HEALTH STUDIES COLLEGIUM

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Magnesium… an essential mineral: Uptake breakthrough.

Low Magnesium (Hypomagnesemia) is associated with…

Situation	Scientific basis
1. Insulin resistance / Metabolic Syndrome	Low magnesium and net acid excess make insulin less effective and reduce cell energy.
2. Diabetes / Obesity	Low magnesium and net acid excess make Insulin less effective and reduce cell energy.
3. Accelerated atherosclerosis	Less repair; more free radical damage; often associated with inflammation due to toxic or immunotoxic effects of toxic minerals (Pb, Hg As, Cd, Ni) or other immune reactivities.
4. 'Essential' Hypertension (High Blood pressure)	Less Mg 2nd message to counter Ca; toxic and immunotoxic effects of toxic minerals or other immunoreactive substances.
5. Coronary spasm	Increased reactivity from relative Ca excess; platelet reactivity, activated by immune complexes or endothelial damaged blood vessel walls, can lead to blood flow impeding clumps. Oxidized fats potentiate this platelet reactivity.
6. Cardiac irritability and arrythmias	Impaired Ca/Mg ratio often with distress linked adrenalines and cortisols sensitizing the heart cells.
7. Preeclampsia of pregnancy	Impaired Ca/Mg ratio; insulin / glucose / energy systems often in dysregulation from toxins (hormone dysregularity) and immune reactivities.
8. Headache	Increased reactivity from relative Ca excess in the presence of cellular acidosis.
9. Pain syndromes	Increased reactivity from relative Ca excess with increased substance P release.
10. Hypokalemia	Impaired Na/K-ATPase pump function; toxic and immunotoxic effects of toxic metals and other immunoreactivities.
11. Hypocalcemia	Impaired Ca/Mg-ATPase pump function.
12. Impaired magnesium uptake	Impaired Ca/Mg-ATPase pump function; see below for ways to overcome this uptake block.
13. Muscle irritability and spasm	"Restless leg syndrome" 2˚ to low cell Mg.

Ionized magnesium, the free form, is the active form of the element in cell functions.

- Total magnesium minus protein bound and ligand complexed magnesium yields the ionized magnesium. Ion-specific electrodes can measure ionized magnesium specifically. Ionized magnesium is in dynamic equilibrium with intracellular, bioactive magnesium. Thus, measurement of ionized magnesium is a more predictive measure of intracellular, functional magnesium status than total Mg, RBC Mg, or sweat Mg in complex cases. Note: **Use of a provocative test of tissue Mg status with d-penicillamine is recommended to assess effective, cellular Mg status**.

Uptake of magnesium is often blocked because the primary uptake mechanism, the calcium/magnesium ATPase enzyme is inhibited. Among the factors that use up magnesium rapidly are:

1. Toxic minerals such as lead, mercury, arsenic, cadmium, and nickel
2. Biocidal hormone mimics
3. Metabolic cellular acidosis
4. Phytates in ingested foods
5. Caffeine intake
6. Alcohol consumption
7. Certain medications such as steroids and oral contraceptives
8. Distress
9. Enteropathy and other intestinal disorders
10. Maldigestion and digestive disorders

Magnesium is the fourth most common cation (divalent mineral ion) in the human body. **Magnesium is the second most abundant cation inside mammalian cells** (after potassium). The **adult** body **contains** an average of 25 grams (**25,000 mg**.) of magnesium. **Half** is found **in** the **bones** where it acts with other minerals to strengthen bones. The remaining half is found in blood, fluid, and cells. According to Vallee, magnesium is involved in over 10,000 enzyme (cell catalysts) actions and is, therefore, essential for many cell and organ functions.

CONSIDERATIONS FOR MAGNESIUM STATUS

Considering the importance of magnesium for optimal body function, there is great value in determining the body's magnesium status. This status can be evaluated by using the following criteria:

1) **How much magnesium is present in the diet?** Magnesium intake through diet has been decreasing. The RDA (Recommended Daily Allowance) for magnesium is 300 to 400 mg per day for a sedentary adult. Physically active or people under distress need more – often twice as much or more. Most of us consume half of that amount or less. Food processing removes much of the magnesium from foods. The most 'white foods' (refined flour, sugar, fat, and processed or synthesized foods) we eat, the more of a magnesium deficit we have.
2) **How efficiently is magnesium being absorbed in the intestine?** There are many factors that inhibit the body's ability to absorb magnesium. Phosphoric acid, which is present in most soft drinks, and oxalates in foods such as spinach or

chocolate, combine with magnesium in the intestines and form insoluble compounds that are not absorbed by the body.

3) **How efficiently can the kidneys recycle magnesium before it is lost in the urine?** Individuals who are using diuretics may have low magnesium levels. Poor digestion and gastrointestinal diseases, such as Crohn's disease can also create deficiency.
4) **Usual blood and urine tests tell us nothing about cell magnesium status.** Properly done balance studies or ionized magnesium levels in the plasma are expensive and cumbersome but can confirm magnesium need.

Considering that magnesium is an activator for so many important body functions, it is not surprising that deficiency can lead to a variety of serious physical and mental problems. Health conditions such as:

- muscle twitches, spasms and tremors
- nerve irritability.
- mood instability.
- high blood pressure (Essential, otherwise unexplained).
- angina (chest pain on exertion).
- heart arrhythmias (magnesium is 'nature's calcium channel blocker')
- calcium loss / osteoporosis risk.
- toxic metals (lead, mercury, cadmium, arsenic, and nickel) are accumulated more rapidly when magnesium stores are low and replacement of magnesium hastens their elimination from the body.
- insomnia.

Basis for discovery of enhanced Magnesium uptake: The concurrent administration of oral ionized magnesium salts such as magnesium glycinate, magnesium ascorbate, magnesium aspartate with choline citrate in glycerol and water allow for neutral micellar droplets to form in the gut facilitating magnesium uptake through neutral cell pores even when the calcium-magnesium ATPase enzyme is inhibited.

Support for observations: In light of the above and to assess the impact of concurrent intake of choline citrate and ionized, soluble magnesium salts on magnesium uptake the following studies were undertaken:

People who have above conditions associated with low magnesium were assessed.

Clinical assessments of remarkable effects of PERQUE

Clinical assessments were done over a periods of one month. Magnesium Salts alone was followed by one month of Choline Citrate alone followed by one month of Magnesium salts along with concurrent administration of Choline Citrate. Functional, clinical end points were assessed.

Case #1: A 26-year-old man suffered from supraventricular arrhythmias that were unresponsive to medication and, despite detailed medical workup, were determined to be 'idiopathic'. The patient was instructed to count the number of irregular heart beats (IHB) over a 2 minute period on rising and before bed.

	AM	PM	Total
Month 1 (ave)	13	22	35
Month 2 (ave)	11	27	38
Month 3 (ave)	1	3	4

Case #2: A 72 year old woman suffered from ectopic heartbeats that were unresponsive to medication and, despite detailed medical workup, were determined to be 'idiopathic'. The patient was instructed to count to count the number of irregular heart beats (IHB) over a 2 minute period on rising and before bed.

	AM	PM	Total
Month 1 (ave)	18	20	38
Month 2 (ave)	22	19	41
Month 3 (ave)	1	2	3

Case #3: A 59 year old man suffered from 'restless legs' and intermittent leg cramps during sleep. The subject was asked to rate the intensity of the problem on a consistent rating scale with '0' indicating no problem and '100' indicating the most severe expression of the condition.

	Ave. intensity of leg cramp related difficulty
Week 1-2	88
Week 3-4	83
Week 5	63
Week 6	44
Week 7	29
Week 8	12
Week 9	7

Laboratory Assessments

In addition to these clinical assessments, the following laboratory evaluations are consistent with enhanced magnesium uptake when the correct magnesium salts are properly combined with high purity choline citrate.

Study of the influence of Magnesium salts ± concurrent choline citrate on ionized magnesium in plasma compared with Magnesium salts alone in people with apparent uptake block of magnesium:

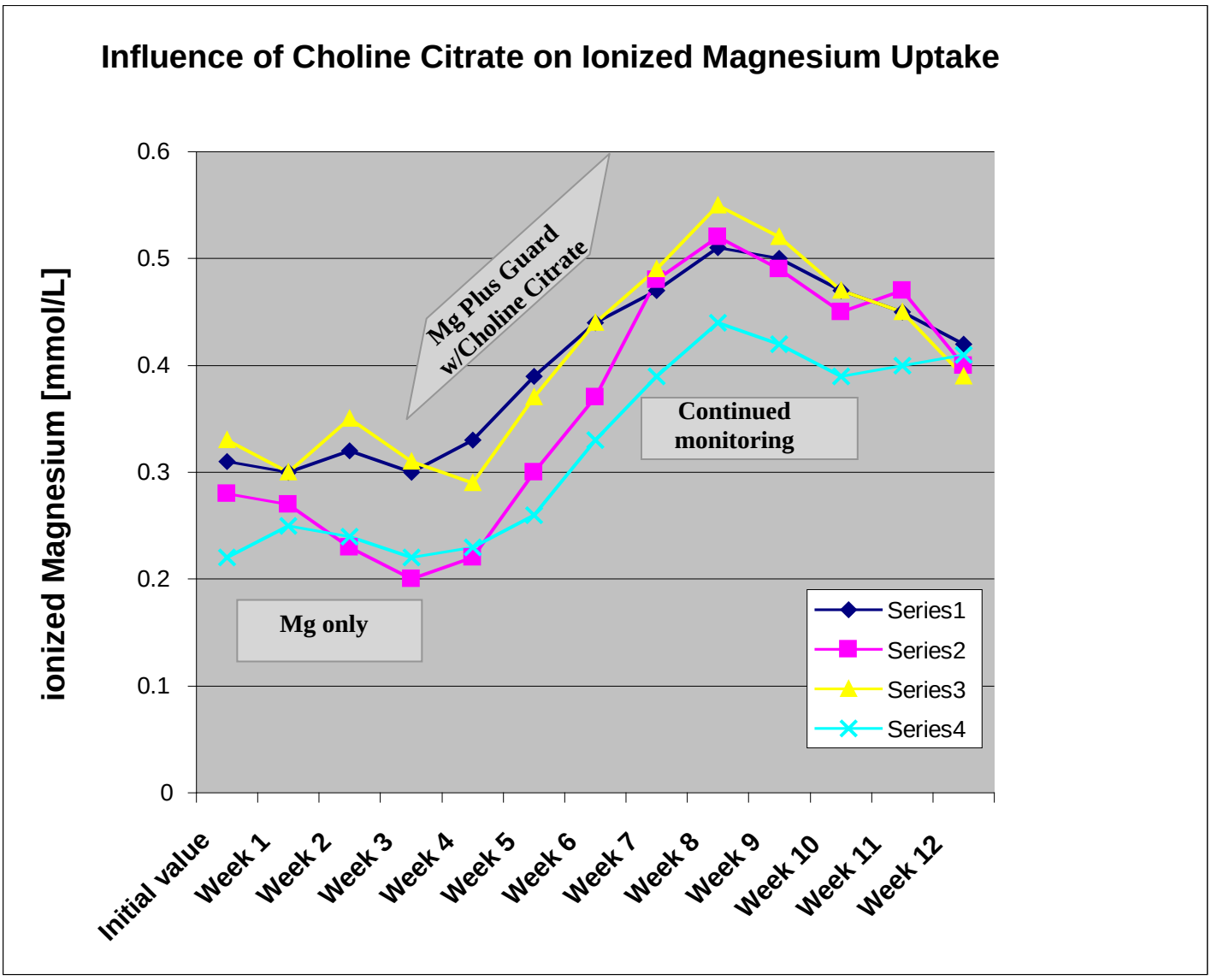
The subjects were selected for signs of magnesium deficit including muscle irritability and fasiculation,.benign cardiac irritability and/or moderate fibromyalgia pain that had previously been unresponsive to magnesium therapy.

Subjects were put on a fixed dose of Magnesium salts, 2 capsules with each meal (6 per day) for one month. For the second month, the same regimen was continued plus addition of 1 teaspoon of choline citrate in juice or water taken at the same time as the Magnesium supplement. For the third month, the subject continued the magnesium regimen but without the additional choline citrate. Diet and fluid intake were kept consistent during the study interval.

Note: the reference range for ionized magnesium using this ion specific electrode (NOVA) is 0.43-0.59 mmol/L. Measurements were made at the end of each study week.

Subject:	Series#1	Series #2	Series #3	Series #4
Results:	Ionized	Ionized	Ionized	Ionized
	Mg [plasma]	Mg [plasma]	Mg [plasma]	Mg [plasma]
Initial value	0.31 mmol/L	0.28mmol/L	0.33 mmol/L	0.22 mmol/L
Week 1	0.30	0.27	0.30	0.25
Week 2	0.32	0.23	0.35	0.24
Week 3	0.30	0.20	0.31	0.22
Week 4	0.33	0.22	0.29	0.23
Week 5	**0.39**	**0.30**	**0.37**	**0.26**
Week 6	**0.44**	**0.37**	**0.44**	**0.33**
Week 7	**0.47**	**0.48**	**0.49**	**0.39**
Week 8	**0.51**	**0.52**	**0.55**	**0.44**
Week 9	0.50	0.49	0.52	0.42
Week 10	0.47	0.45	0.47	0.39
Week 11	0.45	0.47	0.45	0.40
Week 12	0.42	0.40	0.39	0.41

Examining data in graphic form is shown in the next table.



In other studies, the role of choline citrate on magnesium levels in the absence of Magnesium supplementation was evaluated. A modest but statistically insignificant increase in magnesium was noted over a 30-day period of evaluation.

Conclusions:

1. **A previously unknown and unanticipated benefit is observed in the form of facilitated magnesium uptake when choline citrate is concurrently administered.**
2. **Choline citrate alone does not substantially raise ionized magnesium levels.**
3. **In some people with clinical magnesium need, even the most soluble and ionized forms of magnesium are less available, possibly because of inhibition of the Ca/Mg ATPase pump.**
4. **A mechanism of action is the formation of micelles containing 2 molar equivalents of magnesium and choline along with 3 molar equivalents of citrate thus forming an electrically neutral complex.**

Background support from Magnesium research

This site provides information about the magnesium-deficiency catastrophe and its relationship to the beverage industry. Magnesium deficiency appears to be causing 215,000 fatal heart attacks in the U.S. each year, and as many as 20,000,000 fatal heart attacks worldwide. Magnesium deficiency is implicated in many other diseases. Twenty years ago, the U.S. National Academy of Sciences estimated that the U.S. cardiovascular death rate might be reduced by 150,000 deaths per annum by drinking water rich in magnesium and calcium.

"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. The U.S. National Academy of Sciences has estimated that a nation-wide initiative to add calcium and magnesium to soft water might reduce the annual cardiovascular death rate by 150,000 in the United States."
Groundwater and Human Health, Groundwater Resources of British Columbia, BC Ministry of the Environment.

Magnesium and Metabolic syndrome / diabetes risk

Recent studies from academic medical centers highlight the relationship between ongoing magnesium intake, diabetic risk and fasting insulin levels. **We add that overcoming magnesium uptake block is critical to achieving better outcomes. The use of PERQUE MagPlus Guard and Choline Citrate specifically addresses this issue. Clinical results can be monitored through the use of ionized plasma magnesium measurements or, indirectly, through the use of first morning urine pH as an index of buffering capacity in the body since magnesium is a major contributor to the body's cellular buffering capacity.**

The three studies address the following groups:

1. 127,932 adults of both sexes.
2. 39,345 women over 45 years (Women's Health Study).
3. 219 nurses from the Nurses Health Study.

All were considered free of diabetes, cardiovascular disease and cancer at start of the study. Unfortunately, the studies were not designed to exclude metabolic syndrome that is often present in an undiagnosed form.

Method: All three studies were epidemiological, examining the group's responses:

1. Prospective diet history study by food frequency questionnaire every 2-4 years over 12 years (men) and 18 years (women). The careful control for other variables and the size of the study make these results particularly important.
2. Prospective study with baseline dietary history and average follow up of 6 years. A sub-sample of 349 had fasting plasma insulin measured.
3. Dietary magnesium intake was assessed in 1990, and fasting blood insulin measured a decade later (1989 and 1990).

Results: After controlling for potential confounding variables including:

1. BMI,
2. Physical activity,
3. Family history of diabetes

There was a consistent inverse relationship between magnesium intake and both risk of developing type 2 diabetes and fasting insulin levels. Thus reduced magnesium intake is linked to increased risk of metabolic syndrome / diabetes developing.

Table 1: Magnesium intake compared with relative risk for developing diabetes 2 and fasting insulin values (highest vs. lowest quintile of Mg intake)

Study	Result	Significance
1. Women	R=0.66	p<0.001
Men	R=0.67	p<0.001
2. Women	R=0.89	p=0.05
Obese women [BMI >= 25]	R=0.78	p=0.02
Insulin = 53.5 vs. 41.5 pmol/mL		p=0.03
3, Women's Insulin change	9.3 vs. 11.0 µU/mL	p=0.04

Taken together, these studies show that magnesium deficit precedes diabetes, may well predispose to diabetes, and makes the complications of diabetes more severe.

References:
1. *Diabetes Care* 2004;27(1):134-40.
2. *Diabetes Care* 2004;27(1):59-65.
3. *J Am Coll Nutr* 2003;22(6):533-8.

Magnesium and metabolic syndrome

Magnesium deficit is strongly associated with metabolic syndrome based on the following case-controlled observational study.

Subjects: 192 patients with metabolic syndrome, defined as at least two of: hyperlipidaemia, obesity, hypertension, hyperglycemia but not overt diabetes. Controls were 384 healthy age and gender matched people.

Results: Mean serum magnesium in metabolic syndrome subjects was significantly lower. More subjects had values below the usual lab range compared with the control subjects. Study subjects had a mean magnesium value of 1.8 mg/dl (66% below lab lower usual value) compared with controls who had a mean value=2.2 mg/dl (10% below lab lower usual value). This is statistically significant at p<0.00001. **Low serum magnesium was most highly correlated with hyperlipidaemia and hypertension.**

Table 2: Odds ratio (OR) for metabolic syndrome in regard to low vs. usual magnesium

	OR	95% CI
Metabolic syndrome	6.8	4.2-10.9
Dyslipidaemia	2.8	1.3-2.9
Hypertension	1.9	1.4-2.8

Reference: *Acta Diabetol* 2002; 39(4): 209-213.

In addition, a recent Swiss study which found type 2 diabetics to have below usual range magnesium levels compared with 10% of controls (1). Given that total serum magnesium understates deficit in cellular magnesium, these results are particularly striking. This strengthens the case for low magnesium promoting metabolic syndrome and increasing the probability of diabetes emerging.

Why is magnesium low? The best synthesis of the evidence we know of suggests both increased loss (wasting) of magnesium in response to net acid excess in the cells as well as decreased uptake due to block in the calcium/magnesium ATPase enzyme, most likely from accumulation of toxic minerals, hormone mimics, and other toxicants. Diabetic renal disease is likely to aggravate magnesium deficits.

Deficiency can lead to the following problems, particularly in diabetic people:

1. Magnesium is needed for carbohydrate energy metabolism (phosphotransferases that generate ATP are magnesium dependent),
2. Insulin resistance is worse when magnesium low.

This is important for accelerated consequences of hypertension and cardiac arrhythmias and, probably, diabetic retinopathy as well (2-6). This can result in a cycle in which diabetes aggravates the magnesium deficit, which in turn aggravates the diabetes.

In an intriguing Danish study 12 identical twins discordant for diabetes 2 and 12 matched controls. While there was no difference in magnesium status between the groups, insulin mediated glucose disposal and magnesium seen in normal controls was abnormal in the twins (7). We have much to learn. In the mean time, to reduce risk, use **PERQUE MagPlus Guard and Choline Citrate.**

References:
1. *Swiss Med Wkly* 2003; 133(19-20): 289-292.
2. *Clin Chim Acta* 2000; 294(1-2): 1-26.
3. *Neth J Med* 1999; 54(4): 139-146.
4. *Am J Hypertens* 1997; 10(3): 346-355.
5. *Ann Pharmacother* 1993; 27(6): 775-780.
6. *South Med J* 2001; 94(12): 1195-1201.
7. *Diabetes Metab* 2002; 28(3): 201-207.

Oral magnesium improves diabetic control

Oral magnesium supplementation improves metabolic control in type 2 diabetics with low initial serum magnesium, according to new research.

Subjects: 63 type 2 diabetic people with initial serum magnesium <= 0.74 µmol/l taking the common oral hypoglycemic agent (glibenclamide).

Method: Randomized, placebo-controlled trial. Active treatment was 2.5 gm/day of magnesium chloride solution per day for 16 weeks.

Results: Magnesium treated subjects had better diabetic control on all measures. Magnesium vs. placebo after 16 weeks using the Homeostasis Model Assessment for Insulin Resistance index (HOMA-IR), Fasting glucose, and HbA1c as markers of effect:

	Mg	Placebo	Significance
HOMA-IR *	3.8	5.0	p=0.005
Fasting glucose	8.0	10.3 µmol/l	p=0.01
HbA1c	8.0	10.1 %	p=0.04

Reference: *Diabetes Care* 2003;26(4):1147-1152.

No improvement in glucose from low uptake magnesium oxide

No improvement in glucose levels was seen in diabetics given magnesium supplementation in a new Indian trial.

Subjects: 40 type 2 diabetics and 54 controls.

Method: Active treatment of magnesium (600 mg of magnesium oxide/day) was given to both diabetic and control group for 12 weeks.

Results: Diabetics had significantly lower mean serum magnesium levels prior to treatment compared to control subjects, the magnesium supplementation did not result in any significant change in either fasting or post-prandial glucose levels. No documentation of magnesium uptake was included. A favorable change in lipid profile in the diabetics is reported.

Reference: *J Assoc Physicians India* 2003; 51: 37-42.

The prospective study above found clear improvement in several measures of diabetic control after 16 weeks of magnesium supplementation. The other shorter duration study did not document magnesium uptake, found no change in glucose levels, yet did report a benefit to lipid profile. Previous studies had not shown benefits in glucose control from magnesium supplementation, both in people with type 1 and those with type 2 diabetes

(1-7). Further, some studies find improvements in lipid levels and in blood pressure (6, 8); the majority of trials do not (2, 3, 5). Differences in magnesium availability may explain these variances. **If the magnesium does not reach the cell, it is not effective.**

While magnesium deficiency is all too common in diabetics, not all patients will be deficient and improvement from supplementation can only be expected in those patients in whom cellular magnesium is low.

A single positive trial is, of course, not a sufficient basis on which to change clinical practice. In the meantime, it is prudent for clinicians and consumers to use safe, supplemental magnesium (9) and treating magnesium deficiency as if it is present until more sensitive, cost effective tests of intracellular magnesium are available. **The d-penicillamine protocol may provide such a non-invasive yet predictive probe of cellular magnesium status.**

Prospective clinical trials of enhanced magnesium availability following the **PERQUE protocol are needed to document the metabolic syndrome / diabetes risk reduction full potential**. Magnesium deficiency directly induces insulin resistance (10). A plausible mechanism to underlie the protective effects of uptake enhanced magnesium is enhanced correction of metabolic acidosis and enhanced enzyme function.

There is compelling evidence that diabetics often have low magnesium levels. We need to quantify the costs and benefits of taking extra magnesium and better understand the interactions between magnesium and other nutrients, particularly calcium and copper cations, is needed (11) as is the impact on magnesium status of medications affecting insulin resistance) (12).

Diabetes is linked to over 100,000 deaths per year and costs over $100 Bn/year in disease care. By comparison, taking extra magnesium, in a more active form is a simple and cheap solution to an important part of the metabolic syndrome / insulin resistance equation.

As Dr. Mary Ann Block sums it up: First of all, do no harm. Second, use magnesium.

Additional references:

1. *Ugeskr Laeger* 1999; 161(7): 945-948.
2. *Diabet Med* 1998; 15(6): 503-507.
3. *J Hum Hypertens* 1996; 10(8): 517-521.
4. *Diabetes Care* 1995; 18(2): 188-192.
5. *Ann Nutr Metab* 1995; 39(4): 217-223.
6. *Arch Fam Med* 1994; 3(6): 503-508.
7. *Magnes Res* 1999; 12(2): 123-130.
8. *Magnes Res* 1994; 7(1): 43-47.
9. *Circulation* 1995;92(8):2190-2197
10. *J Natl Med Assoc* 2003; 95(4): 257-262.
11. *Nutrition* 2003;19(7-8):617-626.
12. *Exp Clin Endocrinol Diabetes* 2003;111(2):91-96.