DISCUSSION

Magnesium is a ubiquitous alkaline earth element that exists in abundance as an intracellular cation and is so vital to the metabolic functions of cells that the existence of life on earth for a living being without magnesium is impossible. Although several studies confirm the role of magnesium in glucose metabolism, the significance and implications of hypomagnesemia in diabetes is largely unknown. The vigorously contested issue is whether low serum magnesium concentration is prevalent in diabetic patients and whether low serum magnesium concentrations predict excessive morbidity and mortality particularly related with late diabetic complications. The therapeutic effects of magnesium administration in the diabetic patients have also been a matter of great controversy. The present study was undertaken to evaluate the magnesium status in diabetes mellitus in experimental rats and diabetic patients and its implications.

Effect of Magnesium Deficiency and Diabetes on Body and Organ Weight in Experimental Rats

In the present study, experimental rats showed classical signs of magnesium deficiency i.e. hyperemia, hyperexcitability and loss of hairs within first week of feeding the magnesium deficient diet. Hyperemia observed during early phase of magnesium deficiency is due to an increased production and release of circulating pro-inflammatory agents such as cytokines (tumor necrosis factor, interleukin-1, interleukin-6), prostacyclin and histamine (Weglicki et al, 1996; Dickens et al 1992). Magnesium deficiency is also accompanied by increased plasma nitric oxide (NO) levels, which could result in vasodilation (Rock et
shown to strongly correlate with bone magnesium concentration in normal, magnesium deficient and magnesium overloaded animals and human subjects (Alfrey et al, 1974). Thus, serum magnesium levels can be used as an index of body magnesium status.

Time course of magnesium deficient diet on various parameters shows marked effect on serum and RBC magnesium levels in the second week and the there was a progressive decrease in the levels till tenth week. As expected, rats receiving magnesium deficient diet showed drastically reduced urinary magnesium, a finding that agrees with other reports (Kikuchi et al 1998). It has been shown that the urinary magnesium falls markedly when the animals are placed on magnesium deficient diet may approach zero by the third day (Elin et al, 1971).

In diabetic rats, hypomagnesemia was found in confirmation with other studies (Fort et al, 1977; Schneider & Schedl, 1974). Magnesium deficiency has been recognized as a common problem in both types of diabetes and its presence is inversely related to glycemic control and development of complications including hypertension (VanRoelen et al, 1985; Fujii et al, 1982). Urine excretion in the diabetic rats was increased approximately four times that of control rats and so was the magnesium excretion. The renal handling of magnesium in diabetic rats thus may be compromised and failure of renal mechanism in concentrating plasma magnesium may result in perpetuating hypomagnesemia and subsequently magnesium deficiency. An inverse correlation between plasma magnesium and blood glucose concentration has been demonstrated in rats with streptozotocin-induced diabetes (Fort et al, 1977).

**Magnesium Status in Diabetic Patients**

The diabetic patients were chosen as criteria defined by Expert Committee on the Diagnosis and Complications (1997). As expected, there was a marked difference in the mean fasting
Discussion

control and insulin resistance in non-insulin dependent diabetic elderly patients (Tosiello, 1996). Kao et al (1999) found a strong and inverse independent relationship between serum magnesium levels and subsequent development of incident of diabetes in middle-aged adults. The plasma magnesium levels are inversely related to the fasting blood glucose and urinary magnesium excretion in the context of hypermagnesuria. An inverse correlation between serum magnesium concentration and glucose found in this study has also been reported in a study of diurnal profile of diabetic patients and control subjects (Mather et al, 1982). A significantly elevated urine magnesium excretion was observed in the diabetic patients compared with controls subjects in this study. In accordance with the previous studies, this data suggests that the diabetic state per se enhances urine magnesium wasting irrespective of the degree of metabolic control. A modest inverse relationship between urine and plasma/erythrocyte magnesium was found in this study. Similarly, Walter et al (1991) and Gurlek et al (1998) have also reported enhanced urine magnesium losses in diabetic patients. The mechanism responsible for magnesium deficiency in patients with diabetes is not completely known. Osmotic diuresis clearly accounts for a portion of the magnesium loss. It is believed that glycosuria that accompanies the diabetic state, impairs renal tubular reabsorption of magnesium from the glomerular filtrate. Magnesium is reabsorbed principally in the proximal tubule (30%) and thick ascending loop of Henle (65%), with minimal resorption (1-5%) in the distal convoluted tubule. Hypomagnesemia results specifically from a reduction in tubular absorption of magnesium as recently suggested by Garland (1992). The exact site of the resorptive defect is not defined. Renal magnesium handling may be modulated by glucose and insulin even in the non-diabetic individuals where the administration of insulin with or without glucose increase urinary magnesium excretion rate (Kindermann, 1967). A rise in the urinary magnesium excretion rates in the
realizing that maintenance of magnesium levels may be prerequisite to the maintenance of insulin sensitivity.

This data suggests that diabetic patients have reduced erythrocyte magnesium levels indicating to total body magnesium depletion. Insulin has been reported to enhance the transport of magnesium into cells; therefore, lack of insulin or insulin resistance may result in an intracellular magnesium deficit. It has been shown in vitro that even high levels of insulin can not correct the reduced magnesium shift into erythrocytes in insulin-resistant type 2 diabetic patients with hypomagnesemia, which might be explained by a post receptor defect (Paolisso et al 1998). Reduced magnesium content in erythrocyte seems to relate to enhanced urinary loss irrespective of the degree of metabolic control. Data on erythrocyte magnesium levels in diabetes are scarce and conflicting. Levin et al (1981) and Sjorgen et al (1986) reported that erythrocyte magnesium content was similar in diabetic and healthy subjects in spite of reduced plasma magnesium. Rohn et al (1993) and Fujii et al (1982) observed slightly decreased erythrocyte magnesium levels in patients despite significant reduced hypomagnesemia, while, in contrast, VanRoelen et al (1985) reported that half of their diabetic patients had reduced erythrocyte magnesium content, while only 15% of the patients had reduced plasma magnesium levels.

**Magnesium Deficiency and Duration of Disease**

The results presented here show a definite relationship between plasma magnesium concentration and duration of diabetes. The strong correlation of magnesium with duration of disease suggests that elderly diabetic patients are more susceptible to develop magnesium deficiency an observation also noted by Paolisso et al (1990). The strong negative correlation with duration of disease found in this study is in accordance with some of the studies (Gligore et al, 1974; Ewald et al, 1983). However, few studies have also reported no significant correlation between
plasma magnesium levels are diminished, the ability of kidney, particularly loop of Henle to reabsorb progressively more magnesium is increased reflected by increased kidney magnesium levels in magnesium deficiency. It has been observed in the studies that magnesium reabsorption is more complete in the loop of Henle in magnesium-depleted rats (Dirks, 1983).

It has been suggested that analysis of muscle biopsies gives reliable information about the intracellular concentration of magnesium (Johansson et al, 1981; Lim et al, 1969). Muscle magnesium has been found to be decreased in magnesium depleted animals (Forbes, 1966). In the present study, the muscle magnesium was significantly depleted in magnesium deficient as well as diabetic rats, though the extent of loss of magnesium in diabetic rats was comparatively lesser. It has been suggested that clinical magnesium deficiency does not occur in human beings with healthy kidneys, as several mechanisms that come into play are efficient enough to conserve upto one mEq/L of magnesium per day.

In rats, hypomagnesemia was found in experimentally induced diabetes mellitus and depletion of magnesium in organs occurred when the magnesium intake was restricted to the physiological requirement of control rats. In the rats, bone magnesium pool handles most of the buffering, whereas in the human, magnesium pools are available in both bone and skeletal muscle (Fort et al, 1977; Schneider & Schedl, 1974). However, both are insufficient to compensate for long-term magnesium deficiency. Organs other than bone and skeletal muscle contain a relatively small fraction of the body magnesium content and therefore are of little importance in buffering magnesium loss (Wallach, 1988). The liver, heart and brain seem to be particularly susceptible to small and possibly critical losses whereas other organs appear to be relatively immune.
insulin sensitivity via alterations at the insulin receptor-associated tyrosine kinase, while supplementation with this mineral has been shown to slow down the development of non-insulin dependent diabetes models (Balon, 1995). It seems reasonable to speculate that decrease in plasma magnesium interferes with the insulin signaling mechanism involved in glucose transport. Evidences are available that tyrosine kinase activity of muscle is decreased in rats fed a low magnesium diet (Suarez et al. 1995). As reviewed by Jackson (1990), an age related reduction in the activity of numerous enzymes such as hexokinase type II and phosphofructose kinase seems to occur in magnesium deficiency, which might explain the age-related insulin resistance.

A report by McNeil et al. (1982) suggested that magnesium deficiency in rats was accompanied by an increase in phosphoenolpyruvate carboxykinase, an enzyme involved in the production of glucose synthesis from non-carbohydrate precursors. Thus, the importance of magnesium may lie in the regulation of glucose synthesis and breakdown. In addition to these effects of magnesium, magnesium deficiency has been shown to promote insulin resistance in multiple studies. Insulin resistance is a post receptor defect and may be linked to calcium mediation of insulin signaling (Dzurik et al., 1991). In a recent study, the cellular uptake of magnesium, which is normally stimulated by insulin, was shown to be attenuated in diabetics. While insulin insensitivity has been reported in individuals with sub-optimal magnesium status, the focus of this study on magnesium use in diabetes involves interest in the prevention of long-term complications as magnesium deficiency has been associated with oxidative stress, dyslipidemia and ionic alterations, parallel to biochemical alterations occurring in diabetes.

**Oxidative Stress in Magnesium Deficiency**

Lipid peroxidation and derived oxidized products are being intensively investigated because of their potential to cause
vitamin E. Apart from liver magnesium deficiency also leads to a decrease in ascorbate levels in brain and other tissues.

Data presented here clearly show that magnesium deficiency leads to the reduction of GSH in erythrocytes and non-protein thiols in liver. Because of relatively short half-life of intracellular glutathione, de novo synthesis is a mandatory step for maintaining the cellular content of this major intracellular thiol (Minnich et al, 1971). Since rat erythrocyte are able to synthesize and destroy GSH and synthesis of GSH is completely dependent on ATP and magnesium the depletion of magnesium could reduce GSH concentration, which may possibly be the mechanism in increasing oxidative stress in magnesium deficient rats. Freedman et al (1992) have demonstrated that in rats the levels of glutathione in the red blood cells was significantly reduced after 2-3 weeks on magnesium deficiency diet. The fact that GSH concentration decreased in erythrocytes of only magnesium deficient rats and not in normal rats suggests that this ion is directly responsible for the depletion of erythrocyte GSH. In vitro studies have shown that reduced glutathione can protect against peroxidation of lipids in cytosolic and particulate sub-fraction components of rat liver and other tissues (Scholz et al, 1997). Mechanisms that have been proposed to explain the glutathione effects include the removal of species that initiate lipid peroxidation, scavenging of radicals by a glutathione dependent protein (Hill et al, 1984), scavenging of peroxyl radicals by directly by glutathione (Braclay, 1988). GSH is also required for the maintenance of membrane protein thiols and α-tocopherol (Palmandra & Kehrer, 1993). Glutathione-S-transferase responsible for the reduction of lipid hydro peroxide (Tampo, 1990) is glutathione dependent enzyme. Glutathione has also been reported to improve glucose metabolism enhancing glucose-induced insulin secretion in aged patients with impaired glucose tolerance and increasing insulin action in non-insulin dependent diabetic patients (Paolisso, 1992 ). Thus, it may be proposed that
the 4th week of diabetes thus supporting this study. These results are consistent with other reports that oxidative stress is increased in the alloxan diabetic rats due to both increased lipid peroxidation and decreased levels of natural antioxidants, and similar findings have been reported in diabetic patients (Garg et al, 1996; Ceriello et al, 1997). Elevated levels of MDA in the liver, brain and kidney from diabetic animals have also been supported by other studies (Kumar & Menon, 1992; Mukherjee et al, 1994).

Studies evaluating the various serum circulating antioxidants in diabetic patients are still conflicting (Jones et al, 1988; Stankova et al, 1984; Strain, 1991). In the present study, the plasma levels of malondialdehyde (MDA) have been found increased in the diabetic patients and there was a significant reduction in the levels of natural occurring antioxidants (vitamins C & E, uric acid and total thiols). MDA measurement is the most commonly used marker of oxidative stress and reflects a major part of the oxidation of lipid membranes from organs and cell structures in which lipid peroxidation occurs (Weber, 1990). It has been proposed that oxidation of LDL particles in the arterial wall initiates a complex cascade of events that leads to the development of atherosclerotic plaques and eventually leads to stenosis of the arteries or rupture of plaques and heart attack (Duthie & Bellizzi, 1999). In fact, oxidized forms of LDL have been detected in the atherosclerotic lesions from both animals and humans as reported by various studies (Mullarky et al, 1997; Ross, 1986). Elevated free radical activity has also been reported to induce defect in insulin-mediated glucose uptake (Paolisso & Giugliano, 1996). Though the data is in accordance with several other studies, increased levels of vitamin E and uric acid have also been reported by some studies (Ceriello et al, 1997). It has been suggested that the reduction in the antioxidant parameters and increased free radical formation contributes to the development of oxidative stress in diabetes (Giugliano et al, 1996, Garg et al, 1996). The sources of oxygen-
diverse mechanisms for the pathogenesis of complications in diabetes including non-enzymatic glycosylation of proteins and glucose auto-oxidation, enhanced polyol pathway activity. Greater levels of traditional biochemical marker of free-radical activity i.e. malondialdehyde and decreased levels of TRAPc reflect the imbalance between free-radical production and antioxidant defenses in diabetes in favor of the former. Increased oxidative stress may arise either as a result of increased free radical production or reduced activity of antioxidant defense scavengers. Even though it is well known that free radicals are capable of inducing the diabetic complications, how oxidative stress in diabetes initiates complications remain hypothetical. Elevated levels of MDA have been identified in diabetes, and more marked in patients with poor metabolic control. Free radical damage is increased in diabetic patients with nephropathy and retinopathy in comparison to those without diabetic complications.

It has been shown that the plasma total antioxidant capacity is not determined by mere sum of the relative concentration of antioxidants, but is determined also by their synergism. Recently, the assay of the total plasma radical-trapping antioxidant parameter (TRAP) has been proposed to represent a more reliable estimation of plasma antioxidant capacity than the measurement of each known antioxidant (Wayner et al 1987). It has been proposed that TRAP may either be measured directly by a fluorescence-based method (TRAPm) or calculated by formula as proposed by Ghiselli et al, 1995). Ceriello et al, (1997) reported a good correlation between TRAPm and TRAPc and proposed that since TRAPm is long a difficult to perform, TRAPc might be proposed to serve the purpose. The results in this study are in consistent with other studies reporting decreased TRAPc levels in diabetic patients, suggesting the existence of an oxidative stress in diabetes (Cerriello et al, 1997; Tsai et al, 1994).
Furthermore, for the first time the association of hypomagnesemia and oxidative stress in diabetes mellitus was identified in this study. Despite this statistically significant association, a cause-and-effect relationship is unclear. The experimental data presented here suggests that magnesium might be represented as an independent risk factor for increased oxidative stress and decreased antioxidant potential. The increased oxidative stress has been implicated in many free radical mediated diseases including hypertension, diabetes mellitus and accelerated atherosclerosis through oxidative modification of lipoproteins and other biochemical abnormalities. Therefore, it can be postulated that magnesium deficiency leads to reduction of threshold antioxidant capacity and enhanced susceptibility to free radicals, which may eventually culminate in above said disorders.

**Effect of Magnesium Deficiency and Diabetes on Enzymatic Defense Mechanism**

Antioxidant enzymes may play an important role in determining the risk of developing certain diseases such as atherosclerosis and cancer in individuals (Gandy et al, 1971; Andersen et al, 1997), however, little is known about the fate of the activities of these enzymes in magnesium deficiency.

Measurements of tissue-scavenging enzymes in body organs of rats showed clearly that only liver showed significant decrease in the activities of SOD and GST in diabetic and magnesium deficient rats with the exception of kidney SOD, which also decreased slightly but significantly. Similar observations have also been reported by Wohieb & Godin (1987). They observed that the general pattern of changes seen in diabetic animals was tendency of enzyme activities that were low in control tissues to be increased and those high in control tissues to show some degree of reduction.

Measurement of tissue-scavenging enzymes in control rats showed that the lowest activities were found in heart and
to protect against the free radical injury, hypothesis being that magnesium deficiency reduces the threshold antioxidant capacity of the body.

**Magnesium Deficiency and Lipids**

Magnesium deficiency has also been reported to affect lipid metabolism (Rayssiguier et al, 1981). This study has also demonstrated that magnesium deficiency caused elevation of triglycerides and decreased levels of HDL-cholesterol indicating abnormalities in lipoprotein metabolism. The mechanism behind the hypertriglyceridemia may be either due to excessive production and release of lipids into circulation or reduced clearance of triglycerides from the blood or combination of both. It has also been reported that magnesium deficiency decreases the availability of lipoprotein lipase in plasma and that the decrement is inversely correlated with plasma triglycerides concentration (Rayssiguier et al, 1991). Findings of this study are in agreement with other studies, which reported slight variation in total cholesterol in severe magnesium deficiency of short duration and significant increase in total cholesterol during moderate magnesium deficiency for long durations (Rayssiguier, 1986; Gueux et al, 1993).

Observations of dyslipidemia in diabetic rats in this study are also in consistent with the other studies that diabetes mellitus is associated with changes in the lipid metabolism. These observations combined with present knowledge that dyslipidemia is one of the major factors for the development of cardiovascular disease suggest that magnesium deficiency may be one of the contributory factor for the development of cardiovascular diseases associated with diabetes mellitus. The mechanism responsible for the atherogenicity of the hypertriglyceridemic state may be related to increased susceptibility of triglyceride-rich lipoprotein against oxidative modification. Epidemiological surveys have also concluded that populations living in areas having hard water or taking magnesium rich diet are less prone to cardiovascular
Calcium

Severe magnesium depletion has been found to alter calcium metabolism significantly in animals as well as in humans. The mechanism responsible for the calcium imbalance associated with magnesium depletion is elusive. Studies in monkeys and humans have shown that severe magnesium depletion is associated with hypocalcaemia in all the species (Dunn, 1971). Magnesium deficiency has been reported to result in impaired PTH secretion and hypocalcemia (Anast et al, 1976). The rat is unique in this regard that it is the only species that develops hypercalcemia when magnesium is depleted on a normal dietary calcium intake (George & Heaton, 1975). The mechanism responsible for hypercalcemia associated with magnesium depletion in rats is obscure. Alock and MacIntyre (1960) suggested that magnesium and calcium compete for a common absorptive mechanism in both the gastrointestinal tract and in the renal tubule. In this fashion, when less amount of magnesium is available for reabsorption, more calcium will be absorbed, thereby promoting hypercalcemia. Redistribution of calcium between intracellular and extracellular fluid may be another factor causing hypercalcemia in rats. The accumulated evidences indicate that the intestinal transport of calcium, which is apparently dependent upon the intact parathyroid glands, is increased in magnesium deficient rats (Bao et al, 2000; Bunce et al 1974). The parathyroid dependent increased intestinal transport of calcium is a significant factor in the production of hypercalcaemia. It has also been reported that the reduction of calcium content ion in the magnesium deficient diet prevents the development of hypercalcemia (Bao et al, 2000).

Of the many proposed mechanisms to account for the hypocalcemia in magnesium depletion in human, most experimental and clinical studies support an inhibition of parathyroid hormone release and action at the target organs (Rude et al, 1998). Magnesium deficiency impairs parathyroid glandular
mechanisms for potassium depletion coexist with magnesium depletion. The first represents a combination of intracellular and extracellular potassium and magnesium depletion, whereas the second type represents only intracellular depletion. The lack of consistency in the levels of serum potassium between magnesium deficient and diabetic rats suggest the alternative hypothesis that magnesium deficiency may have different influence on the ability of cells to maintain potassium gradient.

The reason for this disrupted potassium metabolism in magnesium deficiency may be related to magnesium dependence of Na⁺, K⁺ ATPase. This enzyme uses the energy derived from ATP hydrolysis to actively pump Na⁺ and K⁺ across the plasma membrane against their respective concentration gradient so as to maintain the physiologically normal intracellular concentration of these cations (Grafton & Baxter, 1992). The lack of energy to fuel the cell membrane cation pump results not only in the leakage of cell potassium but also in the intracellular sodium accumulation. According to the current most widely accepted model of the mechanism for the Na⁺, K⁺ ATPase, cyclic binding and release of magnesium occurs between the enzyme complex and the intracellular milieu during the Na⁺, K⁺ exchange.

Na⁺ K⁺ ATPase activity has been reported low in various tissues of animals with streptozotocin-induced diabetes and in the erythrocytes of Type-I diabetic patients. It has been reported that this impaired enzyme activity plays a role in the pathogenesis of diabetic polyneuropathy. The mechanism leading to the impairment of this enzyme activity in diabetes mellitus is still unclear but the possibility of magnesium deficiency cannot be ruled out.

Magnesium has also been shown to reduce or prevent the net potassium loss from the heart induced by glycosides (Shine, 1979). It has been suggested that this effect of magnesium on intracellular potassium is a result of magnesium enhancing Na⁺, K⁺
magnesium in urine. The marginal but significant decrease in the glucose levels with the supplementation of magnesium confirms the beneficial role of magnesium in diabetes. However, the failure to normalize blood glucose with daily intake of magnesium supplementation in magnesium deficient rats suggests that magnesium deficiency may cause some irreversible defects in the glucose homeostasis causing persistent hyperglycemia. Similar findings were observed by Lima et al (1998) who did not find any improvement in fasting blood glucose with supplementation of magnesium oxide (41.4 mmol/day in three doses for 30 days) but significant fall of fructosamine was reported. Their observations suggest that there was no clinical improvement of insulin resistance and confirm the hypothesis that hypomagnesemia is associated with the insulin resistance state per se. Eibl et al (1995) have shown that magnesium treatment with high dose for 3 months (30 mmol/day) can increase plasma magnesium to nearly normal levels, but did not observe any effect on metabolic control or insulin resistance. By contrast, Paolisso et al (1994) described an improved insulin response and a fall of fasting blood glucose level after magnesium administration in type 2 diabetic patients. Recently it was shown that in obese Zucker rats after 8 weeks of high dietary magnesium intake glycosuria and glycosylated hemoglobin were reduced (Vormann et al, 1997). If hyperglycemia is the main pathophysiological factor in the development of diabetic complications, then positive impact of magnesium supplementation may be expected. Magnesium supplementation, given orally or intravenously, improves insulin sensitivity as well as insulin secretion in patients with diabetes (Kisters et al, 2000) and in this study, also the improvement in the insulin action could be observed. An oral magnesium supplementation has also been reported to reduce the development of type 2 diabetes in predisposed rats (De Valk, 1999). Based on these observations, cautious administration of magnesium salts has been suggested as
(Verlangierii & Busca, 1992), it has been shown that ascorbate has a lower redox potential than α-tocopherol and has been shown to be an efficient co-antioxidant in vitro for the regeneration of α-tocopherol from tocopheroxyl radical (Hamilton et al, 2000; Thomas et al, 1995). Restoration of vitamin C therefore could lead to improve vitamin E status. In addition to scavenging free radical directly, magnesium supplementation may have other benefits; magnesium can reduce the extent of protein glycation, which is known to play an important role in the development of diabetic complications, and this provides an additional rationale for the use of magnesium in diabetes (Vormann et al, 1997). The increased activity of antioxidant enzymes after supplementation of magnesium supplementation indicates that magnesium may restore the decreased overall antioxidant capacity in the diabetic animals. The mechanism by which magnesium affects enzyme activity is not clear. It is possible that magnesium may have been adequate to metabolize the increased cellular peroxide to protect the enzyme activity. Data have shown that tissue antioxidant systems are altered in experimental diabetes as well as in magnesium deficiency and the restoration of these enzyme activities up to some extent by magnesium supplementation seems indicative of the association of magnesium with the process of development of diabetic complications.
and dyslipidemia and supplementation effects, has clinically significant implications.

A possible role of hypomagnesemia in development of diabetic microangiopathy was suggested by the studies of McNair et al (1978). Magnesium may also be implicated in the development of diabetic complications via effects on inositol transport as suggested by Grafton et al (1992). In diabetic patients, hypomagnesemia might represent an independent risk factor for cardiovascular complications (Seeling & Heggtveit, 1974; Mather et al, 1982). They have suggested that magnesium can prevent the development of atherosclerotic disease by counteracting the adverse effects of intracellular calcium, retaining intracellular potassium and contributing both to stabilizing plasma membrane and maintaining the integrity of sub-cellular structures.

Magnesium deficiency has been found to be associated with diabetic microvascular disease. In diabetic children with no clinical evidence of vascular disease, a low serum magnesium level correlated positively with the velocity of regaining basal vascular tone after hyperemia (Ewald et al, 1983). Hypomagnesemia has been well documented in patients with diabetic retinopathy, with lower magnesium levels predicting a greater risk of severe diabetic retinopathy (Cerriello et al, 1982; McNair et al, 1978).

Recognizing the signs of diabetes-induced magnesium deficiency is important, because the deficiency can occur long before it is reflected by the serum values. It could be demonstrated that there is a relationship between hypomagnesemia and late diabetic complications. These evidences stress the concept of evaluating magnesium levels in plasma of diabetic patients particularly with poor glycemic control. The main implication of these results is that low plasma magnesium levels confer increased risk for diabetic complications through increased oxidative stress and altered lipid profile and ionic imbalance.