Diabetologia (1990) 33: 511–514

Diabetologia

Review

Magnesium and glucose homeostasis

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Summary. Magnesium is an important ion in all living cells being a cofactor of many enzymes, especially those utilising high energy phosphate bounds. The relationship between insulin and magnesium has been recently studied. In particular it has been shown that magnesium plays the role of a second messenger for insulin action; on the other hand, insulin itself has been demonstrated to be an important regulatory factor of intracellular magnesium accumulation. Conditions associated with insulin resistance, such as hypertension or aging, are also associated with low intracellular magnesium contents. In diabetes mellitus, it is suggested that low intracellular magnesium levels result from both increased urinary losses and insulin resistance. The extent to which such a low intracellular magnesium content contributes to the development of macro- and microangiopathy remains to be established. A reduced intracellular magnesium content might contribute to the impaired insulin response and action which occurs in Type 2 (non-insulin-dependent) diabetes mellitus. Chronic magnesium supplementation can contribute to an improvement in both islet Beta-cell response and insulin action in non-insulin-dependent diabetic subjects.

Key words: Magnesium, insulin, glucose homeostasis, diabetic complications, dietary magnesium supplements.

Magnesium homeostasis

Magnesium is one of the most abundant ions present in living organisms. It is distributed in three major compartments of the body: about 65% in the mineral phase of skeleton, some 34% in the intracellular space and only 1% in the extracellular fluid [1]. The levels of magnesium in the plasma of healthy people are remarkably constant, being on average 0.85 mmol/l and varying less than 15% from this value [2]. The distribution of normal values for serum or plasma magnesium is similar in men and women and almost one third is bound to plasma proteins. The remaining two-thirds, which is diffusible or ionized, appears to be the biologically active component [2]. As reviewed by Flatman [3] many cells keep their magnesium content well below electrochemical equilibrium, indicating that they possess an active magnesium transport system. This is also true for mitochondria. The source of energy for magnesium transport may be the coupling of magnesium exit to the obligatory entry of either sodium (as in the nerve or muscle cells), protons (as in mitochondria) or potassium (as in synaptosomes or pancreatic Beta-cells), which travel down their electrochemical gradients. In fact there is some evidence that a separate magnesium extrusion pump, driven by metabolic energy directly, does exist [4].

In normal man, daily magnesium intake should be between 240 and 480 mg to maintain an adequate magnesium balance. No single factor appears to play a leading role in the regulation of magnesium metabolism as does, for instance, vitamin D for calcium homeostasis [2]. Data collected from measurements performed in a large series of animal species have shown that the small intestine is the main site of magnesium absorption, but that the pattern of absorption varies with the species studied [5]. Most likely there is a common mechanism for the transport of calcium and magnesium across the small intestinal wall [5], a theory, however, that has been challenged [6]. Magnesium excretion is performed through renal pathways since an amount equivalent to one third of the daily magnesium intake is excreted through the kidney [2].

Magnesium balance appears to be regulated by different hormones known to affect magnesium transport. Among them, calcitonin [7] and parathormone [8] have long been thought to play a major role. Noradrenaline and adrenaline appear to have different effects depending upon the tissue considered, since they stimulate magnesium uptake by fat cells while they reduce magnesium uptake by cardiac muscle cells [2]. Insulin has also been suggested as a regulatory hormone of the magnesium balance. In fact, Lostroh and Krahl [9, 10] were the first

to demonstrate that insulin added in vitro promptly promotes a net increase in the accumulation of magnesium and potassium in uterine smooth muscle cells. These authors [9, 10] suggested that insulin, after interacting with its own receptor on the plasma membrane, can affect an ATPase pump increasing magnesium and potassium cellular entry. Recently reported data support an effect of insulin on magnesium transport. Indeed, during the course of an oral glucose tolerance test, a significant decline in plasma magnesium with a contemporary significant increase in erythrocyte magnesium levels does occur [11]. Such opposite changes in plasma and erythrocyte magnesium levels are also seen during the course of a euglycaemic hyperinsulinaemic glucose clamp [11]. Finally, in vitro investigations have shown that erythrocytes accumulate magnesium in the presence of glucose (5 mmol/l) and insulin (100 mU/l), an effect entirely abolished by ouabain, while glucose alone had no significant effect [11]. These in vivo and in vitro results thus suggest that insulin is an important modulator of intracellular magnesium content; furthermore, there are indications that, as in other energy producing system, an ATPase-dependent pump is involved in the mechanisms by which insulin regulates the erythrocyte magnesium content [11].

Magnesium deficiency in man

The existence of a state of magnesium deficiency has been doubted for many years. However, severe hypomagnesaemia is a well recognized clinical syndrome characterized by: a) muscular symptoms (spasmophilia, gross muscular tremour, ataxia, tetany); b) psychic disorders (agitation, confusion and hallucinations); and, c) cardiological signs (low-voltage T-wave at the ECG). Laboratory data (low serum magnesium levels associated with a normal serum calcium concentration and a normal blood pH) confirm the diagnosis. As recently reviewed by Reinhart [12], measurement of magnesium levels in the plasma or serum is the usual method for determining magnesium homeostasis. However, it is well known that there may be a dissociation between serum and intracellular levels of magnesium [13, 14] and that intracellular levels may indeed better reflect homeostasis. In this respect, erythrocytes or lymphocytes are frequently used while muscle biopsies or magnesium balance studies, although more sensitive indices of magnesium deficiency, are rarely performed [12].

Among all clinical conditions associated with a depletion of magnesium, the most important are: prolonged fasting, excessive losses by the gastrointestinal tract, surgical stress, acute alcoholism and cirrhosis. More recently, diabetes mellitus has been added to the list reported above. In fact, most authors agree that Type 2 (non-insulin-dependent) diabetic patients with poor metabolic control, rather than Type 1 (insulin-dependent) diabetic subjects, are more frequently affected by diabetes-related changes in plasma and erythrocyte magnesium levels [15–18].

Magnesium and insulin action

Numerous in vitro studies have pointed out the major role of magnesium in insulin action [9, 10, 19, 20]. Lostroh and Krahl [9, 10] suggested magnesium as a second messenger for insulin action. In fact, cellular magnesium deficiency is correlated to an impaired function of many enzymes utilising high energy phosphate bonds, which are involved in glucose metabolism, and require magnesium as a cofactor. Furthermore, Tonyai et al. [20] have demonstrated that a low erythrocyte magnesium content per se can increase membrane microviscosity and have suggested that this mechanism may impair the interaction of insulin with its receptor on the plasma membrane.

In vivo, Moles and McMullen [21] have suggested that hypomagnesaemia may contribute to the insulin resistance observed during the treatment of diabetic ketoacidosis, while Durlach and Rayssiguer [22] reported that chronic magnesium deficiency contributes to reduce insulin sensitivity.

Recent studies have also shown that aging and essential hypertension, two classic conditions associated with insulin resistance [23–25], are also associated with an impaired insulin-mediated accumulation of magnesium into erythrocytes. In essential hypertension [26], a significant reduction in plasma and erythrocyte magnesium levels and a reduced erythrocyte magnesium uptake response to incubation in the presence of insulin and high extracellular magnesium levels have been reported; these abnormalities were associated with an increase in erythrocyte membrane microviscosity. It was suggested that changes in the physical state of the plasma membrane as well as in insulin sensitivity were co-responsible for the lower erythrocyte magnesium level found in these patients. In aging [27], the reduced erythrocyte magnesium content was explained on the grounds of the well known insulin-resistant state frequently observed in this condition [23, 24]. The extent to which changes in plasma membrane liquid composition, which frequently occur and impair the interaction of insulin with its receptor in the elderly [28], also contribute remains an open question.

Magnesium and diabetes mellitus

In 1971, Londono and Rosenbloom [29] were the first to demonstrate, in diabetic children, that a glucagon injection induced a significant decline in plasma magnesium and calcium levels. Subsequently, Rosenbloom [30] observed that the decline in plasma magnesium and calcium levels observed during the course of an oral glucose tolerance test was less in children and adolescents with prediabetes mellitus than in healthy control subjects; he concluded that abnormalities in calcium and magnesium handling may occur very early in the course of the development of diabetes mellitus. In 1979, Mather et al. [15] used atomic absorption spectrophotometry to measure plasma magnesium levels in 582 unselected diabetic outpatients and 140 control subjects and observed that mean plasma magnesium levels were significantly lower in the diabetic patients than in the control subjects, while 25% of

the patients had values below those found in all control subjects. Furthermore they showed that, in diabetic subjects, plasma magnesium levels were inversely correlated with metabolic control and directly correlated with plasma albumin levels. Vanroelen et al. [17], and more recently Sjögren et al. [18], have confirmed the high prevalence of hypomagnesaemia in non-insulin-dependent diabetic patients.

The inverse relationship between metabolic control and plasma magnesium levels in diabetic patients has been attributed to increased magnesium urinary losses. Such a mechanism has been investigated by McNair et al. [31] who studied 215 insulin-treated diabetic outpatients aged 7–70 years. These authors reported the occurrence of a definite hypomagnesaemia (below 2 SD of the normal mean) and hypermagnesuria (above 2 SD of the normal mean) in 38.6% and 55% of the patients respectively. They also observed that, in the presence of hypomagnesaemia, the magnesium plasma levels were inversely correlated to the urinary magnesium excretion rate and also to fasting blood glucose values. They concluded that the net tubular reabsorption of magnesium was decreased when severe hyperglycaemia was present. The existence of a close relationship between metabolic control and impaired magnesium balance was confirmed by Fuji et al. [16] who analysed magnesium levels in the plasma, erythrocytes and urine of diabetic patients divided in three groups on the basis of the aspect of their retinal fundi. They observed that a marked depletion in plasma and erythrocyte magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor metabolic control. However, in a recently published study, Ponder et al. [32] reported that the mean urinary magnesium-creatinine ratio was significantly elevated in 220 conventionally treated children with insulin-dependent diabetes compared to 33 healthy non-diabetic siblings; in that study increased losses of magnesium were present even when glycaemic control was considered to be good. These authors concluded that children with insulin-dependent diabetes could be at risk of mineral deficiencies (including magnesium) in the absence of intensive insulin management.

The possible role of magnesium in the development of macro- and microangiopathy has been the subject of several studies. Seelig and Heggtveit [33] and Mather et al. [34] suggested that magnesium can prevent the development of atherosclerotic disease by counteracting the adverse effect of excessive intracellular calcium, retaining intracellular potassium and contributing both to stabilizing plasma membrane and maintaining the integrity of subcellular structures. The negative correlation between a poor erythrocyte magnesium content and the severity of macroangiopathy has been confirmed by Vanroelen et al. [17]. The possibility that magnesium may play a role in the prevention of atherosclerosis is further supported by the finding that chronic magnesium administration decreases collagen and ADP-induced platelet aggregability in non-insulin-dependent diabetic subjects [35].

If many studies have been performed in diabetic patients in an attempt to correlate hypomagnesaemia and reduced erythrocyte magnesium content with metabolic control and development of complications, only a few investigations have dealt with a possible role of a low intracellular magnesium content in the pathophysiology of non-insulin-dependent diabetes mellitus. In fact, one can consider that a low intracellular concentration of magnesium can be both a consequence or a cause of insulin resistance. The relationship between insulin resistance and low intracellular (erythrocyte) magnesium content has been recently studied in a series of 12 non-insulin-dependent diabetic patients [36]. It was observed that the net insulin-mediated increase in erythrocyte magnesium accumulation was inversely correlated with basal plasma insulin levels and body mass index and directly correlated with the Conard's K value after intravenous glucose injection and with the glucose infusion rate calculated in the last 60 min of a euglycaemic hyperinsulinaemic glucose-clamp. Moreover, the in vitro dose-response curve correlating the amount of insulin to the erythrocyte magnesium accumulation was shifted to the right and did not achieve the same maximal effect when erythrocytes of non-insulin-dependent diabetes patients were compared to those of healthy subjects. As for glucose transport [37], this observation suggests that a post-receptor defect is responsible for the impaired insulin-mediated transport of magnesium in non-insulin-dependent diabetic subjects.

These observations prompted a study of the effects of dietary magnesium supplements (3 g/day for 3 weeks) in non-insulin-dependent diabetic patients in whom insulin secretion and action were determined. The results of these studies showed that glucose- and arginine-induced insulin secretion as well as insulin sensitivity were significantly improved by chronic magnesium supplementation [38, 39].

These data, which confirm those previously reported in rats by Legrand et al. [40] might be explained by in vitro studies which have shown that magnesium uptake at the islet Beta-cell level is increased or decreased by agents known to respectively stimulate or inhibit insulin biosynthesis [40]. Moreover, a direct influence of magnesium cannot be excluded, since in vitro variation of extracellular magnesium can modulate both the intracellular potassium and Beta-cell response to glucose [41]. As far as insulin sensitivity is concerned, the slight but significant improvement of this parameter was related to the major regulatory role played by magnesium as a cofactor of many enzymes involved in glucose metabolism (see above).

In conclusion, the results briefly reported here underline the important role played by magnesium in the life of mammalian cells. Moreover, several recent studies on magnesium balance and glucose homeostasis have focused our attention on the potential risks of a poor intracellular magnesium content in diabetic patients as well as on the benefits that patients can get from magnesium supplementation in terms of both insulin secretion and insulin sensitivity.

Acknowledgement. We acknowledge the expert secretarial assistance of Mrs. E. Vaessen-Petit.

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