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Emerging Clinical Significance of Magnesium in Type 2 Diabetes Mellitus

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Abstract

Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 diabetes mellitus. Magnesium, the second most common intracellular cation plays a fundamental role as a cofactor in various enzymatic reactions involving energy metabolism. It is involved at multiple levels in insulin secretion, binding and activity. Magnesium deficiency is common in diabetes mellitus and its late complications. Despite numerous reports linking hypomagnesemia to chronic diabetic complications, attention to this issue is poor among clinicians. The present review discusses the functional role of magnesium in diabetes mellitus and introduces a relatively new concept of magnesium deficiency in diabetic complications.

Key Words: Magnesium, diabetes mellitus, insulin resistance, cardiovascular disease.

Introduction

The discovery of Von Mering and Minkowski in 1889 that pancreatectomy caused spontaneous diabetes followed by the discovery of insulin by Banting and Best in 1921, led to the conclusion that diabetes mellitus was the result of insulin deficiency [1]. Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia [2]. It is a collection of disorders and characterized by defective regulation of carbohydrate, lipid, protein and mineral metabolism. The biochemical hallmark of diabetes mellitus is chronic hyperglycemia which results from an absolute or relative deficiency of insulin. The prevalence of diabetes is higher in the developing countries (6.2% in 2000) as compared to that in developed countries (3.5% in 2000) [3]. The worldwide prevalence of diabetes, especially that of type 2 diabetes mellitus is increasing the awareness about the disease and there has been a rapid growth of ethnic and racial populations who have high prevalence rates of type 2 diabetes mellitus [4]. Interestingly, the prevalence of type 2 diabetes is highest in certain Pacific islands, intermediate in countries such as India and the United States, and relatively low in Russia and China. This variability is likely due to genetic, behavioral and environmental factors. Also, the prevalence varies among different ethnic populations within a given country [2].

Diabetes mellitus is becoming a major epidemic world-wide. Diabetes affects an estimated 16 million people in the United States, as many as half of whom are undiagnosed. Each year, an additional 800,000 individuals develop diabetes in this country and 54,000 die from diabetes-related causes. Diabetes is a leading cause of end-stage renal disease, adult-onset blindness and non-traumatic lower extremity amputations in the United States. In 2000, the estimated life-time risk of being diagnosed with diabetes mellitus was 1 in 5 for females [5]. The risk is 2 to 5 times higher in the African American communities, compared to non-Hispanic Whites. World-wide, more than 140 million people suffer from diabetes, making this one of the most common non-communicable diseases [6].

WHO has predicted that in future the major burden will occur in the developing countries. There will be a 42% increase from 51 million in the year 1995 to 72 million by the year 2025 in developed countries and 170% increase from 84 to 288 million in the developing countries. The countries with largest number of diabetic people are and will be in the year 2025- India, China and the United States [7].

This review is an attempt to bring to focus: Magnesium, as a complicating factor and also a clinically significant electrolyte, for a long term global policy to lower the burden of diabetes mellitus, with new findings

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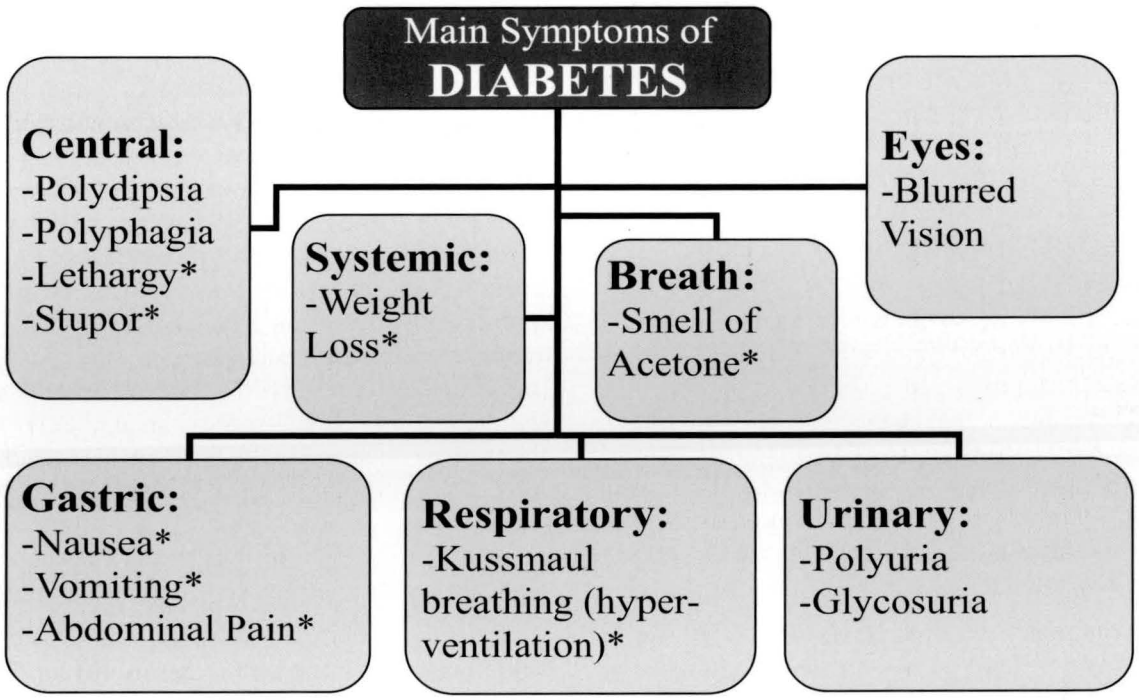
and researches supporting such concerns. Even the international expert committee has given new recommendations for the diagnosis and treatment of diabetes mellitus in this respect [8].

Type 2 Diabetes Mellitus

There are several distinct types of diabetes mellitus but it is broadly divided in to type 1 and type 2. Type 1 diabetes mellitus is characterized by marked deficiency of insulin secretion, whereas Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production [9]. The most prevalent form of diabetes mellitus is type 2, previously called Maturity- onset or Non – insulin dependent diabetes mellitus (NIDDM). Although type 2 diabetes mellitus may be associated with some degree of insulin secretion defect, the patients are often overweight and do not usually have evidence of circulation auto-antibodies against the pancreatic beta-cells [10]. Diabetes mellitus is a common complication of chronic pancreatitis associated with disturbed metabolism of zinc, copper, magnesium and selenium [11]. Major clinical features of diabetes mellitus are depicted in Fig. 1.



*= these symptoms are more common in Type 1 Diabetes.

Fig. 1 Major clinical features of diabetes mellitus.

Type 2 diabetes is an ongoing, chronic and progressive disorder, often asymptomatic in its early stages and remains undiagnosed for many years. Significant hyperglycemia is present on an average for 5-7 years before diagnosis is made. Type 2 diabetes is aptly termed as 'metabolic vascular disease'. The American heart association has stated that from the point of view of cardiovascular medicine, it may be appropriate to say that diabetes is a "Cardiovascular Disease" because major chronic complications of type 2 diabetes affect the macro- as well as microvascular system causing coronary artery disease and peripheral vascular disease or affect microcirculation with devastating results in the form of retinopathy, nephropathy and neuropathy [12].

Magnesium homeostasis

Until recently, the function of magnesium in biological processes was largely ignored to the point where it was described as the "Forgotten Ion". In recent years, there has been an explosion of interest in the physiological and therapeutic properties of this essential element [13]. Magnesium is the fourth most common cation in the body. Magnesium is present in greatest concentration within the cell and is the second most abundant intracellular cation after potassium [14]. Sixty percent of total body magnesium is found in bones, incorporated in the crystal mineral lattice or in the surface-limited exchangeable pool; 20% is located in skeletal

muscle; the remainder exists in other body tissues, especially heart and liver.

Magnesium is required for the activation of many important enzymes including those that involve adenosine triphosphate (ATP). This element is also essential for the transfer, storage and utilization of intracellular energy, for the metabolism of carbohydrates, proteins, fats and nucleic acids, for maintenance of normal cell membrane function and for neuromuscular transmission [15]. Green leafy vegetables such as spinach, cabbage, cauliflower, milk, fruits, cereals, some legumes (peas & beans), and whole, unrefined grains, tap water and among the beverages, coffee, tea and cocoa are rich in magnesium [16].

It has been estimated that refining and processing of food causes a substantial loss of magnesium. For example, the refining and processing of wheat to flour, rice to polished rice and corn to starch depletes magnesium by 82, 83 and 97% respectively [17]. Thus, modern food technology partially explains why a significant segment of the population has intake of magnesium below recommended dietary amounts and may be predisposed to chronic, latent magnesium deficiency. Drinking water on the other hand, remains an important source of magnesium. There are several other factors which have reduced magnesium within the ecosystem as a whole. Acid rain causes exchange between magnesium and aluminium in the soil. This, coupled with intensive farming of the soil, has led to a reduction in magnesium within the food chain [18].

On an average American diet, 250 to 350 mg of Magnesium is consumed daily; 25-60% of dietary Magnesium is absorbed in the gastrointestinal tract. Gastrointestinal absorption occurs predominantly in the small intestines via paracellular simple diffusion at high intraluminal concentrations and active transcellular uptake via Magnesium specific transporters at low concentrations [19]. Active intestinal Magnesium absorption is presumed to involve transient receptor potential channel melastatin 6 (TRPM 6), which is expressed along the brush border membrane of the small intestine. Mutations of TRPM6 have been reported to be associated with hypomagnesemia with secondary hypocalcemia [20].

The ultrafilterability of Magnesium depends on glomerular filtration, volume status, various metabolic states that would enhance the selection for ionized Magnesium (e.g., acidemia, reduced serum content of negatively charged species), and the integrity of the glomerular basement membrane.

Once Magnesium is filtered through the glomerulus, 15 to 25% is reabsorbed in the proximal tubules. Reabsorption at the proximal tubule is mainly passive and proportional to sodium and water reabsorption, although at a lower rate. Approximately 65 to 75% of the filtered Mg load is reabsorbed via the paracellular pathway in the thick ascending limb of the loop of Henle (TAL) [21]. Paracellular Mg reabsorption at this nephron segment has been suggested to be facilitated by claudin 6, also known as paracellin 1. Paracellin 1 is a tight junction protein whose mutation is associated with severe hypomagnesemia with hypercalciuria and nephrolithiasis [22].

Insulin also has been implicated to play a role at this nephron segment by increasing the favorable transepithelial potential difference for Mg reabsorption [23].

The distal convoluted tubule (DCT) reabsorbs approximately 5 to 10% of the filtered Mg via an active and regulated transcellular pathway. Although this is a low percentage of the filtered Mg load, it represents 70 to 80% of Mg that is delivered from the TAL. In addition, because a negligible amount of Mg is reabsorbed distal to this segment, Mg reabsorption at the DCT is of great importance because it determines the final urinary Mg concentration [20]. Recently, Mg reabsorption at the DCT was shown to occur via the transient receptor potential channel melastatin TRPM6. It has been postulated that upon entry into the cells, Mg binds to divalent- binding proteins such as parvalbumin or calbindin- D28K for transport across the cell the basolateral membrane, while Mg is taken into the interstitium by a basolateral Na^{2+}/Mg^{2+} exchanger and/or ATP- dependent Mg pump [24].

Hypomagnesemia and diabetes mellitus

Clinically, hypomagnesemia may be defined as a serum Mg concentration $\leqslant 1.6$ *mg/dl* or SD±2 below the mean of the general population (normal serum Mg concentration is 1.5- 2.5 mg/dl). Early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue and weakness. Magnesium deficiency is common and multifactorial. Magnesium deficit can be categorized in to two types: magnesium deficiency and magnesium depletion. Dietary amounts of magnesium are marginal in the whole population and little alteration in magnesium intake may increase the prevalence of magnesium deficiency [25]. Poor dietary intake, autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, osmotic diuresis, recurrent metabolic acidosis, hypophosphatemia, and hypokalemia are contributory factors. Despite numerous reports linking hypomagnesaemia to chronic diabetic complications, attention to this issue is poor among clinicians.

Hypomagnesaemia has been linked to coronary artery disease, hypertension, poor glycemic control

including diabetic retinopathy, nephropathy, neuropathy and foot ulcerations [26]. Up to 40% of patients with other electrolyte deficiencies are magnesium-deficient as well, whether or not symptoms are present. This finding has led to the suggestion that serum magnesium levels should be obtained routinely when other serum electrolyte levels are ordered [27].

Serum magnesium levels have been shown to be inversely related to the severity of diabetes [28] and hypomagnesemia was commonly associated with sepsis and diabetes mellitus [29]. Magnesium intake was inversely associated with incidence of diabetes in young American adults. This inverse association may be explained, at least in part, by the inverse correlation of magnesium intake with systemic inflammation and insulin resistance [30].

Magnesium is essential for insulin secretion, insulin receptor interaction, post receptor events (involving tyrosine kinase mediated phosphorylation) and normal carbohydrate utilization (by Magnesium dependent enzymes). A compromise in these functions leads to insulin resistance in hypomagnesaemia; the latter is contributed by: (1) Hyperglycemia which leads to decreased cellular Magnesium levels, independent of insulin levels [26], (2) Osmotic diuresis leads to increased urinary Magnesium losses [31] and (3) Concomitant use of diuretics and hypolipidemic agents also increase urinary Magnesium loss [26].

Hypomagnesemia and diabetic complications

Researchers have found an association between magnesium levels and both cardio-vascular disease and hypertension, probably as a result of the common biochemical mechanism underlying the damage observed in each of the diseases (Fig. 2).

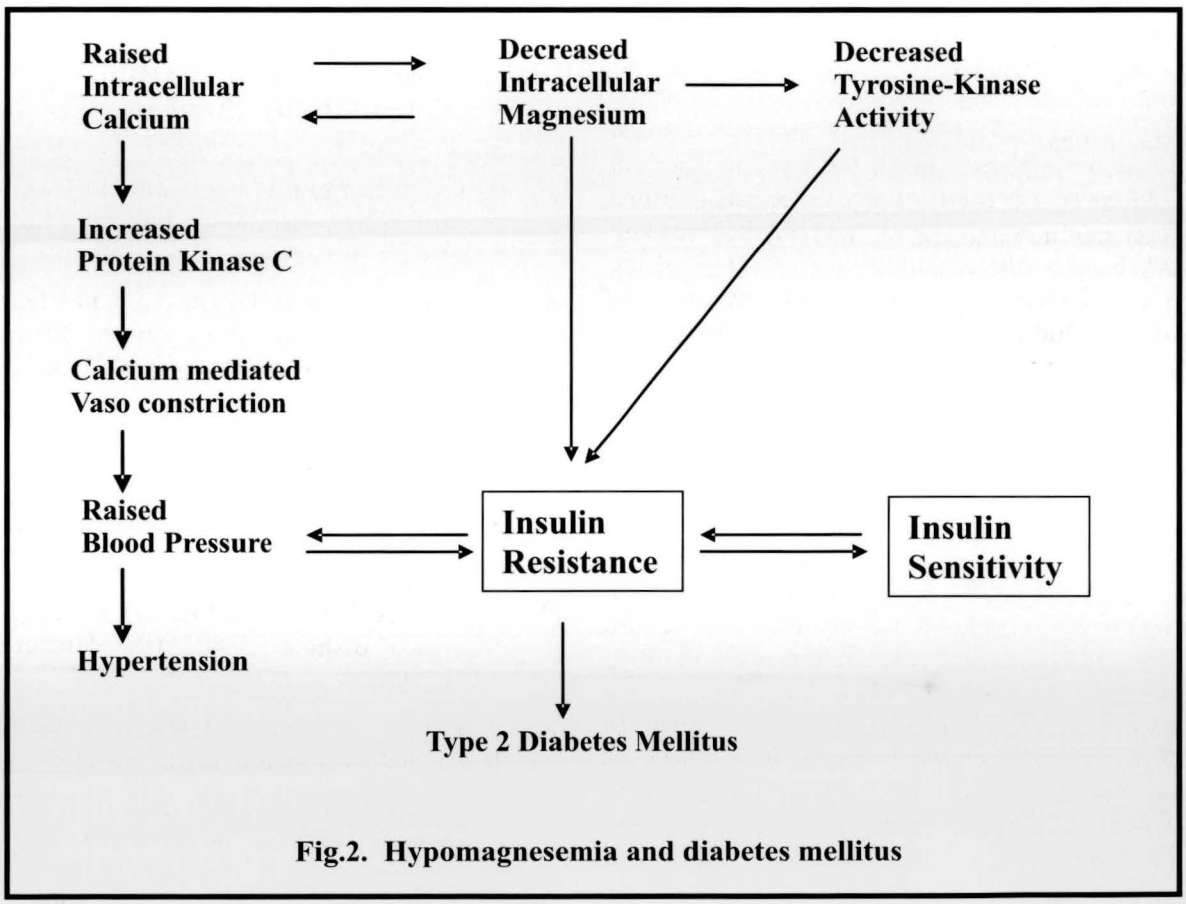


Fig.2. Hypomagnesemia and diabetes mellitus

Sasaki and colleagues demonstrated that the diabetes mellitus patients in their study had lower serum levels of ionized magnesium than healthy controls [32]. As per the Atherosclerosis Risk in Communities (ARIC) Study, a multicenter, prospective cohort study that lasted 4 to 7 years and involved 13,922 middle- aged adults who were free of coronary heart disease at baseline, an inverse association between serum Magnesium and the risk for coronary heart disease was observed among men with diabetes [33].

Pathophysiologically, magnesium depletion can directly cause vasoconstriction and frank hypertension which can predispose to cardiac arrhythmias and sudden death, can increase platelet aggregation and thus the potential for *in situ* thrombosis, and can produce the pathologic lesions of atherosclerosis, all the above occurring clinically to an increased extent in diabetes [34].

. Rodriguez-Moran and Guerrero-Romero suggested that hypomagnesemia may be associated with an increased risk of diabetic foot ulcers. Indeed, they observed a higher incidence of hypomagnesemia among their patients with diabetic foot ulcers compared with those without the condition [35].The existence of a close relationship between metabolic control and impaired magnesium balance was confirmed by Fujii et al. who observed that a marked depletion in plasma and erythrocyte magnesium levels was particularly evident in diabetic patients with advanced retinopathy and poor diabetic control [36].

Corsonello *et al.* observed a significant decrease in serum ionized Magnesium in both the microalbuminuria and overt proteinuria groups compared with the nonmicroalbuminuric group [37]. Accordingly, in a recent retrospective study, an association between low serum Magnesium levels and a significantly faster rate of renal function deterioration in patients with type 2 diabetes was reported [38]. Finally, there also are data to suggest the association between hypomagnesemia and other diabetic complications, including dyslipidemia and neurologic abnormalities [39].

Magnesium supplementation

Because hypomagnesemia has been linked to various micro- and macrovascular complications, a better understanding of Magnesium metabolism and efforts to minimize hypomagnesemia in the routine management of diabetes are warranted [40]. Magnesium supplementation improves insulin mediated glucose disposal and insulin secretion [41]. It also improves insulin action among patients with type 2 diabetes [42]. Oral magnesium supplementation improves insulin sensitivity even in normomagnesemic, overweight, nondiabetics subjects emphasizing the need for an early optimization of Magnesium status to prevent insulin resistance and subsequently type 2 diabetes [43]. Magnesium pidolate at 4.5 g per day (15.8 mmol/day) for 4 weeks significantly improved insulin action and oxidative glucose metabolism, increased erythrocyte magnesium concentration, and decreased erythrocyte membrane microviscosity [44].

Conclusion and future perspective

The treatment of the patients with diabetes requires a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated. Serum magnesium levels are not investigated in routine clinical practice despite its significance. In particular, although hypomagnesemia has been reported to occur with increased frequency among patients with type 2 diabetes mellitus, it is frequently overlooked and undertreated. Oral magnesium restores serum magnesium levels, improving insulin sensitivity and has the potential to partly ameliorate some of the diabetic complications. It is therefore advisable to include serum magnesium in the routine electrolyte panel for the better management of diabetes mellitus.

References

1. Alberti KGMM, Zimmet PZ (1998) For the WHO consultations: Definition, Diagnosis and complications. Part 1 Diabetic Med P 15:533-539.
2. Powers CA (2008) Diabetes mellitus In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo BL, Jameson JL (eds), ,Harrison's principles of internal medicine. 17th edition. United States of America (NY) Mc. Graw Hill Companies, 2275-2304.
3. Wild S, Roglic G, Sicree R, et al (2000) Global prevalence of diabetes: estimation for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053.
4. Burant CF (2004) Diagnosis and classification in Medical management of type 2 diabetes. 5th ed. Virginia. American diabetes Association, 5: 1-16.
5. Narayan KM (2003) Lifetime risk for diabetes mellitus in United States JAMA 14:1884-90.
6. Zimet P, Albert KG and Shaw J (2001) Global and societal implications of diabetes epidemic. Nature 414 : 782-787.
7. King H, Aubert RE and Herman WH (1998) Global burden of diabetes. 1995-2025. Diabetes Care 121: 1414-1419.
8. American Diabetes Associates (2004) Clinical Practice Recommendations: Diabetes Care 6:1-16.
9. Sahay BK and Sahay RK (2003). Type 2 diabetes in the young. Int J Diabetes Dev Ctries. 23:51-4.
10. Miur A, Davies SA and Turner RC (1998) General practice care of non insulin dependent diabetes with fasting blood glucose measurements. Am J Med 73: 610-637.
11. Abbot LG, Rude RK (1993) Clinical Manifestation of Magnesium deficiency. Mineral Electrolyte Metab 19: 314-322.

12. Williams G (2003) Diabetes. In: Warell DA, Cox TM, Firth JD; Benz EJ (eds) Oxford textbook of medicine Oxford University New York 4: 252-53.

13. Laurant P, Touyz RM (2000) Physiological and pathological role of magnesium in cardiovascular system implication in hypertension. J Hypertens 18: 1171-91.

14. Novello N and Blumstein HA (2007). Hypomagnesemia in Ethiopians with diabetes wellitus. Ethn Dis dis 81 (1): 63-68.

15. Chaudhary PD, Sharma R and Bansal DD (2010) Implication of magnesium deficiency in type 2 diabetes. Biol Trace Elem Res 134: 119-129.

16. Wester PO (1987) Magnesium. Am J Clin Nutrition 45: 1305-1312.

17. Marrier JR (1986) Magnesium content of the food supply in modern world. Magnesium. 5 :1-8.

18. Fawcett WJ, Haxby EJ and Male DA (1999). Magnesium physiology and pharmacology. Br J Anaesth 83: 302-320.

19. VoetsT, Nilius B, Hoefs S, et al (2004).TRPM6 forms Voets the Mg2+ influx channel. J Biol Chem 279: 19-25.

20. Schlingmann KP and Weber S (2002). Hypomagnesemia with secondary hypocalcemia is caused by mutations in TRPM6, a new member of the TRPM gene family. Nat Genet 3 :166-170.

21. Walder RY and Landau D (2002). Mutation of TRPM6 causes familial hypomagnesemia with secondary hypocalcemia. Nat Genet 31:171-174.

22. Garber AJ (1996): Magnesium utilization survey in selected patients with diabetes. Clin Ther 18: 285-294.

23. Schnack C, Bauer I, Pregant P, et al (1992) Hypomagnesemia in type2 diabetes mellitus is not corrected by improvement of long term control. Diabetologia35: 77-79.

24. Monteilh- zoller MK, Hermosura MC, Nadler M J, et al. (2003) TRPM7 provides an ion channel mechanism for cellular entry of trace metal ions. J Gen Physiol.121: 49-60

25. Durlach J and Bac P (1998), Magnesium status and aging: an update, Magnes Res 1: 25- 42.

26. Pham PC, Pham PM, Pham SV, et al (2007) Hypomagnesemia in patient with type II diabetes. Clin J Am Soc Nephrol 2: 366-373.

27. Martin DR and Overhot LM. (1996) Disorder of Magnesium, calcium and phosphorous. Harwood Nuss AL, Linden HS, Luten RC , Shepherd SM, Wolfson AB, The clinical practice of emergency medicine. Philadelphia New York (NY): Lippincott Raven Publishers and company; .2: 757-761.

28. Fox C, Ramsoomair D and Carter C (2001), Magnesium: its proven and potential clinical significance South Med J. 94(1): 1195-1201.

29. Limaye CS, Londhey VA, Nadkart MY, et al (2011). Hypomagnesemia in critically ill medical patients. J Assoc Physicians India: 59:19-22.

30. Kim DJ, Xun P, Liu K, et al (2010).Magnesium intake in relation to systemic inflammation ,insulin resistance,and the incidence of diabetes. Diabetes care.12:2604-2610.

31. Hans CP, Sialy R and Bansal DD (2002). Magnesium deficiency and diabetes mellitus. Current Science 83: 12.

32. Sasaki S (2000). Abnormal magnesium status in patients with cardiovascular disease. Clin Sci 20 98: 175-181.

33. Liao F, Folsom AR and Brancati FL (1998) Is low magnesium concentration a risk factor for coronary heart disease the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 136: 480-490.

34. Orimo H and Ouchi Y (1990) Ann NY, Acad Sci 598: 444-464.

35. Moran M and Romero F (2001) Low serum magnesium levels and foot ulcers in subjects with type2 diabetes. Arch Med Res 32: 300-313.

36. Kao WH, Folsom AR, Nieto FJ, et al (1999) Serum and dietry magnesium and the risk of type 2 diabetes mellitus. Arch Intern. Med 159: 2151-2159

37. Corsonello A, Lentile R, Buemi M, et al (2000) Serum ionized magnesium levels in type 2 diabetic patients with microalbuminuria or clinical proteinuria. Am J Nephrol 20: 187-192.

38. Pham PC and Pham PM, Pham PA, et al (2005) Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin Nephrol 63: 429-436.

39. Sales CR, Pedrosa L (2006). Magnesium and diabetes mellitus: Their relation. Clin Nutr 25: 554-562.

40. Quamme GA (2001): Renal handling of magnesium, Massry and Glassock's Textbook of Nephrology, Massry SH (ed), Glassock RJ, Baltimore, 4: 344-350.

41. Lima M, Cruz T, Pausada JC, et al (1998). The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. Diabetes Care 21: 682-686.

42. Drueke TB and Lacour B. (2007) Magnesium homeostasis and disorders of magnesium metabolism. In: Feehally J, Floege J, Johnson RJ (eds) Comprehensive Clinical Nephrology. 3rd ed. Philadelphia, PA: Mosby: PP136-138.

43. Morren FC, Kruger K, Volker K, et al (2011) Oral Magnesium supplementation reduces insulin resistance in non-diabetic subjects–a double blind, placebo–controlled, randomized trial. Diabetes Obese Metab 3: 281-284.

44. Paolisso G, Sgambato S, Gambardella A, et al (1992) Daily Magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr 55: 1161-1167.