Bachelor’s degree

A study of magnesium intake and its possible relation to inflammation

Author: Johanna Hanzon
Supervisor: Anna A. Persson
Examiner: Håkan Andersson
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Abstract
The study was initiated to examine magnesium intake, supplementation and their relation to inflammation. Magnesium is the second most abundant extracellular ion following potassium. Outside the cell, magnesium can be found in bone tissue, cardiac muscle tissue, other tissues and in the blood. Magnesium form compounds which operate in several essential metabolic processes in the body. Magnesium deficiency may have an impact on insulin resistance and endothelial dysfunction, which may result in an increased level of inflammation. Increased inflammation over a longer period has been seen to increase the risk of common lifestyle induced diseases such as diabetes type II and coronary heart diseases. The study of magnesium and its influence on inflammation is thereby becoming important and interesting for all societies and in their effort to find solutions to maintain and increase the well-being of its individuals.

The study is a literature study based on searches made in One Search and Pub Med databases. A total of ten studies were included, five for magnesium intake and five for supplementation. The majority of the studies showed a significant correlation between increased magnesium intake, dietary and supplementary, with decreased levels of inflammatory biomarkers and hints that magnesium might have a role in the inflammation process. What needs to be taken into account is that fiber intake in two studies attenuated magnesium’s inverse relation to inflammation. In addition of a decrease in inflammatory biomarker levels the risk for developing diabetes type II seemed to decrease as well with an increased intake of magnesium in one of the studies. Further studies need to be executed in order to establish the role of magnesium in inflammation and optimal dosage for prevention of metabolic and cardiovascular diseases.

Abstrakt

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1. Introduction
Magnesium (Mg) has been used to treat illness since the late 1600’s when the Epsom salt (magnesium sulphate) from the Epsom spring was discovered (Nishizawa, et al., 2007). Until today magnesium has been utilized in various fields of medicine, for example to reduce renal toxicity during chemotherapy (Kidera, et al., 2014) as migraine prophylaxis (Kropach, et al., 2016) relieve severe asthma (Davendralingam, 2014) and as an anti-convulsant in severe preeclamptic and eclamptic women (Gao, et al., 2013). New fields that are being explored are magnesium and its relation to cardiovascular diseases (CVD), pain relief and anaesthesia, depression and post-traumatic stress disease (PTSD) and the metabolic syndrome (MetS) including hypertension, obesity and diabetes type II (Almoznino-Sarafian, et al., 2007) (Szewczyk, et al., 2008) (Weglicki, 2012).

Magnesium is a cofactor in over three hundred enzymes and has a key role in a great number of functions in the body, two of these are the glucose metabolism and the regulation of insulin (Kim, et al., 2010). Extracellular magnesium competitively inhibit influx of calcium to beta cells. The influx of calcium is needed to excite the cell in order for it to release insulin. When less insulin is released due to the competitive extracellular magnesium the down-regulation of insulin receptors is reversed and the insulin sensibility increases. Intracellular magnesium acts as a cofactor in the transduction of the insulin signal though autophosphorylation of tyrosine kinase receptors and other protein kinases involved in the insulin signal transduction. An interruption in the insulin signal system, caused by magnesium deficiency would make the absorption of glucose to the cell less efficient. With glucose still left in the blood more insulin would have to be produced and released which in turn would lead to down-regulation of insulin receptors as well as induced insulin resistance. (Günter, 2010)

It has been speculated that magnesium deficiency may result in low-grade inflammation and insulin resistance, and contribute to endothelial dysfunction (Bo, et al., 2006) (Kharitonova, et al., 2015). If magnesium has a significant inhibiting effect on C reactive protein (CRP), tumor necrosis factor-alfa (TNF-α) and Interleukin 6 (IL-6) excretion involved in the inflammation process as well as insulin resistance and endothelial dysfunction, magnesium deficiency could increase the risk for development of cardiovascular and other metabolic diseases (diabetes type II and metabolic syndrome (MetS)) (Bo, et al., 2006). The most common cause of death in Sweden and the western part of the world is cardiovascular diseases. Therefore, it is extra interesting to compare magnesium intake in relation to CRP and other biomarkers of chronic and acute inflammation (Aryana, et al., 2014).

Magnesium intake and its relation to inflammation will be investigated through examining how present studies on the subject differ and relate to each other.

2. Aim of the study
The aim of the study is to examine if there is a correlation between magnesium intake and inflammation, which is a contributing factor to cardiovascular and metabolic diseases.

1. Does magnesium intake correlate with significantly decreased levels of common biomarkers of inflammation such as CRP, TNF- α and IL-6?
2. If so, does magnesium supplementation decrease inflammation, which would be explained by a reduction of these biomarkers?
3. Magnesium
Magnesium is the second most abundant intracellular cation followed by potassium, and is naturally in a 2+ oxidation state (Khan, 2013). Magnesium in the human body is stored by 99% intracellularly in bone tissue, the cardiac muscle and other tissues. The remaining 1% is distributed in the blood (FASS, 2016). Free serum magnesium strives to form compounds with adenosine triphosphate (ATP) or other negatively charged ions. The Magnesium-ATP complexes participate in activation of enzymes that are involved in metabolic processes and redox reactions (Kretzinger, et al., 2013). These metabolic processes and redox reactions control vascular contraction and dilation, growth and apoptosis, differentiation and inflammation (Sontia & Touyz, 2007). Magnesium also play a key role in nerve and muscle transmission as well as in synthesis of fatty acids and proteins, phosphorylation of glucose and decarboxylation of citrate. Magnesium is also active in the synthesis of cyclic adenosine monophosphate (cAMP), transcription and replication of DNA and mRNA translation (FASS, 2016) (Musso, 2009).

Magnesium and calcium are antagonists, which affects absorption and reabsorption, efficacy and homeostasis (Dai, et al., 2013). Consequently, magnesium deficiency could lead to coronary arrhythmias, vasoplasms, and reduced heart contractibility, which is regulated by the calcium homeostasis (Almoznino-Sarafian, et al., 2007) (Kretzinger, et al., 2013).

3.1 Magnesium transport mechanism
The transport mechanisms for magnesium are still being explored and knowledge of how magnesium is absorbed and reabsorbed is far from complete. Nevertheless, there are a number of studies, which confirm several transport mechanisms. Magnesium is mainly absorbed in the small intestine by two specific cation channels, transient receptor potential melastatin (TRPM) 6 and TRPM 7. TRPM6 and TRPM7 are called chanzymes for their ability to act as ion channels as well as signalling kinases. TRPM 6 is located in the kidney and small intestine while TRPM7 can be found almost anywhere in the body. Approximately thirty to fifty percent of the total magnesium intake can be absorbed under normal circumstances and if there is a deficiency of magnesium the intestine have the capacity to increase its uptake by forty percent. Reabsorption and regulation of magnesium influx occur mainly in the kidney through TRPM 6 and 7 but also by SLC(solute carrier family) 41a1 and SLC41a2. Magnesium efflux occurs via Na-dependent and Na-independent pathways, one of which is the Na+/Mg2+ exchanger (Nishizawa, et al., 2007) (Sontia & Touyz, 2007) (Touyz, 2008). Most of the filtered magnesium is reabsorbed, generally only 3% is excreted in the urine. In the loop of Henle are calcium receptors that react to altered magnesium and calcium concentrations. The receptors can adjust the excretion of magnesium and calcium by activating the arachidonic acid cascade which inhibit apical NaK2Cl transporter and potassium channels that in turn reduce the positive gradient and induce increased magnesium and calcium losses (Musso, 2009).

Magnesium absorption, resorption and excretion is affected by, to name a few, the total dietary intake of magnesium, bioavailability of different magnesium compounds, intestine and kidney function, and use of medications such as diuretics and cyclosporine (Almoznino-Sarafian, et al., 2007). More magnesium is saved in the body in patients using potassium-sparing diuretics, in patients with renal insufficiency and with an excessive magnesium intake, and at alkalosis. A larger magnesium excretion can be seen when loop diuretics, thiazides and furosemide are used and also at acidosis. Diseases, which increase
excretion, are enteric diseases such as irritated bowels syndrome (IBS), tubular damage on nephrons and chronic alcoholism (Musso, 2009).

3.2 Bioavailability of magnesium compounds
The water solubility is an important factor for the bioavailability of magnesium compounds. Organic salts of magnesium have higher solubility than inorganic salts and are thereby easier absorbed. Magnesium oxide supplements are typically produced and sold commercially but have been shown to have low bioavailability. In studies on animals and humans magnesium citrate, magnesium chloride, magnesium L-aspartate and oxyburate indicate a higher bodily uptake, whereas magnesium sulphate bioavailability was lower (Rylander, 2014) (Kharitonova, et al., 2015).

3.3 Dietary and supplementary magnesium intake
Recommended daily allowance (RDA) in USA is 255-265 mg/day for women, and 330-350 mg/day for men (Nielsen, et al., 2010). The Swedish recommendations from Livsmedelsverket is 120-280 mg/day for children (4-14 years), 280 mg for women and 350 mg for men (FASS, 2016). 60% of American adults do not meet RDI (recommended dietary intake, compatible with RDA) of magnesium. Severe magnesium deficiency is uncommon as the majority of the population consumes at least 50% of RDI (Nielsen, et al., 2010). It is believed that the decreased magnesium intake is a consequence of refined foods, and drinking water, as magnesium rich food include green leafy vegetables, legumes, nuts, seeds and whole grain (Bo, et al., 2006).

3.4 Magnesium deficiency
Magnesium deficiency i.e. hypomagnesaemia is a consequence of low dietary intake of magnesium which does not cover the RDI. Magnesium depletion is the term for a low intake of magnesium due to secondary factors such as diseases, decreased function of the kidney and intestines or medications. Normal serum magnesium range is 1.7-2.3 mg/dL or 0.75-0.95 mmol/L (Musso, 2009). According to farmaceutiska specialiteter i Sverige (FASS) moderate magnesium deficiency is established at plasma magnesium levels at 0.7 mmol/L (17 mg/L) and severe magnesium deficiency at values below 0.5 mmol/L (12 mg/L) (FASS, 2016). Severe deficiency can induce hypokalaemia, neuromuscular irritability, tetany, seizures, hypokalaemia and tachyarrhythmias. Magnesium toxicity is reached at serum concentrations of 4-6 m/dl and 1.74-2.61 mmol/L and symptoms of toxicity are hypotension, vomiting nausea, skeletal muscle paralysis, bradyarrhythmia, which in severe cases could develop to respiratory depression and cardiac arrest (Musso, 2009).

4. Inflammation
Inflammation can be separated into two slightly different responses, acute and chronic inflammation. Distinguishing factors are the time of onset/activation, the duration of the response and a greater accumulation of specific inflammation mediators and leukocytes (Kumar, et al., 2012).

Inflammation is initiated when an alien agent is discovered by macrophages (i.e. a virus or bacteria) or when damaged tissue cells excrete cytokines and other mediators which activate and accumulate a variety of cells involved in the inflammatory process (mast cells, dendritic cells, macrophages and diverse leukocytes). Inflammation results in vascular changes, which include vasodilation, increased permeability due to contraction of endothelial cells and activation of the latter. Adhesion molecules are expressed on the surface of endothelial cells
and enable leukocytes to attach to surface of endothelial cells in order to migrate to the site of injury. Leukocytes clear invaders and eliminate necrotic tissue through phagocytosis and exudation of reactive and toxic agents. Most common in acute inflammation are neutrophils, which arrive at the site of inflammation 6-24 hours after the initiation of the inflammation process. The neutrophils are then replaced by monocytes and macrophages derived from monocytes that have immigrated to injured tissue. This takes place 24-48 hours after initiation of the inflammation process. Macrophages are bigger, live longer and have an improved phagocytosis capacity. They secrete cytokines, which stimulate further inflammation until the necrotic tissue, or the alien agents have been eliminated and the tissue has been repaired. Chronic inflammation can follow acute inflammation. This often occurs in autoimmune diseases where the source of inflammation cannot be extinguished (Kumar, et al., 2012).

4.1 Biomarkers of inflammation
Focus will be on CRP as it is included in the majority of studies investigating magnesium intake in relation to inflammation. Additional biomarkers of inflammation are mentioned and discussed in order to widen the perspective of the study.

4.1.1 Acute phase protein CRP and biomarkers of inflammation.
CRP is a biomarker that reflects vascular inflammation. According to New York Heart Association (NYHA) the risk for cardiovascular diseases rises markedly if CRP exceeds 3 mg/L in serum blood samples (Bo, et al., 2006) (King, et al., 2005).

Acute phase proteins, such as CRP and fibrinogen, are constantly produced by the liver in low concentrations but during acute inflammation the levels may increase hundreds of times. The production of acute phase proteins are stimulated by, amongst others, IL-6. The acute phase proteins bind to microbial cell walls to enhance phagocytosis and promote the elimination of microbes (Kumar, et al., 2012).

4.1.2. IL-1, IL-6 and TNF
Interleukin 1 (IL-1), IL-6 and TNF-a are cytokines which are produced by many different types of cells (i.e. activated macrophages, mast cells, endothelial cells and others). They act locally and have many effects in acute inflammation. For example, they act as chemokines and attract leukocytes to the site of injury and stimulate synthesis of additional cytokines (Kumar, et al., 2012).

5. Material and methods
The study is completely based on literature studies and sources available on University of Lund website LOVISA, Libris, Pub Med and One search. Other sources were available such as Web of science, Cochrane and LUB search but the results from searches did not add any new or different studies in comparison to the sources already used. The search was divided in two parts with slightly differing search criteria. What they had in common was that the studies had to contain both women and men, which were in-between 17-70 years old and where magnesium and CRP-levels or other biomarkers of inflammation were available. The studies from present to those dated back to ten years ago were included, and all trials were made on humans. In the first part of this research at least 1000 subjects had to be observed in each study as well as their magnesium intake and its correlation to CRP. In the second part of this research at least 100 subjects had to be included and the studies would have to focus on magnesium supplement and relation to CRP or and biomarkers of inflammation.

The aim of the study was to see if there was any correlation between magnesium intake and inflammation. Ten studies matched the search criteria, five for each of the two parts. The
search words used was “magnesium CRP” in Pub Med (83 articles) and “CRP magnesium supplement” also in Pub Med (6 articles). The supplement search was also made in One Search (11 articles). The articles that were excluded were animal trials, those lacking information of CRP and magnesium serum levels, studies on children and single gender populations (Table I).

Further searches were performed in One Search on “magnesium CRP” (222 hits 132 without duplicates) “magnesium inflammation biomarkers” (55 hits, 38 without duplicates)”magnesium TNF-a” (129 hits 102 without duplicates) “magnesium IL-6” (156 hits, 103 without duplicates) “magnesium IL-1” (176 hits 130 without duplicates). All studies were sorted after inclusion and exclusion criteria Table I. Additionally, a search was made on “Interferon gamma magnesium” (41 hits, 37 without duplicates) as interferon gamma is a marker of chronic inflammation. The results showed studies made on preeclampsia patients and subjects with acute asthma or were designed as rat models, all of which were excluded. Interferon gamma is therefore not mentioned either in the introduction or later in the text. Previously mentioned searches were made in November 2014.

Cross-searches on Cochrane, Web of science etc. showed the same search results as previous searches. One Search was the database that contained all studies combined. What became clear was the scarcity of extensive studies and population groups in the studies. The limit of 100 subjects on the supplement section was reduced to 50 in order to include more studies. The final amount of studies included were five for part one and five for part two.

Outside the article search complementary material to the introduction was found in LOVISA, Encyclopedia of metalloproteins (Kretsinger, et al., 2013), New perspectives in magnesium research, nutrition and health (Nishizawa, et al., 2007), and also Robbins Basic Pathology (Kumar, et al., 2012).

Table I. Inclusion and exclusion criteria in the article searches

<table>
<thead>
<tr>
<th>Part of search</th>
<th>Inclusion criteria</th>
<th>General inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Search part 1</strong>&lt;br&gt;Magnesium intake and CRP</td>
<td>Dietary intake of magnesium 1000+ subjects</td>
<td>17-70 years&lt;br&gt;Available information of magnesium intake and serum levels of inflammatory biomarkers.</td>
<td>Animal trials&lt;br&gt;Children&lt;br&gt;Single gender populations</td>
</tr>
<tr>
<td><strong>Search part 2</strong>&lt;br&gt;Magnesium supplementation and CRP and other biomarkers</td>
<td>Magnesium supplementation 100+ limit -&gt; lowered to 50+ subjects</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Results

The results will be presented in two sections. Section one covers magnesium intake in correlation to inflammation while section two contains the issue of magnesium supplement and its influence on inflammation.

6.1 Presentation of studies of magnesium intake in relation to inflammation.

Below follows a short presentation of each study included, their aims, study population and results.

6.1.1 Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. (Kim, et al., 2010)

Is a prospective long-term study with the aim to investigate magnesium intake and the incidence of diabetes, insulin resistance and systemic inflammation in young American adults. The study was initiated 1985 and finalized in 2005, a total of 20 years. 5115 subjects, 18-30 years old, were included in the study but were later reduced to 4497 due to exclusion criteria’s of; fasting serum levels of 7 mmol/L glucose or higher at baseline, utilization of anti-diabetic medications, not completing follow up examinations, and subjects with missing information on either magnesium intake or total energy intake, pregnant women, participants with missing data on smoking status, alcohol consumption, physical activity, BMI and waist circumference.

Information of magnesium intake was assessed using validated interviewer-administered CARDIA diet history questionnaires. The questionnaires took approximately 45 minutes to complete and consisted of two parts: first a short questionnaire regarding general dietary practices and second a food frequency questionnaire based on a 24-hour recall where various categories of food, serving size and frequency of consumption were collected. Magnesium supplementation was added to the total intake of magnesium. Dietary data of magnesium intake was collected at baseline, year 7 and year 20. Serum CRP was measured year 7, 15 and 20. IL-6 was measured year 20 and fibrinogen was measured year 5, 7 and 20. Fasting plasma glucose and insulin levels were collected year 0, 7, 10, 15 and 20. The subjects were divided into five groups according to magnesium intake (mg/1000 kcal) ranging from the highest to the lowest intake of magnesium. Those five groups (quintiles) were then adjusted for covariates in three models containing 1) age, sex, ethnicity and study centre 2) years of education, smoking status, alcohol consumption, physical activity and family history of diabetes, BMI, systolic blood pressure, total energy intake 3) dietary intake of saturated fat and crude fiber.

The result of the study showed that from the beginning until the end of the study 330 incidences of diabetes were identified. Determined by a fasting glucose level of 7 mmol/L or more, a non-fasting glucose level of 11.1 mmol/L or more or utilization of anti-diabetic medications. The incidence of diabetes was 47% lower for subjects with the highest intake of magnesium compared to subjects with the lowest intake of magnesium (P value <0.01) Magnesium intake was inversely associated with increased concentrations of hs-CRP, IL-6, fibrinogen and HOMA-IR. The results from the study are presented in Table II.
Table II. Median value (mg/L) of inflammatory markers and HOMA-IR in multivariable adjusted models in association to total intake of magnesium (Quintile 1-5). Adapted from (Kim, et al., 2010)

<table>
<thead>
<tr>
<th>Biomarkers of inflammation and insulin resistance</th>
<th>1 (lowest mg intake)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (highest mg intake)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-CRP (n=4157)</td>
<td>1.60</td>
<td>1.37</td>
<td>1.27</td>
<td>1.00</td>
<td>0.86</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6 (n=3254)</td>
<td>2.26</td>
<td>1.96</td>
<td>1.66</td>
<td>1.54</td>
<td>1.39</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fibrinogen (n=4325)</td>
<td>314</td>
<td>319</td>
<td>319</td>
<td>316</td>
<td>306</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HOMA-IR (n=4239)</td>
<td>2.66</td>
<td>2.63</td>
<td>2.50</td>
<td>2.36</td>
<td>2.11</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The cause of the study was to investigate the incidence of diabetes in correlation to magnesium intake. The authors found an inverse association between the incidence of diabetes and dietary magnesium intake. They believe that the phenomenon could be explained by the inverse correlations between magnesium intake, inflammation and insulin resistance, as an increased magnesium intake decreased the inflammatory biomarkers and lowered the insulin resistance.

6.1.2 Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort (Bo, et al., 2006)

The study was performed in Italy and included 1653 subjects at the age of 45-64. The subjects were patients of 6 family physicians, and representative of the resident population in terms of age group, percentage of men and education level. The subjects were divided into a control group (n=1448) and a subgroup of healthy individuals (n=205). Subjects taking magnesium supplements were excluded. The objective was to study fiber and magnesium intake in relation to diabetes mellitus, the metabolic syndrome, cardiovascular diseases and inflammation. Information of dietary intake of magnesium and fiber was collected using semi quantitative validated food-frequency questionnaires (FFQ) from the European prospective investigation into cancer and nutrition studies. Which is based on recollection of foods consumed during the past 12 months. There were 148 food items to choose from and additionally serving portion and frequency were measured by the assistance of photographs and 10 categories ranging from never to 5 times/day. The FFQ was self-reported. Blood pressure and blood samples were taken in order to detect serum hs-CRP and fasting glucose concentrations, high-density lipoprotein (HDL), insulin, cholesterol, and prealbumin. The subjects were tested for cardiovascular diseases with an electrocardiogram.

As observed in Table III HOMA-IR, hs-CRP and serum glucose decreased with increased intake of magnesium, whereas HDL increased. The prevalence of diabetes and metabolic syndrome decreased from the lowest magnesium intake to the highest. Subjects with the lowest magnesium intake were 3-4 times more likely to have diabetes, MetS and hs-CRP compared to subjects in the highest tertile of magnesium and fiber intake. The association of magnesium intake and diabetes and MetS was attenuated when adjusted for fiber intake. Hs-CRP still had a significant association with low magnesium intake after adjusting for fiber intake. In the subgroup of healthy individual’s magnesium and fiber intake correlated negatively to hs-CRP. Patients with CVD had significantly lower magnesium and fiber intake. Fiber intake had an inverse
significant association to MetS, DM, hs-CRP and HOMA-IR after adjusting for magnesium intake.

Table III. Intake of magnesium in correlation to hs-CRP, fasting glucose, HOMA-IR and HDL. Adjusted from (Bo, et al., 2006)

<table>
<thead>
<tr>
<th>Values of inflammation and insulin resistance</th>
<th>Tertile 1 (lowest intake in mg)</th>
<th>Tertile 2</th>
<th>Tertile 3 (highest intake in mg)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/L</td>
<td>2.3</td>
<td>1.3</td>
<td>1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose mg/dL</td>
<td>112</td>
<td>102</td>
<td>109</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR mmol/LxµU/mL</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL mg/dL</td>
<td>58.9</td>
<td>60.3</td>
<td>61.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

In the recent study a CRP of 3 mmol/L and above was inversely associated to magnesium intake in both study populations even after adjustment for fiber intake, whereas the correlation to diabetes and MetS was attenuated. The researchers suggest that the effect of fiber may be confounded with the effect of magnesium as there was an inverse correlation of fiber intake to metabolic abnormalities.

6.1.3 Dietary magnesium and C-reactive protein levels (King, et al., 2005)
This study was based on National Health and Nutrition Examination Study (NHANES 1999-2000). NHANES was a 12 month long study, executed by National Center for Disease Control and Prevention to gather information about health and diet of noninstitutionalized Americans, 17 or older. The extensive study was constituted of home interviews and health tests made in a mobile center, where blood, urine, hair, air and dust samples were taken. The dietary intakes of magnesium was measured through a computer assisted dietary interview (CADI) which contain several data bases with food lists, brand names and food amount lists.

The aim of the study was to determine if dietary magnesium intake is associated with levels of hs-CRP. 3799 subjects from the NHANES were included in the study. Those taking magnesium supplement were excluded. Covariates that were adjusted for in regression models were age group, race and sex, BMI, smoking status, alcohol consumption, exercise, income level, total caloric intake and medical conditions i.e. angina, heart attack, diabetes, hypertension and coronary heart disease. CRP-levels in relation to magnesium intake was also examined in a subgroup of subjects that were 40 years or older and had a BMI of >25.

Subjects in the lowest quintile of magnesium intake were more likely to have elevated CRP compared to subjects with intake of RDA or more (36.9, 34.9, 33.9 and 28.4%) P =0.045. Adults 40 years and older with a BMI of >25, and an intake of magnesium less than 50% of RDA had a 2.24 time ratio of having elevated CRP levels compared to subjects reaching RDA. Subjects consuming less than 50% of RDA of fiber and magnesium intake were 2.09 times more likely to have elevated CRP.
When adjusted for fiber intake association of magnesium intake and CRP were attenuated. The writers maintain that individuals with magnesium intakes below RDA are more likely to have elevated CRP-value but suggest further research.

6.1.4 Magnesium intake decreases type 2 diabetes risk through the improvement of insulin resistance and inflammation: The Hisayama study (Hata, et al., 2013)

In contrast to the other studies presented, this study was executed in Japan on a cohort of 1999 non-diabetic subjects. The trial lasted from 1988 to 2009 and the mean time of compliance was 15, 6 years. The objective was to investigate magnesium intake in relation to incidence of diabetes type 2, and to measure CRP levels, which could be a possible mechanism for the development of metabolic diseases. The subjects were 40-79 years old and did not use any supplements. At baseline semi quantitative food frequency questionnaires were completed with assistant of trained dieticians and nutritionists. Circa 10 follow-up examinations were made and at these serum insulin levels, HOMA-IR, has-CRP, HDL and triglyceride values were obtained. A self-administered questionnaire concerning smoking habits, alcohol intake, medical history, diabetic and hypertensive treatments and physical activity, were submitted by the subjects.

Results showed a significant decrease in type II diabetes incidence in the 3rd and 4th quintile compared to the 1st with the lowest intake of magnesium. (p=0.01 and 0.03). The results remained significant after adjusting for confounding factors. There was no trend in CRP levels or HOMA-IR in relation to magnesium intake.

6.1.5 Dietary micronutrient intakes are associated with markers of inflammation but not with markers of subclinical atherosclerosis. (Oliviera Otto, et al., 2011)

The aim of the study was to examine associations of dietary micronutrients (magnesium, amongst others) with markers of inflammation and subclinical atherosclerosis. A multi-ethnic cohort of 5181 subjects between 45-84 years was examined. The population sample and tests were collected from the MESA study, the purpose was to examine the prevalence of subclinical CVD and potential affecting factors. Magnesium dietary intake and supplementation was collected from food frequency questionnaires using 24-hour recall. Blood samples were drawn to detect IL-6, hs-CRP, fibrinogen and total homocysteine levels. Coronary artery calcification (CAC) and intima-media thickness of the common carotid artery (CC-IMT) was measured.

In the present study, following subjects were excluded; subjects taking anti-diabetic medications at baseline, those who were diagnosed with diabetes, had inadequate dietary information, or a fasting glucose value of 7 mmol/l or more.

The results showed that magnesium intake was inversely related to plasma total homocysteine (tHcy) levels. High tHcy levels is thought to increase the risk for CVD. There was an inverse relation between magnesium intake and CRP and magnesium was positively associated with fibrinogen. After adjusting for covariates the alterations found in CRP and fibrinogen levels with an increased intake of magnesium lost significance. Magnesium consumption did not show any association with increased levels of IL-6. Magnesium was moderately associated with a reduced risk of CC-IMT.
6.1.6 Summary of magnesium intake in relation to inflammation

The majority of studies on magnesium intake in relation to inflammation had a study population at the age of 40 years and older. Two out of five studies included younger persons. The population size ranged from 1653 to 5181 persons. The examinations and collection of data were made in USA and Italy (not shown in table). The length of the studies varied between 12 months to 21 years. In two of the articles, the time range was not mentioned. Serum CRP and magnesium intake were measured in all studies. Additionally IL-6, fibrinogen, HOMA-IR, HDL, tHcy and fiber intake was registered in several of the articles. In three out of five articles magnesium intake had a significant correlation to serum CRP concentration, whereas two showed no correlation. Fiber attenuated the significant result in article 6.1.3 (Table VI).

<table>
<thead>
<tr>
<th>Article number</th>
<th>Population</th>
<th>Length of study</th>
<th>Measurements</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1.1 (Kim, et al., 2010)</td>
<td>18-30 years 5115 adults</td>
<td>20 years</td>
<td>Hs CRP, IL-6, fibrinogen, HOMA-IR</td>
<td>Inverse relation to incidence of diabetes, hs-CRP, IL-6 and HOMA-IR</td>
</tr>
<tr>
<td>6.1.2 (Bo, et al., 2006)</td>
<td>45-64 years Patients from 6 family physicians 1653 adults</td>
<td>-</td>
<td>CRP, HOMA-IR and HDL</td>
<td>Inverse relation to hs-CRP and HOMA-IR</td>
</tr>
<tr>
<td>6.1.3 (King, et al., 2005)</td>
<td>17+ years, non-institutionalized 3799 adults</td>
<td>12 months</td>
<td>Fiber intake and CRP</td>
<td>Less dietary intake of mg-&gt; more likely to have elevated CRP.</td>
</tr>
<tr>
<td>6.1.4 (Hata, et al., 2013)</td>
<td>40-79 years</td>
<td>21 years</td>
<td>CRP, HOMA-IR and HDL</td>
<td>No correlation of magnesium intake and CRP levels. Risk of diabetes type II seems to decrease</td>
</tr>
<tr>
<td>6.1.5 (Oliviera Otto, et al., 2011)</td>
<td>45-84 years, free from CVD 5181 adults</td>
<td>14 years</td>
<td>CRP, IL-6, fibrinogen and tHcy</td>
<td>Magnesium intake was inversely associated to tHcy, and related to fibrinogen status</td>
</tr>
</tbody>
</table>

Table VI. Summary of articles part 1: Magnesium dietary intake in relation to markers of inflammation.
6.2 Introduction of studies of magnesium supplementation and its influence on inflammation.

In this section studies concerning supplementation of magnesium in relation to inflammation will be presented.

6.2.1 Magnesium supplement intake and C-reactive protein levels in adults (King, et al., 2006)

The study sample was derived from NHANES 99-02, which has been described previously. Subjects were 17 years and older, and the dietary intake of magnesium was collected using 24 hour recall food frequency questionnaires. Serum CRP concentrations were obtained through blood sampling.

The aim was to investigate whether an intake of 50 mg/day or more had a significant effect on CRP levels in comparison to individuals who consumed less than 50 mg/day. A total of 10,024 individuals were included when they had valid measures for magnesium intake and CRP. The subjects were divided into 2 sections, one of which contained subjects supplementing <50 mg/day and subjects who did not use supplement at all, and the other section contained subjects using 50 mg/day or more magnesium supplementation.

The results were controlled for confounding factors (age, sex, BMI, smoking status, exercise and total energy expenditure) in regression models. The outcome of the study showed that individuals taking at least 50 mg supplement/day were 22% less likely to have elevated CRP levels (p = <0.05). A majority of the individuals taking supplements of 50 mg and more reached RDA (60.2%) while in the group with less or no supplementation only 21.9% reached RDA. People who had a daily intake of magnesium below RDA was 40% more likely to have elevated CRP levels (P=<0.05). Table V.

Table V. Difference between supplementation and magnesium deficiency in risk for elevated CRP levels. Adapted from (King, et al., 2006)

<table>
<thead>
<tr>
<th>Magnesium intake</th>
<th>Risk for elevated CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg supplement/day</td>
<td>22% less likely to have elevated CRP levels</td>
</tr>
<tr>
<td>Magnesium intake below RDA</td>
<td>40% more likely to have elevated CRP levels</td>
</tr>
</tbody>
</table>

6.2.2 Magnesium and C-reactive protein in heart failure: an anti-inflammatory effect of magnesium administration? (Almoznino-Sarafian, et al., 2007)

The aim of the study was to observe the relation of serum magnesium to CRP in heart failure patients. 133 patients were transferred from the emergency department to the department of medicine were the examinations took place. In the first part of the study 68 out of the 133 patients had chronic systolic heart failure and they were included in the study. Their serum magnesium and CRP-values were determined after they had been stabilized. In the latter part of the study 35 normomagnesemic heart failure (HF) patients with systolic HF participated. They were divided into group A (n=17) which was treated with 300 mg magnesium citrate/day for 5 weeks and group B (n=18) as untreated controls. Excluding criteria were renal failure, patients receiving magnesium containing drugs, and patients with infectious diseases, thyroid, parathyroid and active liver disease and alcoholism. Values of CRP and serum magnesium levels were obtained before and 5 weeks
after discharge from the hospital. Results: 23 out of the 133 patients observed (17.3%) demonstrated normal serum CRP levels. In patients diagnosed with HF compared with patients with non-HF, mean serum CRP was significantly higher (P=<0.001). In the later part of the study where magnesium administration and its effect on CRP was studied, patients with supplementation showed a significant decrease of CRP (P<0.001) while the non-supplemented group showed a decrease which was not significant (P=0.3). Basal intracellular magnesium increased significantly in group A (P=0.01) but did not reach significance in group B (P = 0.7). 94% of subjects in group A demonstrated lowered CRP values. The authors conclude that magnesium administration might be a way to improve the outcome of heart failure patients through the reduction of CRP.

6.2.3 Magnesium supplementation improves indicators of low magnesium status and inflammatory stress in adults older than 51 years with a poor quality sleep (Nielsen, et al., 2010)

100 adults (22 males and 78 females) were included in a study concerning the effects of magnesium supplementation on sleep disorders and CRP-levels. The subjects included in the study was 51-85 years, had poor quality sleep (sleep disorders or sleep complaints). Excluded were subjects already consuming sleep medications or supplements of at least 100 mg/day. Further exclusion criteria were BMI >40 kg/m², respiratory tract disease, chronic obstructive pulmonary disease and utilization of oxygen apparatus. Subjects taking medications that would retain magnesium and potassium were also excluded when the risk of heart arrhythmia would increase with magnesium supplementation. The experiment lasted 8 weeks, was double blind and placebo-controlled. The subjects were randomly assigned to two groups, a supplementation and a control group. The supplementation group was given 320 mg magnesium citrate/day and the controls were given sodium citrate placebo. Assessment of blood and urine variables, sleep quality, BMI and diet were made at baseline, week 5 and week 7. All subjects kept a three-day food diary for baseline, week 5 and 7 that was used to calculate an estimate of the magnesium intake.

The results of the study indicated that magnesium intake below estimated average requirement (EAR) was significantly associated with higher BMI and increased CRP-levels. Urinary excretion of magnesium increased in subjects taking supplements but not in the placebo group. Sleep quality was improved in both supplement group and placebo group, although in the supplement group participants had a higher score of sleep disturbance. Erythrocyte magnesium increased between baseline and end of the study in both groups (P=0.01). Magnesium supplementation did not have a significant effect on CRP except on participants with a CRP higher than 3.0 mg/L showed a decline with magnesium treatment, while CRP levels in the placebo group rose (P=<0.002).

6.2.4 Acute effect of intravenous administration of magnesium sulphate on serum levels of inter-leukin-6 and tumor necrosis factor-a in patients undergoing elective coronary bypass graft with cardiopulmonary bypass. (Aryana, et al., 2014)

The objective of the study, as written in the headline, was to assess the effect of magnesium sulphate infusion on TNF-a and IL-6, in patients undergoing coronary bypass. 90 patients were enrolled in the study and were randomly assigned to an intervention group (n=45) and a control group (n=45).

Except from getting different solutions i.e. magnesium sulphate saline solution for the intervention group and saline solution for the controls they were given the same treatment. At surgery and 2 hours post surgery blood samples were drawn to assess IL-1, IL-6 and TNF-a. MgSO₄ were injected to subjects in the intervention group with a bolus dose of 30
mg/kg for 5 minutes after the induction of anaesthesia, then the maintenance dose was infused 10 mg/kg/hour. The placebo group was infused with normal saline with the same volume and method used as in the intervention group.

At baseline there was no deviation in TNF-α and IL-6 levels. These concentrations changed significantly post operation. IL-6 values were $67.6 \pm 22.3$ pg/mL in the intervention group and $102.1 \pm 33.7$ pg/mL (P= 0.01) in the placebo group. TNF-α post operation values were $27.4 \pm 4.2$ pg/mL for the intervention group and $44.7 \pm 6.1$ pg/mL in the placebo group (P=0.005).

6.2.5 Evaluation of the Anti-inflammatory effects of peri-operative infusion of magnesium sulfate on the microsurgical procedures for intracranial tumors. (Etezadi, et al., 2014)

The aim of the study was to investigate if a high dose of magnesium infusion before and after neurosurgical operation affect inflammation, by assessing CRP levels. 60 subjects about to undergo elective craniotomy were enrolled. Exclusion criteria involved significant organ disorders, morbid obesity and subjects receiving calcium channel blocking treatment. The patients were divided into an intervention and a control group. The intervention group were treated with 5 grams of magnesium sulphate 2 days prior to operation, the day before and 6 hours within the start of the surgery. MgSO4 was injected using a 10 mL of 50% solution in 1 litre of saline. The placebo group followed the same procedure except that the solution did not contain any magnesium. Throughout the surgery heart rate, blood pressure, electrocardiogram, oxygen saturation, end tidal CO₂, and core temperature values were measured. CRP values were obtained before the first magnesium infusion and 2nd and 3rd day post surgery. Mean arterial blood pressure and heart rate were measured.

CRP increased from the 1st to the 2nd measurement in both the intervention group and in the placebo group, and then it decreased in the 3rd measurement, although the changes were not significant (P=0.435). Heart rate and mean arterial blood pressure were lower in the intervention group compared to the placebo group.

6.2.6 Summary of studies of magnesium supplementation and its relation to inflammation

The subject of the studies were in between 17 to 85 years of age, elderly subjects were overrepresented. The populations contained 60 to 10024 subjects. Examinations took place in USA, Japan, Israel and Iran (not shown in table) and lasted 5 days to 3 years. In all studies except for one, CRP was measured. In that single study CRP was replaced by IL-6 and TNF-α to indicate inflammation. Four out of five studies showed a significant inverse relation of magnesium supplementation and an increased level of biomarkers of inflammation. One of the four articles only showed significance on subjects with already high levels of CRP (3 mg/L and more). One out of five studies showed no significant relation between supplementation and CRP. Table VI
### Table VI. Summary of articles part 2. Magnesium supplementation in relation to CRP and biomarkers of inflammation.

<table>
<thead>
<tr>
<th>Article number</th>
<th>Population</th>
<th>Length of study</th>
<th>Measurements</th>
<th>Results</th>
<th>Significantly decreased CRP levels with increased mg intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2.1 (King, et al., 2006)</td>
<td>17+ years 10024 adults</td>
<td>3 years</td>
<td>CRP, mg intake, dietary and supplement</td>
<td>Supplemented were 22% less likely to have elevated CRP 50% of RDA were 40% more likely.</td>
<td>YES</td>
</tr>
<tr>
<td>6.2.2 (Almoznino-Sarafian, et al., 2007)</td>
<td>57-82 years Institutionalized 133 + 35 patients</td>
<td>5 weeks</td>
<td>Serum and intracellular magnesium and CRP</td>
<td>CRP decreased in both groups but only reached significance in the treatment group</td>
<td>YES</td>
</tr>
<tr>
<td>6.2.3 (Nielsen, et al., 2010)</td>
<td>51-85 years 100 adults</td>
<td>8 weeks</td>
<td>CRP, serum and erythrocyte magnesium</td>
<td>Supplementation decreased CRP with baseline values of &gt; 3mg/L</td>
<td>YES, on adults with high CRP levels</td>
</tr>
<tr>
<td>6.2.4 (Aryana, et al., 2014)</td>
<td>52-72 years 90 patients</td>
<td>12 months</td>
<td>IL-6 &amp; TNF-a</td>
<td>Postop. Levels of IL-6 and TNF-a were significantly higher in placebo group</td>
<td>YES</td>
</tr>
<tr>
<td>6.2.5 (Etezadi, et al., 2014)</td>
<td>45-59 years 60 patients</td>
<td>5 days</td>
<td>Serum CRP</td>
<td>No significant difference in CRP levels</td>
<td>NO</td>
</tr>
</tbody>
</table>

### 7. Discussion
The objective of this literature review was to examine whether magnesium intake and magnesium supplementation are related to increased CRP levels and other biomarkers of inflammation as inflammation is known to increase the risk of metabolic and cardiovascular diseases. The study is divided into two parts, the first part containing prospective long-term studies of magnesium intake in large cohorts and the second part included studies on magnesium supplementation and its acute and chronic effects on inflammatory biomarkers. The main reason for this structure is that the vast population studies rely on food frequency questionnaires, which allow the participants to bias the results. Further, it does not give a complete picture of the magnesium intake in whole as the intake of food may differ in between days, weeks and months. The magnesium supplement studies are better controlled in form of the actual intake of magnesium and its acute effects. On the other hand, the controlled studies exhibit small population samples. Therefore, it was thought that the prospective studies and the minor supplement studies would complement each other.
Results from the studies, as previously described in several review articles, are inconsistent. Three out of five studies showed a significant inverse relation in between magnesium intake and markedly increased CRP concentrations while two did not (Oliviera Otto, et al., 2011) (Hata, et al., 2013). In one of the articles with significant results the correlation was attenuated as fiber was added to the regression model (King, et al., 2005). This sets light on the difficulty of measuring the effects of a single nutrient when food products with high magnesium content is highly correlated to fiber containment. That arises questions, do both magnesium and dietary fiber protect against inflammatory responses, do they activate different anti-inflammatory pathways, or is it a completely different substance in these foods that effect inflammation? The answer differs.

Other interesting associations found in the studies were magnesium intake and its relation to reduced CC-IMT risk (Oliviera Otto, et al., 2011). Also, persons with cardiovascular diseases display low intakes of fiber and magnesium (Bo, et al., 2006). The incidence of diabetes was shown to be 47% lower for subjects with the highest magnesium intake compared with subjects with the lowest intake (Kim, et al., 2010) (Hata, et al., 2013) although in one study the association of magnesium intake and decreased risk for diabetes and MetS was attenuated when adjusting for fiber intake (Bo, et al., 2006). Even though magnesium would not have an anti-inflammatory effect it may still work on functions, which increase the risk for CVD. There are several theories concerning how magnesium influence and suppress inflammation, some of them are inhibition of N-methyl-d-aspartate (NMDA) receptors, the action magnesium has as an antagonist to calcium, and activation of different pathways such as phosphoinositide 3-kinase/Akt (Aryana, et al., 2014). It is still not known if, and to what extent these theories apply.

As seen in most of the prospective studies individuals taking magnesium supplement have a higher total intake of magnesium than non supplementing individuals. It is speculated whether persons taking magnesium supplements also are more health conscious (Kim, et al., 2010). If this is true, magnesium intake might not be the factor responsible for reducing inflammation, instead it might be training and exercise for example.

Further on to the next part of the study, dealing with magnesium supplementation. Four out of five studies showed a significant inverse association between magnesium supplementation and CRP, TNF-a and IL-6 (Almoznino-Sarafian, et al., 2007) (Aryana, et al., 2014) (King, et al., 2006). When supplementing with 50 mg magnesium/day the probability of elevated CRP levels decreased with 22%. While a daily intake below RDA increased the risk of elevated CRP levels with 40%. Patients diagnosed with heart failure had significantly higher levels of CRP in comparison with non-heart failure patients (Almoznino-Sarafian, et al., 2007). Treatment with magnesium sulphate after heart surgery decreased the concentration of TNF-a and IL-6 significantly in the intervention group compared with the placebo group. In another study, the relation of magnesium intake and CRP was only significant in subjects with high serum levels of CRP (Nielsen, et al., 2010).

CRP is often used as a measure of inflammation, mostly because it is more accessible and less expensive than other measures of biomarkers for example TNF-a and IL-6 (Etezadi, et al., 2014). American heart association have in compliance with reliable studies set a threshold of serum CRP where the risk of cardiovascular diseases increase markedly, 3 mg/L (Nishizawa, et al., 2007). It might be an explanation for the amounts of studies measuring CRP and the lack of studies examining magnesium deficiency and supplementation in relation to other biomarkers such as IL-6 and TNF-a.
The strength of this particular literature study is the strict inclusion- and exclusion criteria and the combination of research from different domains such as diabetes-, metabolic syndrome-, nutrition- and cardiovascular research. The weakness of this research is due to the limited resources, biasing covariates and interpretation and presentation of the results. The results in the review are merely a part of the articles on the subject of research and I strongly recommend further reading to get a complete picture.

Magnesium research in relation to human diseases seem to increase. Magnesium, a compound that is thought by some to relieve a vast array diseases and symptoms. These relations though are difficult to assess as a large amount of processes in the body and its internal systems are active simultaneously.

There have been a couple of studies investigating the role of magnesium intake on inflammation but the majority of them are animal trials with rats, rabbits, goats, cows and even bulls. The studies may not present a compliable explanation to how magnesium intake affects humans. Therefore, there is still a need for research on magnesium, its relation to inflammation and effect on humans. Furthermore, it is of importance that the most validated and reliable measure of inflammation is used not just the most cost-effective i.e. food frequency questionnaires and CRP. It seems possible that magnesium intake may have an effect on cardiovascular and metabolic diseases but there is yet extensive research that need to be executed in order to define possible pathway and mechanisms of magnesium and to detect an optimal dose for protection of cardiovascular and metabolic diseases.

8. Conclusion

Studies of magnesium intake in relation to markers of inflammation show inconsistencies. In some there were an inverse association between magnesium intake and CRP, IL-6 and TNF-a, in others there were an association that was attenuated by adjusting for dietary fiber intake and in one study there was no association between magnesium intake and CRP at all. In a majority of the supplement studies magnesium was inversely associated with the risk of increased CRP levels. Extensive research will be required to clarify this relationship further.
References


