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Cellular magnesium as a regulator of glucose homeostasis and insulinmediated signaling and cellular metabolism

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Abstract

The last thirty years have registered a progressive and dramatic increase in the incidence of obesity and type 2 diabetes mellitus world-wide. Metabolic Syndrome, one of the most commonly conditions associated with obesity and insulin resistance, has also increased considerably. The latest releases from the WHO estimate that approximately 1 billion people worldwide are obese, and more than 500 million are diabetic or pre- diabetic. Interestingly, increasing evidence suggest that our current western diet is hypercaloric but hyponutritive, as it is lacking essential micronutrients and minerals. Our laboratory has focused on the possible role of reduced cellular magnesium levels in the dysregulation of cellular and systemic glucose homeostasis. Experimental data obtained in animal and cellular models, including cells of human origin support the conclusion that cellular magnesium regulates transmembrane glucose transport as well as its utilization, and neosynthesis in gluconeogenic tissues, by modulating the activity of specific cellular enzymes and insulin-mediated signaling. Regardless of the tissue considered, decreased cellular and serum magnesium levels impact the proper operation of Glut 4, and Glut 2 transporters, thus limiting the ability of tissues like heart, muscles, liver, and possibly beta-islets, to effectively transport glucose into the cell to support glycolysis, ATP production, and ultimately storage as glycogen. As a consequence, gluconeo-genesis becomes erroneously activated, further enhancing the circulating levels of glucose and resulting in the dysregulation of fatty acids, cholesterol, and protein degradation, to support gluconeogenic activity through increased cortisol production and insulin resistance. Also, decreased cellular magnesium levels appear to contribute directly to increased basal inflammation within tissues, further impairing insulin responsiveness and systemic metabolic homeostasis. Altogether, our results argue for the necessity to better understand the role that micronutrients play in modulating both organ- specific and systemic metabolism and inflammation, to ultimately identifying more effective therapeutic and dietary approaches. A chronic latent Mg deficit or an overt clinical hypomagnesemia is common in patients with type 2 diabetes, especially in those with poorly controlled glycemic profiles. Insulin and glucose are important regulators of Mg metabolism. Intracellular Mg plays a key role in regulating insulin action, insulin-mediated-glucose-uptake and vascular tone. Reduced intracellular Mg concentrations result in a defective tyrosine-kinase activity, postreceptorial impairment in insulin action and worsening of insulin resistance in diabetic patients. A low Mg intake and an increased Mg urinary loss appear the most important mechanisms that may favor Mg depletion in patients with type 2 diabetes. Low dietary Mg intake has been related to the development of type 2 diabetes and metabolic syndrome. Benefits of Mg supplementation on metabolic profiles in diabetic patients have been found in most, but not all clinical studies and larger prospective studies are needed to support the potential role of dietary Mg supplementation as a possible public health strategy in diabetes risk. The aim of this review is to revise current evidence on the mechanisms of Mg deficiency in diabetes and on the possible role of Mg supplementation in the prevention and management of the disease. Diabetes is frequently associated with Mg deficit. The fact that most but not all diabetic subjects have low magnesium (Mg) and that no large randomised controlled trial (RCT) has been specifically focused on subjects with Mg deficit, diagnosed with a reliable technique, may help explain discrepancies of the role of supplemental Mg on glycemic control, and the impact on diabetes risk in prospective epidemiological studies. Different baseline Mg, metabolic control, and age are other potential factors that may contribute. Future prospective RCTs are needed to support the potential role of dietary Mg supplementation as a possible public health strategy to reduce diabetes risk in the population.

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