

The Effect of Magnesium and Zinc on Glycemic Control in Type 2 Diabetic Patients

Arezoo Afkhami-Ardekani¹, Mahmood Reza Motamedzadeh², Saeedeh Jam Ashkezari³,
Mohammad Afkhami-Ardekani^{4*}

1. Medical Student, Faculty of Medicine, Tehran University of Medical Science, Tehran, Iran.
2. MD, Faculty of Medicine, Yazd Azad University, Yazd, Iran.
3. Researcher, Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
4. Professor of Endocrinology, Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

*Correspondence:

Mohammad Afkhami-Ardekani, Department of Internal Medicine, Endocrinology, Shahid Sadoughi University of medical sciences, Yazd, Iran.
Tel: (98) 353 728 0217
Email: Afkhamiam@yahoo.com

Received: 12 May 2016

Accepted: 10 June 2016

Published in August 2016

Abstract

Objective: The aim of this study was to evaluate the effect of zinc and magnesium supplementation on glycemic control and serum insulin in type 2 diabetic patients.

Materials and Methods: In this randomized clinical trial 70 diabetic patients who referred to Yazd Diabetes Center were selected. Subjects received 500 mg/day magnesium oxide or 100 mg/day zinc sulfate randomly for 8 weeks. At the start and end of treatment period fasting blood sugar (FBS), 2 hour postprandial glucose (2-hpp), glycated hemoglobin (HbA1C) and fasting insulin level were measured.

Results: Magnesium and Zinc supplementation for 8 weeks cause significantly decrease in HbA1c ($P=0.005$, $P=0.001$). No significant difference was observed after trial between magnesium and zinc groups in FBS (42.08 ± 7.43 vs. 35.15 ± 6.52) ($P=0.97$), HbA1C (1.22 ± 0.21 vs. 1.77 ± 0.32) ($P=0.07$) and fasting serum insulin (39.81 ± 7.03 vs. 36.68 ± 6.81) ($P=0.83$) respectively.

Conclusion: Results of this study showed that 500 mg/day magnesium oxide or 100 mg/day zinc sulfate administration for 8 weeks could improve HbA1C in type 2 diabetic patients and this effect is same in two groups. But more studies for evaluating effect of magnesium and zinc supplementation on type 2 diabetic patients were suggested.

Keywords: Diabetes type 2, Magnesium, Zinc, HbA1C.

Introduction

Type 2 diabetes accounts for approximately 90 to 95% of all diagnosed cases of diabetes (1). Hypomagnesaemia has been reported to occur in 13.5 to 47.7% of non-hospitalized patients with type 2 diabetes (2). Magnesium is a necessary cofactor for several enzymes that play an important role in glucose

metabolism (3). Some short-term metabolic studies (4-5). Suggested that magnesium supplementation has a beneficial effect on insulin action and glucose metabolism. Magnesium is an important component of many unprocessed foods (6). The over processing of food and some kinds of diet

caused insufficient magnesium intake in industrialized countries during the last century. Moreover, diabetic patients have lower serum levels of zinc (7). Zinc (Zn) is an essential trace element. A wide spectrum of proteins, metalloenzymes, and transcription factors contain this metal ion. It is a micronutrient with known antioxidant activity (8-9). Zinc salts with low toxic profiles (10) have anti-diabetic effects on diabetic mice (11-13). Also, Zn (car)2Cl2 has the in vitro insulin mimetic activity and in vivo blood glucose lowering effect (14). There is this hypothesis that Zn enhances anti-diabetic activity and increases the absorption of glucose by muscle and hepatic cells (15-16). Zn plays a clear role in the synthesis, storage and secretion of insulin, also on conformational integrity of insulin in the hexameric form, the decreased Zn, which affects the ability of the islet cell to produce and secrete insulin, might then compound the problem, particularly in Type 2 diabetes (17-18).

The possible benefits of magnesium and zinc administration as adjuvant factors for the treatment of type 2 diabetes were studied in controlled trial (19-23). However, the benefits of administration of magnesium (24-26) and zinc (27-29) salt in type 2 diabetes is controversial. The aim of this study was to compare the effect of magnesium and zinc administration on glycemic control in type 2 diabetic subjects.

Materials and Methods

The study was conducted with an experimental double-blinded parallel design. The volunteers who met following inclusion criteria were enrolled in the study: type 2 diabetic patients older 30 years old (diagnosed according to ADA criteria) (30) with fasting blood sugar (FBS) between 140-250 mg/dl were recruited from Yazd Diabetes Research Center.

Exclusion criteria were: Cigarette smoking, current treatment with diuretic and/or calcium antagonist drugs or other medication except oral hypoglycemic agent, diabetic complications, using vitamins or minerals

supplements in the previous 2 months, renal failure, ischemic heart disease, congestive heart failure, uncontrolled hypertension, history of stroke, chronic liver disease and major abdominal surgery, pregnancy and lactation.

The institution's Research Ethics Committee of Azad University approved this study. Informed consent was obtained in all cases. At first visit demographic and clinical information were documented.

In this study neither physical activity nor food planning were modified. Adherence to pharmacological treatment and lifestyle intervention were assessed every month by interview.

A total of 70 eligible subjects were enrolled and randomly allocated to receive either magnesium or zinc supplementation daily for 8 weeks. We used the zinc sulfate capsule (Iran, Alhavi) (containing 100 mg zinc) or magnesium oxide (containing 500 mg magnesium) (Iran, Abidi). At baseline and after 8 weeks of treatment, anthropometric measurements, HbA1c, serum glucose, and serum insulin levels were measured.

Laboratory methods:

Serum glucose was measured by colorimetric method (GPO-PAP) with Photometer 5010 (Parsazmon kit, Iran). HbA1C was measured with DS5 analyzer and DS5 Pink Reagent kit. Insulin levels were measured by Elisa (with Insulin AccuBind ELISA Kit, Monobind Inc.). The homeostasis model assessment for insulin resistance (HOMA-IR) (fasting glucose (mmol/l)× fasting insulin (UI/ ml)/22.5) was used for estimating insulin sensitivity (31).

Statistical analysis:

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 12.0, Chicago IL). To compare before and after metabolic responses paired t-test and for compare variable differences between two groups independent t-test were used. Significance was considered $P < 0.05$. Results were given with their 95% confidence interval (CI). All findings were presented as means \pm standard deviation (SD).

Results

In this study 70 type 2 diabetic patients who fulfilled the inclusion criteria were randomized to receive either magnesium oxide or zinc sulfate. Nine subjects dropped-out because of unwilling to continue the study (6 in magnesium oxide group and 3 in zinc sulfate group). Both magnesium oxide and zinc sulfate were well tolerated and there were no serious adverse events or side effects due to drugs. Only in two subjects, mild abdominal pain was seen that did not required any treatment or discontinuation of supplements.

Adherence to treatment was achieved for 32 subjects in zinc sulfate and 29 subjects in magnesium oxide group.

Table 1 and 2 show the parameters before and after trial. The studied parameters did not differ between the groups at the beginning of study. At the end of study HbA1c levels showed a significant decrease in magnesium oxide and zinc sulfate groups. Although fasting insulin and HOMA ratio decreased in magnesium oxide group, but it was not significant at 5% levels.

Table 3 shows there were no significant difference between two groups in studied parameters.

Discussion

This study showed that oral magnesium and zinc supplementation as an adjuvant therapy could reduce HbA1c significantly in type 2 diabetic patients.

Our results showed beneficial effects of magnesium supplementation on long term glycemic control as reflected by HbA1c levels (as an index of overall glycemic control over the preceding 3-4 months) (32). This is in line with the results of several studies as in a clinical randomized double-blinded trial was done by Rodriguez et al, a total of 63 subjects with type 2 diabetes and low level of serum magnesium (serum magnesium levels ≤ 0.74 mmol/l) treated by glibenclamide received either 50 ml MgCl₂ solution (containing 50 g MgCl₂ per 1,000 ml solution) or placebo daily for 16 weeks. At the end of the study, subjects

Table 1. Parameters studied before and after magnesium supplementation

Parameters		Magnesium oxide	P-value*
Weight (Kg)	Before	73.41±10.23	0.53
	After	73.69±10.01	
FBS (mg/dl)	Before	164.19±44.6	0.52
	After	160.1±50.4	
2hpp (mg/dl)	Before	266.2±84.8	0.29
	After	253.6±65.1	
HbA1c (%)	Before	8.4±1.9	0.001
	After	7.7±1.7	
Insulin(IU)	Before	5.6±5	0.85
	After	5.7±4.5	
HOMA	Before	2.2±2.3	0.92
	After	2.2±1.7	

* Independent T-test

Table 2. Parameters studied before and after Zinc supplementation

Parameters		Zinc sulfate	P-value*
Weight (Kg)	Before	74.97±10.94	0.14
	After	74.59±11.13	
FBS (mg/dl)	Before	153.2±48.8	0.99
	After	153.2±50.6	
2hpp (mg/dl)	Before	241.2±65.8	0.72
	After	245.5±83.5	
HbA1c (%)	Before	8.7±1.9	0.005
	After	7.7±2	
Insulin(IU)	Before	6.4±5.4	0.14
	After	5±3.4	
HOMA	Before	2.4±2.3	0.15
	After	1.9±1.6	

* Independent T-test

Table 3. Differences of parameters studied before and after Zinc and Magnesium supplementation

Index	Magnesium oxide	Zinc sulfate	P-value*
Weight (Kg)	-0.27±2.34	0.37±1.43	0.19
FBS (mg/dl)	-4.8±42.1	0.7±35.11	0.62
2hpp (mg/dl)	-12.6±67.5	4.3±65.6	0.32
HbA1c (%)	0.7±1.2	1±1.4	0.57
Insulin(IU)	0.01±5.3	-1.4±4.8	0.24
HOMA	0.04±2.2	0.5±2.1	0.38

* Independent T-test

who received magnesium supplementation showed significant higher serum magnesium concentration and lower HOMA-IR index, fasting glucose levels, and HbA1c than control subjects (33). Similarly, this relation was seen in other studies in type 2 diabetic patients (34) and non-diabetic elderly subjects (35). Nevertheless, results from studies have not been consistent, as in Sjogren study magnesium hydroxide (500 mg/day) was administered orally to the diabetics. Although

requirements of insulin were reduced significantly during the course of the study, but the levels HbA1c and glucose were not changed (36). In Lal study although mean serum magnesium at baseline in the diabetic patients was significantly lower than that in controls fasting and post-prandial blood glucose levels did not show any significant change after 12 weeks of magnesium supplementation (600 mg daily) when compared with baseline (37). Also in de Valk study shows plasma magnesium concentration was higher after supplementation than after placebo, as was Mg excretion. But no significant differences were found in glycemic control (38).

Although it is hypothesized that decrease of insulin levels were a direct effect of magnesium on beta-cell or a consequence of improvement in the insulin-mediated glucose disposal (31), in our study HbA1c decreased significantly without significant changes in serum insulin levels. Also, the decrease of magnesium concentration results in both defective tyrosine-kinase activity and reduction of auto phosphorylation on the at the insulin receptor level (39-40), exerting deleterious effects on glucose metabolism due to insulin sensitivity reduction (41-44), which contributes to poor metabolic control in diabetic subjects (45-48). Lima et al. showing that diabetic subjects who received magnesium oxide (41.4 mmol/l) for 1 month achieved serum magnesium levels similar to those of healthy control subjects (49).

However, current ADA nutrition guidelines recommend the use of magnesium supplements for people with diabetes mellitus who have low serum magnesium levels (50). Our results clearly show that magnesium supplementation significantly decrease HbA1C levels.

The results of current study indicated zinc supplementation could decrease HbA1c significantly, that is in accordance with previous studies. In a prospective, randomized, double blinded study, 56 normal glucose-tolerant obese women were randomized for

treatment with 30 mg zinc daily for 4 week. Insulin did not change in the placebo group, whereas there was a significant decrease of this hormone in the supplemented group. HOMA also decreased in the zinc-supplemented group but did not change in the placebo group (51).

In Partida study patients received 100 mg zinc sulfate treatment in a crossover double-blinded study with starch as placebo. In this study statistically significant differences were found prior to and after zinc treatment in glucose levels as well as in the percentages of glycosylated hemoglobin (23). A randomized, controlled trial on diabetic subjects was done by Afkhami et al. forty patients received randomly either 660mg zinc sulfate or placebo for six weeks. Level of FBS, 2hpp, HbA1C decreased after six weeks treatment with zinc sulfate, but it was not statistically significant. Due to zinc sulfate administration, significant decrease occurred in TG, Chol, LDL and systolic blood pressure. After 12 weeks, there was a significant decrease in HbA1C with zinc sulfate consumption (52). In some studies failed to show beneficial effects of zinc supplementation on glucose homeostasis in type 2 diabetic patients (53,54). In Roussel study zinc supplementation (30 mg/day of zinc gluconate) caused a reduction in lipid pre-oxidation monitored by plasma TBARS after 6 months with no significant changes HbA1C and glucose homeostasis (54). Zinc has numerous potential targets to modulate insulin activity. In rats, zinc deprivation led to plays a role in insulin synthesis and activity (55). Some investigators have also speculated that zinc supplementation could improve insulin sensitivity in type 2 DM (56). As suggested by Preuss (57), there may be improvements in insulin sensitivity that are associated with improved antioxidant status. Despite, in our study zinc supplementation associated with a tendency to a decrease in fasting insulin levels and HOMA, but it was not significant at 5% levels. It might result from low dose or short duration of supplementation in our study.

Our study showed no significant difference between magnesium and zinc supplementation on FBS, HbA1c and fasting insulin levels in type 2 diabetic patients. We could not find any study like this so these results were not conclusive because of scarcity of published information.

We did not measure serum magnesium and zinc levels before the study. An accurate assessment of intracellular magnesium and zinc status is needed to reliably reflect the normalization of hypomagnesaemia and hypozincemia after magnesium and zinc replacement. Although there were no major adverse effects for magnesium and zinc supplements in the trials, optimal dosage to replenish magnesium and zinc deficiency and long-term safety of therapy, particularly at high doses, should also be evaluated in future studies. Moreover, we did not measure pancreatic store or beta cell function, which influence pancreatic insulin secretion.

References

1. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, et al. Prevalence of Obesity, Diabetes, and Obesity-Related Health Risk Factors, 2001. *JAMA* 2003;289(1):76-9.
2. Pham PCT, Pham PMT, Pham SV, Miller JM, Pham PT. Hypomagnesemia in Patients with Type 2 Diabetes. *Clin J Am Soc Nephrol* 2007;2(2):366-73.
3. Paolisso G, Scheen A, D'Onofrio F, Leffebvre P. Magnesium and glucose homeostasis. *Diabetologia* 1990;33(9):511-4.
4. de Valk HW. Magnesium in diabetes mellitus. *Neth J Med* 1999;54(4):139-46.
5. Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesouro P, Varricchio M, et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992;55(6):1161-7.
6. Saris NEL, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium An update on physiological, clinical and analytical aspects. *Clinica Chimica Acta* 2000;294(1-2):1-26.
7. Raz I, Adler JH, Havivi E. Altered tissue content of trace metals in diabetic hyperinsulinaemic sand rats (psammomys obesus). *Diabetologia* 1988;31(5):329-33.
8. Powell SR. The antioxidant properties of zinc. *The Journal of nutrition* 2000;130(5):1447-54.
9. Cruz KJ, de Oliveira AR, Marreiro Ddo N. Antioxidant role of zinc in diabetes mellitus. *World J Diabetes*, 2015;6(2):333-7.
10. Doddigarla Z, Parwez L, Ahmad J. Correlation of serum chromium, zinc, magnesium and SOD levels with HbA1c in type 2 diabetes: A cross sectional analysis. *Diabetes Metab Syndr* 2015;1-4.
11. Chen MD, Liou SJ, Lin PY, Yang VC, Alexander PS, Lin WH. Effects of zinc supplementation on the plasma glucose level and insulin activity in genetically obese (ob/ob) mice. *Biological Trace Element Research* 1998;61(3):303-11.
12. Simon SF, Taylor CG. Dietary Zinc Supplementation Attenuates Hyperglycemia in db/db Mice 1. *Experimental Biology and Medicine* 2001;226(1):43-51.
13. Shisheva A, Gefel D, Shechter Y. Insulinlike effects of zinc ion in vitro and in vivo: preferential effects on desensitized adipocytes and incution of normoglycemia in streptozocin-induced rats. *Diabetes (New York, NY)* 1992;41(8):982-8.
14. Yoshikawa Y, Ueda E, Sakurai H, Kojima Y. Antidiabetes Effect of Zn (II)/Carnitine Complex by Oral Administration. *Chem Pharm Bull* 2003;51(2):230-1.
15. Sakurai H, Kojima Y, Yoshikawa Y, Kawabe K, Yasui H. Antidiabetic vanadium (IV) and zinc (II) complexes. *Coordination Chemistry Reviews* 2002;226(1-2):187-98.

Conclusion

In summary, our results showed that HbA1c levels differ significantly after oral magnesium and zinc supplementation in type 2 diabetic patients. Also, in our study no significant difference was observed between zinc and magnesium supplementation on FBS, HbA1c and fasting insulin. Long term studies are needed to determine usefulness of magnesium and zinc supplementation in the management of type 2 diabetes.

Acknowledgments

This study was supported by Shahid Sadoughi University of Medical Sciences and Yazd Azad Medical University.

Conflict of interest

There is no conflict of interest.

16. Kojima Y, Yoshikawa Y, Ueda E, Kondo M, Takahashi S, Matsukura T, et al. Blood glucose lowering and toxicological effects of zinc (II) complexes with maltol, threonine, and picolinic acid. *Res Commun Mol Pathol Pharmacol* 2002;112(1-4):91-104.
17. Chausmer AB. Zinc, Insulin and Diabetes. *Journal of the American College of Nutrition* 1998;17(2):109-115.
18. Maruthur NM, Clark JM, Fu M, Linda Kao WH, Shuldiner AR. Effect of zinc supplementation on insulin secretion: interaction between zinc and SLC30A8 genotype in Old Order Amish. *Diabetologia*, 2015;58(2):295-303.
19. Eibl NL, Kopp HP, Nowak HR, Schnack CJ, Hopmeier PG, Scherthaner G. Hypomagnesemia in type II diabetes: effect of a 3-month replacement therapy. *Diabetes Care* 1995;18(2):188.
20. WSLti MK, Zimmermann MB, Spinass GA, Hurrell RF. Low plasma magnesium in type 2 diabetes. *Swiss Med Wkly* 2003;133:289-92.
21. Lima M, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Cangucu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 1998;21(5):682.
22. Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential Antioxidant Effects of Zinc and Chromium Supplementation in People with Type 2 Diabetes Mellitus. *J Am Coll Nutr* 2001;20(3), 212-8.
23. Partida-Hernandez G, Arreola F, Fenton B, Cabeza M, Román-Ramos R, Revilla-Monsalve MC. Effect of zinc replacement on lipids and lipoproteins in type 2-diabetic patients. *Biomedicine & Pharmacotherapy* 2006;60(4):161-8.
24. Eibl N, Schnack C, Scherthaner G. Magnesium supplementation in type 2 diabetes. *Diabetes Care* 1998;21(11):2031.
25. Paolisso G, Sgambato S, Pizza G, Passariello N, Varricchio M, D'Onofrio F. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* 1989;12(4):265.
26. Rosolova H, Mayer O, Reaven G. Effect of Variations in Plasma Magnesium Concentration on Resistance to Insulin-Mediated Glucose Disposal in Nondiabetic Subjects 1. *J Clin Endocrinol Metab* 1997;82(11),3783-5.
27. Chausmer AB. Zinc, Insulin and Diabetes. *Journal of the American College of Nutrition* 1998;17(2):109-15.
28. Mooradian AD, Failla M, Hoogwerf B, Maryniuk M, Wylie-Rosett J. Selected vitamins and minerals in diabetes. *Diabetes Care* 1994;17(5):464-79.
29. O'Connell BS. Select Vitamins and Minerals in the Management of Diabetes. *Diabetes Spectrum* 2001;14(3):133-48.
30. American Diabetes Association. Standards of Medical Care in Diabetes-2008. *Diabetes Care* 2008;31(1):12-54.
31. Ascherio A, Rimm EB, Giovannucci E, Willett WC, Stampfer MJ. Blood Donations and Risk of Coronary Heart Disease in Men. *Circulation* 2001;103(1),52-7.
32. Gerich JE. Clinical Significance, Pathogenesis, and Management of Postprandial Hyperglycemia. *Arch Intern Med* 2003;163(11):1306-16.
33. Rodriguez-Moran M, 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;26(4):1147.
34. Meludu SC, Adeniyi FAA. Effect of magnesium supplementation on plasma glucose in patients with diabetes mellitus. *African Journal of Biomedical Research* 2001;4(3):111-3.
35. Paolisso G, Sgambato S, Gambardella A, Pizza G, Tesaro P, Varricchio M, et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992;55(6):1161-7.
36. Sjogren A, Floren CH, Nilsson A. Oral administration of magnesium hydroxide to subjects with insulin-dependent diabetes mellitus: effects on magnesium and potassium levels and on insulin requirements. *Magnesium* 1988;7(3):117-22.
37. Lal J, Vasudev K, Kela AK, Jain SK. Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. *The Journal of the Association of Physicians of India* 2003;51:37.
38. de Valk HW, Verkaarik R, van Rijn HJM, Geerdink RA, Struyvenberg A. Oral Magnesium Supplementation in Insulin-requiring Type 2 Diabetic Patients. *Diabetic Medicine* 1998;15:503-7.
39. Paolisso G, Barbagallo M. Hypertension, diabetes mellitus, and insulin resistance: The role of intracellular magnesium. *American journal of hypertension* 1997;10(3):346-355.
40. Subrez A, Pulido N, Casla A, Casanova B, Arrieta FJ, Rovira A. Impaired tyrosine-kinase activity of muscle insulin receptors from hypomagnesaemic rats. *Diabetologia* 1995;38(11):1262-70.
41. Sheehan JP. Magnesium deficiency and diabetes mellitus. *Magn Trace Elem* 1991-1992;10(2-4):215-9.
42. Lefebvre PJ, Paolisso G, Scheen AJ. Magnesium and glucose metabolism. *Therapie* 1994;49(1):1-7.
43. Curry DL. Magnesium modulation of glucose-induced insulin secretion by the perfused rat pancreas. *Endocrinology* 1977;101(1):203-8.
44. Balon TW, Jasman A, Scott S, Meehan WP, Rude RK, Nadler JL. Dietary magnesium prevents fructose-induced insulin insensitivity in rats. *Hypertension* 1994;23(6):1036-9.

45. Tosiello L. Hypomagnesemia and diabetes mellitus. A review of clinical implications. *Arch Intern Med* 1996;156(11):1143-8.
46. Resnick LM, Altura BT, Gupta RK, Laragh JH, Alderman MH, Altura BM. Intracellular and extracellular magnesium depletion in Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1993;36(8):767-70.
47. Vanroelen WF, Van Gaal LF, Van Rooy PE, de Leeuw IH. Serum and erythrocyte magnesium levels in type I and type II diabetics. *Acta Diabetologica* 1985;22(3):185-90.
48. Crook M, Couchman S, Tutt P, Amiel S, Swaminathan R. Erythrocyte, plasma total, ultrafiltrable and platelet magnesium in type 2 (non-insulin dependent) diabetes mellitus. *Diabetes Res* 1994;27(2):73-9.
49. Lima M, Cruz T, Pousada JC, Rodrigues LE, Barbosa K, Cangucu V. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care* 1998;21(5):682-6.
50. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association Clinical Practice Recommendations Among US Adults With Diabetes, 1999-2002: The National Health and Nutrition Examination Survey. *Diabetes Care* 2006;29(3):531-7.
51. Marreiro DN, Geloneze B, Tambascia MA, Lerbrijo AC, Halpern A, Cozzolino SMF. Effect of zinc supplementation on serum leptin levels and insulin resistance of obese women. *Biological Trace Element Research* 2006;112(2):109-18.
52. Afkhami-Ardekani M, Karimi M, Mohammadi SM, Nourani F. Effect of Zinc Sulfate Supplementation on Lipid and Glucose in Type 2 Diabetic Patients. *Pakistan Journal of Nutrition* 2008;7(4):550-3.
53. Raz I, Karsai D, Katz M. The influence of zinc supplementation on glucose homeostasis in NIDDM. *Diabetes Res* 1989;11(2):73-9.
54. Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant Effects of Zinc Supplementation in Tunisians with Type 2 Diabetes Mellitus. *Journal of the American College of Nutrition* 2003; 22(4):316-21.
55. Faure P, Lafond JL, Coudray C, Rossini E, Halimi S, Favier A, et al. Zinc prevents the structural and functional properties of free radical treated-insulin. *Biochim Biophys Acta* 1994;1209(2):260-4.
56. Marchesini G, Bugianesi E, Ronchi M, Flaminia R, Thomasset K, Pacini G. Zinc supplementation improves glucose disposal in patients with cirrhosis. *Metabolism* 1998;47(7):792-8.
57. Preuss HG. The Insulin System: Influence of Antioxidants. *Journal of the American College of Nutrition* 1998;17(2): 101-2.