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Ferrum, Copper, Zinc and Manganese in Tissues of Patients Treated with Long-Standing Hemodialysis Programme

Żelazo, miedź, cynk i mangan w tkankach pacjentów leczonych przewlekłymi hemodializami

Patients treated with long-standing hemodialyses are particularly exposed to disturbances in electrolyte equilibrium. On the one hand they are deprived of kidneys excretory function, and on the other hand they lack the barrier on the part of digestive system, because the blood dialysed is separated from the dialysing liquid only by an artificial semipermeable membrane. In these conditions all the trace elements may penetrate from the dialysing liquid into the blood and accumulate in tissues, as they are not disposed of through the kidneys.

Most reports concern the behaviour of concentration of trace elements in blood serum (6, 7, 8), however, a few relate to their concentration in tissues (6). For this reason we have undertaken work aimed at postmortem examination of the level of zinc, ferrum, manganese and copper in various tissues of patients treated with long-standing dialyses.

MATERIAL AND METHODS

The subject examined were 5 patients treated with long-standing dialyses — from 2 to 42 months. The patients were 3 women and 2 men aged from 25 to 44 years. The cause of renal failure was chronic glomerulonephritis — in one patient and multicystic kidney — also in one patient. Table 1 presents the selected biochemical examinations of the blood serum of the patients before death. The patients were dialysed by Travenol Ultra-Flo II (3 × 4 hrs a week) with the dialysing liquid of the following composition: Na — 138, K — 2.0, Ca — 3.5, Mg — 1.0, CH_3COO — 35, Cl — 107 mEq/L. All patients were administered Alusal (3—4.5 g/daily). In the first and fifth patient dementia was observed during the process of treatment, with concomitant cachexia in the first patient. Renal osteodystrophy occurred in the third and fourth patient. The control group consisted of 5 people who died suddenly aged 23—37 years (35 on average) with renal function defined as normal.

Table 1. Biochemical test of blood serum of patients treated

Patient	Urea mg %		Creatinine mg %		Uric acid mg %		Na mEq/l	
W.S.	228	146	15.0	11.0	14.0	10.0	140	140
G.E.	200	95	12.0	5.9	9.6	5.9	139	143
R.Z.	115	78	12.0	7.0	13.2	10.7	137	140
K.E.	370	192	18.0	12.1	15.8	13.2	133	142
G.E.	128	57	7.48	4.8	10.4	8.4	127	—

Tissues for examination (from the heart, brain, kidney, liver, quadriceps muscle of the thigh) were sampled postmortem 24 hrs after death both in the group examined and in the control group. Samples of tissues from myocardium (cardiac muscle, heart muscle) were taken 1 centimetre above the cardiac apex, samples of muscle tissues — from the central part of quadriceps muscle of the thigh, renal tissues — 1 cm above the lower pole, liver tissues — from the central part of the lobe, and brain tissues — from the frontal lobe. The arithmetic mean of the level of individual elements in both kidneys was adopted as their level in a kidney, and the mean value from both lobes of the liver. The levels of copper (Cu), ferrum (Fe), zinc (Zn) and manganee (Mn) were determined by the method of atomic absorption spectrophotometry with Evans Electroselenium Limited 240. Mineral substances, i.e. ash, was obtained by dry mineralization at 650°C; the elements examined were selected by the use of 10% hydrochloric acid solution. The results of measurements obtained were analyzed statistically by the SPSS/PC packet. For the independent observations Student *t*-test was applied and the result of $p<0.05$ was adopted as the statistically significant result.

STUDY RESULTS

Table 2 presents the levels of copper and ferrum in the tissues of patients whose death was caused by uraemia, compared with the control group. In the patients dialysed a statistically significant decrease in the level of copper was noted in the kidneys. A similar tendency, but not statistically significant, was found in the skeletal muscles and the liver, however, the level of copper in the brain was insignificantly higher. No statistically significant deviations were noted in the level of ferrum in the tissues of patients with chronic renal failure, with a general tendency towards the decrease of ferrum content in all the samples from those patients.

Table 3 present the levels of manganese and zinc in patients who died of uraemia, compared to the control group. In the patients dialysed manganese showed a statistically higher level in cerebral tissue and in the liver (at the threshold of significance) without observable variations in other tissues. The level of zinc was statistically lower in the skeletal muscles; however, in the liver a decrease in the level of zinc on the threshold of significance was noted. An evident tendency towards the decrease of the level of zinc was observed in all tissues except cerebral tissue.

by long-standing dialyses, before and after dialyse

K mEq/l		Ca mEq/l		P mg %		Serum protein g%	Albumin %
3.5	4.5	3.6	3.9	8.96	5.8	5.13	45
4.9	4.7	4.8	5.8	8.84	5.94	4.56	44
5.3	4.7	2.5	3.95	10.2	8.5	4.3	48
6.3	4.2	4.0	4.0	9.2	5.5	6.4	49
5.5	4.1	3.8	4.2	8.8	6.2	4.75	39.8

Table 2. Levels of copper and ferrum in tissues of patients who died suddenly with normal renal function, and patients treated by long-standing dialyses

Tissue examined	Cu µg/g dry tissue				Fe µg/g dry tissue			
	control		sample		control		sample	
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*
Heart	4.004	1.225	4.338	1.200	25.90	24.40	7.23	1.24
Brain	2.566	0.454	3.416	0.892	37.92	0.69	25.42	33.00
Muscles	3.070	0.427	2.186	0.812	54.77	7.57	43.68	21.94
L. Kidney	5.252	2.309	*1.816	0.620	63.52	30.03	49.22	5.89
R. Kidney	5.168	1.441	*1.724	0.606	66.00	30.84	41.87	6.45
Kidneys	5.210	1.856	*1.770	0.609	64.76	30.30	45.54	3.47
Liver L. L.	4.874	1.332	3.780	1.207	250.16	345.92	30.65	10.36
Liver R. L.	5.574	1.783	4.140	1.016	274.12	386.89	32.42	10.05
Liver	5.224	1.411	3.960	0.865	262.14	365.87	31.53	9.71

$\bar{x}$ — mean value. *SD* — standard deviation. * Statistically significant result.

Table 3. Levels of manganese and zinc in tissues of patients who died suddenly with normal renal function and patients treated by long-standing dialyses

Tissue examined	Mn µg/g dry tissue				Zn µg/g dry tissue			
	control		sample		control		sample	
	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*	$\bar{x}$	*SD*
Heart	1.004	0.491	1.042	0.345	54.17	30.82	44.05	5.09
Brain	0.658	0.165	*1.148	0.327	39.87	11.87	56.01	34.94
Muscles	0.756	0.276	0.758	0.282	55.99	9.66	36.54	6.30
L. Kidney	1.376	0.421	1.212	0.382	52.19	22.58	39.54	14.07
R. Kidney	1.366	0.342	1.176	0.469	48.19	9.88	39.25	13.82
Kidneys	1.371	0.344	1.194	0.423	50.19	12.53	39.40	13.87
Liver L. L.	1.124	0.242	1.54	0.411	55.29	12.50	46.17	8.12
Liver R. L.	1.266	0.240	*1.726	0.290	61.89	16.54	*42.36	10.46
Liver	1.195	0.188	*1.633	0.334	58.59	10.43	*44.27	8.47

$\bar{x}$ — mean value. *SD* — standard deviation. * Statistically significant result.

DISCUSSION

The changes in the content of copper, zinc and manganese noted in selected tissues of patients who died of chronic renal failure are difficult to interpret. They may be caused by uraemia, but they can also be the result of long-standing dialysotheraphy. No definite conclusions can be drawn as to whether the observed disturbances in the level of trace elements are connected with the main disease, because the study did not include a group of patients with renal diseases not treated by dialyses. Thus, we can only make indirect conclusions, based on the relationships between the levels of the metals examined. With only a single examination it is still more difficult to define which was the cause and which was the result.

The present study has shown the simultaneous decrease in the concentrations of Cu and Zn in tissues. We may presume that this relationship suggests the presence of a common factor disturbing the metabolism of these elements in the patients examined. This cannot be the disturbance of absorption, because it has been stressed many times in literature that Zn and Cu are antagonists with relation to absorption; the increase in the level of zinc impairs the absorption of copper (1, 2, 14, 19). A similar effect is observed in the case of intestinal absorption of other heavy metals e.g. cadmium and it is probably connected with the induction or blocking albuminous carrier — metalotionein (2, 10, 16, 17). The situation is different in the serum of alcoholics, in whom the level of zinc decreases, while the levels of ferrum and copper increase (8). However, it should be kept in mind that the lesion associated with renal failure may disturb the absorption of many trace elements (4).

The decrease of the level of Cu in renal diseases is confirmed by many authors (1, 3, 19). An evident decrease in the level of copper in the kidneys, with a significantly smaller decrease observed in the liver, and an insignificant increase in the cerebral tissue is rather equivalent to the reduction of this element together with the substances binding it (in the case of renal diseases for example they may be proteins). A similar effect occurs during administration of penicillamines (12). In certain conditions zinc may substitute for copper as a double positive ion and behaves similarly (2, 3, 4, 10). In the sample investigated its significant loss is observed in the skeletal muscles, which in a healthy condition are, apart from the liver, the most important zinc storage place (2); here, some authors also metion the kidneys (10). In the samples of the liver examined the level of zinc was on the threshold of significance, while in serious liver diseases it always shows a significant increase or decrease (9).

In cerebral tissues we observed a clear increase in the level of manganese and a slight increase in the content of Cu and Zn. This phenomenon is interesting in the light of the fact that several patients in the study suffered from mental disorders. A conclusion may be drawn that chronic renal failure is accompanied

by an accumulation of the above-mentioned elements in the brain. An increased level of aluminium is becoming increasingly important as a cause of postdialytic encephalopathy (13). Our studies suggest that manganese may also influence this complication.

The examinations carried out did not demonstrate a significant change in the content of ferrum in any of the investigated tissues of patients with chronic renal failure. Therefore, it may be presumed that ischemia typical of renal deficiency is not associated with different distribution of ferrum in tissues. However, due to the tendency observed towards the decrease of the level of copper and zinc, we should take these metals into account as the factors increasing ischemia, which is related to their engagement in the process of hemoglobin synthesis (11, 14, 15). The results of the studies allow us to presume that the observed disturbances in the level of Cu, Zn, Mn in tissues may be of some significance in the pathomechanism of chronic renal failure, especially in hemodialysed patients. Wider studies based on a greater number of patients and experiments conducted on animals would enable us to draw more reliable conclusions.

Conclusions

1. In chronically dialysed patients we noted disturbances in the levels of copper, manganese and zinc in tissues.

2. The observed disturbances may be related to the long-standing treatment by dialyses.

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STRESZCZENIE

Przeprowadzono badania poziomu żelaza, miedzi, cynku i manganu w tkankach 5 pacjentów zmarłych z powodu przewlekłej niewydolności nerek. Grupę kontrolną stanowiło 5 nagle zmarłych osób, u których czynność nerek określono jako prawidłową. Oznaczenie pierwiastków w tkankach przeprowadzono metodą spektrofotometrii absorpcji atomowej, aparatem Evans Electroselenium Limited 240. Stwierdzono zaburzenia tkankowego poziomu miedzi, manganu i cynku, co może łączyć się z prowadzonymi u tych chorych wielomiesięcznymi hemodializami.