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INORGANIC PLASMA FLUORIDE CONCENTRATIONS AND ITS RENAL EXCRETION IN CERTAIN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS IN MAN

by

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SUMMARY: In a study involving 2200 patients the inorganic plasma fluoride concentration (IPFC) increased with increasing age. In a fluoridated (1 ppm) community this increase was more pronounced than in a low fluoride (0.2 ppm) community. The mean renal clearance of fluoride and the daily amounts excreted also increased slightly until age fifty, after which a slow decrease was observed. During pregnancy, IPFC decreased significantly until delivery in both fluoridated and non-fluoridated areas. The daily fluoride excretion was also lower during pregnancy than in controls. Patients with renal insufficiency had a mean IPFC of 3.0 ± 0.45 µmol/l in the fluoridated and 2.0 ± 0.14 in the low fluoride community. Their daily fluoride excretion was less than half of that of the control groups. Regularly hemodialyzed patients showed the highest IPFC. In a 6 year-old boy with diabetes insipidus, the IPFC was four times as high as in the corresponding controls. In diabetes mellitus with renal complications, the IPFC was also elevated. Increased water consumption did not cause greater retention of fluoride. In cardiac insufficiency, with normal serum creatinine the IPFC was only slightly elevated.

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During recent years considerable progress has been made in the methodology for measuring the mean free ionized plasma fluoride or inorganic plasma fluoride concentrations in man. The electrometric method first described by Fry and Taves (1) in 1970, slightly modified, has made it possible to make even epidemiological studies on the pharmakinetics of the fluoride ion in man. The aim of our st dy was to try to determine whether or not certain physiological or pathological changes in man also affect fluoride metabolism. For this study we collected about 1,600 plasma samples from patients of a hospital situated in an artificially fluoridated (1 ppm) community. We also collected about 900 samples of plasma from a hospital in a non-fluoridated community with up to 0.2 ppm fluoride in the water in order to compare the results from the two areas. Finally, altogether about 200 urinary samples were collected from both communities in order to estimate the excretion of fluoride in the urine.

Both methods have been described elsewhere in a monograph (2).

As shown in Table 1 we found mean, free ionized plasma fluoride

TABLE 1

Mean Age and Mean Free Ionized Plasma Fluoride

Mean age in years		Plasma F^- in the non-fluoridated area µmol/l ± S.E.M.		Plasma F^- in the fluoridated area µmol/l ± S.E.M.
2	(4)*	0.72 ± 0.078	(3)	1.0 ± 0.00
7	(29)	0.79 ± 0.029	(78)	1.1 ± 0.033
17	(36)	0.83 ± 0.035	(100)	1.1 ± 0.030
27	(58)	0.87 ± 0.023	(189)	1.2 ± 0.023
37	(77)	0.86 ± 0.021	(148)	1.3 ± 0.042
47	(61)	0.86 ± 0.041	(167)	1.4 ± 0.042
57	(98)	0.89 ± 0.037	(146)	1.5 ± 0.039
67	(84)	0.96 ± 0.031	(125)	1.6 ± 0.039
77	(41)	0.93 ± 0.048	(77)	1.7 ± 0.080
87	(13)	1.0 ± 0.080	(14)	1.8 ± 0.14
TOTAL	(501)		(1083)	
MEAN		0.88 ± 0.0093		1.3 ± 0.00048
		MEAN SIGNIFICANCE	P<0.001	

* Number of patients

concentration in the fluoridated community to be 1.3 µM/l (.024 ppm) and 0.88 µM/l (.016 ppm) in the non-fluoridated area. This means that

the concentrations of ionized fluoride in the plasma were only about 50% higher in the fluoridated area although the difference in the fluoride concentrations of drinking water is five-fold. This subject has been discussed in detail (2).

Table 1 also shows that the ionized plasma fluoride concentrations increase significantly with advancing age in patients from both areas. The increase in the fluoridated area is 80% in the fluoride community and 40% in the non-fluoridated area, when the mean ages of patients range from 2 to 87 years. Thus it is understandable that theregression coefficient is significantly larger in the curve from the fluoridated area when compared with that from the non-fluoridated community. The reason for this predominance probably is the increasing amount of fluoride in bones with age because under normal conditions there must be a chemical equilibrium between the concentrations of the skeletal fluoride and the blood fluoride. The method with which we selected the patients for the study is outlined in my monograph (2).

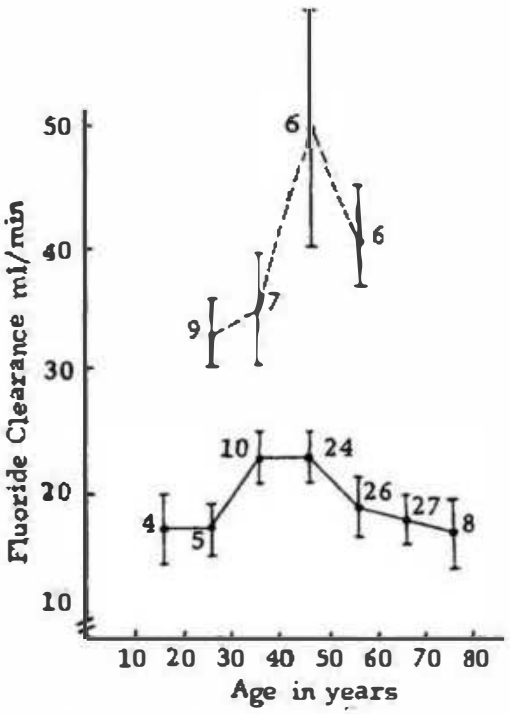
The mean renal clearance of fluoride surprisingly enough was not similar in both areas (Fig. 1). In the fluoridated area it was twice as high as in the non-fluoridated community. Thus the clearance of fluoride differs considerably from clearance of creatinine or inulin probably because fluoride accumulates in the bones in direct proportion to the amount ingested. These mean values are significant when compared with normal control values. It must be remembered however that we measured only plasma ionized fluoride concentrations, but did not correlate the clinical signs of toxicity with fluoride clearance. Another interesting finding was the increase of fluoride clearance with age until about age 50 whereafter a slight decline was found. Our explanation for the increases at the earlier age is a possible slow saturation of bones by fluoride with time which leaves more to be excreted. The decrease in fluoride clearance at an older age could be due to diminishing renal function which is characteristic for older people.

Earlier, Gedalia et al. (3) have shown that the urinary excretion of fluorides decreases significantly during pregnancy. We have also found (Table 2) that ionized fluoride concentration decreased rather steadily until delivery of the baby. Comparison of the earlier finding of Gedalia with ours supports the view that both these results are due to fluoride accumulation in the bones of the developing baby. This finding cannot be the result of a dilution of the plasma volume of the mother during pregnancy which would be more likely to increase than decrease the plasma fluoride concentrations in the mother as seen in preeclamptic patients.

In the non-fluoridated area also the mean, free ionized plasma

Fig. 1

Age and Fluoride Clearance



---- In fluoridated community; —— In low fluoride community.

fluoride concentrations decreased significantly when compared to total "non-pregnant" controls. After delivery the plasma levels of fluoride returned to normal within a few weeks. Women with clinical edema or preeclampsia showed slightly elevated values compared to those whose pregnancy was normal. On the basis of these figures we may conclude that, for the baby which is breastfed, the availability of fluorides is better prior to delivery than after it because of the moderate plasma concentrations. In order to confirm this opinion we also measured the ionized fluoride concentrations of maternal milk and found that after delivery of the baby the ionized plasma fluoride concentrations are the same in maternal milk as in plasma. The fluoride concentrations of the maternal milk are only a fraction of those in the drinking water because these values are in μM/l (1 μM equals 1/3 ppm).

We also studied the effects of certain illnesses on fluoride metabolism, Table 3. In patients with renal insufficiency, we found a correlation between the concentration of serum creatinine and the levels of ionized plasma fluoride, Fig. 2. The mean renal clearance of fluoride was 41 ± 3 ml/min. (S.E.M.) in controls with normal kidney function, which resulted in a mean excretion of 58 μmol/24 hrs.

TABLE 2

Mean Free Ionized Plasma Fluoride Concentrations, Mean Serum Creatinine Values and Mean Ages of Pregnant Women or Women in Labor in Fluoridated Community

		Plasma F^- µmol/l ± S.E.M.	Serum creatinine µmol/l ± S.E.M.	Mean age in years	Significance
In labor	(149)*	0.93 ± 0.023	63 ± 1	26	$p < 0.001$
Pregnant					
0-7 months	(18)	1.15 ± 0.070	64 ± 4	30	$p < 0.05$
8-9 "	(13)	0.87 ± 0.055	67 ± 3	30	$p < 0.001$
10 "	(16)	0.87 ± 0.051	63 ± 3	26	$p < 0.001$
All those pregnant	(48)	0.97 ± 0.039	64 ± 2	29	$p < 0.01$
Edema during pregnancy	(9) (9)	1.1 ± 0.080	66 ± 3	31	$p < 0.05$
Controls of same age	(67)	1.2 ± 0.036	80 ± 2	30	

* Number of patients

TABLE 3

Mean Fluoride Clearance ± S.E.M., Excretion of Fluoride/24 hrs ± S.E.M. and Mean Age of Patient Groups from the Artificially Fluoridated Drinking Water Community

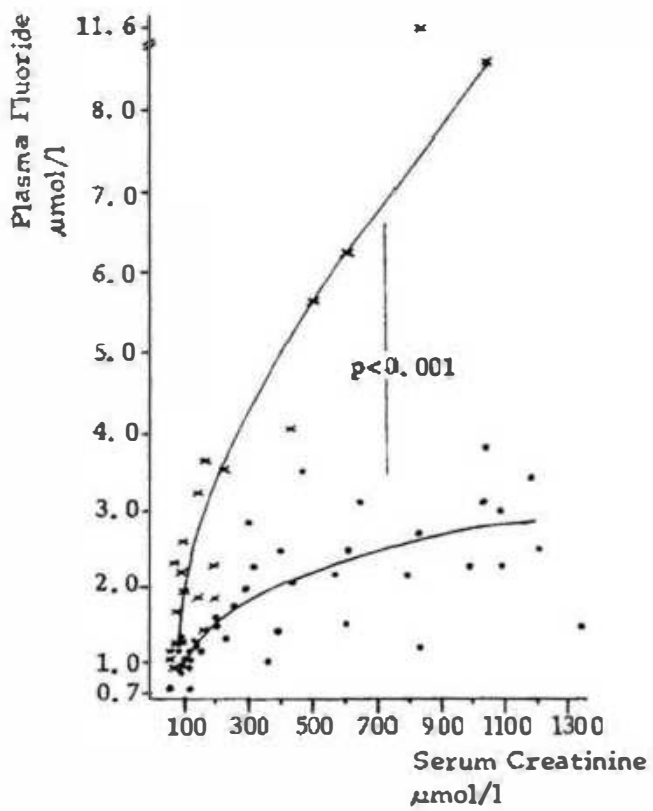
	Renal clearance of fluoride ml/min. + S.E.M.	Daily excretion of fluoride µmol/24 hrs + S.E.M.	Serum creatinine µmol/l + S.E.M.	Mean age in years	N	P_1	P_2
Renal insufficiency	11 ± 3	31 ± 6	649 ± 357	51	5	< 0.001	< 0.05
Diabetes mellitus	16 ± 2	31 ± 10	200 ± 54	35	2		
Pregnancy	44 ± 5	44 ± 4	72 ± 5	27	11		
Controls	41 ± 3	58 ± 5	74 ± 3	38	28		

- Renal insufficiency mean fluoride clearance (P_1) and daily excretion (P_2) are significantly lower than in the controls.

In patients with renal insufficiency, clearance of endogenous fluoride was significantly lower (11 ± 3 ml/min.). The daily urinary fluoride excretion was also lower than in the control group. In two patients with diabetes mellitus, the same tendency was observed as in the group with renal insufficiency. The mean fluoride clearance was 16 ml/min. and the daily excretion 31 µmol/24 hrs. The serum creatinine in these two diabetic patients was higher than normal (105 µmol/l in the woman and 110 µmol/1 in the man). An interesting finding was the slightly lower daily excretion of fluoride in pregnant women. The mean decrease was 14 µmol/24 hrs as compared to the control group. This difference was not significant.

Fig. 2

Correlation Between Serum Creatinine Concentration and Free Ionized Plasma Fluoride in Renal Patients from the Fluoridated Community and Non-Fluoridated Area



(X) represents one patient from the fluoridated community.
(•) represents one patient from the non-fluoridated community.

Table 4 presents data from the artificially fluoridated area. In diabetes mellitus and diabetes insipidus, cardiac insufficiency, liver cirrhosis, LED, cor pulmonale and surprisingly in obstructive icterus we found elevated values. If we excluded patients in whom serum creatinine was elevated the difference from the control group disappeared. Patients with cardiac insufficiency showed elevated values even if serum creatinine was not elevated. Interestingly, patients with hypertension showed significantly lower mean fluoride values than the controls which might be due to the use of diuretic drugs but we did not verify this possibility. Furthermore, sampling in this group was too small for reliable statistical comparisons.

Table 5 shows the corresponding values from the non-fluoridated area with the same disease groups as in Table 3. The only important difference is the fact that here in the cases with hypertension no difference of the free ionized plasma fluoride concentration was noted among those with and without elevated serum creatinine concentration. In patients with LED the mean free ionized fluoride values were significantly higher than in the corresponding control groups.

We also measured the daily excretion of fluoride and the daily renal fluoride clearance in some of the patient groups, (Table 3). The difference between the controls and the patients with renal insufficiency is statistically significant: The mean renal clearance of fluoride was 41 ± 3 in the non-fluoridated controls in subjects with normal kidney function. Endogenous fluoride clearance was significantly lower in patients with renal insufficiency (11 ± 3) and also in diabetes (16 ± 2). However, in both conditions the reduction in fluoride clearance and excretion was more pronounced than in the cases of pregnancy.

In patients with renal insufficiency the mean renal clearance was about one half of that in patients drinking artificially fluoridated water. In addition we found that in patients with cardiac insufficiency the daily excretion of fluoride was somewhat diminished although creatinine values were normal. Therefore it is probable that cardiac disease may also cause at least slight retention of fluoride.

No final conclusions can be made concerning toxicity on the basis of these results because we did not study the clinical phase of fluoride toxicity. However, in patients with severe renal insufficiency the plasma fluoride concentrations were similar to those in patients who received 25 mg of fluoride daily for the treatment of osteoporosis.

TABLE 4

Mean Free Ionized Plasma Fluoride, Mean Serum Creatinine, Mean Ages in the Artificially Fluoridated Drinking Water Community. Comparisons with Control Groups of Same Mean Age and from the Same Community.

		Plasma F^- µmol/l ± S.E.M.	Serum creatinine µmol/l ± S.E.M.	Mean age in years	P
Endocrinic diseases					
Diabetes mellitus (all adult patients)	(70)*	1.7 ± 0.088	118 ± 10	54	<0.05
Diabetes with normal serum creatinine	(46)	1.4 ± 0.058	77 ± 3	52	
Diabetes with elevated serum creatinine	(24)	2.3 ± 0.20	182 ± 27	58	<0.01
Diabetes in children	(18)	1.3 ± 0.056	63 ± 3	11	<0.05
Hyperthyroidism	(10)	1.2 ± 0.11	90 ± 7	54	<0.01
Hypothyroidism	(3)	1.5 ± 0.41	128 ± 21	50	
Diabetes insipidus	(1)	4.0	59 ±	6	
Cardiovascular diseases					
Heart insufficiency (all patients)	(49)	1.9 ± 0.12	117 ± 11	63	<0.05
Heart insufficiency with normal serum creatinine level	(33)	1.8 ± 0.14	84 ± 3	60	<0.05
Heart insufficiency with elevated serum creatinine level	(16)	1.9 ± 0.21	230 ± 66	67	
Heart insufficiency with clinical edema	(8)	2.2 ± 0.33	291 ± 143	62	
Cor pulmonale	(3)	2.6 ± 0.40	121 ± 11	63	
Hypertension (all patients)	(45)	1.2 ± 0.051	91 ± 6	52	<0.001
Hypertension with normal serum creatinine	(34)	1.1 ± 0.045	72 ± 4	45	<0.001
Hypertension with elevated serum creatinine	(11)	1.5 ± 0.11	147 ± 8	59	
Liver diseases					
Liver diseases (all patients)	(7)	2.6 ± 0.33	100 ± 10	52	<0.05
Liver cirrhosis	(5)	2.3 ± 0.33	100 ± 10	53	
Obstructive icterus	(2)	3.5 ± 0.40	100 ± 20	52	
Collagen diseases					
Lupus Erythematos. Dissem.	(3)	2.6 ± 0.70	302 ± 56	56	

* Number of patients

TABLE 5

Mean Free Ionized Plasma Fluoride, Mean Serum Creatinine, Mean Ages in the Non-Fluoridated Drinking Water Community. Comparisons with Control Groups of the Same Mean Age and from the Same Community.

		Plasma F^- µmol/l ± S.E.M.	Serum creatinine µmol/l ± S.E.M.	Mean age in years	P
Endocrine diseases					
Diabetes mellitus (all adult patients)	(36)*	1.1 ± 0.077	174 ± 8	58	<0.01
Diabetes with normal serum creatinine	(18)	0.98 ± 0.052	95 ± 8	57	
Diabetes with elevated serum creatinine	(17)	1.6 ± 0.36	250 ± 48	59	
Hyperthyroidism	(11)	0.95 ± 0.062	67 ± 3	60	
Hyperthyroidism	(5)	1.0 ± 0.14	89 ± 8	67	
Cardiovascular diseases					
Heart insufficiency (all adult patients)	(56)	1.1 ± 0.045	102 ± 6	67	<0.01
Heart insufficiency with normal serum creatinine value	(49)	1.1 ± 0.049	91 ± 3	64	<0.05
Heart insufficiency with elevated serum creatinine value	(7)	1.1 ± 0.10	137 ± 19	70	
Heart insufficiency with clinical edema	(12)	1.3 ± 0.091	134 ± 10	65	<0.05
Hypertension (all patients)	(41)	0.99 ± 0.038	117 ± 9	52	
Hypertension with normal serum creatinine value	(30)	0.95 ± 0.039	91 ± 4	50	
Hypertension with elevated serum creatinine value	(11)	0.94 ± 0.058	147 ± 12	59	
Liver diseases					
Liver diseases (all patients)	(15)	1.1 ± 0.11	105 ± 8	52	
Liver cirrhosis	(10)	0.95 ± 0.095	101 ± 7	51	
Obstructive icterus	(5)	1.4 ± 0.18	107 ± 15	53	
Collagen diseases					
Lupus Erythematos. Dissem.	(9)	1.7 ± 0.20	254 ± 16	43	<0.01

* Number of patients

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Discussion

Dr. Burgstahler: In connection with your analytical studies did you ever look at protein-bound iodine levels as some kind of an index of differences?

Dr. Hanhijarvi: No. We researched only fluoride.

Prof. Jolly: We will have more detailed discussion on renal involvement in tomorrows seminar but I would like to mention that one of the conditions which significantly enhances fluoride toxicity is renal disease of any kind. We have had very few autopsies in our cases but in one case which I remember the patient had originally a polycystic disease of the kidney. He had lived in fluoride areas early in life. In fact, he died of the original disease but the fluoride toxicity was a contributing factor. Similarly the levels of plasma fluoride and fluoride clearances which we have done in our cases along with creatinine clearances are similar to the ones that you have seen in your cases. However, in our cases of fluorosis the levels of plasma fluoride naturally are much higher than yours, namely in the range of 9 to 15 μM of ionic fluoride as compared to about 1.5 in your group.

Question: How does μM compare to mg? I think some of us are not familiar with that.

Prof. Burgstahler: 1/10 mg would be 5.3 μM. .53 would be one hundredth mg.

Dr. Hanhijärvi: Yes we use μM so that there are not so many zeros in the figures.

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