Plasma and erythrocyte magnesium in insulin-dependent and non-insulin-dependent-diabetics: correlations between twelve variables

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Zusammenfassung

Bei 19 bzw. 22 insulin-abhängigen männlichen und weiblichen Diabetikern (IDD) sowie 10 nicht-insulin-abhängigen Diabetikerinnen (NIDD) wurden die folgenden Parameter erfaßt: Plasma-Mg (P-Mg), Erythrozyten-Mg (E-Mg), Alter, Körpermasse, Plasma-Ca (P-Ca), Gesamt- und HDL-Cholesterin, Triglyceride, Albumin, Blutzucker, glycosyliertes Hämoglobin A_1 und die Dauer der Behandlung. Parallel hierzu wurden P-Mg, E-Mg, P-Ca, Gesamt- und HDL-Cholesterin bei 58 männlichen und 53 weiblichen Kontrollpersonen mitbestimmt. Entsprechend der Prüfung auf Normalverteilung und der Homogenität der Varianzen wurden die Ergebnisse mit parametrischen und nicht-parametrischen Tests statistisch ausgewertet. Multiple (R), einfache (r) und Spearman (r) Korrelationskoeffizienten wurden berechnet.

Signifikante multiple Korrelationskoeffizienten ergaben sich zwischen P-Mg von IDD-Männern bzw. E-Mg von IDD-Frauen und den anderen 11 Variablen. Alle signifikanten einfachen Korrelationen ($p \leq 0,05$) sind aufgeführt. Im Vergleich mit den entsprechenden Kontrollen war P-Mg bei IDD-Frauen signifikant erniedrigt ($p < 0,001$) und E-Mg bei IDD-Frauen und Männern (p jeweils $< 0,001$), während P-Ca bei den IDD- sowie NIDD-Patienten jeweils signifikant erhöht war. Verglichen mit IDD-Diabetikerinnen und weiblichen Kontrollpersonen war das HDL-Cholesterin bei den NIDD-Patientinnen erniedrigt.

Bei dem erwählten Signifikanzniveau ($p \leq 0,05$) und trotz des relativ geringen Stichprobenumfanges erscheint es empfehlenswert, Diabetiker nach Geschlecht und Diabetestyp zu unterteilen.

Summary

Plasma and erythrocyte magnesium (P-Mg, E-Mg), age, body mass index, plasma calcium (P-Ca), total- and HDL-cholesterol, triglycerides, albumin, blood glucose, glycosylated hemoglobin Al and duration of treatment were analyzed in 19 insulin-dependent diabetic (IDD) men, 22 IDD women, and 10 noninsulin-dependent diabetic (NIDD) women P-Mg, E-Mg, P-Ca, total- and HDL-cholesterol were simultaneously determined in 58 reference men and 53 reference women. According to the normality of the distributions and the homogeneity of variances, statistical analysis of results was performed using parametric and nonparametric tests. Multiple (R), simple (r) and Spearman (r_s) correlation coefficients were calculated.

Multiple correlation coefficients were significant between P-Mg in IDD men or E-Mg in IDD women and all of the other eleven series of variables. All significant ($p \leq 0.05$) simple correlations are indicated. In comparison with reference subjects, P-Mg decreased significantly ($p < 0.001$) in the group of IDD women and E-Mg in both IDD groups ($p < 0.001$), whereas P-Ca increased significantly in IDD and NIDD patients. NIDD women, in comparison with IDD and reference women, showed a significant drop in HDL-cholesterol.

On the basis of the level of significance adopted ($p \leq 0.05$), and of a relatively small number of subjects, it would seem preferable to separate results in diabetic patients according to sex and type of diabetes.

Résumé

Les magnésium plasmatique et érythrocytaire (Mg-P, Mg-E), l'âge, l'index de corpulence, le calcium plasmatique (Ca-P), les cholestérols total et HDL, les triglycérides, l'albumine, la glycémie, l'hémoglobine glycosylée A_1 et la durée du traitement ont été analysés chez 19 hommes diabétiques insulino-dépendants (DID), 22 femmes (DID) et 10 femmes diabétiques non insulino-dépendants (DNID). Les Mg-P, Mg-E, Ca-P, les cholestérols total et HDL ont été également déterminés chez 58 hommes et 53 femmes de référence. Selon la normalité des distributions et l'homogénéïté des variances, l'analyse statistique des résultats a été effectuée au moyen de tests paramétriques ou nonparamétriques. Les coefficients de corrélation multiple (R), simple (r) et de Spearman (r) ont été calculés.

Les coefficients de corrélation multiple étaient significatifs entre Mg-P chez les hommes DID ou E-Mg chez les femmes DID et les onze autres séries de variables. Tous les coefficients de corrélation simple significatifs ($p \leq 0.05$) ont été indiqués. Par rapport aux sujets de référence, Mg-P était significativement abaissé ($p < 0.001$) dans le groupe de femmes DID et Mg-E dans les deux groupes DID ($p < 0.001$), tandis que le Ca-P était significativement élevé chez les malades DID et DNID. Les femmes DNID, par rapport aux femmes de référence et DID, présentaient une diminution significative du cholestérol-HDL.

Compte-tenu du nombre de sujets et du seuil de signification choisi ($p \leq 0.05$), il serait préférable de séparer les résultats des diabétiques selon le sexe et le type de diabéte.

Introduction

Magnesium (Mg) intervenes in the metabolism of carbohydrates. Diabetes mellitus, even when ketoacidosis is not involved, represents the most common condition for plasma hypomagnesemia [1, 2]. Moreover, chronic Mg deficiency may favor cardiovascular diseases [2]. In diabetic patients, atherosclerosis is very common and occurs early [3].

These factors led us to undertake the present study, which represents an aspect of our continuing work on Mg metabolism reported previously for experimental [4, 5] or clinical [6, 7] investigations relative to atherosclerosis and myocardial infarction and for diabetes mellitus [8].

The biological correlations assumed to exist between different variables generally monitored in hospitalized diabetic patients guided our choice of the following criteria for statistical analyses: age, body mass index, plasma and erythrocyte Mg (P-Mg, E-Mg), plasma calcium (P-Ca), total- and HDL-cholesterol, triglycerides (Tg), albumin, blood glucose, glycosylated hemoglobin A_1 (Hb A_1) and length of treatment. Samples from insulin-dependent diabetic patients were compared first as a function of sex and then with samples from control groups. A similar study was carried out for noninsulindependent diabetic patients. In consideration of the probable interactions between these different variables, simple and multiple correlations were determined.

Materials and Methods

1. Population

The study concerned 162 white-coloured subjects (111 reference subjects and 51 diabetics), all residents of the Nantes area in France, a region supplied with soft tap water. The reference subjects, neither blood donors nor hospitalized, had been studied in a previous work [9]. The 51 hospitalized diabetics, without severe ketoacidosis nor renal failure, diuretics or evident alcoholism, were subdivided into 3 groups: 19 insulin-dependent diabetic (IDD) men, 15 to 72 years of age; 22 IDD women, 13 to 73 years of age, never on oral contraceptives; and 10 non-insulin-dependent diabetic (NIDD) women, 49 to 73 years of age.

2. Assay rechniques

Magnesium and Ca were analyzed by flame atomic absorption spectrometry using a Hitachi 180 – 80 model with Zeeman effect, according to a previously described protocol [9, 10]. The HDL-cholesterol (Boehringer Precipitant No. 400 971: phosphotungstic acid and Mg^{++} ions) and total-cholesterol were determined by the Boehringer enzymatic colorimetric cholesterol C-system, CHOD PAP method [9]. Triglycerides were assessed by the Boehringer enzymatic method on a Cobas automate. Albumin was evaluated after electrophoresis. The blood glucose determination was performed by the glucose-oxidase method, using a Beckman automate. Hb A_1 was assayed according to the microchromatographic technique of *Kynoch* and *Lehmann* [11], and the results were corrected as a function of room temperature.

3. Statistical analysis of results

The normality of distributions was checked by the chi-square test [12] or by the *Shapiro* and *Wilk* test [13]. The homogeneity of variances was then verified [12]. The comparison of means was subjected to appropriate parametric (*Student's* t-test, ANOVA), and nonparametric (*Mann* and *Whitney*) tests [12]. For the comparison of Hb A_1 proportions (P), we used the t-test after an appropriate arc sine transform, defined as = 2 arc sine $\sqrt{P}$ [14]. Multiple (R) and simple (r) correlation coefficients were estimated between series of normal distribution; tests of the significance of the correlation coefficients were performed respectively by the F-test [15] and the t-test [12]. The Spearman correlation coefficient (r_s) was used in case of non-normality of distributions [12].

Results

The results, which to our knowledge provide the only analysis of correlations of this type, are given in Tables 1 to 3 (correlation coefficients have been tabulated only for $p \leq 0.05$). The age of reference subjects and the blood glucose of NIDD women were not distributed normally, so that these variables were obviously excluded from subsequent parametric calculations. It was not considered of interest to compare the means of ages and the duration of insulin therapy.

For reference subjects, (Table 1), the assays indicated were the only ones performed for this group in our laboratory. In men, the multiple correlation between P-Mg and all of the other 4 variables was significant; the same was true for E-Mg. The other results were presented in a previous publication [9]. As far as the levels of Tg, albumin, blood glucose and Hb A_1 are concerned, the reference values given by the hospital laboratory were respectively 0.60 to 1.70 mmol/L, 540 to 650 µmol/L, 4.3 to 5.9 mmol/L and 7.45 ± 0.92 %.

Multiple correlation coefficents (Table 2) were significant between P-Mg in 19 IDD men or E-Mg in 22 IDD women and all of the other 11 variables. The negative correlations were noteworthy in IDD women between P-Ca and total-cholesterol, P-Ca and blood glucose and P-Ca and Hb A_1. The level of HDL-cholesterol, was significantly ($P < 0.05$) higher for IDD women than for IDD men. In comparison with reference subjects, P-Mg decreased significantly ($p < 0.001$) in IDD women, and E-Mg in both IDD groups ($p < 0.001$), whereas P-Ca increased significantly in these same groups.

In NIDD women (Table 3), the rank correlations with blood glucose were never significant ($p > 0.05$). In comparison with reference women, P-Ca increased significantly ($p < 0.005$) and HDL-cholesterol decreased ($p < 0.001$). As compared with IDD women, NIDD women showed significant increases in body mass index ($p < 0.001$), E-Mg ($p < 0.02$) and Tg ($p < 0.01$), and decreases in HDL-cholesterol ($p < 0.01$), blood glucose ($p < 0.01$) and Hb A_1 ($p < 0.001$). The analysis of variance indicated significant differences between the 3 groups of women for P-Mg, E-Mg, P-Ca and HDL-cholesterol.

Discussion

On the basis of the number of subjects and the level of significance adopted ($p \leq 0.05$), the multiple and simple correlations, as well as HDL-cholesterol, showed different conclusions for the two IDD groups. Moreover, the two groups of diabetic women gave different results for 6 variables. As in our preliminary studies [8], these results confirm that it is important to classify diabetics by sex and the clinical form of the disorder. Unfortunately, it was not possible to include a sufficient number of NIDD men in the study to report the results here.

The variation of Mg levels depended on sex and the type of diabetes. No significant decrease in P-Mg or E-Mg was observed for NIDD women; nevertheless, it should be noted that their mean age was elevated (59.2 ± 9.04 years) and that a positive correlation was found between E-Mg and age, a correlation that had been previously established [8]. These data are in agreement with a certain heterogeneity in the results published in the literature [1, 2, 8, 16–19] which show a decrease of P-Mg and/or E-Mg. The P-Mg and E-Mg assays do not have the same biological significance: P-Mg represents the extracellular compartment and depends more on mesologic phenomena, whereas E-Mg represents the intracellular compartment and relates especially to genetic factors [20]. Nevertheless, it should be noted that there was a positive correlation ($p < 0.01$) between these two variables for reference men and IDD women.

The elevation of P-Ca was constant in our 3 groups of diabetics. Results reported in the literature show considerable divergence [2]. Some authors have found high levels of P-Ca in diabetes mellitus [8, 16], others normal levels of total-Ca [21, 22] but lower ionized-Ca levels associated with higher concentrations of complexed-Ca [22]. Moreover, it would certainly be of great interest to assay systematically ionized, complexed and protein-bound Mg and Ca as well as albumin in the plasma of diabetes mellitus patients if the protocols for the procedure, as already described for Mg [23], were not so complicated. Hypomagnesemia probably increases Ca-binding by decreasing the binding competition between Ca and Mg [22]. Furthermore, it would be useful to perform correlations between magnesium parameters, phosphocalcium parameters and their control factors, especially 1,25 dihydroxy-cholecalciferol ($1{,}25-(OH)_2-D_3$), parathormone and calcitonin [8].

In reference subjects and IDD patients, lower HDL-cholesterol levels have been found for men [9], with no difference between normal and IDD groups. On the contrary, NIDD women, in comparison with reference and IDD women, had a very significant decrease in HDL-cholesterol with no rise in total-cholesterol. Moreover, NIDD women as compared with IDD women showed a significant rise in Tg, as previously reported [3, 24].

In IDD women, a negative correlation was noted between P-Mg and albumin, whereas in NIDD women the correlation was negative between E-Mg and albumin. The usual correlations between circulating Mg and albumin indicate that there is a positive correlation [16]. It would appear that increased albumin synthesis leads to a rise in Mg needs.

Table 1: Results in 58 reference men and 53 reference women (mean and SD[a])

	Age (1)	Plasma magnesium (2)	Erythrocyte magnesium (3)	Plasma calcium (4)	Total cholesterol (5)	HDL-cholesterol (6)
— Units	year	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
— *Normal men,* 24–81 years old	42.8 (15.9)	0.77 (0.06)	2.12 (0.25)	2.20 (0.12)	5.23 (1.08)	1.21 (0.28)
— Normality	no	yes	yes	yes	yes	yes
— Multiple correlation coefficient		$R_{2(3,4,5,6)} = 0.41^{*b}$	$R_{3(2,4,5,6)} = 0.42^{*}$			
— Simple correlation coefficient		$r_{(2,3)} = 0.39^{**}$				
— Spearman correlation coefficient	$r_{s(1,4)} = -0.45^{***}$					
— *Normal women,* 22–79 years old	41.4 (13.1)	0.77 (0.05)	2.03 (0.23)	2.18 (0.10)	5.06 (0.97)	1.43 (0.28)
— Normality	no	yes	yes	yes	yes	yes
— Multiple correlation coefficient					$R_{5(2,3,4,6)} = 0.49^{**}$	$R_{6(2,3,4,5)} = 0.44^{*}$
— Simple correlation coefficient				$r_{(4,5)} = 0.29^{*}$	$r_{(5,6)} = 0.38^{**}$	
— Comparison of the means (58 men/53 women)		NS[c]	$p < 0.05$[c]	NS[c]	NS[c]	$p < 0.001$[c]

[a] SD = Estimation of the standard deviation of the population.
[b] Levels of significance: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[c] Student's t-test.

Table 2: Results in insulin-dependent diabetics: 19 men and 22 women (mean and SD[a])

	Age (1)	Body mass index (2)	Plasma magnesium (3)	Erythrocyte magnesium (4)	Plasma calcium (5)	Total-cholesterol (6)	HDL-cholesterol (7)	Triglycerides (8)	Albumin (9)	Blood Glucose (10)	Hb A_1 (11)	Insulin therapy (12)
— Units	year	kg/m^2	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	µmol/L	mmol/L	%	year
— *men,* 21 – 72 years old	40.0 (15.3)	21.2 (2.98)	0.74 (0.08)	1.82 (0.32)[b***]	2.28 (0.08)[b*]	4.70 (1.16)	1.14 (0.38)	1.18 (0.51)	638 (57.8)	10.3 (4.12)	11.9 (3.12)	7.42 (8.12)
— Normality	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
— Multiple correlation coefficient		R = 0.92*[c] $_{2(1\cdots12)}$	R = 0.93* $_{3(1\cdots12)}$			R = 0.93* $_{6(1\cdots12)}$	R = 0.94* $_{7(1\cdots12)}$	R = 0.97** $_{8(1\cdots12)}$			R = 0.94* $_{11(1\cdots12)}$	
— Simple correlation coefficient	r = 0.48* $_{(1,8)}$ r = 0.70*** $_{(1,3)}$	r = 0.48* $_{(2,8)}$ r = 0.70*** $_{(2,6)}$						r = −0.62** $_{(8,9)}$				
— *women,* 13.5 – 73 years old	34.8 (18.3)	20.9 (3.19)	0.71 (0.07)[b***]	1.71 (0.18)[b***]	2.26 (0.12)[b**]	4.82 (1.09)	1.41 (0.41)	1.06 (0.51)	603 (60.9)	12.7 (3.93)	12.0 (2.30)	11.7 (9.21)
— Normality	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
— Multiple correlation coefficient				R = 0.90* $_{4(1\cdots12)}$	R = 0.89* $_{5(1\cdots12)}$			R = 0.88* $_{8(1\cdots12)}$				
— Simple correlation coefficient	r = −0.55** $_{(1,9)}$		r = +0.63** $_{(3,4)}$ r = −0.49* $_{(3,9)}$	r = +0.69*** $_{(4,12)}$	r = −0.61** $_{(5,6)}$ r = −0.50* $_{(5,10)}$ r = −0.45* $_{(5,11)}$					r = 0.59** $_{(10,11)}$		
— Comparison of the means (19 men/22 women)		NS[d]	NS[d]	NS[d]	NS[d]	NS[d]	$p<0.05$[d]	NS[d]	NS[d]	NS[d]	NS[e]	

[a] SD = Estimation of the standard deviation of the population.
[b] Comparison of the means with those of reference subjects of the same sex; *p < 0.05; **p < 0.01; ***p < 0.001.
[c] Levels of significance: *p < 0.05; **p < 0.01; ***p < 0.001.
[d] Student's t-test.
[e] t-test after arc sine transform: $\theta = 2 \text{ arc sine} \sqrt{P}$.

Our investigations revealed no correlation between Mg and blood glucose or Hb A_1, which is in contradiction [16, 25, 26] or agreement [8, 19, 27] with previously reported data.

Conclusion

On the basis of the level of significance adopted ($p \leq 0.05$) and of a relatively small number of subjects, it would seem preferable to separate diabetics according to sex and the clinical form of the disorder. Further studies are necessary, especially concerning the ionized, complexed and protein-bound forms of Mg and Ca, since many factors remain unknown which seem to be necessary for a correct interpretation of all of our results. Nevertheless, diabetic Mg deficiency represents a typical form of Mg "depletion" [2]. Diabetes induces this depletion both by direct effects such as osmotic diuresis and by indirect effects due to hormones, vitamins, ions or porteins. It cannot be considered as a simple deficiency resulting solely from a decrease in Mg supply.

Additional more complete statistical studies are currently being carried out in our laboratory.

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Table 3: Results in 10 noninsulin — dependent diabetic women (mean and SD[a])

	Age (1)	Body mass index (2)	Plasma magnesium (3)	Erythrocyte magnesium (4)	Plasma calcium (5)	Total-cholesterol (6)	HDL-cholesterol (7)	Triglycerides (8)	Albumin (9)	Blood Glucose (10)	Hb A_1 (11)	Duration of treatment (12)
— Units	year	kg/m^2	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	µmol/L	mmol/L	%	years
— Mean (SD)[a]	59.2 (9.04)	27.7 (5.36)	0.75 (0.11)	1.93 (0.26)	2.30 (0.08)	4.97 (0.89)	0.96 (0.29)	1.94 (0.99)	620 (51.0)	8.22 (3.81)	9.49 (2.37)	10.1 (11.9)
— Normality	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes
— Simple correlation coefficient	$r_{(1,4)} = 0.72$*[b] $r_{(1,9)} = -0.77$**	$r_{(2,3)} = 0.65$*		$r_{(4,9)} = -0.88$***				$r_{(8,11)} = 0.63$*				
— Comparison of the means (10 NIDD/ 22 IDD women)		p<0.001[c]	NS[c]	p<0.02[c]	NS[c]	NS[c]	p<0.01[c]	p<0.01[c]	NS[c]	p<0.01[d]	p<0.001[e]	
— Comparison of the means (10 NIDD/ 53 reference women)			NS[c]	NS[c]	p<0.005[c]	NS[c]	p<0.001[c]					
— ANOVA (53 reference/ 22 IDD/10 NIDD)			p<0.05	p<0.001	p<0.01	NS	p<0.01					

[a] SD = Estimation of the standard deviation of the population.
[b] Levels of significance: *$p<0.05$; **$p<0.01$; ***$p<0.001$.
[c] Student's t-test.
[d] Mann and Whitney's test.
[e] t-test after arc sine transform: $\theta = 2 \text{ arc sine} \sqrt{P}$.

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