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Invited review

Magnesium in diabetes mellitus

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Abstract

A tendency for magnesium deficiency in patients with diabetes mellitus is well-established. Glucosuria-related hypermagnesiuria, nutritional factors and hyperinsulinaemia-related hypermagnesiuria all can contribute. The plasma magnesium level has been shown to be inversely related to insulin sensitivity. Magnesium supplementation improves insulin sensitivity as well as insulin secretion in patients with type 2 diabetes. Nevertheless, no beneficial effects of oral magnesium supplementation has been demonstrated on glycaemic control either in patients with diabetes type 1 or 2. Oral magnesium supplementation reduced the development of type 2 diabetes in predisposed rats. There are some indications that magnesium decreases blood pressure, but negative results have been observed in trials that were, however, not designed to test effect on blood pressure as primary parameter. Patients with (severe) retinopathy have a lower plasma magnesium level compared to patients without retinopathy and a prospective study has shown the plasma magnesium level to be inversely related to occurrence or progression of retinopathy. Further study on magnesium (supplementation) is warranted in the prevention of type 2 and of (progression of) retinopathy as well as a means to reduce high blood pressure. © 1999 Elsevier Science B.V. All rights reserved.

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Introduction

It has been well-established that the plasma magnesium level in patients with diabetes mellitus is somewhat decreased [1–3]. Since the magnesium ion is required as co-factor for many enzymatic reactions [4,5], magnesium deficiency may be of clinical importance. This importance requires the demonstration of a link between magnesium deficiency and the occurrence of a chronic complication or a pathophysiological process operative in diabetes and/or the demonstration of a beneficial effect of mag-

nesium supplementation on parameters like glycaemic control, plasma lipids or blood pressure. In this review, the physiology of magnesium in humans and the pathophysiology of magnesium metabolism in diabetes will be described, followed by an evaluation of the available observational and intervention studies.

Physiology of magnesium

There is a specific distribution of magnesium in the body [4,5]. Fifty to 65% of total body magnesium is present in bone, 25% in skeletal muscle, the remainder is found in other tissues like liver and

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heart. The plasma and extracellular magnesium concentration is normally between 0.70 and 1.00 mmol/l. Fifty to 60% of magnesium in blood is in the free, ionised form, the remainder is bound to proteins (30%) or anions like phosphate, citrate and oxalate (10–20%). Recommended daily intake of magnesium is 250–300 mg/day (10.5–12.5 mmol/day) [6,7].

Absorption takes place mainly in the ileum with the stomach and colon playing no major role [4,5,8,9]. The kidney is the main organ in magnesium homeostasis. Magnesium reabsorption takes place in the proximal tubule, thick ascending part of the loop of Henle and the distal tubule [10–12]. The relative contribution of the different nephron segments to the reabsorptive process, expressed as percentage of filtered magnesium in the glomerulus, is shown in Fig. 1. The remaining 5% of filtered magnesium is excreted (3.5–5 mmol/day). Magnesium reabsorption in the proximal tubule depends on the luminal magnesium concentration and is secondary to sodium and water reabsorption [13]. Magnesium reabsorption takes place mainly in the thick ascending part of loop of Henle; at this site it is driven by the transluminal potential difference generated by $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$ co-reabsorption. Magnesium reabsorption increases without ceiling with increasing luminal magnesium concentration; at all luminal concentrations, $\pm 80\%$ of luminal magnesium is reabsorbed [14,15]. The subsequent rise in the

interstitial magnesium concentration inhibits further magnesium reabsorption.

Magnesium balance is mainly regulated at the thick ascending part of loop of Henle by changes in renal excretion, largely influenced by the plasma/extracellular magnesium concentration itself. Renal magnesium excretion rises with increasing and falls with decreasing plasma/extracellular magnesium concentration. During low oral intake, the kidneys are capable of reducing daily excretion to less than 0.5 mmol [16,17]. No hormonal system has been identified which is physiologically important in the long-term regulation of the plasma magnesium concentration in man although some hormones (adrenalin, parathyroid hormone) have a short-term influence [12,18].

The plasma magnesium level is readily and reliably measurable and since several studies have shown that the plasma magnesium concentration is related to the intracellular level, is generally a sufficient parameter in the evaluation of magnesium homeostasis [17,19,20]. The relation between urinary magnesium excretion and the plasma magnesium concentration offers additional information. Hypomagnesaemia by a renal cause is associated with high urinary magnesium excretion, hypomagnesaemia due to a non-renal cause by a low renal magnesium output [14]. The magnesium loading test (MLT) has been developed as another means to identify patients with magnesium deficiency. A magnesium infusion is given and the amount of magnesium from this intravenous load which is excreted, is used for calculating the retention. Covert magnesium deficiency is identified by increased retention. The MLT only offers additional information when the plasma magnesium concentration is normal and there is no renal magnesium wasting (non-renal cause of magnesium deficiency). In those conditions, the kidneys try to preserve magnesium which the MLT can substantiate.

Several cell types have been used for the measurement of the intracellular magnesium concentration: erythrocytes, mononuclear leucocytes, and striated muscle cells. Magnesium levels in erythrocytes are relatively easy to measure but decline with aging of the erythrocyte and are influenced by the ambient insulin concentration [21,22]. Magnesium in leucocytes requires complex methodology and the

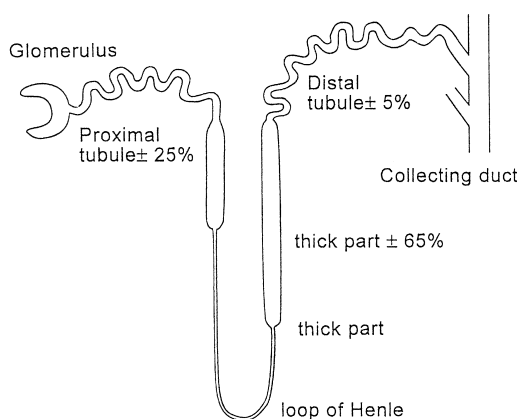


Fig. 1. Reabsorption of magnesium in the kidney.

range of normal values is wide [23,24]. Measurement in striated muscle cells requires an invasive technique making it hardly applicable in clinical medicine. Techniques to determine free intracellular magnesium concentration, like NMR measurements in erythrocytes and intracellular dyes, have been developed but are expensive and laborious.

Magnesium levels in patients with diabetes

Magnesium concentrations have been determined in plasma, erythrocytes, leucocytes, and striated muscle samples, and the free cellular magnesium concentration has been measured in erythrocytes.

Plasma magnesium levels

Mean plasma magnesium concentrations are lower in both patients with type 1 and type 2 diabetes compared to non-diabetic controls [1–3,25–28], although the frequency of hypomagnesaemia may be limited [26,28]. Reported difference in mean magnesium levels between patients and controls range from 0.06 to 0.21 mmol/l. In one study in patients with type 2 diabetes and mild hyperglycaemia without oral glucose-lowering medication, plasma magnesium concentration was similar in patients and controls [29]. However, the relatively small difference and the large standard deviation indicate that this negative result may be caused by insufficient group size (type 2 error).

Intracellular levels

Erythrocyte magnesium levels were similar in patients with type 1 diabetes and controls [2]. In patients with type 2 diabetes, Paolisso et al. found lower erythrocyte levels [30,31], but Sjögren et al. did not [1]. These contradictory results may be related to the patients studied: the patients in the studies by Paolisso had mild type 2 diabetes and were not on insulin therapy, whereas some of the patients in the study by Sjögren were. High insulin

levels stimulate magnesium uptake in erythrocytes in a receptor-independent way [22], and insulin levels will be higher in insulin-treated patients than in non-insulin-treated patients. Striated muscle magnesium content is lowered in diabetic patients, but data are limited owing to the invasive procedure required to obtain tissue [1,2]. Experience with mononuclear leucocytes is likewise limited and without evidence that determinations provide more information than for instance the plasma magnesium concentration [1,25].

Finally, some observations have been made on free intracellular magnesium levels in erythrocytes with the NMR technique. Resnick et al. found decreased levels in type 2 diabetes patients with mild hyperglycaemia and without treatment [29]. Free intracellular magnesium correlated with the total plasma magnesium concentration. Similar results were found in patients with insulin resistance [32]. In patients with untreated essential hypertension, low free intracellular magnesium levels were inversely linked to both the diastolic and the systolic blood pressure and positively to insulin sensitivity [33]. It seems, therefore, that intracellular ionic changes are closely associated with the syndrome of insulin resistance, either as marker or as causal factor.

Pathogenesis of lower magnesium levels in diabetes

Hyperglycaemia and the resulting glycosuria have been traditionally linked to hypermagnesiuria, which in turn causes lower plasma magnesium concentrations and hypomagnesaemia. Glucosuria leads to osmotic diuresis and hypermagnesiuria by attenuating the transepithelial voltage difference in the loop of Henle [25,34,35]. Additional factors may contribute. Evidence from Djurhuus et al. has indicated that hyperinsulinaemia itself augments renal magnesium excretion [36]. Schmidt et al. have drawn attention to the possibility of insufficient amount of magnesium in the diet of patients with diabetes [37]. Finally, Garland has suggested that there may be a specific tubular defect in magnesium reabsorption in patients with diabetes since there is a disproportionate high urinary magnesium (and calcium) loss compared with monovalent ions [38].

Association between magnesium and pathophysiological phenomena

Glycaemic control

An inverse association between fasting glucose and magnesium levels has been observed in patients with non-insulin-treated type 2 diabetes [39]. Plasma magnesium levels were inversely related with HbA_{1c} levels but not with fasting glucose levels in type 1 diabetes [2,27]. In insulin-requiring type 2 diabetes, fasting plasma magnesium levels did not correlate with HbA_{1c} or fasting glucose levels [40]. Another way to assess this relation, circumventing inter-subject differences, is to measure daily glucose and magnesium profiles. These diurnal profiles of patients in a group of nine insulin-requiring patients with type 1 or type 2 diabetes showed a strong inverse association of plasma magnesium and glucose concentrations in seven [41]. The only two exceptions were two type 1 diabetes patients, one with very small fluctuations in the glucose concentrations, one with concurrent other endocrine disease. Therefore, some inverse association between plasma magnesium levels and glycaemic control seems reasonable to assume, irrespective whether this is a causal one and which of the two factors is the primary one.

Insulin sensitivity

The evidence for a positive relation between plasma magnesium concentration and insulin sensitivity comes from *in vitro* studies, animal experiments and clinical data. Theoretically, magnesium can modify insulin sensitivity by acting on insulin binding to the receptor, by influencing receptor activity after binding or by influencing intracellular signalling and processing. Suárez et al. have shown that binding to the insulin receptor in hypomagnesaemic conditions *in vitro* is normal [42], but that insulin receptor (tyrosine kinase) activity is decreased with associated reduced peripheral glucose uptake and glucose oxidation in rats [43]. Induced low intracellular magnesium levels are associated *in vitro* with reduced intracellular consequences of insulin action [44]. Magnesium supplementation can prevent fructose-induced insulin resistance in the rat

as well as reduce the development of spontaneous type 2 diabetes in the Zucker diabetic fatty rat [45,46]. Induction of hypomagnesaemia in healthy adults also leads to decreased insulin sensitivity [47]. In patients with type 2 diabetes a clear inverse association exists between the plasma magnesium concentration and the index of glucose removal after an intravenous glucose load [48]. Therefore, evidence points to an inverse association between plasma magnesium concentrations and insulin resistance, due to intracellular changes, in type 2 diabetes patients.

Additional information can be derived from population-based studies. A recent study in the USA has shown that the fasting plasma magnesium concentration was inversely related to the plasma glucose and insulin concentrations, also after exclusion of the small number of patients with clinically manifest diabetes [49]. When lower magnesium levels are the cause of higher insulin levels as a consequence of increased insulin resistance, this would provide a means of very early intervention with magnesium supplementation. Dietary magnesium intake was inverse related to the plasma insulin concentration in the study by Jing et al. [49]. An inverse association between dietary magnesium and insulin concentration was also observed in young healthy adults by Manolio et al. [50]. Magnesium intake may however be associated with intake of other minerals, fiber, fatty acids and other nutrients [51,52]. Results from the Nurses Health Study have shown that the risk of developing type 2 diabetes decreases with increasing dietary magnesium intake [53]. Therefore, magnesium supplementation seems to be able to favourably alter insulin sensitivity and prevent or retard the development of type 2 diabetes.

Retinopathy and nephropathy

McNair et al. were first to describe a lower mean plasma magnesium level in patients with either type 1 or 2 diabetes and severe background or proliferative retinopathy compared to patients with no or mild background retinopathy [25].

These findings were corroborated by Ceriello et al. [54]. In type 2 diabetes, patients without retinopathy had a higher mean plasma magnesium level than patients with background or proliferative retinopathy

[55]. A prospective study showed that in a group of patients with type 1 or insulin-requiring type 2 diabetes, the plasma magnesium level was inversely related to the development or progression of retinopathy [56]. With additional confirmation, these results warrant further studies to assess the possibility of prevention or postponement of retinopathy with oral magnesium concentration. The plasma magnesium concentration rises with diminishing renal function, beginning with a creatinine clearance of 30 ml/min [57]. Patients with micro-albuminuria or macro-albuminuria without a diminished creatinine clearance have similar plasma magnesium concentrations compared with normo-albuminuric patients [28,58,59].

Intervention studies with oral magnesium supplementation

Table 1 presents the various intervention studies that have been performed [30,31,60–67]. Several parameters of effect can be studied to assess the effect of magnesium supplementation on glucose and

insulin dynamics in patients with diabetes: glycaemic control, insulin requirement, insulin secretion and insulin sensitivity. Generally, an increase in plasma magnesium and erythrocyte magnesium concentrations was observed, but there is no consistent improvement in glycaemic control. In type 2 diabetes, magnesium supplementation both increases insulin secretion and insulin sensitivity; insulin secretion was determined after secretagogues [31], insulin sensitivity with the euglycaemic hyperinsulinaemic clamp technique [30]. Magnesium supplementation in nine patients with type 2 diabetes on diet showed that glucose removal and glucose oxidation increased at the same time that non-oxidative glucose removal and endogenous (hepatic) glucose production did not change [65]. A study performed in elderly subjects without diabetes showed that oral magnesium supplementation again increased glucose removal and glucose oxidation but left endogenous glucose production and non-oxidative glucose metabolism unchanged [68]. To this day, Sjögren et al. have done the only supplementation study in type 1 diabetes patients [66]. However, this was a non-randomised, non-placebo-controlled trial. With 500 mg Mg during

Table 1
Effect of magnesium supplementation in patients with diabetes mellitus

Study	Number of patients	Dose of Mg (mmol/day)	Duration of trial (weeks)	Parameters of effect
<i>IDDM</i>				
Sjögren et al. [66]	16	15	21	No change in HbA _{1c} , decrease in insulin requirement
<i>NIDDM</i>				
Nadler et al. [67] ^a	6	25	6	Decreased thrombocyte aggregability and decreased thromboxane production
<i>Diet/oral medication</i>				
Eibl et al. [61]	40	30	12	No change in HbA _{1c} , lipids or blood pressure
Paolisso et al. [30]	8	15	4	Decreased fasting glucose and improved insulin sensitivity
Paolisso et al. [31]	8	15	4	Decreased fasting glucose and improved insulin secretion
Paolisso et al. [65]	9	15	4	Improved glucose removal and improved glucose oxidation
Paolisso et al. [62]	10	15	10	Decreased thrombocyte aggregability
Parvis et al. [64]	28	16	6	No change in glycaemic control or lipids, decrease in systolic pressure
<i>Diet/oral medication/insulin</i>				
Nadler et al. [60]	20	15	12	Decreased thrombocyte aggregability
Gullestad et al. [63]	56	15	16	No change in glycaemic control, lipids or blood pressure
<i>Insulin</i>				
De Valk et al. [40]	50	15	12	No change in glycaemic control, lipids or blood pressure

^a Medication not detailed.

a 21-week period, insulin requirement fell without change in glycaemic control.

Some studies have shown that magnesium supplementation can reduce platelet aggregability [60,62]. This may be due to a relation between magnesium and prostaglandin synthesis: magnesium deprivation leads to increased thromboxane levels and increased platelet aggregability, whereas magnesium supplementation decreases thromboxane levels with the above-mentioned inhibition of platelet aggregation [47].

The relation between magnesium levels and insulin resistance would suggest that patients with associated lipid disorders, i.e. hypertriglyceridaemia and low HDL, may benefit from magnesium supplementation. Magnesium supplementation to patients with type 2 diabetes did not improve lipid levels in the studies addressing this problem [40,61,63,64]. Three intervention studies failed to show an effect of magnesium supplementation on blood pressure [61,63,64]. In one study a fall in diastolic blood pressure was observed that just failed to reach statistical significance [40]. In this study, as in the other intervention studies cited, it should be borne in mind that patient selection and group size was based on consideration about glycaemic control and not blood pressure. An intervention study in patients with type 2 diabetes has shown that salt restriction with potassium and magnesium substitution was associated with a fall in systolic pressure [69]. The design did not permit clarification which item is (most) responsible. Nevertheless, it seems still worthwhile to test the hypothesis that oral magnesium supplementation has a beneficial effect in patients with diabetes.

Discussion

A tendency for lower magnesium levels in blood and other tissues in patients with diabetes mellitus is well established. Poor glycaemic control with glucosuria and consequently hypermagnesiuria, hyperinsulinaemia-associated urinary magnesium excretion, inadequate nutrition, as well as perhaps a specific renal defect, may contribute to this phenomenon. It may be that patients with diabetes need a higher magnesium intake in view of the possibility of

repetitive and temporary tendency to urinary magnesium loss with hyperglycaemia and glucosuria. Although magnesium supplementation may improve insulin sensitivity and secretion, intervention studies in overt type 2 diabetes have failed to show improvement in glycaemic control. Great benefit may lie in the patient group with impaired glucose tolerance or beginning type 2 diabetes: improving insulin sensitivity by augmenting magnesium intake may decrease or retard the occurrence of these abnormalities in glucose metabolism.

All intervention trials have not been specifically aimed at testing the effect of oral magnesium supplementation on blood pressure. The results from two studies leave the hope alive that with specific patient selection, group size, and intervention medication, some effect may be observed [40,69]. The preliminary data on the relation between plasma magnesium concentration and retinal micro-vascular complications need to be explored since modification of magnesium homeostasis may offer a way to alter the course of disease.

The American Diabetes Association has issued a Clinical Recommendation on magnesium in diabetes [70]. This states that, pending new information on beneficial effect of magnesium supplementation, the plasma magnesium concentration should at least be determined in patients who are considered to be at risk for magnesium deficiency, like patients on thiazide and loop diuretics or patients with inadequate nutrition or alcohol abuse. There are a number of magnesium salts that can be used for oral supplementation; a dose of 15 mmol/day is well-tolerated and can also be given in three divided doses.

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