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Fluoride concentrations in blood were studied in relationship to the renal functions. The concentration of total fluoride in whole blood was linearly correlated with the serum creatinine value of patients who had not undergone hemodialysis ($r=0.70$), while that in serum was not ($r=0.17$). This is due to the increase of nonionic fluoride concentration in the clot. Blood fluoride concentrations of patients with hemodialysis and kidney transplantations are also discussed.

Key words : fluoride, renal function, whole blood

Introduction

In recent years, the use of fluorine containing-compounds has been increasing. Especially, destruction of the ozone layer by chlorofluorocarbons has become a problem on a global scale. In the medical field, too, the opportunity for introducing fluorine into the human body has been increasing markedly, e.g; the use of anti-cancer drugs, and antibiotics containing fluorine atoms. In the dental field the usefulness of fluoride for preventing dental caries by means of fluoride-containing tooth paste and rinsing with fluoride, has attracted much attentions in recent years. Many countries admit the fluoridation of drinking water. Such use of fluoride-containing compounds is applied to patients in pathological conditions, too. However, the fate of fluoride in the human body remains largely obscure.

In order to evaluate the fluoride metabolism, we have been studying the forms in which fluoride is present, their contens, and their distributions in the blood (1). Though ionic fluoride and nonionic fluorides are known to be distributed in the serum and clot, most of the previous studies were concerned with only ionic fluoride in the serum. This is due to the fact that the amount of fluoride in the blood is very small and the handling and analyzing of whole blood is difficult. We succeeded to establish an analytical method for determining trace amounts of fluoride ion (ng F) by gas chromatography and a new method (LOPA) for the ashing of organic fluoride (1,2). This LOPA

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This paper is dedicated to the late Professor Takumi Sato, Shiga University of Medical Science.

method is based on the ashing by activated oxygen and makes it easy to analyze the trace amount of fluoride in both the serum and whole blood. This study revealed that ionic fluoride in the serum accounts for only 8 % of the total fluoride in the whole blood. This finding suggested the importance of the evaluation of fluoride in the clot and nonionic fluoride.

In the previous papers, it was revealed that the dynamics of administered fluoride to rats and humans differed in the serum and the clot (3, 4). It was also found that administered organic fluoride was transferred to the clot through the serum. These results showed the importance of the analysis of not only serum ionic fluoride, which has been primarily studied, but also fluoride in the clot and nonionic fluoride.

Many reports have suggested the dependence of in vivo fluoride metabolism on renal function (5-9). Therefore, as a part of our studies on fluoride metabolism in pathological conditions, fluoride in the blood, both in the clot and nonionic fluoride, was analyzed in patients with renal failure.

Subjects and Methods

The study was conducted on 40 patients undergoing hemodialysis (HD), 10 outpatients under observation after kidney transplantation (KT), 40 outpatients with chronic renal failure who had not undergone hemodialysis (RF), and 11 healthy volunteers (HC), giving a total of 101 subjects. For the 40 patients undergoing hemodialysis, the prior duration of which varied from 6 to 159 months, the blood samples were taken just before dialysis was performed. Additionally, three patients were studied, immediately before and after the first introduction of hemodialysis. The 10 outpatients with transplanted kidneys were under observation for periods of between 5 and 110 months after transplantation.

Ionic and nonionic fluoride are distinguished and total fluoride is defined as the sum of these. Nonionic fluoride was converted to ionic fluoride by ashing with a low-temperature oxygen plasma asher (1). Ionic fluoride was measured by the gas chromatographical method (2). Detailed procedures have been mentioned elsewhere (1). Serum creatinine levels and hematocrit values were measured by a standard blood autoanalyzer.

Results

The serum creatinine levels (Cr values) of all patients are plotted against their whole blood total fluoride levels in Fig.1. For the undialyzed patients with renal failure (RF), the whole blood total fluoride level linearly increased with their Cr values. Although the whole blood total fluoride level of the patients with kidney transplants (KT, 115±14 ng F/mℓ: SD; n=10) was higher than that of the healthy volunteers (HC, 77±8 ng F/mℓ: SD; n=11), it was at the bottom of the renal failure group. The hemodialysis patients (HD) are in the high Cr region and distingushable from others.

The average amounts of total fluoride in the serum and clot for each group are shown in Fig. 2(a). Patients with renal failure who had not undergone hemodialysis, were divided into the three following groups; i) with Cr values below 3 mg/dℓ, ii) with Cr values between 3 and 7 mg/dℓ, and iii) with Cr values above 7 mg/dℓ. Fig. 2(a) shows that for these patients the total fluoride levels in the serum were almost constant, regardless of the Cr values. In contrast, the total fluoride levels in the clot increased together with the Cr values. The serum total fluoride level of the hemodialysis patients (92±5 ng F/mℓ of whole blood: SD; n=40) was similar to that of the undialyzed patients with chronic renal failure (86±5 ng F/mℓ: SD; n=40). The overall average of the serum total fluoride level of the healthy control group (36±3 ng F/mℓ: SD; n=11) and the

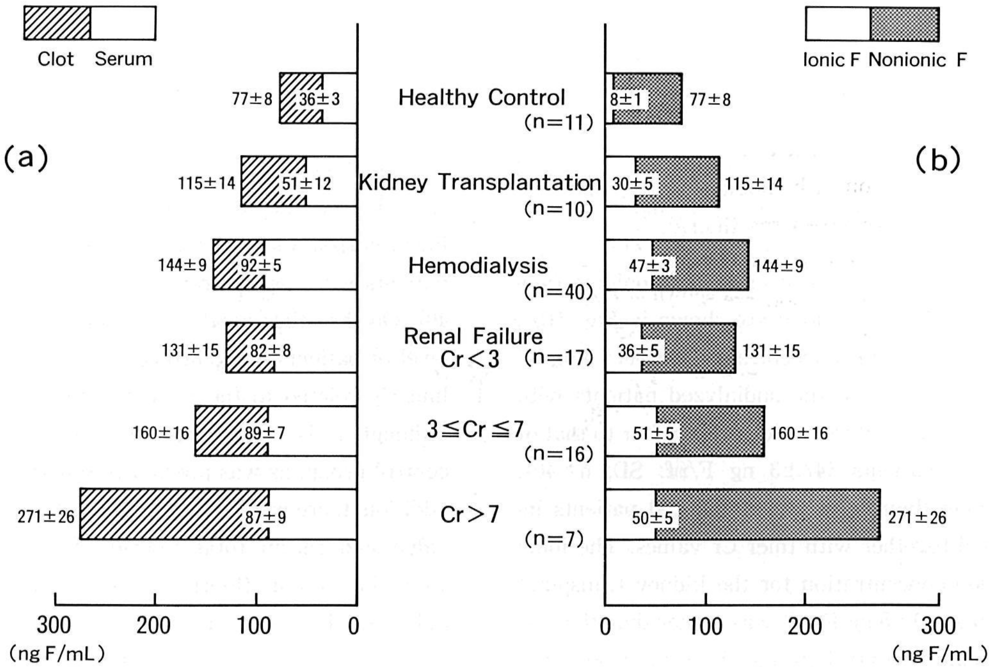

Fig. 1. The relationship between serum creatinine values and whole blood total fluoride levels of patients with renal failure. (The correlation coefficient for Cr and total F of RF=0.70)

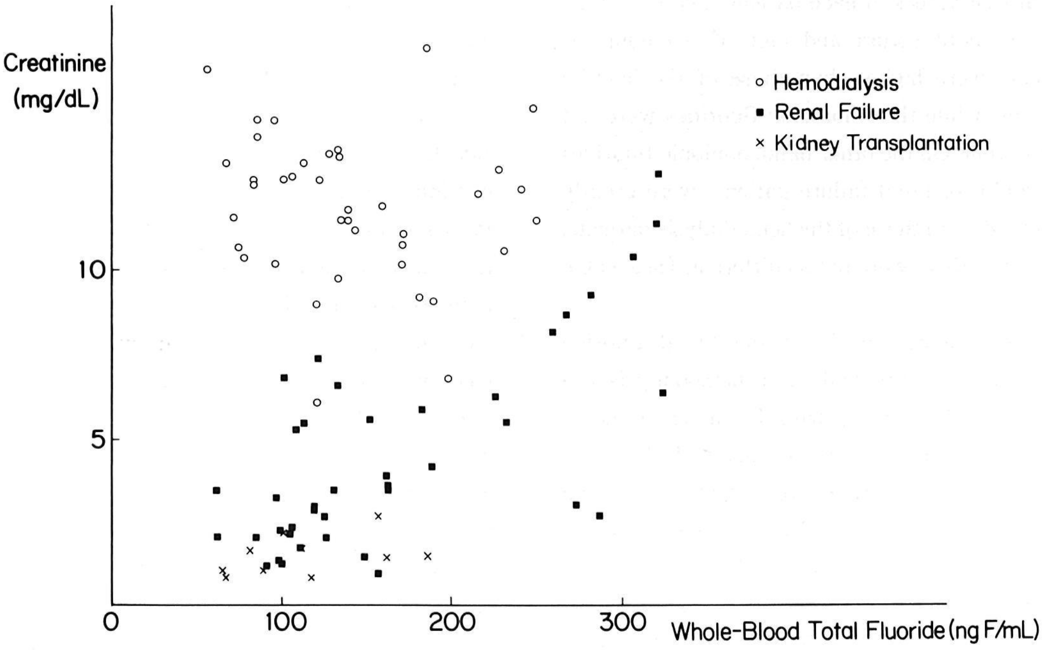

Fig. 2. (a) The distribution of total fluoride in serum and clots of 1 mℓ of whole blood; (b) The distribution of ionic and nonionic fluoride in 1 mℓ of whole blood.

patients with kidney transplants (51±12 ng F/mℓ: SD; n=10) was 43±6 ng F/mℓ of whole blood (SD; n=21), which was much lower than the average values of groups with renal failure (89±3 ng F/mℓ: SD; n=80).

Looking into the detail of the results revealed that the duration of hemodialysis and the age of patients did not affect the fluoride level.

The distributions of ionic and nonionic fluorides in the whole blood are shown in Fig. 2(b). The ionic fluoride concentration was 44±3 ng F/mℓ (SD; n=40) for the undialyzed patients with chronic renal failure, which was similar to that of dialyzed patients (47±3 ng F/mℓ: SD; n=40). Nonionic fluoride of the undialyzed patients increased together with thier Cr values. The ionic fluoride concentration for the kidney transplant patients (30±5 ng F/mℓ) was higher than that for the healthy control group (8±1 ng F/mℓ), but lower than the other groups.

Distributions of ionic and nonionic fluorides in the serum and clot were calculated by using the hematocrit values of each patient. The ionic fluorides in both serum and clot of hemodialysis patients were higher than those of the healthy controls, while thier nonionic fluorides were not so different. On the other hand, nonionic fluorides in the clot of renal failure patients were greatly increased from those of the hemodialysis patients, while the others were not so different. (See Table 1.)

The changes in the whole blood fluoride immediately before and after hemodialysis are shown in Table 2, along with the change in the Cr value and the blood urea nitrogen (BUN) value. The average fluoride concentration of the dialysate used was 6 ng F/mℓ. In contrast to the use of fluoridated water as the dialysate (6,7), no increase was observed in fluoride concentration. The decrease of fluoride levels for the 3 patients measured after one hemodialysis (7-8 ng F/mℓ) was mainly due to the decrease in ionic fluoride, while the Cr and BUN values showed a significant decrease.

Discussion

As shown in Fig. 1, the whole blood total fluoride concentration showed a clear positive linear correlation with the Cr value of undialyzed patients with chronic renal failure (r=0.70; n=40). On the other hand, the serum ionic fluoride level of patients with chronic renal failure is not linearly related to the renal function (r=0.09), although it is higher than that of the healthy control group, as was previously reported (7). In addition, there was no correlation between the Cr value and serum total fluoride (r=0.17) and whole blood ionic fluoride (r=0.03). This result indicates that total fluoride in whole blood is closely related to renal function, since the Cr value is known as one of the major indexes of renal function. Thus, the whole blood total fluoride concentration may serve as a useful index of renal function in judging for starting hemodialysis and following up patients after renal transplantation.

What causes the elevated whole blood fluoride level in patients with renal failure ? One possibility is hypouresis in cases of renal failure. Parson et al. (7) and Spencer et al. (10) reported that urinary fluoride excretion was lower in patients with chronic renal failure than in healthy individuals, and the excretion into sweat and feces were increased. Thus, the elevated blood fluoride level seems to be caused by the decreased urinary fluoride excretion, that is, hypouresis. If hypouresis decreases the urinary fluoride excretion, the excretion of chloride should be also decreased. However, although the increase of chloride level is sometimes found (11), the increase of about 2-3 times relative to the normal is quit rare. Therefore, the increase of fluoride level is not the simple result of hypouresis. Fluoride may be selectively retained against chloride

Table 1. Average distribution and types of fluoride in 1 mℓ whole blood of healthy controls, hemodialysis and renal failure patients

	Serum/ng F		Clot/ng F		
	Ionic	Nonionic	Ionic	Nonionic	Total
Healthy control	6 ± 1	40 ± 4	2 ± 1	29 ± 7	
	46 ± 4		31 ± 6		77 ± 8
Hemodialysis	36 ± 3	56 ± 6	11 ± 1	41 ± 10	
	92 ± 5		52 ± 10		144 ± 9
Renal failure (Cr>7)	35 ± 5	52 ± 10	15 ± 1	169 ± 28	
	87 ± 9		184 ± 28		271 ± 26

Table 2. The changes of fluoride values in the whole blood, the serum Cr and BUN values before and after hemodialysis

Donors	Dialysis	Cr (mg/dℓ)	BUN (mg/dℓ)	Ionic F (ng F/mℓ)	Nonionic F (ng F/mℓ)
1	before	5.2	51	33	134
	after	2.0	15	25	132
2	before	8.9	42	23	98
	after	4.1	18	16	96
3	before	6.7	40	30	91
	after	3.2	15	23	91

in the blood, but to our knowledge there has been no such report.

Another possibility for elevated blood fluoride level is the release of pooled fluoride into the blood. The ingested fluoride is excreted into urine and feces, but at the same time it is stored in bones (12,13). Smith et al. found that fluoride was pooled in bones rather than in soft tissue, in a rabbit model of acute ureteral disturbance (14). Normal fluoride contents in bone are 2000-5000 ppm (15). Renal failure is known to cause bone diseases (16), and thus it may cause fluoride in bone to be released more rapidly.

As shown in Fig. 2(a), the overall average of the serum total fluoride level of the renal failure group (89±3 ng F/mℓ: SD; n=80) was much higher than those of the healthy control group and the patients with kidney transplantations (43±6 ng F/mℓ: SD; n=21). This result indicates that the serum total fluoride level has a maximum value of about 89 ng F/mℓ. Excessive fluoride seems to be accumulated in the clot. However, the accumulated fluoride in patients undergoing hemodialysis and undialyzed patients with chronic-renal-failure was mainly nonionic fluoride (Fig. 2(b)). Ionic fluoride was almost constant at 45±2 ng F/mℓ of whole blood (SD; n=80).

This phenomenon may be well understood by comparing of the ionic and nonionic fluoride distributed in the serum and the clot (Table 1). Only nonionic fluoride in the clot increased as the reduction of renal function (HC<HD<RF). However, other fluorides (ionic fluoride in the serum, ionic fluoride in the clot and nonionic fluoride in the serum) are constant in HD and RF. That is, the reduction in renal function resulted in the increase of nonionic fluoride in the blood clot.

On the other hand, Table 2 shows that only ionic fluoride was decreased by one hemodialysis treatment and nonionic fluoride was unchanged. This indicates that fluoride can be converted from nonionic to ionic. Consequently, repeated hemodialysis gradually reduces nonionic fluoride accumulated. Such transformation of fluoride may take place in the case not only of fluoride decrease in blood but also of fluoride increase.

The structures of substances classified as nonionic fluoride are still unknown. We have reported that the fluoride present in blood could be divided into three types, i.e., ionic fluoride, ionizable fluoride, and covalently bound organic fluoride (1). In this study, nonionic fluoride includes the ionizable fluoride and covalently bound organic fluoride. There is a possibility that most of nonionic fluoride determind in the present study is actually not covalently bound organic fluoride but is "ionizable" fluoride. That is, free ionic fluoride which was overflowed from the serum, might coordinate to protein. Such fluoride may not be analyzed as free ionic fluoride. If it is the case, the blood clot and "nonionic" fluoride play the role of a buffer in preventing too high serum fluoride level. In order to explore the transfer and the conversion of fluoride in blood and thus in order to study the metabolism of fluoride, the ionizable fluoride could a decisive factor. Studies along this line are now in progress.

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腎機能と血中フッ素濃度の相関について

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フッ素の生体内代謝研究の一端として、血中フッ素量と腎機能との関係を検討した。血中フッ素量として全血液中の ionic F と total F および血清中の ionic F と total F を測定した。total F から ionic F を減じたものを nonionic F とした。また腎機能の指標として血清クレアチニン値を用いた。対象は透析患者40名、透析導入には至らない腎不全患者40名、腎移植患者10名および対照としての健常人11名の計101名である。その結果、透析導入には至らない腎不全患者において、全血液中の total F は血清クレアチニン値と正の相関性（r＝0.70）を示し、これは腎機能の低下にともない血餅中の nonionic F が増加するためであることが確認された。また、従来まで検討されてきた血清中の ionic F は濃度の上昇は認められるものの、腎機能との相関性は認められなかった（r＝0.17）。