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REVIEW

Magnesium and diabetes mellitus: Their relation

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Summary The aim of this review was to elaborate a synthesis about the discussions on magnesium and diabetes mellitus, in the last 14 years. The magnesium deficiency has been associated with chronic diseases, amongst them, diabetes mellitus. Epidemiological studies had shown low levels of magnesium ingestion in the general population, as well as a relation between the ingestion of food rich in magnesium and the reduction of diabetes installation and its complications. Hypomagnesemia is frequently present in diabetic patients, however there is not an exact elucidation of the mechanism of magnesium deficiency in diabetes mellitus. On the other hand, in the presence of this illness, it is observed that inadequate metabolic control can affect the corporal concentrations of magnesium, developing hypomagnesemia, which may be still directly related with some micro and macrovascular complications observed in diabetes, as cardiovascular disease, retinopathy and neuropathy. This way, the chronic complications of diabetes can appear precociously. Based on this, the supplementation with magnesium has been suggested in patients with diabetes mellitus who have proven hypomagnesemia and the presence of its complications.

Contents

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Introduction

Along the years it has been observed, in world-wide level, a reduction of micronutrients ingestion among the populations, due to changes on feeding habits.[1] Magnesium (Mg), is one of the most abundant intracellular ions with an essential role in fundamental biological reactions, whose deficiency provokes biochemical and symptomatic alterations in the human organism.[2,3]

Diabetes mellitus (DM), characterized by metabolic disorders related to high levels of serum glucose,[4] is probably the most associated disease to Mg depletion in intra and extra cellular compartments.[5]

Hypomagnesemia has been related as a cause of insulin resistance, also being a consequence of hyperglycemia, and when it is chronic leads to the installation of macro and microvascular complications of diabetes, worsening the deficiency of Mg.[6–9]

The mechanism involving the DM and hypomagnesemia was still unclear, although some metabolic studies demonstrate that Mg supplementation has a beneficial effect in the action of insulin and in the glucose metabolism.[1,10]

The aim of this review was to elaborate a synthesis about the main discussions in literature on Mg and DM, in the last fourteen years (1990–2004), ranging the consensus and controversies.

Magnesium: metabolism, function and deficiency

Mg is the second predominant component in the intracellular compartment, an important regulator of the cellular processes, co-factor of more than 300 essential metabolic reactions, including the ones that produce or use the MgATP complex. However, its functionality is related to the synthesis of tissue constituents, growth and thermogenesis, and with the activity of tyrosine kinase, in the metabolism of glucose.[11]

The homeostasis of Mg depends on the amount of ingestion, of the efficiency of absorption and of the intestinal and renal excretion. The absorption of this mineral occurs along the whole intestinal tract, especially in the ileum and colon, and its regulation is made mainly by the kidney.[10] The homeostatic regulation of Mg is increased by the action of parathormone (PTH), calcitonin, vitamin D, glucagon, antidiuretic hormone, aldosterone and sexual steroids. Beyond these, the insulin is involved in the transport of Mg through the cellular membrane and in the intracellular supply.[2,12]

The average ingestion of Mg, in a world-wide level, has diminished along the years, being frequently below the Recommended Dietary Allowances—RDA, this induces the development of Mg deficiency.[1] However, the specific clinical manifestations of hypomagnesemia are difficult to be diagnosed, due to the frequent associations of this deficiency with biochemical abnormalities as hypokalemia, hypocalcemia and metabolic alkalosis. Patients with hypomagnesemia can present cardiovascular alterations, as ischemic cardiac insufficiency, vascular complications of DM and hypertension. Neurological, hormonal, renal, gastrointestinal and muscular dysfunction also have been associated to hypomagnesemia.[13,14]

There were speculations about a possible relation between Mg deficiency and climatic variations, contributing for the increase of the heart deaths and diabetes. High temperatures would increase sweat losses and, consequently, among the minerals, Mg would be the most affected, because the losses would not be compensated by the diet and water intake, increasing so the risk for these diseases.[15]

Diabetes and dietary ingestion of magnesium

The alimentary source of Mg include the milky products, whole grains, the most of the green leafy vegetables, nuts, seeds, meats, poultries, fishes, dry beans, peas, lentils and products derived from soy.[11]

The Dietary Reference Intakes (DRIs) for Mg varies according to the gender, physiological state and life stage. However, it is important to stand out that these recommendations are for healthful individuals (Table 1).

Epidemiological and multicentric studies have registered an inverse relationship between the ingestion of food rich in Mg and the risk of diabetes.[16]

Table 1 DRIs for magnesium according to the gender, physiologic state and life state.[11]

Gender/physiologic state	Life stage	EAR (mg/d)	RDA (mg/d)	AI (mg/d)	UL* (mg/d)
Male and female	0–6 months	—	—	30	Not certain
	7–12 months	—	—	75	Not certain
	1–3 years	65	80	—	65
	4–8 years	110	130	—	110
Male	9–13 years	200	240	—	350
Female		200	240	—	350
Male	14–18 years	340	410	—	350
Female		300	360	—	350
Male	19–30 years	330	400	—	350
Female		255	310	—	350
Male	31–50 years	350	420	—	350
Female		265	320	—	350
Male	51–70 years	350	420	—	350
Female		265	320	—	350
Male	>70 years	350	420	—	350
Female		265	320	—	350
Pregnancy	14–18 years	335	400	—	350
	19–30 years	290	350	—	350
	31–50 years	300	360	—	350
Lactation	14–18 years	300	360	—	350
	19–30 years	255	310	—	350
	31–50 years	265	320	—	350

*UL of magnesium was established for magnesium supplementation, of nonfood source.

The Iowa Women's Healthy Study, a cohort of postmenopausal women, showed a significant reduction in the relative risk of diabetes, in women with increased intake of whole grains and other food sources of Mg.[17] The Framingham Offspring Study, notified a reduction of the metabolic risk factors for the development of diabetes, associated to the whole grains intake, still demonstrating an inverse association in these grains consumption and fasting insulin.[18]

Other cohort studies carried out with men and women, had also verified an inverse association involving the Mg intake and the risk of type 2 DM; however, in the Women's Health Study, only the women with Body Mass Index (BMI) over 25 kg/m^2 had demonstrated this association.[1,19] Positive correlation between insulin sensitivity and the Mg intake, has been detected, suggesting that the Mg can delay the development of type 2 DM.[12,20]

On the other hand, the relation between ingestion of Mg and the risk of type 2 DM, was not evidenced in ARIC Study, considering blacks and white American individuals[21]; nor in another case-control study accomplished in Switzerland using different methodological procedure.[22]

Magnesium and diabetes mellitus

DM is a metabolic disease of multiple etiology, characterized by hyperglycemia resulting from defects in the insulin secretion and/or the insulin action.[4] According to the American Diabetes Association—ADA, this syndrome is classified as:

1. Type 1 DM—characterized by the β-cells destruction, usually leading to the absolute insulin deficiency, can be of auto-immune or idiopathic nature;
2. Type 2 DM—ranging from predominantly of insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance;
3. Gestational DM—the most common clinical disturbance that affects pregnancy, characterized by glucose intolerance, which onset or first recognition during pregnancy;
4. Other specific types of diabetes as: iatrogenic, specific genetic defects of pancreatic β-cells or insulin action, exocrine diseases of the pancreas,

endocrinopathies, induction by drugs or chemical reagents, infectious, uncommon forms of autoimmune diabetes, and other genetic syndromes associated as, for example, Down syndrome.

Hypomagnesemia in diabetic is usually observed in patients with deficient metabolic control, or associated to the DM chronic complications, according to clinical and epidemiological studies.[6,20]

The responsible mechanisms for Mg deficiency in patients with diabetes have still not been clarified, mainly about the impact in the insulin resistance, in the development of diabetes and its chronic complications.[12,23,24] It is speculated as triggering factors the increase urinary excretion of Mg, specially in patients with unsatisfactory metabolic control, dietary deficiency or absorption reduction.[25–27]

The scientific evidences indicate the role of the calcium and Mg as mediators of the insulin action. In the DM occur chronic alterations of homeostasis of Mg intracellular, unchained by the unbalance between calcium and Mg. The effects result in damages on the tyrosine kinase activity, in level of receptors unchaining the outlying insulin resistance.[28]

Other studies had demonstrated positive effect in the administration of insulin over intracellular Mg concentrations. One of them, demonstrated an improvement of the intracellular Mg concentration in obese children and patients with type 1 and 2 DM, after the stimulation with 100 mU/mL of insulin.[29]

The hyperglycemia, independent of insulin, or other responses due to oral glucose ingestion has potential role in cellular ionic changes of free Ca and Mg. The hyperglycemia per se elevated intracellular Ca and suppressed intracellular Mg in normal human red cells.[30]

In experimental DM has been related alterations in the tissue redistribution of Mg. Spontaneous diabetic rats showed increased urinary excretion of Mg, correspondent to 1,5 times, compared with controls. It was also evidenced an increasing of Mg in the pancreas and reduction in the lungs, kidneys, testicles and adipocytes, in the early stages of the diabetes.[31]

Despite of the deduction that the hypomagnesemia is caused by the diabetes and not the opposite, the Mg deficiency also can influence in the onset of this disease. This was demonstrated in one prospective study (ARIC), predominantly in the white participants.[21] The Mg deficit interferes on enzymatic reactions that use or produce adenosine triphosphate (ATP), in consequence modifies the enzymatic cascade that involves the carbohydrates metabolism, triggering DM. In the same way as observed by Delva et al.,[3] in hyperglycemia, existing ionic alterations in the cells, there is an increase of the intracellular ATP concentration, that induce a reduction of the intracellular ionized Mg levels.

Magnesium and macrovascular chronic complications of diabetes

The chronic complications of diabetes are developed when cells or cellular components are chronically exposed to the high concentrations of glucose. The non-enzymatic glycosylation of proteins and the accumulation of polyol as the sorbitol, result in the formation of end products of the advanced glycosylation in the tissues, causing irreversible changes. This process culminate in cellular damage, being able to trigger macrovascular complications as dyslipidemia and hypertension, associated to the DM; and microvascular as neuropathy, retinopathy and nephropathy.[28]

Abou-Seif and Youssef[32] observed lower Mg concentrations in the plasma of patients with type 2 DM and reduction of antioxidative protection in the two types of diabetes, which can be an increasing factor of the chronic complications. The vascular complications mostly associated to the deficiency of Mg are: heart ischemic disease, atherosclerosis,[20] hypercholesterolemia,[33] hypertriglyceridemia[7] and hypertension,[34,35] and probably the mechanisms of metabolic syndrome.[36]

In type 2 diabetic patients with essential hypertension, have been detected reduced cytosolic free Mg concentrations, when compared to normotensive or non-diabetic individuals. The inverse relation between intracellular ionic disturbs of Mg and the metabolic compensation has been questioned in relation to develop rise of arterial pressure and insulin resistance.[28,34,37]

According to the hypothesis suggested by Paolisso and Barbagallo,[5] the low availability of intracellular Mg diminishes the tyrosine kinase activity and increases the vascular constriction mediated by calcium, hindering the relaxation of cardiac and smooth muscles; and this way, interfering in the usage of the cellular glucose. Such mechanisms contribute to raise the blood pressure and peripheral insulin resistance, suggesting secondary etiological factors of hypertension and type 2 diabetes (Fig. 1).

The Atherosclerosis Risk in Communities (ARIC) Study, indicated that the serum and dietary Mg may be related to the etiology of cardiovascular diseases, hypertension and diabetes. Serum Mg

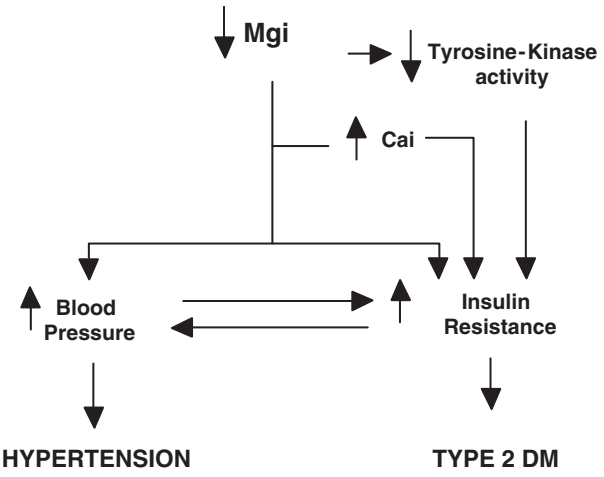

Figure 1 Overall hypothesis in which intracellular Mg deficiency may mediate the relationship between insulin resistance, type 2 DM and hypertension (from Paolisso and Barbagallo,[5] with permission).

was significantly lower in the participants with cardiovascular disease, hypertension and/or diabetes, than in the healthful individuals, registering the lower concentrations in the diabetic patients with hypertension. Moreover, it was observed that patients with cardiovascular disease, the serum Mg was also inversely associated to insulin, fasting serum glucose, systolic arterial pressure and smoking. The Mg dietary ingestion was positively associated to the high density lipoprotein cholesterol (HDL-c) and inversely associated to the fasting insulin, systolic and diastolic pressure.[20]

Sasaki et al.[33] not verified significant difference to the Mg assessed in patients with cardiovascular diseases and in the individuals presenting risk factors for these diseases. Even so, patients with DM and those with cardiac arrhythmia had lower serum levels of ionized Mg, than the healthful controls. On the other hand, the patients with essential hypertension demonstrated higher erythrocyte Mg concentration than control group, which thwart the hypothesis of the Mg deficiency in these patients. It can be deduced however, that serum Mg concentration as a single parameter of evaluation must be carefully interpreted in this kind of study.

Mg deficiency has also been argued as a probable causal factor of dyslipidemias,[38] what constitutes an alert for the chronic complications of DM, as the atherosclerosis. In patients with type 1 diabetes, was demonstrated that the improvement of the metabolic control seems to reduce the renal excretion of Mg, increase HDL-c level and reduce the serum triglycerides. Supplementation with Mg resulted in a negative correlation between serum total Mg and triglycerides concentration; and between the ionized Mg concentration and serum total cholesterol and apolipoprotein A1. These results suggest a probable relation involving the serum Mg concentrations and the lipidic profile.[7]

High concentrations of total cholesterol and low density lipoprotein cholesterol (LDL-c), and low concentrations of HDL-cholesterol had been observed in patients with type 2 diabetes with decompensate fasting glycemia. The HDL-c was positively correlated to serum Mg indicating that hypomagnesemia associates to low levels of HDL-c even in pre-diabetic states.[38]

Magnesium and microvascular chronic complications of diabetes

Experimental researches have shown that patients with diabetic retinopathy present low concentrations of plasma Mg, disposing to a higher risk of advanced retinopathy.[6]

In a prospective study with 61 diabetic patients using insulin (33 type 1 and 28 type 2), it was observed a significant negative correlation between plasma Mg concentration and the retinopathy progression, however, there are doubts if the plasma Mg concentration can be considered a causal factor for the retinopathy development.[39] A transversal study carried out in Brazil with type 1 and type 2 diabetic, did not demonstrate a significant correlation between the severity of retinopathy and Mg concentration in the plasma.[9]

In type 2 diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized Mg levels. Moreover, it was also observed a significant negative correlation between serum ionized Mg and HbA1c and triglycerides, in both microalbuminuria and clinical proteinuria groups. According these results it is possible to associate metabolic control and lipidic profile disturbances with alterations in Mg metabolism in these patients.[40]

In a multicentric study with type 1 diabetic patients it was evidenced that the erythrocyte Mg was in a lesser concentration in the patients with polyneuropathy than in the diabetics without this complication. After intervention with Mg supplementation it was observed an improvement in the nervous conduction, mainly in the young patients who had initial signals of neurological complications.[41]

De Leeuw et al.[42] observed in type 1 diabetic with chronic Mg depletion (supplemented and not supplemented) that the polyneuropathy was

determined by the duration of diabetes and by the low erythrocyte Mg concentration. The supplementation with Mg increased the erythrocyte Mg concentration, as well as reduced the incidence of polyneuropathy.

It has also been suggested that hypomagnesemia is associated with feet ulcers in patients with type 2 DM.[8]

Diabetes and others complications (pregnancy, aging, bone metabolism, hormones)

Some researches involving Mg concentrations have been developed in pregnant women; however the findings are still not consistent.[11]

Bardicef et al.[43] observed lesser ionized and total Mg concentrations in pregnant patients in the third trimester of pregnancy in relation to non-pregnant normal patients, being more accentuated in the gestational diabetes. Beyond this, it was evidenced lower intracellular free Mg levels in pregnancy diabetic women compared with non-pregnant and normal pregnant women. It has been argued that the pregnancy itself induces the losses of this mineral, which are increased in presence of diabetes. On the other hand, none alteration in the ionized Mg concentration was observed in the first trimester of pregnancy of women with and without gestational diabetes.[44]

Beyond pregnancy, aging can also be associated with the reduction of blood Mg concentrations. Patients with type 2 DM, over 65 years old, had presented alterations in the metabolism and compartmentation of Mg, especially in platelets, when compared to plasma and erythrocytes of healthful elderly and young with type 2 DM and healthful young.[45]

Some studies are being developed in the attempt of demonstrating the relation between Mg and the alterations of bone metabolism, common in diabetes. An experiment lead in animals by Yamini et al.,[46] speculated disorders in bone mineral content and in bone bio-mechanism in male rats type spontaneous hypertensive/NIH corpulent—SHR/N-cp (model of rodent that shows many similar characteristics of type 2 DM) obese and thin, submitted to dietary intervention during a period of 8 months. Urinary excretion of Mg was higher in obese rats with bone growth disorders, and before alterations in the concentration of bone Mg.

In humans, the increase of urinary calcium and Mg excretion in relation to the glycemic control of type 1 diabetic patients was verified, mainly in the female gender. This is worried due to the damages on bone mass, predisposing even more the triggering of diabetic osteopenia.[47]

Supplementation with magnesium

In patients with diabetes, the supplementation with micronutrients must be individualized, based on dietary history, clinical features and laboratorial evaluation of the nutritional state.[48]

Even so the oral supplementation with Mg improves the secretion and sensitivity to insulin in type 1 and 2 diabetic patients, there are still controversies based on human and animal studies accomplished. In elapsing of investigations with humans, the oral supplementation with Mg was related to insulin sensitivity and the metabolic control in patients with type 2 DM.[49]

In a clinical randomized study with 128 diabetic patients with unsatisfactory metabolic control (HbA1c $>$ 8.0%), which had been divided into three groups: placebo, supplemented with 20.7 mmol/d of magnesium oxide (MgO) and with 41.4 mmol/d of MgO; it was not verified alterations in plasma and intracellular levels of Mg, nor in the improvement of glycemic control in the group supplemented with the lower dose. Already to the supplemented with 41.4 mmol/d of MgO, it was evidenced a tendency to increase the plasma and urinary Mg, causing a significant decrease in fructosamine.[50] Later, no beneficial effect was demonstrated in the glycemic control of diabetic patients in the studies evaluated by Valk.[10]

Barbagallo et al.[51] demonstrated that the supplementation with Mg improved the circulating glucose levels and the oxidation of the tissue glucose in patients with type 2 DM, besides favoring in the action of the peripheral insulin. Contrary results were verified in type 2 diabetic patients with hypomagnesemia after supplementation with 600 mg of Mg oxide daily. The only beneficial effect observed in this study was on the lipidic profile.[52]

Type 2 diabetics supplemented with nature water with a high Mg content had a significant increase of total serum, urinary and excretion Mg levels. Positive clinical effects was showed by significant decrease of the insulin resistance and fasting immunoreactive insulin.[53]

Still in type 2 diabetics, the Mg associated with Zn, vitamin C and E improved the values of HDL-c and apolipoprotein A; fact not observed when Mg was offered only with zinc.[54] Previously this had been evidenced in humans increasing the positive effect in the carbohydrates metabolism, besides

being co-adjuvant in the treatment of hypertension.[55] It is worth to stand out that, in rats, Baydas et al.[56] had not verified adding beneficial effects of supplementation with zinc, only with Mg.

Although Mg supplementation seems to have beneficial effect in diabetic patients, no rule about dosage and duration of the treatment with this mineral has been established until the moment. In 1992, the ADA[57] suggested the evaluation of serum Mg and supplementation, in cases of proven hypomagnesemia, in diabetic patients with high risk of hypomagnesemia, as, for example, in the case of congestive heart failure, coronarian arterial disease, excessive alcoholic consumption, long term parenteral nutrition, or pregnancy. Nowadays, ADA recommends the replacement of Mg based on the reduction of serum concentrations of this element.[4,58]

Conclusions

According point out the results of epidemiological studies, there are contradictions with relation the low dietary ingestion of Mg to be a predictor factor for type 2 diabetes.

The hypomagnesemia is the mainly focus in studies performed with DM. The diabetic state interferes in the maintenance of the normal concentrations on body Mg, being able to trigger hypomagnesemia easily, mainly in poor metabolic control, which leads more spontaneously the outcome of diabetic chronic complications. Moreover, the hypomagnesemia also to be able to develop DM and its complications, especially when exist other associate risk factors.

About the macrovascular complications, the ARIC study indicated the deficiency of Mg as a etiological factor of the cardiovascular diseases, diabetes and hypertension. So much in this study as in others of clinical base, the mechanisms were interpreted considering the negative effect of the hypomagnesemia in the dyslipidemias and in the metabolic control.

It does not still have epidemiological studies that demonstrate the relation between the hypomagnesemia and microvascular complications of the DM, however, the clinical studies that detected negative correlation between this deficiency and the presence of retinopathy and polyneuropathy, shall be considered in speculations about consequences of alterations on Mg status in diabetes. If the supplementation is responsive in these situations, it is important to do adjustments of clinical management of diabetes.

There are still no consensus regarding of the benefits that Mg supplementation can take to the DM patient with and without complication, however the major of clinical studies had demonstrated positive effects on the insulin resistance and lipidic profile. In this context it is rational to indicate the supplementation to these patients.

It is necessary to accomplish more studies for us to understand better the relation of Mg with the DM.

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References

1. Lopez-Riadura R, Willett WC, Rimm EB, Liu S, Satampper MJ, Manson JE, et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004;**27**(1): 134–40.
2. Saris NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An uptake on physiological, clinical and analytical aspects. *Clin Chim Acta* 2000;**294**:1–26.
3. Delva P, Degan M, Pastori C, Faccini G, Lechi A. Glucose-induced alterations of intracellular ionized magnesium in human lymphocytes. *Life Sci* 2002;**71**:2119–35.
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004;**27**(Suppl. 1):S5–S10.
5. Paolisso G, Barbagallo M. Hypertension, diabetes mellitus, and insulin resistance. The role of intracellular magnesium. *Am J Hypertens* 1997;**10**(3):346–55.
6. Tosiello L. Hypomagnesemia and Diabetes Mellitus. *Arch Intern Med* 1996;**156**:1143–8.
7. Djurhuus MS, Henriksen JE, Klitgaard NAH, Blaabjerg O, Thye-Ronn P, Altura BM, et al. Effect of moderate improvement in metabolic control on magnesium and lipid concentrations in patients with type 1 diabetes. *Diabetes Care* 1999;**22**(4):546–54.
8. Rodríguez-Morán M, Guerrero-Romero F. Low serum magnesium levels and foot ulcers in subjects with type 2 diabetes. *Arch Med Res* 2001;**32**:300–3.
9. Corrêa ZMS, Freitas AM, Marcon IM. Risk factors related to the severity of diabetic retinopathy. *Arq Bras Oftalmol* 2003;**66**:739–43.
10. Valk HW. Magnesium in diabetes mellitus. *Netherlands J Med* 1999;**54**:139–46.
11. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes; Food and Nutrition Board; Institute of Medicine. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*, vol. 6. Washington, DC: National Academy Press; 1997. pp. 190–249.
12. Humphries S, Kushner H, Falkner B. Low dietary magnesium is associated with insulin resistance in a sample of young, nondiabetic black Americans. *Am J Hypertens* 1999;**12**: 747–56.
13. Agus ZS. Hypomagnesemia. *J Am Soc Nephrol* 1999;**10**: 1616–22.
14. Fox C, Ramsoomair D, Carter C. Magnesium: its proven and potential clinical significance. *South Med J* 2001;**94**(12): 1195–201.

15. Franz KB, Bailey SM. Geographical variations in heart deaths and diabetes: effect of climate and a possible relationship to magnesium. *J Am Coll Nutr* 2004;**23**:521S–4S.
16. Nadler JL. A new dietary approach to reduce the risk of type 2 diabetes? *Diabetes Care* 2004;**27**(1):270–1.
17. Meyer KA, Kushi LH, Jacobs Jr DR, Slavin J, Sellers TA, Folsom AR. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000;**71**:921–30.
18. McKeown NM, Meigs JB, Simin L, Wilson PWF, Jacques PF. Whole-grain intake is favorably associated with metabolic risk factors for type 2 diabetes and cardiovascular disease in the Framingham Offspring Study. *Am J Clin Nutr* 2002;**76**: 390–8.
19. Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004;**27**(1):59–65.
20. Ma J, Folsonm AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. *J Clin Epidemiol* 1995;**48**(7):927–40.
21. Kao WHL, Folsom AR, Javier Nieto F, Mo J-P, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 1999;**159**:2151–9.
22. Walti MK, Zimmermann MB, Spinas GA, Jacob S, Hurrell RF. Dietary magnesium intake in type 2 diabetes. *Eur J Clin Nutr* 2002;**56**:409–14.
23. Reis MAB, Velloso LA, Reyes FGR. Alterações do metabolismo da glicose na deficiência de magnésio. *Rev Nutr* 2002;**15**(3): 333–40.
24. Wälti MK, Zimmermann MB, Spinas GA, Hurrell RF. Low plasma magnesium in type 2 diabetes. *Swiss Med Wkly* 2003; **133**:289–92.
25. Eibl N, Schnack C, Schernthaner G. Magnesium supplementation in type 2 diabetes. *Diabetes Care* 1998;**21**(11):2031–2.
26. Mikhail N, Ehsanipoor K. Ionized serum magnesium in type 2 diabetes mellitus: its correlation with total serum magnesium and hemoglobin A_{1c} levels. *Southern Med J* 1999; **92**(12):1162–6.
27. Khan LA, Alam AMS, Ali L, Goswami A, Hassan Z, Sattar S, et al. Serum and urinary magnesium in young diabetic subjects in Bangladesh. *Am J Clin Nutr* 1999;**69**:70–3.
28. Barbagallo M, Resnick LM, Dominguez LJ, Licata G. Diabetes mellitus, hipertensão e envelhecimento: a hipótese iônica das moléstias metabólico-cardiovasculares e o envelhecimento. *Diabetes Metab* 1998;**3**:116–28.
29. Takaya J, Higashino H, Kotera F, Kobayashi Y. Intracellular magnesium of platelets in children with diabetes and obesity. *Metabolism* 2003;**52**(4):468–71.
30. Resnick LM, Barbagallo M, Gupta RK, Laragh JH. Ionic basis of hypertension in diabetes mellitus: role of hyperglycemia. *Am J Hypertens* 1993;**6**:413–7.
31. Takita S, Wakamoto Y, Kunitsugu I, Sugiyama S, Okuda M, Houbara T. Altered tissue concentration of minerals in spontaneous diabetic rats (Goto-Kakizaki rats). *J Toxicol Sci* 2004;**29**(3):195–9.
32. Abou-Seif M, Youssef AA. Evaluation of some biochemical changes in diabetic patients. *Clin Chim Acta* 2004;**346**:161–70.
33. Sasaki S, Osima T, Matsuura H, Ozono R, Higashi Y, Sasaki N, et al. Abnormal magnesium status in patients with cardiovascular diseases. *Clin Sci* 2000;**98**:175–81.
34. Dominguez LJ, Barbagallo M, Sowers JR, Resnick LM. Magnesium responsiveness to insulin and insulin-like growth factor I in erythrocytes from normotensive and hypertensive subjects. *J Clin Endocrinol Metab* 1998;**83**(12):4402–7.
35. Wells IC, Agrawal DK, Anderson RJ. Abnormal magnesium metabolism in etiology of salt-sensitive hypertension and type 2 diabetes mellitus. *Biol Trace Elem Res* 2004;**98**(2): 97–108.
36. Djurhuus MS, Klitgaard NAH, Pedersen KK, Blaabjerg O, Altura BM, Altura BT, et al. Magnesium reduces insulin-stimulated glucose uptake and serum lipid concentrations in type 1 diabetes. *Metabolism* 2001;**50**(12):1409–17.
37. Barbagallo M, Dominguez LJ, Galioto A, Ferlisi A, Cani C, Malfa L, et al. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. *Mol Aspects Med* 2003; **24**:39–52.
38. Guerrero-Romero F, Rodríguez-Morán M. Hypomagnesemia is linked to low serum HDL-cholesterol irrespective of serum glucose values. *J Diabetes Complicat* 2000;**14**:272–6.
39. Valk HW, Hardus PLLJ, Van Rijn HJM, Erkelens DW. Plasma magnesium concentration and progression of retinopathy. *Diabetes Care* 1999;**22**(5):864–5.
40. Corsonello A, Ientile R, Buemi M, Cucinotta D, Mauro VN, Macaione S, et al. Serum ionized magnesium levels in type 2 diabetic patients with microalbuminuria or clinical proteinuria. *Am J Nephrol* 2000;**20**(3):187–92.
41. Engelen W, Bouten A, De Leeuw I, De Block C. Are low magnesium levels in type 1 diabetes associated with electromyographical signs of polyneuropathy? *Magnes Res* 2000;**13**(3):197–203.
42. De Leeuw I, Engelen E, De Block C, Van Gaal L. Long term magnesium supplementation influences favourably the natural evolution of neuropathy in Mg-depleted type 1 diabetic patients (T1dm). *Magnes Res* 2004;**17**(2):109–14.
43. Bardicef M, Bardicef O, Sorokin Y, Altura BM, Altura BT, Cotton DB, et al. Extracellular and intracellular magnesium depletion in pregnancy and gestational diabetes. *Am J Obstet Gynecol* 1995;**172**(3):1009–13.
44. Ertbeg P, Norgaard P, Bang L, Nyholm H, Rudnicki M. Ionized magnesium in gestational diabetes. *Magnes Res* 2004;**17**(1): 35–8.
45. Corica F, Allegra A, Ientile R, Buemi M, Corsonello A, D'Angelo R, et al. Reduced intraplatelet magnesium concentrations in elderly patients with non-insulin dependent diabetes mellitus (NIDDM). *Arch Gerontol Geriatr* 1997; **25**:255–62.
46. Yamini S, Szepesi B, Michaelis OE, Moser-Veillon PB. Bone calcium content and biomechanics in a spontaneous hypertensive/NIH corpulent rat (SHR/N-cp). *Comp Biochem Physiol* 1995;**112A**(3/4):425–31.
47. Brown IR, McBain AM, Chalmers J, Campbell IW, Brown ER, Lewis MJ. Sex difference in the relationship of calcium and magnesium excretion to glycemic control in type 1 diabetes mellitus. *Clin Chim Acta* 1999;**283**:119–28.
48. Mooradian AD, Failla M, Hoogwerf B, Maryniuk M, Wylie-Rosett J. Selected vitamins and minerals in diabetes. *Diabetes Care* 1994;**17**(5):464–79.
49. Rodríguez-Morán M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects. *Diabetes Care* 2003; **26**(4):1147–52.
50. Lima ML, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Canguçu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 1998;**21**(5):682–6.
51. Barbagallo M, Dominguez LJ, Tagliamonte MR, Resnick LM, Paolisso G. Effects of glutathione on red blood cell intracellular magnesium. Relation to glucose metabolism. *Hypertension* 1999;**34**:76–82.

52. Lal J, Vasudev K, Kela AK, Jain SK. Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. *J Assoc Physicians India* 2003;**51**:37–42.
53. Yokota K, Kato M, Lister F, Ii H, Hayakawa T, Kikuta T, et al. Clinical efficacy of magnesium supplementation in patients with type 2 diabetes. *J Am Coll Nutr* 2004;**23**:506S–9S.
54. Farvid MS, Siassi F, Jalali M, Hosseini M, Saadat N. The impact of vitamin and/or mineral supplementation on lipid profiles in type 2 diabetes. *Diabetes Res Clin Pract* 2004;**65**:21–8.
55. Soriano-Carrascosa L, Maldonado-Martín A, Gil-Extremera B, Gonzalez-Gomez L, Jimenez-Lopes P, Arjona-Garcia M. Magnesium supplements in the control of carbohydrate and lipid metabolism, diabetes and obesity. *Am J Hypertens* 1995;**8**(4):134A.
56. Baydas B, Karagoz S, Meral I. Effects of oral zinc and magnesium supplementation on serum thyroid hormone and lipid levels in experimentally induced diabetic rats. *Biol Trace Elem Res* 2002;**88**(3):247–54.
57. American Diabetes Association. Magnesium supplementation in the treatment of diabetes (Consensus Statement). *Diabetes Care* 1992;**15**:1065–7.
58. American Diabetes Association. Nutritional principles and recommendations in diabetes. *Diabetes Care* 2004;**27**(Suppl. 1): S36–46.