Hypomagnesemia, a Risk Factor in Diabetic Retinopathy

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SUMMARY

The serum magnesium concentration was measured in 71 insulin-treated diabetic outpatients who had had the disease for 10 to 20 years. The patients were divided into two subgroups according to the severity of their retinopathy. As a whole the patients exhibited a definite hypomagnesemia ($P < 0.001$) that was most pronounced in the subgroup having the severest degree of retinopathy ($P < 0.01$). The subgroups were comparable regarding known risk factors implicated in diabetic retinopathy. Thus, hypomagnesemia appears to be an additional risk factor in the development and progress of this complication. DIABETES *27*:1075-77, November, 1978.

Although it is generally believed that strict metabolic control delays the development of late complications in diabetes mellitus,[1] it has not been demonstrated conclusively that such control hampers the development of diabetic retinopathy.[2] Therefore, the search for additional risk factors continues. One risk factor of atherosclerosis—cigarette smoking[3]—has recently been found to be associated with the development of proliferative diabetic retinopathy.[4,5]

This directs our attention towards the possible importance of another factor with an atherogenic potential—magnesium depletion. This causes atherosclerosis in experimental animals and possibly also in man.[6] Hypomagnesemia has been reported in diabetes mellitus in the course of recovery from ketoacidosis[7] as well as during insulin maintenance therapy.[8,9] However, the inadequacy[8] or lack[9] of control groups and incomplete information regarding other factors affecting serum magnesium leave considerable uncertainty with respect to the true state of serum magnesium during insulin maintenance therapy of diabetes mellitus.

The aim of this study was to examine whether insulin-treated diabetic patients who were without ketoacidosis or other factors known to affect magnesium metabolism had hypomagnesemia and, if this were the case, whether serum magnesium was related to the degree of retinopathy.

PATIENTS AND METHODS

From the outpatient population of a diabetes hospital (Hvidøre Hospital), insulin-treated patients who had had diabetes for 10 to 20 years were selected. For this subgroup we applied the following criteria of exclusion: serum creatinine > 115 μmol per liter, nephrectomy, renal stone disease, urine incontinence, neck operations, oophorectomy, hysterectomy, endocrine diseases, pregnancy or lactation, gastrointestinal, operations, diseases of the liver or pancreas, intestinal malabsorption, incapacitating diseases of the locomotor system, rheumatoid arthritis, malignant diseases, narcomania, and alcoholism. Patients using hormones (other than insulin), diuretics, anticonvulsants, lithium, neuroleptics, antacids, and cytotoxic agents were also excluded. Seventy-one of the remaining 93 patients were willing to participate. These were divided into two groups on the basis of their retinal findings (see below). Salient data concerning these groups are given in table 1.

As a reference group for serum magnesium, calcium, and protein, 194 normal subjects aged 21 to 70 years (mean 44 years) were used. Grading of the ophthalmoscopic findings was undertaken by one investigator (E.L.). Patients with either normal fundi or

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TABLE 1

Sex, age at onset, and insulin treatment in 71 diabetics, grouped according to the severity of retinopathy

	Number		Age	Age at onset	Duration	Insulin treatment Dose/day	Dose/kg./day
	Men	Women	(yr.)	(yr.)	(yr.)	(I.U.)	(I.U.)
Group A	28	17	37.2* (14–63)†	23.5 (0–53)	13.7 (10–20)	36.1 (14–58)	0.58 (0.22–0.90)
Group B	15	11	42.9 (18–68)	27.9 (4–54)	15.0 (10–20)	38.5 (20–62)	0.60 (0.32–1.07)

*Mean. †Range.

minor changes (microaneurysms and/or exudates smaller than microaneurysms) were classified as group A. Group B included the more severe changes, i.e. microaneurysms plus larger hemorrhages and/or exudates and proliferative retinopathy. The application of high concentrations of serum creatinine as a criterion of exclusion prevented many patients with proliferative retinopathy from participating in the study. Only four patients so affected were included, hence our use of the actual grading.

Patients who smoked daily or had been doing so until less than six months before the study were classified as smokers and the remaining as nonsmokers.

Blood was drawn between 8 and 9 a.m. after fasting and abstinence from smoking, at least since midnight. After a blood sample was drawn, 1 mg. of glucagon was given intravenously and another blood sample was drawn six minutes later. The morning dose of insulin was withheld until after the second blood sample was drawn. Serum concentrations of magnesium and calcium were determined by atomic absorption spectrophotometry and corrected to a constant serum protein level.[10] Serum immunoreactive parathyroid hormone (iPTH) and the spontaneous and glucagon-stimulated C-peptide levels were determined by radioimmunoassay.[11,12] Blood glucose, the 24-hour urinary excretion of glucose, and the serum concentrations of protein, creatinine, potassium, cholesterol, and triglyceride were determined by routine methods. All measurements were made in duplicate, and the coefficients of variation of duplicate measurements of serum calcium, magnesium, proteins, and iPTH were 1.0, 0.7, 0.5, and 4.3 per cent, respectively.

Student's *t* test was used for statistical evaluation of the difference between averages. The outcome of ophthalmoscopic grading remained concealed until the analytic work was completed.

RESULTS

The average concentrations of serum magnesium in controls (n = 194), groups A (n = 45), A + B (n = 71), and B (n = 26) measured 0.83 ± 0.007, 0.75 ± 0.014, 0.74 ± 0.012, and 0.72 ± 0.018 mmol per liter, respectively (means ± 2 S.E.M.) (figure 1). The patients as a group had hypomagnesemia ($P < 0.001$), and the patients in group B had significantly lower serum magnesium than those in group A ($P < 0.01$).

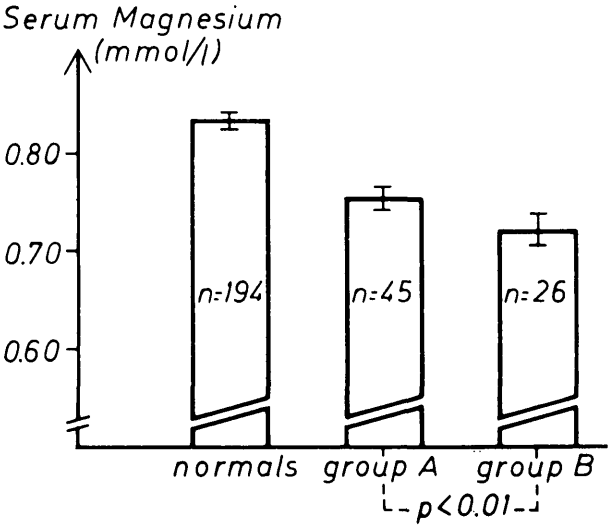

FIG. 1. Serum magnesium level in normal subjects and in 71 diabetics grouped according to retinopathy (see text). Values are given as means ± 2 S.E.M.

Groups A and B were comparable with respect to serum potassium, calcium, iPTH, and renal function, as well as serum lipids, C-peptide, blood glucose, and urinary glucose excretion (table 2). The distribution of smokers in groups A and B was 30/45 (67 per cent) and 20/26 (77 per cent), respectively ($P > 0.05$). Neither within the separate groups nor as a whole did smokers differ from nonsmokers regarding serum magnesium.

DISCUSSION

The possible atherogenic potency of hypomagnesemia[6] prompted this study. Our observations re-

TABLE 2

Biochemical indexes in 71 diabetics, grouped according to retinopathy, and in normal subjects

Biochemical parameter	Group A		Group B		Normal subjects	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Potassium (mmol/liter)	4.5	0.4	4.6	0.4	4.4	0.4
Calcium (mmol/liter)	2.45	0.06	2.48	0.06	2.47	0.07
Creatinine (μmol/liter)	75	11	80	17	80	15
Triglycerides (gm./liter)	0.96	0.10	0.97	0.10	0.82	0.37
Cholesterol (mmol/liter)	5.4	0.5	5.7	0.5	5.1	1.1
C-peptide (nmol/liter)	0.04	0.01	0.03	0.01	0.35	0.11
ΔC-peptide (nmol/liter)	0.02	0.01	0.03	0.02	0.85	0.28
iPTH (μg./liter)	0.28	0.05	0.29	0.04	0.34	0.05
Blood-glucose (mmol/liter)	12.3	4.4	12.5	4.6	4.2	0.5
Urine glucose (mmol/day)	409	417	385	350		

veal a definite lowering of serum magnesium in long-term, insulin-treated diabetic outpatients having a fairly normal renal function ($P < 0.001$). Moreover, patients who had a more severe degree of retinopathy were found to have the lowest concentrations of serum magnesium ($P < 0.01$). The division of our patients according to the severity of their retinopathy yielded groups that were strictly comparable in all respects except serum magnesium (tables 1 and 2). Consequently, we suggest hypomagnesemia as a possible risk factor in the development and progress of diabetic retinopathy.

The cause of diabetic hypomagnesemia is unknown, but an increased urinary loss of magnesium may contribute to it. Two factors may work together in this respect, namely, the osmotic action of glucosuria and the hyperglycemia per se, the latter being known to depress the net tubular reabsorption of magnesium in normal man.[13-15] However, the contribution to hypomagnesemia by these factors remains unknown. Thus, the renal handling of calcium should be affected similarly,[13-15] but we found no evidence of hypocalcemia or secondary hyperparathyroidism (table 2). The contribution by other, as yet unknown, mechanisms is suggested by the observation that groups A and B, being strictly comparable regarding blood glucose and glucosuria, differed significantly with respect to serum magnesium. Future studies should explore the mechanisms that affect the development of diabetic hypomagnesemia and tell us if magnesium supplements hamper the progression of diabetic retinopathy.

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