

CLINICAL STUDY

Lipids in association with serum magnesium in diabetes mellitus patients

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Abstract: *Aim:* To investigate whether and how serum Magnesium (Mg) concentrations influence the serum lipids in diabetes mellitus (DM) patients. The cross-sectional study was conducted on diabetic mellitus (DM) patients with various kidney functions not yet on dialysis.

Patients and methods: Serum lipoprotein(a), glycosylated hemoglobin (HbA1c), serum magnesium (Mg), serum creatinine (creat), serum lipids consisting of triglycerids (Tg), cholesterol (Chol), high-density lipoprotein (HDL) were measured.

Results: Study patients included 122 patients (82F, 40M). The mean patients' age was 63 (± 10) years. The mean length of time they were diabetic was 7.4 (± 5.8) years (median: 6 years). The mean serum Mg was 2 (± 0.4) mg/dl (median: 1.99 mg/dl). The mean creatinine clearance was 64 (± 24) cc/min (median: 64 cc/min). In this study significant inverse correlations of serum Mg with serum cholesterol and LDL as well as non-significant correlations of serum Mg with serum Lp(a), HDL, Tg and with serum HgbA1c were seen. More over a significant inverse correlation of serum Mg with ages of the patients and a significant positive correlation of serum Mg with serum creatinine were seen too.

Conclusions: It seems that in diabetic patients, kidney function is a key role in the regulation of serum Lp(a) levels instead of other factors like serum Mg level. Our finding further supports the importance of Mg supplementation in diabetes mellitus patients. In our study no significant correlation between serum Mg with serum HDL and Tg were found, which needs further investigation (Tab. 1, Fig. 4, Ref. 53). Full Text (Free, PDF) www.bmj.sk.

Key words: serum magnesium, serum lipids, lipoprotein(a), diabetes mellitus.

Within the last years, biological role and properties of metal ions have begun to be reconsidered due to greater importance of inorganic bioions in explanation of numerous biologic processes. Magnesium (Mg) is an important intracellular cation that is distributed into three major compartments: mineral phase of bones (65 %), intracellular space (34 %), and extracellular fluid (1 %) (1). About one third of the circulating magnesium is bound to plasma proteins, with the remaining two thirds free and presumably biologically available (1, 2). In several studies reduced magnesium concentrations have been observed in diabetic adults (3–7) and children (8, 9) despite good nutritional status (10), which probably results from glycosuria-related hypermagnesiuria, nutritional factors or hyperinsulinaemia (3). A large body of evidence shows a link between hypomagnesemia and reduction of

tyrosine-kinase activity at the insulin receptor level. This may result in the impairment of insulin action and development of insulin resistance (11–16). Various evidences suggest that magnesium supplementation could be useful in the treatment of diabetes, and to prevent the development of its chronic complications (17–19).

Experimental studies have also shown that hypomagnesemia inhibits prostacyclin receptor function (20), producing an imbalance between prostacyclin and thromboxane effects (21). Hypomagnesemia can increase platelet reactivity, increase vascular and adrenal responses to angiotensin II, enhance thromboxane A2 (TXA2) release, and lead to organ damage from free radicals (22–25). Magnesium deficiency has also a role in the perturbation of lipid metabolism in the non-uremic population, especially in the diabetic patients (26). Previously we and others have shown that there is a correlation between dyslipidemia and serum magnesium I in end-stage renal failure patients undergoing hemodialysis treatment (27, 28). In light of the evidence of magnesium imbalance in diabetes mellitus, it is important to study the association of serum magnesium with lipids. Indeed controversial reports are available regarding the effect of magnesium (Mg) on lipid profile and glycaemic control in diabetic patients. A number of studies have reported beneficial effects of magnesium supplementation on plasma cholesterol and LDL chole-

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Tab. 1. Minimum, Maximum, Mean +SD and Median values of patients' data also laboratory tests of the patients.

No of pts 122	Minimum	Maximum	Mean±SD	Median
Age (years)	25	84	63±11	64
Duration of DM (years)	0.1	25	7.4±6.8	6
Duration of HTN(years)	0.00	25	3.2±4.5	0.80
BMI (kg/m ²)	19.9	53	25.5±4.5	25.3
Cretinine clearance (cc/min)	10	110	64±24	64
Lp(a) (mg/dl)	0.10	134	22.2±24.8	18.3
Alb (g/dl)	2.5	7.5	4.9±1	4.9
Total protein (g/dl)	5	12.5	7.2±0.9	7
HgbA1C %	3.9	13.3	7.6±1.9	7.6
Chol (mg/dl)	90	388	198±52	192
Tg (mg/dl)	37	580	183±102	155
LDL (mg/dl)	44	210	112±37	112
HDL (mg/dl)	19	128	47±18	44
Mg (mg/dl)	1	3.29	2±0.4	1.99
Creatinine (mg/dl)	0.6	10	1.32±1.34	1

terol, and an increase of HDL cholesterol level (26, 29, 30). This study was designed to investigate whether and how in diabetes mellitus (DM) patients, the serum Magnesium (Mg) concentration influence serum lipids. We designed this study on a group of diabetes mellitus patients who had various kidney functions not yet on dialysis.

Patients and methods

Patients

This cross-sectional study was conducted on diabetic mellitus patients under treatment of either oral hypoglycemic agent with biguanids or Insulin NPH with Insulin crystal injections with various dosages who were admitted to the hospital for controlling the diabetes.

These patients were recruited between January and September of 2005. Among study patients, those who had hypertension, took antihypertensive drugs consisting of calcium channel blocker (amlodine or diltiazem), angiotensin convertin enzyme inhibitors (ACEI) or angiotensin receptor antagonists (ARA) with various doses. Exclusion criteria included taking diuretics, presence of other chronic or acute infections and use of lipid-lowering medications. The study was carried out in Hajar Medical educational and Therapeutic Center of Shahrekord University of Medical Sciences of Iran. All patients signed the consent form for participation in this study.

After admission all patients underwent the history taking consisting of the length of the time they were diabetic, their medications for DM and HTN. Patients were also examined for blood pressure (BP), body mass index measurement as well as heart, lower extremities pulses and feet for ulcer.

Laboratory methods

Blood samples were collected after an overnight fast. Each blood samples were centrifuged within 15 min of venipuncture, and serum lipoprotein(a) (Lp(a)) measurements were determined

by means of a commercial enzyme-linked immunosorbent assay kit (Macrar Lp(a) manufactured by Strategic Diagnostics Inc. for Trinity Biotech USA, Jamestown, NY, USA).

For patients also glycosilated hemoglobine (HbA1c) was measured by chromatography method using Hb-Gold of UK, the normal value in our laboratory is (less than or equal to) 6.1 %. Levels of serum magnesium (Mg), Albumin (Alb), serum creatinine (creat), blood urea nitrogen (BUN), total protein were measured using standard methods. Other lipids consisting of Triglycerids (Tg), cholesterol (Chol), High-density lipoprotein (HDL) was also measured using standard methods. Body mass index (BMI) calculated using the standard formula (weight in kilograms/height in square meters; kg/m²). Serum LDL-C was calculated by Friedewald's formula (31). Creatinine clearance (CrCL) was evaluated from serum creatinine, age and body weight (32).

Statistical analysis

Results are expressed as the mean±SD and median values. Statistical correlations were assessed using a partial correlation test. The comparison between female and male data was assessed using student's t-test. All analyses were performed with the SPSS statistical package (version 11.500 for Windows; SPSS, Chicago, USA). Statistical significance was determined at a p<0.05.

Results

The present study included 122 patients (82 F, 40 M). Base line characteristics of patients are described in Table 1. The mean patient's age was 63 (±10) years. The mean length of the time they were diabetic was 7.4 (±5.8) years (median: 6 years). The mean serum Mg was 2 (±0.4) mg/dl (median: 1.99 mg/dl). The mean creatinine clearance was 64 (±24) cc/min (median: 64 cc/min). Serum Lp (a) levels >30 mg/dl was found in 29 patients (23.8 %). Mean±SD of serum Chol and LDL of the patients were 198±52 and 112±37 respectively.

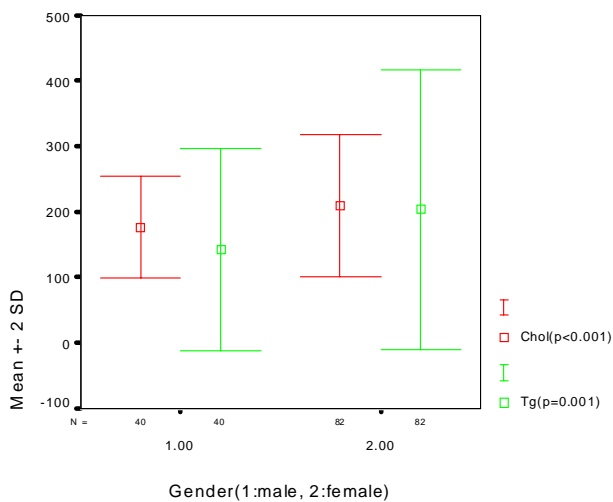


Fig. 1. Significant difference of serum cholesterol and triglyceride between males and females.

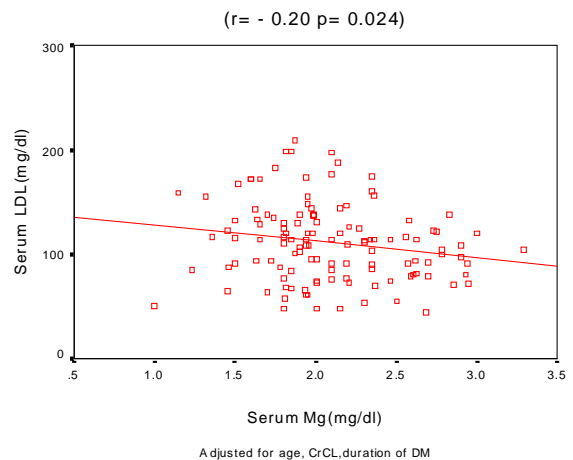


Fig. 3. Significant inverse correlation of serum Mg with serum LDL.

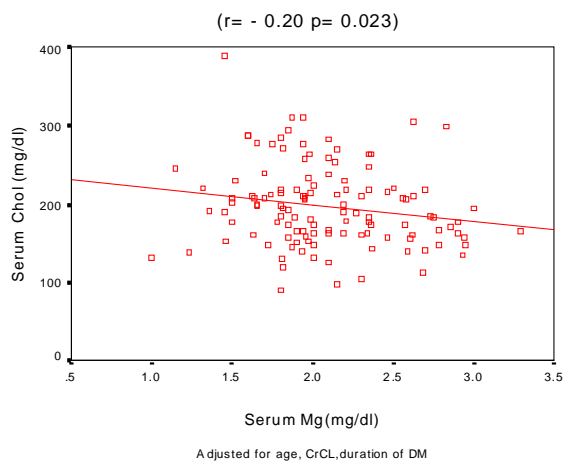


Fig. 2. Significant inverse correlation of serum Mg with serum Cholesterol.

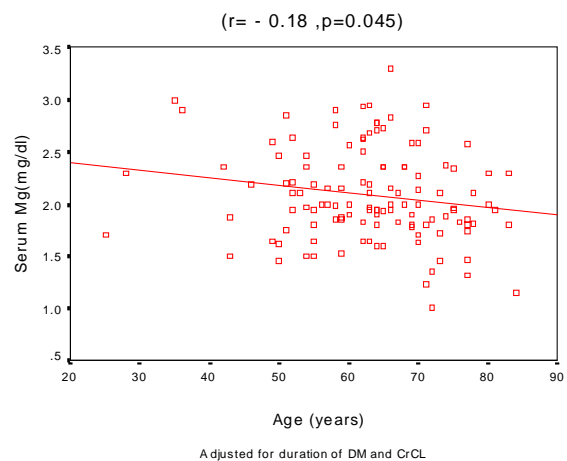


Fig. 4. Significant inverse correlation of serum Mg with the ages of the patients.

In this study no significant difference of duration of DM, age of the patients, CrCL, BMI, HgbA1c and serum Mg serum Alb, Lp(a), LDL, HDL and total protein between males and females were found (P.N.S). A significant difference of serum cholesterol ($p < 0.001$) and triglyceride ($p = 0.001$) between males and females were found (Fig. 1). In this study significant inverse correlations of serum Mg with cholesterol ($r = -0.20$, $p = 0.023$) (Fig. 2) and also with serum LDL ($r = -0.20$, $p = 0.024$) (Fig. 3) were found (adjusted for age, duration of DM and creatinine clearance). No significant correlation between serum Mg with serum Lp(a), HDL, Alb and serum Tg and also with serum HgbA1c were seen (p.N.S). Moreover a significant inverse correlation of serum Mg with ages of the patients ($r = -0.18$, $p = 0.045$) (Fig. 4) (adjusted for duration of DM and creatinine clearance) was seen.

Further more a significant positive correlation of serum Mg with serum creatinine ($r = 0.19$, $p = 0.036$) (adjusted for age, duration of DM and total protein) was seen too. Moreover a weakly negative correlation between serum Mg and duration of DM ($r = -0.18$, $p = 0.055$) (adjusted for age, duration of HTN, BMI, HgbA1C level and chol, LDL, Tg and also serum Creat) was found too.

Discussion

Principle findings of the present study were significant inverse correlations of serum Mg with serum cholesterol and LDL and also non-significant correlations of serum Mg with serum Lp(a), HDL, Tg and with serum HgbA1c were seen. Moreover a significant inverse correlation of serum Mg with ages of the pa-

tients and a significant positive correlation of serum Mg with serum creatinine were seen too. Magnesium is known to play an important role in carbohydrate metabolism, and its imbalance has been implicated in diabetes mellitus both as a cause and a consequence (33–36). Hypomagnesemia has been observed in both animal (35–37) and human subjects with type 1 and type 2 diabetes mellitus (37–41). The etiology of hypomagnesemia in diabetes cannot be clearly explained and serum magnesium levels have been shown to be inversely related to the severity of diabetes (42). Magnesium deficiency in humans is unlikely to occur from a simple lack of foods containing this mineral, except in advanced forms of malnutrition (8). According to the consensus of a panel on magnesium metabolism in diabetes mellitus (43), diabetic patients have additional risk factors for hypomagnesemia and magnesium status, Magnesium may also play a role in the release of insulin and magnesium depletion has an atherogenic potential (44–46). The mechanisms of long-term complications of diabetes are not clearly explained, and hypomagnesemia may be a contributing factor to these complications, particularly ischemic heart disease (14, 47), retinopathy (4, 48), and bone loss (49, 50). In a study conducted by Lal et al on 40 patients of type 2 diabetes mellitus (DM) and 54 age and sex matched non-diabetic controls, the diabetic patients (study group) were supplemented with 600 mg of Mg oxide daily for 12 weeks. They were followed up every four weeks (for a total duration of twelve weeks) and investigated for the above parameters. Mean serum magnesium at baseline in the diabetic patients was significantly lower than that in controls (1.44 ± 0.48 mg/dl vs 2.29 ± 0.33 mg/dl). A significant fall in serum total cholesterol, LDL cholesterol and triglycerides and a rise in HDL cholesterol levels was observed 4 to 8 weeks after the initiation of magnesium supplementation and continued till the end of the study i.e. 12 weeks. They concluded that Mg supplementation resulted in a beneficial effect on the lipid profile of these patients (30). Usefulness of chronic magnesium supplementation on reduction of plasma cholesterol and LDL cholesterol, and an increase of HDL cholesterol was also shown by Corica (29) and Baydas et al (51). The study of previous investigators were mainly on the effect of Mg supplementation on lipid profiles of diabetic patients. To our best knowledge this is the first report serving the association of serum Lp(a) with serum magnesium in diabetic patients with various kidney functions not yet on dialysis. The mean creatinine clearance of our study patients were 64 ± 24 cc/min (median: 64 cc/min). In our study we adjusted the results with kidney function of the patient, while with decreasing the renal function, dyslipidemia might also supervene distinct the effects of serum Mg or poorly controlled diabetes. While we previously showed the positive association of serum Lp(a) with serum Mg in hemodialysis patients (28), in this study even after adjusting for multiple confounding factor, no significant association between serum Mg and serum Lp(a) was seen. Taking >30 mg/dl as the cut-off value for Lp(a), we had serum Lp (a) levels >30 mg/dl in 29 patients (23.8 %). It seems that kidney function is a key role in the regulation of serum Lp(a) levels instead of other factors (52) in diabetic patients. We also showed inverse corre-

lations of serum Mg with serum cholesterol and LDL levels, a finding which further supports the importance of Mg supplementation in diabetes mellitus patients. In our study no significant correlation between serum Mg with serum HDL and Tg were found, which needs further investigation. Recent studies in rats have shown that magnesium deficiency produces hypertriglyceremia, hypercholesterolemia, increased low-density lipoproteins (LDL), and reduced high-density lipoprotein (HDL) through reduced triglyceride clearance, diminished activity of lecithin cholesterol acetyltransferase (LCAT) and lipoprotein lipase, and increased activity of HMG-COA reductase (53). The association between hypomagnesemia and hypertriglyceremia has been confirmed in studies of pigs (53). While the association between lipid abnormalities and hypomagnesemia has not been fully understood in human studies. Our results emphasize the importance of serum Magnesium level and clinical impact of these findings merit further investigation.

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