; and the decreased adipogenic differentiation capacity of human adipose-derived stem cells by the effect of sodium pentaborate pentahydrate in a dose-dependent manner without formation of cytotoxic effects [14], all these results support our present results.

4.3. Serum and hematologic parameters

Boron is found in human blood as boric acid (98%) and borate anion (2%) and its level is under control by renal excretion [36]. In this study, the serum boron level was not affected as much as urine from the changes in dietary boron and, when the amount of dietary boron was increased 8-fold, the serum boron level increased significantly to 1.3 times. Similarly, in a clinical study, the plasma boron level of 43 healthy women who received 2.5 mg/day boron for 60 days via sodium borate capsule increased 1.5 fold (from 0.033 to 0.052) [37]. Plasma boron level increased by 1.5 times in a study by Hunt et al. [38] where the amount of boron intake was increased 9-fold with boron supplementation. Unlike our study, in Hunt et al.'s study, healthy participants (n = 11), at the beginning, had taken a low boron diet for 167 days, then it was followed by a 48 days of boron supplementation. For the determination of boron in the samples, the ICP-AES method was used. However, in our study the ICP-MS method was used; participants did not consume a boron-poor diet at the beginning and boron supplement was not used, the boron amount was increased only via the diet.

In Koc et al.'s study, the serum boron level was determined in 105 healthy people by ICP-MS method and it was found as 0.07 ± 0.08 ppm [39]. The serum boron level of our participants was about 0.06 ± 0.02 ppm at the beginning. After the one-month boron-rich diet, the serum boron level increased to 0.08 ± 0.03 ppm.

There are several studies in the literature showing that boron can affect insulin and glucose metabolism [40,41]. In our study, as a result of a one-month boron-rich diet, the levels of FBG and fasting insulin decreased significantly. This decrease may be important in terms of clinical aspects when the boron-rich diet applied for a long time. Although its mechanism was not elucidated yet, it has been suggested that boron will decrease NADPH production and decrease fasting insulin level and may decrease pancreatic beta cell stress [41].

Cakir et al. have shown that oral administration of boric acid decreased serum TC and LDL-C levels and increased HDL-C, in streptozotocin-induced diabetic rats [42]. The rats were given two different compounds containing 8 mg/kg/day boron for 14 days in another study and were shown to cause decreased serum LDL-C and TG levels. Considering these results, it was suggested that boron may have beneficial effects on atherosclerosis [43]. It was also found that serum apolipoprotein-B and TG levels decreased significantly in 10 dogs that were fed 4 g/day (pharmacologic intake) borax added to their diet for 30 days [44]. Serum TC, TG, LDL-C, homocysteine, CRP, interleukin-1β and interleukin-6 levels of healthy subjects (n = 27) who were given 112 mg/day calcium fructoborate supplements (3 mg boron and 5.26 mg calcium) for 30 days were shown to decrease. It has been suggested that calcium fructoborate is important in providing a healthy lipid profile and decreases the levels of inflammation markers and has an anti-inflammatory effect [9]. In our study, after the one-month boron-rich diet, serum total, LDL-C and VLDL-C levels were found to decrease significantly and the increase in serum HDL-C levels were not significant. Based on negative and significant correlation between serum TC and serum boron concentration, the clinically important reduction (16 units) in TC levels, and the literature data, it can be concluded that boron-rich diet may be beneficial for lipid metabolism and may regulate serum lipid profile. The significant decrease in serum lipid values may have arisen from high fiber content of diet rich in boron consumed in the present study.

One of the important health problems is the increase in the number of people with coronary heart disease. It has been reported that the risk of coronary heart disease decreases in people consuming more fiber in their diet [45]. Dietary fiber consists of nutrients, such as pectin, gum, hemicellulose, cellulose, β-glucan, inulin, lignin, that are resistant to digestive enzymes and are mainly found in cereal, dried fruit, and vegetables. Dietary fiber decreases the cholesterol level by providing the use of more cholesterol in the bile acid synthesis pathway and increasing the excretion of bile salts from the intestine [27]. Foods with high amount of boron are usually those with high amount of fiber. It has been suggested that nutrition with boron-rich foods may be an important contributor to prevention from cardiovascular diseases [46]. Increasing the boron intake via diet can only be achieved by consuming fruits, vegetables, dried fruits, and nuts. Therefore, diets arranged to increase the amount of boron intake are largely similar to the Mediterranean diet. Vegetables, fruits, grains, dried legumes, and oilseeds, are frequently found in the Mediterranean diet that is known to reduce the risk of cardiovascular diseases, type 2 diabetes, obesity, and cancer [47].

SREBP is a key transcription factor that regulates the genes in the *de novo* lipogenesis and glycolysis pathways [48]. It has been shown that boron can inhibit SREBP activity and regulate lipid biosynthesis [35,49]. In our study, a significant positive correlation was found between serum SREBP level and LDL-C levels while a significantly negative correlation was found with HDL-C levels. However, there was no significant difference between serum SREBP levels before (20.59 ± 11.39 ng/mL) and after the one-month boron-rich diet (20.96 ± 8.48 ng/mL) ($p = 0.844$). In contrast to our study, Mohammadi et al. found a negative correlation between the plasma SREBP and serum TC and LDL-C levels [50] in which plasma SREBP expressions were investigated in 120 healthy subjects. Since SREBP is a new parameter that has been studied recently, there has been no clinical study yet related with boron and SREBP. Therefore, this contradictory result between the two studies is expectable. Very soon, more accurate results will be achieved by conducting more detailed studies and increasing the number of similar studies.

It has been shown that vitamin D levels of individuals (n = 13) with vitamin D deficiency (< 12 ng / mL) who have been given calcium

fructoborate supplement containing 6 mg of boron per a day for 60 days, increased by 20% [51]. Although the mechanism of action is not known yet, it is thought that boron may have repressed the catabolic activity of the 24-hydroxylase enzyme [52]. In our study, there was 11% increase in serum vitamin D levels after the one-month boron-rich diet. However, there was no significant difference between serum vitamin D levels before (23.17 ± 17.24 ng/mL) and after the one-month boron-rich diet (26.03 ± 13.07 ng/mL) ($p = 0.236$). This may be due to the fact that the initial vitamin D levels of the participants were not very low and the one-month boron-rich diet period was not sufficient.

In another study, it has been shown that orthoboric acid supplementation containing 5 and 25 mg/kg/day boron for 45 days in vitamin D deficiency decreased serum ALP level in chicks [53]. In our study, the serum ALP level also decreased significantly after a one-month diet, but this decrease was not clinically significant.

Serum TSH levels of our participants reduced 25% significantly after the one-month boron-rich diet. This result may have been due to the change in the diet iodine. The amount of dietary iodine can not be calculated in BeBis programme. Therefore, the dietary iodine amount was not calculated in our study. Boron-rich diet may be beneficial for some types of thyroid patients. In a study conducted in our country, a significant positive correlation was determined between serum TSH level and both with body weight and BMI in 226 obese and 38 healthy non-obese people [54]. Moreover, TSH is known to affect adipogenesis in adipose tissue [55]. The decrease in TSH levels may be due to the decrease in body fat mass in our study. In the light of this information, the relation between dietary boron and TSH should be examined in detail and supported by clinical studies.

In middle-aged women and men, a low-boron diet (0.25 mg / 2000 kcal) for 63 days and then 49 days boron supplementation (3 mg/day boron) significantly reduced blood urea level and platelets count; increased hemoglobin, MCH, and MCHC levels significantly [56]. It has been emphasized that these changes are not clinically important since they were among the reference values. In our study, blood urea level and MCH decreased significantly at the end of the one-month boron-rich diet; however, it does not have a clinical importance, there was a negative significant correlation between serum urea and boron concentrations. The experimental protocol of our study was quite different from the above study of Nielsen. Boron intake of our participants was increased by 10 mg via the diet, and they were not fed with a boron-poor diet.

The boric acid given at 40 and 80 ppm with drinking water to the rats for 60 days significantly increased the RBC and hemoglobin values, but at 160 and 640 ppm it decreased RBC, WBC, and hemoglobin values significantly [57]. Similarly, blood WBC count and MCH significantly decreased with the boron-rich diet in our study. However, there was no clinical importance. It has been reported that intraperitoneally boric acid supplementation (5, 10, 20 mg/kg/day boron) for 14 days did not prevent the decrease in WBC level caused by gentamicin while it increased blood hematocrit level in rats [58]. In another study, obese rabbits were fed with a high energy diet and given borax decahydrate supplemented with 10, 30, and 50 mg/kg in 96 h intervals orally for 7 months and hematological parameters were not affected [59].

Little is known about boron homeostasis in humans. There are contradictory expressions in the literature related to the relationship between NaBC1 and boron. In Park et als' study, it has been suggested that NaBC1 is a transporter related with boron homeostasis, it functions as an electrogenic, voltage-regulated, Na^+-coupled $B(OH)_4^-$ transporter in the presence of borate, and it transports Na^+, H^+ in the absence of borate [60]. Liao et al. reported that mRNA expression levels of NaBC1 in the gut may be affected by boron addition to diet [61]. However, according to Zhang et als' study, NaBC1 is not a transporter related with borate [62]. In the present study, no significant difference was found between the serum NaBC1 levels before (2.40 ± 2.01 (2.89) ng/mL) and after the one-month boron-rich diet (1.9 ± 1.7 (1.4) ng/mL) ($p = 0.754$). All these results show that boron homeostasis should be researched in details in point of NaBC1.

4.4. Urine parameters

It has been reported that the urine boron level may widely reflect the dietary boron intake [24]. The first study that investigated the relationship between boron intake and urine boron level belonged to Culver et al. in 1994. Urine boron level has been found to correlate with daily boron intake level [63].

The urine boron levels of 18 men who took 10 mg of boron supplementation for 4 weeks were determined as 1.6 ± 0.3 mg/day at the beginning of the study and increased to 10.13 ± 0.92 mg/day at the end of the study [17]. In another study, daily boron intake and serum, urine boron levels of 155 people who work in boron processing plant in Bandırma, Turkey, were evaluated. They found that the urine boron level increased with the increased exposure of boron and a positive correlation was found between urine and the serum boron concentration [64].

In our study, the urine boron level was determined as 1.46 ± 0.8 (1.20) mg/day at the beginning of the study. After the one-month boron-rich diet it increased to 8.65 ± 3.17 (8.07) mg/day. These findings support the knowledge that urine boron concentration increases together with the increase in boron intake. In our study, when the dietary boron intake increased 8-fold, the urine boron level increased 6-fold. Also, a significant and positive correlation was found between urine and serum boron concentrations. The reason for the increase in urine densities may be due to excessive perspiration because of the rising temperature in summer.

4.5. Salivary parameters

The data about the salivary boron level is very limited in the literature. In a study conducted in Canada, the mean salivary boron level of 16 healthy participants have been found to be 0.016 ± 0.005 ppm with the ICP-MS method [65] and the daily dietary boron intake have not been calculated. In our study, the mean salivary boron level was 0.06 ± 0.04 ppm at the beginning. After boron-rich diet for a month, it increased to 0.10 ± 0.09 ppm.

This study is the first study showing that the salivary boron level is increased when daily dietary boron intake increases. In recent years, biological samples taken with non-invasive methods such as saliva, instead of serum, have been preferred in the determination of biochemical parameters. The fact that salivary and serum boron values are very close to each other and the difference between them is statistically insignificant shows that salivary boron level can be used instead of serum boron level assay.

Saliva buffering capacity is the best predictor of caries activity. Patients with high buffering capacity are reported to be resistant to caries [66]. In our study, saliva buffering capacity significantly increased to 5.21 ± 0.78 from 4.42 ± 0.69 at the end of the one-month boron-rich diet. It has been thought that the boron may have a cariostatic effect [67]. The boron level of carious teeth were determined to be lower than those of healthy teeth [68]. The increase in salivary boron may have a beneficial effect on oral and dental health indirectly and may reduce the formation of caries.

Park et al. detected NaBC1 in basolateral membranes of salivary gland acinar cells of rat [60]. In our study, at the end of the one-month boron-rich diet, the saliva NaBC1 concentration was not increased significantly. Our study is the first study that examined level of salivary NaBC1 depending on a diet.

5. Conclusion

Our study is the first clinical study in which the dietary boron level was increased via foods. When daily dietary boron amount was increased 10 mg, serum, saliva, and urine boron values increased 1.3, 1.7,

and 6 times, respectively. A positive correlation was found between serum, urine and salivary boron values. It was shown that saliva samples could be used for boron determination instead of serum samples which requires invasive application. At the end of the one-month diet, the number of blood WBC, eosinophil ratio, MCH, FBG, ALP, TSH, serum urea, and fasting insulin levels decreased significantly, while serum creatinine level and salivary buffering capacity were increased significantly. Significant changes in TSH and salivary buffering capacity may have clinical importance. The most important change was related with the lipid profile. Serum TC, LDL-C and VLDL-C and TG levels decreased significantly after the one-month boron-rich diet. The body weight, body fat mass and BMI of the participants decreased significantly.

6. Limitations

The first limitation of this study was the use of changes in the total diet, and not of specific dietary supplements (possibly placebo-controlled and administered blindly) to increase the dietary boron intake. Second, although macronutrients and caloric values were preserved, it was not possible to control the other dietary nutrients such as fiber, vitamin C, A, and E. Third, multivariate analysis was necessary to differentiate the effects of these nutrients. However, for this analysis, the number of participants were not enough as the number of parameters were quite high in our study.

Declarations of interest

None.

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