Original Article JCDR

# Relation of magnesium with insulin resistance and inflammatory markers in subjects with known Coronary artery disease

**Mahalle N, PhD*, Garg MK, MD, DM†, Kulkarni MV, PhD‡ and Naik SS, PhD***

**Deenanath Mangeshkar Hospital and Research Center, Biochemistry Section, Department of Pathology, Erandawane, Pune 411004, India*
*† Department of Endocrinology, Command Hospital (Southern Command), Pune*
*‡ Division of Biochemistry, Department of Chemistry, University of Pune, Pune*

## ABSTRACT

**Background:** Magnesium plays an important role in regulating insulin action and secretion. Dietary magnesium deficiency and hypomagnesemia have been associated with inflammation. There is paucity of data regarding this in Indian subjects. Hence, we studied the relation of serum and dietary magnesium with insulin resistance (IR) and inflammatory markers. **Methods & Results:** We studied the relation of serum high sensitive C-Reactive Protein (hsCRP), interlukin-6 (IL-6) and tumor Necrosis Factor (TNF-α) with cardiovascular risk factors in three hundred coronary artery disease patients. Nutrition assessment was done at the time of recruitment. Patients were evaluated for anthropometry, cardiovascular risk factors, and blood samples were collected. Patients were divided into three groups according to serum magnesium levels; ≤1.6 (Group 1), >1.6–2.6 (Group 2) and: >2.6 mg/dl (Group 3) and into two groups according to recommended dietary allowance (RDA) for magnesium (≤350 mg/day and >350 mg/day). More than half of patients (58.6%) were having hypomagnesemia and 62% were consuming magnesium below RDA. Insulin and IR was significantly higher and insulin sensitivity was significantly lower in group 1 compared to group 2 and 3. Insulin and IR was correlated negatively; and insulin sensitivity was correlated positively with serum magnesium. Similarly inflammatory markers were significantly higher in group1 when compared with group 2 and 3 and they were correlated negatively with serum magnesium. Dietary magnesium was positively correlated with serum magnesium. Insulin and IR were significantly higher and insulin sensitivity was significantly lower in subjects with low RDA for magnesium. Insulin and IR were correlated negatively and sensitivity was correlated positively with dietary magnesium. Inflammatory markers; IL-6, TNF-α, and hs CRP were significantly high in subjects with low RDA for magnesium and were correlated negatively with dietary magnesium. **Conclusion:** Hypomagnesemia and low dietary magnesium is associated with IR and inflammatory markers in patients with coronary artery disease.

**Keywords:** Inflammatory markers; Hypomagnesemia; C-reactive protein; Interleukin-6; Tumor necrosis factor–alpha; Coronary artery disease

## INTRODUCTION

Magnesium is the second most abundant intracellular cation and is an essential element that has numerous biological functions. Magnesium is plentiful in green leafy, cereal, grain, nuts and legumes, however, refining or processing of food may deplete magnesium content by nearly 85%[1]. About 30% of ingested magnesium is absorbed by distal small intestine. Magnesium acts as a cofactor in many of enzymatic reactions in the human body. Magnesium is essential for the synthesis of nucleic acids and proteins, for intermediary metabolism particularly related to the neuromuscular and cardiovascular systems. Over 300 enzymes are dependent on magnesium. Magnesium influences the enzymatic activity by binding to legends such as ATP in ATP-requiring enzymes, enolase, pyruvate kinase, and pyrophosphatase, leading to conformational change during

**Corresponding address:**
Namita Parikshit Mahalle
Pathology Department
Deenanath Mangeshkar Hospital and Research Center
Erandawane, Pune 411004, India
E-mail: pnmahalle@gmail.com
Mobile: 09689935996

**DOI:** 10.5530/jcdr.2014.1.4

the catalytic process, eg. Na+,K+-ATPase, or aggregation of multi-enzyme complexes eg. Aldehyde dehydrogenase[2]. Hence, magnesium plays an important role in regulating insulin action, insulin-mediated glucose uptake, and insulin secretion. Magnesium depletion may result in a defective tyrosine kinase activity at the insulin receptor level causing impairment in insulin action, and aggravation of insulin resistance[3]. This becomes more relevant in Indians as there is high prevalence of magnesium deficiency[4]; and Indians have higher prevalence of insulin resistance and type-2 diabetes mellitus (T2DM)[5]. Dietary magnesium deficiency and hypomagnesemia have also been associated with inflammatory response leading to endothelial dysfunction and insulin resistance[6–7]. High levels of inflammatory markers have been reported in Indian adolescents[8].

There are a few studies which evaluated the relation of dietary and serum magnesium with cardiovascular risk factors in Indian patients[8–9], however, no study has evaluated the relation of dietary and serum magnesium with insulin resistance and inflammatory markers in Indian subjects. The study among post-menopausal women from United States which also included Asians, found no association of magnesium intake with inflammatory markers; though it was inversely related among whites and blacks[10].

In view of this, we have measured markers of insulin resistance and inflammatory markers in a angiographically proven coronary artery disease. We hypothesized that serum and dietary magnesium will be inversely related with inflammatory markers and insulin resistance.

## Methods

This was an extension of study conducted previously; where we have studied association of magnesium and traditional cardiovascular risk factors[9]. Three hundred patients with known coronary disease above the age of 25 years were included in this study. Patients, who were admitted in cardiology department for evaluation of chest pain and found angiography positive, were selected in the study consecutively. Exclusion criteria were presence of chronic kidney disease, hepatic dysfunction, known endocrinal or rheumatologic diseases, chronic infections or alcoholism. All cases were interviewed using a questionnaire, which included data on smoking, physical activity. Height, weight, waist, hip circumference were measured. Body mass index (BMI) and waist hip ratio (WHR) was calculated.

Nutrition assessment was done once at the time of recruitment; based on previous two days 24 hour dietary recall. Mean of recall of two days was taken. Diet was assessed using a computer based comprehensive diet assessment known as Diet soft software, version: 1.1.7 [developed by Invincible IDeAS (www.invincibleideas.com) based on book Nutritive value of Indian Foods by C. Gopalan, B.V.Rama Sastri and S.C.Balasubrsmanian, National Institute of Nutrition, Indian council of Medical Research, Hyderabad, India][11]. Questionnaires and diet assessments were administered via interview by trained staff. Portion size estimation was undertaken using volume measures, circular measures, numbers and linear measures. To help participants estimate portion sizes, interviewers provided commonly used serving plates, bowls, utensils, cups and spoons. If measurements could not be given we recorded in three sizes: small, medium or large and any unusual intake was noted on the recall. For each nutrient, we used a standardized unit of measurement and reported values per 100 grams of edible portion of food product. There was no significant change in the dietary pattern of these participants and no change in lifestyle also.

Fasting blood samples were collected after 14 hour fasting. Magnesium was measured by Xylidyl blue method, which has no interference due to calcium. Patients were divided into three groups according to serum magnesium levels; group-1: ≤ 1.6 mg/dl (n=176, 58.6%), group 2: > 1.6–2.6 mg/dl (n=102, 34%) and group 3: > 2.6 mg/dl (n=26, 8.6%) and into two groups according to Recommended Dietary Allowance of magnesium[11]; group-1 with dietary intake of magnesium ≤ 350 mg/day (n = 186, 62%) and group 2 (n = 114 , 38%) with dietary intake of magnesium levels > 350 mg/day. Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and highly sensitive C-reactive protein (hsCRP), were measured with kits manufactured by Gen-probe Diaclone, France and Biochek, CA, USA, respectively. Insulin was done by Microparticle enzyme immunoassay (MEIA). Insulin resistance and sensitivity was calculated by using homeostatic model analysis (HOMA) model [HOMA-IR=fasting insulin (μIU/ml)*fasting glucose (mmol/l)/22.5 and quantitative insulin sensitivity check index (QUICKI) [QUICKI=1/(log(fasting insulin μU/mL)+log(fasting glucose mg/dL)] respectively. Intra assay and inter assay precision was <5% and <10% respectively for above parameters. The study was approved by Institutional ethics committee of Deenanath Mangeshkar Hospital. Informed consent was obtained from all subjects.

## Statistical method

Statistical analysis was carried out using SPSS Version 20 (SPSS Inc. Chicago, USA) and EPI INFO 3.5.3 (CDC, Atlanta, GA, USA). Data were presented as mean ± SD (95% confidence interval) unless specified. All non-parametric data involved were analyzed by chi-square test. All parametric data were analyzed by student's t-test. Pearson correlation was used to evaluate the correlation between dependent variables like serum and dietary magnesium and independent variables like cardiovascular risk factors. A p value of $< 0.05$ was considered statistically significant.

## Results

Three hundred patients with known cardiovascular disease (M:216; F:84, age:25–92) were studied. A comparison of cardiovascular risk factors according to serum magnesium levels are given in table 1. Mean age of patients was 60.92±12.48 years. There was no age difference between males and females (M: 60.95 ± 12.34; F: 61.03 ± 12.92; p=0.10). (Table 1) In present study more than half of patients (58.6%) were having low magnesium level and 62% were taking dietary magnesium below recommended dietary allowance (350 mg/day).

**Table 1 Basic characteristics**

| Parameters | Male (N=216) | Female (N=84) | P value |
|---|---|---|---|
| **Age (years)** | 60.95 ± 12.34 (62.00) | 61.03 ± 12.92(62.00) | 0.102 |
| **Smoking n(%)** | 82 (38.0%) | 29 (34.5%) | 0.673 |
| **BMI (kg/m2)** | 27.65 ± 3.69 (27.04) | 28.52 ± 4.07 (27.94) | 0.076 |
| **WHR** | 0.92 ± 0.05 (0.93) | 0.91 ± 0.06 (0.93) | 0.118 |
| **Less physical activity n(%)** | 87 (40.3%) | 29 (34.5%) | 0.431 |
| **Insulin (mU/L)** | 49.35 ± 41.58 (36.40) | 52.27± 48.21 (42.40) | 0.601 |
| **HOMA-IR** | 16.61 ± 17.16 (12.15) | 22.28 ± 28.80 (12.01) | 0.502 |
| **QUICKI** | 0.28 ± 0.04 (0.27) | 0.27 ± 0.05 (0.21)å | 0.464 |
| **hsCRP (mg/L)** | 11.87 ± 10.02 (11.78) | 11.18 ± 8.72 (12.30) | 0.578 |
| **IL-6 (pg/ml)** | 62.36 ± 73.85 (25.10) | 70.15 ± 78.92 (25.00) | 0.421 |
| **TNF-α (pg/ml)** | 23.82 ± 41.87 (9.75) | 29.01 ± 38.15 (11.45) | 0.324 |

Median is given in parentheses
BMI-Body mass index; WHR-Waist hip ratio; HOMA-IR: homeostatic model analysis – insulin resistance; QUICKI: quantitative insulin check index; hsCRP: highly sensitive C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α

## Serum Magnesium

Insulin and insulin resistance were significantly higher and insulin sensitivity was significantly lower in group 1 when compared with group 2 and group 3. There was no significant difference between group-2 and group-3. (Table 2) Insulin and insulin resistance was correlated negatively; and insulin sensitivity was correlated positively with serum magnesium. (Table 4 & Figure 1). This significant association was maintained even after adjustment with age, sex, waist hip ratio and BMI. (Table 5)

Similarly IL-6, TNF-α and hsCRP was significantly higher in group1 when compared with group 2 and group 3. There was no significant difference between group-2 and group-3. Inflammatory markers were correlated negatively with serum magnesium (Table 4, Figure 1) This significant association was maintained even after adjustment with age, sex, waist hip ratio and BMI (Table 5).

## Dietary Magnesium

Dietary magnesium was positively correlated with serum magnesium and this was maintained even after adjustment with age and sex in multiple regression analysis. Insulin and insulin resistance was significantly higher and insulin sensitivity was significantly lower in group-1 when compared with group-2 (Table 3). Insulin and insulin resistance were correlated negatively and sensitivity was correlated positively with dietary magnesium. (Figure 1) This significance remained for insulin resistance and sensitivity but not for insulin levels (Table 4). This significant association was maintained even after adjustment with age, sex, waist hip ratio and BMI (Table 5). Inflammatory markers; IL-6, TNF-α and hsCRP were significantly higher in group 1 compared to group 2 and were correlated negatively with dietary magnesium. Inflammatory markers were negatively correlated with dietary magnesium levels; which were maintained even after adjustment with age, sex, BMI and waist hip ratio in multiple regression analysis (Table 4–5 & Figure 1).

**Table 2 Insulin resistance and inflammatory markers according to serum magnesium levels**

| Parameters | Group 1 (≤ 1.6 mg/dl) N=176 | Group 2 (> 1.6–2.6 mg/dl) N=102 | Group 3 (> 2.6 mg/dl) N=22 | p-value# |
|---|---|---|---|---|
| **Insulin (mU/L)** | 61.43 ± 46.20 (54.55–68.31) | 36.27 ± 34.70 (29.94–43.61) | 22.25 ± 22.70 (12.15–32.36) | <0.0001 |
| **P-value** | | <0.0001* | <0.0001†, 0.136ffi | |
| **HOMA-IR** | 24.60 ± 24.70 (20.92–28.28) | 9.61 ± 9.14 (7.82–11.41) | 6.80 ± 7.58 (3.44–10.16) | <0.0001 |
| **P-value** | | <0.0001* | <0.0001†, 0.546ffi | |
| **QUICKI** | 0.26 ± 0.02 (0.25–0.26) | 0.30 ± 0.04 (0.29–0.31) | 0.31 ± 0.04 (0.27–0.28) | <0.0001 |
| **P-value** | | <0.0001* | <0.0001†, 0.144ffi | |
| **IL-6(pg/ml)** | 98.00 ± 77.18 (86.52–109.48) | 18.62 ± 41.20 (10.53–26.72) | 9.81 ± 7.99 (6.27–13.36) | <0.0001 |
| **P-value** | | <0.0001* | <0.0001†, 0.558ffi | |
| **TNF-α (pg/ml)** | 33.84 ± 49.98 (26.40–41.27) | 13.57 ± 16.95 (10.24–16.90) | 11.10 ± 9.35 (6.96–15.25) | <0.0001 |
| **P-value** | | <0.0001* | <0.012†, 0.792ffi | |
| **hsCRP (mg/L)** | 17.11 ± 8.34 (15.87–18.35) | 3.94 ± 5.21 (2.92–4.97) | 4.06 ± 4.66 (1.99–6.13) | <0.0001 |
| **P-value** | | <0.0001* | <0.0001†, 0.945ffi | |

All values are given as mean± SD (95%CI)
*P value between Group-1 and Group-2, † P value between Group-1 and Group-3, ffi P value between Group-2 and Group-3, #P value among all groups

HOMA: homeostatic model analysis – insulin resistance; QUICKI: quantitative insulin check index; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; hsCRP: highly sensitive C-reactive protein

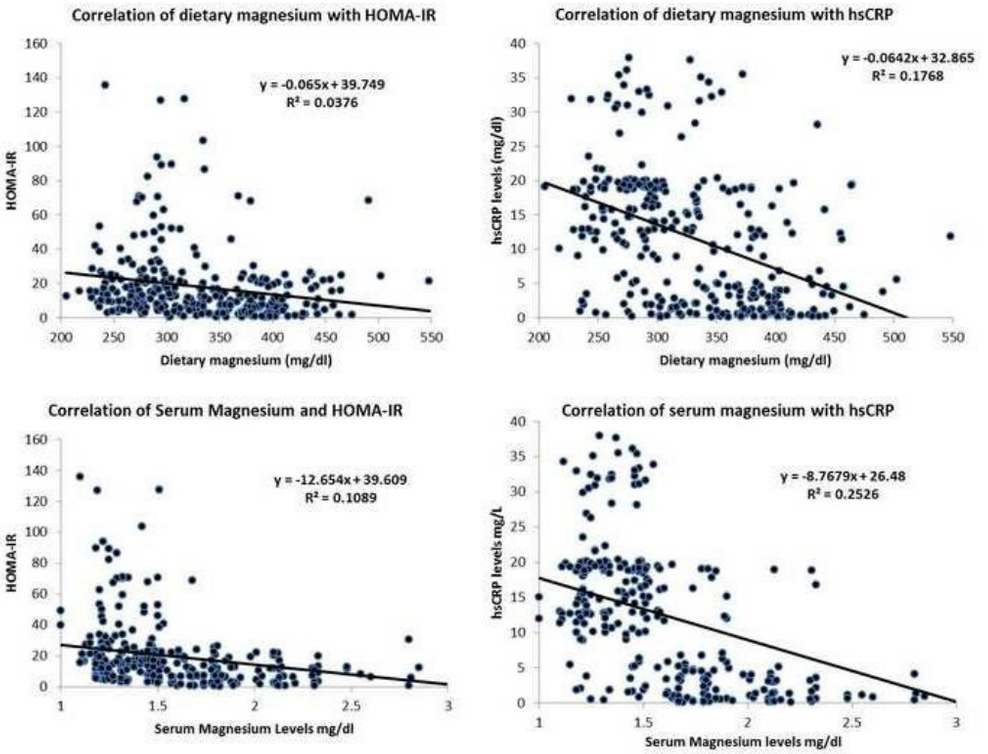


**Figure 1:** Relation of serum and dietary magnesium with insulin resistance (HOMA-IR) and inflammatory marker (hsCRP)

**Table 3 Insulin resistance and inflammatory markers according to dietary magnesium levels**

| Parameters | Dietary magnesium intake | | P Value |
|---|---|---|---|
| | ≤ 350 mg/day N=186 | >350 mg/day N=114 | |
| **Insulin (mU/L)** | 54.16 ± 42.30 (48.04–60.29) | 43.65 ± 44.69 (35.37–51.95) | 0.0420 |
| **HOMA-IR** | 22.07 ± 24.24 (18.56–25.58) | 11.88 ± 12.66 (9.53–14.23) | <0.0001 |
| **QUICKI** | 0.27 ± 0.03 (0.26–0.27) | 0.29 ± 0.04 (0.28–0.30) | <0.0001 |
| **IL-6 (pg/ml)** | 84.38 ± 78.82 (72.97–95.78) | 32.19 ± 55.76 (21.84–42.53) | <0.0001 |
| **TNF-α (pg/ml)** | 32.12 ± 49.38 (24.98–39.27) | 14.11 ± 14.93 (11.34–16.88) | <0.0001 |
| **hsCRP (mg/L)** | 14.90 ± 9.41 (13.59–16.32) | 6.33 ± 7.45 (4.94–7.71) | <0.0001 |

All values are given as mean± SD (95%CI)
HOMA: homeostatic model analysis – insulin resistance; QUICKI: quantitative insulin check index; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; hsCRP: highly sensitive C-reactive protein

**Table 4 Correlation of serum and dietary magnesium with insulin resistance and inflammatory markers**

| Parameters | Serum magnesium | | Dietary magnesium | |
|---|---|---|---|---|
| | r value | P-Value | r value | P-Value |
| **Insulin** | -0.301 | <0.0001 | -0.086 | 0.138 |
| **HOMA IR** | -0.323 | <0.0001 | -0.180 | 0.002 |
| **QUICKI** | 0.416 | <0.0001 | 0.252 | <0.0001 |
| **IL-6** | -0.420 | <0.0001 | -0.285 | <0.0001 |
| **TNF-α** | -0.212 | <0.0001 | -0.212 | <0.0001 |
| **hsCRP** | -0.495 | <0.0001 | -0.404 | <0.0001 |

HOMA: homeostatic model analysis – insulin resistance; QUICKI: quantitative insulin check index; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; hsCRP: highly sensitive C-reactive protein

**Table 5 Multiple regression analysis of Serum and dietary magnesium with insulin resistance and inflammatory factors after adjusting with age, sex, BMI and WHR**

| Parameters | Serum magnesium | | Dietary magnesium | |
|---|---|---|---|---|
| | Beta coefficient | P-Value | Beta coefficient | P-Value |
| **Insulin** | -0.004 | <0.0001 | -0.125 | 0.1559 |
| **HOMA-IR** | -0.008 | <0.0001 | -0.567 | 0.0017 |
| **QUICKI** | 5.545 | <0.0001 | 393.9 | <0.0001 |
| **IL-6** | -0.003 | <0.0001 | -0.250 | <0.0001 |
| **TNF-α** | -0.003 | 0.0001 | -0.365 | 0.0001 |
| **HsCRP** | -0.029 | <0.0001 | -2.783 | <0.0001 |

HOMA: homeostatic model analysis – insulin resistance; QUICKI: quantitative insulin check index; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; hsCRP: highly sensitive C-reactive protein

## Discussion

Coronary artery disease is well-known for its association with various metabolic abnormalities such as hypertension, dyslipidemia, and a reduction in glucose tolerance, which are associated with underlying insulin resistance and inflammatory markers[12]. Exact mechanism of underlying insulin resistance and chronic low grade inflammation is unknown. This has been explained by genetic and epigenetic mechanisms[13]. Genetic changes have long gestational period before the biological effect takes place. With recent epidemic of non-communicable disease, changes in environmental factors are more likely the cause. Environmental factors include environmental toxins[14] and life style factors[15]. Among life style factors, physical activity is related to insulin resistance and inflammatory markers[16]. Another aspect of life style is nutritional factors, which has been changed considerably with change in economic progress and modernization[17]. Several studies have evaluated relation of nutritional factors with insulin resistance and inflammation[18–20].

Magnesium, being the second abundant intracellular caution and its involvement in more than 300 enzymatic reactions, has been studied for its relation with insulin resistance and inflammation[1]. In the present study, insulin resistance, and insulin levels were higher and insulin sensitivity was lower in subject with hypomagnesaemia as compared to subjects with normal serum magnesium levels. Similar observation has been made by others, where serum magnesium was inversely related to HOMA IR[3], and insulin levels[2].

Serum magnesium levels were positively correlated with insulin sensitivity (QUICKI) and negatively with insulin levels and insulin resistance (HOMA-IR), which persisted after adjustment for age, sex, BMI and WHR in this study. Studies in American adults[3] and obese non diabetic children[2] have also reported positive correlation with quantitative insulin sensitivity check index with serum magnesium. Serum magnesium deficiency in this study may be secondary to decreased dietary magnesium intake as serum magnesium was positively related to dietary magnesium intake[9]. Studies among women with polycystic ovarian syndrome did not show any correlation between serum magnesium and insulin resistance[21–22]. This may be due to hormonal alteration in women with polycystic ovarian syndrome. Sometimes, serum magnesium may not accurately reflect intracellular magnesium levels, which may be low, even when serum levels are within the normal range[3,15].

In present study, patients with low dietary magnesium intake had significantly higher insulin levels and insulin resistance (HOMA-IR) and lower insulin sensitivity (QUICKI). Univariate analysis confirmed this correlation, but in multiple regression analysis, correlation of dietary magnesium was significant for insulin resistance but not for insulin after adjustment for age, sex, BMI, and smoking. Most of epidemiologic studies have shown an inverse association between magnesium intake and fasting insulin concentration[23–24].

In healthy postmenopausal women study red blood cells magnesium was directly correlated with insulin and HOMA-IR[25]. Magnesium deficit may independently lead to a higher risk for insulin resistance and cardiovascular disease. Insulin resistance is implicated in progression of type-2 diabetes mellitus along with decreased insulin secretion. In follow up studies magnesium intake was inversely associated with incidence of diabetes in young American adults[3], Chinese[26], and Australian adults[27]. A large prospective cohort study of older Iowa women showed strong inverse associations with incidence of diabetes[28]. A Meta-analysis of prospective cohort studies also demonstrated similar results[25]. Contrary to this, in a few studies no association was detected between dietary magnesium intake and the risk for incident type 2 diabetes[29–30].

This can possibly be explained by the other dietary components such as fibres in food that are high in magnesium[31]. Magnesium supplementation in subjects with insulin resistance and type 2 diabetes mellitus resulted in improvement of insulin sensitivity[32–33] and beta-cell response to glucose[32]. These findings suggest that increased consumption of magnesium-rich foods such as whole grains, beans, nuts, and green leafy vegetables may reduce the risk of type 2 diabetes mellitus.

Intracellular magnesium plays a key role in regulating insulin action, insulin-mediated-glucose uptake and vascular tone[34]. Reduced intracellular magnesium concentrations result in a defective tyrosine-kinase activity, post-receptor impairment in insulin action, and worsening of insulin resistance in diabetic patients[1]. It was observed that autophosphorylation of the beta-subunit of the insulin receptor was significantly reduced by 50% in magnesium-deficient rats and the tyrosine kinase activity of insulin receptors by hypomagnesaemia[35].

Clinical and animal studies have described influence of magnesium on inflammation[36–37]. In present study, hypomagnesaemia was associated with increased levels of inflammatory markers suggesting associated low grade inflammation. Other studies have also reported strong correlation of low serum magnesium with low grade systemic inflammation demonstrated by elevated CRP[38–39] and TNF-α concentrations[40–41]. In children elevated hsCRP levels were independently associated with hypomagnesemia[42]. In Indian children and adolescents, high levels of inflammatory markers have been reported,[12] which can partially be explained by low magnesium levels.

Serum magnesium levels are reflection of dietary intake[9]. Several studies have assessed relation of dietary magnesium with inflammatory markers[39–44]. In this study, higher inflammatory markers were observed among patients with magnesium intake lower than RDA. Inflammatory markers were negatively correlated with dietary magnesium intake. One study reported lower CRP concentration (12%), in the subjects in the highest quintiles when compared with lowest quantiles[39]. In our study, this difference was more marked with hs CRP levels, 42.8% lower in patients that high magnesium intake compared to lower intake. Similar observation was also reported by other studies among different population: Italian population[44], Nurses' Health Study[45], and postmenopausal women[13]. However, magnesium supplementation did not significantly attenuate inflammatory markers compared to placebo in intervention studies[31,46]. This further suggests probable role of other dietary constituents associated with magnesium intake significantly modulate observed relation between magnesium and inflammation[47]. In National Health and Nutrition Examination Survey (NHANES) survey, individual with intake of magnesium below the RDA were 1.48–1.75 times more likely to have elevated CRP[39].

Dietary magnesium deficiency increases proinflammatory neuropeptides such as substance P which acts through neurokinin-1 receptors of inflammatory and endothelial cells, and may stimulate release of inflammatory mediators[48]. Magnesium acts as a natural calcium antagonist, the molecular basis for the inflammatory response is probably the result of a modulation of the intracellular calcium concentration. Potential mechanisms includes the priming of phagocytic cells, the opening of calcium channels, activation of N-methyl-D-aspartate (NMDA) receptors, the activation of nuclear factor-kappa B (NFkB)[37,38].

Limitation of this study is that intracellular magnesium, a more sensitive indicator of magnesium balance, was not measured. Magnesium is primarily an intracellular cation; roughly 1% of whole-body magnesium is found extracellular space, and the free intracellular fraction is the portion regulating enzyme pathways[49]. However, serum magnesium exhibits a good correlation with intracellular free magnesium measured by nuclear magnetic resonance spectroscopy[50].

## ACKNOWLEDGEMENT

We thank Deenanath Mangeshkar Hospital and Research Centre, Pune, for providing necessary facilities.

**Conflict of Interest:** None of the authors have any conflicts of interests

## Conclusion

Lower serum and dietary magnesium is associated with insulin resistance and inflammatory markers in Indian patients with coronary artery disease. Higher insulin resistance has been observed in Indian children[51]. Increased dietary intake since childhood may positively modify insulin resistance and chronic low grade inflammation, and may decrease the impact of non-communicable diseases associated with these pathogenetic mechanisms.

## REFERENCES

1. Musso CG. Magnesium metabolism in health and disease. Int Urol Nephrol. 2009; 4: 357–62.
2. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000; 294: 1–26.
3. Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs DR Jr, He K. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. Diabetes Care. 2010; 33: 2604–10.
4. Yajnik, CS, Smith RF, Hockaday TD, Ward NI, Fasting plasma magnesium concentrations and glucose disposal in diabetes. Br Med J (Clin Res Ed). 1984; 288: 1032–4.
5. Isharwal S, Misra A, Wasir JS, Nigam P. Diet & insulin resistance: a review & Asian Indian perspective. Indian J Med Res. 2009; 129: 485–99.
6. Brilla LR. Magnesium Influence on Stress and Immune Function in Exercise. J Sports Med Doping Stud, 2012; 2:3.http://dx.doi.org/10.4172/2161-0673.1000111
7. Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. Nutr Rev.2010; 68:333–40.
8. Misra A. C-reactive protein in young individuals: problems and implications for Asian Indians. Nutrition. 2004; 20: 478–81.
9. Mahalle N, Kulkarni MV, Naik SS. Is hypomagnesaemia a coronary risk factor among Indians with coronary artery disease? J Cardiovasc Dis Res. 2012; 3: 280–6.
10. Chacko SA, Song Y, Nathan L, Tinker L, de Boer IH, Tylavsky F, Wallace R, Liu S. Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. Diabetes Care. 2010; 33: 304–10.
11. Gopalan C, Rama Sastri BV, Balasubramanian SC. Nutritive value of Indian Foods (3rd edition). Revised & updated by Narasinga Rao BS, Deosthale YG, Pant KC. Publisher-National Institute of Nutrition, Indian council of Medical Research, Hyderabad, India. (1989) Reprint-2005. p.1–156.
12. Mohan V, Venkatraman JV, Pradeepa R. Epidemiology of cardiovascular disease in type 2 diabetes: the Indian scenario. J Diabetes Sci Technol. 2010; 4: 158–70.
13. Choi SW, Friso S. Epigenetics: A New Bridge between Nutrition and Health. Adv Nutr.2010; 1: 8–16.
14. Norman RE, Carpenter DO, Scott J, Brune MN, Sly PD. Environmental exposures: an under recognized contribution to noncommunicable diseases. Rev Environ Health. 2013; 28: 59–65.
15. Cahill F, Shahidi M, Shea J, Wadden D, Gulliver W, Randell E, Vasdev S, Sun G. High dietary magnesium intake is associated with low insulin resistance in the Newfoundland population. PLoS One, 2013; 8: e58278. doi: 10.1371/journal.pone.0058278. Epub 2013 Mar 5.
16. Kelishadi R, Mirghaffari N, Poursafa P, Gidding SS. Lifestyle and environmental factors associated with inflammation, oxidative stress and insulin resistance in children. Atherosclerosis, 2009; 203: 311–9.
17. Ulijaszek S. Modernisation, migration and nutritional health of Pacific Island populations. Environ Sci. 2005; 12: 167–76.
18. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, Jacobs DR Jr. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2006; 83:1369–79.
19. Galland L. Diet and inflammation. Nutr Clin Pract.2010; 25: 634–40.
20. Mahalle N, Kulkarni MV, Naik SS, Garg M K. Dietary factors responsible for insulin resistance and inflammation in subjects with coronary artery

disease in Indian population. Journal of Diabetes and its Complications (accepted for publication) Year
21. Sharifi F, Mazloomi S, Hajihosseini R, Mazloomzadeh S. Serum magnesium concentrations in polycystic ovary syndrome and its association with insulin resistance. Gynecol Endocrinol, 2012; 28: 7–11.
22. Kauffman RP, Tullar PE, Nipp RD, Castracane VD. Serum magnesium concentrations and metabolic variables in polycystic ovary syndrome. Acta Obstet Gynecol Scand. 2011; 90: 452–8.
23. Lopez-Ridaura R, Willett WC, Rimm EB, Liu S, Stampfer MJ, Manson JE, Hu FB. Magnesium intake and risk of type 2 diabetes in men and women. Diabetes Care. 2004; 27:134–40.
24. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. J Intern Med. 2007; 262: 208–14.
25. Laires MJ, Moreira H, Monteiro CP, Sardinha L, Limão F, Veiga L, Gonçalves A, Ferreira A, Bicho M. Magnesium, insulin resistance and body composition in healthy postmenopausal women. J Am Coll Nutr.2004; 23: 510S–3S.
26. Villegas R, Gao YT, Dai Q, Yang G, Cai H, Li H, Zheng W, Shu XO. Dietary calcium and magnesium intakes and the risk of type 2 diabetes: the Shanghai Women's Health Study. Am J Clin Nutr, 2009; 89: 1059–67.
27. Simmons D, Joshi S, Shaw J. Hypomagnesaemia is associated with diabetes: Not pre-diabetes, obesity or the metabolic syndrome. Diabetes Res Clin Pract. 2010; 87: 261–6.
28. Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr. 2000; 71: 921–30.
29. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. Arch Intern Med. 1999;159: 2151–59.
30. Aguilar MV, Saavedra P, Arrieta FJ, Mateos CJ, González MJ, Meseguer I, Martínez-Para MC. Plasma mineral content in type-2 diabetic patients and their association with the metabolic syndrome. Ann Nutr Metab. 2007; 51: 402–6.
31. Lee S, Park HK, Son SP, Lee CW, Kim IJ, Kim HJ. Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. Nutr Metab Cardiovasc Dis. 2009; 19: 781-8.
32. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. Diabetes Care. 1989; 12: 265–9.
33. Guerrero-Romero F, Tamez-Perez HE, Gonzalez-Gonzalez G, Salinas-Martinez AM, Montes-Villarreal J, Trevino-Ortiz JH, Rodriguez-Moran M. Oral magnesium improves insulin sensitivity in nondiabetic subjects with insulin resistance. Diabetes Metab. 2004; 30: 253–8.
34. Rosolova H, Mayer O Jr, Reaven GM. Insulin-mediated glucose disposal is decreased in normal subjects with relatively low plasma magnesium concentrations. Metabolism. 2000; 49:418–20.
35. Suarez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A. Impaired tyrosinekinase activity of muscle insulin receptors from hypomagnesaemic rats. Diabetologia.1995; 38:1262–70.
36. Tejero-Taldo MI, Kramer JH, Mak IuT, Komarov AM, Weglicki WB. The nerve-heart connection in the pro-oxidant response to Mg-deficiency. Heart Fail Rev. 2006; 11: 35–44.
37. Malpuech-Bruge`re C, Nowacki W, Dav-eau M, Gueux E, Linard C, Rock E, Lebreton J, Mazur A, Rayssiguier Y. In-flammatory response following acute magnesium deficiency in the rat. Biochim Biophys Acta.2000;1501: 91–8.
38. Rayssiguier Y, Gueux E, Nowacki W, Rock E, Mazur A. High fructose consumption combined with low dietary magnesium intake may increase the incidence of the metabolic syndrome by inducing inflammation. Magnes Res. 2006; 19: 237–43.
39. King DE, Mainous AG III, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. J Am Coll Nutr, 2005; 24: 166–71.
40. Rodriguez-Morand M, Guerrero-Romero F. Elevated concentrations of TNF-alpha are related to low serum magnesium levels in obese subjects. Magnes Res. 2004; 17: 189–96.
41. Guerrero-Romero F, Bermudez-Peña C, Rodríguez-Morán M. Severe hypomagnesemia and low-grade inflammation in metabolic syndrome. Magnes Res. 2011; 24: 45–53.
42. Rodríguez-Morán M, Guerrero-Romero F. Serum magnesium and C-reactive protein levels. Arch Dis Child. 2008; 93: 676–80.
43. Isasi CR, Deckelbaum RJ, Tracy RP, Starc TJ, Berglund L, Shea S. Physical fitness and C-reactive protein level in children and young adults: The Columbia University BioMarkers Study. Pediatrics. 2003;111: 332–8.
44. Bo S, Durazzo M, Guidi S, Carello M, Sacerdote C, Silli B, Rosato R, Cassader M, Gentile L, Pagano G.Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. Am J Clin Nutr. 2006; 84: 1062–9.
45. Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. Am J Clin Nutr. 2007; 85:1068–74.
46. Moslehi N, Vafa M, Rahimi-Foroushani A, Golestan B. Effects of oral magnesium supplementation on inflammatory markers in middle-aged overweight women. J Res Med Sci. 2012; 17: 607–14.
47. Lopez-Garcia E, Schulze MB, Fung TT, Meigs JB, Rifai N, Manson JE, Hu FB. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. Am J Clin Nutr. 2004; 80: 1029 –35.
48. Kramer JH, Spurney C, Iantorno M, Tziros C, Mak IT, Tejero-Taldo MI, Chmielinska JJ, Komarov AM, Weglicki WB. Neurogenic inflammation and cardiac dysfunction due to hypomagnesemia. Am. J. Med. Sci. 2009; 338: 22–7.
49. Nadler JL, Rude RK. Disorders of magnesium metabolism. Endocrinol Metab Clin North Am. 1995; 24: 623– 41.
50. Ryzen E, Servis KL, DeRusso P, Kershaw A, Stephen T, Rude K. Determination of intracellular free magnesium by nuclear magnetic resonance in human magnesium deficiency. J Am Coll Nutr.1989; 8: 580–7.
51. Yajnik CS. Nutrition, growth, and body size in relation to insulin resistance and type 2 diabetes. Curr Diab Rep. 2003; 3: 108–14.