

# The Therapeutic Effects of Magnesium in Insulin Secretion and Insulin Resistance

## Abstract

Insulin resistance (IR) is a chronic pathological condition that is related to reduce the rates of glucose uptake, especially in the liver, muscle, and adipose tissue as target tissues. Metabolic syndrome and type 2 diabetes mellitus can occur following progression of the disease. The majority of prior research has applied that some cations such as magnesium ( $Mg^{2+}$ ) have important physiological role in insulin metabolism.  $Mg^{2+}$  is the fourth most abundant mineral in the human body that gets involved as a cofactor of various enzymes in several metabolic events, such as carbohydrate oxidation, and it has a fundamental role in glucose transporting mechanism of the cell membrane. This cation has numerous duties in the human body such as regulation of insulin secretion in pancreatic beta-cells and phosphorylation of the insulin receptors in target cells and also gets involved in other downstream signal kinases as intracellular cation. On this basis, intracellular  $Mg^{2+}$  balancing is vital for adequate carbohydrate metabolism. This paper summarizes the present knowledge about the therapeutic effects of  $Mg^{2+}$  in reducing IR in liver, muscle, and pancreases with different mechanisms. For this, the search was performed in Google Scholar, PubMed, Scopus, and Web of Science by insulin resistance, skeletal muscle, liver, pancreases, magnesium,  $Mg^{2+}$ , and inflammation keywords.

**Keywords:** Diabetes, glucose, insulin resistance, magnesium

## Introduction

Type 2 diabetes (T2D) is very common in human societies and the most important feature of this disease is insulin resistance (IR). The complications of this disease can severely affect the quality of human life. On the other hand, long-term use of insulin leads to increased IR, so today there is a need for alternative drugs or supplements that, in addition to lowering blood sugar, maintain the integrity of cell pathways and also maintain the survival of pancreatic beta cells. In this regard, in the present study, we decided to investigate the effects of magnesium ( $Mg^{2+}$ ) as a complementary drug to reduce IR on important issues involved in glucose metabolism.

## Insulin Resistance

Insulin resistance is a chronic pathological condition that is related to reduce the rates of glucose uptake, especially in the liver, muscle, and adipose tissue as target tissues, and it occurs when insulin receptors (INRs) lose their sensitivity

to insulin.<sup>[1]</sup> Insulin controls energy homeostasis and glucose metabolism by stimulating glucose uptake from skeletal muscle and, to a lesser degree, liver and adipose tissue. It was reported in the literature that a family of glucose transport proteins, which are expressed in specific tissues and known as glucose transporter (GLUTs), contributes to the glucose uptake process. In adipose tissue and skeletal muscle, GLUT4 is the main isoform of GLUTs that participate in insulin-stimulated glucose uptake based on translocation of GLUT4 from an intracellular pool to the plasma membrane.<sup>[2,3]</sup> Hence, IR and type 2 diabetes in rodents and humans are associated with defects at the level of GLUT4 content in skeletal muscles and adipose tissue<sup>[2,3]</sup> that leads to enhancing the concentration of insulin in the circulatory system as a compensatory mechanism.<sup>[4,5]</sup> Following these conditions, IR occurs with downregulating INR and desensitizing postreceptor pathways.<sup>[6]</sup> IR is widely recognized as an important risk factor for cardiovascular disease, metabolic syndrome (MetS), obesity, cancer, and T2D.<sup>[5,7]</sup>

**How to cite this article:** Hosseini Dastgerdi A, Ghanbari Rad M, Soltani N. The therapeutic effects of magnesium in insulin secretion and insulin resistance. *Adv Biomed Res* 2022;11:54.

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**Received:** 20 November 2021

**Revised:** 26 January 2022

**Accepted:** 08 February 2022

**Published:** 29 June 2022

### Access this article online

**Website:** www.advbiores.net

**DOI:** 10.4103/abr.abr\_366\_21

### Quick Response Code:



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## Diabetes Mellitus

DM is a common metabolic disorder that can change people's life due to high morbidity and mortality. This disease is associated with pancreatic dysfunction in insulin secretion or low insulin-directed fostering of glucose by target cells which cause hyperglycemia in the blood. DM is divided into two general types: insulin-dependent diabetes mellitus (IDDM) or type 1 and non-IDDM or type 2. IDDM is known as an autoimmune disorder because T-lymphocytes reactivity against pancreatic  $\beta$ -cells induced hypoinsulinemia and thus hyperglycemia.<sup>[8,9]</sup> T2D as a chronic disease is characterized by hyperglycemia due to impaired insulin secretion, insulin function, or both.<sup>[10,11]</sup>

Chronic hyperglycemia is the main risk factor for heart disease, stroke, kidney disease, blindness, and amputation.<sup>[10,12]</sup> Unfortunately, the World Health Organization reported that the prevalence of diabetes is rapidly increasing all around the world and there has been an epidemic increase in mortality from T2D.<sup>[10]</sup> It is expected that the number of people suffering from diabetes will reach 25%–28% by 2050. To overcome this situation, some approaches have been made to find some medications that may increase insulin sensitivity and improve T2D complications. Quite recently, considerable attention has been paid to magnesium as a potential option for balancing glucose uptake.<sup>[13]</sup>

## Mg<sup>2+</sup>

Mg<sup>2+</sup> is the fourth most important element in the human body and the second most abundant intracellular cation,<sup>[1]</sup> with 99% distribution in the intracellular compartment and only 1% distribution in the extracellular fluid.<sup>[14]</sup> The normal serum of Mg<sup>2+</sup> concentration is reported to be in the range of 0.76–1.15 mmol/L.<sup>[1]</sup> Mg<sup>2+</sup> involves in more than 300 enzymatic reactions and numerous physiological processes by acting as a cofactor for many enzymes such as energy metabolism, glucose transport across cell membrane, hepatic gluconeogenesis, pancreatic functions, insulin secretion, and action in pancreatic cells and target tissues through interaction with receptors of this hormone.<sup>[5,15-17]</sup> On this basis, intracellular Mg<sup>2+</sup> balancing is vital for adequate carbohydrate metabolism.<sup>[10,18]</sup> Studies have indicated that daily Mg<sup>2+</sup> supplements may improve glycemic response among T2D patients<sup>[10]</sup> and also prevent MetS.<sup>[19]</sup> With this aim in mind, in this paper, we reviewed Mg<sup>2+</sup> performance in improving IR.

## The Role of Mg<sup>2+</sup> in Improving Insulin Resistance and Blood Glucose

There have been numerous studies that investigate the benefits of Mg<sup>2+</sup> supplementation in IR and diabetic subjects. Nevertheless, contradictory opinions have been presented in the literature throughout the years. For instance, a number of studies have found that Mg<sup>2+</sup> supplementation

has beneficial effects on metabolic control in individuals with T2D,<sup>[3,20,21]</sup> while other observations provided insufficient data about the effects of Mg<sup>2+</sup> supplementation on T2D.<sup>[10,22]</sup> Guerrero-Romero has stated that the intake of supplements containing 50 mL MgCl<sub>2</sub> for 16 weeks remarkably improved homeostatic model assessment for IR (HOMA-IR), fasting blood sugar (FBS), and hemoglobin A1c (HbA1c) in individuals with T2D.<sup>[23]</sup> More recent evidence highlights that higher levels of Mg<sup>2+</sup> serum are associated with a greater degree of sensitivity to insulin,<sup>[1,24,25]</sup> and this justifies the improvement of the glycemic control indicators after Mg<sup>2+</sup> supplementation. However, this improvement could be interpreted by different mechanisms.<sup>[10]</sup> More recent evidence reveals that increasing Mg<sup>2+</sup> intake is related to not only lowering fasting glucose (FG) and insulin<sup>[10]</sup> but also decreasing the risk of T2D.<sup>[21,26]</sup> Considering the positive effects of Mg<sup>2+</sup> on mechanisms involved in IR, the prescription of a healthy Mg<sup>2+</sup>-rich diet can be effective for individuals with MetS and T2D. In addition, a meta-analysis was conducted on T2D individuals highlighting that Mg<sup>2+</sup> supplementation improves glycemic control in T2D patients.<sup>[27]</sup> Different doses of Mg<sup>2+</sup> have been suggested by researchers in diabetic patients. ELDerawi *et al.* have indicated that daily administration of 250 mg of Mg<sup>2+</sup> in T2D patients group improved HbA1c, insulin levels (ILs), C-peptide, and HOMA-IR and subsequently reduced IR and also improved the glycemic control indicators after 3 months of intervention.<sup>[10]</sup> As well, a meta-analysis that was carried out in 2006 to evaluate the effect of oral Mg<sup>2+</sup> supplementation on glycemic control revealed that a median Mg<sup>2+</sup> dose of 360 mg/day was associated with significantly lower FG in treatment groups, suggesting improved glucose control.<sup>[27]</sup> A recent small, randomized, placebo-controlled trial in obese, nondiabetic, IR individuals demonstrated that 365 mg/day of Mg<sup>2+</sup> for 6 months significantly lowered FG, fasting insulin (FI), and IR and improved insulin sensitivity.<sup>[28,29]</sup> Solati *et al.* have demonstrated that oral Mg<sup>2+</sup> supplementation, during 4 months or more, reduced the FG concentrations as compared with people who received Mg<sup>2+</sup> supplementation for less than 4 months. They also stated that Mg<sup>2+</sup> supplementation is related to significant decrease in low-density lipoprotein (LDL) and cholesterol,<sup>[30]</sup> as mentioned by other studies.<sup>[31]</sup> In explaining this issue, it should be stated that Mg<sup>2+</sup> increases the activity of lipoprotein lipase enzyme as described by Rayssiguier and Gueux. In other words, increased secretion of catecholamines due to Mg<sup>2+</sup> deficiency in the body is associated with increases in lipolysis.<sup>[32]</sup> With increasing lipolysis and subsequent enhancement in plasma free fatty acids, a series of reactions lead to an increase in very LDL and the synthesis and secretion of triglycerides (TGs) and also enhance plasma TG concentration.<sup>[30,32]</sup> Table 1 lists a number of studies that have examined the role of Mg<sup>2+</sup> in improving IR.

**Table 1: Studies that have examined the role of magnesium in improving insulin resistance**

Source	Doses	Time of administration	Protective effects of Mg <sup>2+</sup>	
			Effect	References
MgSO <sub>4</sub>	1 or 2 mg/kg diet	4 weeks	Mg <sup>2+</sup> supplementation improved glucose tolerance, lowered BG levels, lipid perturbations and HOMA-IR index. Mg <sup>2+</sup> , on the other hand, was able to increase insulin sensitivity and INR and GLUT4	[2]
MgSO <sub>4</sub>	10 g/l drinking water	12 weeks	MgSO <sub>4</sub> lowered BG, glucose tolerance and HbA1c relative to the diabetic group. Also Mg <sup>2+</sup> increased GIR in diabetics	[3]
Elemental high-potency, highly absorbable magnesium (oxide, gluconate, lactate)	250 mg/d tablet	3 months	Administration of Mg <sup>2+</sup> indicated a significant improvement in HbA1C, insulin levels, C-peptide, HOMA-IR and HOMA-β%	[10]
MgCl	300 mg/day (50 gr of MgCl <sub>2</sub> by 1000 ml of solution)	12 weeks	Mg <sup>2+</sup> -supplemented subjects significantly increased their serum Mg <sup>2+</sup> levels and reduced HOMA-IR index	[23]
Mg <sup>2+</sup> supplementation	360 mg/day	4–16 weeks	Oral Mg <sup>2+</sup> supplementation was effective in reducing plasma fasting glucose levels and raising HDL cholesterol in patients with T2D diabetes	[27]
Mg–aspartate–hydrochloride	365 mg/day	6 months	Mg <sup>2+</sup> supplementation resulted in a significant improvement of fasting plasma glucose and some insulin sensitivity indices. Mg <sup>2+</sup> prevent IR and subsequently T2D diabetes	[28]
MgSO <sub>4</sub>	300 mg/d	3 months	Administration of Mg <sup>2+</sup> significantly improved fasting BG, 2 h postprandial glucose, lipid profile, and hepatic enzymes	[30]
Magnesium oxide	250 mg/day	6 weeks	Mg <sup>2+</sup> significantly improved glycemic control and lipid profiles	[31]
MgSO <sub>4</sub>	10 g/l of	16 weeks	Administration of MgSO <sub>4</sub> improved IPGTT, lowered BG levels, and decreased FoxO1 and PEPCK genes and proteins expression in muscle and liver	[57]

IR: Insulin resistance, HOMA-IR: Homeostatic model assessment for IR, BG: Blood glucose, INR: Insulin receptor, HbA1c: Hemoglobin A1c, GLUT: Glucose transporter, T2D: Type 2 diabetes mellitus, HDL: High-density lipoprotein, Mg<sup>2+</sup>: Magnesium, MgSO<sub>4</sub>: Magnesium sulfate IPGTT: Intraperitoneal glucose tolerance test: for measures the clearance of an intraperitoneally injected glucose load from the body. It is used to detect disturbances in glucose metabolism that can be linked to condition such as diabetes or metabolic syndrome., GIR: Glucose infusion rate: shows the rate at which glucose enters the cell and is inversely related to IR

Taken together, these findings suggest that Mg<sup>2+</sup> supplementation in the diet of people with IR can help enhance insulin sensitivity. In the following of this study, we reviewed the effectiveness of Mg<sup>2+</sup> in reducing IR and mechanisms involved in this process.

### Search Strategy

To identify relevant studies, the search was performed in Google Scholar, PubMed, Scopus, and Web of Science. The search was carried out from 1983 until 2021. The keywords used in the search were insulin resistance, skeletal muscle, liver, pancreases, magnesium, Mg<sup>2+</sup>, and inflammation without language or date restrictions. The title and abstract of all the articles were studied and those describing mechanisms of IR and therapeutic effects of Mg<sup>2+</sup> in reducing IR were finally selected.

### The Role of Mg<sup>2+</sup> on Insulin Secretion from Pancreatic Beta-Cells

Some studies found evidence about the significant effect of Mg<sup>2+</sup> on insulin secretion and BG control in diabetic and nondiabetic patients,<sup>[1,6]</sup> whereas other studies have found

no significant association between normal intracellular Mg<sup>2+</sup> concentrations and insulin secretion.<sup>[33-36]</sup> Therefore, based on some studies, Mg<sup>2+</sup> has a fundamental role in the function of many enzymes in these metabolic pathways.<sup>[37,38]</sup>

As an initial step in insulin secretion, glucose uptake into the pancreatic β-cell via GLUT2. In cellular metabolism, adenosine triphosphate (ATP) is generated through glycolytic pathway from glucose.<sup>[39]</sup> In the path of ATP synthesis in beta-cells, glucose converts to glucose-6-phosphate (G6P) by glucokinase (GK). The rate of GK activity depends on magnesium ATP (Mg<sub>ATP</sub>).

On the other hand, with the binding of ATP to the Kir6.2 subunits, the K<sub>ATP</sub> channels are closed and opening of these channels depends on the binding of Mg<sub>ATP</sub> to the sulfonylurea receptor subunit (SUR1). After closing K<sub>ATP</sub> channels, pancreatic beta-cell membranes depolarize. These events stimulate electrical activity that opens the voltage-gated calcium (Ca<sup>2+</sup>) (L-type) channels to stimulate insulin secretion.<sup>[1,11]</sup> The role of Mg<sup>2+</sup> in the regulation of various stages of insulin secretion is discussed below.

## Glucokinase

In the path of ATP synthesis in beta-cells, glucose converts to G6P by GK. The rate of GK activity depends on Mg<sub>ATP</sub>.<sup>[11,40]</sup>

## Glycolysis

After converting glucose to G6P via glycolysis and the Krebs cycle, the level of ATP significantly increases. In this metabolic process, Mg<sub>ATP</sub> acts as a cofactor for numerous enzymes.<sup>[11,25]</sup> A number of studies have found that Mg<sup>2+</sup> acts as an essential cofactor in all ATP-transfer reactions. In addition, this cation is known as rate-limiting enzyme of glycolysis.<sup>[41,42]</sup>

## K<sub>ATP</sub> Channel

The first investigations into K<sub>ATP</sub> channels in 1984 found that these channels are the important regulators of the membrane potential in pancreatic beta-cells.<sup>[43]</sup> The pancreatic K<sub>ATP</sub> channel is composed of four Kir6.2 subunits and four SUR1 subunits. The activity of these channels is controlled by the intracellular ATP-to-adenosine diphosphate (ADP) ratio. In the presence of Mg<sup>2+</sup>, binding of Mg<sub>ATP</sub> and Mg<sub>ADP</sub> to the SUR1 subunits promotes channel opening. High glucose levels stimulate glycolysis that shifts the balance toward ATP, which simultaneously reduces the level of Mg<sub>ADP</sub> and consequently closed K<sub>ATP</sub> channels that increased insulin secretion.<sup>[11,25,44]</sup> The role of Mg<sup>2+</sup> on insulin secretion can be justified by its Ca<sup>2+</sup> antagonism, and this role may be dependent on the cytosolic Ca<sup>2+</sup>/Mg<sup>2+</sup> ratio and not exclusively on Mg<sup>2+</sup> concentration.<sup>[25,45,46]</sup>

## L-Type Ca<sup>2+</sup> Channel

Following the increasing ATP levels and closure of K<sub>ATP</sub> channels, the pancreatic beta-cell membrane becomes depolarized. This causes activating Ca<sup>2+</sup> influx via the voltage-dependent L-type Ca<sup>2+</sup> channel.<sup>[11]</sup> It has now been suggested that hypomagnesemia decreases the expression of L-type Ca<sup>2+</sup> channels that reduces insulin secretion indirectly.<sup>[47]</sup> Another plausible role of Mg<sup>2+</sup> is controlling L-type Ca<sup>2+</sup> channel opening via blocking Ca<sup>2+</sup> uptake into adipocytes.<sup>[5]</sup>

## Insulin Vesicle Release

Insulin-containing vesicles exocytose out of the cell by increasing Ca<sup>2+</sup> levels and binding this cation to these vesicles.<sup>[25]</sup> Mg<sup>2+</sup> blocks L-type Ca<sup>2+</sup> channels, thus regulating insulin secretion.<sup>[11]</sup> Atwater *et al.* have mentioned that Ca<sup>2+</sup>/Mg<sup>2+</sup> ratio is the most important factor in induced insulin secretion in perfused rat pancreas and mouse islets.

The results emphasize that stimulation of insulin secretion depends on decreasing in physiological Mg<sup>2+</sup> concentrations, but insulin secretion was inhibited only by decreased

Ca<sup>2+</sup> levels. In this regard, as long as the Ca<sup>2+</sup>/Mg<sup>2+</sup> ratio remains constant, the amount of insulin secretion does not change. Decreasing the level of Mg<sup>2+</sup> without changing the level of Ca<sup>2+</sup> changes this ratio, which can affect insulin secretion.<sup>[48]</sup>

## Effects of Mg<sup>2+</sup> on Insulin Signaling Kinases Activity

A growing body of literature has been introduced Ras–MAPK pathway as a regulator for gene expression and insulin-associated mitogenic effects. Some metabolic processes such as glucose uptake mobilization, lipogenesis, and also glycogen and protein synthesis are stimulated by PI3K/Akt kinase pathway. With the binding of insulin to the INR, plasma membrane subunits of the INR (insulin receptor substrate [IRS] and Shc proteins) undergo phosphorylation that changes receptor conformation.<sup>[1]</sup> Shc phosphorylation activates the Ras–MAPK pathway. IRS phosphorylation, on the other hand, triggers a cascade of events through the phosphoinositide 3-kinases-protein kinases (PI3K–Akt) pathway which eventually leads to the production of a second messenger phosphatidylinositol-3,4,5-triphosphate (PIP3). PIP3 induces phosphorylation of 3-phosphoinositide-dependent protein kinase-1 that activates downstream Akt. Akt has an essential role in the regulation of glucose transport, lipid synthesis, gluconeogenesis, and glycogen synthesis.<sup>[1,49]</sup>

In this regard, Mg<sub>ATP</sub> acts as a phosphorylation factor for INR tyrosine kinase (IRTK) and other signal kinases that initiate a cascade of phosphorylation events. On the other hand, Mg<sup>2+</sup> has a central role in the regulation of glucose control and metabolic effects of insulin via interacting with TK of INR and other enzymes. Evidence highlights that Mg<sup>2+</sup> level is the important factor in inducing downstream signal kinases after binding the insulin to the INR.<sup>[1]</sup> Moreover, Mg<sup>2+</sup> by binding to the regulatory site of the IRTK induces regulatory influence. The affinity of this site to Mg<sub>ATP</sub> is dependent on free Mg<sup>2+</sup> concentration.<sup>[1,6]</sup> A growing body of studies reveals that a decrease in Mg<sup>2+</sup> concentration is associated with an increase in IR.<sup>[50,51]</sup> In IR cell models, there is an impaired response of the TK to insulin stimulation.<sup>[50-52]</sup> In addition, Mg<sup>2+</sup> acts as a limiting factor in carbohydrate metabolism. Because Mg<sup>2+</sup> is necessary for phosphorylation activities of some enzymes such as glutathione peroxidase, superoxide dismutase, and catalase.<sup>[50,52]</sup> It is by now generally accepted that Mg<sup>2+</sup> has a central role for autophosphorylation of the b-subunits of the INR. In this regard, two Mg<sup>2+</sup> ions bind to the TK domain that enhancing the affinity of TK for ATP molecules.<sup>[11,53]</sup> Siddiqui *et al.* demonstrated that enhancing intracellular Mg<sup>2+</sup> concentration improves some biological processes such as TK activity, glucose transport, and consequently insulin secretion.<sup>[54]</sup>

## Effects of Mg<sup>2+</sup> on Glucose Metabolism in the Muscle

Skeletal muscle uptake approximately 80% of dietary glucose via GLUT4.<sup>[11,55]</sup> Many literatures highlights that Mg<sup>2+</sup> could stimulate GLUT4 gene expression.<sup>[2,56]</sup> For example, a recent study in diabetic rats has indicated that oral Mg<sup>2+</sup> supplementation enhanced muscle *GLUT4* gene expression that decreases serum glucose levels to the normal range.<sup>[57]</sup> A group of researchers from Korea has been proved that diabetic mice fed with Mg<sup>2+</sup>-rich seawater have shown enhanced GLUT1 and GLUT4 expression in the skeletal muscle.<sup>[58]</sup> Insulin and also insulin-like growth factor 1 induced Akt cascade through PI3K by phosphorylation of IRS1.<sup>[59,60]</sup> The Akt protein kinase is consists of three isoforms that have a major contributor to tumor initiation and also tumor metastasis. These isoforms have been found in rodent muscle while insulin is a ligand for Akt1 and to a lesser extent Akt2.<sup>[59,61]</sup> Previous research showed that Mg<sup>2+</sup> administration increases Akt2 transcription ~2.6 fold higher in the diabetic animal case group, compared with the diabetic control group via enhancing in *IRS1* gene expression.<sup>[59]</sup> Some scientists demonstrate that Mg<sup>2+</sup> administration in diabetic animal models for 16 weeks enhances Akt2 transcription.<sup>[59]</sup> Following research in this area, researchers stated that Mg<sup>2+</sup> supplementation increases INR and GLUT4 level, whereas before Mg<sup>2+</sup> therapy, the levels of these proteins were low in uncontrolled diabetic conditions.<sup>[2]</sup> One investigation not only confirmed other studies that demonstrated that Mg<sup>2+</sup> induces glucose metabolism in muscle cells by transporting GLUT4-containing vesicles to the plasma membranes.<sup>[2]</sup> This result was also confirmed by experiments performed on rats by Morakinyo *et al.*<sup>[2]</sup> A study in 2019 showed that daily administration of 1000 mg/kg MgSO<sub>4</sub> was associated with an increase in GLUT4 gene expression in all the diabetic groups.<sup>[8]</sup> Solaimani *et al.* provided further evidence that magnesium sulfate (MgSO<sub>4</sub>) supplementation increase GLUT4 mRNA expression about 23%.<sup>[56]</sup>

Various approaches have been suggested that nuclear receptors called peroxisome proliferator-activated receptors (PPARs) play a controlling role in glucose metabolism in diabetics.<sup>[62,63]</sup> PPAR has three isoforms including PPAR- $\alpha$ , PPAR- $\beta/\delta$ , and PPAR- $\gamma$ <sup>[63,64]</sup> that expressed in adipose, muscle, and liver tissues.<sup>[63]</sup> Each isoform plays different roles *in vivo*.<sup>[63,65]</sup> For instance, PPAR- $\gamma$  is mainly synthesized in white adipose tissue and muscle<sup>[63,66]</sup> and has essential roles in glycemic control via decreasing plasma ILs and increasing insulin sensitivity.<sup>[63,67]</sup> In addition, its ligand increases the expression of GLUT4 mRNA and fatty acid storage in fat tissues. Scientists believe that PPAR- $\gamma$  agonist receptor therapy improves muscle glucose homeostasis by inducing insulin cell signaling. It was reported in the literature that MgSO<sub>4</sub> supplementation for 16 weeks in diabetic rats enhances PPAR- $\gamma$  transcription and expression.<sup>[63]</sup> These studies provide support for the

central role of the Akt2 gene in glucose homeostasis after Mg<sup>2+</sup> therapy. This is because the intracellular level of Mg<sup>2+</sup> concentration is inversely related to BG levels. In summary, Mg<sup>2+</sup> mediates effective metabolic control by autophosphorylation and stimulation of insulin.

## Effects of Mg<sup>2+</sup> on Glucose Metabolism in the Liver

Scientists believe that the main reason for the rapid rise in BG is the high production of glucose by the liver.<sup>[57,68]</sup> According to research findings, Mg<sup>2+</sup> is an essential factor in the function of liver enzymes. For instance, it has a fundamental function in gluconeogenesis and glycogenesis pathways in the liver. In this regard, seawater Mg<sup>2+</sup> administration in diabetic mice model decreases phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) mRNA expression.<sup>[25]</sup> Findings from one study demonstrated that gluconeogenic genes such as PEPCK are inhibited by Mg<sup>2+</sup><sup>[57]</sup> and hepatic glucose production is diminished by Mg<sup>2+</sup> supplementation to maintain BG levels near normal.<sup>[8,25]</sup> In the same way, Mg<sup>2+</sup> supplement therapy has positive effects on the ISI-HOMA and fasting plasma glucose, as an indicator of hepatic IR and hepatic glucose production, respectively.<sup>[28,69,70]</sup> Mg<sup>2+</sup> acts as a significant cofactor for catalytic activity of phosphofructokinase-1 (PFK-1). This enzyme is a key enzyme and rate-limiting step that catalyzes glycolysis.<sup>[8,11]</sup> In general, it can be stated that Mg<sup>2+</sup> has cofactor activity for a large number of enzymes that involve in the glycolytic pathway as kinases or phosphorylase. By enhancing the level of intracellular Mg<sup>2+</sup>, these enzymes keep their activated form that this situation reduces the risk of hyperglycemia by increasing the ATP production through converting glucose to pyruvate and eventually ATP via citric acid pathway. Results from one study support the idea that the activated form of protein kinase (AMPK) system acts as a key factor in regulating energy balance in the cell and consequently the whole body. AMPK inhibits gluconeogenic gene expression and hepatic glucose production and thus maintains BG concentrations at a normal level. Mg<sup>2+</sup> can activate AMPK in a Ca<sup>2+</sup>-dependent manner that activates PFK-1 in the glycolytic pathway.<sup>[8,71]</sup> In addition, this cation can decrease the effect of glucagon in the liver.<sup>[13,25]</sup> Glucagon upregulates hepatic glucose production, glycogenolysis, gluconeogenesis, fatty acid oxidation, and lipolysis.<sup>[25]</sup> In diabetic animals model, Mg<sup>2+</sup> supplementation downregulates the glucagon receptor that leads to improve insulin sensitivity.<sup>[71]</sup>

Forkhead box protein O1 (FoxO1) is a transcription factor that increases hepatic glucose production by regulating target gene expression.<sup>[25,72]</sup> This factor is controlled by Akt-mediated phosphorylation at three highly conserved Akt phosphorylation sites (Thr-24, Ser-253, and Ser-316) on its genome.<sup>[25,73]</sup> Phosphorylation of this factor causes it to leave the nucleus and thereby inactivating transcription

of gluconeogenic enzymes. This situation increases the chance of glucose uptake by cells and ultimately balances glucose levels. On the other hand, FoxO1 binds to insulin-response elements in the promoters of PEPCK and G6Pc genes and increases the expression of these genes.<sup>[73,74]</sup> In this regard, overexpression of FoxO1 induces gluconeogenesis, hyperglycemia, and IR. More recent evidence reveals that Mg<sup>2+</sup> supplementation in diabetic animal models decreases the expression of hepatic FoxO1 and consequently suppresses gluconeogenic genes, such as PEPCK.<sup>[25,57]</sup> Figure 1 summarizes the role of Mg<sup>2+</sup> in reducing IR in the pancreas, muscle, and liver.

### Effects of Mg<sup>2+</sup> on Low-Grade Systemic Inflammation

Inflammation is a key factor in the development of IR.<sup>[1,75]</sup> Interleukin-1 (IL-1) is an inflammatory cytokine that secretes by multiple tissues, particularly adipose tissue. This factor reduces the expression of IRS-1 and GLUT4 that eventually causes IR.<sup>[1,76]</sup> Production of IL-1 regulated by diet-induced metabolic stress. IL-1 is involved in the production of another inflammatory factor called IL-6 that in turn causes IR by inhibiting the PI3K pathway.<sup>[75,77]</sup>

A major factor involved in the production and secretion of some inflammatory mediators such as IL-1, IL-6, IL-8, IL-18, and cyclooxygenase-2 is a mediator called tumor necrosis factor-alpha (TNF $\alpha$ ). TNF $\alpha$  induces gene expression of the mentioned factors. Some recent studies have suggested positive associations between the serum level of TNF $\alpha$  and pathophysiology of IR. The authors of these studies have believed that TNF $\alpha$  is one of the most important factors in the development of IR.<sup>[77]</sup> Inhibition of TNF $\alpha$  stimulates some pathways such as

nuclear factor kappa B (NF- $\kappa$ B) and c-Jun NH2-terminal kinases (JNK).<sup>[1,26,77]</sup> On the other hand, some studies provide several reasons for the role of TNF $\alpha$  in the development of diabetes and its complications.<sup>[63]</sup>

It has been suggested that hyperglycemia induces NFKB gene expression as a proinflammatory agent which leads to IR.<sup>[63]</sup>

It was reported in one article that drinking Mg<sup>2+</sup>-enriched water could not inhibit the expression of the *NFKB* gene in animal diabetic models, but Mg<sup>2+</sup> administration for 16 weeks could enhance GLUT4 expression and consequently decrease BG level via decreasing NFKB protein.<sup>[63]</sup> Activated NFKB and JNK induce ser307 phosphorylation in IRS-1 that leads to blocking Tyr phosphorylation of IRS-1.<sup>[77]</sup> In addition, TNF $\alpha$  could decrease Akt activity and GLUT4 gene expression simultaneously which consider as important pro-inflammatory factors.<sup>[78]</sup> The majority of prior suggested that Mg<sup>2+</sup> therapy reduces production of some pro-inflammatory factors such as interleukins (IL1, IL-6), TNF, vascular cell adhesion molecule-1, and plasminogen activator inhibitor-1. Furthermore, this cation can enhance production and activity of the antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, catalase, and also cellular and tissue levels of some antioxidants such as glutathione, Vitamin C, Vitamin E, and selenium.<sup>[1,25,79]</sup> According to the above and based on the results of studies, Mg<sup>2+</sup> decreases the development of chronic low-grade inflammation by blocking the production of inflammatory mediators.<sup>[79]</sup>

### Effects of Mg<sup>2+</sup> on Oxidative Stress

Persistent and prolonged chronic hyperglycemia promotes progressive accumulation of nonenzymatic glycation

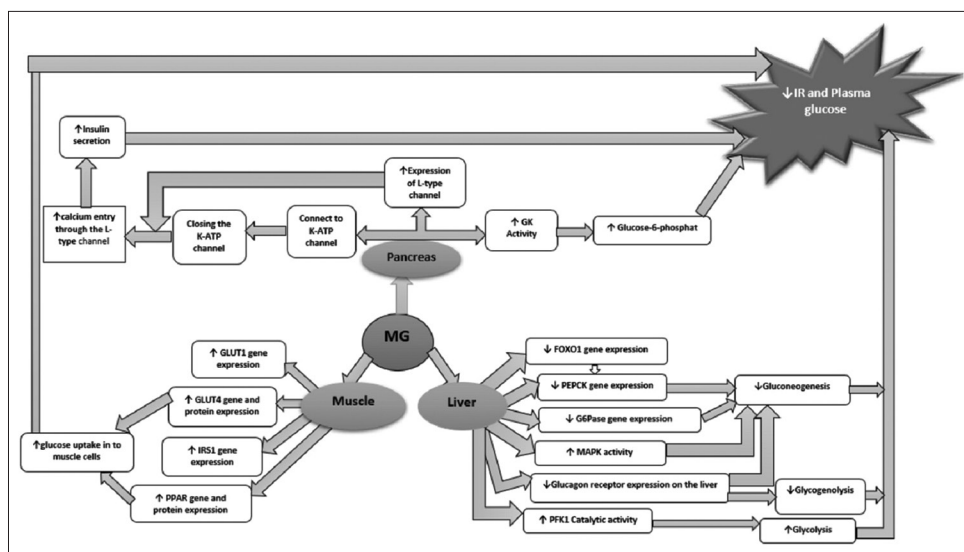


Figure 1: Role of magnesium in reducing insulin resistance in the pancreas, muscle, and liver. GLUT1: Glucose transporter 1, GLUT4: Glucose transporter 4, IRS1: Insulin receptor substrate 1, Mg: Magnesium, PPAR: Peroxisome proliferator-activated receptors, FOXO1: Forkhead box protein O1, PEPCK: Phosphoenolpyruvate carboxykinase, G6Pase: Glucose 6-phosphatase, MAPK: Mitogen-activated protein kinase, PFK-1: Phosphofruktokinase-1, GK: Glucokinase

of proteins and oxygen-free radical production<sup>[80-84]</sup> that leads to an increase in oxidative stress (OS) and also can produce permanent chemical alterations in proteins.<sup>[81]</sup> It has been proven that overproduction of reactive oxygen species (ROS) and inadequate antioxidant protection create metabolic and cellular imbalance that plays an important role in the development of DM.<sup>[85]</sup> Mg<sup>2+</sup> therapy can decrease oxidative damage by reducing ROS production.<sup>[86]</sup> This element can prevent the OH formation from hydrogen peroxide via counteracting the redox-active transition metals.<sup>[87]</sup> In diabetic individuals, the concentrations of free radicals are higher than normal.<sup>[88,89]</sup> Damage caused by ROS excessive production for repair causes inflammation. This involves the activation of the NF-κB pathway.<sup>[90]</sup> Mg<sup>2+</sup> therapy blocks the production of pro-inflammatory cytokines by inhibiting NF-κB production.<sup>[91]</sup> Furthermore, Mg<sup>2+</sup> plays a critical role as an anti-inflammatory agent and acts as a Ca<sup>2+</sup> antagonist.<sup>[46]</sup> In the light of previous studies on the relationship between Mg<sup>2+</sup> and mitochondrial function, it has been proven that Mg<sup>2+</sup> improves mitochondrial function through increasing ATP production, decreasing the mitochondrial production of ROS and intracellular Ca<sup>2+</sup> overload, and repolarizing the mitochondrial membranes, as well as by reducing OS.<sup>[25]</sup>

Figure 2 shows the role of Mg<sup>2+</sup> in reducing inflammation and OS, which leads to a decrease in IR.

### Effects of Mg<sup>2+</sup> on Key Mg<sup>2+</sup>-Dependent Enzymes of Carbohydrate and Energy Metabolism

Mg<sup>2+</sup> acts as a rate-accelerating factor in numerous metabolic pathways because Mg<sup>2+</sup> or Mg<sub>ATP</sub> has a crucial role as a cofactor for many enzymes such as gluconeogenesis

enzymes in the liver PEPCK, fructose-1,6-bisphosphatase, pyruvate carboxylase (PC), and G6Pase.<sup>[1,92]</sup> For example, in the path of ATP synthesis in beta-cells, glucose converts to G6P by GK and the rate of GK activity depends on Mg<sub>ATP</sub> concentration.<sup>[93]</sup>

On the other hand, glycogen synthase kinase 3 (GSK3) is a potential regulator for glycogen synthase (GS) activity. Insulin signaling activates PI3K and Akt that lead to enhancing the inhibitory serine phosphorylation of GSK3.<sup>[94]</sup> Mg<sup>2+</sup> ions bind to GSK3 that neutralizing the negative charge on the aspartic acid side chains.<sup>[95]</sup> In addition, Mg<sup>2+</sup> has an important regulatory role in numerous metabolic activities such as glycolysis and the Krebs cycle.<sup>[96,97]</sup> It regulates glycolytic enzymes, such as hexokinase, PFK, phosphoglycerate kinase, and pyruvate kinase.<sup>[96,98]</sup>

Mg<sup>2+</sup> is involved in increasing the activity of three important mitochondrial dehydrogenases: isocitrate dehydrogenase and 2-oxoglutarate dehydrogenase complex that stimulated directly by Mg<sup>2+</sup> isocitrate complex and free Mg<sup>2+</sup>, respectively, and pyruvate dehydrogenase complex that is stimulated indirectly by the effect of Mg<sup>2+</sup> on pyruvate dehydrogenase phosphatase. Studies show that Mg<sup>2+</sup> is a rate limiting factor for oxidative phosphorylation when 2-oxoglutarate is the oxidizable substrate.

### Conclusions

Based on the research reviewed in this article, it can be concluded that normal Mg<sup>2+</sup> serum level is essential for optimal functioning of many enzymes in insulin secretion and also glucose and energy metabolism. Mg<sup>2+</sup> is associated with improvement in beta-cell function, decreasing IR, accelerating glucose tolerance, and ultimately, clinical

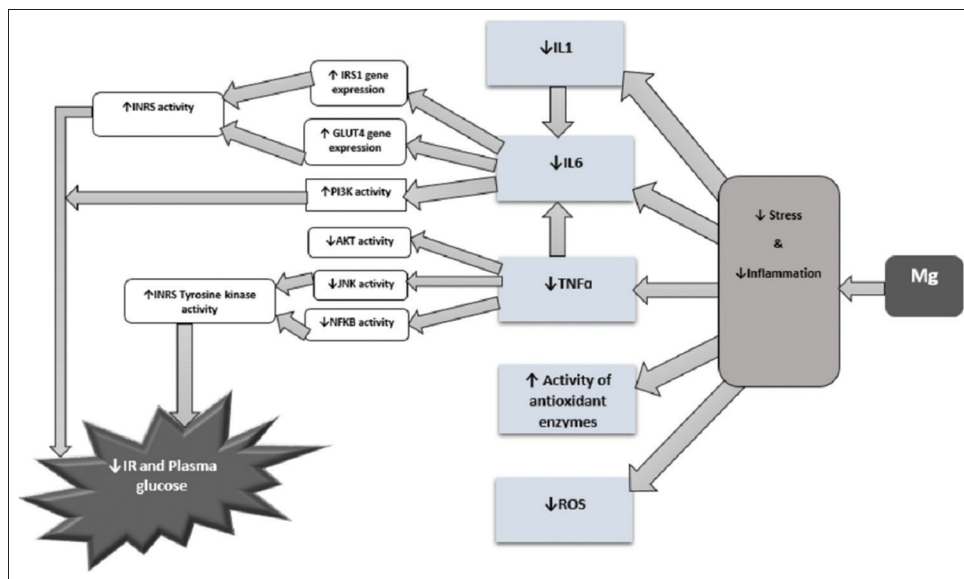


Figure 2: Role of magnesium in reducing inflammation and oxidative stress. INR: Insulin receptor, NFKB: Nuclear factor-kappa B, JNK: c-Jun N-terminal kinases, TNF $\alpha$ : Tumor necrosis factor-alpha, IL1: Interleukin-1, IL6: Interleukin-6, PI3K: Phosphoinositide 3-kinases, GLUT4: Glucose transporter 4, AKT (PKB): Protein kinase B, ROS: Reactive oxygen species, Mg: Magnesium

improvement of T2D. Oral Mg<sup>2+</sup> supplementation and appropriate dietary patterns improve insulin sensitivity and metabolic control in individuals with T2D, suggesting that Mg<sup>2+</sup> is an important factor in the etiology and management of this widespread socially significant disease. In addition, it is worth highlighting that Mg<sup>2+</sup> acts as the insulin sensitizer by regulating TK activity of the receptor of this hormone and autophosphorylation of this receptor b-subunit, with ensuing phosphorylation of its substrates mediators, and favors the manifestation of IR. Mg<sup>2+</sup> improves glucose consumption and glucose tolerance, at least in part, via stimulation of GLUT4 gene expression and translocation and also suppression of the gluconeogenesis pathway and glucagon receptor gene expression by targeting the liver and muscle. According to the results of our study and the previous ones, we can conclude that not only Mg<sup>2+</sup> supplementation can be helpful in diabetes control, but also the effective dosage and duration of supplementation, and the patients who need the supplementation should be considered. Therefore, Mg<sup>2+</sup> is also recommended as an inexpensive, easy-to-use, natural adjuvant therapy for patients with T2D.

### Acknowledgment

The authors would like to express their gratitude to Isfahan University of Medical Sciences, Isfahan, Iran.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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