



**ADDIS ABABA UNIVERSTY**

**FACULTY OF MEDICINE**

**DEPARTMENT OF MEDICAL BIOCHEMISTRY**

**Serum magnesium level and magnesium supplementation on Type 2  
Diabetes Mellitus: systematic review**

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**Addis Ababa University**  
**College of Health Science**  
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As Senior Paper advisor, I hereby certify that I have read and evaluated this senior paper Prepared under our guidance, by **SEFEALEM ASSEFA** entitled: Serum magnesium level and magnesium supplementation on Type 2 Diabetes Mellitus:

I recommended that it can be submitted as fulfilling Master's Degree requirements.

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As member of the Board of examiners of senior paper defense examination, we certify that we have read and evaluated the senior paper prepared by **SEFEALEM ASSEFA** and examined the candidate. We recommend that the Paper be accepted as full filling the Master's Degree requirement for Medical Biochemistry.

Board of examiners

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**Acronyms:**

ADA -American Diabetes Association

ARIC -Atherosclerosis Risk in Communities (Study)

ATP- adenosine triphosphate

cAMP- cyclic adenosine monophosphate

cTAL -cortical thick ascending limb of the loop of Henle (kidney)

DCT -distal convoluted tubule (kidney)

FPG- fasting plasma glucose ,

FIRI - fasting immunoreactive insulin

HbA1c- glycosylated hemoglobin A1c

HDL –C- high density lipoprotein cholesterol

HOMA-IR = homeostasis model assessment for insulin resistance

IRS- insulin-receptor substrates.

LDL -low density lipoprotein

Na/K-ATPase sodium/potassium-adenosine triphosphatase (enzyme)

NIDDM- Non Insulin Dependent Diabetes Mellitus

RDA- Recommended Dietary Allowances (USA)

RDI- recommended dietary intake

TG- triglyceride

UKPDS -United Kingdom Prospective Diabetes Study

VLDL very low density lipoprotein

**Abstract:**

**Objective:** To assess the association between serum magnesium levels and risk of type 2 diabetes and to evaluate the effect of magnesium supplementation on diabetes status.

**Design:** Systemic review

**Data Sources:** By the electronic databases searches journals and retrieved studies published in English language by systematically searching Medline, JCEM, European journals of Clinical Nutrition and American Medical Association from 1992 to Feb 2011 and by manually examining the references of the original articles.

**Study Selection:** includes prospective cohort studies and random case control trials reporting relative risks with 95% confidence intervals for the association between magnesium intake and incidence of type 2 diabetes.

**Results:** Most of the studies included in this review comprising patients of type 2DM showed significantly lower serum magnesium levels compared to the controls. Magnesium supplementation studies also showed resulted in significant improvement in serum levels of Mg, FGL, HDL-C; serum TG levels were found to decrease significantly while plasma cholesterol levels were not affected.

**Conclusions:** Serum magnesium levels were significantly low in type 2 DM compared to the controls group. A direct relationship between the status of Diabetes and Mg levels was also noted. A significant improvement in serum Mg levels, FGL and HDL-C concentration was observed after Mg supplementation. No significant difference in levels of serum cholesterol was noted.

Over all the Magnesium supplementation appeared to have improved the insulin sensitivity and metabolic control in type 2 diabetes mellitus.

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## **1. Introduction:**

Diabetes mellitus (DM) is a group of metabolic disorders, characterized by metabolic disorders related to high levels of serum glucose. The most prevalent form of DM is type 2, previously called maturity-onset or non-insulin-dependent diabetes mellitus (NIDDM), and is generally characterized by insulin resistance. Over the last decades, there has been a rapid increase in the prevalence of type 2 diabetes in parallel with the obesity epidemic. Although obesity is the strongest risk factor for type 2 diabetes, evidences mounting that certain foods and dietary factors may be associated with this disease [1, 2]. In particular, high consumption of whole grains, beans, nuts, fruits and vegetables has been related to a reduced risk of type 2 diabetes [1]. These food items are rich sources of magnesium. Nearly 99% of the total body magnesium is located in bone or the intracellular space. Magnesium is a critical cation and cofactor in numerous intracellular processes, for multiple enzymes involved in glucose metabolism and is suggested to play a role in glucose homeostasis, insulin action [2].

Low magnesium status has repeatedly been demonstrated in patients with type 2 diabetes, which appears to have a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes as well as on the evolution of complications such as retinopathy, thrombosis, and hypertension [27, 34]. The reasons why magnesium deficiency occurs in diabetes are not clear. However, several studies have reported increased urinary magnesium excretion in type 1 and 2 diabetes compared to healthy individuals as the reason of hypomagnesaemia [1, 2, 27]. Some studies also reporting a correlation between glycemic control and urinary magnesium loss [28, 34]. Low dietary intake may also contribute to low magnesium status in diabetics, that patients with type 2 diabetes are often overweight, and may consume a diet higher in fat and lower in magnesium density than non-diabetics. Impaired intestinal absorption might also contribute to low magnesium status in diabetics.

In the Atherosclerosis Risk in Communities (ARIC) Study, a dose response inverse relation between serum magnesium concentrations and the incidence of type 2 diabetes was observed amongst white participants [28]. Several subsequent large prospective cohort studies have

reported a statistically significant reduction in risk of type 2 diabetes associated with increased magnesium intake.

In humans, several experimental metabolic studies, have suggested that magnesium supplementation has beneficial effects on glucose metabolism, insulin action and / or insulin sensitivity [3, 4, 39]. In addition, cross-sectional studies have found an inverse association between magnesium intake and fasting insulin concentrations, a good marker of insulin resistance.

The aim of this review is to evolve a clear evidences from different controlled and cohort studies about the association between magnesium intake and risk of type 2 diabetes following the main discussions in literatures compiled on Magnesium and diabetic, in the last nineteen years (1992–2011), ranging the consensus and controversies.

## **2. Review of Literatures:**

### **2.1 Magnesium: metabolism, function and deficiency:**

Magnesium: Magnesium is the fourth most abundant mineral element and it is the most abundant cation in the body and within the cell second only to potassium. The adult human body ( 70 kg) contains 21 to 28 gm of magnesium ( approximately 1 mol). Of this about 60% is in bone, 20% in skeletal muscle, 19% in other cells and 1% in extra cellular fluid [11].

### **2.2 Biochemistry:**

An alkaline earth metal, magnesium has chemical properties distinctly different from those of the transition metals. Compared with transition metals magnesium interacts with other chemical species with a stronger electrostatic bonding component and a relative preference for oxygen over nitrogen atoms. There are two major roles for magnesium in biological systems:

- It can compete with calcium for binding sites on proteins and membranes.
- It can form chelates with important intracellular anionic ligands, notably adenosine triphosphate (ATP).

Magnesium catalyses or activates more than 300 enzymes in the body, acts as a n essential cofactor for enzymes concerned with cell respiration, glycolysis and transmembrane transport of other cations. Notably, It is a cofactor for ATP, an important membrane stabilizing agent, required for the structural integrity of numerous intracellular proteins and nucleic acids, a substrate or cofactor for important enzymes such as adenosine triphosphatase, guanosine triphosphatase, phospholipase C, adenylate cyclase, and guanylate cyclase; a regulator of ion channels; an important intracellular signaling molecule; and a modulator of oxidative phosphorylation [6]. Magnesium can affect enzyme activity by binding the active site of the enzyme ( pyruvate kinase, enolase ) by ligand binding (ATP-requiring enzymes), by causing conformational changes during the catalytic process (Na-K ATPase) and by promoting aggregation of multi enzyme complexes[6,9].

Finally, magnesium is intimately involved in nerve conduction, muscle contraction, potassium transport, and calcium channels. Because turnover of magnesium in bone is so low, the short-term body requirements are met by a balance of gastrointestinal absorption and renal excretion.

Therefore, the kidney occupies a central role in magnesium balance. Factors that modulate and affect renal magnesium excretion can have profound effects on magnesium balance. In turn, magnesium balance affects numerous intracellular and systemic processes [6].

### 2.3 Magnesium Distribution:

The total body Mg content is approximately 24 g (1 mol) per 70 kg is predominantly distributed in bone, muscle, and soft tissue, with the highest concentrations being found in skeletal and cardiac muscle cells (about 55%). Mg in bone is adsorbed to the surface of hydroxyapatite crystals, and only about one third is readily available as an exchangeable pool and probably serves as a reservoir for maintaining a normal extracellular magnesium concentration. About 45% of the body's magnesium is intracellular [6].

Table 2.1: Total distribution of magnesium (Mg) in the body.

TOTAL BODY MAGNESIUM (MG) DISTRIBUTION			
Location	Percent of Total	Mg Content, mmol*	Mg Content, mg*
Bone	53	530	12720
Muscle	27	270	6480
Soft tissue	19.2	192	4608
Erythrocyte	0.5	5	120
Serum	0.3	3	72
Total		1000	24000

\*data typical for a 70 kg adult

(James T. McCarthy Rajiv Kumar Divalent Cation Metabolism: Magnesium)

#### FIGURE 4-2

#### Intracellular distribution of magnesium:

Only 1% to 3% of the total intracellular Mg exists as the free ionized form of Mg, which has a closely regulated concentration of 0.5 to 1.0 mmol, by intracellular sequestration and complexation. Very little change occurs in the concentration of intracellular free Mg, even with large variations in the concentrations of total intracellular or extracellular Mg [6, 7, 8].

Our understanding of the concentration and distribution of intracellular Mg has been studied by the development of electron microprobe analysis techniques and fluorescent dyes using microfluorescence spectrometry in addition to the flame atomic absorption spectroscopy (FAAS) technique.

Intracellular Mg is predominantly combined with organic molecules (eg. ATPase, cell and nuclear membrane-associated proteins, DNA and RNA, enzymes, proteins, and citrates or sequestered within sub-cellular organelles (mitochondria and endoplasmic reticulum). A

heterogeneous distribution of Mg occurs within cells, with the highest concentrations being found in the perinuclear areas, which is the predominant site of endoplasmic reticulum.

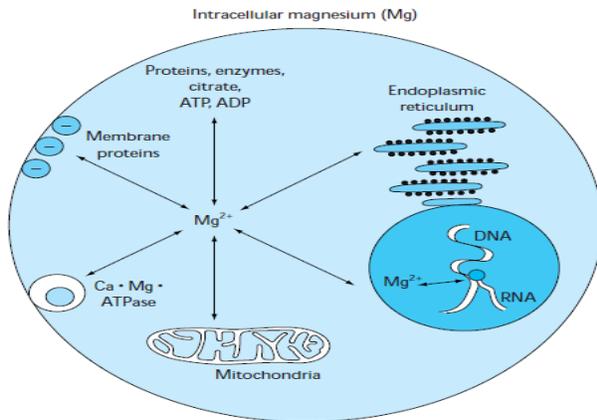


Figure 2.1: Intracellular distribution of magnesium

(James T. McCarthy Rajiv Kumar Divalent Cation Metabolism: Magnesium)

**FIGURE 4-3**

Movement of  $Mg^{2+}$  between intracellular and extracellular space and within intracellular compartments. Stimulation of adenylate cyclase activity (eg, through stimulation of  $\beta$ -adrenergic receptors) increases cAMP. Increase in cAMP induces extrusion of Mg from mitochondria by way of mitochondrial adenine nucleotide translocase, which exchanges one  $Mg^{2+}$ -ATP for ADP. This slight increase in cytosolic  $Mg^{2+}$  can then be extruded through the plasma membrane by way of a Mg-cation exchange mechanism, which may be activated by either cAMP or Mg.

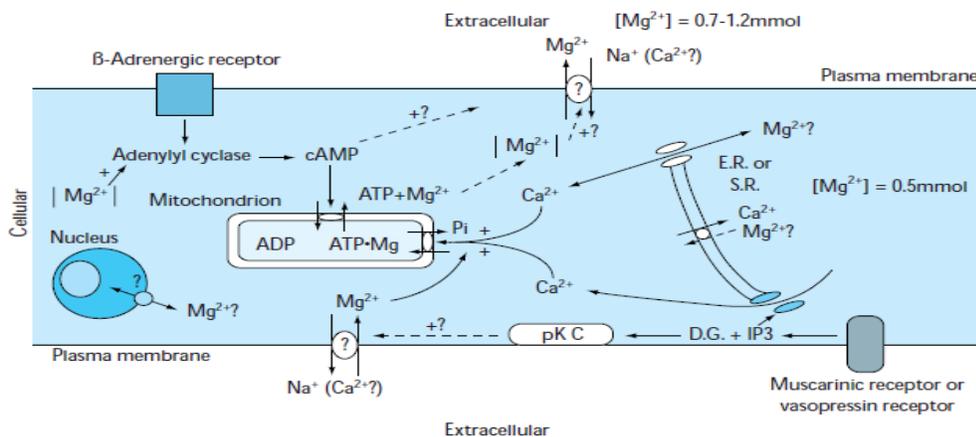


Figure 2.2: Regulation of intracellular magnesium ( $Mg^{2+}$ ) in the mammalian cell.

(James T. McCarthy Rajiv Kumar Divalent Cation Metabolism: Magnesium)

Activation of other cell receptors (*eg*, muscarinic receptor or vasopressin receptor) may alter cAMP levels or produce diacyl- glycerol (DAG). DAG activates Mg influx by way of protein kinase C (pK C) activity. Mitochondria may accumulate Mg by the exchange of a cytosolic Mg<sup>2+</sup>-ATP for a mitochondrial matrix Pi molecule. This exchange mechanism is Ca<sup>2+</sup>-activated and bidirectional, depending on the concentrations of Mg<sup>2+</sup>-ATP and Pi in the cytosol and mitochondria [7].

Inositol 1,4,5-trisphosphate (IP3) may also increase the release of Mg from endoplasmic reticulum or sarcoplasmic reticulum (ER or SR, respectively), which also has a positive effect on this Mg<sup>2+</sup>-ATP-Pi exchanger. Other potential mechanisms affecting cytosolic Mg include a hypothetical Ca<sup>2+</sup>-Mg<sup>2+</sup> exchanger located in the ER and transport proteins that can allow the accumulation of Mg within the nucleus or ER. A balance must exist between passive entry of Mg into the cell and an active efflux mechanism because the concentration gradient favors the movement of extracellular Mg (0.7–1.2 mmol) into the cell (free Mg, 0.5 mmol). This Mg extrusion process may be energy requiring or may be coupled to the movement of other cations. The cellular movement of Mg generally is not involved in the transepithelial transport of Mg, which is primarily passive and occurs between cells [7, 8].

#### **Transport systems of magnesium (Mg):**

Specific membrane associated Mg transport proteins only have been described in bacteria such as *Salmonella*. Although similar transport proteins are believed to be present in mammalian cells based on nucleotide sequence analysis. Both MgtA and MgtB (molecular weight, 91 and 101 kDa, respectively) are members of the adenosine triphosphatase (ATPase) family of transport proteins.

Both of these transport proteins have six C-terminal and four N-terminal membrane-spanning segments, with both the N- and C-terminals within the cytoplasm. Both proteins transport Mg with its electrochemical gradient, in contrast to other known ATPase proteins that usually transport ions against their chemical gradient. Low levels of extracellular Mg are capable of increasing transcription of these transport proteins, which increases transport of Mg into *Salmonella*. The Cor A system has three membrane-spanning segments. This system mediates Mg influx; however, at extremely high extracellular Mg concentrations, this protein can also mediate Mg efflux.

Another cell membrane Mg transport protein exists in erythrocytes (RBCs). This RBC Na<sup>+</sup>-Mg<sup>2+</sup> antiporter facilitates the outward movement of Mg from erythrocytes in the presence of extracellular Na<sup>+</sup> and intracellular ATP. ADP, C-carbon, N-nitrogen[6 ,8].

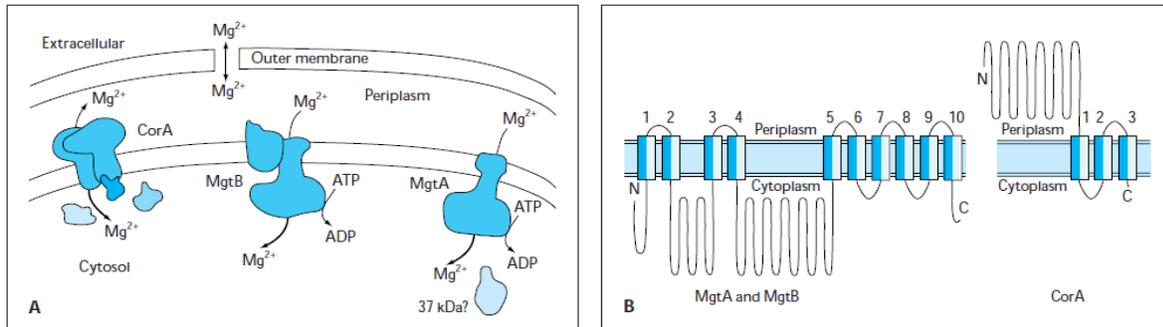


Figure 2.3: Transport systems of magnesium (Mg) (From Smith and Maguire [8])

#### 2.4 Metabolism:

Magnesium intakes vary appreciably an approximate range for US and Western European population being 140 to 180 mg/d. The recommended dietary allowance (RDA) for magnesium is listed in table below and is 270 – 350 mg/d for adults and an intake of about 3.6 mg/kg/d is necessary to maintain Mg balance [11]. Foods high in Mg content include green leafy vegetables (rich in Mg-containing chlorophyll), legumes, nuts, sea foods, and meats. Hard water contains about 30 mg/L of Mg. Dietary intake is the only source by which the body can replete Mg stores [6, 9, 11].

Table 2.2 : Recommended dietary intakes of magnesium [11]

Recommended dietary allowances (RDA)		
Age		Magnesium
Infants	0.0 - 0.5	40
	0.5 - 2.0	60
Children	1 - 3	80
	4 - 6	120
Males	7 - 10	170
	11 - 14	270
	15 - 18	400
	19 - 50, 51 +	350
Females	11 - 14	280
	15 - 18	300
	19-50 ,51+	280
Pregnant	320	
Lactating	355	

Magnesium is absorbed by the body mainly in the small intestine or in the acidic stomach environment. The body may absorb 25% to 75% of dietary magnesium, depending on the body's needs and dietary habits. However this may vary widely because intestinal absorption is inversely related to magnesium intake.

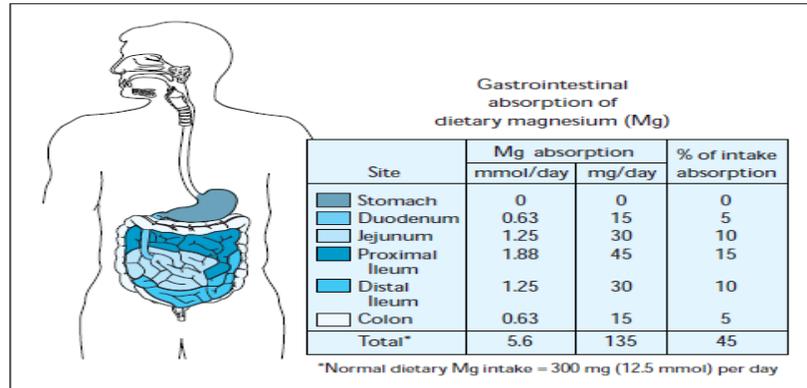


Figure 2. 4: Gastrointestinal absorption of dietary intake of magnesium (Mg)

Magnesium absorption is increased or decreased by certain nutrients and factors.

**Absorption is increased by:**

- ✓ Body needs -growth, pregnancy, lactation, Exercise
- ✓ Vitamin D3 , Lactose & Phosphorus balance
- ✓ Acid environment-hydrochloric acid, citric acid, ascorbic acid (vitamin C)
- ✓ Protein intake and amino acids such as lysine and glycine & Fat intake

**Absorption is decreased by:**

- ✓ Vitamin D deficiency
- ✓ Gastrointestinal problems - in states of nausea, vomiting, or nasogastric suction, mild to moderate losses of Mg occur. In diarrheal states, Mg depletion can occur rapidly owing to both high intestinal secretion and lack of Mg absorption
- ✓ Hypochlorhydria (low stomach acid)
- ✓ Stress, Lack of exercise
- ✓ High fat & protein intake
- ✓ Oxalic acid foods (beet greens, chard, spinach, rhubarb, cocoa)
- ✓ Phytic acid and fibre (present in whole grains)
- ✓ High dietary phosphorus & calcium intake or calcium supplements [6,9].

**Proposed pathways for movement of magnesium across the intestinal epithelium.**

Two possible routes exist for the absorption of Mg across intestinal epithelial cells:

1. **The transcellular route:** its existence is inferred from several observations. No large chemical gradient exists for Mg movement across the cell membrane; however, a significant uphill electrical gradient exists for the exit of Mg from cells. This finding suggests the existence and participation of an energy-dependent mechanism for extrusion of Mg from intestinal cells. If such a system exists, it is believed it would consist of two stages.
  - a. Mg would enter the apical membrane of intestinal cells by way of a passive carrier or facilitated diffusion.
  - b. 2) An active Mg pump in the basolateral section of the cell would extrude Mg.
2. **The intercellular pathway:** Movement of Mg has been demonstrated to occur by both gradient-driven and solvent-drag mechanisms. This path may be the only means by which Mg moves across the intestinal epithelium. The change in transport rates at low Mg concentrations would reflect changes in the “openness” of this pathway. High concentrations of luminal Mg (*eg*, after a meal) are capable of altering the morphology of the tight junction complex. High local Mg concentrations near the intercellular junction also can affect the activities and affect its permeability of local membrane- associated proteins (*eg*, [Na-K ATPase]) [10].

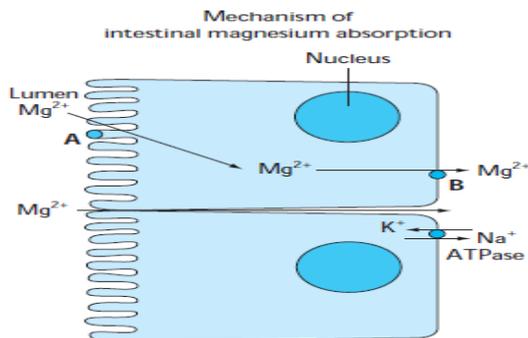


Figure 2.5: Proposed pathways for movement of magnesium (Mg) across the intestinal epithelium.

(From Kayne LH, Lee[10])

Mg homeostasis is maintained by absorption in the gastrointestinal tract and eliminated primarily through urinary excretion, to a smaller extent through gastrointestinal excretions and to a negligible part through sweat, menstrual losses and other corporal secretions. The homeostasis is maintained by increased fractional absorption of Mg in the kidney and the gastrointestinal tract, and by release from internal Mg stores such as bone and skeletal muscle. About one third of bone

Mg resides on the surface of bone either within the hydration shell or on the crystal surface. This fraction is surface exchangeable and is thought to serve as a reservoir to maintain extracellular Mg concentration. Bone provides the highest buffering potential, but skeletal muscle Mg contributes to the buffering and can lose an average of 15 % of its total Mg. Together, the bone and skeletal muscle pools can provide an average of 1.7 mmol/kg body weight equivalents to 15 % of total body Mg to maintain Mg homeostasis.

## 2.5 Renal Handling of Magnesium:

Mg is filtered at the glomerulus, with the ultrafilterable fraction of plasma Mg entering the proximal convoluted tubule (PCT) and about 20% of the filtered Mg has been reabsorbed. The kidneys are the main organs of magnesium homeostasis in maintaining plasma homeostasis in maintaining plasma concentrations.

During periods of magnesium depletion kidney magnesium excretion can be markedly reduced. Only 3 to 5% of the filtered load in the kidney is excreted. Mg reabsorption occurs passively through paracellular pathways and Approximately 20% of the filtered magnesium is reabsorbed in the proximal tubule and whereas nearly 65% of the filtered load is absorbed in the cortical thick ascending limb of the loop of Henle in both juxtamedullary and superficial cortical nephrons. In states of normal hydration, however, very little Mg reabsorption occurs in the PST. A small amount of Mg is absorbed in the distal convoluted tubule. Mg transport in the connecting tubule has not been well quantified. Little reabsorption occurs and no evidence exists of Mg secretion within the collecting duct. Normally, 95% of the filtered Mg is reabsorbed by the nephron. In states of Mg depletion the fractional excretion of Mg can decrease to less than 1%; whereas Mg excretion can increase in states of above-normal Mg intake, provided no evidence of renal failure exists [1, 6–10].

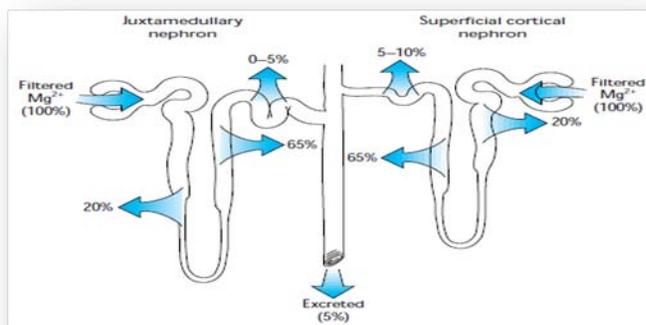


Figure 2.6: The renal handling of magnesium ( $Mg^{2+}$ ).

## 2.6 Clinical Significance:

The best defined manifestation of magnesium deficiency is impairment of neuromuscular junction; examples are hyperirritability, tetany, convulsions and electrocardiographic changes. Magnesium deprivation has been associated with cardiovascular disease through epidemiological evidence that relates low magnesium intake to a high incidence of cardiac deaths, particularly in soft water areas where waterborne magnesium is low and a low incidence of cardiac deaths in hard water areas where magnesium intakes are higher. Hypertension, myocardial infarction, cardiac dysrhythmias, coronary vasospasm and premature atherosclerosis also have been linked to magnesium depletion [12]

Conditions that have been associated with hypomagnesaemia include [15,18 & 21]:

- Primary metabolic disturbances: Inadequate intake , Total parenteral nutrition ,Refeeding syndrome .
- Endocrine disorders: Hyperparathyroidism, Hyperthyroidism, Primary hyperaldosteronism , Bartter's syndrome ,Diabetic Ketoacidosis , Alcoholic Ketoacidosis.
- GIT disorders: Specific absorptive defects, Malabsorption syndromes, Prolonged diarrhoea, Prolonged nasogastric suction , Pancreatitis and Cellulose phosphate ingestion.
- Cellular uptake or redistribution: Administration of epinephrine , Acute pancreatitis, Following correction of respiratory acidosis and Massive blood transfusion
- Chronic alcoholism, alcohol withdrawal
- Increased renal Excretion: Ethanol ingestion , Idiopathic, Following renal transplantation ,Cyclosporine therapy, Aminoglycoside therapy and Diuretic administration such as-Furosemide, Ethacrynic acid ,Bumetanide , Acetazolamide, Thiazides

The treatment should focus on correcting the cause. Those due to inadequate intake or to disorders that reduce intestinal absorption or cause excessive losses into the urine can be corrected by oral supplementation. For example 2 ml of 50% magnesium sulfate heptahydrate every 6<sup>th</sup> hourly-1<sup>st</sup> day, 1 ml of 50%  $MgSO_4 \cdot 7H_2O$  for the following 3-4 days, Cardiac arrhythmias patients with nausea and vomiting magnesium therapy 4.2 mmol  $Mg SO_4$  (1 gm) every 6 hours.

Increased serum magnesium concentrations have been observed in dehydration, severe diabetic acidosis and Addison's disease. Conditions that interfere with glomerular filtration, mainly caused by : Ingestion of magnesium containing compounds like antacids , Rhabdomyolysis , Adrenal insufficiency, Familial benign hypocalciuric hypercalcemia results in retention of magnesium and hence elevation of serum concentrations. Hypermagnesemia leads to an increase in atrioventricular time of the electrocardiogram and end stage renal disease [10, 12].

Treatment: Symptoms and findings can reverse by infusion of calcium salts. Administration of saline and furosemide may help promote excretions of magnesium and also Haemodialysis

## **2.7 Diabetes Mellitus:**

**Definition:** Diabetes mellitus is a group of metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [9,13]. Pathogenic process involved in the development of diabetes range from auto-immune destruction of the beta cells of the pancreas with consequent insulin deficiency to abnormalities in carbohydrate, fat and protein metabolism in diabetes is deficient action of insulin on target tissues [13,14].

American Diabetes Association, delineated DM into categories including type 1, type 2, gestational and several others. Type 1 DM (juvenile-onset) is typically a result of an autoimmune- mediated process in which pancreatic beta-cells in the Islets of Langerhans are destroyed resulting in little or no any insulin production (IDDM). The most prevalent form of DM is type 2, (maturity-onset) or called non-insulin-dependent DM (NIDDM), and is generally characterized by insulin resistance [14].

### **2.7.1 Type 2 Diabetes:**

This form of diabetes is characterized by insulin resistance and usually relative (rather than absolute) insulin deficiency. Most patients with this form of diabetes are obese. Ketoacidosis seldom occurs spontaneously. These patients are at increased risk of developing macrovascular complications. The basis of this form can be genetic factors, environmental factors, malnutrition in utero, age etc.

### **2.7.2 Etiology and Pathogenesis of Type 2 Diabetes:**

Type 2 diabetes, also called adult-onset diabetes or NIDDM, is caused by insulin resistance which is characterized by a decreased effectiveness of insulin. In contrast to type 1 diabetes in which the pancreatic islets are destroyed and no insulin can be synthesized anymore, in type 2 diabetes insulin secretion is normal, elevated or reduced [13,55].

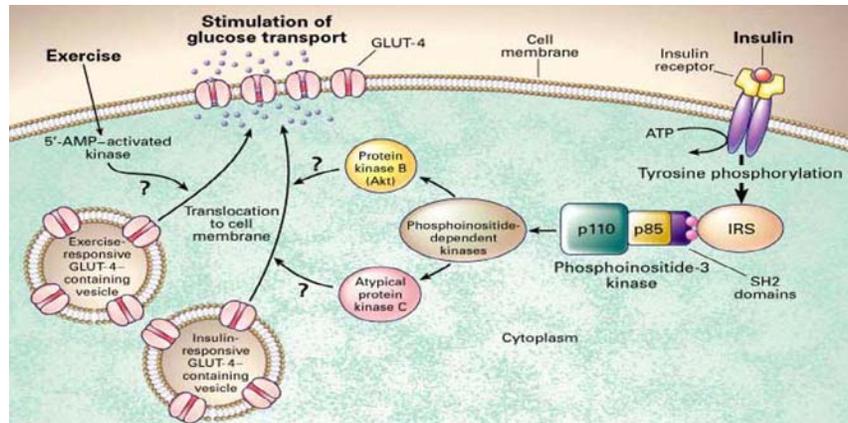
#### **Insulin resistance:**

Insulin resistance is characterized by a decreased effectiveness of insulin. Himsworth & Kerr (1939) [13] were the first to describe insulin resistance, based on glucose infusion. They observed that in obese, older patients insulin injections had a reduced impact. In general, defects of both insulin action and insulin secretion must be present to produce overt type 2 diabetes, Several conditions are related to insulin resistance, ranging from normal (aging, starvation, puberty, pregnancy) to abnormal (obesity, diabetes, polycystic ovarian syndrome, Cushing syndrome, acromegaly [13].

#### **Mechanism of insulin resistance:**

Insulin was discovered in 1921, but only recently the mechanism by which it promotes glucose uptake into the cells has been understood. Insulin resistance primarily affects skeletal muscle, adipose tissue and the liver. There are different families of glucose transporters with different substrate specificities, kinetic properties, and tissue distributions. The Na-linked glucose transporters are restricted to the intestine and the kidney where they actively transport glucose against a glucose concentration gradient. The other groups of transporters convey glucose by facilitated diffusion down glucose-concentration gradients [14].

GLUT-4 is the main insulin-responsive glucose transporter and is located primarily in muscle cells and adipocytes. The most likely explanation for the development of insulin resistance is a post-receptor defect in propagation of the message induced by the binding of insulin to its receptor.



**Figure2. 7:** Insulin-signaling pathway (Shepherd & Kahn, 1999) [56]

In the absence of insulin, about 90 % of GLUT-4 is sequestered intracellularly in vesicles. In response to insulin or exercise, the vesicles containing GLUT-4 move to the plasma membrane, fuse with it, and increase thus the rate of glucose transport into the cells. On removal of insulin stimulation, GLUT-4 is re-internalized into intracellular storage pools. Insulin acts by binding to its receptor in the plasma membrane resulting in phosphorylation of the receptor and different insulin-receptor substrates (IRS). These substrates form complexes with docking proteins leading to the activation of phosphoinositide-3 kinase. This enzyme activates phosphoinositide-dependent kinases participating in the activation of protein kinase B and atypical forms of protein kinase C. Both these kinases are involved in promoting the vesicles containing GLUT-4 to move to the plasma membrane. In contrast, exercise stimulates glucose transport by pathways that are independent of the insulin-signaling pathway and may involve 5'-AMP-activated kinase [56].

It is thought that insulin resistance arises from a defect in the insulin-signaling pathway that regulates the translocation of GLUT-4 containing vesicles to the plasma membrane. Studies have shown that the concentrations of phosphorylated insulin receptor and IRS-1, and the activity of phosphoinositide-3 kinase are reduced in skeletal muscle of obese subjects with insulin resistance and of patients with type 2 diabetes [57].

In response to the increased blood glucose levels, the pancreatic islets produce greater and greater quantities of insulin. The resulting hyperinsulinemia may additionally worsen the situation by a 'down-regulation' of the number of insulin receptors. Although increased insulin secretion may at first compensate the reduced insulin action, the pancreatic  $\beta$ -cells eventually

become overstressed, thus leading to decreasing insulin production and type 2 diabetes. Both, reduced insulin sensitivity and reduced insulin secretion must be present to produce overt type 2 diabetes [13, 56, 57].

Moreover, the chronic elevation of serum free fatty acids due to high fat diets or obesity may contribute to insulin resistance. In obese subjects, especially those with visceral obesity, circulating free fatty acid levels are elevated due to lipolysis of stored triglyceride. In a study with healthy subjects, lipid infusion over 5 hours decreased insulin-mediated glucose uptake in association with a loss of the ability of insulin to stimulate phosphoinositide-3 kinase activity in muscle. Findings from a rat study confirm that high-fat feeding produces impaired activity of phosphoinositide-3 kinase associated with alterations in both protein kinase B and atypical protein kinase C activities in skeletal muscle. The aggravation of insulin resistance is probably caused by oxidation of the free fatty acids into acetyl CoA which stimulates glucose production in the liver and inhibits glucose oxidation in skeletal muscle, thus aggravating hyperglycemia [13, 58].

The hyperglycemia of diabetes develops because of an absolute (type 1 diabetes) or a relative (type 2 diabetes) deficiency insulin, resulting in decreased anabolic and increased catabolic effects. In both type-1 and type-2 diabetes, insulin's actions are also impaired by insensitivity of target tissues. While this is the fundamental defect in type-2 diabetes, hyperglycemia can also induce insulin resistance through glucose toxicity [15].

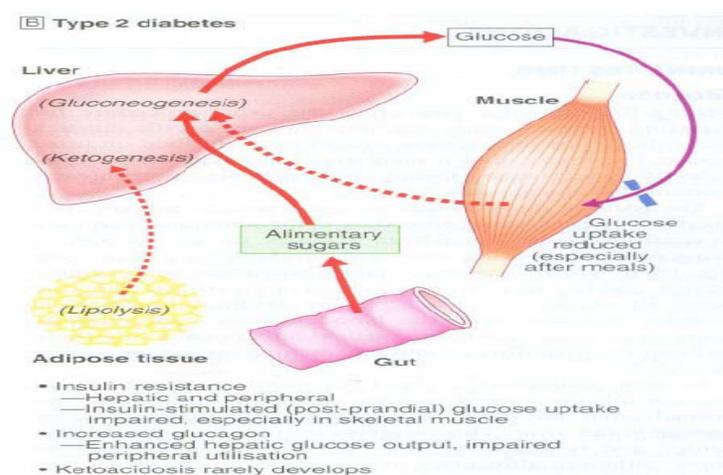


Figure2. 8: metabolic disturbance in diabetes [15]

## 2.8 Tracing Magnesium and Diabetes mellitus Connection

Magnesium plays an important role in carbohydrate metabolism. It may influence the release and activity of insulin, the hormone that helps control blood glucose (sugar) levels. Low blood levels of magnesium (hypomagnesaemia) are frequently seen in individuals with Type 2 diabetes. However, the evidence showing magnesium or adequate magnesium status as having a preventive effect or therapeutic effect on diabetes is inconclusive. Various researches' indicates that the association between blood magnesium levels, dietary magnesium intake, and Type 2 diabetes [9, 27, 34].

The earliest suggestion, made in 1952 by Stutzman and Amatuzio, was based on their observation of lower serum magnesium levels in DM patients [16]. Studies in experimental animals demonstrate that magnesium can retard or prevent the induction of insulin resistance and DM, while a magnesium deficit can predispose to hyperglycemia.

Based on studies in humans, we can estimate that a significant proportion of patients (25 to 40%) with DM are hypomagnesemic, or have suboptimal magnesium status. In the Atherosclerosis Risk in Communities (ARIC) study, Ma and colleagues (1999) investigated the relationship between serum and dietary magnesium and DM [17]. The researchers tested 15,248 subjects and found significantly lower serum magnesium levels in those with DM compared to those without the disease. Researchers also found associations between magnesium levels and both cardiovascular disease and hypertension, probably as a result of the common biochemical mechanisms underlying the damage observed in each of the diseases.

Duplicating the results of the above study, Sasaki and colleagues (2000) demonstrated that the DM patients in their study had lower serum levels of ionized magnesium than healthy controls [18].

In another study (in 1999) from Bangladesh, researchers examined the serum levels of magnesium in patients with malnutrition-related diabetes mellitus (MR-DM) [19]. This type of DM is further divided into two categories- fibrocalculus pancreatic diabetes and protein-deficient DM, and constitutes 55% of all patients with DM in Bangladesh. Patients with MR-DM had significantly decreased serum magnesium levels compared with controls or malnourished patients without DM. Almost 70% of those patients with MR-DM had clinically defined

hypomagnesaemia (serum levels < 0.70 mmol/L) and 90% had hypermagnesuria (urinary magnesium > 335 mmol Mg/mol creatinine).

The researchers suggested these patients' observed alterations in magnesium status resulted primarily from urinary loss of the mineral associated with an osmotic diuresis, which is characteristic of this disease. Malnutrition, with its associated diet poor in vitamins and minerals, further contributes to the magnesium deficit in MR-DM patients.

Many investigations have demonstrated an association between mortality rates among DM patients and the magnesium content of drinking water. Foster H (1987) and Yang CY, et al. (1999) in the U.S reported a significant negative correlation between the magnesium content of drinking water and the mortality rate of DM patients ( $r=0.56$ ) [20, 21]. Similarly, patients with DM from more than 2,633 individual's at different locations in Canada demonstrated a negative correlation between the magnesium content of their drinking water and DM-related mortality rates.

### **2.8.1 Magnesium and Insulin Action**

In support of clinical findings showing an association between hypomagnesemia and poor glucose control observed in diabetic patients, numerous studies have demonstrated an important relationship between magnesium and insulin release and activity. An intracellular enzyme called tyrosine kinase requires magnesium to allow insulin to exert its blood-sugar-lowering effects. Insulin, via its interaction with ligand-activated tyrosine protein kinase-associated receptors, initiates a cascade of biochemical interactions that result in several physiological, biochemical and molecular events that are involved in carbohydrate, lipid and protein metabolism.

Although the binding of insulin to its receptor does not appear to be altered by magnesium status, the ability of insulin once bound to the receptor to activate tyrosine kinase is reduced in hypomagnesemic states [22]. As a result, reduced peripheral glucose uptake and oxidation are often noted in subjects with hypomagnesemia. Decrements in the enzymatic activities of several metabolic pathways are seen in DM patients as a result of the relative magnesium deficiency [22, 23].

### **2.8.2 Magnesium and insulin secretion:**

Magnesium deficiency may play an important role in both insulin sensitivity and insulin secretion processes. The release of insulin caused by a glucose challenge is partly dependent on adequate magnesium. Without magnesium, our pancreas won't secrete enough insulin—or the insulin it secretes won't be efficient enough to control our blood sugar. Available data strongly suggest that the calcium/magnesium ratio is a primary regulator of the insulin secretory process [24]. It has been shown that magnesium may competitively inhibit the voltage-dependent calcium channel, which is known to play a role in insulin secretion. These findings strongly support the hypothesis that magnesium plays an important role in the regulation of insulin secretion.

In addition, it has been reported that the acetyl-CoA carboxylase enzyme that catalyses the formation of malonyl-CoA, which is implicated in physiological insulin secretion, is stimulated by magnesium in a concentration-dependent manner [25].

Magnesium deficiency also led to increased urinary thromboxane levels and enhanced aldosterone-secreting effects of angiotensin II, decreases levels of vasodilatory prostaglandins (PGs), increases levels of vasoconstrictive PGs increases vascular smooth muscle cytosolic calcium, impairs insulin release, produces insulin resistance, and alters lipid profile and growth factors,. The changes on both of these observed indices probably reflect increased activity of processes that can contribute to the underlying pathological changes associated with microvascular and macrovascular damage, therefore, these suggests that magnesium deficiency may be a common factor in both insulin resistance and vascular diseases.

**General objective:**

To conduct a systematic review of the published literatures on the serum magnesium level and benefits of magnesium supplements for glucose control ,insulin sensitivity and improvements in patients with type 2 diabetes.

**Specific Objective:**

1. To review the association of serum magnesium level in patients with type 2 diabetes mellitus.
2. To assess the association between serum magnesium and risk of type 2 diabetes.
3. To determine whether oral magnesium supplementation improves both insulin sensitivity and metabolic control in type 2 diabetic subjects with decreased serum magnesium levels.

### **3. Methods:**

#### **3.1 Selection of Studies:**

I searched the literatures for all reports of Data from large epidemiological studies , Health Professionals Follow-up Study ,from prospective cohort studies randomized controlled trials and randomized double-blind trial that evaluated the effects of hypomagnesaemia in type 2 diabetes mellitus oral supplementation and dietary intake of magnesium on glycaemic parameters and/or lipids in patients with Type 2 diabetes.

All relevant clinical trials were identified from searches of journals and retrieved studies published in English language by systematically searching Medline, JCEM, European journals of Clinical Nutrition and American Medical Association Original-research studies that were published in 1992 to Feb 2011 were selected. It was included diagnostic studies that compare the Serum level of Mg in diabetic patients over several durations of time of the study population. We The search were used combinations of key words relating magnesium, non insulin dependent DM cohort studies, the association of magnesium and NIDDM, dietary approach in type 2 DM prevention, and glycaemic control. In addition, the reference lists of the retrieved articles helped us to find relevant to the present articles that did not allocate through the searching procedure. And language restrictions were applied.

#### **3.2 Selection criteria:**

Studies were included if they met the following criteria: (i)randomly assigning treatment and a control (ii) presented original data from prospective cohort, case control clinical trials and cohort studies; (iii)placebo or alternative treatment used as control group;(iv) the exposure of interest was the association of diabetes and hypomagnesaemia and improvement due to Intake of magnesium from foods (dietary) or oral supplements, (v)Measurements for glycated hemoglobin (HbA 1c ), fasting glucose levels, lipids, blood pressure, or blood, serum magnesium levels ; (vi) full journals published in English language.

#### **3.3 Data extraction:**

The data we collected included the first author's name, year of publication, country of origin, mean of patients' age, diabetic treatment, sample size, sex proportion, the number of randomized groups, duration of treatment, magnesium formulation and dosage and mean serum magnesium level in cases and control groups.

### 3.4 Data analysis:

The data obtained are analysed using in tables and figures according to their data extraction and compared by using their average values. All statistical analyses were performed using Excel software (Version 7.0) The analysis was to compare oral magnesium supplementation with placebo for the outcome of glycaemic control, or fasting blood glucose, which included whole blood, plasma or serum glucose levels. The secondary analysis was to evaluate the effects of oral magnesium supplementation on high-density lipoprotein (HDL) cholesterol, total cholesterol, triglyceride, systolic and diastolic blood pressure,, serum magnesium levels. I also calculated the difference between the means of the treatment and placebo groups.

### 4. Result:

The electronic search yielded 85 citations. One publication, on the the hypomagnesemia and type 2 diabetes is in Chinas was not in English and was excluded. Fourteen studies were retrieved for further examination. These included seven studies on the serum magnesium level in type 2 diabetes in different case control studies and the rest seven studies on the oral magnesium supplementation and improvement of the serum Mg and metabolic adjustments published between 1992 and 2011. Five studies were excluded because they are reviews and meta analysis.

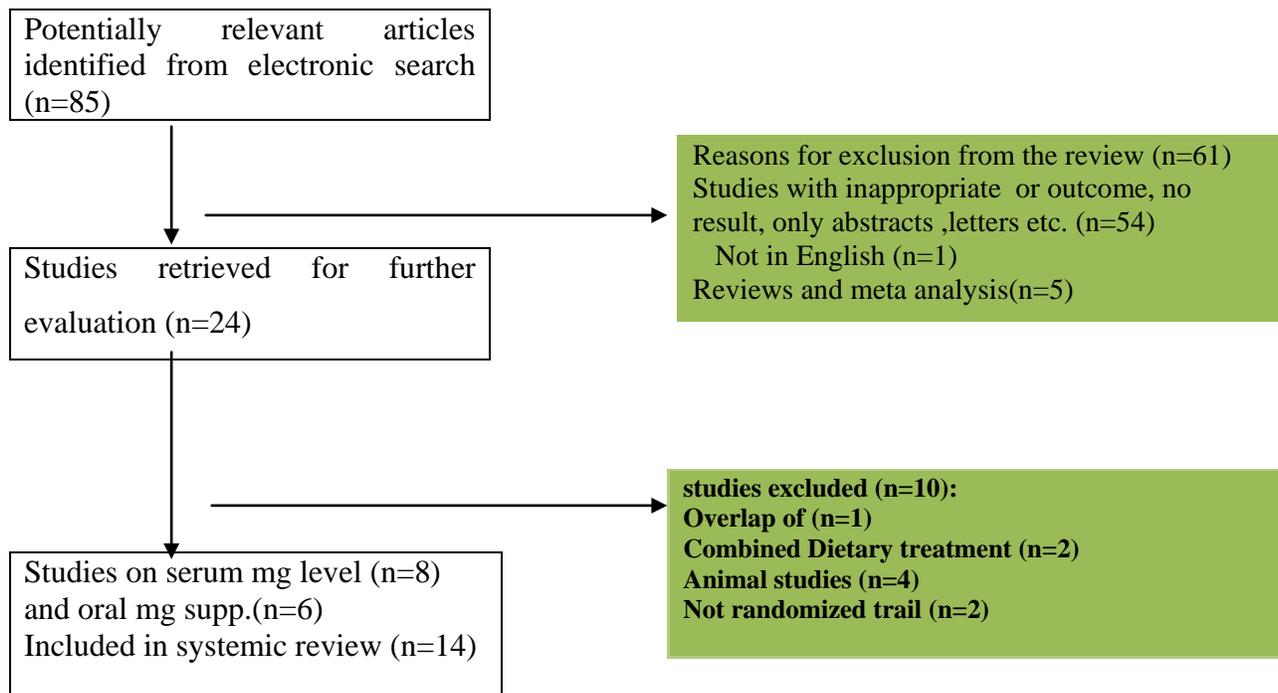


Figure3.1: Flow chart of study selection.

#### 4.1 Characteristics of studies and participants:

Of the 24 trials identified, 14 randomized controlled trials and prospective cohort studies met the inclusion criteria (Table 3&4). I did not include any unpublished trials, abstracts' and animal models or non-English language studies. Figure 10 describes the study selection process that led to the final 15 studies in this in this review. Of these, some of were cross-over design and the rest most of them are parallel design. The first eight studies which shows the association of the level of the serum magnesium and type 2 diabetes, one of them were cohort studies and the rest six were controlled trials (Table 3.1).

The second table (table 3.2) which represents 6 studies evaluating oral magnesium supplementation as conventional treatment /or medication for Type 2 diabetes. The number of participants ranged from 9 to 128[with the median of 47]. The range of treatment period was from 4 to 16 weeks (median 12 weeks). In most of the trials, treatment was with diet or oral glucose-lowering medication.

#### 4.2 Hypomagnesaemia in type 2 diabetes:

Table 3.1: Characteristics of controlled trials and prospective cohort studies showing the serum magnesium depletion in and type 2 diabetes

Authors	Country	Study design	Diabetes type	N. Diabetics /controls	Age	Duration of Diabetes	Mean serum Mg	p
Resnick <i>et al.</i> 1993 [26]	US	Parallel	2	22/30	NS	10.7	0.81 vs.0.86	NS
Ma <i>et al.</i> 1995 [27]	US		1, 2	282/ 6707			0.79 vs.0.83	Ns
Kao <i>et al.</i> , 1999[28]	US ARC Study	Crossover cohort	2	10 871 M &F) 6Years	45–64 Yrs		black 0.80 white 0.83	<i>P</i> <.001
de Lenardis 1999 [29]	Germany	Parallel	2	114 /116	53-77 yrs	7.2	0.84 vs. 0.88	<i>P</i> <0.001
Wälti. <i>et.al.</i> 2003[30]	Swiss	Parallel	2	109/156	61.3 / 58.3 yrs		0.77 Vs 0.83	<i>p</i> < 0.001
Huerta <i>et.al.</i> 2005[31]	University of Virginia	Parallel	Ob, none DM	24/24	8–17 yrs		0.74 Vs 0.801	<i>P</i> <0.009
Kauser M ,2006[15]	Gandhi University	Parallel	2	50/50	38-80 yrs		0.69 Vs 0.83	NS
Diwan. <i>et.al.</i> , 2006[33]	India	Parallel	2	40/40	40-60yr		0.68 Vs 0.85	<i>P</i> <0.05

\*NS-not specified.

The above table shows an overview of the studies which have compared mean serum or plasma Mg concentrations between type 2 diabetics and healthy control subjects. The reference range for serum/plasma Mg determined by FAAS is between 0.75 to 0.95 mmol/l [30,33]. Of the studies listed above, all shows a decreased serum Mg concentration in the diabetic group compared to the control group, and in most cases the difference is significant. Two studies de Lenardis [26] and Resnick *et al.*[29] found no significant difference when analyzing total serum Mg, however when they analyzed serum ionized Mg they found a significantly lower concentration in the diabetic group (184.1 vs. 223.3  $\mu$  mol/l,  $p < 0.01$  average b/n the two studies). Moreover, they noted a correlation between serum ionized Mg and intracellular free Mg in erythrocytes. One study which is in none diabetic but, obese also shows reduction in serum Mg level.

Even if the mean serum Mg concentration is decreased in the Diabetic groups, it is still well within the reference range. However, the mean serum Mg concentrations of the control groups also vary considerably between the different studies, although mean serum Mg of a healthy population would be expected to be around 0.85 mmol/l [34]. The results showed the extracellular and intracellular Mg ion concentration of diabetic patients was significantly reduced compared with values in healthy controls.

#### **4.3 Effects of magnesium supplementation on type 2 diabetic mellitus patients:**

Six of the included trials reported on the presence or absence of adverse events among participants receiving oral magnesium supplements [35-40]. However, the small numbers of participants in these trials do not allow to rule out rare side-effects. Treatment compliance was similar in both groups.

No severe adverse effects, such as cardiovascular events or deaths, were reported. Two trials showed that treatment with magnesium at doses up to 15.8 mmol/day and for periods as long as 4–12 weeks did not result in any adverse effects [35, 37, 40]. Overall, the most common side-effects were gastrointestinal symptoms, including mild abdominal pain, diarrhoea and nausea among diabetic patients in the magnesium treatment group.

Table 3.2 :Characteristics of controlled studies showing Mg supplementation studies in patients with type 2 diabetes.

Authors	type Diabetes	No.of subjects	Study design	Dose of Mg [mmol/d]	Durati on[weeks]	End point measures
Paolisso <i>et al.</i> (1992)[35] Italy	2	37 12Y 25Old	Parallel	15.8 Mg pidolate	4	Serum & erythrocyte magnesium, Glucose levels and Insulin values; plasma lactate and pyruvate levels.etc
Mooren et.al ,2010 [36] Germany	2	27/25	Parallel	Mg-asp- hydrochlorid e	24	blood pressure total cholesterol, HDL-C, TG, total extracellular and intracellular Mg concentration was determined.
Rodriguez- Moran et.al (2003)[37] Mexico	2	32 Mg 31 p	Parallel	26.3  Mg Cl <sub>2</sub>	16	Homeostasis model ,insulin resistance, fasting glucose, HbA 1c , blood pressure, LDL, HDL and total cholesterol, triglyceride
Yokota.et.al 2004[38] Australia	2	6 male and 3 female ,	Crossover	300mL/d  MAG21	4	Fasting plasma glucose, fasting immunoreactive insulin, homeostasis model insulin resistance index: TG systolic BP ; diastolic BP, MBP mean blood pressure.
deValk et.al., 1998 [39] Netherlands ,	2	25/25	Parallel	15mg or P	12	plasma glucose, homeostasis model insulin resistance index: TG systolic BP ; diastolic BP, MBP mean blood pressure.
Rodriguez Moran et.al 2011[40] Mexico	No	97  49 Mg 48 p	parallel	50 5%MgCl <sub>2</sub>	12	insulin level, fasting glucose, HbA 1c , blood pressure, LDL, HDL and total cholesterol, triglyceride, insulin, homeostasis model insulin resistance index:

*Note: FPG- fasting plasma glucose ,FIRI - fasting immunoreactive insulin, HbA1c - glycated hemoglobin, GA-glycated albumin 1,5-AG -1,5-anhydroglucitol, and total cholesterol (TC), and high density lipoprotein cholesterol (HDL-C) were measured. HOMA-IR = homeostasis model assessment for insulin resistance (fasting glucose [mmol/l] x fasting insulin [ $\mu$ UI/ml] /22.5)*

### 4.3.1 Effect of magnesium on blood, erythrocyte or urinary magnesium levels

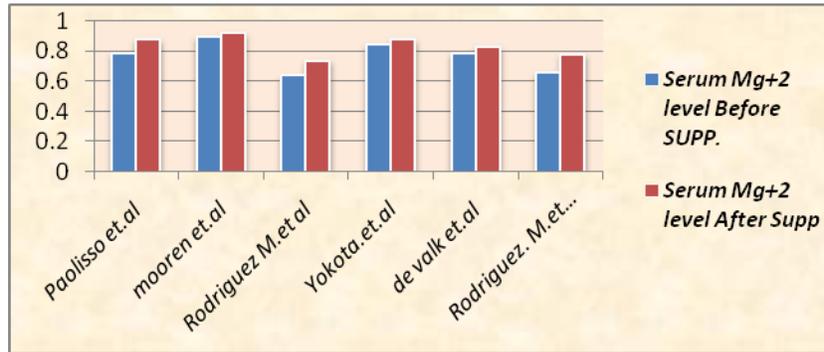


Figure3.2: Change in serum Mg in Type 2 diabetic patients and the magnesium treatment group compared with those in the control group

As this review showed that groups after oral supplemental of magnesium there is an average 0.06733mmol/l increase of blood magnesium levels, Figure 3.2 shows the empirical relationship between magnesium treatment and the time course of response in blood magnesium levels based on information from six trials. There was still a trend toward an increase in blood magnesium. Additionally, oral magnesium supplementation for 4–16 weeks significantly predicted an increase in urinary magnesium levels but the increase in erythrocyte magnesium levels was not significant [35-40].

### 4.3.2 Effect of Magnesium supplementation on mean blood pressure:

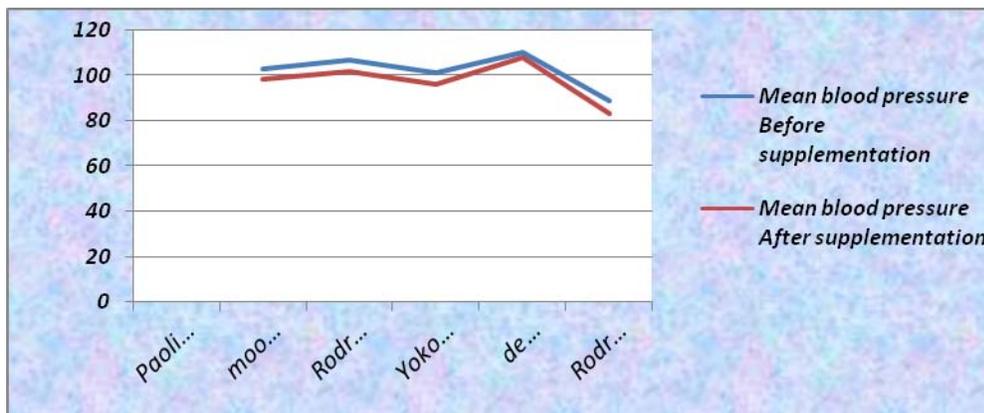


Figure3.3: mean blood pressure change before and after magnesium supplementation.

An increase in plasma magnesium concentration, irrespective of trial medication, was associated decreased Diastolic pressure and systolic blood pressure, but this was might not statistically significant in one study, but in the other studies shows constant reduction, with an average of (4.26mmol/Hg) reduction in mean blood pressure with increase in plasma magnesium.

#### 4.3.3 Fasting plasma glucose and insulin level:

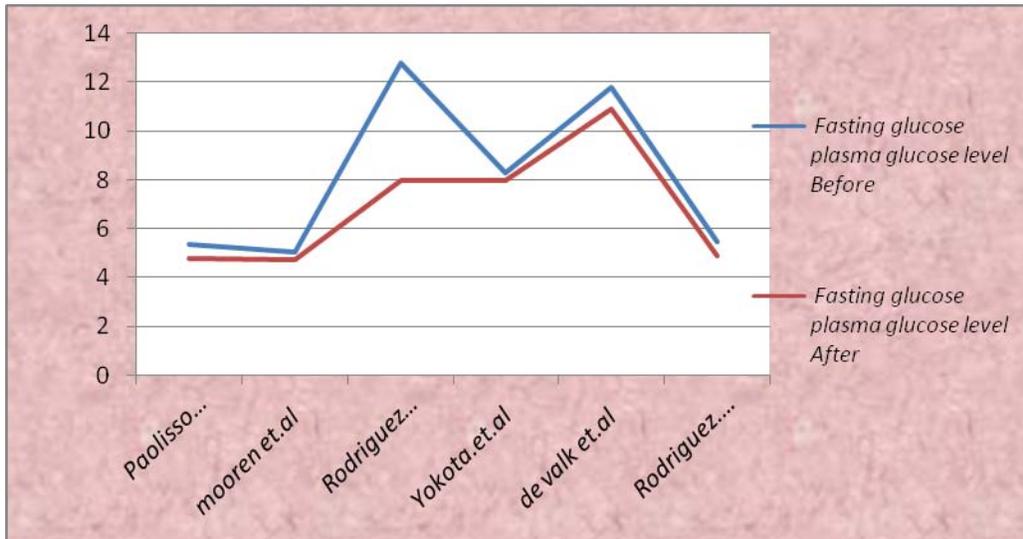


Figure3.4: Fasting glucose level before and after magnesium supplementation.

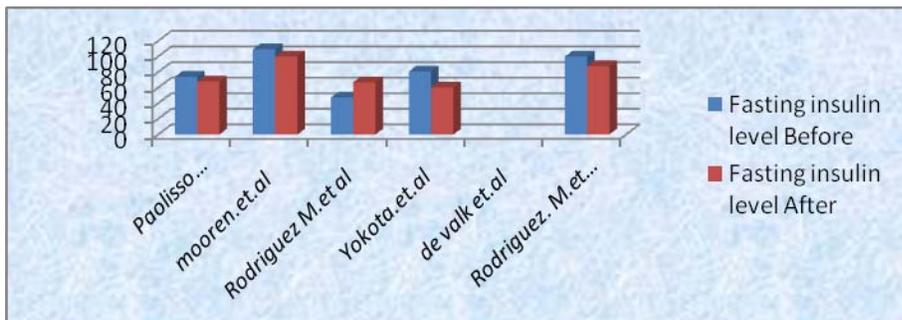


Figure3.5: Fasting insulin level before and after magnesium supplementation.

In these studies, subjects who received magnesium supplementation showed a significant reductions of Fasting plasma glucose level in the Magnesium supplement group than those observed in control subjects, (figure3.4). In this regard, although serum glucose and HbA1c levels were reduced in control subjects.

On the other hand, at the end of the study as can be seen in (Figure 3.5) insulin levels in the magnesium supplemented group were lower than those in the control group. This is a controversial finding because there are some reports showing a high insulin response in subjects with low serum magnesium levels, and yet other reports show an impairment of insulin secretion in magnesium deficiency subjects. However, the results lower insulin levels that I documented in the magnesium supplemented subjects were a direct effect of magnesium on beta-cell or a consequence of improvement in the insulin- mediated glucose disposal [35-40].

In addition, magnesium-supplemented subjects showed a significant reduction in homeostasis model assessment for insulin resistance (HOMA-IR) index values. The decrease of magnesium concentration results in both defective tyrosine-kinase activity and reduction of autophosphorylation on the beta-subunit at the insulin receptor level, exerting deleterious effects on glucose metabolism due to insulin sensitivity reduction, which contributes to poor metabolic control in diabetic subject [35,36].

#### 4.3.4 Magnesium effects on Lipid profile:

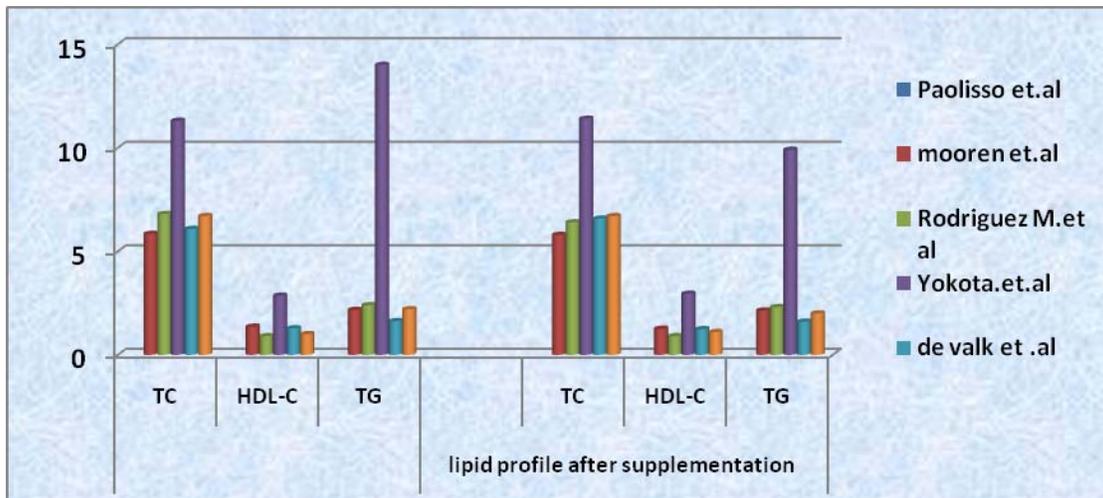


Figure3.6: the compression of TC=total cholesterol, HDL-cholesterol and triglycerol level before and after magnesium supplementation:

Figure 3.6 presents the effects of magnesium supplementation on lipid profiles, and Overall, compared with placebo group. Magnesium intake increased HDL cholesterol levels by average of 0.01mmol/l (1.48 to 1.49) and the TG level is reduction by average of 1.212mmol/l(4.48 to

3.588mmol/l) and the total cholesterol levels is not statically significant changed, reduced from 7.344 to 7.374mmol/l by average. However, the results from the studies showed no significant effects on other parameters for different magnesium doses among patients with Type 2 diabetes.

## **5. Discussion:**

### **5.1 Serum /plasma/ magnesium level:**

The interrelationship between diabetes and various micronutrients is characterized by a certain reciprocity. Chronic hyperglycemia can cause significant alterations in the status of some micronutrients and on the other hand, some of these nutrients can directly modulate glucose homeostasis [41]. Especially deficiencies of certain minerals such as Mg, Zn and Cr have been shown to predispose a person to glucose intolerance and to promote the development of diabetic complications [39,41, 44]. The implication of magnesium one of the nutrients in diabetes is reviewed more in detail as follows.

Several studies might be argued that the effect could be due to dietary fiber rather than Mg because both are found in large quantities in whole-grain cereals and vegetables. However, in the Iowa Women's Health Study, the association remained after adjustment for cereal fiber and grain intakes and the Nurses' Health Study did not even find an association between dietary fiber and diabetes risk. Humphries *et al.* [42] compared dietary Mg intake with insulin resistance in non-diabetic adults and found a negative correlation. Also in another study shows that There was a significant inverse association between magnesium intake and risk of type 2 diabetes, independent of age and BMI [43].

In addition, results from the Atherosclerosis Risk in Communities (ARIC) study [28] and Swiss Federal Institute of Technology [29] indicated low serum Mg to be a strong, independent predictor of the development of type 2 diabetes.

Early evidence of Mg deficiency such as 1946, hypomagnesaemia was noted in patients with diabetic Keto acidosis [44]. In 1968, a survey of 5'100 consecutive patients at a diagnostic clinic in the USA, revealed diabetes to be the most common condition associated with hypomagnesaemia [45] 20% of the patients with hypomagnesaemia (Mg < 0.74 mmol/l) were diabetics. And 17.5 % was arteriosclerotic heart disease of the patients. Also, In 1995, the

American Diabetes Association (ADA) stated in its clinical practice recommendations that Mg deficiency may play a role in insulin resistance, carbohydrate intolerance and hypertension, and that Mg deficiency should be corrected but only if hypomagnesaemia could be demonstrated [46].

In reference to this review type 2 Diabetics patients have low levels of serum Mg. low serum Mg levels have been also reported in type 1 and 2 diabetes in number of studies in European countries [26,42, 46]. Of the studies listed in the result almost all shows a decreased serum Mg concentration or serum ionized magnesium in the diabetic group compared to the control groups, and in most of the Differences noted were statically significant [26-33].

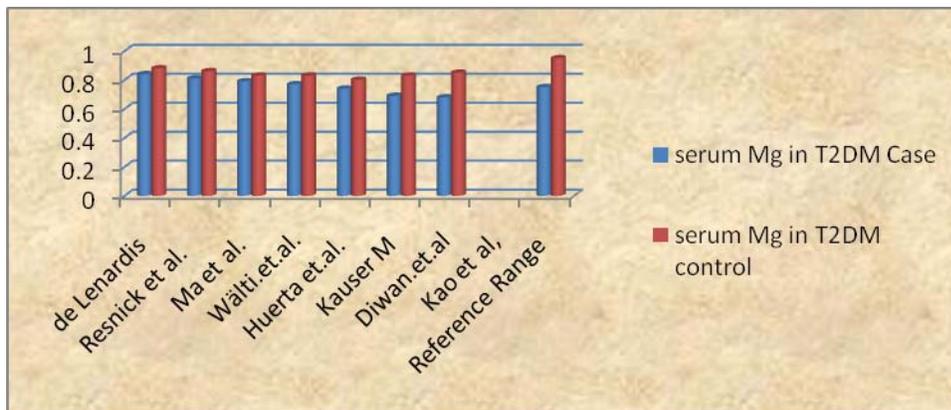


Figure 5.1: comparison of serum mg in T2DM patients.

### 5.1.1 Etiology of Mg deficiency in diabetes:

The reasons for the high prevalence of Mg deficiency in diabetes are not clear, but may include increased urinary loss, lower dietary intake, or impaired absorption of Mg compared to healthy individuals. Since Diabetes mellitus has been suggested to be the most common metabolic disorder. Hypomagnesemia in diabetes represents secondary magnesium depletion which requires more or less specific correction of the different perturbations of the control mechanisms of magnesium deficit that are involved with diabetes. Osmotic diuresis clearly accounts for a portion of the magnesium loss. It is believed that glycosuria which accompanies the diabetic state, impairs renal tubular reabsorption of magnesium from the glomerular filtrate [46, 47].

Renal magnesium handling may be modulated by glucose and insulin even in non-diabetic individuals, where the administration of insulin with or without glucose increases urinary magnesium excretion rate. A rise in the urinary magnesium excretion rates in diabetic patients with increasing insulin dosage has been reported despite maintenance of serum levels, suggesting the effect of insulin on renal magnesium handling[12,47].

Glucose itself is a crucial part of cellular ion homeostasis, increasing intracellular calcium and decreasing intracellular magnesium. Recent evidences suggest that insulin can increase free magnesium entry into the cell. Furthermore, in the state of insulin resistance, insulin-induced entry of magnesium is also impaired. Glycemic control in patients with type-2 diabetes, however, may not correct low magnesium concentration, suggesting that other factors may regulate magnesium levels in diabetic patients [33, 47].

The existence of a close relationship between metabolic control and impaired magnesium balance was confirmed that a marked depletion in plasma and erythrocyte magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor diabetic control.

The relationship between magnesium and glucose metabolism is supported by a recent epidemiological studies showing that deficient magnesium intake is a risk factor for the development of type-2 diabetes independent of age, body mass index, alcohol intake and family history of diabetes [30, 33, and 47].

### **5.1.2 Consequences of Mg deficiency in type 2 diabetes:**

#### **Glucose homeostasis and insulin sensitivity:**

Magnesium depletion has shown to have a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes. It was further demonstrated that this abnormality was associated with an increase in erythrocyte membrane micro viscosity and therefore suggested that changes in the physical state of the plasma membrane as well as insulin resistance were both responsible for the lower erythrocyte Mg level found in these patients [27]. Also, these changes in plasma membrane liquid composition might impair the interaction of insulin with its receptor and thus decrease glucose tolerance have studied the effect of Mg deficiency on glucose disposal and insulin action in rats and have found an impairment of both insulin secretion and sensitivity[48,49].

The impairment of insulin sensitivity seems to be related, at least in part, to a defective tyrosine kinase activity of the insulin receptor. Also in human non-diabetic subjects, low plasma Mg has been associated with relative insulin resistance, glucose intolerance, and hyperinsulinemia [52]. In fact, intracellular Mg deficiency appears to be associated with an impaired function of several enzymes involved in glucose metabolism, which need high energy phosphate bonds and thus require Mg as a cofactor[51]. This may lead to impairment of insulin action and worsening of insulin resistance in diabetic and hypertensive patients [51]. The same seems to happen in obesity; two studies show insulin resistance along with reduced erythrocyte Mg accumulation after glucose loading in non-diabetic obese subjects [51]

In summary, the relationship between Magnesium deficiency and insulin resistance is a vicious circle. Low Mg status contributes to the development of insulin resistance, which in turn attenuates Mg uptake in insulin-sensitive tissues. Metabolic syndrome, Hypertension, Atherosclerotic disease, myocardial infarction, Micro vascular complications and Osteoporosis are also diseases which are prevalent in hypomagnesaemia [27, 34, and 53].

## **5.2 Mg supplementation:**

The effect of Mg supplementation on Mg status has mostly been assessed by measuring serum and erythrocyte Mg concentrations. In all of cases, an increase in serum Mg and erythrocyte Mg concentrations was observed after Mg supplementation [34-40]. However, erythrocyte Mg had not shown to be a very reliable indicator of intracellular Mg status, and because tissue Mg uptake might be diminished in type 2 diabetes, other parameters such as muscle Magnesium concentration would probably provide better information.

Because low Magnesium status has a negative impact on glucose homeostasis and insulin sensitivity, as well as on the evolution of diabetic complication, oral Magnesium supplementation is expected to have a positive effect in patients with diabetes. The results of most published intervention studies are summarized in in this review (figures above see pages 25-27) of randomized controlled trials. I found that oral magnesium supplementation for 4– 16 weeks may be effective in reducing plasma glucose levels and raising HDL cholesterol in Type 2 diabetic patients[35-40].

Magnesium supplements have been advocated as an attractive option for improving glycaemic control in diabetic patients because of their relative safety and affordability. Almost all

individual published trials were underpowered and used different doses and formulations of magnesium supplements. Given inconsistent results from previous trials, this review increased statistical power for testing the hypothesis whether overall magnesium intake from various supplements exerts any beneficial effect on glycaemic control or metabolic parameters in patients with Type 2 diabetes. Magnesium supplementation has many beneficial effects on insulin sensitivity, lipid profiles, platelet aggregation and blood pressure [34-40]. These findings tend to support the notion that oral magnesium supplementation may help maintain magnesium homeostasis in the human body and thereby exert a beneficial effect on fasting glucose and HDL cholesterol in patients with Type 2 diabetes [36,37,38].

Further supporting results come from a very recent study of a randomized placebo-controlled study performed in 63 type 2 diabetics in Mexico. They found not only increased serum Mg, but also improved metabolic control and insulin sensitivity after supplementation for 16 weeks [40].

Magnesium supplementation may be more effective in the prevention of type 2 diabetes since low Magnesium intakes seem to be associated with an increased risk of diabetes. A study performed in elderly subjects without diabetes has shown that oral Mg supplementation improved both insulin sensitivity and secretion [35]. Furthermore, Magnesium supplementation was able to reduce the development of diabetes in obese Zucker1 diabetic fatty rats [54]

Although Mg may have a positive effect on insulin sensitivity and secretion, most intervention studies in type 2 diabetics have failed to show an improvement of glycemic control or diabetes-related complications [37, 39]. It seems that the disorders resulting from magnesium deficit in diabetics are due to intracellular depletion of the ion, which is not controllable by oral supplementation alone. If tissue Mg uptake is decreased due to insulin resistance, the effect of supplementation may be limited due to low availability of the supplemental Magnesium to the cells. A greater benefit may lie in subjects with impaired glucose tolerance or beginning type 2 diabetes, in which improving insulin sensitivity by increasing Mg intake may retard or attenuate the disease.

### **5.2.1 Limitations:**

Current American Diabetes Association (ADA) nutrition guidelines recommend the use of magnesium supplements for people with diabetes mellitus who have low serum magnesium levels [55]. The results clearly show that magnesium supplementation significantly increases plasma or serum or erythrocyte magnesium levels and thereby normalized the hypomagnesaemia in diabetes. Nevertheless, it should be noted that serum or plasma magnesium measurements are poor indicators for total body magnesium status. An accurate assessment of intracellular magnesium status is needed to reliably reflect the normalization of hypomagnesaemia after magnesium replenishment [55].

In addition, optimal dosage to replenish magnesium deficiency and long-term safety of magnesium therapy, particularly at high doses, should also be evaluated in future studies, although there were no major adverse effects reported for different doses and forms of magnesium supplements in the included trials.

Given most of the studies were short-term trials (4- 11 weeks), these results may underestimate the true effect of magnesium supplementation on long-term glycaemic response. Although a single measurement of fasting glucose levels is a less accurate and stable indicator of glycaemic control than HbA1c, our results for the effect of magnesium intake on fasting glucose levels may be an indication of favourable effects on glucose homeostasis in diabetic patients.

Magnesium supplements have been advocated as an attractive option for improving glycaemic control in diabetic patients because of their relative safety and affordability. However, there is limited empirical data to evaluate whether magnesium supplements should or should not be recommended to patients with diabetes.

## **6. Conclusion and recommendation:**

These findings show that serum magnesium levels were significantly lower in type 2 diabetic patients when compared to controls groups. Levels of serum magnesium in uncontrolled type 2 diabetic patients were further lower than those in whom diabetes was under control and hypomagnesaemia is a factor in type 2 diabetes mellitus patients leading to various complications. Hence it is worthwhile estimating magnesium levels in type 2 diabetes mellitus patients.

In this review, a growing body of evidence from experimental, epidemiological and clinical studies supports the hypothesis that magnesium plays an important role in modulating insulin mediated glucose uptake. In this regard, a low intracellular magnesium concentration may result in defective tyrosine kinase activity at the insulin receptor level and cause the increase in intracellular calcium concentration, both of which are events that are involved in the impairment of insulin sensitivity. The requirement of magnesium for insulin signaling highlights the clinical relevance of the possible effects of magnesium deficiency on states of altered glucose metabolism.

On the other hand, Oral magnesium supplementation can improve insulin sensitivity and secretion in patients with Type 2 diabetes mellitus; as various studies showing the effect of Magnesium supplementation on glycaemic control, blood pressure, and plasma lipids in insulin-requiring patients with Type 2 DM strengthen this hypothesis.

As findings suggest that a significant inverse association between magnesium level and diabetes risk. Therefore this study supports the oral magnesium supplementation or the dietary recommendation to increase consumption of major food sources of magnesium, such as whole grains, nuts, and green leafy vegetables that improving insulin sensitivity and metabolic control in type 2 diabetic patients with decreased serum magnesium levels.

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