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## **Magnesium Metabolism in Insulin Resistance, Metabolic Syndrome, and Type 2 Diabetes Mellitus**

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Magnesium plays a key role in regulating insulin action, insulin-mediated glucose uptake, and vascular tone. Intracellular magnesium depletion may result in a defective tyrosine-kinase activity at the insulin receptor level, in a postreceptorial impairment in insulin action, and clinically in a worsening of insulin resistance. Intra- and extracellular alterations of magnesium metabolism have been identified in clinical states characterized by insulin resistance, such as metabolic syndrome, hypertension, altered glucose tolerance, type 2 diabetes, and aging. Several studies, from our and other's groups, have confirmed the clinical relevance of alterations of magnesium homeostasis in these conditions and have highlighted the importance of an accurate definition of the magnesium status. While measurements of total serum magnesium levels have been proven inadequate for this purpose because important magnesium depletions are required before total serum level decreases, two technologies,  $^{31}\text{P}$  nuclear magnetic resonance ( $^{31}\text{P}$ -NMR) spectroscopy and magnesium-specific ion-selective electrodes, that, respectively, measure intracellular and extracellular free levels of magnesium, have a higher sensitivity in detecting magnesium deficits. A number of evidences have confirmed that magnesium supplementation is indicated in conditions associated with magnesium deficit, although well-designed therapeutic trials with oral magnesium supplements to study the beneficial effects in metabolic syndrome and in type 2 diabetes are needed.

An increasing number of evidences have suggested a clinical relevance for the altered magnesium (Mg) metabolism present in states of increased peripheral insulin resistance. As discussed below, we have suggested a role for Mg deficit as a possible unifying mechanism of the insulin resistance of hypertension and conditions associated with altered glucose tolerance, including metabolic syndrome and type 2 diabetes mellitus.<sup>1</sup> Our group has used a ion-based approach to demonstrate: (1) the critical importance of Mg metabolism in regulating insulin sensitivity, as well as vascular tone and blood pressure homeostasis; (2) that Mg deficiency, defined on the basis of intracellular free magnesium levels (Mgi), and or serum ionized magnesium (MgI) is a common feature of insulin resistant-states, as well as various cardiovascular and meta-

bolic processes and aging; (3) the ability of environmental factors such as dietary nutrient sugar and mineral content to alter the set point of steady-state cell ion activity.<sup>2,3</sup>

## Magnesium and Glucose Metabolism

Magnesium is the second most abundant intracellular cation (after potassium) present in living cells and its plasma concentration is remarkably constant in healthy subjects. Ninety-nine percent of Mg is distributed in the intracellular fluid, and 1% is distributed in the extracellular fluid. The levels of Mg in the plasma of healthy people are remarkably constant, being on average 0.85 mmol/L and varying less than 15% from this value. Circulating Mg exists in three forms: a protein-bound fraction (25% bound to albumin and 8% bound to globulins), a chelated fraction (12%), and the physiologically active ionized fraction (MgI, 55%).<sup>4</sup> Because Mg is predominantly an intracellular ion, and in the serum only the ionized active form is metabolically available, its total serum concentrations (MgT) may not reflect the Mg status or intracellular pool, and intracellular Mg depletion can be seen with normal MgT concentrations.<sup>5-8</sup>

Magnesium is directly involved in numerous important biochemical reactions, and particularly is a necessary cofactor in over 300 enzymatic reactions and specifically in all those processes that involve the utilization and transfer of adenosine triphosphate (ATP). Thus, intracellular Mg is a critical cofactor for several enzymes in carbohydrate metabolism, and because of its role as part of the activated Mg-ATP complex required for all of the rate-limiting enzymes of glycolysis, regulates the activity of all enzymes involved in phosphorylation reactions. Intracellular free magnesium concentration is critical in the phosphorylation of the tyrosine-kinase of the insulin receptor, as well as all other protein kinases, and all ATP and phosphate transfer-associated enzymes, such as the CaATPases in plasma membrane and endoplasmic reticulum. Magnesium deficiency may result in disorders of tyrosine-kinase activity on the insulin receptor, an event related to the development of a of postreceptorial insulin resistance and decreased cellular glucose utilization<sup>9</sup>; that is, the lower the basal Mgi, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity. Specifically, in skeletal muscle and fat tissue, insulin resistance would be the expected outcome in the presence of suppressed cellular Mg. Significant decrements in these enzyme activities can already be observed at the range of Mg values seen in disease states such as type 2 diabetes and hypertension.<sup>10</sup>

## Diagnostic Tools Available to Define Magnesium Status of Magnesium-Deficient Subjects

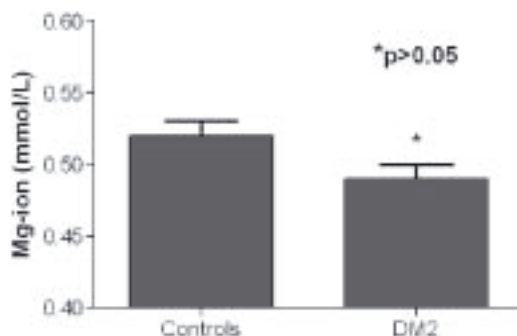
One of the principle reasons Mg metabolism has not become more the focus of routine attention in clinical practice has been the absence of an easily available, accurate, and reproducible measure of Mg status. Measurements of MgT

levels, which includes the protein-bound, chelated, and ionized fractions, that are the clinical measurement routinely used for assessing circulating Mg are not useful, and have been proven inadequate for this purpose because important Mg depletion is required before its total serum levels decrease.<sup>5,11</sup> Two technologies, <sup>31</sup>P-NMR spectroscopy and Mg-specific ion-selective electrodes (ISE), that measure Mgi and extracellular MgI, respectively, are a major advance in this regard, and have a higher sensitivity in detecting Mg deficits. This is because MgT levels are a late marker of a depletion of Mg stores (the complexed serum MgT is the last store to be depleted when an already important Mg depletion has occurred), while the declines in ionized unbound MgI may occur significantly earlier. While <sup>31</sup>P-NMR techniques are a research-based test because of the expenses in setting up and maintaining the NMR equipment, the development of a Mg-selective electrode apparatus may be particularly useful in routine clinical use. Using these techniques, a deficiency of intra- and ionized extracellular Mg levels have been consistently demonstrated in diabetes, often when MgT levels were within normal limits,<sup>5</sup> and significant relationship have been found with blood pressure, and cardiovascular and metabolic parameters.<sup>3</sup> From the intracellular point of view, these relations appear to be continuous, and do not display a threshold value within the range of clinically observable cellular free Mg levels, that is, the lower the free Mgi, the stiffer the blood vessels, the higher the blood pressure, the greater the insulin resistance, etc.<sup>1,3,12</sup>

## Magnesium Deficiency in Type 2 Diabetes Mellitus and Metabolic Syndrome

The presence of a Mg deficit in diabetic patients has long been recognized.<sup>13,14</sup> Epidemiological studies have found a high prevalence of hypomagnesaemia in subjects with diabetes, especially in those with poor glycemic control.<sup>15,16</sup> Because of the lack of sensitivity of serum total MgT, a suppressed level of intracellular Mgi and serum ionized MgI can be found in many subjects with total serum MgT still in the normal range (see above). Using the Nova-8 Mg ISE to measure serum ionized Mg in a preliminary sample of 50 subjects with type 2 diabetes, we have recently found significantly lower MgI levels compared to normal controls ( $0.49 \pm 0.01$  mmol/L vs.  $0.52 \pm 0.01$  mmol/L,  $p < 0.05$ ), without significant changes in MgT (Figure 17.1). When MgI and Mgi levels were measured concurrently in the same subjects using <sup>31</sup>P-NMR and the ISE Mg-selective electrode, Resnick and colleagues found that both Mgi and MgI (but not serum total MgT) were significantly reduced in type 2 diabetes subjects, and that a close direct relationship was present between the ionized extra- and the intracellular Mg measurement.<sup>5</sup>

Low dietary Mg intake and increased Mg urinary losses<sup>17-19</sup> are the main causes of the Mg deficit in diabetic subjects. The use of loop and thiazide



**FIGURE 17.1.** Ionized Mg levels (MgI, mmol/L) in type 2 diabetic subjects versus normal controls.

diuretics, which promote Mg wasting, may worsen Mg depletions. A Mg-deficient diet has been found to be associated with a significant impairment of insulin-mediated glucose uptake.<sup>20</sup> Hyperglycemia and hyperinsulinemia may have a role in the increased urinary Mg excretion, thus contributing to Mg depletion, and the reduced sensitivity to insulin may affect Mg transport.

Magnesium deficiency, which may take the form of a chronic latent Mg deficit rather than clinical hypomagnesemia, may have clinical importance because of the crucial role of Mg as a cofactor in many enzymatic reactions regulating glucose metabolism. A deficient Mg status may not just be a secondary consequence of diabetes, but experimental and epidemiological data suggest that it may precede and cause insulin resistance and altered glucose tolerance, and even type 2 diabetes.<sup>21</sup> However, independent to the cause of poor plasma and intracellular Mg content, a depletion of Mg seems to be a cofactor for a further derangement of insulin resistance.<sup>1,22</sup>

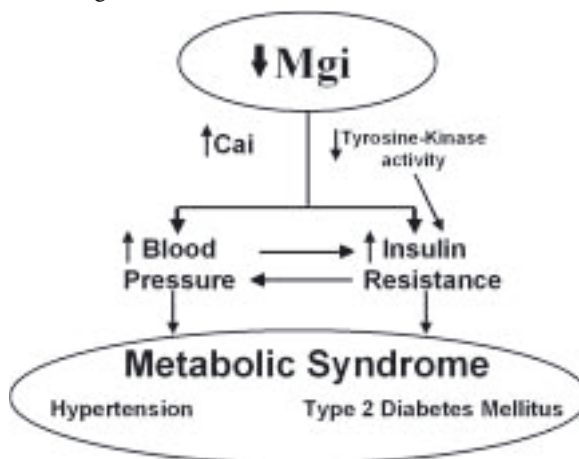
At the cellular level, using gold-standard NMR techniques, our group have shown lower steady-state Mgi and reciprocally increased Cai levels in subjects with type 2 diabetes mellitus, compared with young nondiabetic subjects.<sup>23–25</sup> We have recently extended our experience with NMR technique to study cytosolic free Mg directly in situ, in vivo, and in human living tissues, such as muscle and brain, and have shown that in living tissues Mgi values are quantitatively and inversely related to both systolic and diastolic blood pressures.<sup>26</sup>

Intracellular free magnesium levels quantitatively predict the fasting and postglucose levels of hyperinsulinemia, as well as peripheral insulin sensitivity. Specifically, (1) fasting insulin levels<sup>27</sup>; (2) the integrated insulinemic response to a standard oral glucose tolerance test<sup>28</sup>; (3) the steady-state plasma glucose response to insulin infusion; and (4) indices for peripheral insulin sensitivity derived from euglycemic hyperinsulinemic clamps, are all inversely related to Mg levels, whether measured as Mgi in situ in brain, free or total Mg in peripheral red cells,<sup>21,29,30</sup> or even as circulating Mg.<sup>31,32</sup> Furthermore, direct and inverse relations, respectively, are observed between Mgi and Cai levels and HbA1c, fasting blood glucose, and the glycemic response to oral glucose loading in normal, hypertensive, and diabetic subjects.<sup>33</sup>

## Aging, Insulin Resistance, and Magnesium

Old age is frequently associated with insulin resistance and glucose intolerance. We have specifically studied the behavior of ion content with age and have shown a continuous age-dependent fall of Mgi levels in peripheral blood cells of healthy elderly subjects,<sup>25</sup> these alterations being indistinguishable from those occurring, independently of age, in essential hypertension or diabetes.<sup>25</sup> In other terms, essential hypertension and/or type 2 diabetes appear to determine an acceleration of natural age-dependent Mg depletion, suggesting that these ionic changes may be clinically significant, underlying the predisposition in elderly subjects to cardiovascular and metabolic diseases, and might therefore help to explain the age-related increased incidence of these diseases. At the same time, the naive concept of both hypertension and type 2 diabetes as diseases of accelerated vascular aging may be more literally true than previously thought, because both of these diseases display these same ionic changes at all ages. Thus, having these conditions is ionically the same as getting older, for example, a 48-year-old diabetic having cellular ionic alterations indistinguishable from a healthy 84-year-old, suggesting a role for Mg deficit in the increased incidence of hypertension and glucose intolerance with age.<sup>2,25</sup>

Altogether, this accumulating evidence of the relevance of altered cellular Mg metabolism to tissutal insulin sensitivity suggests a critical role of Mg metabolism in contributing to the clinical coincidence of Mg depletion to states of insulin resistance, such as hypertension, metabolic syndrome, type 2 diabetes, as well as the increased incidence of each of these conditions with age, a condition itself characterized by a tendency to intracellular Mg depletion. Thus, pathophysiologically, Mgi depletion can directly promote tissutal insulin resistance and altered vascular tone, thus helping to understand the mechanisms underlying the clinical association among these apparently different conditions (Figure 17.2).



**FIGURE 17.2.** Overall hypothesis in which intracellular Mg deficiency may mediate the relationship between insulin resistance, hypertension, and type 2 diabetes mellitus.

## Insulin and Glucose Acute Effects on Dynamic Changes of Cellular Magnesium

Although these data suggest that cellular free ion content may determine clinically relevant biologic outcomes such as blood pressure, cardiac mass, and cellular insulin responsiveness,<sup>2</sup> it is also concomitantly true that metabolic and dietary factors have a role in contributing to insulin sensitivity and in regulating intracellular ion metabolism. Thus, dietary salt<sup>34</sup> or sugar loading allowed us to assess the role of different dietary circumstances in regulating blood pressure and cellular ion metabolism. Specifically, the transient hyperglycemia of oral glucose loading reproduces in normal subjects the same altered ionic profile of depleted Mgi/increased Cai levels that occurs chronically in diabetic subjects,<sup>27</sup> which dynamically appears to be equally and inversely true for serum ionized Mg. The contribution of hyperglycemia and hyperinsulinemia to the intracellular Mg depletion of diabetes has been confirmed by in vitro studies from our group showing that both glucose and insulin may, in turn, alter Mgi levels. Thus, glucose in a specific, concentration- and time-dependent manner, at concentrations achieved clinically, and independent of insulin lowered Mgi and reciprocally elevated Cai.<sup>35</sup> Barbagallo and colleagues reported that hyperglycemia also alter ionic content in cultured vascular smooth muscle cells, suggesting an ionic mechanism for the increased vasoconstriction present in chronic diabetic states.<sup>36</sup> This glucose-mediated effects are independent of insulin action, because hyperglycemia induces these changes both in vascular smooth muscle cells, and in erythrocytes, where glucose transport is unaffected by insulin.<sup>35,37,38</sup> Among its many actions, insulin has specific ionic effects to stimulate the transport of Mg from the extracellular to the intracellular compartment, thus increasing Mgi content.<sup>39</sup> Using NMR techniques to measure Mgi, we have shown that the ionic action of insulin is specific, dose-related, and independent of cellular glucose uptake. Insulin in the incubation medium was able to induce an accumulation of Mgi which shifted from a basal values of  $177 \pm 11$  mmol/L to  $209 \pm 19$  mmol/L.<sup>39</sup> The ionic effects of insulin were time and dose dependent. In the dose-response study, the dose of insulin at which we observed these ionic effects started at  $10 \mu\text{U/mL}$  and peaked at  $200 \mu\text{U/mL}$ , this dose corresponding roughly to the maximal physiological response in humans, adding to the physiological relevance of this effect. Such results further suggest that insulin is an important modulator of intracellular Mg content; furthermore, there are indications that, as in other energy producing systems, an ATPase-dependent pump is involved in the mechanism by which insulin regulates the erythrocyte Mgi content.

The overall hypothesis that Mgi content is a crucial determinant of cellular responsiveness is supported by other data from our group showing that the ability of insulin at physiologically maximal concentrations to stimulate Mgi is impaired in cells from hypertensive individuals, in which the basal Mgi

content is reduced,<sup>21</sup> confirming that insulin action is strictly dependent from the cellular Mgi content; for all subjects, independently of their designation as normotensive or hypertensive, cellular Mgi responsiveness to insulin was closely and directly related to basal cellular Mgi levels; that is, the lower the basal Mgi, the less responsive was the cell to insulin. Furthermore, a blunting of Mgi responses to insulin could be reproduced in normal cells that were Mg depleted by prior treatment either with A23187 in a calcium-free medium or with high glucose concentrations (15 mmol/L).<sup>40</sup> Once again, insulin responsiveness followed basal Mgi levels ( $r = 0.637$ ). Altogether, these data demonstrating ionic aspects of cellular insulin resistance has led us to hypothesize that the insulin resistance, currently defined by measurements of tissue glucose uptake, might equally well be defined on the basis of altered cellular ion responsiveness. Similar cellular behavior was found in cell responsiveness to glucose action. As was the case for insulin the lower the Mgi, the less responsive is the cell to glucose.<sup>37</sup> Thus, this ionic insulin resistance is probably not specific for insulin, but may rather be one tissue manifestation of a general property of cells in which steady-state Mgi and/or Cai level may determine cell responsiveness to insulin, glucose, or to other external stimuli. It is possible to hypothesize therefore, that the insulin resistance of hypertension and diabetes, currently defined by measurements of tissue glucose uptake, might equally well be defined on the basis of altered cellular ion responsiveness (Figure 17.2).

The link between Mg deficiency and the development of insulin resistance and type 2 diabetes is strengthened by the observation that several treatments for diabetes appear to increase Mg levels. Metformin, for example, raises Mg levels in the liver. Pioglitazone, a thiazolidinedione anti-diabetic agent that increases insulin sensitivity, increases free Mg concentration in adipocytes.<sup>41</sup> Other research of our group have demonstrated that the action of the insulin mimeting substances vanadate and IGF-1 are both associated to a direct effect to stimulate intracellular free Mg levels,<sup>42</sup> and that the effects of antioxidants glutathione and vitamin E to improve glucose and insulin metabolism may derive at least in part from their action on Mg metabolism. Barbagallo and coworkers demonstrated that the action of glutathione and vitamin E to increase insulin sensitivity in hypertensive subjects is associated with a concurrent increase in Mgi, and that a significant direct relationship between glucose disposal increase and Mgi levels was present.<sup>29,30</sup>

## Is Providing Oral Magnesium Supplementation Effective in Reversing the Magnesium and Clinical Abnormalities?

The effects of Mg supplements on the metabolic profile of type 2 diabetic subjects are still controversial,<sup>43</sup> benefits having been found in some,<sup>44-46</sup> but not all, clinical studies.<sup>47-49</sup> Differences in baseline Mg status and metabolic control may explain the differences among these studies. Thus, a recent clinical trial



specifically conducted among diabetic subjects with low total serum Mg levels (index of an already advanced Mg deficit) found a beneficial effect of oral Mg supplementation on fasting and postprandial glucose levels and insulin sensitivity<sup>43</sup> and we have shown an improvement in insulin-mediated glucose uptake measured by euglycemic insulin clamp in diabetic subjects after oral Mg supplementations.<sup>21</sup> A significant relationship was found between the increase in plasma and erythrocyte Mg concentration and the parallel progressive increase in the insulin sensitivity in diabetic patients that were supplemented with increased dosage of Mg supplements (5.1–11.5 mmol of elemental Mg).<sup>21</sup> Among nondiabetic, apparently healthy subjects, there are also some evidences of a relatively small but significant beneficial effects of Mg supplements on insulin sensitivity.<sup>32,50</sup> Recent epidemiological data have showed a significant inverse association between Mg intake and diabetes risk supporting the priority of Mg deficit in the development of glucose intolerance and diabetes.<sup>51</sup> Thus, taking into account that both dietary Mg and serum plasma Mg content have been associated with an increased risk to develop glucose intolerance and diabetes,<sup>13</sup> the use of Mg supplements could be an alternative tool for the prevention of type 2 diabetes,<sup>52</sup> a hypothesis that needs to be confirmed by specific and well-designed trials with Mg that are needed in the near future.<sup>21,53</sup>

Altogether, with the recent advances in the accurate measurement of intracellular and extracellular Mg levels, we have now the tools to translate what is known of the critical importance of Mg in glucose and insulin metabolism into clinical practice, both in routinely monitoring Mg status and in the therapeutic use of Mg supplementation in those conditions and those subjects in whom Mg deficiency can be demonstrated.

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