ORIGINAL RESEARCH ARTICLE

Assessment of Effect of Magnesium Intake on Blood Pressure Control in Hypertensives: A Case-control Study with a Nested Intervention of Flax Seeds Administration to Increase Magnesium Intake

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Abstract

Aim and background: A significant proportion of hypertensive patients do not achieve good blood pressure (BP) control despite optimal medications and salt restriction. Considering the BP-lowering effect of magnesium reported in some previous studies, we wanted to assess the correlation between magnesium intake and control of BP in Indian hypertensives. Twenty-four-hour urinary magnesium excretion was used as a surrogate marker of magnesium intake. Further, the effect of supplementation of magnesium-rich flaxseeds on control of BP was assessed, in a subset of the study subjects.

Methodology: In this case-control study, 40 patients of essential hypertension with poor BP control as per JNC-8 BP goals were enrolled as cases and 40 patients of essential hypertension with good BP control were enrolled as controls. Twenty-four-hour urinary samples were collected in both cases and controls and urinary magnesium-creatinine (Mg/Cr) ratios were estimated. The urinary Mg/Cr ratios of patients of the two groups were compared using the Mann–Whitney *U* test. A subset of 23 patients was given an intervention of three tablespoons of roasted whole flaxseeds daily for 4 weeks, and the significance of the change in mean BP, before and after the intervention, was assessed using a paired *t*-test.

Results: The urinary Mg/Cr ratio in the good BP-control group [median = 77.05 [interquartile range (IQR)] = 23.51–101.80] was higher, compared to the poor BP-control group [median = 56.49 (IQR = 44.19–69.97)], with *p*-value = 0.02852, when tested with Mann–Whitney *U* test. In the subset of consenting participants, who took 3 Tbsp flax seeds daily, the average systolic BP and diastolic BP decreased significantly, from 141.13 (SD = 11) mm Hg and 87.65 (SD = 9.19) mm Hg to 134.22 (SD = 11.50) mm Hg and 84.65 (SD = 8.17) mm Hg, respectively (Paired *t*-test; *p*-value for SBP = 0.005, DBP = 0.013).

Conclusion: Hypertensive patients with good BP control have higher levels of 24-hour urinary magnesium excretion when compared to patients with poor BP control. Flaxseeds can be used in hypertensive patients as an adjuvant to drug therapy to improve BP control.

Clinical significance: Hypertensive patients can be advised to consume flax seeds regularly to maintain healthy magnesium levels and control hypertension.

Keywords: Hypertension, Indian, Magnesium, Magnesium deficiency, Poor BP control, 24-hour urinary flaxseeds.

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Introduction

Hypertension, a highly prevalent chronic lifestyle disease, can be called the "the silent killer" due to its often asymptomatic presentation, leading to complications like stroke and myocardial infarction. It is now the most prevalent chronic disease in India and 2.6 lakh Indians die because of this.[1] Considering its multi-factorial pathophysiology, it is often difficult to manage optimally leading to increased morbidity and mortality. The mainstay of management is pharmacologic. However, it is scientifically proven that lifestyle modifications aid its management. The National Heart, Lung and Blood Institute (NHLBI) had sponsored clinical trials on the DASH diet (Dietary Approaches to Stop Hypertension) for hypertension management, which the World Health Organization (WHO) also later added to its guidelines on hypertension management.[2,3] The DASH diet recognizes the importance of minerals like sodium and potassium in blood pressure (BP) control. Another, less-recognized mineral that has been linked to BP control is magnesium.[4–8]

Magnesium is an important intracellular mineral in our bodies. The magnesium intake depends on the magnesium content of drinking water and food consumed. Approximately 30–40% of dietary magnesium is absorbed via the jejunum and ileum.

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Parathyroid hormone and 1, 25-dihydroxy Vitamin D have been reported to be the main regulators of magnesium absorption. Kidneys maintain magnesium homeostasis, and the urinary magnesium excretion usually matches with the net intestinal absorption and is approximately 100 mg/day.

Many research articles discuss the effect of magnesium on cardiovascular health from the early 1900s.[4,9–17] Banjanin and Belojevic, in a single-arm study ($n = 48$), observed the reduction of mean systolic BP (SBP) by 8.97 (SD = 2.01) mm Hg and mean diastolic BP (DBP) by 5.87 (SD = 1.49) mm Hg from baseline (p-value < 0.001) after 1-month supplementation of 300 mg oral magnesium oxide.[4] In another clinical trial ($n = 198$), Rodriguez-Moran and colleagues reported significant changes in components of metabolic syndrome after a 16-week supplementation of 30 mL magnesium chloride 5% solution (382 mg elemental magnesium); −3.6 (SD = 3.3) mm Hg (p-value = 0.001) for SBP; −5.5 (SD = 1.7) mm Hg (p-value = 0.005) for DBP; −12.4 (SD = 3.6) mg/dL (p-value < 0.005) for fasting glucose; −61.2 (SD = 24) mg/dL (p-value = 0.003) for triglycerides.[10]

Even though magnesium is abundantly available through dietary sources like drinking water, cereals, nuts, legumes, green leafy vegetables, flaxseeds, pumpkin seeds, etc., there is still a documented deficiency of magnesium around the world.[18] Subclinical magnesium deficiency may be defined as a state of asymptomatic deficiency because of low dietary magnesium intake over a period of time. It is highly prevalent throughout today's world due to changes in dietary practices, the use of water softeners and purifiers, etc.[18–22] Such magnesium deficiency going unnoticed for years contributes to poor cardiovascular health and the development of various chronic inflammatory pathologies.[7,8]

Various observational studies have reported significant differences in magnesium levels in the hypertensive population compared to the normal population.[23,24] The WHO-coordinated cardiovascular diseases and alimentary comparison (CARDIAC) study (involving 50 population samples from 22 countries) observed, in a linear regression analysis, that Mg/Cr ratio was inversely associated with BMI, SBP, DBP, and TC (P for linear trend < 0.001 for each). They concluded that a higher 24-hour urinary Mg/Cr ratio was associated with lower cardiovascular disease risk factors, including BMI, TC, obesity, hypertension, and hypercholesterolemia.[24] In another cross-sectional study on Indian hypertensives, Chidambaram et al., reported a significantly lower average Mg/Cr ratio (as mg/gm) in middle-aged hypertensives (mean Mg/Cr ratio: 85.35 mg/g with SD of 7.72 mg/gm) compared to normotensives (mean Mg/Cr ratio: 112.95 mg/gm with SD of 6.80 mg/gm) with p-value < 0.05.[23–28]

The above observations raised the hypothesis that differences in BP control, among hypertensives on treatment, could be related to differences in magnesium intake. This was the origin of our research question, "Does the level of magnesium intake contribute to the control of BP in hypertensives on treatment?".

Therefore, we designed this study to assess the correlation between magnesium intake and BP control among Indian hypertensives on anti-hypertensive medication. Since the urinary Mg/Cr ratio is a reliable indicator of magnesium intake, we evaluated the correlation of 24-hour urinary magnesium levels to BP control (categorized as per JNC-8 BP goals) in study participants.

Subsequently, a subset of patients willing to participate further in the study were given supplementation of three tablespoons of flaxseeds daily (because flaxseeds contain high magnesium levels) for 4 weeks. After 4 weeks, the 24-hour urinary magnesium and BP were again evaluated, to assess changes in magnesium excretion and correlation with changes in BP.

The objectives of the study were:

- Assessment and comparison of 24-hour urinary magnesium excretion in hypertensive patients with good and poor BP control.
- Assessment of correlation between 24-hour urinary magnesium excretion and BP in study participants, following intake of three tablespoons of flax seeds, for 4 weeks.

Methodology

The study was conducted in a Tertiary Health Center after approval from the Institutional Ethics Committee. The first part of the study involved participation by patients of essential hypertension aged between 30 and 80 years, who were visiting for hypertension treatment follow-up in the medicine Out Patient Department (OPD). The exclusion criteria were: Patients who were on diuretics (because diuretics decreased magnesium excretion in urine and in that case measuring urinary magnesium excretion would not be a reliable marker of magnesium intake) or proton-pump inhibitors (it decreased gastrointestinal absorption of magnesium), patients with chronic kidney disease (confounding factor), or who were critically ill or morbidly obese (ethical reason).

The sample size of 80 was calculated using www.openepi.com, from observations of a previous study on mean 24-hour urinary magnesium levels in Indian hypertensives vs normotensives.[23] The final power calculated for the study using GPower 3.1 was 80%.

The participants were explained about the objectives of the study, the duration, and the method of 24-hour urinary collection using Patient Information Sheets. Signed written consent was obtained. Their demographic details were noted in Case Record forms. They were provided with 5-L air-tight cans (pre-filled with 20% dilute HCL as a preservative) and explained about the method of 24-hour urine collection, that is, voiding of the first urine in the morning and then collecting all the urine up until the same time next day (exact 24 hours). Urine creatinine and magnesium estimation was done at the biochemistry lab. All biochemical investigations were performed on the EM360, Erba Fully-Automated Chemistry Analyzer. Urinary creatinine was estimated using Jaffe's Alkaline Picrate method and urinary magnesium was estimated by Calmagite dye binding method.

For the BP readings, the Auscultatory method using a standard mercury sphygmomanometer was used to record the SBP and the DBP. An average of four readings (SBP/DBP) with two readings each on two separate occasions was used. BP measurement was done as per JNC-8 guidelines.

After the first part of the study was completed, a cohort of 23 patients was formed from the original 80. The patients were selected based on their willingness to participate further and were counseled regarding the benefits of a magnesium-rich diet. They were specifically advised to consume three tablespoons of flax seeds daily, for 4 weeks. The flax seed supplementation was as whole, roasted, flax seeds, provided as measured sachets of three tablespoons each. As per the U.S. Department of Agriculture, the magnesium content of three tablespoons of flaxseeds are approximately 120 mg. After 4 weeks, their BP was recorded again, along with 24-hour urine collection. The average BP of the 23 patients before and after the dietary flax seeds supplementation was compared to assess changes in BP following the intervention.

Table 1: JNC-8 guidelines for goal BP in hypertensives[25]

	Goal BP (SBP/DBP)	*Good control*	*Poor control*
Age 18–59 years without major comorbidities	Average BP <140/90 mm Hg	If average BP < 140/90 mm Hg	If average BP ≥140/90 mm Hg
Age 18–59 years with major comorbidities			
Age ≥60 years with diabetes/chronic kidney disease			
Age ≥60 years without diabetes/chronic kidney disease	Average BP <150/90 mm Hg	If average BP < 150/90 mm Hg	If average BP ≥150/90 mm Hg

Table 2: Demographics of patients in the two groups

Groups	*Control group (Good control of BP) (n = 40)*	*Case group (Poor control of BP) (n = 40)*	*p-value*
Average age (years) as mean (SD)	60 (8.9)	54.3 (10.8)	0.011
Male-Female ratio	3:5	1:3	0.228
Mean SBP (SD) mm Hg	131.5 (8.84)	152.1 (9.37)	*
Mean DBP (SD) mm Hg	81.45 (6.06)	93.22 (8.14)	*
% Having diabetes	42.5	52.5	0.37
Urinary magnesium/creatinine ratio (mg/gm) median/IQR	77.05 (IQR = 23.51–101.80)	56.49 (IQR = 44.19–69.97)	0.0285

**p*-value is not calculated for these parameters as they are the basis of grouping of study subjects

Table 3: Logistic regression coefficients

	Coeff	*SE*	*z-stat*	*Lower z0.025*	*Upper z0.975*	*Exp (b)*	*p-value*
b0	4.0020	1.5029	2.6628	1.0563	6.9476	54.7057	0.007749
X_1	–0.01238	0.006429	–1.9256	–0.02498	0.0002209	0.9877	0.05415
X_2	–0.05409	0.02491	–2.1713	–0.1029	–0.005265	0.9473	0.0299

Variable X_1 is urinary Mg/Cr ratio and X_2 is age

Microsoft Excel was used to record all data and to perform preliminary statistical analysis such as calculation of mean, SD, median, etc. Means are compared with a *t*-test to estimate the significance of the difference between the groups and medians were compared by non-parametric Mann–Whitney *U* test. The proportions between the two groups were compared by Chi-square test. These statistical tests were performed on www.socscistatistics.com.

Results

The study included 80 patients, aged 36–78 years, divided into a case group and a control group based on their BP. Patients ($n = 40$) with mean SBP/DBP who met the BP goal for hypertension, given in the JNC-8 guidelines (Table 1), were categorized as the control group. The patients ($n = 40$) whose mean BP exceeded the cut-off for good control were categorized as case group.

The mean BP of both groups with other demographics is presented in Table 2. The age distribution of participants is significantly different in both groups. The male-to-female ratio and percentage of individuals with diabetes are similar in the two study groups.

Urinary Mg/Cr ratios of the 24-hour urine samples were used to look for the effect of magnesium intake on BP control. The median of Mg/Cr ratios of the whole study population ($n = 80$) was 65.93 mg/gm (IQR = 45.66–87.81 mg/gm). Non-parametric Mann–Whitney *U* test (a.k.a. Wilcoxon-Rank-Sum test) was used to compare the median values of urinary Mg/Cr ratio of the two study groups as the data had a non-Gaussian distribution. The urinary Mg/Cr ratio of patients in the good control group is significantly higher when compared to the patients in the poor control group (*p*-value 0.0285).

Since the two groups were found to be significantly different in terms of age ($p = 0.011$), we wanted to check whether the difference in urinary Mg/Cr ratio between the two study groups is confounded by the difference in age distributions and for this purpose a logistic regression was performed. Urinary Mg/Cr ratio and age of the patient were the independent variables and the categories of BP control were the dependent variables. The results of the analysis show that the difference in urinary Mg/Cr ratio between the two groups is not significant when adjusted for age (Table 3).

The second part of the study included 23 participants, who were given flax seeds to be consumed daily, three tablespoons for 4 weeks. This group had a mean age of 57.7 (SD = 10.9) years and a male-female ratio of 9:14. Their anti-hypertensive medications were unchanged since enrolment into the study. The BP measurements and urinary Mg/Cr ratios of these participants after intervention are shown in Table 4. The average SBP and DBP were reduced significantly after 4 weeks, *p*-value = 0.005 and 0.013, respectively. The 24-hour urinary magnesium excretion also showed a significant increase in urinary Mg/Cr ratios (Table 4).

Discussion

The median of Mg/Cr ratios of the whole study population ($n = 80$) was 65.93 mg/gm (IQR = 45.66–87.81 mg/gm), which is slightly

Table 4: Comparison of mean BP and Mg/Cr ratio before and after 4 weeks of increased dietary intake of magnesium

	Before intervention	*After intervention*	*p-values*
Mean SBP (SD) mm Hg	141.13 (11)	134.22 (11.50)	0.005
Mean DBP (SD) mm Hg	87.65 (9.19)	84.65 (8.17)	0.013
Mean Mg/Cr ratio (SD) mg/gm	45.98 (15.05)	112.73 (53.17)	<0.00001

lower than the observation in a similar study by Chidambaram and colleagues, who showed urinary Mg/Cr ratios in a South Indian hypertensive population as 85.35 (SD = 7.72) mg/g compared to a normotensive population 112.95 (SD = 6.8) mg/g; *p*-value = 0.014.[23] The urinary magnesium levels have not been previously compared among hypertensive subjects, sub-grouped based on BP-control, as done in our study.

The median urinary Mg/Cr ratio in patients with poor BP-control [56.49 (IQR = 44.19–69.97) mg/gm] was significantly lower compared to those with good BP-control [77.05 (IQR = 23.51–101.80) mg/gm] with *p*-value = 0.0285. This observation suggests that the role of magnesium in BP control extends to hypertensive patients too. The above hypothesis is supported by the review article titled "The role of magnesium in hypertension and cardiovascular disease" wherein the combination of increased magnesium and potassium intake with reduced sodium intake was found to be effective in reducing BP. Magnesium intake was reported to increase the effectiveness of all classes of anti-hypertensive agents.[28]

The BP-lowering effects of magnesium are reported to be related to the effect on vascular smooth muscle cell (VSMC). Magnesium causes a decreased influx of calcium and increased cGMP levels, which together help in the relaxation of the VSMC.[29]

Due to the difference in mean age between the two study groups, we applied logistic regression to assess the correlation between urinary Mg/Cr ratio, age, and BP control of the study groups. The statistical significance of the observation changed to not significant. This observation highlights the need for age-matched study groups, to equivocally assess the contribution of magnesium intake in achieving BP targets, in hypertensive patients on treatment.

The observations in the second part of the study, where 23 consenting participants were asked to increase their magnesium intake through three tablespoons of flaxseeds (120 mg magnesium) for 4 weeks, show an improvement in BP associated with increased urinary Mg/Cr ratio. There was a significant reduction in mean SBP, that is from 141.13 (SD = 11) mm Hg to 134.22 (SD = 11.50) mm Hg (*p*-value = 0.005) and in mean DBP, that is from 87.65 (SD = 9.19) mm Hg to 84.65 (SD = 8.17) mm Hg (*p*-value = 0.013). After this intervention, the mean Mg/Cr ratios increased significantly from 45.98 (SD = 15.05) mg/gm to 112.73 (SD = 53.17) mg/gm. Such BP reduction after magnesium supplementation has been observed by various researchers in the past.[4,9–11] This study has results similar to the study by Banjanin and Belojevic, who observed a reduction of mean SBP by 8.97 (SD = 2.01) mm Hg and mean DBP by 5.87 (SD = 1.49) mm Hg from baseline (*p*-value < 0.001) after oral supplementation of 300 mg magnesium-oxide product for 1-month.[4]

Flax seeds are rich in dietary fibers and omega-3 fatty acids, in addition to being a rich source of magnesium. Dietary supplementation of flax seed flour along with chia flour has been reported to have anti-inflammatory effects.[30]

Considering the reduction in BP after this dietary intervention and the general beneficial effects of flax seed reported in other studies, we recommend dietary intake of three tablespoons of flaxseeds daily for better control of BP in hypertensive patients. As per the U.S. Department of Agriculture, 100 gm of flax seeds has a magnesium content equal to 392 mg, hence, three tablespoons contain approximately 120 mg of magnesium.

Limitations of the Study

Due to the difference in age distribution between the study populations, it is impossible to prove comprehensively that the difference in urinary Mg/Cr ratio is associated with BP control. As flax seeds are rich in dietary fiber and omega-3 fatty acids, the association of BP control with the intake of flax seeds could be secondary to other nutrients in flax seeds. However, the benefit of flax seed consumption in BP management is conclusively proved in the study.

Conclusion

Decreased intake of magnesium is associated with poor control of Hypertension. An increase in the magnesium intake by supplementation of flax seeds is effective in promoting the control of BP.

Clinical Significance

Flax seed intake is an effective method for promoting BP control in hypertensive patients.

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