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**ASSOCIATION BETWEEN MAGNESIUM AND CARDIOVASCULAR DISEASE RISK:
SYSTEMATIC REVIEW AND META-ANALYSIS OF COHORT
STUDIES UPDATED TO JULY 2016**

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Received on 27-07-2016

Accepted on 04-09-2016

Abstract

The cardiovascular disease is one of the most important reasons for death worldwide. Some studies have shown that magnesium can reduce the risk of cardiovascular diseases, but these studies do not have the similar results. Hence in this study we tried by doing a systematic review and meta-analysis to investigate the effect of magnesium intake through the drinking water and food as well as the serum level of magnesium on the pulmonary heart disease risk. For finding the studies conducted in Iran and the world, we used the databases Pubmed, Scopus, Irandoc, SID and ISI. 22 articles (23 cohort studies) in all of which an almost similar methodology had been used and all of them had been done in the time interval from 1995 up to 2016, were investigated. Heterogeneity of the studies was high both in adsorption studies ($I^2 = 62\%$, p value = 0.002) and in the serum ones ($I^2 = 51\%$, p value = 0.029). Hence the random effect model was used for overall meta-analysis of studies. Meta-analysis of 13 intake studies showed there is not any significant relationship between magnesium intake through the water and food and the cardiovascular risk (RR = 0.91%, 95% CI (0.81-1.03), P value = 0.13). Meta-analysis of 10 cohort studies showed there is a significant relationship between the serum magnesium and the cardiovascular risk. An increase in serum magnesium reduced significantly the cardiovascular risk by 27% (RR = 0.73%, 95% CI (0.64-0.84), P value < 0.001). Eggers' test showed

there is no considerable release of error (p value < 0.001) in the intake studies (Intercept:-0.64, 95% (-3.6, 2.3) and serum studies (Intercept:-2.2, 95% (-4.6, 0.64). The results of this study supported the reduction of the risk of cardiovascular diseases resulting from an increase in serum level of magnesium (P value <0.001).

1. Introduction

Cardiovascular disease (CVD) is one of the most important reasons for death and disability around the world [1,2]. The prevalence of CVD is increasing day by day; it requires the spread of this disease to be stopped [3,4]. Increase in the physical activities, tobacco control, weight control and nutrition are the factors affecting the control of CVD [5-9]. Magnesium is an essential mineral element for the body; it has several roles in biological functions of cardiovascular system. At the sub-cellular level the magnesium regulates modulates trans membrane transport of Ca, Na, and K, contractile proteins; it is an essential factor for activity of ATP ase [10,11]. Magnesium is a thing naturally abundant in the human body and there is observed that it reduces the risk of CVD [12]. However, due to its reduction in resources for drinking water and food, the consumption of magnesium in the world has been declined [13]. In the United States the prevalence of magnesium deficiency in adult men and women is 64% and 67% respectively and by male and female individuals more than 71 years it is respectively 81% and 82% [14]. An increase in blood pressure causes CVD [15]. Studies have shown that a change in the serum level of magnesium can affect the blood pressure [16,17]. Recently it has been obtained some evidences that a deficiency of magnesium can cause the effects of genotoxins on the cardiopulmonary tissues and cells [18,19]. Magnesium deficiency in drinking water (light water) as well as in the territory is associated with hypertension, coronary vasospasm, ischemic heart disease (IHD), atherosclerosis and sudden-cardiac death [10,20-23]. The current guidelines for CVD control are to increase the amount of magnesium intake through the enrichment of food which has a positive effect on pressure [24-26]. Recently some review studies and meta-analysis have been done in the field of the relationship between serum magnesium and magnesium intake on the one hand and CVD. These studies showed that CVD can be caused by a deficiency of serum level of magnesium in food or water (intake). These results showed that CVD can be associated with magnesium [27-29]. Although some studies have shown that high level of magnesium in the water and food as well as high level of serum reduces the risk of CVD [30-33], but in this field the results is not of enough correlation. For example, in a study of Ohira an increase in the magnesium intake reduced CVD risk by 35%, but in Abbott et al study it increased that by 70% [30, 34]. On the other hand, the latest meta-analysis and review study in this field was carried out in 2013 by Xinhua et al [29]. Hence in this study we have tried to do a systematic review on the databases

and meta-analysis of studies till 2016 and reexamine the relationship between serum level and the intake of magnesium on the one hand and CVD risk on the other.

2. Materials and methods

This study was a meta-analysis and systematic review of the relationship between intake and serum level of magnesium on the one hand and CVD risk on the other. For finding the studies conducted in Iran and the world we used the databases Pubmed, Scopus, Irandoc, SID and ISI.

1.2. Selection of studies

At the beginning, a list of titles and abstracts of all studies available at the databases mentioned by three researchers (Ya.F, Ha.K, Ya.Z) was prepared for preventing the researchers bias. Related titles were examined independently; then the search was done on the studies that were published from 1990 up to 2016. Search was done for 2 weeks from 15/05/2016 to 2016/06/30; then the related studies were entered into the research process by method of initial blinding and independent from each other. The main Inclusion Criterion for participation of different articles in this research was a reference to the level of magnesium in serum, food and water with the risk of CVD. The investigations that did not belong to the initial researches or had as subject the clinical decision-making and were the investigations non-associated with CVD, were considered out of the research. In the second stage the abstract of the various selected studies was investigated by the researcher using a checklist STROBE¹ that is a standard checklist. This checklist includes 43 diverse sections and evaluates the various aspects of methodology including the sampling methods, measurement of variables, statistical analysis and the objectives of the study [35].

In this checklist, the least achievable score was considered the score 40 and 45 as the maximum score. Finally, the superior articles that had achieved the least score (40) given to the checklist questions, were entered into research and for meta-analyzing their data were extracted. For determining the Publication Bias the drawing Funnel Plot and Eggers' test was used [36].

2.2. Data extraction

In this study, 22 articles (23 cohort studies) in all of which an almost similar methodology had been used and all of them were done in the time interval from 1995 up to 2016, were examined. The important information required for analyzing data, including information related to the topic, title, study type, the time of study, location of study, sex, the number of participants, duration of the measurement period, score of each study in the system of Newcastle-Ottawa scale (NOS), the relative risk and the results was gathered.

3.2. Evaluation of studies quality

Based on the quality evaluation criterion NOS which includes Selection, Comparability and Exposure, the cohort studies were scored. The score range in system of NOS is 0 to 9. The studies were classified into two groups of low score (< 7) and high score (≥ 7) [37].

4.2. Synthesis and statistical analysis of data

Meta-analysis of data was done by software of Comprehensive Meta-Analysis V. 2.2.064. For calculating the heterogeneity of the studies we used I^2 Higgins. In studies that I^2 was more than 50%, we made use of the random effect model and where that was less than 50%, meta-analysis we used the fixed effect model. In this study the significance level was P value < 0.05 .

3. RESULTS

1.3. Identification of the related studies

At this stage by searching databases Scopus, Embase, SID, Irandoc, ISI web of science and PubMed, 1352 articles in general were obtained. Based on the Title and abstract, Duplicates removed, Review, editorial, Review, protocol and Nonhuman, 1051 articles were set aside at stage of Eligibility. 301 remaining articles were put aside from meta-analysis for some reasons such as lack of data, analysis of indicators HR and OR etc. Finally, 22 articles (23 cohort studies) in which the relative risk had been calculated were meta-analyzed (Figure 1).

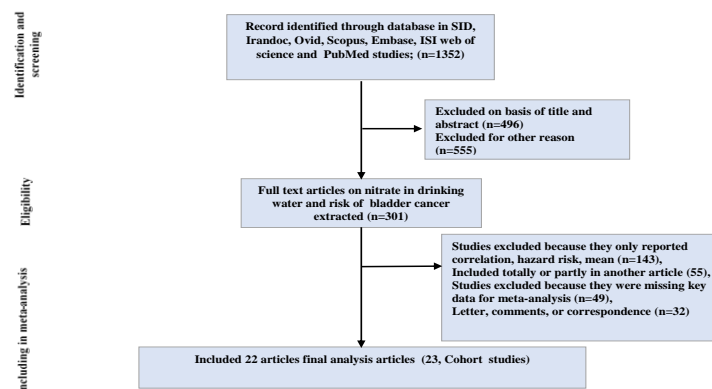


Figure1. Flow diagram for identification of relevant cohort studies.

2.3. Features of studies

General characteristics of studies such as the year of publication, place, the measurement period, the number of participants, gender, kind of magnesium (intake or serum) have been shown in terms of the relative risk and results in Table 1. The scope of the study years was 1995 to 2016. 12 studies were done on women and men, 5 studies on women and 6 studies on men.

Table-1: General characteristics CVD and magnesium studies evaluated for meta-analysis.

First Author	Year	Location	Follow-up	Study P	Sex	Age (range or mean)	Outcomes Assessment	Magnesium	RR	Low	High	
Ascherio et al	1998	United States	8	4378	Male		They are consistent with the hypothesis that diets rich in potassium, magnesium, and cereal fiber reduce the risk of stroke, particularly among hypertensive men	Intake	0.92	0.58	1.46	[38]
Liao et al	1998	United States	7	13922	Female/Male	45-64	Low magnesium concentration may contribute to the pathogenesis of coronary atherosclerosis or acute thrombosis	Intake	0.69	0.45	1	[39]
Iso et al	1999	United States	14	85764	Female	34-59	Low calcium intake, and perhaps low potassium intake, may contribute to increased risk of ischemic stroke in middle-aged American women. It	Intake	0.8	0.63	1.01	[40]

							remains possible that women in the lowest quintile of calcium intake had unknown characteristics that made them susceptible to ischemic stroke					
Abbott et al	2003	United States	30	7172	Male	45-68	Intake of dietary Mg is associated with a reduced risk of CHD. Whether increases in dietary Mg intake can alter the future risk of disease warrants further study	Intake	1.7	1.2	2.4	[30]
Al-Delaimy et al	2004	United States	12	39633	Male	40-75	Magnesium intake and risk of coronary heart disease among men	Intake	0.82	0.65	1.05	[41]
Song et al	2005	United States	10	39876	Female	39-89	-	Intake	1	0.82	1.23	[27]
Larsson et al	2008	Finnish	13.6	26556	Male	50-69	In male smokers suggest that a high magnesium intake may play a role in the primary prevention of cerebral infarction	Intake	0.92	0.8	1.07	[31]
Weng et al	200	China	10.6	1772	Female/Ma	>=40	The protective association of dietary	Intake	0.6	0.4	1.04	[42]

al	8				le		folate on IS risk may be in part through that of other correlated nutrients or other dietary components		8	5]
Ohira et al	2009	United States	15	14221	Female/Male	45-64	Low serum magnesium levels could be associated with increased risk of ischemic stroke, in part, via effects on hypertension and diabetes	Intake	0.75	0.59	0.95	[34]
								serum	1.04	0.82	1.32	
Kaluza et al	2010	Swedish	10	23366	Male	45-79	Men with relatively high intakes of dietary calcium and magnesium showed that intake of calcium above that recommended daily may reduce all-cause mortality	Intake	1.25	0.96	1.61	[43]
Chiuvetal	2011	United States	10	88375	Female	30-55	Higher plasma concentrations and dietary magnesium intakes were associated with lower risks of SCD. If the observed association is causal, interventions directed at increasing	Intake	0.66	0.46	0.95	[33]

							dietary or plasma magnesium might lower the risk of SCD					
Larsson et al	2011	Swedish	10.4	34670	Female	49-83	Dietary potassium intake is inversely associated with risk of stroke, in particular ischemic stroke	Intake	0.92	0.58	1.46	[44]
Zhang et al	2012	Japan	14.7	58615	Female/Male	40-64	Dietary magnesium intake was associated with reduced mortality from cardiovascular disease in Japanese, especially for women	Intake	1.02	0.85	1.22	[45]
Gartside et al	1995	United States	10	8251	Female/Male	25-74	Associations emphasize the important role of modifiable dietary and behavioral characteristics in the causation and prevention of CHD	serum	0.68	0.54	0.87	[32]
Ford et al	1999	United States	19	12340	Female/Male	>=40	Serum magnesium concentrations were inversely associated with mortality from IHD and all-cause mortality	serum	0.69	0.52	0.9	[46]
Leone et al	2006	France	18	4035	Male	30-60	Low serum magnesium contribute to an increased mortality risk in middle-aged	serum	0.6	0.2	1.2	[47]

							men					
Khan et al	2010	United States	20	3531	Female/Male	>=40	Data from this large, community-based cohort do not support the hypothesis that low serum magnesium is a risk factor for developing hypertension or CVD	serum	0.91	0.72	1.17	[48]
Peacock et al	2010	United States	12	14232	Female/Male	45-64	Low levels of serum Mg may be an important predictor of SCD. Further research into the effectiveness of Mg supplementation for those considered to be at high risk for SCD is warranted	serum	0.62	0.42	0.93	[49]
Reffelman et al	2011	Germany	10.1	3910	Female/Male	20-79	Low serum Mg levels are associated with higher all-cause mortality and cardiovascular mortality. This corresponds well with recent findings that hypomagnesaemia is associated with the increase of left ventricular mass over the following years	serum	0.61	0.41	0.88	[50]

Taveira et al	2016	United States	4	4916	Female/Male	55.3	Magnesium intake <2.3 mg/kg was related to increased risk of subsequent HF hospitalizations. Future studies are needed to test whether serum magnesium levels predict risk of HF	serum	0.47	0.27	0.82	[51]
Kieboom et al	2016	Holland	8.7	9882	Female/Male	65.1	Low serum magnesium is associated with an increased risk of CHD mortality and SCD	serum	0.82	0.7	0.96	[52]
Chiuvetal	2013	United States	6	86323	Female	30-55	Dietary and plasma magnesium were not associated with total CHD incidence in this population of women. Dietary magnesium intake was inversely associated with fatal CHD, which may be mediated in part by hypertension	serum	0.61	0.45	0.84	[53]

In 22articles (23 cohort studies)625100 participants were generally diagnosed. The scope of the measurement period was between 4 and 30 years (12.5 ± 5.5). From total studies 15 studies have been carried out in the United States and the rest in other countries. Based on the criterion of quality evaluation of scale (NOS) Newcastle-Ottawa, the studies of Iso et al and Ford et al (6 score) have low score andother 21 studies had high score (Table 2).

Table 2. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa scale for**assessing the quality of cohort.**

Study	Year	Selection (Score)				Comparability (Score)	Exposure (Score)			Total Score
		Representativeness of the exposed cohort	Select ion of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Ascherio et al	1998	1	1	1	1	1	0	1	1	7
Liao et al	1998	1	1	1	1	2	0	1	1	8
Iso et al	1999	1	1	1	1	1	0	0	1	6
Abbott et al	2003	1	1	1	1	2	0	1	1	8
Al-Delaimy et al	2004	1	1	1	1	2	1	1	1	9
Song et al	2005	1	1	1	1	2	0	1	1	8
Larsson et al	2008	1	1	1	1	1	0	1	1	7
Weng et al	2008	1	1	1	1	2	1	1	1	9
Ohira et al	2009	1	1	1	1	1	0	1	1	7
Kaluza et al	2010	1	1	1	1	2	1	1	1	9

Chiuv et al	2011	1	1	1	1		1		1	1	1	9
Larsson et al	2011	1	1	1	1		1		0	1	1	7
Zhang et al	2012	1	1	1	1		1		0	1	1	7
Gartside et al	1995	1	1	1	1		1		0	1	1	7
Ford et al	1999	1	1	1	1		1		0	0	1	6
Leone et al	2006	1	1	1	1		1		0	1	1	7
Khan et al	2010	1	1	1	1		1		1	1	1	8
Peacock et al	2010	1	1	1	1		1		0	1	1	7
Reffelman n et al	2011	1	1	1	1		2		1	1	1	9
Taveira et al	2016	1	1	1	1		1		0	1	1	7
Kieboom et al	2016	1	1	1	1		2		1	1	1	9
Chiuv et al	2013	1	1	1	1		1		0	1	1	7

3.3. meta-analysis of Studies

Heterogeneity of the studies was high both in adsorption studies ($I^2 = 62\%$, p value = 0.002) and in the serum ones ($I^2 = 51\%$, p value = 0.029).

Hence the Random effect model was used for overall meta-analysis of studies. Meta-analysis of 14 intake cohort studies showed there is not any significant relationship between the magnesium intake through food and water with the CVD risk, but the magnesium intake reduced CVD risk by 9% (RR = 0.91%, 95% CI (0.81-1.03), P value = 0.13) (Figure 2).

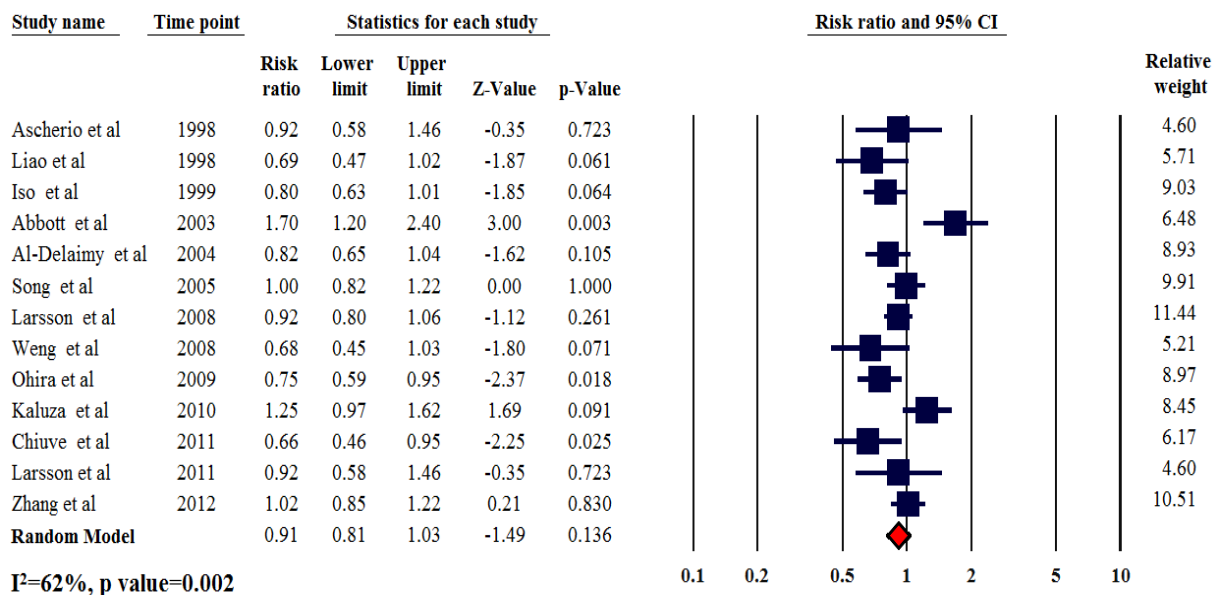


Figure 2. Forest plot of meta-analysis on intake magnesium and CVD.

Meta-analysis of 10 serum cohort studies showed a significant relationship between the serum magnesium and CVD risk. An increase in serum magnesium reduced significantly the CVD risk by 27% (RR = 0.73%, 95% CI (0.64-0.84), P value < 0.001) (Figure 3).

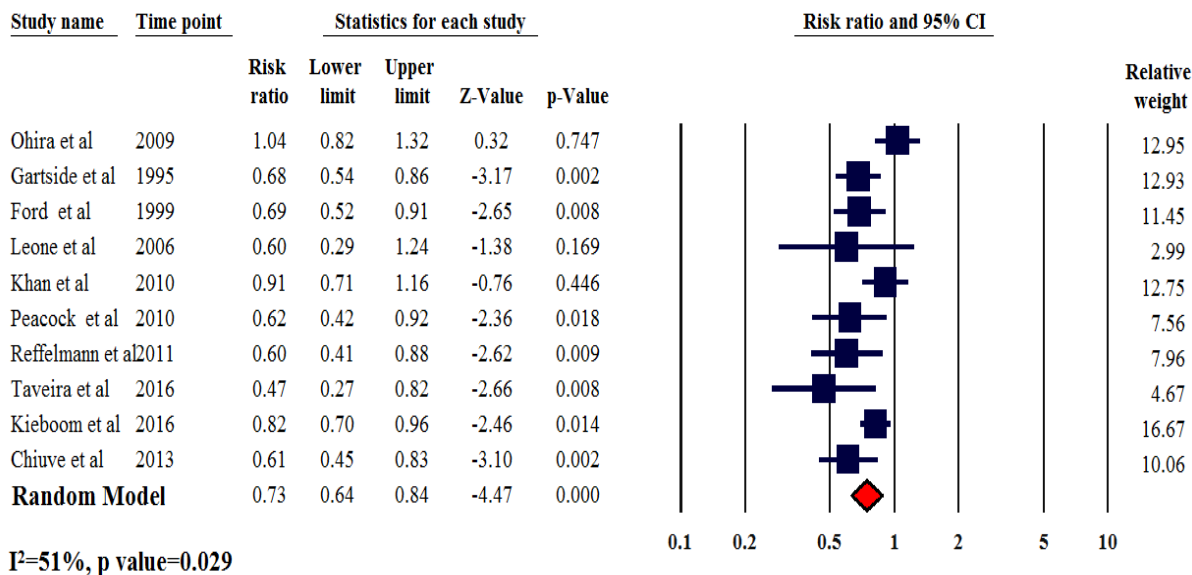


Figure 3. Forest plot of meta-analysis on serum magnesium and CVD.

Reversibility of Funnel in both studies (intake and serum) revealed there is not a general publication bias. Eggers' test also showed there is no significant publication bias (p value < 0.001) (Figure 4) in the intake studies (Intercept:-0.64, 95% (-3.6, 2.3) and serum studies (Intercept:-2.2, 95% (-4.6, 0.64).

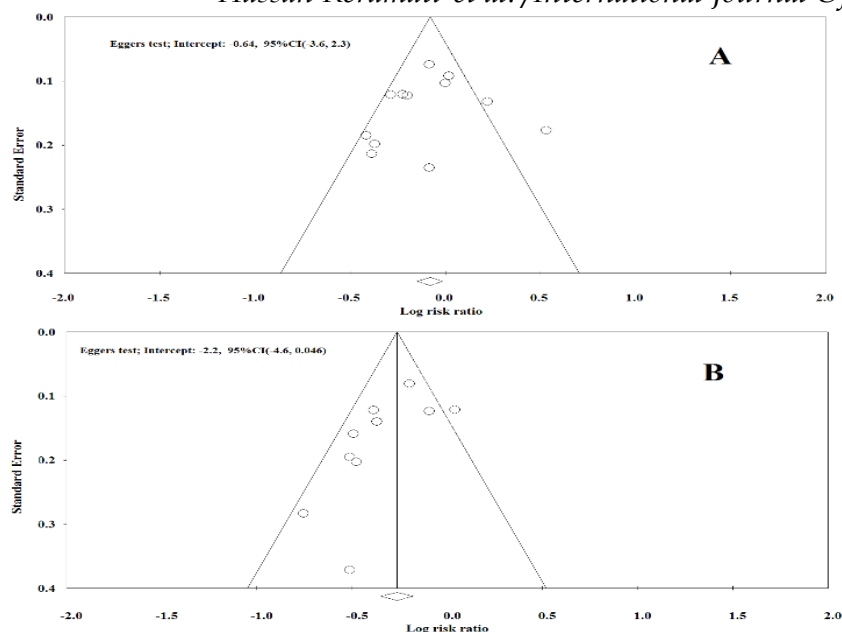


Figure-4. Funnel plot of the intake (A) and serum (B) magnesium studies included in the meta-analysis.

4. Discussion

The results of this study supported the reduction the risk of cardiovascular diseases resulting from an increase in serum level of magnesium (P value<0.001). A significant association was found between dietary magnesium and total CVD incidents risk in the nonlinear model. The greatest risk reduction was observed when dietary magnesium intake increased from 150 mg/d to 400 mg/d. An increase of 0.1 meq/L in serum magnesium was relationships with a 9% decrease in the risk for CVD incidents. Analyses stratified by individual CVD outcomes propose that adequate dietary magnesium intake decrease the risk of stroke, CHD, and CVD death equally. as of limited data on the individual CVD results, should be interpreted carefully and verified by further studies. During the past 8 decades, dietary and serum magnesium have received increased attention and have been the subject of comprehensive studies in cardiovascular health. Magnesium deficiency is considered an main risk factor for various types of CVD. The prevalence of magnesium deficiency is much higher among patients with CVD than among other patients [13, 54, 55]. But, more than half (nearly 65%) of the United States population consumes less than the daily requirement of magnesium from foods[14]. Current guidelines from the WHO and several epidemiological studies have demonstrated that intake of magnesium from drinking water may decrease the risk of several types of CVDs [14, 56]. However, compared to magnesium from dietary sources, the amount of magnesium consumed from drinking water is negligible. This fact has weakened the interest in the inclusion of drinking water in preventive strategies for CVD [27]. Dietary magnesium intake is an important

component for the primary prevention of CVD. Several admissible mechanisms have been suggested for the relationship between magnesium and cardio metabolic benefits including improvement in endothelial function; induction of direct and indirect vasodilation; improved BP; beneficial effects on arrhythmias, inflammatory reactions, and platelet aggregation; and improvement of insulin homeostasis and lipid metabolism [57, 58]. Furthermore, experimental and epidemiological studies considered that hypertension may serve as an effect modifier of the magnesium and CVD association [28, 59]. According to WHO, 62% of all strokes and 49% of CHD incidents are attributable to high BP [60]. A previous meta-analysis of 12 randomized clinical trials that analyzed the effects of magnesium supplementation on BP showed that each 10 mmol/day increase in magnesium was relationships with a 4.3 mm Hg reduction in systolic BP¹ and a 2.3 mm Hg reduction in diastolic BP[25, 61]. In the present meta-analysis, most included cohort studies were adjusted for basic BP or hypertension status; only 1 study [38] assessed the impact of hypertension on the association between dietary magnesium intake and CVD risk. This study found more enunciated associations among hypertensive individuals than among non-hypertensive individuals; this results supports the useful effect of magnesium on CVD outcomes.

Larsson et al [62] performed a systematic review combining 7 research papers and performed a dose-response meta-analysis to determine the relationship between magnesium intake. They showed that an increase of 100 mg a day in magnesium intake is linearly relationships with 9% decrease in the risk for total stroke (0.88 to 0.97). But, all but 1 of 7 individual studies detected non-significant linear trends between magnesium intake and CVD risk [38]. In contrast to previous meta-analyses, which showed a linear association between magnesium intake and stroke risk, we found evidence of a nonlinear inverse association between magnesium intake and total CVD incidents risk, with the greatest risk reduction occurring when intake was increased from low levels.. This is consistent with the finding of a significant inverse association in our highest vs. lowest meta-analysis.

Limitations of the study

Although the results of this study showed the relationship between the serum magnesium and CVD risk, butthis study had some limitations that include: putting aside the case control studies, limitation of language (except English and Farsi), putting aside the studies that have used the method of blinding, not getting separated of the studies on smokers and non-smokers, not being isolated of studiesbased on of sex and location.

5. Conclusion

The results of the meta-analysis and systematic review showed that an increase in magnesium intake through the consumption of drinking water and food reduces CVD risk. On the other hand, an increase in magnesium serum level reduces CVD risk some more compared with the intake of magnesium (Pvalue < 0.001). The results of this study supported the reduction of CVD risk resulting from magnesium.

6. References

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