Changes in Selenium, Zinc, Magnesium, Calcium, Potassium, Cholesterol and Creatine-kinase Levels during the Twelve Days Following Acute Myocardial Infarction in Men. Correlation and Regression Studies

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Zusammenfassung

Aufgrund vermutlicher Interaktionen und Beziehungen zum akuten Myokardinfarkt wurden in Plasma (P) und/oder Erythrozyten (E) die folgenden Parameter bestimmt: Selen (P-Se); Zink (P-Zn; E-Zn); Magnesium (P-Mg; E-Mg); Calcium (P-Ca); Kalium (E-K); Gesamt- und HDL-Cholesterin sowie die Gesamt-Creatin-Kinase. Untersucht wurden 32 Männer unmittelbar nach der Aufnahme sowie an den Tagen (T): 2; 3; 6; 10 und 12. 21 gesunde Männer dienten als Kontrollen. Am T 1 fand sich bei den Patienten ein Abfall von P-Ca ($p < 0,005$), P-Zn ($p < 0,001$) und HDL-Cholesterin ($p < 0,025$). Während den folgenden 12 T blieben nur P-Se und HDL-Cholesterin unverändert. Für die anderen Variablen fanden sich bei inter-individuellem Vergleich signifikante Veränderungen. Aufgrund vermuteter Interaktionen wurden einfache, *SPEARMAN* und multiple Korrelationskoeffizienten errechnet sowie schrittweise Regressionsgleichungen aufgestellt. Hierbei fand sich bei den Kontrollen ein Haupteinfluß von E-Zn und HDL-Cholesterin und bei den Patienten von P-Mg, E-Zn und HDL-Cholesterin am T 12 auf die abhängige Variable (P-Se). Von T 1 bis T 12 fanden sich beträchtliche Schwankungen für P-Se mit einer Dominanz für P-Mg und/oder E-Mg.

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Summary

The supposed biological relations between different variables in acute myocardial infarction (MI) led us to determine plasma (P) and/or erythrocyte (E) levels of selenium (P-Se), zinc (P-Zn; E-Zn), magnesium (P-Mg; E-Mg), calcium (P-Ca), potassium (E-K), total- and HDL-cholesterols and total creatine-kinase in 32 men upon admission to hospital and then on day (D) 2, 3, 6, 10 and 12. The same variables were measured in 21 reference men. Comparison of patients on Dl with controls showed a decrease in P-Ca ($p < 0.005$), P-Zn ($p < 0.001$) and HDL-cholesterol ($p < 0.025$). During the next 12 days, only P-Se and HDL-cholesterol levels remained unchanged. For the other variables, individual comparison of means by the least-significant difference indicated the dates of significant changes in concentration. In view of the probable interactions between these different variables, simple, *Spearman* and multiple correlation coefficients were searched for as well as stepwise regression equations. The equations demonstrated the major influence of E-Zn and HDL-cholesterol in reference men, and of P-Mg, E-Zn and HDL-cholesterol in patients at D 12, on the dependent variable (P-Se). From D 1 to D 12 the mainly representative variables of P-Se differed considerably, with a predominance for P-Mg and/or E-Mg.

Résumé

Les relations biologiques supposées entre différentes variables, après un infarctus aigu du myocarde, nous ont conduits à déterminer les taux plasmatique (P) et/ou érythrocytaire (E) de sélénium (Se-P), zinc (Zn-P; Zn-E), magnésium (Mg-P; Mg-E), calcium (Ca-P), potassium (K-E), cholestérols total et HDL et créatine kinase totale chez 32 hommes au moment de l'entrée à l'hôpital, puis aux jours (J) 2, 3, 6, 10 et 12. Les mêmes variables furent analysées chez 21 hommes de référence. La comparaison des malades, à Jl, aux témoins a montré une diminution de Ca-P ($p < 0,005$), Zn-P ($p < 0,001$) et cholestérol HDL ($p < 0,025$). Au cours des 12 jours d'hospitalisation, seuls les taux de Se-P et de cholestérol HDL ne varièrent pas. Pour les autres variables, la comparaison individuelle des moyennes par la méthode de la plus petite différence significative a indiqué les jours de changement significatif de concentration. Compte tenu des interactions probables entre ces différentes variables, les corrélations simples, de *Spearman* et multiples ont été recherchées ainsi que les équations de régression pas à pas. Ces équations ont mis en évidence l'influence majeure, sur la variable dépendante Se-P, du Zn-E et du cholestérol HDL chez les hommes de référence, et du Mg-P, du Zn-E et du cholestérol HDL chez les malades, à J 12. De J 1 à J 12, les variables les plus représentatives du Se-P variaient considérablement, avec une prédominance pour Mg-P et/ou Mg-E.

Many prospective studies have implicated metallic elements and lipids in the genesis of cardiovascular diseases [1–4]. The purpose of the present study was to investigate changes in concentrations of some of these elements after myocardial infarction (MI) in order to determine whether any significant relations exist. Accordingly, plasma (P) and/or erythrocyte (E) levels of selenium (P-Se), zinc (P-Zn; E-Zn), magnesium (P-Mg; E-Mg), calcium (P-Ca), postassium (E-K), total- and HDL-cholesterols and total creatine-kinase (CK: E.C.2.7.3.2) were measured in men admitted to hospital with acute MI from day (D) 1 to D 12. In view of possible relationships between these variables, simple, Spear-

man and multiple correlations were searched for.
With respect to Se, the question has been raised as to whether it is essential to humans [5], and there has also been increasing interest in its role in coronary heart disease [6–8]. As there has been little investigation of changes in P-Se within the first 12 days after MI, it was decided in our study to provide stepwise regression equations with Se as dependent variable.

Patients and methods

Populations

Samples were obtained from 53 white men (32 patients with acute MI and 21 reference subjects), all residents of the Nantes area in France, a region supplied with soft tap water. The 32 patients (32 to 82 years of age) were hospitalized in an intensive care unit for acute MI with clinical, biological and electrical signs. During the 12 days of the study these patients were treated essentially with heparin and nitroglycerine in venous form. The 21 reference men (36 to 78 years of age) were neither blood donors nor hospitalized patients, were free of metabolic or cardiovascular affections and were not receiving any form of medicine.

Assay techniques

Blood specimens (5 ml) were drawn into Terumo Venoject Tubes (Ref. T206 LH, Code VT 050 HLl) containing lithium heparin. On the first day, specimens were consistently taken from patients upon admission to hospital. On subsequent days [2, 3, 6, 10 and 12], blood was collected from fasting patients between 0800 and 0900h, conditions which were the same for reference men. Selenium was determined by electrothermal atomic absorption spectrometry using a Philips SP 2900 (Philips, Division Science et Industrie, 105, rue de Paris, F-93002 Bobigny) equipped with a Se electrodeless discharge lamp (Perkin-Elmer) (Perkin-Elmer, Division Instruments, 1, rue Franklin, B.P. 67, F-78391 Bois d'Arcy Cédex) and a deuterium background correction. Measurements were performed at 196.0 nm, using a nickel matrix modifier solution [9]. The dilution ratio was 1/3, and the graphite tube was pyrolytically coated. Fifteen µl of diluted plasma were injected into the graphite tube and the following program adopted: dry at 110°C (60 s), ash at 1200°C (20 s) and atomize at 2500°C (3 s). Tests were done in duplicate using the standard additions technique.
Magnesium, Ca and Zn were analyzed by flame atomic absorption spectrometry using a Hitachi 180–80 model with Zeeman effect (Skalar Analytique, 40 quai d'Issy-les-Moulineaux, F-75015 Paris). Potassium was measured by emission spectrometry using the same apparatus. The details of the operating procedure have been described previously [10]. Precision for Se was < 5 % for a concentration of 1 µmol/L. Precision (CV) for other cations, both "within day" and "between day" was < 1 %; accuracy exceeded 99 %. HDL-cholesterol (Boehringer Precipitant No 400971: phosphotungstic acid and Mg ions) and total-cholesterol were determined by the Boehringer enzymatic colorimetric cholesterol C-system, CHOD-PAP method [10]. Measurement of CK activity was performed using the R CK NAC-activated Merckotest (Ref. 14317) and CK-MB activity on D 1 and D 2 using the R CK-MB NAC-activated Merckotest (Ref. 14333; reagents containing CK-M inhibitory antibodies) at 25°C and 334 nm.

Statistical analysis

The normality of distributions was checked by the chi-square test [11] or the Shapiro and Wilk's test [12]. The homogeneity of variances was then verified [11]. The changes in the different variables from D 1 to D 12 was analyzed by one-way ANOVA, with repeated measurements, or by the Friedman test [13]. Individual comparison of means from D 1 to D 12 was performed by the least significant difference (LSD) method when F was significant [11].
Simple and multiple correlation coefficients were estimated between series of normal distributions; their significance was tested by t and F tests [11, 14]. The Spearman correlation coefficient was used in case of nonnormality [11]. Stepwise regression equations [14] for reference men and patients from D 1 to D 12 were also calculated, with P-Se chosen as dependent variable. Only normally distributed variables common to both patients and reference men were retained as mainly representative variables: P-Mg, E-Mg, P-Ca, E-Zn, total- and HDL-cholesterols.

Results

The different results are given in Tables 1, 2 and 3. To our knowledge, these results provide the first analysis of correlation and regression of this type in this field of pathology.
Comparison of patients on D 1 with reference men (not given in Tab. 1) showed a decrease in P-Ca ($p < 0.005$), P-Zn ($p < 0.001$) and HDL-cholesterol ($p < 0.025$). During the next 12 days, only P-Se and HDL-cholesterol concentrations remained

Tab. 1: Means and SD for Results in 21 Reference Men and 32 Men Patients Hospitalized after Acute Myocardial Infarction at Days 1, 2, 3, 6, 10 and 12

	Plasma selenium µmol/L (1)	Plasma magnesium mmol/L (2)	Erythrocyte magnesium mmol/L (3)	Plasma calcium mmol/L (4)	Plasma zinc µmol/L (5)	Erythrocyte zinc µmol/L (6)	Erythrocyte potassium mmol/L (7)	Total cholesterol mmol/L (8)	HDL-cholesterol mmol/L (9)	Total creatine-kinase I.U./L (10)
Reference men (n=21)	1.05 (0.26)	0.77 (0.06)	2.10 (0.27)	2.23 (0.13)	10.9 (2.36)[a]	157 (18.8)	88.7 (12.6)[a]	5.80 (1.15)	1.40 (0.36)	
Myocardial Infarcted men (n=32)		c								
day 1	1.01 (0.31)	0.74 (0.09)	2.20 (0.24)	2.10 (0.15)	7.93 (1.70)	167 (23.5)	86.3 (6.94)	5.58 (1.29)	1.14 (0.35)	364 (272)
day 2	1.03 (0.25)	0.75 (0.09)	2.18 (0.24)	2.09 (0.15)	7.60 (1.50)	165 (21.4)	89.4 (8.15)	5.26 (1.00)	1.12 (0.31)	333 (329)[a]
day 3	1.04 (0.27)	0.79 (0.09)	2.22 (0.25)	2.09 (0.17)	7.75 (1.43)	168 (21.8)	89.2 (10.5)	5.06 (1.07)	1.15 (0.30)	127 (111)[a]
day 6	1.04 (0.32)	0.86 (0.11)	2.31 (0.26)	2.14 (0.14)	9.47 (1.52)	167 (21.3)	91.1 (7.18)	5.12 (1.05)	1.09 (0.36)	37.1 (21.5)
day 10	1.07 (0.31)	0.86 (0.09)	2.39 (0.27)	2.15 (0.15)	10.9 (1.42)	173 (22.3)	88.6 (7.73)	5.29 (1.08)	1.05 (0.38)	25.6 (21.1)[a]
day 12	1.09 (0.34)	0.84 (0.10)	2.42 (0.25)	2.18 (0.12)	10.7 (1.23)	172 (19.6)	90.8 (8.10)[a]	5.23 (0.84)	1.08 (0.35)	23.0 (13.4)[a]
ANOVA[b]	NS	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$	$p<0.005$		$p<0.01$	NS	
Friedman test							$p<0.01$			$p<0.001$

[a] Nonnormal distribution
[b] One-way analysis of variance, repeated measures, from day 1 to day 12
[c] Individual comparison of means by the least significant difference (days with significant variation: $p<0.05$)
SD = Estimation of the standard deviation of the population

unchanged. For the other variables, the individual comparison of means by LSD indicated the dates of significant changes in their concentrations. The vertical square brackets in Tab. 1 mark the days of significant variation ($p < 0.05$) in the levels of the different variables. Thus, for P-Mg a first variation occured on D 3 and then, as of D 6, the level remained constant. P-Zn did not vary significantly from D 1 to D 3, changed at D 6 and then became constant again at a higher value from D 10 to D 12.

Owing to the relatively small number of subjects and the level of significance adopted ($p < 0.05$), only significant simple (r), Spearman (r_s) and multiple (R) correlation coefficients are given in Tab. 2 in order to simplify the presentation. It is necessary to add certain results for r_s correlations not shown in the table between CK and CK-MB ($p < 0.001$) on D 1 ($r_s = + 0.916$) and D 2 ($r_s = + 0.833$) and between P-Zn and CK-MB ($p < 0.05$) on D 1 ($r_s = - 0.338$). The stepwise regression equation provided evidence in the reference group of major influence of E-Zn and HDL-cholesterol on the P-Se level. In patients, the stepwise regression equations differed from D 1 to D 12. However, P-Mg and/or E-Mg were generally the mainly representative variables. For patients at D 12, as for reference men, E-Zn and HDL-cholesterol were among the mainly representative variables found.

Discussion

With respect to P-Se, our findings in reference men are comparable to those previously reported for a similar technique [15–17]. Gluthathione peroxidase is a tetrameric enzyme (E.C.1.11.1.9) which requires a selenocysteine at each of its 4 catalytic sites for its activity [18]. It utilizes reduced glutathione as a hydrogen donor to remove hydrogen peroxides and other lipid hydroperoxides. This inactivating role prevents the formation of free radical products and lipid peroxides that could alter arterial endothelium. Beyond this recognized role, Se deficiency has also been involved in platelet aggregation owing to its possible role in the metabolism of thrombocyte prostaglandin [19]. This could account for the association between MI and low Se levels mentioned by *Salonen* et al. [20] and for the significant inverse correlation between P-Se and severity of coronary atherosclerosis [21]. However, our own re-

Tab. 2: Study of Simple (r), Spearman (r_s) and Multiple (R) correlations[a]

Reference men	MI-Day 1	MI-Day 2	MI-Day 3	MI-Day 6	MI-Day 10	MI-Day 12
r = +0.484 3,6[b]	r = +0.355 2,5	r = −0.449** 1,2	r = +0.472** 4,7	r = 0.647**** 4,7	r = +0.366 1,5	r = −0.438* 3,4
	r = +0.469** 5,7	r = +0.381 4,5	r = +0.514*** 4,8	r = +0.472** 5,8	r = +0.527*** 4,8	r = −0.355 3,9
	r = +0.365 5,8	r = +0.620**** 4,7	r = +0.434* 5,8	r = −0.442* 5,10	r = +0.396* 8,9	r = +0.376 4,8
	r = −0.479** 5,10	r = +0.417* 4,8	r = +0.496*** 6,8	r = +0.395* 6,8		r = +0.370 6,9
	r = +0.570**** 6,8	r = +0.391* 4,9	r = +0.477** 7,9	r = +0.432* 6,9		
	r = −0.366 7,10	r = +0.376 5,6				
		r = +0.501*** 5,7				
		r = +0.457** 6,8				
		r = +0.375 7,8				
		r_s = −0.592**** 5,10	r_s = −0.428* 4,10		r_s = −0.336 6,10	r_s = −0.348 3,7
			r_s = −0.682**** 5,10			
	R[c] = 0.679* total-chol.	R = 0.635 total-chol.	R = 0.750**** total-chol.		R = 0.648* total-chol.	
			R = 0.703** P-Ca		R = 0.629 P-Ca	R = 0.688** P-Ca
			R = 0.685** E-Zn	R = 0.653* E-Zn		R = 0.667* E-Zn

[a] Only significant correlation coefficients ($p < 0,05$) are indicated
[b] Column numbers from table 1
[c] Multiple correlations between normally distributed variables common to reference men and men patients with myocardial infarction: P-Se, P-Mg, E-Mg, P-Ca, E-Zn, total-, and HDL-cholesterol
* $p < 0.02$
** $p < 0.01$
*** $p < 0.005$
**** $p < 0.001$

Tab. 3: Stepwise Regression Equations[a]

Reference subjects:
P-Se = 2.408 − 0.007 E-Zn − 0.218 HDL-cholesterol (R = 0.444; F = 2.21)
Myocardial Infarction Subjects:
Day 1: P-Se = 0.162 − 1.089 P-Mg + 0.379 E-Mg + 0.392 P-Ca (R = 0.438; F = 2.22)
Day 2: P-Se = 1.635 − 1.19 P-Mg + 0.055 total-cholesterol (R = 0.503; F = 4.90; $p < 0.05$)
Day 3: P-Se = 0.372 + 0.300 E-Mg (R = 0.270; F = 2.36)
Day 6: P-Se = −0.0958 − 0.981 P-Mg + 0.299 E-Mg + 0.604 P-Ca (R = 0.446; F = 2.32)
Day 10: P-Se = 0.400 + 0.280 E-Mg (R = 0.246; F = 1.93)
Day 12: P-Se = 1.459 − 1.225 P-Mg + 0.006 E-Zn − 0.337 HDL-cholesterol (R = 0.515; F = 3.37; $p < 0.05$)

[a] P-Se (μmol/L): dependent variable;
P-Mg (mmol/L),
E-Mg (mmol/L),
P-Ca (mmol/L),
E-Zn (μmol/L),
total- and HDL-cholesterols (mmol/L):
mainly representative variables

sults obtained in patients with MI did not differ significantly from control values, which is in agreement with the data of *Miettinen* et al. [22]. It must be emphasized, as do *Sartiano* et al. [23], that most of these relations, and others as well [24, 25], have been reported at very low mean P-Se levels, not obtained for our control and patient values nor for those of *Miettinen* et al. [22]. This would seem to suggest that only severe Se depletion increases the risk of cardiovascular diseases.

With respect to Mg movements after acute MI, our earlier studies and review of the literature

[26–28] indicated that Mg is released not only by the infarcted left ventricle but also by the nonnecrotic left ventricle and the right ventricle. Magnesium apparently enters the extracellular compartment, which would account for the transient increase ($p < 0.005$) in P-Mg noted then on D 12 [26]. The E-Mg concentration modified more slowly than the P-Mg concentration and not exactly in the same way [26], and the changes in these two variables between D 1 and D 12 were not studied then.

Our present results are not in disagreement with these earlier studies but confirm a significant increase in P-Mg and E-Mg from D 1 to D 12. It is of interest to note that changes in serum Mg levels after MI close to ours have been recently reported [29, 30]. A decrease ($p < 0.05$) in serum Ca level in patients after acute MI as compared to control subjects has also been noted [31].

After MI a significant decrease in P-Zn or serum Zn is consistently observed [31–33]. Moreover, in patients with MI a significant inverse correlation has been noted between P-Zn level and the value of plasma enzymes [33]. A drop in P-Zn is generally a reliable diagnostic test for acute MI, and the extent of the drop has prognostic implications [33, 34]. Several hypotheses have been advanced to account for the drop in P-Zn after MI [34–36]. Our own results relative to men who died after MI indicate that only the Zn level of the necrotic area is decreased ($p < 0.001$) as compared to that of the left ventricle of reference men [37]; in the right ventricle and the nonnecrotic left ventricle, Zn levels were even slightly higher than those of control men. Accordingly, in view of the drop in P-Zn from D 1 to D 3, the hypothesis would seem feasible that circulating Zn is taken up by nonnecrosed myocardial tissue, in proportion to the extent of the necrotic area, as part of the reparative process. However, the nature of the metabolic route between plasma and the heart is uncertain.

Our data presented in Tab. 2 indicate that positive and significant simple correlation coefficients between P-Zn or E-Zn and total-cholesterol were often found from D 1 to D 6, which is in agreement with findings in recent studies [38]. No significant r correlations were found between P-Zn and HDL-cholesterol, which is in agreement [39, 40] and disagreement [41] with reported studies. After MI, stability in HDL-cholesterol levels has already been reported [42] as well as significant changes in cholesterolemia [42, 43].

Our stepwise regression equations differed in patients from D 1 to D 12, perhaps as a result of the adaptation process (metabolic reactions) in response to stress caused by MI. Out of all of the correlated variables acting on a given phenomenon, the stepwise regression equation selects the most representative. This equation is admittedly less predictive than that of regression for all the variables measured, but it is simpler (only the essential factors are included) which accounts for its value [14].

Many unknown factors remain to be accounted for. As a number of variables are involved in acute MI, the study of a single variable is of relatively little interest. Our team is currently working on further, more complete statistical studies relative to other variables in this sector of pathology.

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