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The multifaceted and widespread pathology of magnesium deficiency

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Summary Even though Mg is by far the least abundant serum electrolyte, it is extremely important for the metabolism of Ca, K, P, Zn, Cu, Fe, Na, Pb, Cd, HCl, acetylcholine, and nitric oxide (NO), for many enzymes, for the intracellular homeostasis and for activation of thiamine and therefore, for a very wide gamut of crucial body functions. Unfortunately, Mg absorption and elimination depend on a very large number of variables, at least one of which often goes awry, leading to a Mg deficiency that can present with many signs and symptoms. Mg absorption requires plenty of Mg in the diet, Se, parathyroid hormone (PTH) and vitamins B6 and D. Furthermore, it is hindered by excess fat. On the other hand, Mg levels are decreased by excess ethanol, salt, phosphoric acid (sodas) and coffee intake, by profuse sweating, by intense, prolonged stress, by excessive menstruation and vaginal flux, by diuretics and other drugs and by certain parasites (pinworms). The very small probability that all the variables affecting Mg levels will behave favorably, results in a high probability of a gradually intensifying Mg deficiency. It is highly regrettable that the deficiency of such an inexpensive, low-toxicity nutrient result in diseases that cause incalculable suffering and expense throughout the world. The range of pathologies associated with Mg deficiency is staggering: hypertension (cardiovascular disease, kidney and liver damage, etc.), peroxynitrite damage (migraine, multiple sclerosis, glaucoma, Alzheimers disease, etc.), recurrent bacterial infection due to low levels of nitric oxide in the cavities (sinuses, vagina, middle ear, lungs, throat, etc.), fungal infections due to a depressed immune system, thiamine deactivation (low gastric acid, behavioral disorders, etc.), premenstrual syndrome, Ca deficiency (osteoporosis, hypertension, mood swings, etc.), tooth cavities, hearing loss, diabetes type II, cramps, muscle weakness, impotence (lack of NO), aggression (lack of NO), fibromas, K deficiency (arrhythmia, hypertension, some forms of cancer), Fe accumulation, etc. Finally, because there are so many variables involved in the Mg metabolism, evaluating the effect of Mg in many diseases has frustrated many researchers who have simply tried supplementation with Mg, without undertaking the task of ensuring its absorption and preventing excessive elimination, rendering the study of Mg deficiency much more difficult than for most other nutrients. © 2001 Harcourt Publishers Ltd

THE CHEAPEST OUNCE OF PREVENTION

In an age of sky-rocketing medical costs due to astronomical investments in high-tech gadgets that allow us to look inside the body in a myriad of ever more complicated ways, and in miracle drugs that can achieve amazing feats, it seems incredible that a deficiency of one of the cheapest nutrients may be at the roots of a colossal tree of pathologies that inflict untold pain and monetary losses worldwide.

Yet, a magnesium deficiency is common and does have a legion of devastating effects and correcting it costs pennies a day per person. Therefore, eliminating it may produce a higher return on investment and a higher reduction of disease and pain, in a shorter time, than any miracle drug or high-tech development.

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MAGNESIUM, THE CONSUMMATE DIVA

Mg is very similar to a great opera singer: it is very demanding, but when everything is right, it can perform

wonders. It is demanding in that its absorption requires a host of conditions and is inhibited by several factors. Moreover, Mg will leave the body, without hesitation, if any of a series of conditions are not met.

ENTICING THE DIVA

In contrast to Ca, which requires either parathyroid hormone (PTH) or vitamin D for its absorption, Mg requires both PTH and vitamin D (1,2). Therefore, we can say that the main function of vitamin D in a euparathyroid person is not Ca but Mg absorption.

Since vitamin D must either be produced by exposure to sunlight or ingested in the few foods that contain it (vitamin D enriched milk, cod liver oil, etc), it can be seen that people with limited exposure to sunlight and without access to food rich in vitamin D are likely to suffer from a Mg deficiency. Similarly, severely hypoparathyroid individuals would automatically be deficient in Mg. Furthermore, a small amount of Mg is indispensable for the release of PTH, and since PTH is necessary for Mg uptake, when very low levels of Mg are reached, PTH is not released and Mg levels can no longer recover, unless a small amount of Mg is administered intravenously, in order to prime the release of PTH.

Finally, a diet rich in saturated fats and/or low in vitamin B6 hinders Mg absorption. Unfortunately, the modern American diet: hamburgers, French fries, coffee and sodas is not only relatively low in Mg, it is very rich in saturated fats, which hinder its absorption and, as we shall see next, coffee and phosphoric acid (sodas) increase Mg elimination.

HOLDING ON TO THE DIVA

Many substances increase renal elimination of Mg, when consumed in excess: ethanol, diuretics, coffee, tea, salt, phosphoric acid (sodas), Ca, K and sugar as can many drugs, foscarnet (a Mg chelator), aminoglycosides, amphotericin B, cyclosporine, azathioprine, cisplatin, citrated blood, excess vitamin D, etc. (see Fig. 1).

Serum Mg levels may also decrease suddenly, when the Mg enters the cells because of alcohol withdrawal, hungry bone syndrome or refeeding syndrome after starvation (3). Delirium tremens is caused partly by very low serum levels of glucose, Mg, P and B vitamins. Mg greatly affects muscle by inhibiting the release of acetylcholine, the neurotransmitter that triggers muscle contraction (4). Accordingly, in delirium tremens, the low levels of Mg increase the release of acetylcholine, producing massive involuntary contractions.

Furthermore, prolonged, intense stress, especially in the absence of Mg-rich foods and sun light, increases considerably Mg elimination (and therefore, Ca and K elimination). The extreme case being the shell-shock inflicted on thousands during the repeated and prolonged bombardments of WW I.

Several conditions can also increase Mg elimination (3): prolonged diarrhea or vomiting, biliary fistulas, chronic pancreatic insufficiency, acute tubular necrosis (diuretic phase), aldosteronism, diabetic ketoacidosis, syndrome of inappropriate antidiuretic hormone following renal transplantation (the hormonally induced Mg losses are exacerbated by the administration of cyclosporine, which we listed above as contributing to Mg elimination).

Moreover, a Se deficiency also increases Mg elimination and causes Fe accumulation (5).

Very heavy menstruation, vaginal flux or sweating also increase Mg elimination. Some parasites, such as the quite common pinworm (*Enterobius vermiculares*), can deprive the body of Mg (6).

Finally, insufficient water intake, a very common phenomenon, has the same effect as high sodium intake, causing increased elimination of Mg, in order to increase the salinity of the urine.

THE ENIGMATIC DIVA

Because there are so many variables involved in Mg absorption and elimination, it is very difficult to study the effect of Mg supplementation in clinical trials, in which only Mg is administered. So that a person with minimal exposure to sunlight or a fat-rich diet or enterobiosis or high ethanol consumption or under considerable stress, receiving 100 mg of Mg may experience a minimal effect, while the rare person in which all the variables are favorable, may experience a considerable effect. Since most people are much more likely to have at least one faulty variable than they are to have all the variables operating favorably, the clinical study would conclude that Mg has no noticeable effect on the condition.

THE DIVERSE PATHOLOGY OF MG DEFICIENCY

Mg is far smaller, less electropositive and less abundant in serum than Na, Ca or K and it plays a myriad crucial roles in electrolyte, hormonal and enzymatic homeostasis with an extremely wide range of repercussions throughout the body.

Diseases caused by electrolyte imbalances

Mg is necessary for activation of most of the ATPases, so that low Mg levels result in impaired transport of K, H, Na, Ca, etc.

Because the kidneys require Mg in order to recycle Ca, P and K and to eliminate excess Na, Cl, Pb and Cd. A Mg deficiency eventually leads to low levels of Ca and K and to high levels of Na, Cl, Cd and Pb. This electrolytic imbalance leads to hypertension and to intracellular

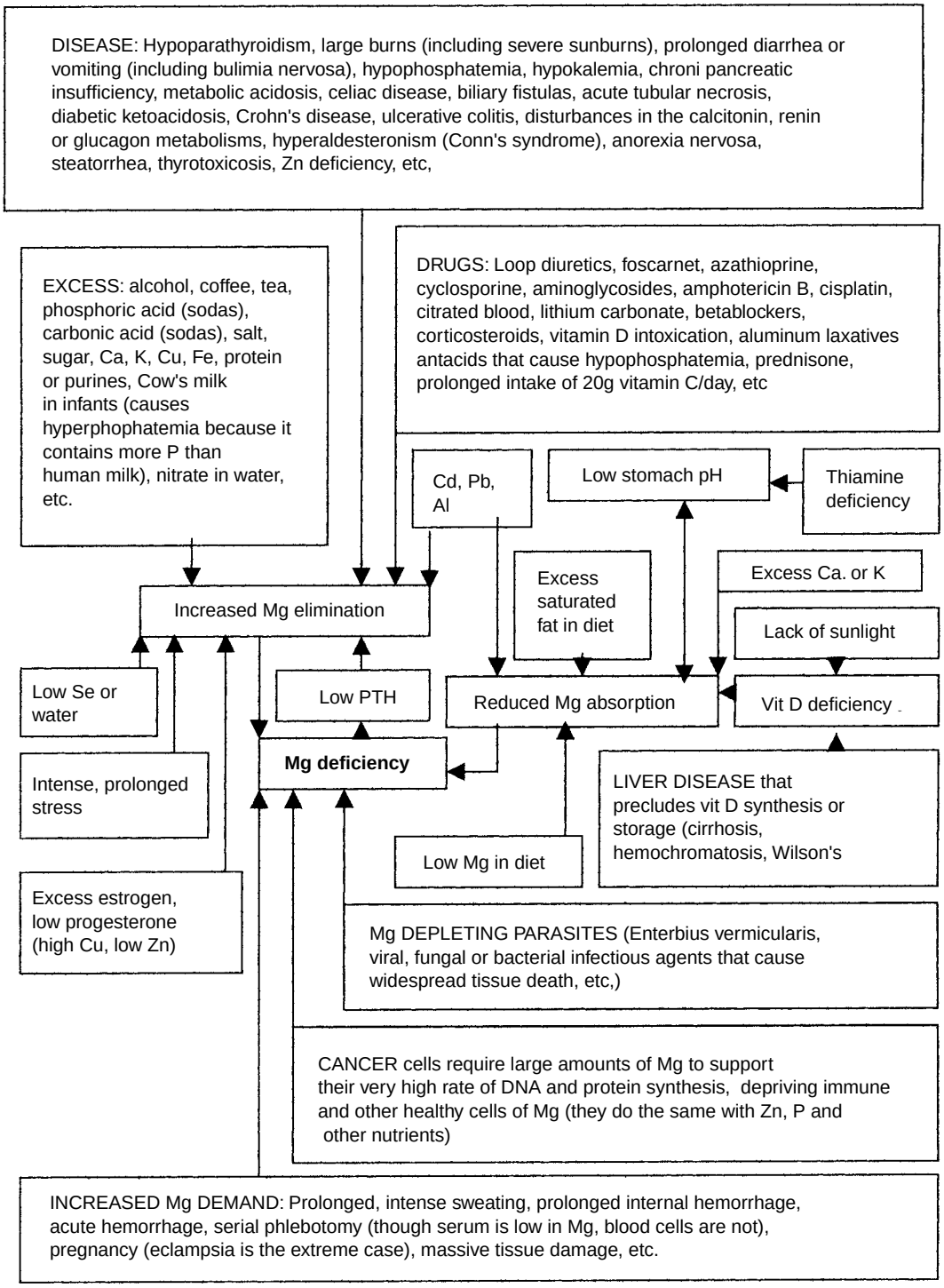

Fig. 1 The multiple factors conspiring to produce a Mg deficiency.

disturbances at the mitochondrial level. In turn, the hypertension eventually leads to cardiovascular damage, renal and hepatic damage, increased risk of aneurysms and internal hemorrhages, and many other diseases.

Hypertension is further exacerbated by low Mg and vitamin B6 levels in hypercholesterolemia, because they result in diminished endothelial cell response to the vasodilators histamine and acetylcholine and increased response to the vasoconstrictors 5-hydroxytriptamine, angiotension and noradrenaline, leading to atherosclerosis. The abnormal response to these vasodilators and vasoconstrictors can be corrected with magnesium

pyridoxal 5-phosphate glutamate (7). The guilt of Mg in coronary atherosclerosis and hypertension is supported by epidemiological data from apparently healthy individuals (8) and from renal transplant patients, who experience Mg deficiency induced by cyclosporine (9).

Diseases caused by inactive thiamine

Thiamine (vitamin B1) forms thiamine pyrophosphate in the presence of Mg. When the latter is not available, thiamine cannot perform properly (10) (see Fig. 4). The result is an apparent thiamine deficiency, even when the body has enough or excess thiamine. The lack of performance of thiamine results in low levels of gastric acid (low levels of secretin, leading to autism), leading to increased risk of GI infections and to impaired digestion and in damage to the hypothalamus (confusion, delusions, hallucinations, disorientation, Wernicke's encephalopathy (11), Alzheimer's disease, etc.). The lack of Mg also leads to the formation of calcium pyrophosphate, instead of thiamine pyrophosphate. Calcium pyrophosphate can precipitate in painful crystals (pseudogout).

Diseases caused by faulty NO release from the cells

Magnesium also plays a crucial role in the release of nitric oxide (NO) from the cell. NO serves many functions (see Figs 2, 3 and 6), among the most important is preventing

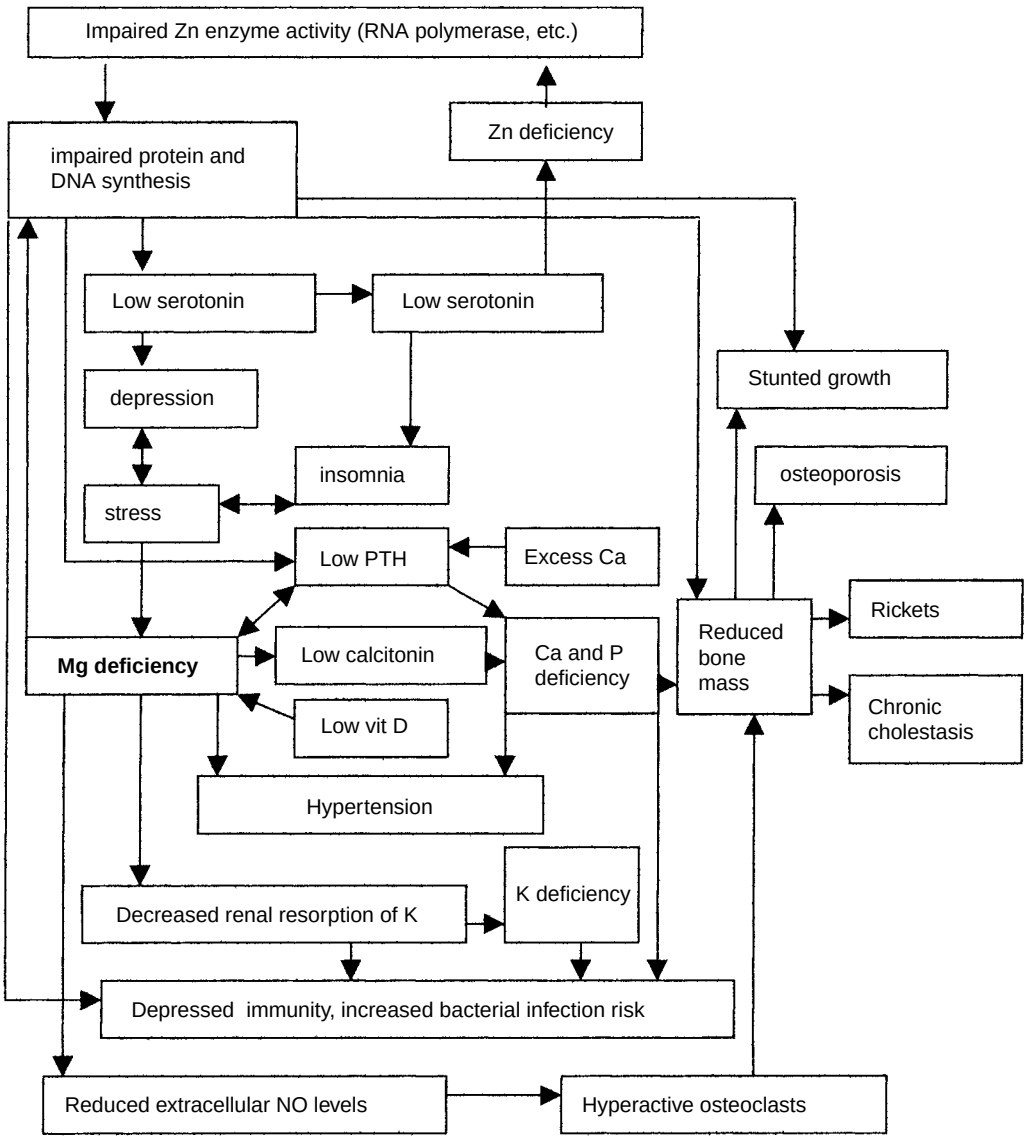

Fig. 2 Interaction between Mg, Ca, Zn and K.

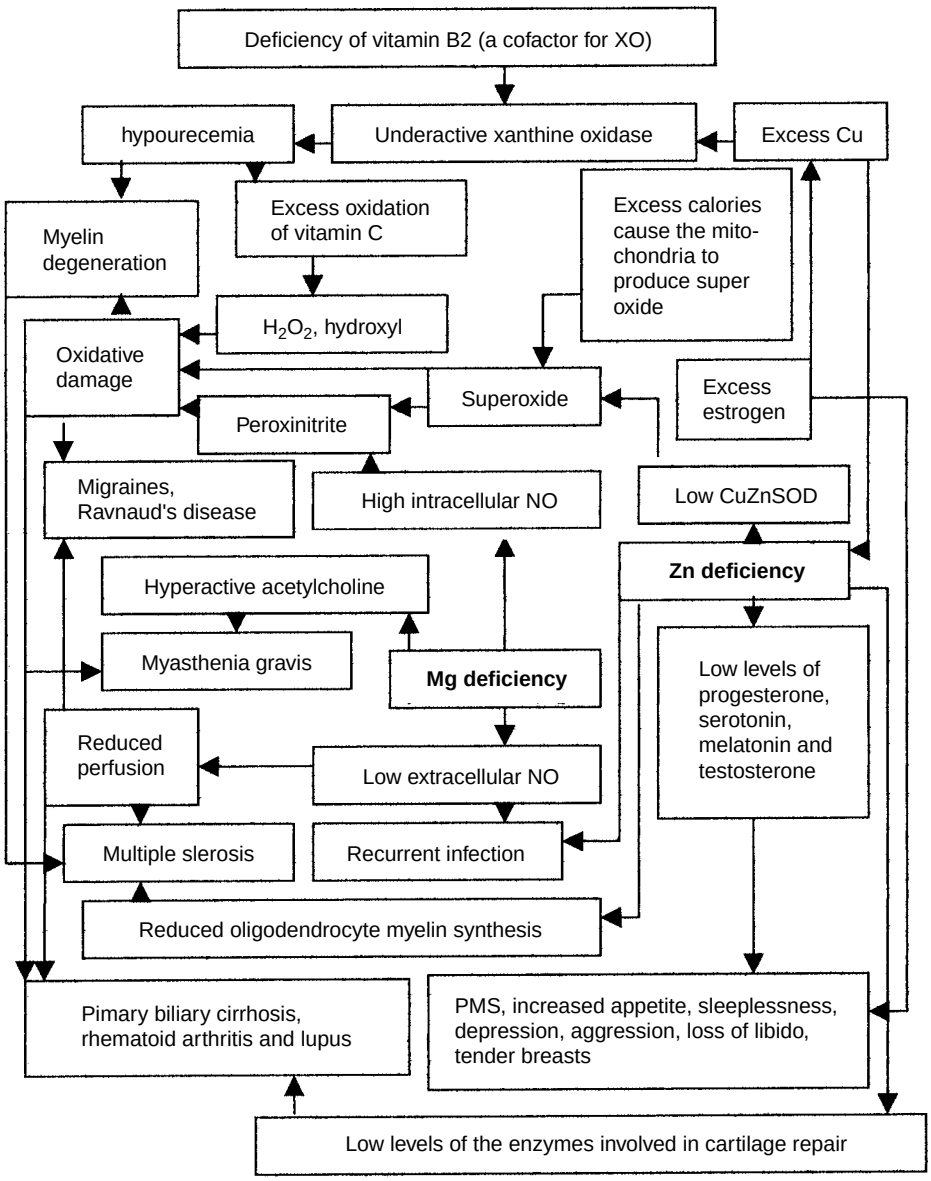

Fig. 3 Combined Mg and Zn deficiency and excess Cu in menstruating women.

infections in the body cavities, such as the sinuses, throat, lungs, vagina, larynx, etc.

Another mayor function of NO is vasodilatation, which is the reason for administering nitroglycerin to a stroke patient.

NO, vitamin K, Mg and Sr inhibit the osteoclasts (12), greatly increasing bone deposition. Therefore, Mg greatly affects osteoporosis by increasing Ca serum levels and by inhibiting bone removal by the osteoclasts, which are inactivated both by Mg and by NO released thanks to Mg.

NO deficiency may also play a role in arteriosclerosis induced by low Mg levels, since *Chlamydia p*, is suspected of contributing this disease, and low NO levels may favor this bacterium.

Since Mg is necessary to activate thiamine in order to prevent excessive aggression and since Mg is also necessary for the neurons to release NO, which also plays a role in aggression in males, it is obvious that a Mg deficiency should be considered as part of the etiology of highly aggressive behavior in males by psychiatrists. On the other hand, Mg deficiency in females is often part of the etiology of depression.

When Mg is deficient, the cell cannot release its NO, so that the bacteria can thrive and blood vessels cannot dilate properly, resulting in increased risk of recurring

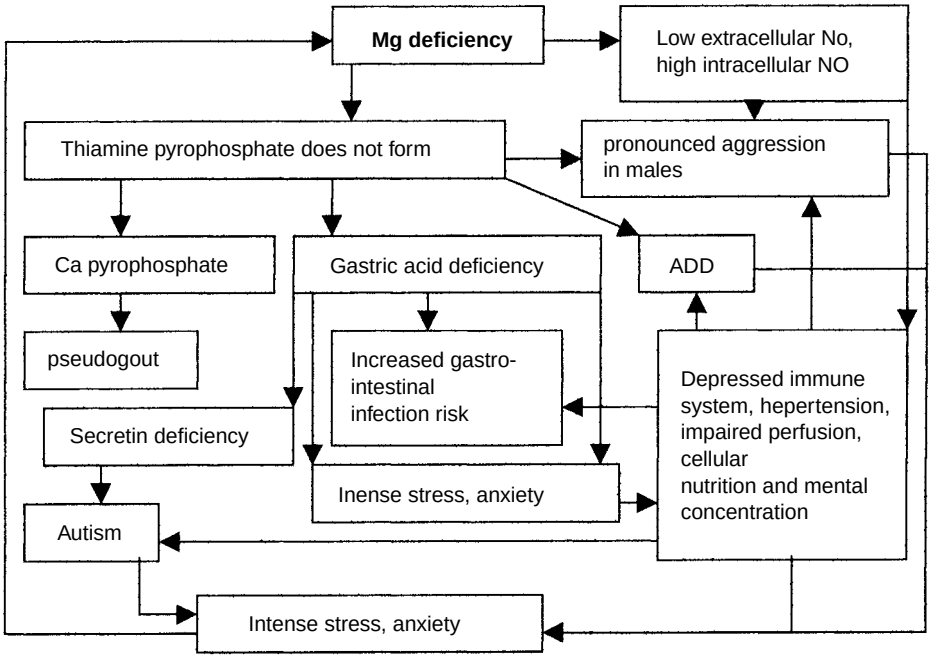

Fig. 4 The pathologic effects of a Mg deficiency on the thiamine metabolism.

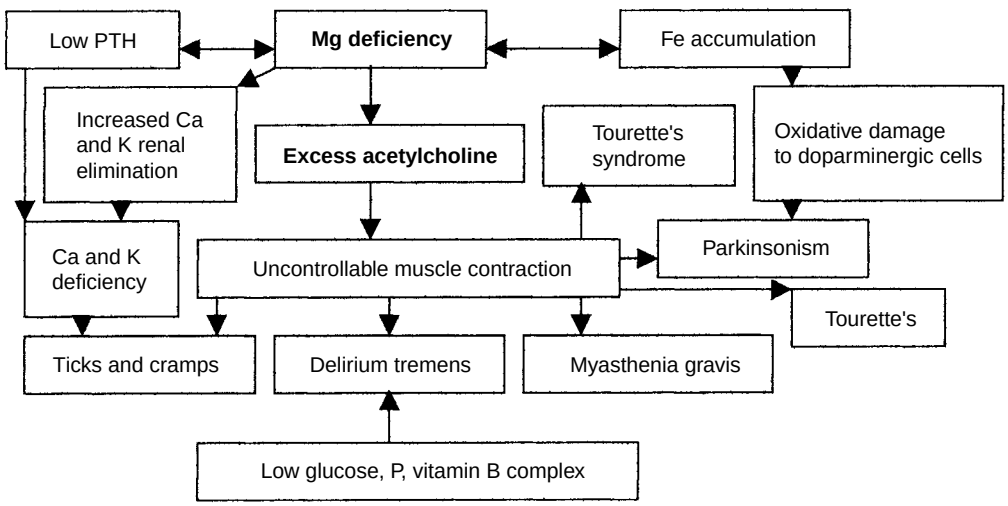

Fig. 5 Mg and acetylcholine release in skeletal muscle.

infection and exacerbating the hypertension caused by the low plasma levels of Ca and Mg and high levels of Na. Furthermore, the accumulation of NO in the cell causes formation of peroxynitrite, an extremely reactive substance formed by the reaction of NO with superoxide, which causes massive oxidative damage to the cell.

The combination of hypertension, impaired perfusion, and cellular damage leads to migraines (13), multiple sclerosis, impotence (NO causes the vasodilation responsible for an erection), glaucoma, strokes, etc. (see Fig. *6*).

Diseases due to excess acetylcholine release at the neuro-muscular junction, by deficient Mg

As we mentioned above, Mg inhibits the release of acetylcholine, so that low Mg levels lead to uncontrollable muscle contractions (see Fig. *6*). This can be seen in delirium tremens, myasthenia gravis, Guillain-Barre syndrome, etc.

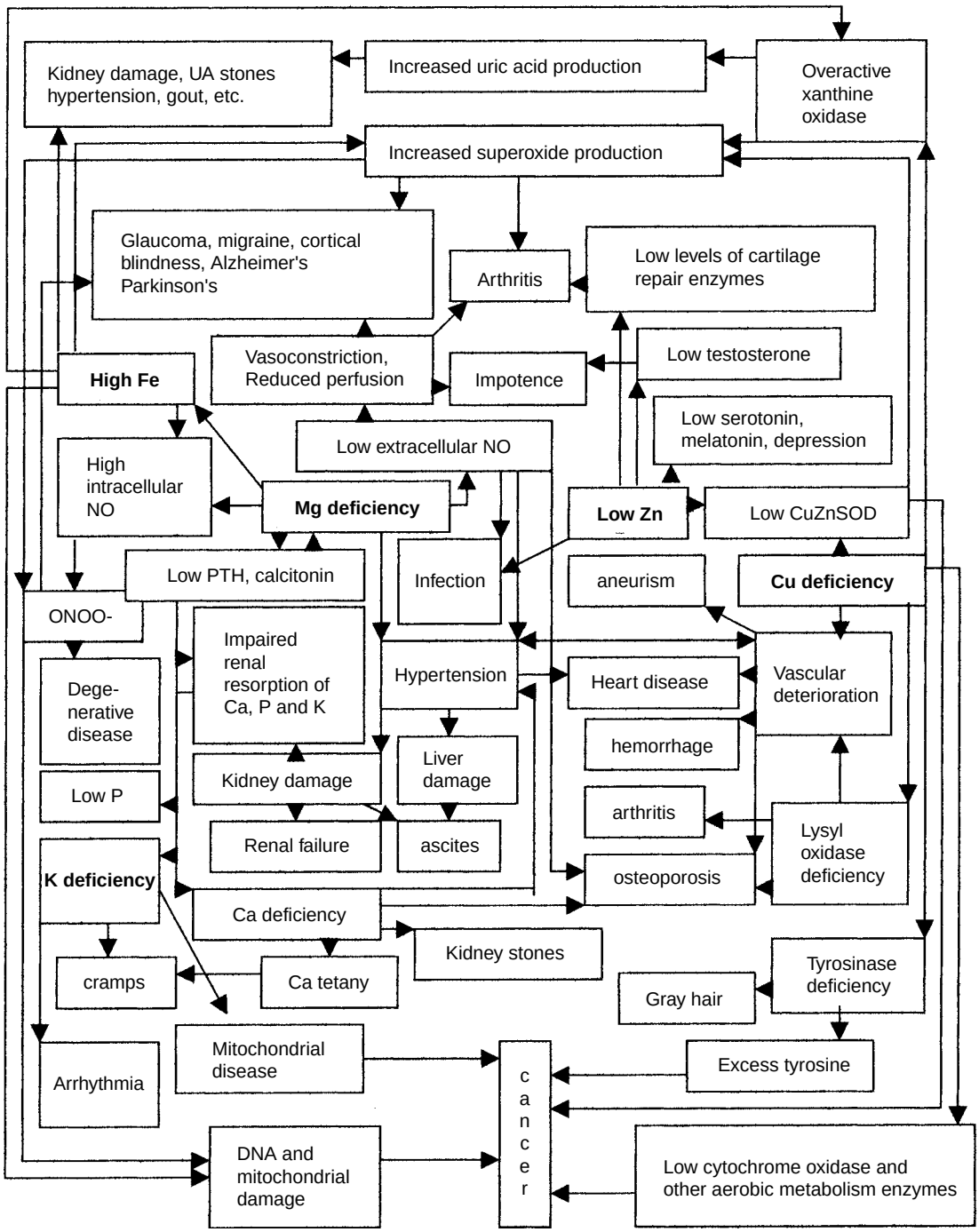

Fig. 6 Combined Mg, Zn and Cu deficiencies and Fe accumulation, leading to degenerative disease in men and postmenopausal women.

Diseases due to trace metal accumulation, caused by deficient Mg

A Mg deficiency affects greatly the distribution of several minerals in the body, for example, it increases Fe levels in liver, spleen and kidney at the same time that it reduces Cu levels in the liver (14).

The accumulation of Fe, Cd, Al and Pb in the kidneys, liver and brain, that results from, and exacerbates, a Mg deficiency, leads to considerable oxidative damage of these crucial organs. The brain damage eventually manifests itself as many devastating diseases such as autism (15–17), Parkinson's disease, etc.

Al may be ingested in well water or in the form of Al laxatives. While Cd is often derived from cigarette smoking and Pb from occupational hazards. Fe accumulates with age in men and postmenopausal women.

CORRECTING A MG DEFICIENCY

In order to correct a moderate Mg deficiency, a person with a low Mg diet and limited exposure to sunlight, who ingests 2 cups of coffee and 2 beers per day, may require 250 mg Mg, 100 micrograms Se, 400 IU vitamin E, 25 mg vitamin B6, 6 glasses of water and reducing the saturated fat in the diet. On the other hand, a person with plenty of exposure to sunlight all year around and with a diet rich in B6 and Mg (legumes, nuts, vegetables, fruits), and low in saturated fats, and 1 cup of coffee or beer per day, and taking plenty of water, may need only 50 mg Mg per day.

However, since Mg and vitamins D and B6 have low toxicity, providing 100 mg Mg, 100 micrograms Se, 400 IU vitamin D and 25 mg vitamin B6 a day in the winter to all the people living beyond 35° of latitude seems justified.

On the other hand, when there is a severe Mg deficiency, the lack of the low levels of Mg needed to cause the release of PTH, requires that the parathyroid gland be primed with a small parenteral dose of Mg, so that PTH be released and Mg levels may begin to recover from Mg in the diet.

Since the liver is involved in vitamin D synthesis and storage, vitamin D deficiency and the deficiencies that derive from it (Mg, Ca, K and P), must be addressed in patients suffering from cirrhosis, hemochromatosis, Wilson's disease and other major liver diseases.

Finally, since Pb and Cd antagonize Mg, patients with high levels of these elements would benefit from chelation therapy with succimer, which only removes these toxic metals, sparing Cu, Zn and other essential metals.

CONCLUSIONS

Even though Mg is readily available in food, the large number of favorable conditions required for its absorption and retention often result in a deficiency, which can manifest itself in a myriad symptoms and signs, encompassing an extremely wide range of pathologies.

Unfortunately, evaluation of the Mg status is complicated by the fact that most of the Mg is stored in tissues, so that serum values are not truly representative. For example, a patient with an apparently healthy serum Mg of 2 mg/dl may have low intracellular Mg stores, because cellular Mg uptake may be impaired.

Furthermore, the same large number of conditions required for the maintenance of proper Mg levels greatly complicates the evaluation of the effect of Mg during clinical trials. Therefore, it is essential that researchers understand all these conditions very well.

Finally, since Mg is very inexpensive and has an extremely low toxicity, and since vitamin D and B6 are also very inexpensive (in most cases, vitamin D can be increased by simple exposure to sun light) it is deplorable that Mg deficiency should still be the cause of so much suffering and expense, even in the most advanced societies.

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