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Magnesium deficiency as a contributing factor to type 2 diabetes: a review of the literature

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Abstract

Magnesium deficiency is a vital contributing factor to the happening and arising of insulin resistance, metabolic syndrome, and type 2 diabetes mellitus. Magnesium has a critical function in controlling the level of glucose in the blood and insulin sensitivity, acting as a cofactor for various enzymes such as enzymes involved in carbohydrate oxidation, glucose transport mechanisms of the cell membrane, cell replication, and lipid metabolism. Studies have indicated that reduced magnesium levels in the blood are connected with a significant decline in insulin-mediated glucose uptake which is a vital part of the cell's metabolism. In people with type 2 diabetes, plasma magnesium concentration was inversely associated with markers of insulin resistance. This means as magnesium levels in plasma decrease, the risk of insulin resistance increases. Additionally, magnesium deficiency can play a role in the development of diabetes by affecting the activity of the Na/K-ATPase enzyme, pancreas inflammation, reactive oxygen species (ROS) modification, lipid metabolism, and causing genetic instability, as the main contributors to type 2 diabetes. Therefore, early detection of magnesium deficiency can help prevent further complications. Physicians should be aware of the connection between magnesium deficiency and diabetes and monitor patients with magnesium deficiency for diabetes symptoms and make sure that the patient is getting adequate amounts of magnesium from their diet. Further research is needed to reveal the exact mechanisms underlying magnesium deficiency-induced type 2 diabetes and the curative effects of magnesium supplementation.

Keywords: Sodium potassium pump, Insulin resistance, Lipid metabolism, Pancreatitis, GLUT4, Genetics

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Introduction

Type 2 diabetes is a widespread metabolic ailment occurring as a result of increased blood sugar, due to insulin resistance or deficiency. This disease is associated with the occurrence of several symptoms, including hyperhidrosis, dry mouth, hunger, extreme weakness, blurred vision, chronic non-healing wounds, hands and feet paresthesia, itching, and fungal infections. Over time, high blood sugar levels can lead to various circulatory, nervous, and immune disorders, including heart disease, nerve damage, kidney disease, eye damage, skin conditions, hearing impairment, sleep apnea, and dementia. Clinical risk factors associated with type 2 diabetes include family history, nationality, being overweight, fat distribution, and smoking.

According to the International Diabetes Federation, nearly 537 million people worldwide lived with diabetes in 2021, with 90%-95% of them having type 2 diabetes. This disease affects both developed and developing countries, and certain ethnic groups, including South Asians, Pacific Islanders, Latinos, and Native Americans, seem to be at greater risk. Rates of diabetes have been increasing over the past few decades, from an estimated 30 million in 1985 to 135 million in 1995 and 217 million in 2005, largely due to global aging, decreasing exercise, and increasing obesity rates. India, China, the United States, Indonesia, and Japan are the five countries with the most significant number of people with diabetes as of 2000. The World Health Organization recognizes diabetes as a global epidemic.

Type 2 diabetes is described by two main events: (a) the beta cells of the pancreatic Langerhans's islets fail to produce and secrete insulin, and (b) body cells become resistant to insulin and cannot respond to it. In the second case, the pancreas produces excess insulin to keep blood glucose levels stable, leading to beta cell exhaustion and decreased insulin levels, ultimately resulting in diabetes and rapid weight loss.

Beta cells produce insulin, which initially takes the form of pre-proinsulin. Various endoplasmic reticulum (ER) proteins assist in conformational modifications of pre-proinsulin to produce proinsulin. ER proinsulin then

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Implication for health policy/practice/research/ medical education

Insufficient magnesium levels may play a role in the onset of diabetes by inducing insulin resistance, influencing the functioning of the Na/K-ATPase enzyme, triggering inflammation of the pancreas, resulting in type 2 diabetes via ROS alteration, disrupting lipid metabolism, leading to hypertriglyceridemia, which increases the risk of atherosclerosis and cardiovascular disorders, and causing genetic instability, a key factor in the development of type 2 diabetes.

enters the Golgi apparatus, where it cleaves into C-peptide and insulin in the immature secretory vesicles. Historically, beta cell dysfunction has been linked to the death of beta cells. Recently, it has been suggested that this phenomenon is the result of a complex integration of the environment with various molecular pathways in cell biology. Improper diet and increased daily consumption of lipids and sugar result in obesity, promoting long-term inflammation and insulin resistance. Under these circumstances, beta cells are subject to toxic pressures, including inflammation, inflammatory stress, ER stress, metabolic/oxidative stress, and amyloid stress, with the potential to ultimately lead to a loss of islet integrity.

Diagnosing diabetes is done by checking blood sugar levels using different methods. Three tests are routinely prescribed to measure blood glucose levels: 1- Fasting blood glucose test, where the patient should not eat any food except water for 8 hours before the test to see the baseline blood sugar level; 2- Random blood glucose test, which can be taken at any time, regardless of fasting; and 3- A1c test, in the other words, HbA1c or glycated hemoglobin test, which shows the patient's blood sugar status for 3 months.

The predominant pharmacological approach to type 2 diabetes involves oral medications, although insulin injections and other injectable agents may also be employed. Metformin, a medication taken orally in tablet form either with or after meals, is the most commonly prescribed drug for this condition. Its use is associated with improved maintenance of healthy blood glucose levels, although its common side effects include nausea and diarrhea.

Magnesium is a mineral that participates in the functioning of over 300 enzymes, which facilitate various chemical reactions within the body. This essential nutrient regulates blood sugar levels, and blood pressure reduction, and lowers the risk of heart disease and stroke. Meanwhile, magnesium contributes to maintaining healthy bones, decreasing the frequency of migraine attacks, improving exercise performance, reducing symptoms of anxiety and depression, and easing premenstrual syndrome. It is present in certain fortified foods as well as naturally in many foods. A varied diet, including the following sources, can supply the recommended amounts of magnesium:

- Whole grains, seeds, nuts, legumes, and green leafy vegetables, such as cabbage
- Enriched breakfast foods and cereals
- Dairy products, such as milk and yogurt

In both types of diabetes, magnesium levels tend to be lower than normal, but this decrease happens more commonly in type 2 diabetes, because of the link to insulin resistance. Individuals with insulin resistance may excrete magnesium in their urine, causing a decline in magnesium levels. This mineral seems to have a role in enhancing insulin secretion and sensitivity. Diabetic patients have an increased risk of magnesium deficiency due to elevated magnesium excretion and subsequent insulin resistance. However, the contribution of magnesium deficiency is not limited to the aforementioned factor. In this article, we explore the literature to review the correlation of magnesium insufficiency with type 2 diabetes.

Insulin resistance

Insulin resistance is a chronic disease defined by decreased glucose uptake rates in target tissues, leading to metabolic syndrome and type 2 diabetes. Several studies have shown magnesium deficiency as a vital influencer in insulin resistance and a prevalent occurrence in people with type 2 diabetes (1,2).

Magnesium is a critical cation involved in numerous physiological actions, containing insulin metabolism (3). It serves as a metabolic intermediate for various enzymes in carbohydrate oxidation and the glucose transport chain of the cell membrane (4). Moreover, it regulates the secretion of insulin from the beta-cells of the pancreas and participates in downstream signaling kinases as an intracellular cation. Thus, intracellular magnesium balancing is crucial for adequate carbohydrate metabolism (5).

A recent investigation examined the function of magnesium in insulin-dependent glucose uptake in 3T3-L1 adipocytes. The results displayed that approximately 50% of insulin-dependent glucose uptake is reduced by magnesium deficiency (6). This discovery promotes the notion that magnesium plays a crucial role in glucose handling and insulin sensitivity.

Further analysis of the molecular mechanisms revealed that magnesium deficiency did not affect insulin receptor phosphorylation or PIP3 mass. Nonetheless, live microscopy imaging revealed a decrease in the nucleus to the cytosol transportation of FoxO1, thereby indicating reduced AKT activation in adipocytes experiencing magnesium deficiency (7). Additionally, results from immunocytochemistry utilizing a Lectin membrane marker and Myc-epitope-tagged glucose transporter 4 (GLUT4) revealed that GLUT4 translocation in magnesium-deficient adipocytes was decreased under insulin stimulation, and insulin stimulation decreased glycolysis in magnesium-deficient adipocytes (8).

Interestingly, in people with type 2 diabetes, plasma magnesium level was conversely associated with markers

of insulin resistance, showing that lower magnesium is related to more insulin resistance. This finding suggests that magnesium supplementation may have therapeutic effects in reducing insulin resistance in the liver, muscle, and pancreas with different mechanisms (9, 10).

In that way, magnesium deficiency appears to take a significant part in insulin resistance and glucose handling. More research is needed to clarify the accurate mechanisms underlying magnesium deficiency-induced insulin resistance and the therapeutic effects of magnesium supplementation (11).

Sodium/potassium pump malfunction

Research has demonstrated that magnesium concentration impacts the interior of the red blood cells' surface in a manner that is dependent on concentration. When intracellular levels of ionized magnesium go below 0.8 mm, the activation of ouabain-sensitive sodium-potassium exchange can be categorized into two or three distinct components. These components include a minor element that is not dependent on the concentration of ionized magnesium, a saturated component, and a component that increases in proportion to the concentration of ionized magnesium. Within this range, the sodium-sodium exchange speed also stays steady lat its maximal point (12, 13).

The Na/K-ATPase is an enzyme that actively extrudes Na+ from cells in exchange for K+. It provides the driving force for the secondary active transport of solutes such as amino acids, phosphate, vitamins, and glucose (14). Its activity is regulated by many hormones, including insulin, which controls the Na/K-ATPase activity tissue- and isoform-specifically. Insulin controls Na/K-ATPase activity through non-reversible covalent modification of catalytic subunits, activation by a rise in intracellular Na+ concentration, altered Na+ sensitivity, and expression changes of subunit genes and proteins. Evidence suggests that the phosphatidylinositol-3-kinase and mitogen-activated protein kinase arms of the insulin-stimulated intracellular signaling networks are involved in this regulation (15).

Magnesium's effect on the sodium-potassium pump cycle can have implications for diabetes (16-18). If the pump does not work normally, the level of insulin will be affected. Magnesium deficiency may reduce the magnesium content of cells, decreasing intracellular ATP concentration, and increasing ADP concentration. Sprague-Dawley rats that were fed a basal diet consisting of different amounts of magnesium displayed a slight boost in ATP and a slight decline in ADP levels when the magnesium volume exceeded normal levels. Studies have shown that sodium-sodium and sodium-potassium exchange are suppressed by the concentration of ionized magnesium exceeding 0.8 mm, with sodium-sodium exchange being suppressed more strongly (19, 20).

In conclusion, magnesium deficiency may assign to the development of diabetes by affecting the function of this pump. Sodium and potassium ions are exchanged across the cell membrane by the Na/K-ATPase enzyme, which also drives the secondary active transport of many solutes. Its activity is regulated by many hormones, including insulin, which controls Na+/K+-ATPase activity in a tissue- and isoform-specific manner (21). The analytic relevance of Na+/K+-ATPase control by insulin in diabetes and related disorders is an area of ongoing research.

Pancreatitis and ROS accumulation

Magnesium deficiency can be linked to pancreas inflammation (22). Pancreas is one of the most important organs of the body producing insulin into the bloodstream, and when it does not work correctly, it leads to diabetes. Pancreatitis is a disorder that changes pancreas cell functions, and it occurs when the pancreas becomes inflamed (23). Magnesium acts as a cofactor of pancreatic enzymes in protein synthase, and it has been observed that in severe pancreatitis, hypomagnesemia and hypocalcemia may occur alone or in combination, resulting in part from the deposition of these cations in areas of fat necrosis. Magnesium deficiency similarly occurs in patients with diarrhea and pancreatic insufficiency. Since serum levels of magnesium are sufficient indicators of magnesium deficiency, routine evaluation of magnesium status could allow suitable supplementation and conceivably symptomatic improvement in patients with severe chronic pancreatitis. Additionally, chronic alcoholics tend to be magnesium-depleted, and pancreatic dysfunction aggravates that deficiency. Overall, patients with long-term pancreatitis could develop a magnesium deficiency due to malabsorption, diabetes, or chronic alcoholism.

There is a strong relationship between diabetes and pancreas-related disorders, such as pancreatitis (24). However, having the same signs does not mean that we are positive about being diabetic. In pancreatitis, the patient will experience pain in the belly, especially in the upper part. The other symptoms that are going to appear are fever, backache, tachycardia, nausea, and vomiting. The result of inflammation of pancreas cells is interfering with islet cell functions. Then glycoside is presented in urine and hyperglycemia would be submitted. It is not usual but there are cases in which, pancreatitis produces permanent diabetes mellitus either by producing sufficient permanent islet cell damage or by precipitating clinical evidence of the disease in the person hereditarily predisposed to it.

One of the important reports of pancreatitis is ROS (25). There are many ways ROS can damage a cell, such as lipids, which are produced in the cell membrane, proteins, nucleic acids, and DNA substrate in living cells, resulting in impaired insulin gene expression, insulin secretion, or increased apoptosis (26-29). Excess glucose metabolites promote the formation of ROS, leading to chronic oxidative stress, which contributes to healing diabetes side effects. These side effects would be

observed by alternating in the biomarkers of oxidative stress, including glutathione levels, superoxide dismutase, vitamins, lipid peroxidation, glutathione peroxidase, and nitrite concentration. Hyperglycemia-induced superoxide overproduction seems to be the main role in the activation of all pathways involved in the pathogenesis of complications of diabetes, resulting in acute endothelial dysfunction and inflammation pathways activation in the veins and arteries of diabetic sick people (30).

In addition to metabolic disorders, the next problem of magnesium deficiency is related to oxidative stress, resulting in impaired insulin activity through several pathways that generate ROS such as hydrogen peroxide and superoxide anions. ROS has a vital role in signaling pathways videlicet NF-κB and PKC, which interfere with insulin signaling pathways, which can make the resistance of insulin more serious. Deficiencies in magnesium have been linked to oxidative stress markers, including oxidative modification products of lipids, proteins, and DNA, as well as weakened antioxidant defenses. Mechanisms associated with magnesium deficiency involve inflammation, endothelial dysfunction, mitochondrial inability, and lavish fatty acid production.

Magnesium deficiency is linked to the development of diabetes and its complications. Some factors affect magnesium which is going to receive through meals, such as stress, high levels of alcohol consumption, inherited renal magnesium transport disorders, and endocrine diseases such as diabetes mellitus and metabolic syndrome (31). Diabetic patients with low serum magnesium levels are at risk of increased oxidized LDL concentrations and poor DNA repair content, leading to gain genomic variables and pancreatitis.

Diabetes is a relatively common complication of chronic pancreatitis, and around 50 percent of people with chronic pancreatitis will go on to develop diabetes. In conclusion, magnesium deficiency contributes to pancreas inflammation, which can lead to type 2 diabetes, through ROS modification. It is important to monitor magnesium levels, especially in patients with chronic pancreatitis, to prevent complications associated with diabetes. Physicians should be aware of the connection between pancreatitis and diabetes and monitor patients with pancreatitis for diabetes symptoms. Magnesium supplementation may help prevent magnesium deficiency and reduce the risk of diabetes and its complications. Finally, early detection of diabetes and appropriate treatment can help prevent further complications.

Genetic instability

Magnesium is essential for maintaining genomic stability, regulating cell cycle control, and apoptosis. It acts as an intracellular regulator, required for the shifting of DNA harm generated by environmental mutagens, internal processes, and DNA replication (32). Magnesium deficiency can reduce membrane uprightness and function, rise oxidative stress, and accelerate maturing. Furthermore, marginal magnesium deficiencies are very common in most industrialized countries. Genetic instability plays a crucial role in the development and progression of diseases by affecting gene expression, mRNA stability, and translational efficiency. Diabetes is a complex and diverse metabolic disorder that is often accompanied by challenges such as cardiovascular disease, hypertension, inflammation, chronic kidney disease, diabetic retinopathy, and nephropathy. Several single nucleotide polymorphisms (SNPs) including rs5186, rs1800629, rs1799983, and rs1800795 in genes AGTR1 (33, 34), TNFA (35), NOS3 (36), and IL6 (37) respectively, have been linked to an increased risk of diabetes, diabetic nephropathy and retinopathy, cardiovascular disease, inflammation, hypertension, and kidney diseases. Furthermore, these loci exhibit variations in allele and haplotype frequencies specific to different populations. These discoveries have implications for understanding the causes of diabetes and related complications and the population-specific response to medications.

Diabetes mellitus is a metabolic disorder characterized by chronically high blood sugar levels due to insufficient insulin production and/or resistance to insulin in peripheral tissues. Genetic instability is closely associated with various diseases as it regulates gene expression, mRNA stability, and translational efficiency. Diabetes is a complex and diverse metabolic dysfunction often accompanied by complications such as cardiovascular disease, hypertension, inflammation, chronic kidney disease, diabetic retinopathy and nephropathy. The occurrence rates of these complications vary among individuals and different populations, and specific genetic variations may frequently contribute to the development of these conditions (38, 39).

While the identified SNPs provide some insight into the genetic basis of diabetes and its associated complications, further research is needed to fully understand the complex interplay between genes, environmental factors, and disease development. In the future, population-specific genetic architecture should be considered before developing drugs or treatment strategies for diabetes and its associated complications. Additionally, strategies to ensure adequate magnesium intake should be promoted to prevent magnesium deficiency and its potential role in contributing to genetic instability and disease development.

Lipid metabolism interference

Magnesium is an essential mineral required for numerous biochemical reactions in the body, including those involved in lipid metabolism (40). The deficiency of this ion can also cause type 2 diabetes through dyslipidemia, which is a condition characterized by abnormal levels of lipids, including cholesterol and triglycerides, in the blood (41).

Lipid metabolism plays a crucial role in the development of type 2 diabetes (42). It has been observed that individuals with type 2 diabetes have abnormal lipid metabolism (43,44), particularly hypertriglyceridemia, which increases the risk of atherosclerosis and cardiovascular diseases (45). Hypertriglyceridemia is caused by an increase in triglyceride-carrying lipoproteins, chylomicrons, and very low-density lipoproteins (VLDL) (46). In type 2 diabetes, VLDL-triglyceride-synthesis in the liver is increased, leading to hypertriglyceridemia (47).

Magnesium plays a vital role in lipid metabolism by regulating the activity of enzymes involved in lipid metabolism, such as lecithin cholesterol acyltransferase (LCAT) and lipoprotein lipase (LPL). LCAT is an enzyme that converts free cholesterol to cholesteryl ester, which is then transported to the liver for excretion. LPL is an enzyme that breaks down triglycerides in the blood and converts them into energy. Magnesium is required for the activation of LCAT and LPL, and its deficiency can lead to impaired lipid metabolism (48).

Studies have shown that magnesium deficiency is prevalent in patients with dyslipidemia, hypertension, diabetes, and obesity, which are risk factors for atherosclerosis (49). Magnesium deficiency has been found to increase triglyceride and free cholesterol levels and decrease esterified cholesterol levels in plasma (50-52). In addition, as a result of magnesium deficiency, triglyceride levels in VLDL and LDL fractions increase, as do cholesterol levels in VLDL and LDL fractions, with HDL levels significantly decreasing. This disturbance in lipid metabolism ultimately leads to atherosclerosis and increases the risk of cardiovascular diseases (53).

In conclusion, magnesium deficiency can contribute to the development of type 2 diabetes by interfering with lipid metabolism. Magnesium is required for the activation of enzymes involved in lipid metabolism, and its deficiency leads to impaired lipid metabolism, particularly hypertriglyceridemia. Hypertriglyceridemia is a risk factor for atherosclerosis and cardiovascular diseases. Therefore, adequate magnesium can be considered for the prevention and treatment of type 2 diabetes.

Conclusion

Insulin resistance is a persistent medical condition that contributes to metabolic syndrome and type 2 diabetes mellitus. Many studies emphasize the vital role of magnesium deficiency in the development and progression of insulin resistance. Magnesium, an essential cation involved in numerous physiological processes, including insulin metabolism, serves as a cofactor for various enzymes in carbohydrate oxidation and glucose transport mechanisms of the cell membrane. Studies have shown that magnesium deficiency significantly decreased insulin-dependent glucose uptake, supporting the notion that magnesium plays a crucial role in glucose handling and insulin sensitivity.

Further investigation revealed that the deficiency of magnesium did not affect insulin receptor phosphorylation or the mass of PIP3. However, it did lead to a decrease in the movement of FoxO1 from the nucleus to the cytosol, indicating reduced activation of Akt in magnesium-deficient adipocytes. Additionally, the study demonstrated that the translocation of GLUT4 was impaired in magnesium-deficient adipocytes stimulated by insulin, resulting in decreased glycolysis and altered energy metabolism in these cells. Interestingly, people with type 2 diabetes, demonstrated a negative correlation between plasma magnesium concentration and markers of insulin resistance, thus indicating that reduced levels of magnesium are linked to increased insulin resistance.

Additionally, it is postulated that magnesium deficiency may contribute to the development of diabetes by affecting the activity of the Na/K-ATPase enzyme, which regulates the exchange of sodium and potassium ions across the cell membrane and provides the driving force for the secondary active transport of many solutes. The clinical relevance of Na/K-ATPase control by insulin in diabetes and related disorders is an area of ongoing research.

Furthermore, magnesium deficiency contributes to pancreas inflammation, which can lead to type 2 diabetes, through ROS modification. This discourse underscores the significance of monitoring magnesium levels, particularly in patients with chronic pancreatitis, to prevent complications associated with diabetes. Physicians should be aware of the connection between pancreatitis and diabetes and monitor patients with pancreatitis for diabetes symptoms.

Magnesium deficiency is potentially a factor that causes type 2 diabetes by contributing to genetic instability. Magnesium is vital for maintaining genomic stability and is a crucial cofactor in enzymatic systems involved in DNA processing. Furthermore, marginal magnesium deficiencies are prevalent in most industrialized countries. In addition, common SNPs in IL6, AGTR1, NOS3, and TNFA genes that are associated with diabetes may be caused by the deleterious consequences of magnesium deficiency on genetic stability.

Finally, it is important to highlight the role of magnesium deficiency in interfering with lipid metabolism, leading to hypertriglyceridemia, which is a risk factor for atherosclerosis and cardiovascular diseases. Adequate magnesium intake can be considered for the prevention and treatment of type 2 diabetes.

In conclusion, the evidence presented in this discourse demonstrates the vital role of magnesium deficiency in the development and progression of insulin resistance and type 2 diabetes mellitus. Magnesium, an essential cation involved in numerous physiological processes, including insulin metabolism, serves as a cofactor for various enzymes in carbohydrate oxidation, glucose transport mechanisms of the cell membrane, cell replication, and lipid metabolism. Further studies are necessary to elucidate

the exact mechanisms underlying magnesium deficiency-induced type 2 diabetes and the therapeutic effects of magnesium supplementation. Adequate magnesium intake can be considered for the prevention and treatment of type 2 diabetes and its associated complications. Physicians should be aware of the connection between magnesium deficiency and diabetes and monitor patients with magnesium deficiency for diabetes symptoms. Early detection of magnesium deficiency can help prevent further complications.

Authors' contribution

Conceptualization: MB.
Validation: GAK.
Formal analysis: EA.
Investigation: AR, SC.
Writing–original draft preparation: AR, SC.
Writing–review and editing: EA.
Supervision: GAK.
Project administration: GAK.

Conflicts of interest

The authors declare no financial or personal conflict of interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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