Deficit in Magnesium and Type II Diabetes Interaction

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Abstract

The research and the body of knowledge on the relationship between diabetes and magnesium status is constantly expanding. This systematic literature review investigated the effects on type II diabetes (T2DM) patients with low levels of magnesium (Mg). The keywords of “Magnesium” and “Type II diabetes mellitus” were submitted through the EBSCOHost abstract database platform to identify all related articles pertaining to the hypothesis that Mg deficit impacts T2DM in the past five full years. The results of this review confirm that low levels of magnesium are associated with a negative impact on those with type II diabetes. With an intervention of magnesium either through supplementation or dietary means insulin sensitivity and glucose metabolism may be improved. However, more research is required on the subject to come to a final conclusion on the causality, especially with regard to whether magnesium deficit precedes or follows the condition of abnormal serum glucose.

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Deficit in Magnesium and Type II Diabetes Interaction

Type II diabetes (T2DM) is becoming one of the most serious global health challenges of the 21st century (Ankush, Suryakar & Ankush, 2009). The main pathophysiological change in an individual with T2DM is insulin insensitivity with the presence of hyperglycemia, dyslipidemia and endothelial dysfunction (Sampaio, et al. 2014). In order to delay or prevent the complications of T2DM an individual must maintain adequate blood glucose, blood pressure and blood lipid levels (Huang, et al. 2012). Magnesium (Mg) has been associated with T2DM and may be one of the most important factors in the disease's prevention or treatment (Huang, et al. 2012). Being the fourth most abundant mineral in the body Mg has been recognized as a cofactor for more than 300 metabolic reactions within the body. Mg is involved in glucose metabolism, glucose homeostasis, and insulin sensitivity (Volpe, 2013). Mg consumed through the diet has shown a beneficial association with T2DM (Hruby, et al. 2013). Mg plays a role in the metabolism of insulin and glucose by impacting tyrosine kinase activity (Volpe, 2013). Degradation of insulin sensitivity and a dysfunction in tyrosine kinase activity is thought to be a result of a lowered concentration of Mg within the body (Dasgupta, et al. 2012). Insulin resistance promotes urinary excretion of Mg thus leading to an excess loss of Mg within the body causing Mg deficiency (Lecube, et al. 2012). Causes of low levels of Mg within the body can be due to a diet low in Mg, osmotic diuresis leading to a high renal excretion of Mg and an insensitivity of insulin affecting intra-cellular Mg transport causing an increased loss of the extra-cellular Mg (Dasgupta, et al. 2012). Observational studies and clinical trials have shown a consistent beneficial relationship between adequate amounts of dietary Mg and individuals with T2DM (Hruby, et al. 2013). Recent studies have found that changes in metabolism of the macro-mineral Mg have been linked to oxidative stress found in persons with T2DM (Sampaio, et al.

2014). It is predicted that hypomagnesemia has a negative impact on individuals with T2DM and a dietary intervention or supplementation of Mg is needed to improve the management of the disease. What remains unclear is does a Mg deficit precede or cause insulin resistance or is a Mg deficit simply a result of increased urinary excretion. The purpose of this review is to examine the accumulation of evidence supporting a relationship between Mg deficit and T2DM.

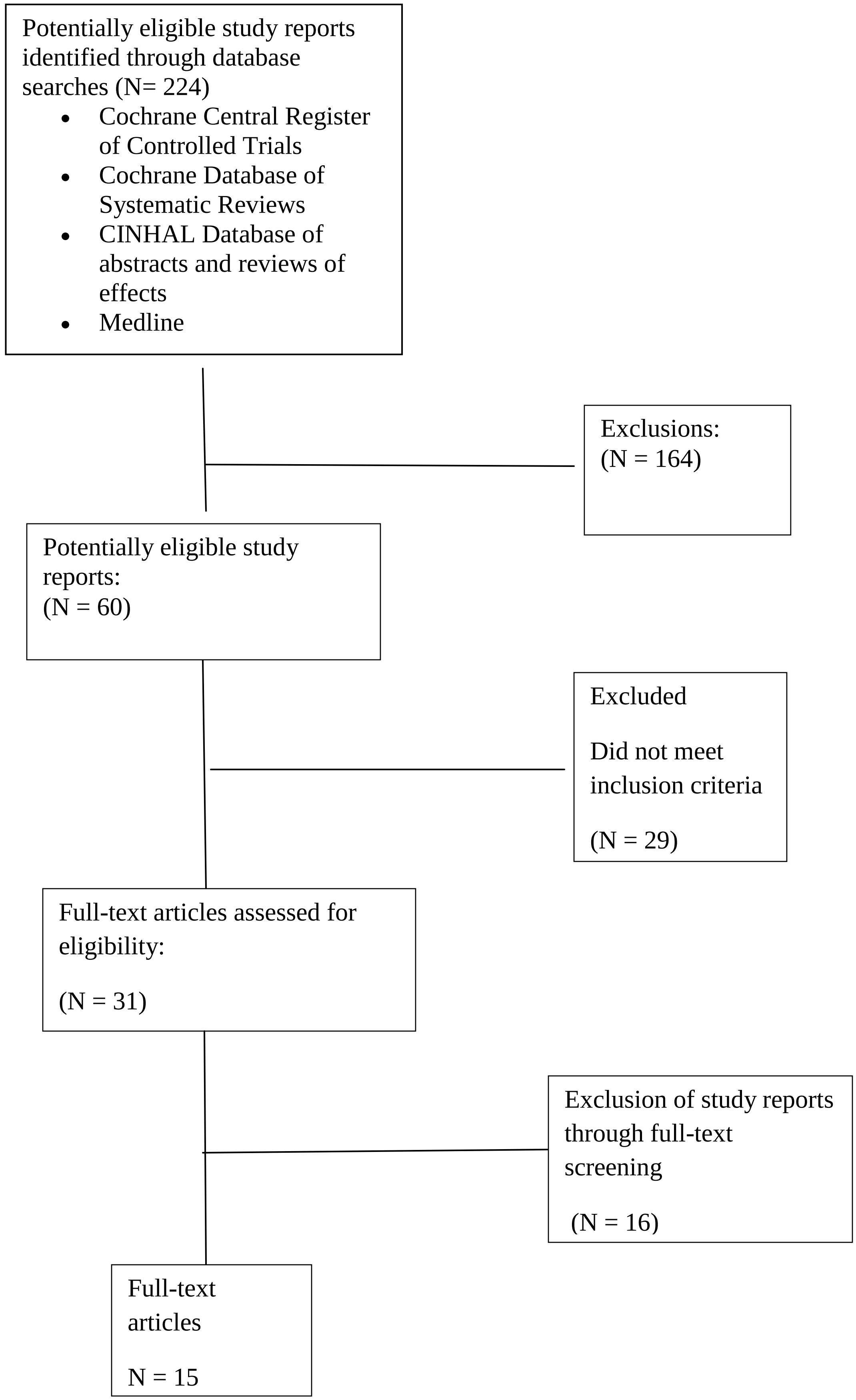
Methods

This systematic literature review was completed on September 2015 utilizing the abstract database platform of EBSCOHost to search MedLine, CINHAL, Cochrane Random Control Trials and Cochrane Systematic Reviews from 2009 through September 2015. All potential articles identified with the keywords Mg, type 2 diabetes, insulin resistance, hypomagnesaemia, oxidative stress and hyperglycemia. Abstract articles had to meet the following inclusion criteria: (1) Human adult studies (2) T2DM (3) English articles (4) studies within the last five years (5) isolated Mg studies. Exclusion criteria included: (1) Type I diabetes mellitus (2) children (3) pregnant women (4) non-human studies (5) insufficient study group numbers (6) non-English articles. Steps included title review, abstract review and full-text article review. Full-text articles were selected if the abstracts met the keyword criteria.

Results

The initial search resulted in 224 title entries that matched the keywords “Magnesium” and “Type 2 diabetes”. Within the 60 abstracts that were reviewed 31 abstracts were considered in the selection procedure. Of the 31 abstracts only 15 full-text articles were used due to others lacking relevant information or matching inclusion criteria. (See Figure 1).

Figure 1: Details of Search Process



There were 15 articles included in this review. The types of studies included five case-control studies, four cross-sectional studies, three reviews, one combined cross-sectional case control with subsequent intervention study, one retrospective cohort study, and one random control trial. Of the 12 available trials reviewed there were nine that were of high quality without evident limitations.

The case-control and cross sectional studies performed trials to measure Mg levels to test whether or not those with T2DM had lower levels of Mg than those who did not have the disease. Results from the studies reported that Mg levels in patients with T2DM were lower compared to non-T2DM patients. Patients with the disease long-term were also an independent risk factor to have hypomagnesemia (Dasgupta et al 2012, Haglin et al 2011, Huang et al2012, Hyassat et al 2014, Ismail et al 2015, Lecube et al 2012, Masood et al 2009, Sampaio et al, 2014).

In a prospective study 90 participants were examined on whether or not individuals with T2DM had an abnormal level of plasma glucose, Mg, plasma malondialdehyde (MDA), and nitric oxide (NO). Blood samples were taken to identify these levels and results show plasma Mg concentrations were lower in T2DM patients. Hypomagnesemia were more pronounced in those with the disease as well. Poor control of T2DM results in an increased loss of Mg through urinary excretion, low levels of plasma Mg and other factors such as diarrhea, vomiting and sodium intake. The study included three separate groups and were measured for their HbA_1c (%), erythrocyte membrane MDA (nM/ml), erythrocyte superoxide dismutase (SOD) activity (U/mg protein), and erythrocyte reduced glutathione (GSH) (uM/gm Hb). The three groups in the study represented different variables: Group I: 30 healthy individuals; Group II: 30 T2DM patients with no complications; Group III: 30 T2DM patients with complications including cardiovascular disease, nephropathy, neuropathy, and retinopathy). Results from the study shows that levels of plasma glucose ($p<0.001$), HbA_1c ($p<0.001$), plasma NO end products ($p<0.05$), plasma MDA ($p<0.001$), erythrocyte membrane MDA ($p<0.001$) were significantly higher in group III, as compared to group II (See table 1.) (Ankush, Suryakar & Ankush, 2009).

A retrospective study was conducted to include a total 455 participants (144 T2DM mellitus individuals; 311 non-T2DM individuals) to assess whether or not low levels of Mg affected the risk of end-stage renal disease. Individuals were grouped into either a high Mg or low Mg level according to their serum Mg concentration. The study reported that those with low levels of Mg were 2.12 times more likely to develop end-stage renal disease. This study explores the risk factors of end-stage renal disease with having T2DM and/or having low Mg levels (Sakaguchi, et al. 2012).

A two tailed T test was performed comprising of 30 type II diabetic patients that were split into one of two groups (Group A; Group B). The test included a comparison of the means of tri-glycerol, HbA_1c and Mg levels between the two groups. Both groups had T2DM and were assigned to either Group A or Group B. Group A had hypomagnesemia while Group B did not have the condition. The study reported that Group A had significantly higher triglyceride levels in comparison to group B (Srinivasan, et al. 2012). (See table 2).

Table 1: Literature Search Results for Mg and T2DM

Author (s)	Type of Study	#Subjects N=	Outcome/ Measures Used	Findings	Limitations
Ankush, R. D., Suryakar, A. N., & Ankush, N. R	Prospective Case Control	N = 90	Blood samples identifying levels of plasma glucose, Mg, MDA and NO.	Plasma Mg levels were positively correlated with erythrocyte GSH and erythrocyte SOD activity.	N/A
Dasgupta, A., Sarma, D., & Saikia	Cross-Sectional	N = 150	Photometric method was used to assess Serum Mg levels	17 subjects had hypomagnese-mia (low Mg) and 133 had normal levels of Mg. Mean duration of diabetes was 6.8 years in patients with low Mg	N/A
Håglin, L., Bäckman, L., & Törnkvist, B.	Case control study	N = 1339	Serum Mg (S-Mg)	Women with T2DM lower S-Mg than non diabetic	N/A
Hruby, A., McKeown, N. M., Song, Y., & Djoussé, L.	Narrative review	85 citations	N/A	Failed to yield consistent and robust results	Not systematic review, high potential for bias.
Huang, J. H., Lu, Y. F., Cheng, F. C., Lee, J. N., & Tsai, L. C	Cross sectional study	N = 210	Anthropo-metric measurement, blood pressure, and biochemical determination of blood and urine samples.	Among all patients, 88.% had Mg intake less than recommended and 37.1% had low Mg	N/A
Hyassat, D., Al Sitri, E., Batieha, A., EL-Khateeb,	Cross sectional study	N = 210	Anthropo-metric measurement, diabetes	210 patients (19%) had low Mg. Patients with diabetes duration	Most participants were treated with

M., & Ajlouni, K.			mellitus, and Mg was measured	over five years were independent risk factors for low Mg.	antidiabetic and or anti-hypertensive drugs. Suggested ionized Mg more sensitive measure
Ismail, T.S.T., Yaacob, N.M., Omar, J., Mustapha, Z, Yusuff, H. & Nordin, H	Cross sectional study	N = 150	Serum Mg level and Hb	8.6% had low serum Mg level	54+ y/o w T2DM
Lecube, A., Baena-Fustegueras, J. A., Fort, J. M., Pelegrí, D., Hernández, C., & Simó, R	Cross sectional case-control study with subsequent interventional study	N = 200 obese subjects (50 T2DM + 150 without diabetes)	Serum Mg levels	T2DM showed lower serum Mg level than non-diabetics	N/A
Masood, N., Baloch, G. H., Ghori, R. A., Memon, I. A., Memon, M. A., & Memon, M. S.	Case control study	N = 5000 including T2DM + healthy subjects	Serum zinc and Mg levels	Mean serum zinc was significantly lower in diabetic patients, no significantly difference in serum Mg level	N/A
Nasri, H.	Review	N = 122 T2DM patients	15 citations	Referenced study in 2008	N/A
Niranjan, G., Mohanavalli, V., Srinivasan, A. R., & Ramesh, R.	Randomized controlled clinical trial	N = 63	Pioglitazone (15mg) in addition to usual doses of sulfonylureas	No significant difference between FPG, serum total Mg, HbA1c and MDA levels before and after the treatment with pioglitazone.	N/A

Sakaguchi, Y., Shoji, T., Hayashi, T., Suzuki, A., Shimizu, M., Mitsumoto, K., ... & Tsubakihara, Y.	Retrospective cohort study	N = 455 (144 w/ T2DM + 311 non diabetic)	Serum Mg level categorized into low Mg or high Mg group	Low Mg group had a 2.12 higher risk of ESRD	Patients w/ < 3 months follow up data
Sampaio, F. A. Feitosa, M. M. Sales, H. C., Costa e Silva, D. M., Clímaco Cruz, K. J., Oliveira, F. E., . . . Colli, C.	Case control study	N = 88	Plasma erythrocyte and urinary levels of Mg, serum iron, ferritin, total iron binding capacity, fasting glucose, glycated hemoglobin, insulin, creatinine, clearance and plasma thiobarbituric acid reactive substances	Mg intake and plasma Mg were lower in diabetic subjects. Diabetes induced hypomagnesemia and this may have enhanced oxidative stress	N/A
Srinivasan, A. R., Niranjan, G., Velu, V. K., Parmar, P., & Anish, A	Case Control Two-tailed t-test study	N = 30	Fasting blood glucose, triacylglycerol, and Mg	Group A (Mg level <1.2 mg/dl) group B (Mg level >1.2 mg/dl)	N/A
Volpe, Stella	Narrative review	N/A	N/A	N/A	Not systematic review, high potential for bias

Discussion

Some studies in the review did not concentrate on Mg individually but had relevant information to support the hypothesis that Mg deficit is associated with T2DM. The studies in this review identified how low level of Mg negatively affects individuals with T2DM.. When a Mg intervention was performed the disease improved and negative effects subsided. A prospective study consisting of three groups measured the levels of Mg between those with T2DM (no complications), T2DM (with complications) and healthy individuals. The study concluded that those with T2DM (with complications) had the most adverse levels of plasma glucose, HbA_1c, plasma NO end products, plasma MDA and erythrocyte membrane MDA than those in the other groups. Mg does not only affect the body's tyrosine-kinase activity but also plays a role in glucose metabolism and insulin sensitivity. This shows that the low levels of Mg have an impact on those with T2DM. The information extracted from these studies supports the hypothesis in that Mg may improve the state of an individual with T2DM mellitus. The question still remains on what caused these individuals to have low levels of Mg. What caused the low levels of Mg within the body was it due to dietary behaviors or some metabolic effect of T2DM?

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