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NUTRITION

Comparative effects of daily and weekly boron supplementation on plasma steroid hormones and proinflammatory cytokines

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ABSTRACT

Boron possesses widespread properties in biochemistry and nutrition. Acute supplementation with 11.6 mg of boron resulted in a significant increase in plasma boron concentration. Given such a fast bioavailability, the objective was to determine whether acute (hourly or daily), and weekly supplementation could have any significant biological effects on the steroid hormones and further on some inflammatory biomarkers. Eight healthy male volunteers attended the laboratory on three occasions (days 0, 1 and 7). On the first day (day 0), a blood sample collection at 8.00 A.M was followed by ingestion of placebo with the breakfast. On the next day (supplementation-day 1), similar procedure was followed by ingestion of a capsule containing 10 mg of boron. On both occasions blood was collected every 2 h for the next 6 h. Subjects were requested to consume a capsule of 10 mg boron every day with their breakfast, and on the day 7, the blood collection was carried out at 8.00 A.M, again. Boron in plasma increased significantly following hours and weekly consumption. Six hours supplementation showed a significant decrease on sex hormone binding globulin (SHBG), high sensitive CRP (hsCRP) and TNF-α level. After one week (in samples taken at 8.00 A.M, only), the mean plasma free testosterone increased and the mean plasma estradiol decreased significantly. Dihydrotestosterone, cortisol and vitamin D was elevated. Also, concentrations of all three inflammatory biomarkers decreased after supplementation. Of note, despite decreased proinflammatory cytokines, based on recent clinical data, this must be the first human study report to show an increase level of free testosterone after boron consumption.

Introduction

Boron has not been generally accepted as being essential for humans; however, it is accepted as being a beneficial bioactive element for humans. In summary, the biochemical function of B is still speculative. Future research should be focus on determining this function, as this would help research in other areas, such as identifying B-status indicators and the nutritional importance of B in some pathological conditions, such as arthritis and osteoporosis. Even without this defined function, however, it is apparent that B enhances optimal function throughout the life cycle. It is reported that boron is necessary for the formation of specific steroid hormones. A clinical trial has demonstrated that both 17-beta-estradiol and testosterone levels significantly increase in postmenopausal women consuming 3 mg/day of boron for 7 weeks. In this study, boron supplementation caused a twofold increase in testosterone concentrations and a significant increase in calcium retention [1]. In another study, men given 10 mg of boron a day for 4 weeks experienced a significant increase in 17-beta-estradiol levels and an increase in plasma testosterone [2]. The results of a study by Wallace et al. [3] suggest that acute supplementation with 11.6 mg of boron, as 102.6 mg sodium tetra borate decahydrate, given in combination with meal, resulted in a significant increase in plasma boron concentration compared with placebo in healthy middle-aged men. This showed that boron in the supplements was bioavailable and effectively absorbed. Overall, there was a 10-fold increase in plasma boron from fasting concentrations. Plasma boron was significantly elevated from baseline values 1 h after consumption of the boron supplement and the concentration peaked at 4 h postprandial. At 6 h postprandially, the plasma boron concentration was still significantly higher than the baseline concentration (0.124 ± 0.02 mg/l vs. 0.008 ± 0.01 mg/l; $P \leq 0.001$) [3].

Having such a fast bioavailability, the objective of the present study was to determine if acute or daily supplementation with boron could have any significant biological effects on the synthesis of steroid hormones and to rule out the possibility that longer-

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term (weekly) supplementation of boron may exert such a function. While boron supplementation can alleviate arthritic and inflammation signs [4–6] and may have anti-carcinogenic properties [7–11]; therefore its effect on proinflammatory biomarkers (cytokines) in plasma was assessed.

Materials and methods

This study was approved by the Research Ethics Committee of the University and informed consent was obtained from each subject at the time of recruitment to the study.

Subjects

Eight apparently healthy male volunteers from academic staff and students participated in the study. They were non-smokers with a mean age of 41.3 ± 7.5 (range 29–50) years and body mass index (BMI) of 25.5 ± 2.2 kg/m^2. None of the volunteers was adhering to any form of special diet or taking medications or dietary supplements, and had no previous history of endocrine disease.

Initially, we started with 10 subjects and had 2 exclusions; due to the hyperandrogenecity in one subject and sudden back pain in other one. Other reason was lack of funding which allowed us to design the study with only 10 subjects.

Study design

This study was an experimental (pre and post supplemental) controlled design. Subjects attended the laboratory on three occasions (days 0, 1 and 7), each following an overnight fast for 12 h. (1) On the first day (day 0), they were admitted at 8.00 A.M, blood was collected and was followed by ingestion of a capsule containing lactose powder as placebo along with their breakfast. (2) On the next day as the first day of supplementation (day 1), they were admitted at 8.00 A.M, blood was collected and was followed by ingestion of a capsule containing 10 mg of boron as sodium tetra borate along with their breakfast. The boron supplements were prepared from sodium tetra borate and lactose (Sigma Chemical Co., St. Louis, Mo). Samples of blood were collected every 2 h for the next 6 h. Each sample was centrifuged, separated and plasma then fractionated and stored at −20 °C until hormone assay. (3) Subjects were requested to maintain their habitual diet and activity throughout the next week and consume a capsule of 10 mg boron everyday with their breakfast. Upon arrival at the center on day 7, one blood collection was carried out at 8.00 A.M after an overnight fasting and plasma were also stored at −20 °C, again. Adherence of the subjects with supplementation was determined in a way that boron capsules were provided in 1-week lots with a number of surplus capsules and the subjects were asked to return the leftovers so as to allow gauging the number of capsules returned, the degree of apparent adherence could be estimated.

Biochemical analysis

Pre samples of the day 0, and daily supplemented samples of the day 1 and weekly supplemented plasma samples were analyzed for boron. Boron concentration in plasma was determined using inductively coupled plasma-optical emission spectrometry [(ICP-OES), Perkin Elmer-Optima 2100 DV, USA]; with the operating conditions of plasma gas flows (L/min): plasma 15, auxiliary 0.2, nebulizer 0.5; Rf power at torch of 1300 watts and pump flow rate of 1.5 ml/min. Samples were diluted with 1 ml of 200 mM nitric acid without heating as described in Usuda et al. (1997). The detection limit of the assay for boron was 0.01 μg/g for the plasma samples [12].

Baseline and all hourly (2 h intervals; day 1) and weekly plasma samples were analyzed for testosterone (T), free testosterone (FT), dihydrotestosterone (DHT), estradiol (E2), sex hormone binding globulin (SHBG), cortisol, 25-hydroxy vitamin D, luteinizing hormone (LH), Interleukin-6 (IL-6), high sensitive CRP (hsCRP) and tumor necrosis factor-alpha (TNF-α).

T, FT, DHT, E2, SHBG, cortisol, LH, and hsCRP were analyzed by ELISA (Diagnostics Biochem Canada Inc., Ontario, Canada). The intra-assay coefficients of variation (CVs) % and assay sensitivity were 5.1 and 0.022 ng/ml for T; 2.0 and 0.17 pg/ml for FT; 2.1 and 6 pg/ml for DHT; 6.1 and 10 pg/ml for E2; 4.8 and 0.1 nmol/L for SHBG; 3.1 and 0.4 μg/dl for cortisol; 5.4 and 0.2 IU/L for LH; and 1.4 and 10 ng/ml for hsCRP, respectively.

25-Hydroxy vitamin D was analyzed by EIA (Immuno Diagnostic Systems Ltd., Boldon, Tyne Wear, UK), with the intra-assay coefficients of variation (CVs) % and assay sensitivity of 6.9 and 5 nmol/L; and IL-6 and TNF-α were analyzed by ELISA, Diaclone, Besancon, France, with the intra-assay coefficients of variation (CVs) % and assay sensitivity of 4.2 and <2 pg/ml for IL-6, and 3.3 and <8 pg/ml for TNF-α, respectively.

Statistical analysis

Data are expressed as mean ± SD and a statistical package (SPSS 17.0) was used to perform all comparisons. The paired sample Student's *t*-test was used to determine the statistical significance between mean values for boron concentrations and to test for significant hourly mean (average of 3 measurements) of day 0 vs. day 1, mean of the three time intervals in day 0 vs. day 1 (supplemented time points), and mean of samples of 8.00 A.M in day 0 vs. day 7 (weekly) variation in pre and post treatment occasions for hormones and inflammatory biomarkers.

Results

(1) All subjects participated in this study completed the investigation with full adherence on boron consumption. They reported no adverse effects. The baseline and supplemented mean ± SD of plasma boron concentrations (ppm) of subjects are shown as follow:

Plasma boron:

At baseline or unsupplemented period (placebo): 0.036 ± 0.021 ppm;

After hourly or daily supplementation of boron (10 mg): 0.066 ± 0.028 ppm;

After weekly supplementation of boron (10 mg/d): 1.32 ± 0.057 ppm.

Plasma boron increased significantly ($P = 0.002$) following hours consumption of boron compared to the placebo. It elevated from baseline values 4–6 h after consumption. After one week, the plasma boron concentration peaked largely and was significantly ($P = 0.000$) higher than the baseline and daily concentrations. The magnitude of the boron elevation for baseline vs. daily and weekly supplement was 1.83 and 36-fold and for daily vs. weekly supplement was 20-fold, respectively.

(2) The average baseline (placebo/day 0) and average hourly (day 1) supplemented mean ± SD of plasma hormones and inflammatory biomarkers are shown in Table 1. For Vit. D and inflammatory biomarkers, the results of the blood samples taken only at 14.00 P.M are presented.

Six hours boron supplementation had no major effect on hormone concentrations except SHBG showed significantly ($P = 0.000$) lower concentrations following boron consumption. Among the inflammatory biomarkers, plasma hsCRP concentration decreased significantly ($P = 0.005$). Also, the TNF-α

Table 1
Mean ± SD[a] of 6 h unsupplemented baseline (placebo/day 0) and boron supplemented periods (day 1) for the hormones and inflammatory biomarkers.

Variable	Mean ± SD (day 0)	Mean ± SD (day 1)	*P* value*
Total testosterone (ng/ml)	2.52 ± 0.62	2.60 ± 0.52	0.30
Free testosterone (pg/ml)	9.42 ± 4.59	9.58 ± 4.32	0.70
Dihydrotestosterone (pg/ml)	645 ± 137	658 ± 142	0.40
Estradiol (pg/ml)	36.90 ± 13.50	35.80 ± 13.30	0.70
Sex hormone binding globulin (nmol/L)	32.20 ± 9.40	29.70 ± 8.00	0.000
Cortisol (μg/dl)	4.63 ± 2.29	4.07 ± 1.73	0.06
Luteinizing hormone (IU/L)	2.29 ± 1.42	2.16 ± 1.21	0.70
Vitamin D[b] (nmol/L)	36.20 ± 15.90	35.70 ± 12.60	0.9
hsCRP (ng/ml) (*n* = 7)	1372 ± 1182	909 ± 783	0.005
IL-6[b] (pg/ml)	1.32 ± 0.65	1.17 ± 0.65	0.6
TNF-α[b] (pg/ml)	10.50 ± 4.14	8.58 ± 3.86	0.04

[a] Values are mean of the average of the 3 measurements for each subjects (*n* = 8) obtained from blood samples taken at 10.00 A.M, 12.00 and 14.00 P.M (24 readings). Samples of the 8.00 A.M excluded due to unsupplementation.
[b] Analysis for Vit. D, IL-6, and TNF-α was conducted with the data obtained from only one blood sample taken at 14.00 P.M (mean of 8 readings; one outlier value excluded for hsCRP).
* A value of $P \leq 0.05$ was considered statistically significant.

levels showed a significant decrease ($P = 0.04$) in the average readings of the two different days (10.50 ± 4.1 pg/ml vs. 8.58 ± 3.8 pg/ml).

(3) The comparison of the mean ± SD of baseline (placebo) hormones and inflammatory biomarkers concentration vs. boron supplementation of the three time intervals (every 2 h) in day 0 vs. day 1 are shown in Table 2.

Comparison of each time interval in day 0 with the corresponding time point in day 1 for each variable showed no significant difference, except for SHBG and TNF-α showing significantly ($P \leq 0.05$) lower concentrations, hours after boron consumption. The above data indicated that except these two, there was no significant hourly effect for boron supplementation on the corresponding time point for the variables shown in Table 2.

(4) The comparison of the baseline (placebo/day 0) and weekly supplemented mean ± SD of plasma hormones and inflammatory biomarkers plus hormone ratios of the subjects (samples taken at 8.00 A.M, only) are shown in Table 3.

The mean plasma FT concentration increased significantly from 11.83 ± 4.60 to 15.18 ± 3.07 pg/ml, and the mean plasma E2 concentration decreased significantly from 42.33 ± 16.47 to 25.80 ± 11.25 pg/ml after one week supplementation, while DHT, cortisol and Vit. D showed a non significant, but higher level at weekly post supplementation period. Also, all three inflammatory biomarkers decreased after supplementation, showing a significant difference for TNF-α levels ($P \leq 0.05$), and a marked non-significant decrease (approximately 50%) for hsCRP and IL-6 levels. The reason for this non-significancy may lie within the broad value of the standard deviations.

Discussion

The mechanism whereby boron influences bone mineral balance has not been determined. However, past studies by Nielsen et al. (1987) indicate that dietary boron repletion in postmenopausal women, who were previously on a low-boron diet, increased their serum 17B-estradiol (E2) and testosterone levels, particularly in those whose dietary Mg intake was low [1]. Similar increase in serum E2 levels was found in healthy males after 4 weeks of dietary boron supplementation [2]. Accordingly, it is possible that boron may modify bone mineral balance by

Table 2
Hourly comparison of hormones and inflammatory biomarkers (mean ± SD, *n* = 8) following placebo (day 0) and boron supplementation (day 1).

Variable	Placebo (h)				Boron supplementation (h)			
	8.00 A.M	10.00 A.M	12.00 P.M	14.00 P.M	8.00 A.M[a]	10.00 A.M	12.00 P.M	14.00 P.M
Total testosterone (ng/ml)	3.20 ± 0.60	2.59 ± 0.61	2.48 ± 0.68	2.48 ± 0.64	–	2.63 ± 0.44	2.48 ± 0.52	2.69 ± 0.62
Free testosterone (pg/ml)	11.83 ± 4.60	9.45 ± 5.10	9.01 ± 4.80	9.81 ± 4.30	–	8.55 ± 4.30	8.92 ± 4.20	11.25 ± 4.30
Dihydrotestosterone (pg/ml)	741 ± 152	652 ± 145	641 ± 155	643 ± 129	–	636 ± 131	631 ± 119	707 ± 176
Estradiol (pg/ml)	42.33 ± 16.47	40.30 ± 16.00	33.50 ± 13.00	36.80 ± 12.30	–	41.60 ± 12.90	32.0 ± 11.20	33.80 ± 15.30
Sex hormone binding globulin (nmol/L)	32.99 ± 9.97	31.90 ± 10.10	32.50 ± 9.80	32.30 ± 9.40	–	30.08 ± 9.50*	29.50 ± 7.60*	29.40 ± 7.60*
Cortisol (μg/dl)	7.93 ± 4.62	5.70 ± 2.80	4.18 ± 1.69	4.01 ± 2.12	–	4.55 ± 1.71	3.70 ± 1.52	3.96 ± 2.05
Luteinizing hormone (IU/L)	1.74 ± 0.70	2.18 ± 1.39	2.47 ± 1.62	2.22 ± 1.40	–	2.16 ± 1.35	2.13 ± 1.38	2.20 ± 1.35
Vitamin D (nmol/L)	35.82 ± 13.49	–	–	36.27 ± 15.30	–	–	–	35.70 ± 12.60
hsCRP (ng/ml) (*n* = 7)	1460 ± 1233	1545 ± 1342	1287 ± 1192	1284 ± 1175	–	942 ± 874	894 ± 831	892 ± 767
IL-6 (pg/ml)	1.55 ± 1.05	–	–	1.32 ± 0.65	–	–	–	1.17 ± 0.65
TNF-α (pg/ml)	12.32 ± 3.13	–	–	10.50 ± 4.10	–	–	–	8.50 ± 3.80*

[a] 8.0 A.M is baseline (unsupplemented) time point in day 1.
* Significantly different $P \leq 0.05$ from corresponding (similar) time point in placebo (day 0); placebo vs. supplemented time point.

Table 3
Hormones and inflammatory biomarkers concentration (mean ± SD) plus hormone ratios following consumption of placebo (day 0) and weekly boron supplementation (day 7) [comparison was performed for the samples taken at 8.00 A.M, $n = 8$].

Variable	Mean ± SD (day 0)	Mean ± SD (day 7)	*P* value*
Total testosterone (ng/ml)	3.20 ± 0.60	3.32 ± 0.56	0.73
Free testosterone (pg/ml)	11.83 ± 4.60	15.18 ± 3.07	0.02
Dihydrotestosterone (pg/ml)	741 ± 152	791 ± 120	0.34
Estradiol (pg/ml)	42.33 ± 16.47	25.81 ± 11.25	0.01
Sex hormone binding globulin (nmol/L)	32.99 ± 9.97	31.44 ± 9.06	0.27
Cortisol (μg/dl)	7.93 ± 4.62	10.10 ± 4.88	0.25
Luteinizing hormone (IU/L)	1.74 ± 0.70	2.06 ± 1.01	0.4
Vitamin D (nmol/L)	35.82 ± 13.49	38.36 ± 12.09	0.32
hsCRP (ng/ml) ($n = 7$)	1460 ± 1233	795 ± 734	0.11
IL-6 (pg/ml)	1.55 ± 1.05	0.87 ± 0.15	0.09
TNF-α (pg/ml)	12.32 ± 3.13	9.97 ± 3.23	0.05
FT/T (pg/ml/ng/ml)	3.62 ± 1.02	4.66 ± 1.08	0.001
FT/E2 (ng/ml)	0.31 ± 0.15	0.67 ± 0.29	0.004
T/E2 (ng/ml)	91.68 ± 54.8	148.8 ± 58.7	0.009
T/SHBG (ng/dl)	31.13 ± 14.7	33.21 ± 13.4	0.48
DHT/T (ng/ml)	0.23 ± 0.01	0.24 ± 0.02	0.29

* A value of $P \leq 0.05$ was considered statistically significant.

increasing the synthesis and/or actions of sex hormones. Nevertheless, because boron treatment appears to increase serum E2 level in postmenopausal women, it has been suggested that dietary boron supplementation may reduce some of the adverse effects of E2 deficiency that is associated with menopause and cessation of ovarian function, such as bone mineral deficits and bone loss. On the other hand, in as much as the possibility that the effect of boron on bone mineral homeostasis is mediated through interaction between boron and sex hormones (particularly E2) is attractive, supporting evidence for this hypothesis is currently lacking [13]. Estrogen levels drop after menopause causing osteoclasts to become more sensitive to parathyroid hormone, which signals them to break down bone. Recent evidence, suggests that boron modifies the action of the hormones (estrogen and vitamin D) at the cell membrane level, which ultimately might affect bone turnover.

It is reported that dietary boron influences the activity of several micronutrients, including calcium, magnesium, and vitamin D, and boron supplementation in rats and chicks has been shown to increase bone strength [14]. In athletic subjects boron supplementation modestly affected mineral status, and exercise modified the effects of boron supplementation on serum minerals [15]. However, it was also found that 3 mg boron/d for 10 months altered serum mineral levels but did not affect circulating hormones [16].

In this study, it was found that boron is bioavailable and effectively absorbed. Generally, there was several folds increase in plasma boron from fasting conditions. The findings for hourly supplementation were in keeping with results of study reported by Wallace et al. [3]. Supplementation of healthy males with 10 mg/d after one week resulted in a significant rise in plasma free testosterone concentration. Based on recent clinical data, this is the first human study report to show an increase level of free testosterone after boron consumption. Previously, supplementation of healthy males with 10 mg/d after several weeks resulted in a significant rise in plasma 17-B estradiol concentration [17] and the increase was consistent with some animal reports, as well [18,19]. It was shown that changes in plasma testosterone is achievable by boron in rats [20] and also in rats fed a range of dietary boron for 30 or 60 days, which appear to be time- and dose-dependent [21]. However, the significant decrease in plasma estradiol after one week supplementation indicates a higher rate of conversion of total testosterone to free testosterone in the testosterone metabolic pathway. In support of the above findings, the ratios of FT/T, T/E2, and FT/E2 were all significantly increased, indicating an androgen amplifier condition. It is known that the major circulating androgen in males is testosterone and about 98% of testosterone molecules are bound to proteins in the blood, principally to sex hormone-binding globulin (SHBG) and also to albumin and cortisol-binding globulin, as well. It is assumed that bound hormones cannot exit blood capillaries and are therefore not bioavailable. Thus, elevation of unbound free testosterone by boron supplementation supports the hypothesis that boron has an important biological role or change in steroid utilization. The free hormone hypothesis states that the biological activity of a given hormone is affected by its unbound (free) rather than protein-bound concentration in the plasma. This hypothesis is likely to be valid for free testosterone showing its level to be under the influence of boron. This free testosterone is considered the biologically active form of the hormone, as this portion of the hormone can interact at the target tissue receptors. Given the effect of boron on plasma steroid hormone concentrations and their diverse roles in metabolism, it is not surprising that boron has been implicated with a number of diseases. It might have a role in some disorders of unknown etiology, such as osteoporosis in post-menopausal women that exhibit disturbed major mineral metabolism [1] under the influence of hormonal variations. Boron is beneficial for optimal calcium and bone metabolism [22,23] and in particular via hormonal elevations in post-menopausal women [1] and vitamin D synthesis or up-regulation [24,25].

In cross-sectional and longitudinal studies of men aged 30 or 40 years and above, total, bioavailable and free testosterone concentrations fall with increasing age with a steeper decline in bioavailable and free compared with total testosterone concentrations [26,27]. In older men above the age of 65 or 70 years, the changes in total testosterone are overshadowed by more significant declines in free testosterone levels [28,29].

The fact that boron changed steroid levels suggests that boron may now appear to play a role in human nutrition, particularly in relation to bone health, as well.

Furthermore, one week supplementation resulted in a significant decrease in plasma TNF-α concentration (12.32 pg/ml vs. 9.97 pg/ml) and a remarkable decrease (about 50%) in plasma concentration of hsCRP (1460 ng/ml vs. 795 ng/ml) and IL-6 (1.55 pg/ml vs. 0.87 pg/ml), respectively. This is also, the first human study reporting the effect of boron supplementation on reducing the inflammatory biomarker levels. The observed lack of significance for hsCRP and IL-6, regardless of 50% decrease might have been due to the broad values of the standard deviations obtained for the two variables.

Recent findings also indicate that boron and borates have attracted scientific attention due to recent reports indicating that they may possess anti-carcinogenic properties [7,8]. It has also been reported that boric acid inhibits human prostate cancer cell proliferation [9,10] and ingestion of boron in drinking water decreases

the incidence of cervical cancer-related histopathological findings [11]. Hormone replacement therapy (HRT) is known to reduce lung cancer and dietary boron may also have actions similar to those of HRT. In a study on the joint effects of boron intake and HRT use on lung cancer risk, it was reported for the first time that boron intake was inversely associated with lung cancer in women, whereas women who consumed low boron and did not use HRT were at substantially increased odds [30]. Also, evidence exists that boron may have antioxidants and anti-inflammatory properties [31,32]. It might be interesting to study further the above effects simultaneously with alterations in steroid hormone concentrations as a result of boron deficiency or supplementation states.

In healthy persons, lowering the level of C-reactive protein, a key biomarker of inflammation, has been shown to elicit a reduction in cardiac events. Therefore, the decreased level of hsCRP after boron supplementation is clinically plausible. Drug companies are actively developing medications aimed specifically at reducing CRP levels [33]. In addition, both TNF-α and IL-6 which are considered as risk factors for coronary heart disease and cardiovascular function and morphology, shown as ectopic fat accumulation in various tissues [34–36], were reduced by boron supplementation in this study, as well.

Among several nutrients, the role of boron on sex hormone status is not completely known; however, increased levels of sex steroids have been demonstrated in both males and females after boron supplementation and it seems to be required for the formation of activated (hydroxylated) forms of certain steroid hormones. The mechanism of action and its function seems to be time and dose dependent. Based on available data, experts have concluded that the level of testosterone and estradiol have been changed after long term therapy, however, the present study showed an increase level of free testosterone and decreased level of estradiol, after short term consumption. Based on systemic review, there seems to be a possible association between endogenous steroids and boron which is found rich in nuts, legumes, dried/fresh fruits and vegetables.

Finally, further studies are required (a) to establish the feasibility of modulating steroid hormones by boron supplementation in males and females, especially in older adults, and (b) decreasing proinflammatory cytokines and in turn (c) the possible impacts or protective roles in a number of diseases or pathological conditions. Thus, additional research is necessary to further clarify boron's influence in a 6–8 weeks supplementation trial with a weekly blood sampling.

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References

[1] Nielsen FH, Hunt CD, Mullen LM, Hunt JR. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women. FASEB J 1987;1:394–7.
[2] Naghii MR, Samman S. The effect of boron supplementation on its urinary excretion and selected cardiovascular risk factors in healthy male subjects. Biol Trace Elem Res 1997;56:273–86.
[3] Wallace JMW, Hannon-Fletcher MPA, Robson PJ, Gilmore WS, Hubbard SA, Strain JJ. Boron supplementation and activated factor VII in healthy men. Eur J Clin Nutr 2002;56:1102–7.
[4] Newnham RE. Arthritis or skeletal fluorosis and boron. Letter. Int Clin Nutr Rev 1991;11:68–70.
[5] Hunt CD, Idso JP. Dietary boron as a physiological regulator of the normal inflammatory response: a review and current research progress. J Trace Elem Exp Med 1999;12:221–33.
[6] Newnham RE. How boron is being used in medical practice. In: Goldbach HE, Rerkasem B, Wimmer MA, Brown PH, Thellier M, Bell RW, editors. Boron in plant and animal nutrition. New York: Kluwer Academic/Plenum Publishers; 2002. p. 59–62.
[7] Gallardo-Williams MT, Chapin RE, King PE, Moser GJ, Goldsworthy TL, Morrison JP, et al. Boron supplementation inhibits the growth and local expression of IGF-1 in human prostate adenocarcinoma (LNCaP) tumors in nude mice. Toxicol Pathol 2004;32:73–8.
[8] Cui Y, Winton MI, Zhang ZF, Rainey C, Marshall J, De Kernion JB, et al. Dietary boron intake and prostate cancer risk. Oncol Rep 2004;11:887–92.
[9] Gallardo-Williams MT, Maronpot RR, Wine RN, Brunssen SH, Chapin RE. Inhibition of the enzymatic activity of prostate-specific antigen by boric acid and 3-nitrophenyl boronic acid. Prostate 2003;54:44–9.
[10] Barranco WT, Eckhert CD. Boric acid inhibits human prostate cancer cell proliferation. Cancer Lett 2004;216:21–9.
[11] Korkmaz M, Uzgoren E, Bakirdere S, Aydin F, Ataman OY. Effects of dietary boron on cervical cytopathology and on micronucleus frequency in exfoliated buccal cells. Environ Toxicol 2007;22:17–25.
[12] Usuda K, Kono K, Yoshida Y. Serum boron concentration from inhabitants of an urban area in Japan. Reference value and interval for the health screening of boron exposure. Biol Trace Elem Res 1997;56:167–78.
[13] Sheng MH, Taper LJ, Geit H, Veit H, Qian H, Ritchey SJ, et al. Dietary boron supplementation enhanced the action of estrogen, but not that of parathyroid hormone, to improve trabecular bone quality in ovariectomized rats. Biol Trace Elem Res 2001;82:109–23.
[14] Devirian TA, Volpe SL. The physiological effects of dietary boron. Crit Rev Food Sci Nutr 2003;43:219–31.
[15] Meacham SL, Taper LJ, Volpe SL. Effect of boron supplementation on blood and urinary calcium, magnesium, and phosphorus, and urinary boron in athletic and sedentary women. Am J Clin Nutr 1995;61:341–5.
[16] Volpe SL, Taper LJ, Meacham S. The effect of boron supplementation on bone mineral density and hormonal status in college female athletes. Med Exerc Nutr Health 1993;2:323–33.
[17] Naghii MR, Mofid M. Elevation of biosynthesis of endogenous 17-B oestradiol by boron supplementation: one possible role of dietary boron consumption in humans. J Nutr Environ Med 2008;17:127–35.
[18] Sisk DB, Colvin BM, Bridges CR. Acute, fatal illness in cattle exposed to boron fertilizer. J Am Vet Med Assoc 1998;193:943–5.
[19] Sisk DB, Colvin BM, Merrill A, Bondari K, Bowen JM. Experimental acute inorganic boron toxicosis in the goat: effects on serum chemistry and CSF biogenic amines. Vet Hum Toxicol 1990;32:205–11.
[20] Naghii MR, Samman S. The effect of boron supplementation on the distribution of boron in selected tissues and on testosterone synthesis in rats. J Nutr Biochem 1996;7:507–12.
[21] Lee IP, Sherins RJ, Dixon RL. Evidence for induction of germinal aplasia in male rats by environmental exposure to boron. Toxicol Appl Pharmacol 1978;45:577–90.
[22] Nielsen FH. Dietary fat composition modifies the effect of boron on bone characteristics and plasma lipids in rats. Biofactors 2004;20:161–71.
[23] Naghii MR, Torkaman G, Mofid M. Effects of boron and calcium supplementation on mechanical properties of bone in rats. Biofactors 2006;28:195–201.
[24] Naghii MR, Samman S. The effect of boron on plasma testosterone and plasma lipids in rats. Nutr Res 1997;17:523–32.
[25] Miljkovic D, Miljkovic N, McCarty MF. Up-regulatory impact of boron on vitamin D function—does it reflect inhibition of 24-hydroxylase? Med Hypotheses 2004;63:1054–6.
[26] Litman HJ, Bhasin S, Link CL, Araujo AB, McKinlay JB. Serum androgen levels in black, Hispanic, and white men. J Clin Endocrinol Metab 2006;91:4326–34.
[27] Liu PY, Beilin J, Meier C, Nguyen TV, Center JR, Leedman PJ, et al. Age-related changes in serum testosterone and sex hormone binding globulin in Australian men: longitudinal analyses of two geographically separate regional cohorts. J Clin Endocrinol Metab 2007;92:3599–603.
[28] Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, et al. Testosterone and estradiol among older men. J Clin Endocrinol Metab 2006;91:1336–44.
[29] Yeap BB, Almeida OP, Hyde Z, Norman PE, Chubb SA, Jamrozik K, et al. In men older than 70 years, total testosterone remains stable while free testosterone declines with age. The Health in Men Study. Eur J Endocrinol 2007;156:585–94.
[30] Mahabir S, Spitz MR, Barrera SL, Dong YQ, Eastham C, Forman MR. Dietary boron and hormone replacement therapy as risk factors for lung cancer in women. Am J Epidemiol 2008;167:1070–80.
[31] Nielsen FH. The emergence of boron as nutritionally important throughout the life cycle. Nutrition 2000;16:512–4.
[32] Armstrong TA, Spears JW. Effect of boron supplementation of pig diets on the production of tumor necrosis factor-alpha and interferon-gamma. J Anim Sci 2003;81:2552–61.
[33] Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40.
[34] Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. PLoS Med 2008;5(April (4)):e78.
[35] Arkhipova SV, Zorin NA, Iankin MIu, Podkhomuthnikov VM, Zorina VN, Zorina RM, et al. Cytokine and acute phase inflammation reactant levels in men with myocardial infarction. Klin Med (Mosk) 2009;87:20–3.
[36] Gustafson B. Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17. February 3 [Epub ahead of print].