Article ID: WMC003878 ISSN 2046-1690

Hypomagnesemia and its implications in Type 2 Diabetes Mellitus- A Review Article

Corresponding Author:
Dr. Namrata Chhabra,
Professor and Head, Biochemistry, SSR Medical College, Mauritius, 5, Loretto convent street, 742CU001 - Mauritius

Submitting Author:
Dr. Namrata Chhabra,
Professor and Head, Biochemistry, SSR Medical College, Mauritius, 5, Loretto convent street, 742CU001 - Mauritius

Article ID: WMC003878

Article Type: Review articles

Submitted on:10-Dec-2012, 06:06:26 AM GMT **Published on:** 10-Dec-2012, 01:58:07 PM GMT

Article URL: http://www.webmedcentral.com/article_view/3878

Subject Categories: Diabetes

Keywords: Hypomagnesemia, Type 2 Diabetes Mellitus, atherogenic dyslipidemia and coronary heart disease.

How to cite the article: Chhabra S, Chhabra S, Ramessur K, Chhabra N. Hypomagnesemia and its implications in Type 2 Diabetes Mellitus- A Review Article . WebmedCentral Diabetes 2012;3(12):WMC003878

Source(s) of Funding:

Self funding by the authors

Competing Interests:

None

Hypomagnesemia and its implications in Type 2 Diabetes Mellitus- A Review Article

Author(s): Chhabra S, Chhabra S, Ramessur K, Chhabra N

Abstract

Hypomagnesemia has been implicated in adversely affecting diabetic complications. Magnesium is a cofactor for over 300 enzymes particularly for those concerned with ATP and energy production. It is also required for normal DNA function, cell permeability regulation and neuromuscular excitability. Clinically, hypomagnesemia has been related to hypertension, atherogenic dyslipidemia, impaired clotting, increased inflammatory burden, oxidative stress, carotid wall thickness and coronary heart disease. Type 2 Diabetes Mellitus facilitates low serum magnesium levels and this in turn worsens glycemic control in diabetes, thus establishing a vicious circle that leads to a progressive impairment in metabolic control and more risk of diabetic complications.

Conclusion: Hypomagnesemia is a cause or consequence of type 2 diabetes mellitus remains yet to be ascertained , but it is a cardiovascular risk factor and favors diabetic complications. Periodic determination of magnesium levels and appropriate magnesium replacement can promote a better glycemic control, healthy life style and delay the onset of diabetes related complications.

Keywords: Hypomagnesemia, Type 2 Diabetes Mellitus, atherogenic dyslipidemia and coronary heart disease.

Introduction

Diabetes mellitus is a chronic disease that requires long-term medical attention to limit the development of its devastating complications. The incidence of diabetes is increasing worldwide. A 2011 Centers for Disease Control and Prevention (CDC) report estimated that nearly 26 million Americans have diabetes. Additionally, an estimated 79 million Americans have prediabetes (1).

The International Diabetes Federation predicts that the number of people living with diabetes will rise from 366 million in 2011 to 552 million by 2030. It is a disproportionately expensive disease; in the United States in 2007, the direct medical costs of diabetes were $116 billion, and the total costs were $174 billion (2). The treatment of the patients with diabetes requires a multidisciplinary approach whereby every potential complicating factor must be monitored closely and treated.

Hypomagnesemia has been reported to occur at an increased frequency among patients with type 2 diabetes compared with their counterparts without diabetes. Hypomagnesemia occurs at an incidence of 13.5 to 47.7% among patients with type 2 diabetes. The increased incidence of hypomagnesemia among patients with type 2 diabetes presumably is multifactorial (3).

Physiological Role Of Magnesium

Magnesium is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It may exist as a protein-bound, complexed, or free cation. Magnesium (Mg) is involved in more than 300 enzymatic reactions and is essential for life. Magnesium may be required for substrate formation, as an allosteric activator of enzyme activity, and for membrane stabilization. Adenylate cyclase (4) and the sodium- potassium-adenosine triphosphatase (Na, K, ATPase) (5) are enzymes that are critically dependent on Mg. It is also an essential enzyme activator for neuromuscular excitability and cell permeability, a regulator of ion channels and mitochondrial function, a critical element in cellular proliferation and apoptosis, and an important factor in both cellular and humoral immune reactions. The effects of Mg on enzymes, as well as on other important biological processes such as glycolysis, oxidative phosphorylation, nucleotide metabolism, protein biosynthesis, and phosphoinositol turnover, underscore the importance of Mg in cellular metabolism (6-10).

Basic studies suggest that Mg^{2+} ions modulate immunological functions such as granulocyte oxidative burst, lymphocyte proliferation, and endotoxin binding to monocytes(11). Furthermore, Mg deficiency is correlated with increases in interleukin-1, tumor necrosis factor-α, interferon-γ, and substance P

(12-14).

Assessment Of Magnesium Status and Hypomagnesemia

Magnesium deficiency refers to a total body deficiency of Mg (15). Clinically, hypomagnesemia may be defined as a serum Mg concentration ≤1.6 mg/dl or >2 SD below the mean of the general population(16). However, because serum only contains 0.3% of the total body Mg, it is a poor reflection of total body Mg content(17).Thus, total serum Mg concentration may not adequately reflect body Mg stores, and patients may have a normal serum Mg and total-body Mg depletion.

Intracellular Mg^{2+} can also be estimated using circulating red blood cells, mononuclear cells, and skeletal muscle cells. Intracellular Mg^{2+} has been assessed as an index of Mg status [18] and is generally a more accurate indicator of Mg status than the total serum Mg concentration (19). However, a great deal of overlap with the normal range is seen, and intracellular Mg^{2+} is not a sufficiently discriminatory test to diagnose Mg deficiency in any given patient (20).Therefore, the clinical assessment of patients at risk for Mg deficiency remains vital for making a timely diagnosis.

Clinically, it has been suggested that in a patient with suspected Mg deficiency, a low serum Mg concentration is sufficient to confirm the diagnosis. If the serum Mg level is normal in the same patient, then other more sensitive tests should be performed (21). Although controversies still exist as to how hypomagnesaemia is best gauged, current understanding on the clinical impact of hypomagnesaemia in human is influenced by studies that have relied predominantly on the measurements of serum Mg concentrations (3)

Hypomagnesaemia In Type 2 Diabetes Melltus- A Cause Or Consequence?

The magnesium homeostasis is tightly regulated and depends on the balance between intestinal absorption and renal excretion (22) {Table}. In addition, genetic determinants and sex hormones can also modulate serum magnesium levels (23). The mechanisms whereby hypomagnesemia may induce or worsen existing diabetes are not well understood. Nonetheless, it seems that both insulin secretion and insulin action can be affected (24).

Because insulin has been implicated in enhancing renal magnesium reabsorption, insulin deficiency or resistance could promote urinary magnesium excretion (3). In addition, hyperglycemia and glycosuria may also interfere with renal magnesium handling, mainly by reducing the tubular reabsorption of the cation (25).

In diabetic patients the ultrafilterable Mg load may be enhanced by glomerular hyperfiltration, recurrent excessive volume repletion after hyperglycemia-induced osmotic diuresis, recurrent metabolic acidosis associated with diabetic ketoacidosis, and hypoalbuminemia (26). The last two conditions may increase the serum ionized Mg fraction and, hence, ultrafilterable Mg load and subsequent urinary loss. In addition, it is conceivable that significant microalbuminuria and overt proteinuria among patients with diabetic nephropathy may contribute to renal Mg wasting as a result of protein-bound magnesium loss (3).

Other potential causes of lower serum magnesium in obese type 2 diabetic patients include reduced intestinal magnesium absorption secondary to higher fat intake and lower fiber intake(27), and diabetic autonomic neuropathy that may reduce oral intake and gastrointestinal absorption (3). Insulin may induce a shift of magnesium from the plasma to the erythrocytes and smooth muscle cells, both in vivo and in vitro, helping to explain the abnormalities in magnesium circulating levels frequently reported in diabetic patients (28).

In addition to its role in increasing serum ionized Mg concentration and, hence, ultrafilterable Mg load for renal excretion, metabolic acidosis has been suggested to enhance protonation of the Mg channel in the DCT and subsequent inhibition of cellular Mg uptake(29)- Table.

Implications Of Magnesium Deficiency

Low circulating magnesium levels have been related to elevated blood pressure, atherogenic dyslipidemia, impaired clotting, increased inflammatory burden, oxidative stress, carotid wall thickness and coronary heart disease (30-31). Therefore, hypomagnesemia could be considered an additional source of cardiovascular risk in T2DM. In addition, hypomagnesemia has been implicated in adversely affecting diabetic complications (3). Lower $[Mg^{2+}]$ is associated with a faster renal function deterioration rate in DM2 patients.(16). Furthermore, it has recently been shown that low serum magnesium concentrations increase the risk of all-cause mortality in T2DM(32).

Insulin Release: Apart from diabetic complications

and the mortality rate, reduced intracellular magnesium concentrations result in an altered cellular glucose transport, a defective tyrosine-kinase activity, post-receptor impairment in insulin action by influencing intracellular signaling and processing, and reduced pancreatic insulin secretion (24, 33).

Insulin Resistance: In addition, chronic magnesium deficiency has also been associated with elevated concentrations of TNF-alpha, and this fact may also contribute to post-receptor insulin resistance (34). Therefore, T2DM could facilitate low serum magnesium levels and this could in turn worsen glycemic control of diabetes, thus establishing a vicious circle that could lead to a progressive impairment in metabolic control and more risk of diabetic complications (35).

Clinical Manifestations and Biochemical Alteartions Associated With Hypomagnesemia

Symptomatic magnesium depletion is often associated with multiple biochemical abnormalities such as hypokalemia, hypocalcemia, and metabolic alkalosis. As a result, it is often difficult to ascribe specific clinical manifestations solely to hypomagnesaemia (36).

Hypokalemia is a common event in hypomagnesaemia patients, occurring in 40 to 60% of cases(37). This relationship is in part due to underlying disorders that cause both magnesium and potassium loss, such as diuretic therapy and diarrhea. There is also evidence of renal potassium wasting in hypomagnesemic patients (38). Potassium secretion from the cell into the lumen in the cells of the thick ascending limb and cortical collecting tubule is mediated by ATP-inhibitable luminal potassium channels (39) . Hypomagnesemia is associated with a reduction in cell magnesium concentration, which may then lead to a decline in ATP activity, and, due to removal of ATP inhibition, an increase in the number of open potassium channels (40)). In addition, decreasing cytosolic magnesium has been shown to directly increase the activity of potassium channels of ascending limb cells (41).Given the very high cell potassium concentration, these changes would promote potassium secretion from the cell into the lumen and enhanced urinary losses. The hypokalemia in this setting is relatively refractory to potassium supplementation and requires correction of the magnesium deficit (42).

Hypocalcemia: The most classical sign of severe hypomagnesaemia (<1.0 mEq/L, 0.5 mmol/L, or 1.2 mg/dl) is hypocalcemia. Suppressive effect of hypomagnesaemia on PTH secretion, bone resistance to PTH and Low plasma levels of calcitriol (1,25-dihydroxyvitamin D), are the important causes of hypocalcemia associated with hypomagnesaemia in type 2 DM (36).

Neuromuscular Hyperexcitability: Although hypocalcemia may contribute to the neurological signs, Mg deficiency without hypocalcemia has been reported to result in neuromuscular hyper excitability (43). Lowering the serum Mg concentration decreases the threshold of axonal stimulation and increases nerve conduction velocity (44) . Mg2+ has also been shown to influence the release of neurotransmitters, such as glutamate, at the neuromuscular junction by competitively inhibiting the entry of calcium into the presynaptic nerve terminal [45,46]. It is likely that a decrease of extracellular Mg2+ would allow a greater influx of calcium into the presynaptic nerves and the subsequent release of a greater quantity of neurotransmitters, resulting in hyperresponsive neuromuscular activity (47).

Cardiovascular Implications: Dysrhythmias, hypertension, vasospasm, electrocardiographic changes-prolonged QT interval, prolonged PR interval ,wide QRS peaked T waves are observed in hypomagnesemia(48). Based on data from the Atherosclerosis Risk in Communities (ARIC) Study, an inverse association between serum Mg and the risk for coronary heart disease was observed among men with diabetes (49).

Management Of Hypomagnesemia In Type 2 Diabetes Mellitus

Poor dietary intake as a result of gastrointestinal autonomic dysfunction must be controlled. Tight glycemic control is recommended to minimize recurring renal Mg wasting in association with osmotic diuresis and metabolic acidosis. Associated hypophosphatemia and hypokalemia must be corrected. Finally, control of glomerular hyperfiltration with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or both may offer additional benefits in reducing renal Mg wasting. When hypomagnesemia persists despite all measures, oral Mg supplementation is indicated (3). Oral magnesium replacement therapy corrects hypomagnesemia after a minimum treatment period of 3 months (50).

Conclusion

Hypomagnesemia, can result in disturbances in nearly

every organ system and can cause potentially fatal complications . It is necessary that routine screening for hypomagnesemia be done and the condition be treated as early as possible.

Acknowledgement

I am thankful to Professor(Dr) A.K. Lavania and Professor(Dr). Kuldip Singh Sodhi for their unconditional support and guidance**.**

References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011.

2. One adult in ten will have diabetes by 2030. International Diabetes Federation. November 14, 2011.

3. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT (2007) Hypomagnesemia in patients with type 2 diabetes. Clin J Am SocNephrol 2: 366–373.

4. Grubbs RD, Maguire ME. Magnesium as a regulatorycation: criteria and evaluation. Magnesium. 1987;6:113-127.

5. Hexum T, Samson FE Jr, Himes RH. Kinetic studies of membrane (Na+-K+-Mg2+)-ATPase. Biochim Biophys Acta.1970;212:322-331.

6. Sanders GT, Huijgen HJ, Sanders R: Magnesium in disease: A review with special emphasis on the serum ionized magnesium. Clin Chem Lab Med37 :1011– 1033,1999.

7. Saris NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A: Magnesium: An update on physiological, clinical and analytical aspects. Clin Chem Acta294 :1– 26,2000

8. Elamin A, Tuvemo T: Magnesium and insulin-dependent diabetes mellitus. Diabetes Res Clin Pract10 :203– 209,1990.

9. White JR, Campbell RK: Magnesium and diabetes: A review. Ann Pharmacother27 :775– 780,1993.

10. Sales CR, de Fatima Campos Pedrosa L: Magnesium and diabetes mellitus: Their relation. Clin Nutr25 :554– 562,2006

11. Johnson JD, Hand WL, King-Thompson NL. The role of divalent cations in interactions between lymphokines and macrophages. Cell Immunol. 1980;53:236-245.

12. Weglicki WB, Phillips TM. Path biology of magnesium deficiency: a cytokine/neurogenic inflammation hypothesis.Am J Physiol. 1992;263:R734-R737.

13. Weglicki WB, Phillips TM, Freedman AM, Cassidy MM,Dickens BF. Magnesium-deficiency elevates circulating levels of inflammatory cytokines and endothelin. Mol Cell Biochem. 1992;110:169-173.

14. Weglicki WB, Mak IT, Stafford RE, Dickens BF, CassidyMM, Phillips TM. Neurogenic peptides and the cardiomyopathy of magnesium-deficiency: effects of substance Preceptor inhibition. Mol Cell Biochem. 1994;130:103-109.

15. Welt LG, Gitelman H. Disorders of magnesium metabolism. Dis Mon. 1965;47:1-32.

16. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM, Yanagawa N, Pham PT: Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus type 2. Clin Nephrol63 :429– 436,2005 [published erratum appears in Clin Nephrol 64: 248, 2005].

17. Rude RK. Minerals—magnesium. In: Stipanuk MH, ed. Biochemical and Physiological Basis of Human Nutrition. Orlando, Fla: Saunders; 2000:671-685.

18. Martin HE. Clinical magnesium deficiency. Ann N Y Acad Sci. 1969;162:891-900.

19. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. Crit Care Med. 1985;13:19-21.

20. Basso LE, Ubbink JB, Delport R. Erythrocyte magnesium concentration as an index of magnesium status: a perspective from a magnesium supplementation study. ClinChimActa. 2000;291:1-8.

21. Tosiello L: Hypomagnesemia and diabetes mellitus. Arch Intern Med156 :1143– 1148,1996

22. Topf JM, Murray PT (2003) Hypomagnesemia and hypermagnesemia. Rev Endocr MetabDisord 4: 195–206.

23. Shuen AY, Wong BY, Wei C, Liu Z, Li M, et al. (2009) Genetic determinants of extracellular magnesium concentration: analysis of multiple candidate genes, and evidence for association with the estrogen receptor alpha (ESR1) locus. ClinChimActa 409: 28–32.

24. Barbagallo M, Dominguez LJ (2007) Magnesium metabolism in type 2 diabetes mellitus, metabolic syndrome and insulin resistance. Arch BiochemBiophys 458: 40–47.

25. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbol I (1982) Renal hypomagnesaemia in human diabetes mellitus: its relation to glucose homeostasis. Eur J Clin Invest 12: 81–85.

26. Quamme GA: Renal handling of magnesium. In: Massry and Glassock's Textbook of Nephrology, 4th Ed., edited by Massry SH, Glassock RJ, Baltimore,

Lippincott Williams & Wilkins,2001 , pp344– 350
27. Schulze MB, Schultz M, Heidemann C, Schienkiewitz A, Hoffmann K, et al. (2007) Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. Arch Intern Med 167: 956–965.
28. Paolisso G, Sgambato S, Passariello N, Giugliano D, Scheen A, et al. (1986) Insulin induces opposite changes in plasma and erithrocyte magnesium concentrations in normal man. Diabetologia 29: 644–647.
29. Dai LJ, Friedman PA, Quamme GA: Acid-base changes alter Mg2+ uptake in mouse distal convoluted tubule cells. Am J Physiol Renal Physiol272 :F759–F766,1997.
30. Ma J, Folson AR, Melnick SL, Eckfeldt JH, Sharrett AR, et al. (1995) Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J ClinEpidemiol 48: 927–940.
31. Guerrero-Romero F, Rodriguez-Moran M (2006) Hypomagnesemia, oxidative stress, inflammation, and metabolic syndrome. Diabetes Metab Res Rev 22: 471–476.
32. Haglin L, Tornkvist B, Backman L (2007) Prediction of all-cause mortality in a patient population with hypertension and type 2 DM by using traditional risk factors and serum-phosphate, -calcium and –magnesium. ActaDiabetol 44: 138–143.
33. Takaya J, Higashino H, Kobayashi Y (2004) Intracellular magnesium and insulin resistance. Magnes Res 17: 126–136.
34. Rodriguez-Moran M, Guerrero-Romero F (2004) Elevated concentrations of TNF-alpha are related to low serum magnesium levels in obese subjects. Magnes Res 17: 189–196.
35. Larsson SC, Wolk A (2007) Magnesium intake and risk of type 2 diabetes: a meta-analysis. J Intern Med 262: 208–214
36. Zalman S. Agus. Hypomagnesaemia. JASN July 1, 1999 vol. 10no. 7 1616-1622
37. Whang R, Ryder KW: Frequency of hypomagnesemia and hypermagnesemia: Requested vs routine. JAMA 263:3063 -3064, 1990.
38. Shils ME: Experimental human magnesium depletion. Medicine (Baltimore)48:61 -85, 1969
39. Nichols CG, Ho K, Hebert S: Mg(2+)-dependent inward rectification of ROMK1 channels expressed in Xenopus oocytes. J Physiol (Lond) 476:399-409, 1994.
40. Kelepouris E: Cytosolic Mg2+ modulates whole cell K+ and Cl- currents in cortical thick ascending limb (TAL) cells of rabbit kidney [Abstract]. Kidney Int37 : 564,1990.
41. Whang R, Whang DD, Ryan MP: Refractory potassium depletion: A consequence of magnesium deficiency. Arch Intern Med152 : 40-45,1992.
42. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. Clin Endocrinol. 1976; 5:209-224.
43. Wacker WE, Moore FD, Ulmer DD, et al. Normocalcemic magnesium deficiency tetany. JAMA. 1962;180:161-163.
44. Mordes JP, Wacker WE. Excess magnesium. Pharmacol Rev. 1977;29:273-300.
45. Del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. J Physiol. 1954;124:370-384.
46. Jenkinson DH. The nature of the antagonism between calcium and magnesium ions at the neuromuscular junction.J Physiol. 1957;138:434-444.
47. Augustine GJ, Charlton MP, Smith SJ. Calcium action in synaptic transmitter release. Annu Rev Neurosci. 1987;10:633-693.
48. Garrison M. Tong, Robert K. Rude, Magnesium Deficiency in Critical Illness :J Intensive Care Med 2005 20: 3.
49. Liao F, Folsom AR, Brancati FL: Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J136 :480– 490,1998.
50. Eibl NL, Kopp HP, Nowak HR, Schnack CJ, Hopmeier PG, Schernthaner G. Hypomagnesemia in type II diabetes: effect of a 3-month replacement therapy. Diabetes Care. 1995 Feb;18(2):188-92

Disclaimer