Effects of Taking Magnesium Supplements for Diabetics and Those with A High Risk of Diabetes

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Abstract. Diabetes is a common disease occurring around the world. Patients usually have high blood sugar and many complications. Diabetes is typically caused by an inability to use insulin or damage to beta-cells. Magnesium is a co-factor involved in glycolysis and activation of insulin use, so by examining trials including magnesium supplementation in individuals with all forms of diabetes, this research investigated if taking magnesium supplements had an association with blood glucose and insulin resistance in diabetics or those with a high risk of diabetes. Ten trials in this paper are analyed to figure out whether magnesium supplement is associated with blood sugar and insulin resistance in diabetics and those with high risk of this diseased. Eight trials showed an association between consuming Mg supplement and lower blood sugar and insulin resistance, but two trials concluded there was no association. The differences in the results may be caused by different blood magnesium levels or ethnic groups of participants, which needs further analysis.

Keywords: Magnesium supplements, diabetes, insulin resistance, glycolysis

1. Introduction

Nowadays, there is a widespread public health problem that influences people's life a lot, which is diabetes. Diabetes is not only incurable, but also has a number of side effects that significantly lower patients' quality of life. The Western diet consists of large consumption of red meat, high sugar desserts/drinks, refined carbohydrates, and small consumption of vegetables, fruits, and whole grains, while most people who eat unhealthy diets also lack exercise. Both of these factors are associated with the development of this disease.

Whole grains, vegetables with green leaves, and nuts are all high in magnesium, and meat and fish also contain some magnesium, but recent dietary surveys have shown that Westerners do not consume enough magnesium to meet the recommended intake.

Most diabetic patients suffer from hypomagnesemia. Since magnesium is the cofactor of many enzymatic reactions, so Mg deficiency has been linked to the pathogenesis of many diseases, including the development of diabetes. Mg not only controls the efficiency of insulin use but also participates in glycolysis, so Mg deficiency increases insulin resistance and aggravates the condition of diabetic patients.

There was one meta-analysis study that have shown an association between taking Mg supplements and lowering blood glucose and insulin resistance [1]. The researchers suggested that taking Mg supplements is a good way to manage the progression of diabetes and prevent diabetes, However, these meta-analyses only looked at patients with T2D, and none of the trials analyzed lasted longer than 16 weeks, so it is not clear whether Mg supplementation has a long-term effect on glycemic control on all types of diabetes [1].

In this paper, through analysis of several trials that explore the relationship between Mg supplements and blood glucose and insulin resistance in all types of diabetic patients/patients at high risk of diabetes, which can help to find an association between taking Mg supplements and reducing blood glucose and insulin resistance.

2. What is Diabetes and the Pathology of Diabetes

Type I diabetes (T1D), type II diabetes (T2D), and gestational diabetes (GDM) are the three primary kinds of the disease. Diabetes affects 422 million people globally and the proportion of people with diabetes is still rising [2]. In addition, the prevalence is higher among high-income people living in urban areas than among low-income people in rural areas. People who are overweight, have high blood pressure or cholesterol, or have a positive family history of diabetes are also more likely to get the disease. Hemoglobin A1C (HbA1C), Fasting glucose (FPG) and Insulin Resistance (HOMA-IR) are the main methods to detect diabetes. Diabetics will have HbA1C higher than 6.5% (48 mmol/l), HOMA-IR higher than 1.9 and FPG higher than 126 mg/dl [2, 3].

Normal individuals experience a rise in blood sugar levels after eating, which causes the pancreatic beta cells to generate insulin, allowing the glucose to enter the liver through the GLUT4 channel, where it can be stored or converted to energy. However, because diabetics either don't have insulin or are unable to use it, diabetics' blood sugar levels do not decrease after having food.

T1D is an autoimmune disease that accounts for about 10% of the total incidence of diabetes and is mainly associated with genetic factors, but also with environmental factors [4]. T1D occurs mainly in children between the ages of 4 to 14, especially in monozygotic twins [4]. The pathogenesis of T1D is due to the failure of pancreatic beta cells to produce insulin. The patient's antigen-presenting cell (APC) interprets the patient's beta-cell peptide as an antigen and delivers it to CD4 helper T cells, which activate CD8 T cells and induce cytokine release, leading to the destruction of beta-cell.

The incidence of T2D is the highest of all diabetes, and it is usually adults who are more likely to develop T2D. It often affects β cell function and insulin resistance through dietary factors, exercise factors, and genetic factors. The mechanism of T2D is caused by insulin resistance and the destruction of pancreatic β cells. Insulin resistance occurs when the liver or fat or muscle cells are not sensitive to insulin and cannot convert glucose in the blood into energy or store it. For T2D patients, insulin is unable to transport glucose to liver cells, so the pancreas produces more insulin to try to transport glucose to the liver, which leads to the accumulation of blood glucose. Therefore, insulin resistance will cause the destruction of pancreatic β cells. Studies have shown that when beta cells work too hard, they can't produce insulin and suffer insult and apoptosis. So, insulin resistance and β cells work together to control the progression of diabetes. Furthermore, some studies show that vegetarianism has a negative association with the incidence of T2D, and there is a positive relationship between overweight and obesity and the incidence of T2D. There is also an association between those who enjoy fitness and exercise in general and reduced T2D incidence.

Gestational diabetes is now a common complication of pregnancy, and pregnant women who are overweight or who are elderly parturient women or who have a positive family history for T2D are more likely to have GMD [5]. Gestational diabetes has a similar pathogenesis to T2D and is caused by insulin resistance or disruption of β-cell function. However, it is essential to note that if gestational diabetes is left untreated in the mother, it can predispose the fetus to hyperinsulinaemia, which can lead to fetal overweight in the short term and possibly lead to type 2 diabetes in the long term in both the fetus and the mother [5].

Diabetes is a serious disease not only because of its high incidence but also because it can lead to many complications. Regardless of the type of diabetes, it can result in kidney disorders such as end-stage renal disease, diabetic retinopathy, and cardiovascular diseases such as coronary heart disease and atherosclerosis. So how treating diabetes is a serious and continuing problem. Generally, people with diabetes use insulin injections or oral insulin to control their blood sugar, but people with diabetes can also improve their conditions by changing their lifestyles. For example, doing more exercise and having a healthy and balanced dietary pattern is associated with preventing diabetes or preventing its progression. Some researchers have stated that taking magnesium supplements is associated with lowering blood sugar in diabetics or those with a high risk of developing this disease.

3. Mechanism of How Mg Influences Glycolysis

Mg is an essential cation in the body because Mg is involved in approximately three hundred enzymatic processes in the body such as protein synthesis and blood sugar regulation [6]. The normal adult body Mg content is about 1,000 mmol (21-28 g), with a blood magnesium range from 0.75 - 0.96 mmol/L. The bones are where the majority of the magnesium is kept, and the remaining magnesium can be freely exchanged between extracellular fluid and intercellular fluid to maintain the serum magnesium balance. Meanwhile, the recommendation of daily intake of Mg for adults is 4.5 mg/kg/day, but it varies from person to person [6].

Magnesium can shield the negative charge of the ATP phosphate group and forms the Mg-ATP complex. This complex is involved in all phosphorylation reactions in glycolysis, and magnesium can affect glycolysis in two ways. The first is to affect insulin sensitivity. If the concentration of Mg is too low, it will have an impact on the insulin receptor's tyrosine kinase-mediated phosphorylation, which prevents insulin from releasing sufficient signals for glucose consumption.

The other way is that Mg affects hexokinase and phosphofructokinase during glycolysis as shown in Figure 1. Hexokinase converts glucose to glucose-6-phosphate with ATP and its phosphate group, whereas phosphofructokinase uses fructose-6-phosphate to produce fructose-1-6-bisphosphate. These two processes all need Mg to take part in, so if the serum Mg concentration is too low, glycolysis will be inhibited, and glucose cannot be stored in the liver as glycogen or enter the tricarboxylic acid cycle to produce energy. Diabetes will result from this since blood glucose levels rise.

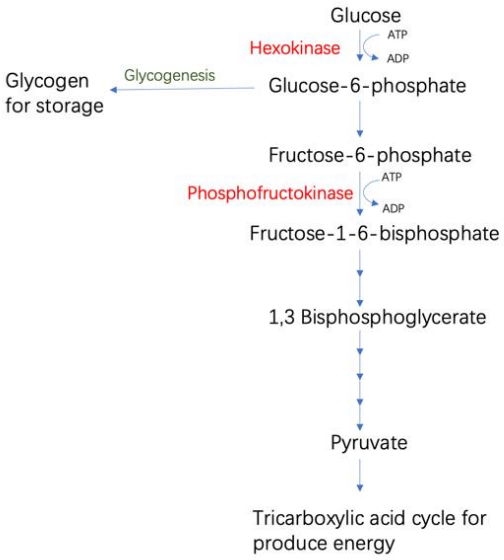

Figure 1. The process of glycolysis. The kinases that can be influenced by Mg are shown in red. Glucose that enters glycolysis can be stored or enter the tricarboxylic acid cycle to produce energy.

4. Trials for Diabetics and Those at High Risk for Diabetes with Taking Magnesium Supplements

4.1. For Diabetics

Five studies that are shown in Table 1, involving 385 people and including T1D, T2D, and gestational diabetes, included men and women in five studies and only women in one [2, 7-10]. Three trials (including three with T2D) showed that magnesium supplementation is associated with reducing FPG in diabetics and only one trial done by Navarrete-Cortes et al observed that FPG increased by 0.02, which is quite small [2, 7-10]. For HbA1C, 3 trials (including two with T2D and one with T1D) showed that magnesium supplementation is associated with reducing HbA1C in diabetics and only 2 trials done by Navarrete-Cortes et al (2004) and Sadeghian et al (2020) detected that HbA1C

increased for about 6.56 and 1.9 [2, 7-10]. For HOMA-IR, two trials (including two with T2D) showed that magnesium supplementation is associated with reducing HOMA-IR, but in 2 trials, HOMA-IR increased by 0.353 and 0.1 [2, 7-9].

4.2. For People with A High Risk of Diabetes

As shown in Table 2, five studies involved 445 people, all at high risk for diabetes, who were either overweight, hypomagnesia or insulin resistant [11-15]. All five studies included men and women. In trials with people with a high risk of diabetics, 3 trials (including people with hypomagnesaemia, people who are overweight and people who have insulin resistance) showed that Mg supplementation is associated with reducing HOMA-IR in people with a high risk of diabetics [11-13]. Only one trial done by Lee et al demonstrated that taking Mg supplements cannot improve the insulin resistance status [14]. Lee et al stated that this result could be different from others because the participants in this trial were all Korean, while most of the other trials were European/American, and it is possible that the effects of Mg supplements vary by race. At the same time, 4 trials showed that treating prediabetes with Mg supplements can help reduce FPG and only one trial done by Lee et al observed that taking Mg supplements cannot improve the blood glucose level for prediabetes [11-15].

Table 1. Patients with diabetes

Author (year)	Type of diabetes	HbA1c for Intervention group (%)	FPG for Intervention group (mg/dL)	HOMA-IR for Intervention group	Daily Mg supplement dosage	Conclusion
ELDerawi et al [2].(2018)	T2D	8.32 to 7.6.	158.6 to 148.05.	6.16 to 4.44.	Had Jamieson magnesium tablet (250mg) daily for 3 months.	Taking Mg supplements was inversely associated with blood glucose and insulin resistance.
Solati et al [7]. (2014)	T2D	8.33 ± 1.47 to 7.90 ± 1.68	183.9 ± 15.43 to 125.8 ± 6.52	2.47 ± 2.71 to 5.01 ± 2.47	Took capsules containing MgSo4 three times a day (300 mg Mg total) for 3 months.	Use of Mg supplements was negatively associated with blood glucose and insulin resistance.
Navarrete-Cortes et al [8]. (2014)	T2D	7.9 to 8.5.	153.9 to 154.26	4.45 to 4.51	Subjects in intervention group took magnesium lactate (360mg Mg).	Taking Mg supplements was positively associated with blood glucose and insulin resistance.
Shahbah et al [10].(2017)	T1D	10.11% ± 0.87% to 7.88% ± 0.42%	——	——	Took 300mg magnesium oxide daily for 3 months.	Use of Mg supplements was negatively associated with blood glucose and insulin resistance.
Sadeghian et al [9]. (2020)	T2D with nephropathy	7.6 ± 1.4 to 7.7 ± 1.6	166.6 ± 45.9 to 156.8 ± 53	2.4 ± 2.4 to 4.3 ± 3.8	Took one capsule of MgO (250 mg of Mg) daily for 3 months.	Use of Mg supplements was inversely associated with blood glucose and insulin resistance.

Table 2. People with a high risk of diabetes

Author (year)	Type of diabetes	HbA1c for Intervention group (%)	FPG for Intervention group (mg/dL)	HOMA-IR for Intervention group	Daily Mg supplement dosage	Conclusion
Guerrero-Romero et al [11]. (2015)	Prediabetes with hypomagnesaemia.	____	113.5 ± 7.5 to 86.9 ± 7.9	4.03 ± 2.8 to 2.85 ± 1.0	Took 30 mL of 5% MgCl2 solution (382mg Mg) daily for four months	This trial shown that Mg supplement is associated with decreasing blood glucose.
Guerrero-Romero et al [12].(2004)	Non-diabetic subjects with insulin resistance and hypomagnesemia.	____	104.4 ± 15.2 to 90 ± 10.8	4.6 ± 2.8 to 2.6 ± 1.1	Subjects in the intervention group took oral 2.5g MgCl2 (632 mg of Mg) every day for 3 months.	Mg supplement is associated with decreasing insulin sensitivity in hypomagnesemic in prediabetics.
Mooren et al. [13]. (2011)	Overweight non-diabetic patients with insulin resistance.	____	91.26 ± 12.24 to 85.5 ± 18.72	3.488 ± 1.983 to 2.974 ± 1.682	Took 365 mg of magnesium aspartate HCl orally every day for six months.	Mg supplements can reduce glycemia and insulin resistance in patients with prediabetes.
Lee et al [14]. (2009)	Overweight prediabetes.	____	91.26 ± 9 to 92.52 ± 9.36	2.54 ± 1.08 to 2.74 ± 1.76	The intervention group was given magnesium oxide (300 mg Mg) daily for three months.	Mg supplementation was not associated with improved glycemia and insulin resistance in patients with prediabetes.
Simental-Mendía et al [15]. (2014)	Prediabetes with hypomagnesemia.	____	108 ± 25.2to 99 ± 18	____	Took 30 ml of MgCl2 solution (382 mg magnesium) was injected daily for 3 months.	Taking Mg supplements is associated with lower fasting glucose in patients with prediabetes.

5. Discussion

These randomized controlled trials' analysis demonstrated that magnesium supplementation considerably lowers the HOMA-IR, FPG, and HbA1C in individuals at high risk for developing diabetes and only modestly lowers these markers in diabetic patients with hypomagnesemia. In the trial done by Navarrete-Cortes et al., the participants were patients with normal magnesium blood levels for T2D, they did not improve their blood glucose and insulin resistance after taking magnesium supplements. This means that adequate intake of magnesium supplements, which affect serum magnesium levels, improved glycemic index and insulin sensitivity only when a person had hypomagnesemia. In addition, 8/10 of the trials were randomized controlled double-blind trials, which improved the accuracy and credibility of the trial results. In conclusion, after taking magnesium supplements, most diabetics have improved their glycemic index and insulin resistance, so magnesium supplements are related to lower glycemic index and insulin resistance in diabetics with hypomagnesemia.

In the contrast, these trials also had a lot of limitations. First of all, the number of subjects in each trial was not very large, and the main age group was between 18 and 65, so it was not considered whether Mg supplements had sufficient effects on children and elderly. At the same time, the small number of participants could not include people of all races. As Lee et al. concluded that Mg supplementation did not help prevent diabetes in Korean patients, but for Western prediabetes, Mg

supplementation was associated with effective blood glucose reduction. In addition, in one trial, diabetic patients who smoked were excluded. Some studies have proved that smoking is positively associated with diabetes, so the exclusion of patients who smoked may make the results more favorable to the negative correlation between taking Mg supplements and lowering blood glucose [7]. Finally, only one trial examined children with T1D, no trial examined gestational diabetes, and four trials examined T2D. However, one meta-analysis trial specifically analyzed 54 trials of various types of supplements for glycemic control in patients with GDM, including analysis of vitamin D, magnesium, probiotics, etc., and concluded that supplementing with magnesium was linked to a decrease in both FPG and HOMA-IR [5]. In order to identify whether magnesium supplements are connected to glycemic and insulin resistance in all diabetic individuals, further research is necessary.

Secondly, different trials used different magnesium supplements and consumed different doses. For example, in the trial done by ELDerawi et al., they used Jamieson magnesium tablet (250mg), but in the trial done by Navarrete-Cortes et al., they used magnesium lactate (360mg Mg), this might potentially result in variations in the trials' findings. Moreover, in the trial done by ELDerawi et al, the subjects' diets were regulated, with lots of fruit and vegetables and a small amount of fat, so a change in diet could change the results [2].

Thirdly, the duration for all trials is between 6 weeks to 6 months, which is short, extending the duration to 6 months will be better to detect whether magnesium supplements are helpful.

6. Conclusion

In diabetics with hypomagnesemia or those at high risk for developing diabetes with hypomagnesemia, analysis of these trials revealed a relationship between magnesium supplementation and reduced blood glucose and insulin resistance, but more trials are needed to see if magnesium is helpful in diabetic patients with normal magnesemia. For diabetic patients, Mg supplement only improved parameters in patients with hypomagnesemia, so more research still need to explore whether it is useful for diabetic patients with normomagnesemia. It appears possible that racial disparities in patients at high risk for diabetes could affect how well a magnesium supplement improves blood sugar and insulin resistance.

This study mainly contributed to judging if Mg supplementation is linked to lowering blood sugar and insulin resistance in a variety of diabetic individuals, but the existing research have a number of drawbacks. First of all, there are not enough research data. Secondly, most of the studies were done for T2D and only a few studies were done for TD1 and GDM. Third, all trials were no longer than 6 months, so there is a band discussion as to whether Mg supplementation can improve blood sugar in diabetic patients over the long term. Finally, there is a possibility of different effects due to the different types of Mg supplements. Future studies should focus more on how to improve blood glucose in T1D and GDM populations and what type of magnesium supplementation is most effective. For all people, elemental Mg can be obtained through magnesium supplements along with daily dietary intake of magnesium.

To sum up, a higher magnesium intake can protect diabetics and those at high risk for developing it, as well as lessen the likelihood of diabetes complications.

References

[1] Dong J. Y., Xun P., He K., et al. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. Diabetes Care, 2011, 34(9): 2116-2122.

[2] WA E. LDerawi, Naser I. A., Taleb M. H., et al. The Effects of Oral Magnesium Supplementation on Glycemic Response among Type 2 Diabetes Patients. Nutrients, 2018, 11(1): 44.

[3] Prevention. Centers for Disease Control and. All About Your A1C. 2021. www.cdc.gov/diabetes/basics/type2.html.

[4] Paschou S. A., Papadopoulou-Marketou N., Chrousos G. P., et al. On type 1 diabetes mellitus pathogenesis. Endocr Connect, 2018, 7(1): R38-R46.

[5] Jin Shixiao, Sha Liyan, Dong Jianli, et al. Effects of Nutritional Strategies on Glucose Homeostasis in Gestational Diabetes Mellitus: A Systematic Review and Network Meta-Analysis. Journal of Diabetes Research, 2020, 2020: 6062478.

[6] Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev, 2003, 24(2): 47-66.

[7] Solati M., Ouspid E., Hosseini S., et al. Oral magnesium supplementation in type II diabetic patients. Med J Islam Repub Iran, 2014, 28: 67.

[8] Navarrete-Cortes A., Ble-Castillo J. L., Guerrero-Romero F., et al. No effect of magnesium supplementation on metabolic control and insulin sensitivity in type 2 diabetic patients with normomagnesemia. Magnes Res, 2014, 27(2): 48-56.

[9] Sadeghian Mehdi, Azadbakht Leila, Khalili Noushin, et al. Oral Magnesium Supplementation Improved Lipid Profile but Increased Insulin Resistance in Patients with Diabetic Nephropathy: a Double-Blind Randomized Controlled Clinical Trial. Biological Trace Element Research, 2020, 193(1): 23-35.

[10] Shahbah D., Hassan T., Morsy S., et al. Oral magnesium supplementation improves glycemic control and lipid profile in children with type 1 diabetes and hypomagnesaemia. Medicine (Baltimore), 2017, 96(11): e6352.

[11] Guerrero-Romero F., Simental-Mendía L. E., Hernández-Ronquillo G., et al. Oral magnesium supplementation improves glycaemic status in subjects with prediabetes and hypomagnesaemia: A double-blind placebo-controlled randomized trial. Diabetes Metab, 2015, 41(3): 202-207.

[12] Guerrero-Romero F., Tamez-Perez H. E., González-González G., et al. Oral magnesium supplementation improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. Diabetes Metab, 2004, 30(3): 253-258.

[13] Mooren F. C., Krüger K., Völker K., et al. Oral magnesium supplementation reduces insulin resistance in non-diabetic subjects - a double-blind, placebo-controlled, randomized trial. Diabetes Obes Metab, 2011, 13(3): 281-284.

[14] Lee S., Park H. K., Son S. P., et al. Effects of oral magnesium supplementation on insulin sensitivity and blood pressure in normo-magnesemic nondiabetic overweight Korean adults. Nutrition, Metabolism and Cardiovascular Diseases, 2009, 19(11): 781-788.

[15] Simental-Mendía L. E., Rodríguez-Morán M.,Guerrero-Romero F. Oral magnesium supplementation decreases C-reactive protein levels in subjects with prediabetes and hypomagnesemia: a clinical randomized double-blind placebo-controlled trial. Arch Med Res, 2014, 45(4): 325-330.