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Lipids in association with serum magnesium in diabetes mellitus patients

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Abstract

Background. *The aim of the study was to investigate if and how, in diabetes mellitus (DM) patients, serum Magnesium (Mg) concentration influences serum lipids. A cross-sectional study was conducted on diabetic mellitus (DM) patients with various kidney functions, not yet on dialysis.*

Material and methods. *Serum lipoprotein (a), glycosylated haemoglobin (HbA_{1c}), serum magnesium (Mg), serum creatinine (creat) and serum lipids, consisting of triglycerides (Tg), cholesterol (Chol) and high density lipoprotein (HDL) were measured.*

Results. *Study patients included 122 patients (82 F, 40 M). The mean patient's 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, and also non significant correlations of serum Mg with serum Lp (a), HDL, Tg and with serum HbA_{1c} were seen. Moreover, a significant inverse correlation of serum Mg with the patients' ages and a significant positive correlation of serum Mg with serum creatinine were also seen.*

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 findings further support 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.*

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

Introduction

In recent years, the biological role and properties of metal ions have begun to be reconsidered due to greater importance of inorganic bioions in the 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 that shows a link between hypomagnesemia and reduction of tyrosine-kinase activity at the insulin receptor level, which may result in the impairment of insulin action and development of insulin resistance, has

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been progressively accumulated in previous years [11–16]. Various evidence suggests that magnesium supplementation could be useful in the treatment of diabetes and to prevent the development of its chronic complications [17–19], and 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 A_2 (TXA_2) release, and lead to organ damage from free radicals [22–25]. Magnesium deficiency also has a role in the perturbation of lipid metabolism in the non-uremic population, especially in diabetic patients [26]. Previously, we and others have shown that there is a correlation between dyslipidemia and serum magnesium l in end-stage renal failure patients undergoing haemodialysis 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 cholesterol, and an increase of HDL cholesterol level [26, 29, 30]. This study was designed to investigate if 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, and were not yet on dialysis.

Material and methods

Patients

This cross-sectional study was conducted on diabetic mellitus patients under treatment of either an oral hypoglycaemic agent with /- biguanides or insulin NPH with/- Insulin crystal injections with various dosages who were admitted to the hospital to control their diabetes.

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

After admission all patients' medical histories were examined concerning the length of the time they were diabetic and their medicament for DM and HTN. Patients were also examined for blood pressure (BP), body mass index, heart and lower extremities pulse and their feet were examined for ulcers.

Laboratory methods

Blood samples were collected after an overnight fast. The blood samples were centrifuged within 15 min of venopuncture, and serum lipoprotein(a) [Lp(a)] measurements were determined by means of a commercial enzyme-linked immunosorbent assay kit [Macra® Lp(a) manufactured by Strategic Diagnostics Inc. for Trinity Biotech USA, Jamestown, NY, USA].

The patients' glycosilated hemoglobine (HbA_{1c}) was also measured by chromatography 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) and total protein were measured using standard methods. Other lipids consisting of triglycerides (Tg), cholesterol (Chol) and high density lipoprotein (HDL) were also measured using standard methods. Body mass index (BMI) was calculated using the standard formula (weight in kilograms/height in metres squared: kg/m^2). 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. Comparison between female and male gender data was assessed using Students' *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-value < 0.05.

Results

The present study included 122 patients (82 F, 40 M). Baseline characteristics of the patients are described in Table I .The mean patient's 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). 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.

Table I. Minimum, maximum, mean ± SD and median values of patients' data and laboratory tests of the patients

Patients (n = 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
Creatinine 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
HbA_{1c} (%)	3.9	13.3	7.6 ± 1.9	7.6
Cholesterol [mg/dl]	90	388	198 ± 52	192
Triglycerides [mg/dl]	37	580	183 ± 102	155
LDL [mg/dl]	44	210	112 ± 37	112
HDL [mg/dl]	19	128	47 ± 18	44
Magnesium [mg/dl]	1	3.29	2 ± 0.4	1.99
Creatinine [mg/dl]	0.6	10	1.32 ± 1.34	1

DM — diabetes mellitus; HTN — hypertension; BMI — body mass index; LDL — low density lipoprotein, HDL — high density lipoprotein; Lp(a) — lipoprotein A; Alb — albumin; SD — standard deviation

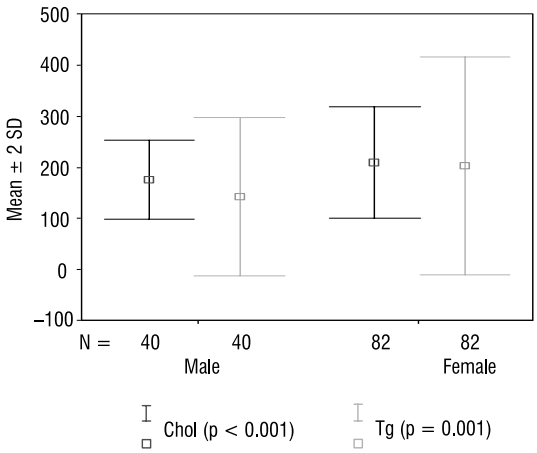

Figure 1. Significant difference of serum cholesterol and triglyceride between males and females

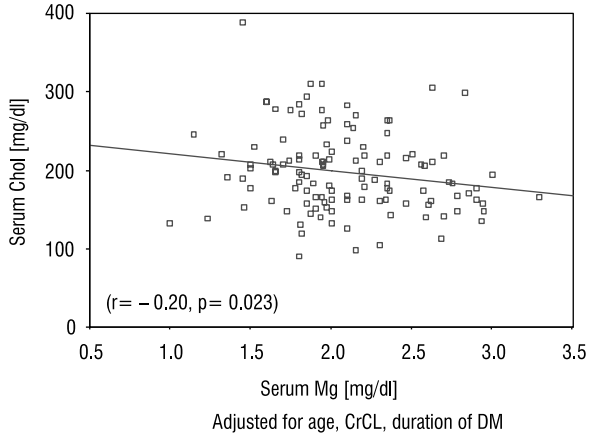

Figure 2. Significant inverse correlation of serum Mg with serum cholesterol

In this study no significant difference of duration of DM, age of the patients, CrCL, BMI, HbA_{1c} and serum Mg, serum Alb, Lp(a), LDL, HDL and total protein between males and females was found (P.N.S). A significant difference of serum cholesterol ($p < 0.001$) and triglyceride ($p = 0.001$) between males and females was found (Figure 1). In this study significant inverse correlations of serum Mg with cholesterol ($r = –0.20$, $p = 0.023$) (Figure 2) and also with serum LDL ($r = –0.20$, $p = 0.024$) (Figure 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 or with serum HbA_{1c} were seen (P.N.S). Moreover, a significant inverse correlation of serum Mg with ages of the patients ($r = –0.18$, $p = 0.045$) (Figure 4) (adjusted for duration of DM and creatinine clearance) was seen. Furthermore, 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. Also, a weak negative correla-

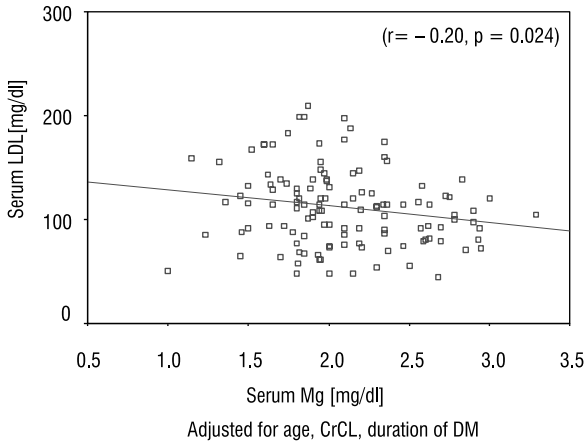

Figure 3. Significant inverse correlation of serum Mg with serum LDL

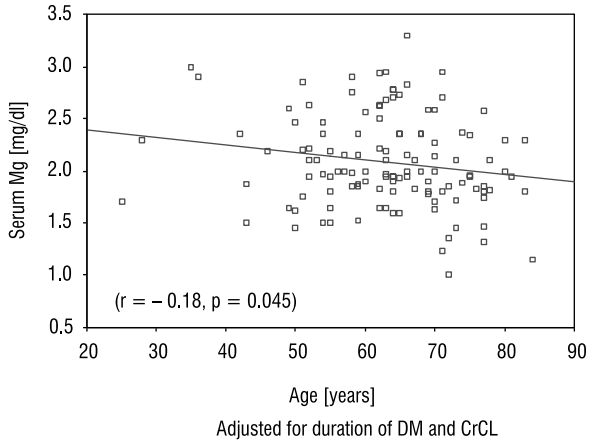

Figure 4. Significant inverse correlation of serum Mg with the patients age

tion between serum Mg and duration of DM (r = –0.18, p = 0.055) (adjusted for age, duration of HTN, BMI, HbA_{1c} level and Chol, LDL, Tg and also serum creat was found too).

Discussion

The 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 $HgbA_{1c}$. Moreover, 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 as well. 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 48 weeks after 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]. The usefulness of chronic magnesium supplementation in reducing plasma cholesterol and LDL cholesterol, and in increasing HDL cholesterol was also shown by Corica et al. [29] and Baydas et al. [51].The subject of study of previous investigators was mainly the effect of Mg supplementation on lipid profiles of diabetic patients. To our best knowledge this is the first report investigating 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 according to the kidney function of the patients, although, by decreasing the renal function, dyslipidemia might also supervene the effects of serum Mg or poorly controlled diabetes.

While we previously showed the positive association of serum Lp(a) with serum Mg in haemodialysis patients [28], in this study even after adjusting for multiple confounding factors, 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, 53] in diabetic patients. We also showed inverse correlations 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 [54]. The association between hypomagnesemia and hypertriglyceremia has been confirmed in studies of pigs [54]. However, 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 the clinical impact of these findings merit further investigation.

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