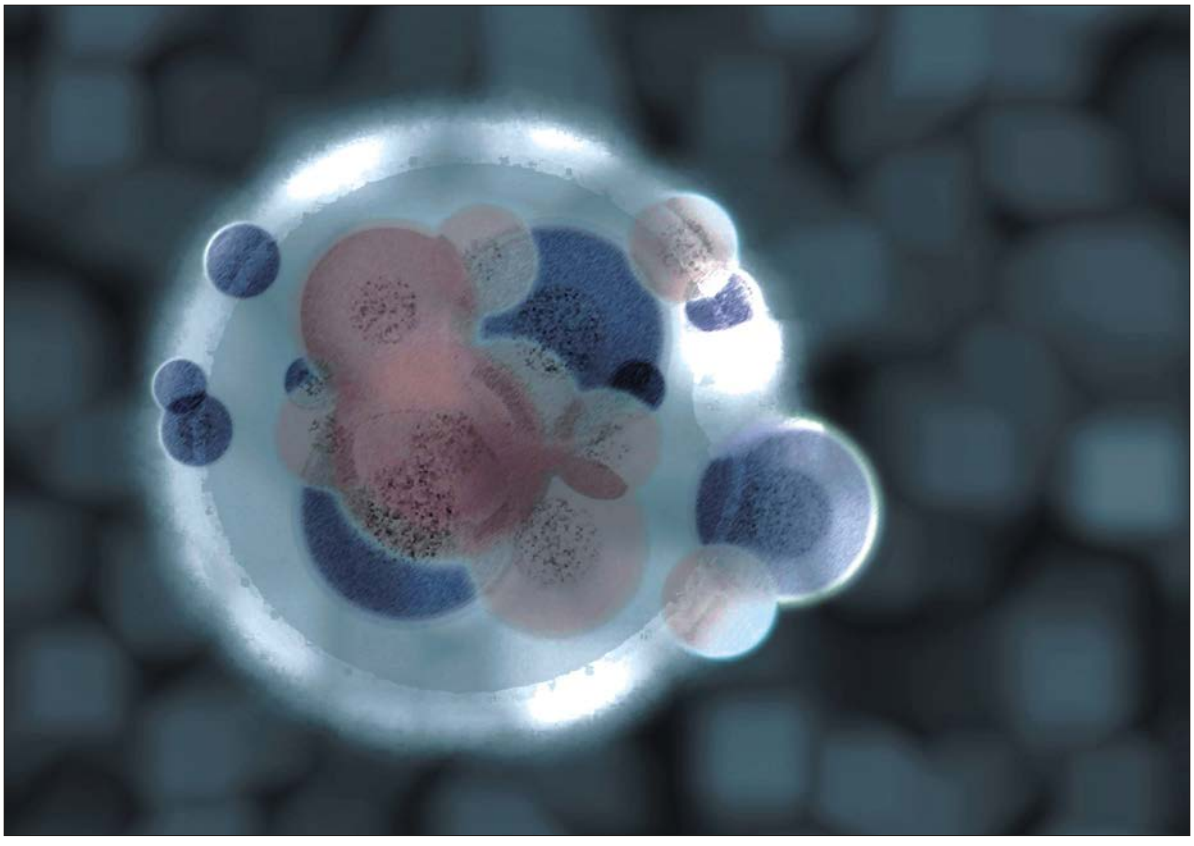

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Effect of Calcium Supplementation on Blood Pressure in Overweight or Obese Women

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Abstract: The aim of this trial was to determine the effect of short term calcium supplementation for 30 days on systolic and diastolic blood pressure in overweight or obese women. A double blind randomized clinical trial was conducted in 44 overweight or obese women (age: 25±6 years) assigned to 1000 mg day^{-1} elemental calcium or placebo groups. Systolic and diastolic blood pressures were measured using digital wrist monitor at baseline and after the intervention. Dietary calcium and energy intakes were estimated using 24 h recall for 3 days. No significant differences were observed in age, blood pressure, calcium and energy intakes between the groups at the baseline. No differences were observed between blood pressures before and after the intervention and also between the study groups. It seems that short term calcium supplementation (1000 mg day^{-1}) would not have any significant effect on blood pressure in overweight or obese women.

Key words: Calcium, blood pressure, over-weight, obesity

INTRODUCTION

The epidemic of obesity took off from about 1980 and in almost all countries has been rising inexorably ever since (James, 2008).The limited available data indicates that the prevalence of obesity in Middle Eastern countries is high, particularly in women who appear in general to have a higher prevalence of obesity than women in most western countries (IOTF/WHO, 2006). Obesity is an important risk factor for many diseases, including cardio-vascular disease, which is among the most important determinants of mortality (Finkelstein *et al*., 2003). It is estimated that hypertension is contributor of seven million deaths annually, which is equal to 13% of global mortality rate (WHO, 2002).

The prevalence of hypertension increase markedly with Body Mass Index (BMI), such that a BMI of 30-34.9 is associated with a 2.5 fold increase in prevalence of hypertension in adults under the age of 55 (Must *et al*., 1999). A reverse relationship between blood pressure and calcium intakes has been reported in epidemiological studies (Wang *et al*., 2008; Kamso *et al*., 2007; Azadbakht *et al*., 2005; Geleijnse *et al*., 2004) but some studies have not affirmed such relation (Burgess *et al*., 1999; Cappuccio *et al*., 1995; Culter and Brittain, 1990; Hamet, 1995).

Inadequate dietary calcium intakes have been reported from countries of different geographic regions or socioeconomic status (Dolega-Cieszkowski *et al*., 2006; Harinarayan *et al*., 2004; Lombardi-Boccia *et al*., 2003). It is estimated that in USA calcium intakes typically do not meet the recommended adequate intakes for all ages beyond 11 years, especially females (NHANES, 2007). The National Nutrition Survey Study in Iran (2000-2002) has showed that average calcium intake in Iran is below 70% of the recommended amount (Kalantari *et al*., 2005). With this background, the use of calcium supplements could be justified in overweight or obese populations in order to decrease blood pressure. Although the effect of calcium supplementation has been investigated in many studies, but due to unsatisfactory methodologies of some of them, conceived conclusions have not been achieved yet (Dickison, 2006). Recent evidence based reviews tend to conclude that the relationship between calcium and risk of hypertension is inconsistent and inconclusive (Trumbo and Ellwood, 2007; Myers and Champagne, 2007; Dickinson *et al*., 2006).

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Based on the World Health Organization (WHO) recommendation for the exertion of nutritional Randomized Controlled Trials (RCTs) in various populations (de-Onis *et al*., 1998), we decided to perform a double blind RCT to determine the effect of short term calcium supplementation on blood pressure in overweight or obese women.

MATERIALS AND METHODS

The methodology of the study has been described elsewhere (Karandish *et al*., 2007). Briefly, this double blind randomized clinical trial was conducted on a group of premenopause, overweight or obese women {Body Mass Index (BMI) ≥ 25 kg m^{-2}; age >18 years}, with no recent history of weight loss medications and without evidence of existing chronic diseases, pregnancy, lactation, or oral contraceptive use. The study was conducted during 2005 in Ahwaz, located in south-west of Iran. Subjects with recent calcium supplement intake were excluded from the study. Compliance rates need to be estimated in clinical trials, because participants with low compliance rates may confound the results. We selected intake of at least 100 capsules arbitrarily as a cut-off point to recognize participants likely to be poor complaints. No participant was excluded due to this reason.

From 150 volunteers who were screened for eligibility, 53 female subjects were selected; fully informed about the project and were randomly assigned in supplement (n = 26) or placebo (n = 27) groups. During the study, nine subjects were excluded and 44 participants (24 subjects in the calcium supplement group and 20 subjects in the placebo group) completed the study. All participants were students of medicine or allied health.

Subjects were assigned to receive 1000 mg day^{-1} calcium as four calcium carbonate capsules for 30 days. For every participant who attended randomly in the calcium supplement group, another participant was enrolled in the placebo group. The capsules were taken twice daily. Nine subjects were excluded during the study: two subjects from calcium group (because of starting weight loss diet therapy or dislike to continue the study protocol) and seven subjects from the placebo group (because of nausea or vomiting, dislike to continue the study protocol, renal infection, starting to consume multivitamin and mineral supplement, moving from the city, or undergoing an operation on mouth).

Each calcium carbonate capsule contained 250 mg of elemental calcium (625 mg calcium carbonate) and the placebo contained 625 mg lactose. Quality control of 10 randomly selected capsules was carried out. Mean calcium content was measured by volumetric method (James, 1995) and the results were 237.5 and 0.6 mg in the calcium supplement and placebo capsules, respectively. The capsules were taken twice daily (two with lunch and two with dinner or any time during the day if they fail to meet the schedule) while they pursue their normal lifestyle.

Blood pressures were measured after at least 12 h night fasting and being 15 min rest. Electronic wrist blood pressure monitor (Samsung Corporation, Gyeonggi-Do, Korea) was used for blood pressure measurements. Mean of three measurements (on right hand) was calculated and used for statistical analyses.

Body weight and height were determined using Seca scale and stadiometer, respectively. All anthropometric measurements were done according to WHO protocols (WHO, 1995). BMI was calculated from weight divided by height squared (kg m^{-2}).

Dietary calcium and energy intakes were estimated using mean of three 24 h recalls (2 working days and one weekend).

SPSS software (version 9) was used for statistical analyses. Statistical distribution of variables was analyzed by One-Sample Kolmogorov-Smirnov test; and normal distribution of all variables was confirmed. Comparisons between groups were made by using independent-samples t-test. Paired samples t-test was used for comparing variables (within each group) before and after the intervention. All statistical tests were done in 2 tails format and p-value <0. 05 was the level of significance.

Written consents were signed by the volunteers. According to the latest revision of dietary reference intakes (IOM, 1997), there is no threat of side effects for the subjects from receiving calcium supplements or lactose in the doses used in this study. The present study was approved by the local Committee of Ethics in Biomedical Research.

RESULTS AND DISCUSSION

No significant differences were observed between the calcium supplement and the placebo groups regarding demographic or dietary variables.

As it is presented in the Table 1, mean of dietary calcium intake was lower than the recommended adequate intake (1000 mg day^{-1}) (IOM, 1997) in both groups.

Results of blood pressure measurements are shown in Table 2. No statistically significant differences were observed between the two study groups and in each group before and after the intervention.

The results of this clinical trial showed that consuming 1000 mg day^{-1} calcium supplement for 30 days can not affect blood pressure in overweight or obese women. The results which are shown in Table 1 indicate that the two groups were comparable with regard to the possible confounding factors, e.g., anthropometric or dietary intake variables.

Table 1: Baseline anthropometric and dietary intakes of overweight or obese women in calcium supplement and placebo groups*

Variable	Calcium supplement (n = 24)	Placebo (n = 20)
Age (year)	24.5±6.1	25.4±6.0
Weight (kg)	71.7±8.7	71.7±8.5
Height (Cm)	158.8±5.2	159.5±5.7
BMI (kg m^{-2})	28.4±3.1	28.2±3.0
Energy (kcal day^{-1})	2208±595	1954±404
Calcium (mg day^{-1})	690±419	584±260

*Results are presented as Mean±SD. There was no statistically significant difference between the groups (tested by t-Student test)

Table 2: Systolic and diastolic blood pressures of overweight or obese women in calcium supplement and placebo groups*

	Calcium supplement (n = 24)		Placebo (n = 20)	
Variable	Before	After	Before	After
Systolic blood pressure (mm Hg)	97±11	96±12	99±9	100±9
Diastolic blood pressure (mm Hg)	66±9	66±9	68±8	66±6

*Results are presented as Mean±SD. There was no statistically significant difference between the groups

A few mechanisms have been proposed about the effect of calcium intake on blood pressure, but an agreement about the accuracy of these mechanisms has not been achieved yet. The mechanisms (very briefly) are as follows: 1. Natriuretic effects of calcium (Reid *et al*., 1986); 2. Effects of calcium on parathyroid hormone and 1, 25 di-hydroxy Vitamin D_3 (Pfeifer *et al*., 2001; Resnick *et al*., 2000), the two hormones, which increase blood pressure via effect on smooth muscles (Zemel, 2001); 3. Possible increase of vasodilatory agent, calcitonin gene-related hormone (Wimalawansa *et al*., 1995) and effects on renin-angiotensin system (Resnick, 1999).

Effects of five weeks oral calcium supplementation on blood pressure in a rural Chinese population were studied by Pan *et al*. (2000) and statistically significant decreases in systolic and diastolic blood pressures were reported. There is lack of agreement between this study and our finding. It should be noted that the disagreement between results of these two studies can be explained by the differences between recruited subjects. Subjects of Pan *et al*. (2000) study had been recruited from a rural area with higher average blood pressure and prevalence of hypertension and with high salt and low calcium intake.

Although many clinical trials have been carried out in different countries, but not only the results of these trials are inconsistent but also there is no consistency between systematic reviews or meta analyses about the relation between calcium intake and blood pressure (MacMahon *et al*., 1990; Griffith *et al*., 1999; Bucher *et al*., 1996; Allender *et al*., 1996; van Mierlo *et al*., 2006). A recent meta analysis by van Mielor *et al*. (2006) estimated the highest decrease in blood pressure resulted from calcium supplementation (-1.9 mm Hg in systolic blood pressure and -1.0 mm Hg in diastolic blood pressure, respectively). Previous meta analyses had reported a decrease of -0.8 to -1.4 mmHg and a -0.2 to -0.8 mm Hg in systolic and diastolic blood pressures, respectively.

MacMahon *et al*. (1990) showed that sustainable blood pressure control could decrease the risk of stroke and coronary heart disease by 34 and 21%, respectively. But such an effect has not been found in any other meta analysis; and to our knowledge, decrease of blood pressure more than 5 mmHg have been reported by only 4 studies (Belizan *et al*., 1983; Lyle *et al*., 1987; Takagi *et al*., 1991; Zhou *et al*., 1994). These studies suffer from small sample sizes. There are two important notes about the meta analysis published by van Mielor *et al*. (2006). Firstly, when the analysis was limited to the populations with low calcium intakes, the effect on blood pressure was stronger (-2.6 and -1.3 mmHg in systolic and diastolic blood pressures, respectively). Secondly, no stronger effect was found with supplement doses higher that 1 g day^{-1}. Authors of the meta analysis suggested further studies particularly in populations accustomed to low dietary calcium intakes. We suggest future studies in such populations with same calcium dose but for longer duration. Apparently, Zemel (2001) conclusion that dietary calcium plays a key role in blood pressure is not consistent with finding of this study, but it should be noted that as the author states: those with elevated blood pressure are likely to respond favorably to calcium intervention (Zemel, 2001). In addition, food sources of calcium exert greater effects than supplemental sources. Zemel (1998) demonstrated that dietary calcium modulation of intracellular calcium, mediated by suppression of calcitrophic hormones, attenuate the risk of hypertension.

From the Reid (2005) study similar results to the above mentioned meta analyses were reported. The observed statistically significant effect on systolic blood pressure in the Reid (2005) study could be due to the large sample size (732 and 739 in calcium supplement and placebo groups, respectively). It is noteworthy that although such effect had been statistically significant, but it seems that 1 mmHg decrease in systolic blood pressure would not be important from the biological and medical points of view. In other word, the degree of decline in blood pressure is so small that there is little clinical benefit (Sakhaee and Maalouf, 2005).

Because being overweight or obese was the main inclusion criterion of this study and also because of the age range, participants were not hypertensive patients. As findings of studies about the relation between calcium and hypertension are not conclusive (Trumbo and Ellwood, 2007; Myers and Champagne, 2007;

Dickinson *et al*., 2006), conducting more RCTs on overweight or obese patients with hypertension is strongly recommended.

It can be concluded that 1 g day^{-1} calcium supplement in short term does not affect blood pressure in over weight or obese women. Keeping in mind the high prevalence of iron deficiency anemia on the one hand and interaction between calcium and iron or other minerals (van de Vijver *et al*., 1999) on the other hand; and also the side effects of calcium supplements, e.g., constipation (Prince *et al*., 2006), we do not suggest doses higher that 1 g day^{-1}. In addition, due to possible relation of calcium with prostate cancer (Kurahashi *et al*., 2008; Allen *et al*., 2008; Ahn *et al*., 2007; Mitrou *et al*., 2007) and with vascular events (Bolland *et al*., 2008), it is recommended that clinicians and mass media be more cautious about calcium supplement use. These potentially detrimental effects should be balanced against the likely benefits of calcium.

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