## DIABETES:

**"Low cellular magnesium with high cellular calcium is the key to metabolic syndrome X. Type II Diabetes is really magnesium deficiency that manifests as metabolic syndrome X."** The Magnesium Factor, Mildred Seelig MD. Avery Books, 2003 - Ch 2.
***http://www.amazon.com/Magnesium-Factor-Mildred-Seelig/dp/1583331565***

### Ionic basis of hypertension, insulin resistance, vascular disease, and related disorders. The mechanism of "syndrome X".

http://www.ncbi.nlm.nih.gov/pubmed/8507440
Am J Hypertens. 1993 Apr:6(4):123S-134S. Resnick LM. Cardiovascular Center, New York Hospital, Cornell Medical Center, New York.

Great pathophysiological significance has recently been placed on the association of metabolic abnormalities, such as hyperinsulinemia, insulin resistance, obesity, and frank diabetes mellitus, with essential hypertension and coronary artery disease, and the clinical coincidence of these features has been termed "syndrome X." Despite the suggestion that insulin itself mediates this clinical linkage, the specific mechanisms underlying this syndrome remain poorly understood. We have attempted to understand these phenomena at the cellular level, and have investigated the role of cellular mineral ion species such as cytosolic free calcium (Cai), free magnesium (Mgi), and intracellular pH (pHi) in various insulin resistant states, including essential hypertension, obesity, and type II (non-insulin-dependent) diabetes mellitus (NIDDM). Utilizing nuclear magnetic resonance spectroscopic techniques to noninvasively assess intracellular concentrations of these ions, we observed that each of these disease states is characterized, in whole or in part, by common abnormalities of cellular ion metabolism, including elevated Cai levels and suppressed levels of Mgi and pHi. Furthermore, despite the predominant use of red cells as a tissue source, the measured levels of Cai, Mgi, and pHi were closely related to the ambient blood pressure, the degree of cardiac hypertrophy, and to the hyperinsulinemic response to oral glucose challenge. Altogether, these data suggest an integrated "ionic hypothesis" in which the frequent clinical coexistence of hypertension and altered insulin metabolism derives from common abnormalities of cellular ion handling, resulting in excess steady-state levels of Cai, reciprocal depletion of Mgi, and lowered pHi. These cellular ion alterations would be expected to have tissue-specific consequences, appearing in vascular tissue as vasoconstriction and elevated blood pressure, in skeletal muscle and fat as insulin resistance, in pancreatic beta-cells as hyperinsulinemia, and in neural tissue as potentiated neurotransmitter release and increased sympathetic nerve activity. Thus, according to this hypothesis, essential hypertension, insulin resistance, hyperinsulinemia, and NIDDM are in reality different clinical components of what should be better designated as "generalized cardiovascular-metabolic disease" (GCMD)

### Magnesium Metabolism in Hypertension and Type 2 Diabetes Mellitus

http://journals.lww.com/americantherapeutics/Abstract/2007/07000/Magnesium_Metabolism_in_Hypertension_and_Type_2.12.aspx
American Journal of Therapeutics: July/August 2007 - Volume 14 - Issue 4 - pp 375-385
doi: 10.1097/01.mjt.0000209676.91582.46 Barbagallo, Mario MD; Dominguez, Ligia J MD; Resnick, Lawrence M MD

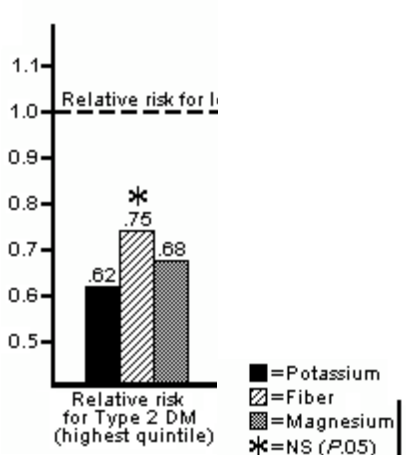
The increasing evidence for the clinical relevance of altered magnesium metabolism to states of altered insulin resistance confirms the role of magnesium deficit as a possible underlying common mechanism of the insulin resistance of hypertension and altered glucose tolerance. The pioneer work of Lawrence M. Resnick and his group using the cellular ion-based approach that we are only partially presenting here has consistently contributed to the progress of the field, demonstrating (a) the critical importance of magnesium metabolism in regulating insulin sensitivity as well as vascular tone, and blood-pressure homeostasis; (b) that magnesium deficiency, defined on the basis of intracellular free magnesium levels, and or serum ionized magnesium is a common feature of both diabetic and hypertensive states as well as various other cardiovascular and metabolic processes and aging; (c) the ability of environmental factors such as dietary nutrient-sugar and mineral content to alter the set point of steady-state cell ion activity; and (d) that magnesium supplementation is indicated in conditions associated with magnesium deficit although well-designed therapeutic trials of magnesium in essential hypertension and type 2 diabetes mellitus are needed in the near future.

## Diet and risk of clinical diabetes in women

***http://www.ajcn.org/cgi/content/abstract/55/5/1018***

American Journal of Clinical Nutrition, Vol 55, 1018-1023, Copyright © 1992 by The American Society for Clinical Nutrition, Inc GA Colditz, JE Manson, MJ Stampfer, B Rosner, WC Willett and FE Speizer , Channing Laboratory, Harvard Medical School, Boston, MA 02115-5899.

To determine the relations of diet with risk of clinical noninsulin- dependent diabetes, we analyzed data from a prospective cohort of 84360 US women. During 6 y of follow-up we identified 702 definite incident cases. Because body mass index (BMI) is a powerful risk factor for diabetes, we examined the relations of fat (including type), fiber, sucrose, and other components of diet to risk of diabetes, among women with BMIs (in kg/m2) less than 29 kg/m2. After controlling for body mass index, previous weight change, and alcohol intake, we observed no associations between intakes of energy, protein, sucrose, carbohydrate, or fiber and risk of diabetes. Compared with women in the lowest quintile of energy-adjusted intake, and relative risks (and tests for trend) for those in the highest quintile were 0.61 (P trend = 0.03) for vegetable fat, 0.62 (P trend = 0.008) for potassium, 0.70 (P trend = 0.005) for calcium, and 0.68 (P trend = 0.02) for magnesium. These inverse associations were attenuated among obese women (BMIs greater than or equal to 29).



## Carbohydrates, dietary fiber, and incident type 2 diabetes in older women[1,2,3]

http://www.ajcn.org/cgi/content/abstract/71/4/921

American Journal of Clinical Nutrition, Vol. 71, No. 4, 921-930, April 2000 © 2000 American Society for Clinical Nutrition Katie A Meyer, Lawrence H Kushi, David R Jacobs, Jr, Joanne Slavin, Thomas A Sellers and Aaron R Folsom

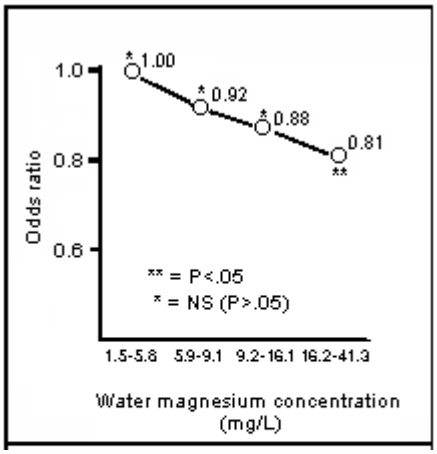
**Background:** Dietary carbohydrates may influence the development of type 2 (non-insulin-dependent) diabetes, for example, through effects on blood glucose and insulin concentrations.
**Objective:** We examined the relations of baseline intake of carbohydrates, dietary fiber, dietary magnesium, and carbohydrate-rich foods and the glycemic index with incidence of diabetes.
**Design:** This was a prospective cohort study of 35988 older Iowa women initially free of diabetes. During 6 y of follow-up, 1141 incident cases of diabetes were reported.
**Results:** Total grain, whole-grain, total dietary fiber, cereal fiber, and dietary magnesium intakes showed strong inverse associations with incidence of diabetes after adjustment for potential nondietary confounding variables. Multivariate-adjusted relative risks of diabetes were 1.0, 0.99, 0.98, 0.92, and 0.79 (*P* for trend: 0.0089) across quintiles of whole-grain intake; 1.0, 1.09, 1.00, 0.94, and 0.78 (*P* for trend: 0.005) across quintiles of total dietary fiber intake; and 1.0, 0.81, 0.82, 0.81, and 0.67 (*P* for trend: 0.0003) across quintiles of dietary magnesium intake. Intakes of total carbohydrates, refined grains, fruit and vegetables, and soluble fiber and the glycemic index were unrelated to diabetes risk.
**Conclusion:** These data support a protective role for grains (particularly whole grains), cereal fiber, and dietary magnesium in the development of diabetes in older women.

## Magnesium in drinking water and the risk of death from diabetes mellitus.

http://www.ph.kmu.edu.tw/teacher/cs723a.htm

Magnesium Res 1999; *12:131-137*. Yang CY, Chiu HF.

The odds ratio for dying from diabetes decreases as the concentration of magnesium in drinking water increases.



## Magnesium Intake and Incidence of Metabolic Syndrome Among Young Adults

J AHA, Circulation 2006;113:1675-1682
http://circ.ahajournals.org/cgi/content/abstract/113/13/1675 Ka He MD, ScD; Kiang Liu, PhD; Martha L. Daviglus, MD, PhD; Steven J. Morris, PhD; Catherine M. Loria, PhD; Linda Van Horn, PhD; David R. Jacobs, Jr, PhD; Peter J. Savage, MD

***Background—*** Studies suggest that magnesium intake may be inversely related to risk of hypertension and type 2 diabetes mellitus and that higher intake of magnesium may decrease blood triglycerides and increase high-density lipoprotein (HDL) cholesterol levels. However, the longitudinal association of magnesium intake and incidence of metabolic syndrome has not been investigated.

***Methods and Results—*** We prospectively examined the relations between magnesium intake and incident metabolic syndrome and its components among 4637 Americans, aged 18 to 30 years, who were free from metabolic syndrome and diabetes at baseline. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program/Adult Treatment Panel III definition. Diet was assessed by an interviewer-administered quantitative food frequency questionnaire, and magnesium intake was derived from the nutrient database developed by the Minnesota Nutrition Coordinating Center. During the 15 years of follow-up, 608 incident cases of the metabolic syndrome were identified. Magnesium intake was inversely associated with incidence of metabolic syndrome after adjustment for major lifestyle and dietary variables and baseline status of each component of the metabolic syndrome. Compared with those in the lowest quartile of magnesium intake, multivariable-adjusted hazard ratio of metabolic syndrome for participants in the highest quartile was 0.69 (95% confidence interval [CI], 0.52 to 0.91; *P* for trend <0.01). The inverse associations were not materially modified by gender and race. Magnesium intake was also inversely related to individual component of the metabolic syndrome and fasting insulin levels.

***Conclusions—*** Our findings suggest that young adults with higher magnesium intake have lower risk of development of metabolic syndrome.

## Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X

Molecular Aspects of Medicine Vol 24, Issues 1-3, 6 Feb 2003, Pages 39-52
http://www.sciencedirect.com/science/journal/00982997 purchaseMario Barbagallo, Ligia J. Dominguez, Antonio Galioto, Anna Ferlisi, Calogero Cani, Loriano Malfa, Antonella Pineo, Adele Busardo and Giuseppe Paolisso

**Abstract**

Magnesium (Mg) is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular Mg concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In vitro and in vivo studies have demonstrated that insulin may modulate the shift of Mg from extracellular to intracellular space. Intracellular Mg concentration has also been shown to be effective in modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation–contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli. A poor intracellular Mg concentration, as found in noninsulin-dependent diabetes mellitus (NIDDM) and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both

events are responsible for the impairment in insulin action and a worsening of insulin resistance in noninsulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily Mg administration, restoring a more appropriate intracellular Mg concentration, contributes to improve insulin-mediated glucose uptake. The benefits deriving- from daily Mg supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily Mg intake are predictive of a lower incidence of NIDDM. In conclusion, a growing body of studies suggest that intracellular Mg may play a key role in modulating insulin-mediated glucose uptake and vascular tone. We further suggest that a reduced intracellular Mg concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension.

## HYPERTENSION:

**Drinking Water and Health**, Pages 440 through 447 of the Report of the Safe Drinking Water Committee of the National Academy of Sciences, 1977
**http://books.nap.edu/openbook.php?record_id=1780&page=441**

According to the U.S. National Academy of Sciences (1977) there have been more than 50 studies, in nine countries, that have indicated an inverse relationship between water hardness and mortality from cardiovascular disease. That is, people who drink water that is deficient in magnesium and calcium generally appear more susceptible to this disease.

**Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium** Am J Hypertens (UNITED STATES) Mar 1997, 10 (3) p346-55
http://www.nature.com/ajh/journal/v10/n3/abs/ajh1997759a.html

Magnesium is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular magnesium concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In fact, in vitro and in vivo studies have demonstrated that insulin may modulate the shift of magnesium from extracellular to intracellular space. Intracellular magnesium concentration has also been shown to be effective on modulating insulin action (mainly oxidative glucose metabolism), offset calcium-related excitation-contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli, by stimulating Ca2+-dependent K+ channels. A poor intracellular magnesium concentration, as found in non-insulin-dependent diabetes mellitus (NIDDM) and in hypertensive (HP) patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening of insulin resistance in non-insulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily magnesium administration, restoring a more appropriate intracellular magnesium concentration, contributes to improve insulin-mediated glucose uptake. Similarly, in HP patients magnesium administration may be useful in decreasing arterial blood pressure and improving insulin-mediated glucose uptake. The benefits deriving from daily magnesium supplementation in NIDDM and HP patients are further supported by epidemiological studies showing that high daily magnesium intake to be predictive of a lower incidence of NIDDM and HP. In conclusion, a growing body of studies suggest that intracellular magnesium may play a key role on modulating insulin-mediated glucose uptake and vascular tone. We further suggest that a reduced intracellular magnesium concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension. (74 Refs.)

**Relationship of magnesium intake and other dietary factors to blood pressure: the Honolulu heart study.** Am J Clin Nutr (UNITED STATES) Feb 1987, 45 (2) p469-75 http://www.ajcn.org/cgi/content/abstract/45/2/469

Associations between blood pressure and intakes of 61 dietary variables assessed by 24-h recall method were investigated in 615 men of Japanese ancestry living in Hawaii who had no history of cardiovascular disease or treated hypertension. Magnesium, calcium, phosphorus, potassium, fiber, vegetable protein, starch, Vitamin-C, and vitamin D intakes were significant variables that showed inverse associations with blood pressure in univariate and a multivariate analyses. Magnesium had the strongest association with blood pressure, which supports recent interest in its relation to blood pressure. Nevertheless, it was not possible to separate the effect of magnesium from that of other variables because of the problem of high intercorrelation among many nutrients. While recommendations based upon cross-sectional studies must be viewed cautiously, these results suggest that foods such as vegetables, fruits, whole grains, and low-fat dairy items are major sources of nutrients that may be protective against hypertension.

# RESTLESS LEGS SYNDROME (RLS):

## Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study.

http://www.ncbi.nlm.nih.gov/pubmed/9703590

Sleep. 1998 Aug 1;21(5):501-5. Hornyak M, Voderholzer U, Hohagen F, Berger M, Riemann D. Department of Psychiatry and Psychotherapy, Albert-Ludwigs-University, Freiburg, Germany.

Periodic limb movements during sleep (PLMS), with or without symptoms of a restless legs syndrome (RLS), may cause sleep disturbances. The pharmacologic treatments of choice are dopaminergic drugs. Their use, however, may be limited due to tolerance development or rebound phenomena. Anecdotal observations have shown that oral magnesium therapy may ameliorate symptoms in patients with moderate RLS. We report on an open clinical and polysomnographic study in 10 patients (mean age 57 +/- 9 years; 6 men, 4 women) suffering from insomnia related to PLMS (n = 4) or mild-to-moderate RLS (n = 6). Magnesium was administered orally at a dose of 12.4 mmol in the evening over a period of 4-6 weeks. Following magnesium treatment, PLMS associated with arousals (PLMS-A) decreased significantly (17 +/- 7 vs 7 +/- 7 events per hour of total sleep time, $p < 0.05$). PLMS without arousal were also moderately reduced (PLMS per hour of total sleep time 33 +/- 16 vs 21 +/- 23, $p = 0.07$). Sleep efficiency improved from 75 +/- 12% to 85 +/- 8% ($p < 0.01$). In the group of patients estimating their sleep and/or symptoms of RLS as improved after therapy (n = 7), the effects of magnesium on PLMS and PLMS-A were even more pronounced. Our study indicates that magnesium treatment may be a useful alternative therapy in patients with mild or moderate RLS-or PLMS-related insomnia.

## Clinical, EEG, electromyographic and polysomnographic studies in restless legs syndrome caused by magnesium deficiency.

http://www.ncbi.nlm.nih.gov/pubmed/8363978

Rom J Neurol Psychiatry. 1993 Jan-Mar;31(1):55-61. Popoviciu L, Aşgian B, Delast-Popoviciu D, Alexandrescu A, Petruţiu S, Bagathal I. Academy of Medical Sciences, Department of Neurology, Tirgu-Mures, Romania.

The present paper reports biochemical and neurophysiological investigations in ten cases with restless leg syndrome. Other neuropsychiatric affections and factors which could generate the symptomatology of restless legs syndrome were not included. The EEG recordings demonstrated evident reticular neuronal hypersynchrony generated by hyperpnoea (sinusoidal slow waves). The classical EEG investigations pointed out neuromuscular hyperexcitability, but some modifications of the functional parameters of the neuromuscular excitability and conductibility (signs of neuropathy) were also noticed. In all the cases, continuous 8-hour polysomnographic recordings and monitorization on infrared TV screen were performed. Investigations reported: important disorders of sleep organization, agitated sleep with frequent periods of nocturnal awakenings, increase of the durations and percentages of light slow-wave sleep (LSWS) and rapid and frequent changes of various stages of LSWS, a decrease of duration and percentage of DSWS, a decrease of duration and percentage of REM sleep (as in other parasomnias caused by magnesium deficiency) and nocturnal EEG anomalies (long discharges of sinusoidal slow waves, of sharp waves and of sharp slow waves appearing in the LSWS stages with the disappearance in the REM sleep).

## CRAMPS – MUSCLE, LEG:

Dr Skantze http://www.drskantze.com/health/legcramps.htm

Leg cramps are powerful contractions of the muscles in the lower leg which causes great pain. It often occurs in the middle of the night and therefore wakes up the patient. The pain persist for hours thereafter although of lower intensity. Anyhow, it can disturb the sleep to a great extent. … Increasing the extracellular $Ca^{2+}$ enhances transmitter release; lowering it reduces and ultimately blocks synaptic transmission. The facilitating effect of $Ca^{2+}$ on synaptic transmission is inhibited by $Mg^{2+}$, a blocker of $Ca^{2+}$ channels.
There is little knowledge of the exact nature of leg cramps and as an effect of this there is no primary cure. I will mention a few of which magnesium have been of help for me.
Water intoxication and hyponatremia (low concentration of sodium (salt) in the blood) can cause cramps. ...
Hypomagnesemia (low concentration of magnesium in the blood) causes neuromuscular hyperexcitability. NMDA (N-methyl-D-Aspartate) receptors are involved in generating the locomotor pattern. NMDA receptor-channel's voltage-dependent blockade by $Mg^{2+}$ is responsible for the inhibition by magnesium. Too low $Mg^{2+}$ will make the inhibition too small.

http://www.health911.com/remedies/rem_cramp.htm
Magnesium will help the smooth muscles that surround your arteries to relax, and your body uses it to process calcium.

http://www.digitalnaturopath.com/cond/C466089.html
Low levels of certain minerals known as electrolytes - magnesium, potassium, calcium and sodium - have long been linked to leg cramps. (Marathon runners sweating out the miles are particularly prone to this variety.) …
To prevent cramping consider the regular use of supplements, especially calcium, magnesium, potassium …

## CHRONIC FATIGUE SYNDROME:

### Red blood cell magnesium and chronic fatigue syndrome.

http://www.ncbi.nlm.nih.gov/pubmed/1672392 Lancet Mar 30, 1991;Vol 337(8744):757-60.
Cos IM, Campbell MJ, Dowson D. Medical School, University of Southampton, UK.

The hypotheses that patients with chronic fatigue syndrome (CFS) have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such patients were tested in a case-control study and a randomised, double-blind, placebo-controlled trial, respectively. In the case-control study, 20 patients with CFS had lower red cell magnesium concentrations than did 20 healthy control subjects matched for age, sex, and social class (difference 0.1 mmol/l, 95% confidence interval [CI] 0.05 to 0.15). In the clinical trial, 32 patients with CFS were randomly allocated either to intramuscular magnesium sulphate every week for 6 weeks (15 patients) or to placebo (17). Patients treated with magnesium claimed to have improved energy levels, better emotional state, and less pain, as judged by changes in the Nottingham health profile. 12 of the 15 treated patients said that they had benefited from treatment, and in 7 patients energy score improved from the maximum to the minimum. By contrast, 3 of the 17 patients on placebo said that they felt better (difference 62%, 95% CI 35 to 90), and 1 patient had a better energy score. Red cell magnesium returned to normal in all

patients on magnesium but in only 1 patient on placebo. The findings show that magnesium may have a role in CFS.

### Treating chronic fatigue syndrome by repleting mineral deficiencies - Nutritional Influences on Illness

http://findarticles.com/p/articles/mi_m0ISW/is_247-248/ai_113807056/?tag=content;col1

**Townsend Letter for Doctors and Patients, Feb-March, 2004 by Melvyn R. Werbach**

Patients with chronic fatigue syndrome (CFS) are usually stressed, and stress hormones can promote a reduction in tissue magnesium levels. Moreover, CFS has much in common with magnesium deficiency (1):

1. Neuromuscular and psychiatric disorders
2. Immunologic disorders with an inappropriate response to viral infections.
3. Increase in substance P (a neuropeptide which promotes inflammation, bronchospasm and capillary permeability.)
4. Increase in NMDA (n-methyl-d-aspartate) receptor activity.

To explain the last point, the NMDA receptor is part of the brain's neuroexcitatory pathway. Upregulation of the receptor, which is found in CFS, causes neuromuscular and psychiatric symptoms. Since magnesium inhibits the NMDA receptor, an increase in NMDA receptor activity is also found in magnesium deficiency.

Magnesium deficiency, even despite normal dietary intake, is common, (2), (3) and it appears that deficient patients may benefit from supplementation, probably because it corrects the deficiency syndrome. (2-5)

If fibromyalgia is prominent, magnesium has been combined with malic acid, since malate plays an important role in energy metabolism. When primary fibromyalgia patients were treated for an average of 8 weeks with 200 to 600 mg of magnesium and 1200 to 2400 mg of malate daily, their mean tender point index significantly decreased from 19.6 to 6.5. Six of the patients were switched to placebo. Within 2 days, their muscle pain had worsened. After 2 weeks, the mean tender point index had risen from 6.8 to 21.5. (6)

However, in a subsequent double-blind crossover study of similar patients who received 300 mg of magnesium and 1200 mg of malic acid for 4 weeks, there were no significant improvements in pain or tenderness or in functional or psychological measures. (7)

In clinical practice, pain from fibromyalgia appears to respond in about 2 days compared to about 2 weeks for fatigue. About 40% of CFS patients are said to show improvement. (8)

### Review and Hypothesis: Might Patients with the Chronic Fatigue Syndrome Have Latent Tetany of Magnesium Deficiency

*http://bubl.ac.uk/archive/journals/jcfs/v04n0298.htm#7review*

Journal of Chronic Fatigue Syndrome, Vol. 4(2) 1998 page 77-108The Haworth Press, Mildred Seelig

ABSTRACT:

The latent tetany syndrome (LTS) parallels CFS in its neuromuscular and psychiatric manifestations, as well as in inner ear disturbances: vestibular in CFS and FM, as well as in LTS, and increased vulnerability to noise-induced deafness in LTS. Microvascular damage to the cochlea is seen in Mg deficiency, noise-induced deafness, and might be a factor in migraine and other severe headaches in both LTS and CFS; impaired cognition more in CFS than in LTS. However, some brain and neurotransmitter dysfunctions seen with Mg deficiency might be contributory to cognitive disorders of CFS. Mg loss caused by enhanced catecholamine release produced by stress may well be contributory to stress-induced acute episodes of CFS. Malfunctions of the cellular and humoral immunological systems are caused by experimental Mg deficiency. Whether allergies in CFS patients and abnormal response to antigenic challenge are results of low Mg remains to be proven. Mitral valve prolapse is seen in many LTS and CFS

patients, whether a putative Mg deficiency predisposes to this abnormality is not known. Clinical improvement with Mg treatment has been proven in LTS, and seemed helpful in the rare cases of CFS and FM in whom it has been tried. The Mg status should be determined in patient with CFS and FM, but methodology is a handicap. Serum Mg is an inaccurate index. Three methods show promise. Percentage retention of a Mg load is accurate but requires ion-selective electrodes. Blood cell Mg is reliable in a little more than half the patients; sublingual cell Mg seems more accurate. More intensive, and controlled studies of the Mg status of CFS and FM patients, and of their response to Mg therapy is desirable.

## INTRODUCTION

Chronic fatigue syndrome (CFS) is widely recognized, is of uncertain etiology (1), and has created diagnostic confusion for centuries (2,3). Numerous environmental, metabolic, infectious, immunologic, and psychiatric disturbances have been implicated in the many complaints. When the syndrome was found to be associated with abnormal immunologic responses to infection, it was termed postinfectious neuromyasthenia, chronic virus infection, myalgic encephalomyelitis, "chronic fatigue immune dysfunction syndrome" (CFIDS), and fibromyalgia (FM) (1-9). Possibly pertinent to such disturbances are the abnormal immunologic findings in Mg deficiency (10- 13). There are many parallels in clinical manifestations and dysfunctions in the latent tetany syndrome (LTS) of marginal magnesium (Mg) deficiency, and those of CFS, an observation made in 1992 (14), following publication of a small study that reported low erythrocyte Mg levels in patients with CFS and their favorable response to a six-week trial of weekly intramuscular Mg injections in most of them (1*5).* Chronic fatigue, weakness, depression and anxiety, sleep disturbances, paresthesias and sensorineural hearing loss, as well as neuromuscular irritability and myalgias have long been known to respond to long-term Mg supplementation (16-21). That stress commonly precedes acute CFS events is another indication that Mg inadequacy might be a factor, because stress hormones cause Mg loss, and low Mg levels increase secretion of catecholamines (22,23). A few reports of CFS and FM improvement with Mg administration support the premise that low Mg or abnormality in its utilization might be contributory to their pathogenesis. Thus, it is important to determine the Mg status in CFS and FM, a need which has created difficulties because of methodological problems. Diagnostic tests to determine whether Mg deficiency exists, should allow for documentation of the possible value of Mg treatment in these conditions. Serum Mg levels, the easiest to measure, are least reliable (unless an ion-selective electrode is used to measure physiologically active free ionic Mg) since most Mg is intracellular. Mg levels in blood cells or sublingual cells have provided better results, and percentage retention of a Mg load has been accurate, but cumbersome. Carefully controlled, large clinical trials, with measurement of the Mg status before, during and after Mg supplementation, might clarify the pathogenesis, as well as providing a new therapeutic approach to those patients with CFS who have low Mg levels.

# CARDIOVASCULAR DISEASE:

## Serum magnesium and ischaemic heart disease: findings from a national sample of US adults.

http://www.ncbi.nlm.nih.gov/pubmed/10480691?dopt=Abstract Int J Epidemiol. 1999 Aug;28(4):645-51. Ford ES. Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA.

BACKGROUND: Animal and human data suggest that magnesium may play an important role in ischaemic heart disease. Few prospective epidemiological studies have related serum magnesium concentrations to mortality from ischaemic heart disease (IHD) or all-causes. METHODS: Data from the National Health and Nutrition Examination Survey Epidemiologic Followup Study were used to examine the association between serum magnesium concentration, measured between 1971-1975, and mortality from IHD or all-causes in a national sample of 25-74-year-old participants followed for about 19 years. RESULTS: The analytical samples for IHD and all-cause-mortality included 12 340 and 12 952 participants, respectively (1005 IHD deaths, 2637 IHD deaths or hospitalizations, 4282 total deaths). Hazard ratios for IHD mortality from proportional hazards analysis comparing the second (1.59-<1.68 mEq/l), third (1.68-<1.77 mEq/l), and fourth (> or =1.77 mEq/1) quartiles of serum magnesium concentration with the lowest quartile were 0.79 (95% CI: 0.58-1.08), 0.66 (95% CI: 0.47-0.93), 0.69 (95% CI: 0.52-0.90), respectively. For all-cause mortality, hazards ratios were 0.82 (95% CI: 0.72-0.93), 0.84 (95% CI: 0.73-0.96), 0.85 (95% CI: 0.75-0.95). No significant interactions between serum magnesium concentration and age, sex, race, and education were observed. CONCLUSION: Serum magnesium concentrations were inversely associated with mortality from IHD and all-cause mortality.

## Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study.

http://www.ncbi.nlm.nih.gov/pubmed/9736141?dopt=Abstract Am Heart J. 1998 Sep;136(3):480-90. Liao F, Folsom AR, Brancati FL. Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis 55454-1015, USA.

BACKGROUND: Hypomagnesemia has been hypothesized to play a role in coronary heart disease (CHD), but few prospective epidemiologic studies have been conducted. METHODS AND RESULTS: We examined the relation of serum and dietary magnesium with CHD incidence in a sample of middle-aged adults (n=13,922 free of baseline CHD) from 4 US communities. Over 4 to 7 years of follow-up, 223 men and 96 women had CHD develop. After adjustment for sociodemographic characteristics, waist/hip ratio, smoking, alcohol consumption, sports participation, use of diuretics, fibrinogen, total and high-density lipoprotein cholesterol levels, triglyceride levels, and hormone replacement therapy, the relative risk of CHD across quartiles of serum magnesium was 1.00, 0.92, 0.48, and 0.44 (P for trend=0.009) among women and 1.00, 1.32, 0.95, and 0.73 (P for trend=0.07) among men. The adjusted relative risk of CHD for the highest versus the lowest quartile of dietary magnesium was 0.69 in men (95% confidence interval 0.45 to 1.05) and 1.32 in women (0.68 to 2.55).
CONCLUSIONS: These findings suggest that low magnesium concentration may contribute to the pathogenesis of coronary atherosclerosis or acute thrombosis.

**Role of dietary magnesium in cardiovascular disease prevention, insulin sensitivity and diabetes** ***http://journals.lww.com/co-lipidology/Abstract/2008/02000/Role_of_dietary_magnesium_in_cardiovascular.10.aspx***

Current Opinion in Lipidology: February 2008 - Volume 19 - Issue 1 - p 50-56 Bo, Simona; Pisu, Elisabetta

Purpose of review: This review summarizes the evidence for benefits of magnesium on metabolic abnormalities, inflammatory parameters, and cardiovascular risk factors and related-potential mechanisms. Controversy due to contrasting results in the literature is also discussed.

Recent findings: Increased dietary magnesium intake confers protection against the incidence of diabetes, metabolic syndrome, hypertension, and cardiovascular disease. It ameliorates insulin resistance, serum lipid profiles, and lowers inflammation, endothelial dysfunction, oxidative stress, and platelet aggregability. Magnesium acts as a mild calcium antagonist on vascular smooth muscle tone, and on postreceptor insulin signaling; it is critically involved in energy metabolism, fatty acid synthesis, glucose utilization, ATPase functions, release of neurotransmitters, and endothelial cell function and secretion. Prospective studies, however, have found only a modest effect for dietary magnesium on incident pathologies. Furthermore, magnesium supplementation on glucose metabolism, blood lipid levels, and ischemic heart disease has given inconsistent results.

Summary: There is strong biological plausibility for the direct impact of magnesium intake on metabolic and cardiovascular risk factors, but in-vivo magnesium deficiency might play only a modest role. Reverse causality, the strong association between magnesium and other beneficial nutrients, or the possibility that people who choose magnesium-rich foods are more health-conscious may be confounding factors.

# OSTEOPOROSIS

## Magnesium and osteoporosis

http://dietary-supplements.info.nih.gov/factsheets/magnesium.asp
Magnesium Office of Dietary Supplements National Institutes of Health

Bone health is supported by many factors, most notably calcium and vitamin D. However, some evidence suggests that magnesium deficiency may be an additional risk factor for postmenopausal osteoporosis [4]. This may be due to the fact that magnesium deficiency alters calcium metabolism and the hormones that regulate calcium (20). Several human studies have suggested that magnesium supplementation may improve bone mineral density [4]. In a study of older adults, a greater magnesium intake maintained bone mineral density to a greater degree than a lower magnesium intake [56]. Diets that provide recommended levels of magnesium are beneficial for bone health, but further investigation on the role of magnesium in bone metabolism and osteoporosis is needed.

## Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women

http://www.ajcn.org/cgi/content/abstract/69/4/727 American Journal of Clinical Nutrition, Vol. 69, No. 4, 727-736, April 1999 Katherine L Tucker, Marian T Hannan, Honglei Chen, L Adrienne Cupples, Peter WF Wilson and Douglas P Kiel

Background: Osteoporosis and related fractures will be growing public health problems as the population ages. It is therefore of great importance to identify modifiable risk factors.
Objective: We investigated associations between dietary components contributing to an alkaline environment (dietary potassium, magnesium, and fruit and vegetables) and bone mineral density (BMD) in elderly subjects.
Design: Dietary intake measures were associated with both cross-sectional (baseline) and 4-y longitudinal change in BMD among surviving members of the original cohort of the Framingham Heart Study. Dietary and supplement intakes were assessed by food-frequency questionnaire, and BMD was measured at 3 hip sites and 1 forearm site.
Results: Greater potassium intake was significantly associated with greater BMD at all 4 sites for men and at 3 sites for women ($P < 0.05$). Magnesium intake was associated with greater BMD at one hip site for both men and women and in the forearm for men. Fruit and vegetable intake was associated with BMD at 3 sites for men and 2 for women. Greater intakes of potassium and magnesium were also each associated with less decline in BMD at 2 hip sites, and greater fruit and vegetable intake was associated with less decline at 1 hip site, in men. There were no significant associations between baseline diet and subsequent bone loss in women.
Conclusion: These results support the hypothesis that alkaline-producing dietary components, specifically, potassium, magnesium, and fruit and vegetables, contribute to maintenance of BMD.

# MAGNESIUM, THE NUTRIENT THAT COULD CHANGE YOUR LIFE

http://www.mgwater.com/rod15.shtml PYRAMID BOOKS NEW YORK 1968 Ch15 **MAGNESIUM FIGHTS OSTEOPOROSIS** J. I. RODALE with HARALD J. TAUB

For many years osteoporosis has been a mystery disease, striking most frequently in old age, often crippling and always bringing pain. When it strikes, bones gradually lose density and become more porous. They break easier, and are proportionately harder to mend. Osteoporosis attacks 20 to 30 percent of post-menopausal women, and between 5 to 10 percent of men more than 50 years old.

For a long time nothing was known of its cause. It was considered an unavoidable part of aging. Researchers now know that the bones of the body are continually "shedding" cells and being rebuilt. Osteoporosis results when the shedding or breaking down and resorbing of the bone occurs faster than the building-up process.

Here are several theories for-why this takes place. One is that the building blocks of the bone-calcium, vitamin D, etc.-are lacking. Sometimes, dietary supplements of these elements can reestablish a normal balance so that the bone is replaced as quickly as it is resorbed.

Studies have also shown that prolonged lack of exercise can cause deterioration of the bone. In these cases, a simple exercise program along with adequate dietary therapy can block the disease's progress.

A more recent finding is that osteoporosis can be caused by overproduction of adrenal steroids and large doses of corticosteroids. At the same time, certain other hormones (estrogens) appear to combat osteoporosis.

All of the facts have been jangling around in the files of medical researchers for months and years- making no sense to many of them, and leaving osteoporosis as much a mystery disease as ever. Now Dr. Lewis B. Barnett, a retired orthopedic (bone) surgeon living in Center, Colorado, whose work we have cited in previous chapters, has advanced a theory that takes into account and explains all these random facts. What's more, Barnett has successfully tested his theory.

In a personal interview at his Colorado home, Meadow Ranch, Dr. Barnett told us, "One of the most important aspects of the disease osteoporosis has been almost totally overlooked. That aspect is the role played by magnesium."

### *Health from Minerals in Water*

Dr. Barnett first became interested in the role of magnesium in bones and osteoporosis in 1950. At that time he began a series of investigations in Hereford and Dallas, Texas. One purpose of the study was to find out why people in later years frequently have fractures of the cervical neck of the femur, and why in certain areas these heal with great difficulty. These fractures rarely occurred in the Hereford area but were common in Dallas.

When the fractures did occur in the Hereford area, at an average age of 82.5, the healing time was eight weeks. In Dallas, the fractures occurred at the average of age 63, and, if they healed at all, took in the vicinity of 6.3 months.

Barnett analyzed the soil and water content of the two areas, and concluded the major factor in bone health was the mineral content of the water supply. Analysis of the water showed that calcium alone could not be the element responsible for combating osteoporosis. The Hereford water contained only four parts per million of calcium while the Dallas water contained 23 p.p.m. There were only slight differences in the fluorine, iodine, and phosphorus content of the water. Barnett considered these differences statistically insignificant.

The one really outstanding difference was in the magnesium content of the two water supplies. The Dallas supply contained eight p.p.m. of the mineral, while the Hereford water contained 16 p.p.m. Although the medical literature then contained very little on the virtues of magnesium, Barnett did locate some reports on the subject. In the publication, *Vital Facts About Foods,* by Otto Carque (1933) is the statement. "Bones average about 1 per cent phosphate of magnesium and. teeth about 1% per cent phosphate of magnesium. Elephant tusks contain 2 per cent of phosphate of magnesium and billiard balls made from these are almost indestructible. The teeth

of carnivorous animals contain nearly 5 per cent phosphate of magnesium and thus they are able to crush and grind the bones of their prey without difficulty."
Barnett decided to analyze the bone content of people in Dallas and Hereford. He chose for his study 500 women, average age 55. All were his patients, undergoing lumbar and cervical vertebrae surgery. Except for slipped disks and related problems, they considered themselves healthy individuals.

***More Magnesium, Stronger Bone***

The findings bore out the results of the previous studies: the major difference was in the magnesium content of the bone. In the Dallas area where bone weakness was evident because of the high number of cases of osteoporosis, the magnesium content of bone was .05 percent; in Hereford, 1.76 percent.
Still Barnett was not satisfied. He decided on another study. He examined the bone content of healthy people and compared it with the content of people suffering from severe osteoporosis. Again he found there was little difference among the calcium, phosphorus, and fluoride content of the bones of the individuals. The magnesium content of the healthy people, however, was 1.26 percent. That of the osteoporosis victims was .62 percent.
'The mechanism whereby magnesium functions to strengthen bone and combat osteoporosis is, like many functions of the body, quite complex," Dr. Barnett explained. "Our studies, however, have convinced us that the mineral is important-perhaps the most important single element-in bone health."
The theory behind it is that magnesium is needed, by the pituitary gland**.** This gland regulates all the other glands of the body, and to do this regulating it uses magnesium. This mineral acts as a sedative, counteracting the stimulant effect of the adrenal glands. These glands must be restrained in their production, or else their secretions will speed up the breaking down and resorption of bone tissue.
Another function of magnesium is to act as an enzyme or catalyst. In effect, it acts as the glue that binds calcium and fluorine to build bone. Thus, even though calcium and fluorine may be abundant in the diet, they cannot be used and are flushed out of the system unless the binding element, magnesium, is also present.

***Deficiency Widespread***

"A test we conducted on 5,000 people found about 60 percent of them deficient in magnesium," Barnett told us.
"Perhaps it wouldn't be a bad idea, since they are adding things to the water supply anyway, if they considered magnesium." At any rate, Barnett does not consider osteoporosis a necessary accompaniment of old age. A diet high in magnesium, calcium, phosphorus, and fluorine is definitely an important preventive measure.
There is no official recommendation on how much magnesium one should get in his daily diet. Not only is magnesium the mystery mineral, but it is also, to a large degree, the ignored one. However, Dr. Barnett advocates that 600 mg. a day will provide a safety margin and will not be wasted.

# MULTIPLE SCLEROSIS:

## Multiple sclerosis: decreased relapse rate through dietary supplementation with calcium, magnesium and vitamin D

http://www.ncbi.nlm.nih.gov/pubmed/3537648 Med Hypotheses. 1986 Oct;21(2):193-200. Goldberg P, Fleming MC, Picard EH.

A group of young patients having multiple sclerosis was treated with dietary supplements containing calcium, magnesium and vitamin D for a period of one to two years. The experimental design employed self-pairing: the response of each patient was compared with his/her own case history as control. The number of exacerbations observed during the program was less than one half the number expected from case histories. No side effects were apparent. The dietary regimen may offer a new means of controlling the exacerbation rate in MS, at least for younger patients. The results tend to support a theory of MS which states that calcium and magnesium are important in the development, structure and stability of myelin.

## Magnesium concentration in brains from multiple sclerosis patients.

http://www.ncbi.nlm.nih.gov/pubmed/2353567?dopt=Abstract Acta Neurol Scand. 1990 Mar;81(3):197-200. Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K. Division of Neurological Diseases, Wakayama Medical College, Japan.

Magnesium (Mg) concentrations were studied in the brains of 4 patients with definite multiple sclerosis (MS) and 5 controls. The magnesium contents were determined by inductively coupled plasma emission spectrometry in autopsy samples taken from 26 sites of central nervous system tissues, and visceral organs such as liver, spleen, kidney, heart and lung. The average Mg content in the CNS tissues, as well as visceral organs except for spleen, of MS patients showed a significantly lower value than that seen in control cases. The most marked reduction of Mg content was observed in CNS white matter including demyelinated plaques of MS samples. Whether or not these significantly lower Mg contents found in CNS and visceral organs of MS patients may play an essential role in the demyelinating process remain unclear, requiring further studies on MS pathogenesis from the point of metal metabolism.

## Comparative findings on serum IMg2+ of normal and diseased human subjects with the NOVA and KONE ISE's for Mg2+.

http://www.ncbi.nlm.nih.gov/pubmed/7939388?dopt=Abstract Scand J Clin Lab Invest Suppl. 1994;217:77-81. Altura BT, Bertschat F, Jeremias A, Ising H, Altura BM. Department of Physiology, State University of New York, Health Science Center at Brooklyn 11203.

It is clear now that although different ionophores for ionized Mg (IMg2+) have been designed by several groups, each of these has a distinctly different KMgCa. In view of this, it is important to determine whether each of these ion selective electrodes (ISE's) yield identical results for IMg2+ in sera from healthy and diseased humans. Using such an approach, we determined, in a blinded-and random manner, IMg2+ with both the NOVA and KONE ISE's for IMg2+ in two independent laboratories. No significant differences were found either for sera from healthy human volunteers or diseased patients. We did, however, note several interesting findings: 1. randomly, selected hospitalized patients exhibit a much higher incidence of abnormalities for IMg2+ (57-71%) than that noted previously for total Mg (TMg) measurements; and 2. coronary heart disease, rectal cancer and multiple sclerosis patients exhibit extracellular deficits in ionized free Mg.

# MITRAL VALVE PROLAPSE:

## Clinical Symptoms of Mitral Valve Prolapse Are Related to Hypomagnesemia and Attenuated by Magnesium Supplementation

Am J Cardiol. Volume 79, Issue 6, Pages 768-772 (15 March 1997)
Barbara Lichodziejewska, MDa, Jadwiga K—loś, MDa, Joanna Rezler, MDa, Katarzyna Grudzka, MDa, Maria D—lużniewska, MDa, Andrzej Budaj, MDa, Leszek Ceremużyński, MD, PhDa

Mitral valve prolapse syndrome (MVP) is a frequent disorder characterized by a number of complaints which lessen the quality of life. The pathogenesis of MVP symptoms has not been fully elucidated. Hyperadrenergic activity and magnesium deficiency have been suggested. This study was designed to verify the concept that heavily symptomatic MVP is accompanied by hypomagnesemia and to elucidate whether magnesium supplementation alleviates the symptoms and influences adrenergic activity. We assessed serum magnesium in 141 subjects with heavily symptomatic primary MVP and in 40 healthy controls. Decreased serum magnesium was found in 60% of patients and in 5% of controls ($p < 0.0001$). Patients with low serum magnesium were subjected to magnesium or placebo supplementation in a double-blind, crossover fashion. Typical symptoms of MVP ($n = 13$), intensity of anxiety, and daily excretion of catecholamines were determined. After 5 weeks, the mean number of symptoms per patient decreased from 10.4 ± 2.1 to 5.6 ± 2.5 ($p < 0.0001$), and a significant reduction in weakness, chest pain, dyspnea, palpitations, and anxiety was observed. Increased noradrenaline excretion before and after magnesium was seen in 63% and 17% of patients, respectively ($p < 0.01$). Mean daily excretion of noradrenaline and adrenaline was significantly diminished after magnesium. It is concluded that many patients with heavily symptomatic MVP have low serum magnesium, and supplementation of this ion leads to improvement in most symptoms along with a decrease in catecholamine excretion.

This study reveals a high incidence (60%) of hypomagnesemia in 141 patients with symptomatic mitral valve prolapse. After controlled oral magnesium supplementation for 5 weeks in 70 patients, most symptoms were significantly alleviated along with diminution of catecholamine excretion.

### Common Conditions Linked to a Magnesium Deficiency: Mitral valve prolapse *http://www.ctds.info/magnesium.html#mitral*

Connective Tissue Disorder Site Sandy Simmons

Many studies show that most people (60 - 85%, depending on the study) with mitral valve prolapse are low in Mg. Not surprisingly, magnesium supplementation has been shown to alleviate the symptoms of mitral valve prolapse.
Heart valves with mitral valve prolapse show abnormalities of hyaluronic acid. People with many chronic disorders, especially the connective tissue disorders, commonly have mitral valve prolapse and studies show they always have hyaluronic acid abnormalities. Hyaluronic acid depends upon Mg for its synthesis.

A review of the studies on Medline shows that hyaluronic acid is linked to mitral valve prolapse, mitral valve prolapse is linked to a wide variety of disorders, especially connective tissue disorders, and most connective tissue disorders are linked to anomalies of hyaluronic acid.
If you put these events into a logical sequence, then you can come up with a theory that low Mg levels impacting hyaluronic acid, especially mitral valve prolapse, are are a common link in many of the disorders in which mitral valve prolapse occurs.
People with mitral valve prolapse have been found to have higher instances than normal of anxiety related disorders. This is thought to be because of higher adrenaline levels, as measured by increased catecholamine (a by-product of adrenaline) levels in their urine. Not surprisingly, elevated adrenaline levels and increased urinary catecholamines are also caused by low magnesium levels.
People who have mitral valve prolapse are hypermobile at a higher rate than controls.
People who are hypermobile have been found to be anxiety prone. In fact, people who have anxiety disorders are 16 times more likely to have joint laxity than controls. Hypermobility is a feature of rickets, which can also be caused by a magnesium deficit.
Mitral valve prolapse, anxiety disorders and hypermobility all frequently occur together, whether they occur as isolated conditions, or as a part of many connective tissue disorders such as mitral valve prolapse syndrome, Marfan syndrome and Ehlers-Danlos syndrome.
Some people with mitral valve prolapse have a characteristic body habitus that includes pectus excavatum, hypermobility, pectus carinatum, scoliosis, bowed limbs and other distinctive features. These conditions are called rachitic skeletal features, which can also be caused by a magnesium deficiency.
Many studies have noted associations between mitral valve prolapse and migraines, another disorder closely linked to Mg deficits.
People with mitral valve prolapse also have significantly higher rates of keratoconus, another disorder that has also been linked to low magnesium levels, hyaluronic acid abnormalities and hypermobility.

**Arthritis**

**Asthma**

**Cardia arrhythmias**

**Cardomyopathy**

**Celiac disease**

**Chronic obstructive pulmonary disease**

**Congestive heart failure**

**Dysmenorrhea (4).**

**Eosinophilia-myalgia syndrome**

**Epilepsy**

**Fibromyalgia**

**Glaucoma**

**Hearing Loss**

**Kidney stones**

**Low HDL-cholesterol**

**Mental illness**

**Migranes**

**Multiple sclerosis**

**Muscular excitability**

**Nephritis**

**Nervousness**

**Neuritis**

**Parkinson's Disease**

**Pregnancy toxemia**

**Premature delivery**

**Premenstrual syndrome**

**Psoriasis**

**Stroke**