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Role Of Magnesium In The Regulation Of Type 2 Diabetes

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Abstract
Magnesium is an important mineral very essential for glucose homeostasis and insulin sensitivity. Magnesium is involved in reactions like kinases, protein synthesis, oxidation and insulin secretion. Magnesium is an intracellular cation plays a role in physiological and biological process like regulating insulin action, insulin mediated glucose uptake. Hypomagnesemia leads to tyrosine kinase activity impairment in insulin receptor levels leads to defective insulin action, insulin resistance and oxidative stress in type 2 DM and further development of chronic condition like heart diseases, macrovascular defects like stroke, myocardial infarction and peripheral artery diseases, microvascular defects like nephropathy, neuropathy and retinopathy. The Homeostasis of magnesium is highly regulated by absorption in the intestine, storage of bone and renal excretion. The observation of this review is serum magnesium levels strongly correlated to glycemic control and recommends monitoring serum magnesium levels in type 2 diabetes and supplementation should be considered in the management of diabetes.

Keywords: Hypomagnesemia, Type 2 Diabetes mellitus, Metabolic Syndrome.

Introduction

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycemia, defect with carbohydrate metabolism caused by either a deficiency in insulin secretion from pancreas, a failure of cells to respond effectively to insulin or a combination of both factors. [1] Type 2 Diabetes mellitus (T2DM), before called non-insulin-dependent diabetes mellitus, is the most common type of diabetes, recording for approximately 90% of these cases worldwide. [2] Both insulin resistance and impaired insulin secretion gradually disrupt metabolic process leading rearrangement of carbohydrate, lipid and protein metabolisms. [3] In 2024, it is estimated that 589 million adults aged 20-79 were living with diabetes and this number is projected to increase significantly, reaching about 853 million by 2050 worldwide. According to the estimates, the number of adults aged 20-79 with diabetes is projected to rise from approximately 89.8 million to about 156.7 million by 2050 in India. [4]

Magnesium (Mg^{2+}) second most abundant intracellular cation after potassium and it is the fourth most abundant cation in the human body. Approximately 60% of Mg^{2+} stored in bones providing structural support and mineralization. About 40% found in soft tissues, where it participate various metabolic activities. Only about less than 1% of Mg^{2+} circulates in the blood. Mg^{2+} functions as a vital cofactor for hundreds of enzymatic reactions, interact enzymes by serving structural or catalytic component and also influences substrates involved in these reactions. The prime role of Mg^{2+} is stabilizing the Mg-ATP complex, which crucial for kinases-enzymes that transfer phosphate group. Because of this, Mg^{2+} is considered regulatory factor many enzymes involved in the carbohydrate metabolism and energy production. Moreover Mg^{2+} plays an essential role intermediary metabolism, supporting the synthesis of macromolecules nucleic acid, lipids, proteins and carbohydrates to ensure the and facilitating overall cellular function and growth.[5] Mg^{2+} helps regulate the excitation-contraction coupling in muscles, ensuring proper contraction and subsequent relaxation, it is contributes to maintaining nerve stability and conduction supporting nervous system and plays a role in facilitating the release of neurotransmitters.[6] The aim of this review is to propose insights into the Mg^{2+}

consumption, homeostasis, supplementation, mechanism, deficiency connected to type 2 diabetes mellitus.

Homeostasis of Magnesium

The adult daily recommended intake for Mg^{2+} is 420 mg for men and 320 mg for women.[7] Foods rich in Mg^{2+} include peas, beans, spinach, nuts, whole-grain cereals, leafy vegetables and seeds.[8] Homeostasis of Mg^{2+} is maintained by intestine, bone and kidney by absorption, storage and excretion respectively.[9] The absorption of Mg^{2+} primarily take place in the small intestine of ileum and jejunum by enterocytic pathway depends on electrochemical gradient.[10] The secondary absorption of Mg^{2+} takes place at the large intestine by transcellular pathway using the transient receptor potential metastatin (TRPM) which is an cation receiving channels.[11] After absorption of Mg^{2+} enter into the blood stream and the fate decided by serum it's concentration. The reference range of Mg^{2+} in the serum is 1.2 -2.3 m.Eq/L.[12] Mg^{2+} is then distributed entire the body and mainly stored in bone as a major pool. Resorption of Mg^{2+} takes place in the bone while required. The reabsorption of Mg^{2+} takes in the kidney. [13]

Mg^{2+} Deficiency

Mg^{2+} deficiency occurs in insufficient dietary supplement, intestinal absorption defects, increased urinary output.[14] Most of the lab investigations regularly to estimate Mg^{2+} status in regular clinical practice is magnesemia due to easy availability and cost effective.[15] Serum Mg^{2+} levels represent the magnesemia actually tissue pools like intracellular content of Mg^{2+} higher side.[6] For this reason Mg^{2+} deficiency is misjudged electrolyte imbalance.[16] Mg^{2+} content is only 1% of total Mg^{2+} in the human body and can't represent for entire intracellular status of Mg^{2+} for this basis deficiency underestimated for years. [17] Hypomagnesemia is as well connected with mechanisms of molecular level with use of medications such as diuretics, receptor inhibitors of epithermal growth factor, calcineurin inhibitors, cisplatin and antibiotics. Usage of proton pump inhibitors certain medical conditions and abuse of alcohol results in Mg^{2+} deficiency. [18, 19] Hypomagnesemia reported in conditions like depression, fatigue, muscle spasms and arrhythmias and prolonged low levels Mg^{2+} standing associated with osteoporosis and sarcopenia. [20, 21] Rigorous Mg^{2+} exhaustion defined by serum Mg^{2+} at very low concentration 0.3 – 0.4 mmol/L might lead to cardiac arrhythmias, tetany and seizures. [22] Mg^{2+} depletion is present in impaired gastrointestinal absorption caused by celiac disease, inflammatory bowl disease and colon cancer and gastrectomy.[23] Renal insufficiency and electrolytes imbalance may leads to Mg^{2+} depletion.[24] A lo Mg^{2+} status found in genetic levels by the mutation of genes like TRPM6, CLDN16-19, KCNA1 and CNNM2 and severe hypomagnesemia accomplished to renal failure, seizures and mental retardation. [22]

Mg^{2+} and obesity

Several studies have observed that individuals with obesity tend to have lower serum Mg^{2+} levels compared with non obese individuals.[25] Mg^{2+} influences inflammation, oxidative stress, endothelial function all of which are involved in the obesity pathophysiology.[26] Unhealthy diets, junk foods, high calorific value food substance and very poor in essential nutrients and its results Mg^{2+} deficiency.[27]

Animal trial of diet induced obesity Mg^{2+} supplementation obstruct the accumulation of adipose tissue.[28] Human demonstrated that Mg^{2+} supplementation improves insulin sensitivity and reduced waist circumference in overweight women.[29] Another study demonstrated that Mg^{2+} supplementation combined with dietary counselling resulted in significant reduction of body fat percentage.[30] In obese individuals, energy from diet mostly derived from grains and sugars that reflects very active glucose catabolism takes place in liver. Most of the key enzymes of oxidation pathway of glucose are depends on Mg^{2+} and activation thiamine into thiamine diphosphate (TDP) that is another critical coenzyme of oxidative metabolism depends on Mg^{2+}. [31] As a result of low intracellular concentrations of Mg^{2+} or TDP can revise the oxidative metabolism of glucose. In hepatic, a reduce of the activity of the Mg^{2+} and TDP dependent enzyme pyruvate dehydrogenase may redirect metabolism of glucose into oxidative phase of the pentose phosphate pathway, leads to increased production of NADPH. [31] NADPH offers essential redox potential for synthetic pathways, like fatty acid biosynthesis, leads to increased production of triglycerides and LDL and subsequently, excessive triglycerides storage in adipocytes that leads to obesity and risk of obesity co-morbidities such as Dyslipidemia, metabolic syndrome and

type 2 diabetes mellitus. [32] Mg^{2+} is essential for the synthesis and activation of vitamin D. [33] Thus, Mg^{2+} is essential for hydroxylation of vitamin D into active of calcitriol takes place liver and kidney. [34] Vitamin D is important for the maintain optimal Mg^{2+} levels, where as deficiency may impair Mg^{2+} absorption and utilization. Vitamin D and Mg^{2+} are synergistic elements and deficiency can impair over all health.[35]

Insulin Resistance

Increased insulin resistance is the major pathophysiological reason for the progress of T2DM. In healthy individuals, insulin enhances glycogen production in the liver, lipid synthesis by adipose tissue and glucose uptake in muscle. [36] Insulin resistance is often the consequence of condensed sensitivity of the insulin receptor that is composed of two insulin binding alpha-subunits and beta–subunits. Specifically, upon insulin binding, the tyrosine residues of the beta-subunits become autophosphotylated, activating a wide signaling network in the cell. Depending on the target tissue, direct substrate of the insulin receptor may be recruited to the receptor, of which insulin receptor substrates -1-4 are the most studied. These IRSs, in turn, phosphorylate downstream signaling pathways leading to glucose uptake, glycogenesis, lipid synthesis and other insulin-dependent actions. Alternatively, the insulin receptor can activate IRS-independent pathways via Src homology 2 domain containing transforming protein causing the activation of mitogen-activated protein kinase signaling and regulation of cell proliferation. [37]

Role of Mg^{2+} in Insulin Sensitivity

Most of the studies shown that hypomagnesemia is linked with increased insulin resistance in T2DM individuals. [38] In other study patients with metabolic syndrome, it was shown that insulin resistance associates with decreased serum Mg^{2+} concentration. [39] Another study of black Americans of adults showed that Mg^{2+} deficiency contributes to an insulin-resistant state. [40] An identical results shown again in the study of induced Mg^{2+} deficiency reduced insulin action and secretion. [41]

Insulin Secretion

Insulin secretion from pancreatic β-cells is necessary to the control of blood glucose homeostasis. Enhanced blood glucose levels stimulate the entry of glucose in pancreatic β-cells by GLUT2, where it is converted to glucose-6-phosphate (G6P) by the enzyme glucokinase.[42] The enzymatic reaction role as a glucose sensor to decide the required quantity of insulin secretion. G6P is further metabolized by glycolysis to generate ATP, which directly induces closure of KATP channel Kir6.2. [43] Shutting of these channels induces depolarization of the plasma membrane and as a result opening of voltage-dependent Ca^{2+} channels. [44] The invasion of extracellular Ca^{2+} triggers the release of insulin by exocytosis. [45]

Role of Mg^{2+} in insulin Secretion

The studied evidence for a role of Mg^{2+} in insulin secretion is partial and not as much of well studied than the effect of Mg^{2+} on insulin sensitivity, but several at the present studies suggest that T2DM patients with hypomagnesemia display reduced insulin secretion. In individuals without diabetes, decreased serum Mg^{2+} concentrations are associated with a reduced insulin secretion. [46] On the other hand, HOMA of β-cell activity was negatively linked with the serum Mg^{2+} concentration with T2DM at Canadian cohort study.[47] Supplementation of individuals without diabetes with Mgcl2 significantly raised β-cell activity in a small randomized clinical trial.[48]

Mg^{2+} in Metabolic Syndrome

Accumulation of excess of fat in body is the characteristic feature of obesity and metabolic syndrome (MetS). In obesity involves excess accumulation of fat, but in MetS is a disorder of accumulation and use of energy, supported by low-grade systemic inflammation and follow-on in central adiposity, hypertension, dyslipidemia and insulin resistance. Most of the studies have found a positive relationship between low dietary Mg^{2+} intake and MetS risk independently from other risk factors like exercise, smoking, BMI, race, gender, alcoholism. [49] An another study showed in the meta-analysis presented that the dietary Mg^{2+} intake inversely coupled with the prevalence of MetS. [50] Dietary Mg^{2+} intake

and prevalence of MetS a cross sectional analysis done in china that results inversely correlated.[51] According to the recent studies higher Mg^{2+} intake may lower significant the risk of progressing from prediabetes to manifest diabetes.[52] MetS rapid change and enhance the threat of developing T2DM, cardiovascular disease. Regular Mg^{2+} intake decreases cardiometabolic risk and is connected with a reduced risk of cardiovascular disease, diabetes and all cause mortality. [53] Similarly higher levels of circulating Mg^{2+} are interlinked with diminish the risk of cardiovascular disease, mostly coronary artery disease.[54] Prolonged Mg^{2+} deficiency leads to hypomagnesemia and intracellular Mg^{2+} deficiency shows obesity with MetS in old age group of non-white people along with insulin resistance. [55] More over individuals meet the recommended daily allowance of Ca^{2+} and Mg^{2+} have lowering the exposure of MetS. [56]

Mg^{2+} in Type 2 Diabetes Mellitus

Diabetes Mellitus of type 1 and type 2 are among the most general causes of magnesium deficiency. [57] Type 2 diabetes (T2D) is frequently connected with altered Mg2+ homeostasis and Mg2+ intake is inversely associated with the risk of T2D in a dose-response manner. [58] The occurrence of hypomagnesemia in patients with T2DM ranges widely, from 13.5% to 47.7%. [57] Study of epidemiology shown a high prevalence of hypomagnesemia in individuals with T2DM. [59] Sources contain reduced oral intake, increased renal loss and the chronic diarrhea related with autonomic neuropathy. Medications such as proton-pump inhibitors can damage the gastrointestinal absorption of magnesium. This outcome may be the result of a drug-induced decrease in the pH of the intestinal lumen that alters the affinity of transient receptor potential melastatin-6 and melastastin-7 (TRPM6, TRPM7) channels on the apical surface of enterocytes for magnesium.[60] Probably one of the most studied chronic diseases with respect to magnesium is type 2 diabetes mellitus and the metabolic syndrome. Magnesium plays a crucial role in glucose and insulin metabolism, mainly through its impact on tyrosine kinase activity of the insulin receptor, by transferring the phosphate from ATP to protein. Magnesium may also affect phosphorylase b kinase activity by releasing glucose-1-phosphate from glycogen. In addition, magnesium may directly affect glucose transporter protein activity 4 (GLUT4), and help to regulate glucose translocation into the cell. [61,62] The influence of Mg^{2+} on glucose metabolism, insulin sensitivity and action could explain the negative relationship between Mg^{2+} intake and T2DM. [63] To understand this, it is value recalling that insulin secretion is started by a Ca2+ `influx that is competitively inhibited by extracellular Mg^{2+} and, as a result, insulinemia is inversely related with magnesemia. Circulating glucose is easily taken from cells through the glucose transporter 2 (GLUT2), and then converted in glucose-6-phosphate (G6P) by glucokinase (GK). The oxidation of G6P in glycolysis determines an increase in the ATP/ADP ratio leading to the closure of ATP-sensitive K+ channels (KATP channels) and, consequently, to the depolarization of the membrane, followed by the opening of voltage-dependent Ca2+ channels.[64] The increase in intracellular concentrations of Ca^{2+} triggers the fusion of insulin-containing granules with the membrane and the subsequent release of their content. The molecular mechanisms by which Mg^{2+} contributes to insulin resistance are mostly unrevealed. However, it is accepted that Mg^{2+} deficiency has a significant impact on insulin secretion and may contribute to dysfunction of pancreatic beta cells in T2D. [65] This depends on the key roles played by Mg^{2+} in the glucose-dependent signaling inducing insulin release. The activities of GK and many glycolytic enzymes depend on Mg-ATP complex, thus, a low intracellular Mg^{2+} concentration results in decreased ATP level in the cells. In addition, the closure of KATP channels depends on ATP binding to the Kir6.2 subunit, while the opening of these channels depends on Mg-ATP binding to the SUR1 subunit. The reduction in the intracellular levels of both ATP and Mg-ATP deranges the fine regulation of KATP channels. This leads to an increase in the basal secretion of insulin and induces hyperinsulinemia, thus contributing to a chronic exposure of cells to insulin and to the development of insulin resistance fostered also by the concomitant low grade inflammation. [65] Furthermore, the chronic hyperinsulinemia typical of insulin resistance induces an increase in renal excretion of Mg^{2+}, thus perpetuating a vicious cycle. [37] In gathering, we remind that physiological concentration of insulin and glucose induces Mg^{2+} transport, hence increasing intracellular Mg^{2+} level. It is significant that low intracellular Mg^{2+} impairs cell sensitivity to insulin, because low intracellular Mg^{2+} alters the tyrosine-kinase activity of the insulin receptor (INSR), leading to the development of post-receptor insulin resistance and decreased cellular glucose uptake. [66] In exacting, Mg^{2+} and Mg-ATP complex is regulatory evaluator of the PI3K/Akt kinase pathway downstream to the INSR. This pathway begins

with INSR auto-phosphorylation that activates the downstream kinase cascade. Insulin receptor substrate (IRS) primarily triggers phosphatidylinositol-4,5-bisphosphate-3-kinase (PI3K) and it form the second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 activates 3-phosphoinositide dependent protein kinase-1 (PDK1), which activates Akt. Akt control the metabolic performance of insulin, including glucose utilization by GLUT4 mobilization in skeletal muscle and adipose tissue, glycogen and protein synthesis and lipogenesis. Therefore, the lower is the basal intracellular Mg2+ concentration, the higher is the amount of insulin required to metabolize the same glucose load, indicative of reduced insulin sensitivity. [66] All of the data described that insulin action is dependent on the intracellular Mg^{2+} concentration. Hypomagnesemia can also contribute to T2DM through the variation of Na+/K+-ATPase that is critical for sustaining the membrane potential and low cytoplasmic sodium concentration. Mg^{2+} ions make the conformational alter of the sodium pump whose dysfunction has been correlated to T2DM. [67] In addition, some individual nucleotide polymorphisms in the TRPM6 gene are connected with an increased risk of developing T2DM because TRPM6 cannot be activated by insulin in the occurrence of these mutations.[68] The study that numerous pharmacological management for diabetes such as metformin, appear to increase Mg^{2+} levels further supports this postulation and propose a substantial interdependence between Mg^{2+} deficiency and the improvement of insulin resistance and T2DM. Mg^{2+} deficiency may not be a secondary significance of T2DM, but it may contribute to insulin resistance and changed glucose tolerance, thereby leading to T2DM.[69] Some of study have consider the relationship between hypomagnesemia and metabolic disorders in childhood and adolescence. Mg^{2+} deficiency in obese children may be secondary to reduced dietary Mg^{2+} intake. Obese children show lower serum Mg^{2+} levels than the normal-weight control group. In obese children and adolescents, Mg^{2+} blood concentration is oppositely linked with the degree of obesity and is related to an unfavourable serum lipid profile and higher systemic blood pressure than healthy controls.[70] The association between Mg^{2+} deficiency and insulin resistance have been described also in childhood. [71]

Conclusion

Mg^{2+} is an necessary element for maintaining electrolyte balance for all living organisms. Mg^{2+} deficiency is related with various disorder and diseases. Mg^{2+} deficiency leads to chronic low grade inflammation results of obesity, T2DM and MetS. Mg^{2+} deficiency is associated with cardiovascular diseases, hypertension, pre-eclampsia, arrhythmias, atherosclerosis and heart failure. A relationship is offered between T2DM and the prevalence of Mg^{2+} deficiency parameters, including reduced circulating and tissue concentrations and increased urinary Mg^{2+} excretion. In addition a lower intake of Mg^{2+} and lower levels in circulation are associated with a higher risk of developing T2DM. Mg^{2+} deficiency is connected with poor glycemic control and greater insulin resistance in patients with T2DM. More over Mg^{2+} supplementation seems to generate the correction of this vicious loop, but at the moment this is hard to understand whether Mg^{2+} beneficial effects occur through a direct effect on metabolic pathway or indirect action on inflammation or both. However, the study is still far from complete and future prospective more studies are required to support the possible inclusion of Mg^{2+} supplements and fully understand the complex in dynamic role of Mg^{2+} in T2DM.

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