MAGNESIUM AND SELENIUM IN DIABETICS WITH PERIPHERAL ARTERY DISEASE OF THE LOWER LIMBS

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Abstract

Background and aims. *Knowing that diabetes mellitus (DM) often leads to cardiovascular injury such as peripheral artery disease (PAD) of the lower limbs and that some microelements like magnesium (Mg) and Selenium (Se) might be involved in the alterations entailed by these complications, we aimed to investigate the behavior of those microelements in these diseases.*

Methods. *We studied 114 patients with type 2 DM, treated not with insulin but only by diet or oral antidiabetics, mean aged 56.6 having a mean duration of the diabetes of 14.5 years, mostly men (80), 64 of them (40 men) having also PAD stage 2 without severe complications. We had a control group of 40 similarly-aged subjects without DM or PAD. The measurements were performed on a Konelab 30I device and serum selenium was quantified by atomic absorption spectroscopy. All patients underwent clinical, paraclinical and arterial Doppler echography for establishing the diagnosis of PAD.*

Results. *The results for controls were 2.2±0.4 mg/dl for Mg, 130±6 µg/dl for Se; diabetics had 1.68±0.4 mg/dl Mg, 88±6 µg/dl Se; diabetics with PAD had significantly lower levels: 1.36±0.6 mg/dl Mg, 66±6 µg/dl Se ($p<0.05$). Age inversely correlated with the values of both microelements especially in women. Mixed dysipidemia, present in DM, correlated with PAD. Blood pressure also inversely correlated with Mg and Se. Coronary heart disease (ischemia) linked to lower blood values of Mg and Se. Left Ventricle Hypertrophy (as proved by echography) also correlated to lower blood values of Mg and Se, as did glycated hemoglobin (HbA1c).*

Conclusion. *We may conclude that in DM there is a Mg deficit which becomes significant in DZ+PAD especially in forms with high blood pressure (HBP), severe dyslipidemia and in the presence of early microvascular complications, our paper suggesting the opportunity of a substitutive treatment with Mg and Se in selected cases.*

Keywords: serum magnesium, selenium, type 2 diabetes mellitus, peripheral artery disease.

Introduction

Diabetes mellitus (DM) is an important disease with increasing incidence and strong medical and social impact especially through severe cardiovascular complications. Peripheral artery disease (PAD) of the lower limbs is frequently seen in diabetics and tends to have a more severe evolution. Some trace-elements like magnesium (Mg) and selenium (Se) have modified values in diabetic patients' blood revealing a potential involvement in the appearance of the disease and its complications.

Objectives

We aimed to measure the serum values of Mg and Se in a group of type 2 diabetics, mean age 58 and with a duration of the disease of approx. 8.5 years, metabolically balanced without specific severe complications or morbid associations; from those we delimited a group of 64 diabetics which also had PAD in the second degree of

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evolution showing signs of claudication with medium-efforts. We tried to identify some potential relation between clinico-biological data and also possible prognostic and therapeutic relations in these diseases.

Material and methods

This was a clinical study related to paraclinical investigations including serum Se and Mg measurement in type 2 diabetics admitted in a hospital during the last 3 years. The clinical group consisted of 114 type 2 diabetics, mean aged 56.6±0.5 years having a mean duration of the disease of 14.5±0.5 years, mostly men (80 cases) with metabolically compensated disease at the moment of investigation. From those we separated a group of 62 diabetics that also had PAD in the 2nd stage with intermittent claudication of approx. 80±20 m. In this group as well the majority were men (40 cases). A group of 40 healthy individuals (blood donors) of similar age were the control group. We obtained the paticipation consent from those included in the study and also the approval from the University Ethical Comitee.

The clinical study included a thorough physical examination, with body weight, blood pressure measurement, pulse taking etc. Laboratory investigations included current data hematological and bioclinical (cholesterol, triglycerides, HDL-cholesterol, glycemia, nitrates, creatinin, glycated hemoglobin etc.). They also were subject to ECG, chest Xray, retinal exam, microalbuminuria, echocardiography examination. Investigation of the peripheral arteries was performed by Doppler echography of the lower limbs by the same examiner. Serum Mg was assessed by an automated method in a Konelab multianalyser and the serum Se was quantified by atomic absorption spectroscopy in the Chemistry Laboratory of the Babes-Bolyai University in Cluj (Prof. Frentiu and coworkers). Results were statistically analysed, their significance being assessed by the T Student test.

Results

We noted below the serum levels of Mg and Se in diabetics as compared to controls and those with PAD (see table I).

Table I. Values by disease.

Group	DM	DM+PAD	Controls
Mg (mg/dl)	1.68±0.4	1.36±0.6	2.2±0.4
Se (µg/dl)	88±0.6	66±0.6	160±6

Compared values of Mg in diabetics vs.the control group showed statistically significant differences and also in diabetics vs. the PAD group, with a $p<0.05$. We also noted severe hypomagnesiemia in diabetics, more intense in the presence of PAD of the lower limbs. We state that PAD was only of the second degree with a quite stable claudication index. According to gender the values of Mg and Se were noted below ($p<0.05$) (table II).

Table II. Values by gender.

Gender	DM males	DM females
Mg (mg/dl)	1.86±0.4	1.64±0.4
Se (µg/dl)	93±0.6	82±0.6

Values of serum Mg were notably lower in women, also the mean values of serum Se were lower in that group. Related to age we found the following (table III).

Table III. Values by age.

Age (years)	< 45	45-65	>65
Mg (mg/dl)	1.72±0.4	1.48±0.4	1.28±0.4
Se (µg/dl)	98±0.6	82±0.6	66±0.6

Mean values of Mg but also Se became lower with ageing, with statistical significance ($p<0.01$)

Analyzing the duration of the diabetes we had the following data ($p<0.05$) (table IV).

Table IV. Values by duration of diabetes.

Duration (years)	<8	>8
Mg (mg/dl)	1.76±0.6	1.52±0.4
Se (µg/dl)	96±0.6	72±0.6

Usually the duration of the diabetes was associated with statistically significant low values for Mg but also for Se. It is know the fact that DM evolves in the presence of dyslipidemia, often severe, which is present in PAD and usually associates with mixed dyslipidemia which is a marker but also a pathogenetic element of generalized atherosclerosis. The values for classic lipidic parameters in DM and in DM+PAD were associated with the decrease of serum Mg and Se (*$p<0.01$) (table V).

Table V. Values of lypids.

Test	Cholesterol	Triglycerides	HDL-cholest	Mg	Se
DM	232±10	248±10	32±4	1.68±0.6*	86±4
DM+PAD	264±12	284±10	28±2	1.34±0.6*	62±4
Controls	184±10	160±10	36±2	2.24±0.6*	130±4

The DM group we investigated had no severe microvascular or macrovascular complication (e.g. myocardial infarction). Despite this fact, paraclinical investigation such as retinal exam, microalbumiuria allowed us to note some early alterations such as diabetic retinopathy and values of microalbuminuria, which correspond to the initial changes found in nephropathy. The presence of these initial changes was related to some Mg and Se changes. Among the type 2 diabetics we studied the presence of retinopathy was seen in approximately 25% of them and 30% had signs of nephropathy, while the DZ+PAD group had even higher percentage: 40% retinopathy and 50% nephropathy. The long lasting metabolic imbalance was assessed by the levels of HbA1c which had lower values in case of severe aggravation (*$p<0.01$, **$p<0.05$) (table VI).

Table VI. Values by glycated Hb.

	DM	DM	DM+PAD	DM+PAD
HbA1c (mg/dl)	< 7.5	>12	<7.5	>12
Mg (mg/dl)	1.74±0.4	1.68±0.4	1.44±0.4	1.32±0.4**
Se (µg/dl)	96±0.4*	72±0.4*	82±0.4*	62±0.4*

In PAD patients the severe and long lasting metabolic imbalance (HbA1c>12%) revealed significantly lower values of the studied parameters. Vascular ultrasound examination evidenced multiple arterial obstructions that could not be related to the values of Mg or Se in blood.

Discussion

DM is a metabolic disease with increasing incidence, affecting around 4% of the general population; diabetes is a disease that leads to micro and macrovascular changes like the frequent PAD. Mg is a microelement that plays an important role in biology and pathology, being involved in multiple biological and metabolic processes. Recent literature offers ample examination regarding the role of magnesium. First were Durlach et al., then Mc Nair, Paolisso, Rayssignier, Classen, Seelig and others – all of them proving Mg deficit in DM, its role and importance being vastly studied [1-8,10,11,17,19,20]. There is also a relation between Mg values and the duration of DM revealed also by our findings: blood serum Mg decreases almost parallel to the duration of disease especially in aging women. Our DM+PAD group proved to have even lower values for Mg (proved statistically significant) than the controls or DM group; basically the PAD group had the lowest values of all; also the Mg dropped above 65 years. In Romania, interesting data regarding the role and the importance in pathology of the Mg were published decades ago by Szantay, Porr, Nechifor, Miu and Dragatoiu, Zeana and others that showed the importance role played by hypomagnesemia in various diseases like DM, digestive illnesses, HBP, CAD and others [4-6,8,14-17,21,29]. McNair considers that hypomagnesemia is a pathogenetic factor in diabetic retinopathy [1]. Also hypomagnesemia correlated often with severe dyslipidemia from PAD, in which case its pathogenetic role in the evolution of atherosclerosis may be discussed [1,2,6,13,14,19]. Long term imbalanced diabetes, proved by very high levels of HbA1c correlated with very low MG values [14,16,17,20]. Many authors plead for the existing underlying Mg deficit in DM, intensified in the presence of PAD. The causes of this phenomenon are not fully known yet: it is considered there is also a lower intake, a low absorption or a higher loss of Mg possibly by medication like diuretics or malnutrition [2,7,8,11,21,26,41]. Our data add up to prove the severe hypomagnesemia in DM, especially complicated with PAD with a significant lowering in the presence of microangiopathy [19,20]. Serum Se is an essential microelement for antioxidative and immunomodulatory processes, involved in many metabolic processes and defense, being vasoactive and antitumoral. Recent data showed low blood Se in the onset of hypertension, coronary heart disease but also neoplasia of the liver, colon or prostate. Although the importance of dietary supplements of Se is vastly discussed the results of prophylaxis of neoplasia are controversial [22-25,31,32,37,42]. Our data revealed low values of Se in DM, intensely decreased in DM+PAD. In various papers the data regarding the Se behaviour in various diseases are often contradicting other data but most of those shows a direct relation between serum Se and dislypidemia and CHD, AMI, HBP [12,22-24,32-35,42]. Our data are close to those results, Se values being significantly lower in DM+PAD, related to the duration of diabetes, its long metabolic imbalance, dyslipidemia or atherosclerosis. In fact hyposelenemia often correlated with hypomagnesemia in DM and DM+PAD. Its reduction was more expressed by ageing but also by the duration of the disease. Selenium is also involved in the pathogenesis of HBP, systemic atherosclerosis, lots of published works identifying a Se deficit when CHD or atherosclerosis was present including PAD [3,22-24,31,32,42,43]. Some authors found almost a parallel between the intensity of the Se deficit and the seriousness of CHD or HBP; many works tested the value of some food supplements or drugs containing Se without getting significant results [9,31,32,37,38,42,43]. It is already known that Se binds to certain proteins and plays a role in attenuating the inflammatory effects besides other antioxidative mechanisms. Kok (1987) noted that very low values of Se in blood (blow 45 µg/l) were markers for a significant increase in cardiovascular mortality [22]. On the other hand, other authors noted that very high levels of Se also associate with increased cardiovascular mortality. Experimental data (Manati – 2009) noted the protective role of a Se supplementation against drug-induced injuries on rabbit liver [37,42,43]. Our data obtained from the studied group revealed the existence in DM of a Se deficit, but even more a Mg one, augmented in the presence of PAD.

Conclusions

Serum Mg and Se are significantly lower in type 2 DM metabolically compensated. Presence of PAD (2nd stage) leads to significant lowering of Mg and Se, the decreased values progressing with age and duration of the disease. Mixed dyslipidemia tends to relate with a decrease of Mg and Se in DM+PAD, suggesting an associated mechanism of aggravation. Long-standing metabolic imbalance of DM in PAD is associated with low Se and Mg values. Microangiopathy in its early stage tends to relate to low values of Mg and Se in patients. This significant deficit of Mg and Se suggests the involvement of these oligoelements in the atherosclerotic process and in the metabolic imbalance of DM, suggesting that a corrective supplementation with Mg and Se may prove useful in selected cases.

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