CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2529253

Available online at: http://www.iajps.com *Review Article*

RELATIONSHIP OF HYPOMAGNESEMIA AND DIABETIC FOOT ULCERS: A LITERATURE REVIEW

Waddah Abdulsattar Abu-Talib[1],Omar Abdullah Alfarhan[2],Razan Mohammad Aljohani[3], Sara Ahmed Aledreesi [4],Mariam Hussain Alabndi [5], Muna Darwish Fadhel[6]

[1]M.D, SBGS, Consultant General Surgery , King Abdulaziz Hospital , Makkah, Saudi Arabia
[2]MBBS, Ministry of Health, Jeddah, Saudi Arabia
[3]MBBS, Ibn Sina National College, Jeddah, Saudi Arabia
[4]MBBS, Umm Al-Qura University, Jeddah, Saudi Arabia
[5]MBBS, Mansoura University, Mansoura, Eygpt
[6]MBBS, Ibn Sina National College, Jeddah, Saudi Arabia

Abstract:
Hypomagnesemia has been suggested to be associated with diabetes, its pathogenesis, complications, and comorbidities. This fact has been explained as a link between hypomagnesemia and decreasing of tyrosine-kinase activity at the insulin receptor level, which may lead to the impairment of insulin action and the occurrence of insulin resistance. Hypomagnesemia is correlated o the incidence of neuropathy and abnormal platelet activity, both of which are risk factors for the progression of the feet ulcer. There is also evidence that magnesium supplementation may be related to decreasing in the occurrence of diabetes mellitus and diabetic complications and comorbidities.

Keywords: *Hypomagnesemia, Diabetes Mellitus, Diabetic Foot Ulcer.*

Corresponding author:
Waddah Abdulsattar Abu-Talib
M.D , SBGS , Consultant General Surgery ,
King Abdulaziz Hospital,
Makkah, Saudi Arabia

QR code

Please cite this article in press Waddah Abdulsattar Abu-Talib et al., ***Relationship of Hypomagnesemia and Diabetic Foot Ulcers: A Literature Review.,*** *Indo Am. J. P. Sci, 2018; 05(12).*

INTRODUCTION:

Magnesium is the fourth abundant mineral in the human body, is a coenzyme for more than three hundred enzymatic reactions, and is critical for adenosine triphosphate (ATP) metabolism [1]. Magnesium is an essential mineral mostly present in fibrous foods, non-starchy vegetables, fruits, nuts, and dairy products [2]. Due to recent changes in eating habits, decreasing the magnesium level has become abundant, especially diabetic patients. Hypomagnesemia has been investigated in 13.5% to 47.7% of non-hospitalized type 2 diabetic patients contrasted with the incidence of 2.5% to 15% in non-hospitalized non-diabetic patients [3]. Decreased levels of magnesium have been related to increasing resistance of insulin, the occurrence of type 2 diabetes mellitus, or even diabetes medication [4]. Dietary supplementation with magnesium may decrease insulin resistance and diabetes risk. In a study which concerned with the resistance of insulin atherosclerosis, dietary magnesium supplementation was directly associated with increased insulin sensitivity after adjusting for confounding factors [5]. Besides the association between hypomagnesemia and the risk of developing type 2 diabetes, hypomagnesemia is correlated with chronic diabetic complications and elevated mortality rate betweensevere type 2 diabetic patients [6]. Wang et al. reported a negative correlation between serum magnesium levels and diabetic macrovascular complications, including cardiovascular disease and peripheral artery disease [6]. Foot ulcers are a major problem in type 2 diabetic patients [8]. Development of ulcers of the feet is mainly due to diabetic neuropathy and peripheral vascular disease [9, 10]. Perhaps one-third of foot ulcers have a mixed etiology, i.e., neuropathic and ischemia [9].

MATERIAL AND METHODS:

We used scientific websites such as PubMed, Google Scholar, and Research Gate to get related articles about this subject. The research process involved specific keywords "Hypomagnesaemia and diabetes mellitus, foot ulcer related to hypomagnesemia in diabetic patients, complications of hypomagnesemia in diabetic patients and ect" to discover more articles regarding the matter. We were more interested in English published articles just which from 1995 to 2018.

Biological functions of Magnesium ions:

The normal adult has about 25 grams of magnesium. More than 60% of all the magnesium in the body is concentrated in the skeleton, about 27% in muscle, while 6 to 7% is located in other cells and less than 1% is found outside cells. Magnesium contributed to more than 300 essential metabolic reactions[11].

- Magnesium acts as an intracellular regulator of cell cycle control and apoptosis [12].
- Glycolysisgluconeogesis and lipolysis require high concentrations of magnesium.
- Magnesium is needed by the adenosine triphosphate (ATP) synthesizing protein in mitochondria.
- Magnesium is needed at many steps during the synthesis of nucleic acids (DNA and RNA) and proteins.
- Glutathione, an essential antioxidant requires magnesium for its formation.
- Magnesium plays a critical role in bone formation, building the structure of cell membranes and structure of chromosomes[13].
- Cell signaling requires Magnesium adenosine triphosphate (MgATP) for the addition of phosphorus (phosphorylation) of proteins and the synthesis of the cell signaling molecule, cyclic adenosine monophosphate (cAMP)[14].

Possible causes of hypomagnesemia in diabetes:

1. Dietary deficiency
   - The major sources of magnesium in the food supply are dairy products (20%), grain products (20%), meat, poultry and fish (15%), legumes, nuts and soya products (13%)
   - Most of these have been restricted in a diet prescribed for diabetics, which could be contributing to the higher prevalence of hypomagnesemia in diabetics [15].
2. Decreased intake

- Secondary to diabetic autonomic neuropathies, which may reduce consumption and absorption[16]
- Poor oral intake -esophageal dysfunction -diabetic gastroparesis
- Enhanced gastrointestinal loss
- Diarrhea as a result of autonomic dysfunction

3. Enhanced renal magnesium loss

- Enhanced filtered load by glomerular hyperfiltration
- Osmotic diuresis (glucosuria) -metabolic acidosis (diabetic ketoacidosis)
- By increasing the serum ionized Mg fraction [17]
- Hypoalbuminemia- by increasing the serum

ionized Mg fraction [17]
- Microalbuminuria and overt proteinuria- as a result of protein-bound magnesium loss [18].

4. Enhanced tubular flow
- Increasing the volume as a result of large volume replacement
- Induce renal Mg wasting and may reduce tubular reabsorption due to high tubular flow [17].

5. Reduced renal reabsorption
- Endocrinologic dysfunction: insulin deficiency or resistance, causing decreased Mg reabsorption at the TAL [19]
- Metabolic acidosis (diabetic ketoacidosis)
- Diuretics [3]

Diagnosis of Hypomagnesemia:

Traditionally, hypomagnesemia isdefined as decreasing the concentration of serum magnesium (Mg) since this estimation has for some time been promptly accessible. Clinically, hypomagnesemia might be characterized as a serum Mg concentration 1.6 mg/dl or 2 SD less than the mean of the general population [20]. Mostly the Mg is an intracellular cation; it has been questioned if one can utilize measurements of serum Mg concentrations to study the effect of Mg on different physiologic conditions. Some specialists, instead, have utilized investigations of intracellular Mg concentrations. Clinically, it has been proposed that in a patient with suspected Mg insufficiency, a low serum Mg concentration is adequate to confirm the diagnosis. On the off chance that the serum Mg level is normal in a similar patient, then other more sensitive tests ought to be performed [21].

Role of insulin in the regulation of plasma and intracellular Mg concentrations:

In vitro and in vivo studies have reported that insulin may regulate the shift of Mg from extracellular to intracellular space. The concentration of intracellular Mg has also been appeared to be viable in balancing insulinactivity(essentially oxidative glucose digestion), offset calcium-related excitation-contraction coupling and reduction smooth cell responsiveness to depolarizing stimuli[12].

A low intracellular Mg concentration, as found in noninsulin-dependent diabetes mellitus (NIDDM) and hypertensive patients may lead to an impairment of tyrosine-kinase action at the insulin receptor level and exaggerated intracellular calcium concentration. The two occasions are responsible for weakness in insulin activity and a worsening of insulin resistance in noninsulin-dependent diabetic and hypertensive patients[13].

On the other hand, the daily administration of Mg in NIDDM patients, restoring a more suitable intracellular Mg concentration contributes to enhancing insulin-mediated glucose administration[14]. The benefits deriving from daily Mg supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily Mg intake is predictive of a lower incidence of NIDDM[22].

The relationship between hypomagnesemia and diabetic foot ulcer:

The diabetic foot ulcer (DFU) is characterized as signs of an attack and duplication of microorganisms in soft tissues or bone anywhere below the malleoli in a person with type 2 diabetes mellitus (T2DM) [23]. Advancement of foot ulcers is fundamental because of diabetic neuropathy and peripheral vascular infection [24]. It is accounted for that up to 25% of diabetic subjects are in danger of creating DFU amid their lifetime and poor injury healing is a critical purpose for morbidity and mortality [25]. Several studies have suggested that hyperglycemia, insulin resistance, dyslipidemia, increased inflammation, and reactive oxygen (ROS)/nitrogen classes play a vital role in the pathogenesis of DFU [26, 27]. Hypomagnesemia due to low magnesium intake and increased magnesium loss is common in poorly controlled diabetes [28]. Previous studies have shown that low serum magnesium levels are associated with DFU [29, 30]. Hypomagnesemia has been correlated with the development of neuropathy and abnormal platelet function [30, 31], which both are risk factors for the incidence of DFU [32].

Treatment of Magnesium deficiency:

The beneficial effects of magnesium supplementation on metabolic profiles and biomarkers of irritation and oxidative stress have recently been investigated between patients without DFU. It has been recently reported that the daily administration of 250 mg magnesium oxide for six weeks among patients suffered from gestational diabetes (GDM) had beneficial effects on metabolic profiles and biomarkers of inflammation and oxidative stress [33]. Also, another study demonstrated that magnesium intake causemarkedly decreases in the fasting glucose, triglyceride levels, and insulin resistance in normal-weight subjects; however, no significant effect had been found on mean HDL cholesterol levels [34]. But, the administration of Mg for 16 weeks has been reported

to haven't an effect on lipid profiles among T2DM patients [35] and inflammatory factors among healthy middle-aged, overweight women [36]. Improvement of indices of insulin metabolism, lipid profiles,biomarkers of irritation, and oxidative stress by magnesium may be because of their impacts on the acetyl-CoA carboxylase that catalyzes the development malonyl-CoA and is implicated in physiological insulin secretion [37], and inhibiting nuclear factor-kappa B (NF-kappa B) [38]. As there is proof that taking magnesium enhancements may quicken wound healing and has an antidiabetic impact, we theorized that magnesium supplementation might assist patients with DFU to heal their injury quicker and better affect metabolic profiles, and biomarkers of irritation and oxidative stress. The point of the present investigation, in this manner, was to assess the impacts of magnesium supplementation on wound healing and metabolic in patients with DFU [23].

CONCLUSION:

The levels of magnesium should be controlled in diabetic patients, especially in those with foot ulcers, and magnesium supplementation can be a complementary treatment for these patients. Also, magnesium supplementation can decrease the mortality rate in critically ill patients with type 2 diabetes mellitus.

REFERENCES:

1. Gröber U, Schmidt J, Kisters K. Magnesium in prevention and therapy. Nutrients. 2015;7(9):8199-226.
2. Wark PA, Lau R, Norat T, Kampman E. Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis–. The American journal of clinical nutrition. 2012 Aug 1;96(3):622-31.
3. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. Clinical journal of the American Society of Nephrology. 2007 Mar 1;2(2):366-73.
4. Bertinato J, Xiao CW, Ratnayake WN, Fernandez L, Lavergne C, Wood C, Swist E. Lower serum magnesium concentration is associated with diabetes, insulin resistance, and obesity in South Asian and white Canadian women but not men. Food & nutrition research. 2015 Jan 1;59(1):25974.
5. Ma B, Lawson AB, Liese AD, Bell RA, Mayer-Davis EJ. Dairy, magnesium, and calcium intake in relation to insulin sensitivity: approaches to modeling a dose-dependent association. American journal of epidemiology. 2006 Jul 21;164(5):449-58.
6. Curiel-García JA, Rodríguez-Morán M, Guerrero-Romero F. Hypomagnesemia and mortality in patients with type 2 diabetes. Magnesium research. 2008 Sep 1;21(3):163-6.
7. Wang S, Hou X, Liu Y, Lu H, Wei L, Bao Y, Jia W. Serum electrolyte levels in relation to macrovascular complications in Chinese patients with diabetes mellitus. Cardiovascular Diabetology. 2013 Dec;12(1):146.
8. Morrish NJ, Stevens LK, Fuller JH, Keen H, Jarrett RJ. The incidence of macrovascular disease in diabetes mellitus: the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics. Diabetologia. 1991 Aug 1;34(8):584-9.
9. Laing P. The development and complications of diabetic foot ulcers. The American journal of surgery. 1998 Aug 1;176(2):11S-9S.
10. Guerrero-Romero F, Rodríguez-Morán M. Relationship of microalbuminuria with the diabetic foot ulcers in type II diabetes. Journal of Diabetes and its Complications. 1998 Jul 1;12(4):193-6.
11. Celio MR, Pauls TL, Schwaller B. Guidebook to the calcium-binding proteins. Sambrook & Tooze Publication at Oxford University Press; 1996.
12. Allan CB, Clarke MJ. Less common metals in proteins and nucleic acid probes. Springer-Verlag; 1998.
13. Hartwig A. Role of magnesium in genomic stability. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2001 Apr 18;475(1-2):113-21.
14. Barbagallo M, Dominguez LJ, Galioto A, Ferlisi A, Cani C, Malfa L, Pineo A, Paolisso G. Role of magnesium in insulin action, diabetes and cardio-metabolic syndrome X. Molecular aspects of medicine. 2003 Feb 6;24(1-3):39-52.
15. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, Hutchinson RG, Metcalf PA. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Journal of clinical epidemiology. 1995 Jul 1;48(7):927-40.
16. Boulton AJ VA, Arezzo JC, Bril V, Feldman EL,

Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D. American Diabetes Association. Diabetic neuropathies: A Statement by the American Diabetes Association. Diabetes Care. 2005;28:956-62.
17. Massry SG, editor. Massry & Glassock's Textbook of Nephrology. Philadelphia: Lippincott Williams & Wilkins; 2001 Jan.
18. Corsonello A, Ientile R, Buemi M, Cucinotta D, Mauro VN, Macaione S, Corica F. Serum ionized magnesium levels in type 2 diabetic patients with microalbuminuria or clinical proteinuria. American journal of nephrology. 2000;20(3):187-92.
19. Mandon BE, Siga ES, Chabardes DA, Firsov DM, Roinel NI, De Rouffignac CH. Insulin stimulates Na+, Cl-, Ca2+, and Mg2+ transports in TAL of mouse nephron: cross-potentiation with AVP. American Journal of Physiology-Renal Physiology. 1993 Sep 1;265(3):F361-9.
20. 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. Clinical Nephrology. 2005 Jun 1;63(6).
21. Tosiello L: Hypomagnesemia and diabetes mellitus. Arch Intern Med 156: 1143–1148, 1996
22. Manuel y Keenoy B, Moorkens G, Vertommen J, Noe M, Neve J, De Leeuw I. Magnesium status and parameters of the oxidant-antioxidant balance in patients with chronic fatigue: effects of supplementation with magnesium. Journal of the American College of Nutrition. 2000 Jun 1;19(3):374-82.
23. Jain AK, Viswanath S. Distribution and analysis of diabetic foot. OA Case Reports. 2013;2(21):117.
24. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, Driver VR, Frykberg R, Carman TL, Marston W, Mills Sr JL. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. Journal of vascular surgery. 2016 Feb 1;63(2):3S-21S.
25. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. Jama. 2005 Jan 12;293(2):217-28.
26. Karadurmus N, Sahin M, Tasci C, Naharci I, Ozturk C, Ilbasmis S, Dulkadir Z, Sen A, Saglam K. Potential benefits of hyperbaric oxygen therapy on atherosclerosis and glycaemic control in patients with diabetic foot. Endokrynologia Polska. 2010;61(3):275-9.
27. Van Dam PS, Cotter MA, Bravenboer B, Cameron NE. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms. European journal of pharmacology. 2013 Nov 5;719(1-3):180-6.
28. Garland HO. New experimental data on the relationship between diabetes mellitus and magnesium. Magnesium research. 1992 Sep;5(3):193-202.
29. Keşkek ŞÖ, Kırım S, Karaca A, Saler T. Low serum magnesium levels and diabetic foot ulcers. Pakistan journal of medical sciences. 2013 Nov;29(6):1329.
30. Rodríguez-Morán M, Guerrero-Romero F. Low serum magnesium levels and foot ulcers in subjects with type 2 diabetes. Archives of medical research. 2001 Jul 1;32(4):300-3.
31. Tosiello L. Hypomagnesemia and diabetes mellitus: a review of clinical implications. Archives of Internal Medicine. 1996 Jun 10;156(11):1143-8.
32. Bresäter LE, Welin L, Romanus B. Foot pathology and risk factors for diabetic foot disease in elderly men. Diabetes research and clinical practice. 1996 Apr 1;32(1):103-9.
33. Asemi Z, Karamali M, Jamilian M, Foroozanfard F, Bahmani F, Heidarzadeh Z, Benisi-Kohansal S, Surkan PJ, Esmaillzadeh A. Magnesium supplementation affects the metabolic status and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. The American journal of clinical nutrition. 2015 May 27;102(1):222-9.
34. Rodríguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves the metabolic profile of metabolically obese, normal-weight individuals: a randomized, double-blind placebo-controlled trial. Archives of Medical Research. 2014 Jul 1;45(5):388-93.
35. RODRiguez-MORan MA, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. Diabetes care. 2003 Apr 1;26(4):1147-52.
36. Moslehi N, Vafa M, Rahimi-Foroushani A, Golestan B. Effects of oral magnesium supplementation on inflammatory markers in middle-aged, overweight women. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2012 Jul;17(7):607.

37. Kowluru A, Chen HQ, Modrick LM, Stefanelli C. Activation of acetyl-CoA carboxylase by a glutamate-and magnesium-sensitive protein phosphatase in the islet β-cell. Diabetes. 2001 Jul 1;50(7):1580-7.

38. Mazur A, Maier JA, Rock E, Gueux E, Nowacki W, Rayssiguier Y. Magnesium and the inflammatory response: potential physiopathological implications. Archives of biochemistry and biophysics. 2007 Feb 1;458(1):48-56.