IONIC, NONIONIC, AND TOTAL FLUORIDE IN HUMAN SERUM

by

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SUMMARY: 97 healthy adults and 13 fluorosis patients living in Tianjin Yangliuqing area were investigated for serum ionic fluoride (F⁻), nonionic fluoride (NF), and total fluoride (TF) concentrations. No sex-related differences in serum F⁻, NF, TF, and the ratios of F⁻/NF and F⁻/TF were observed in healthy adults. Serum F⁻ concentration and F⁻/NF, F⁻/TF of fluorosis patients were significantly higher than those of healthy adults. Both F⁻/NF and F⁻/TF are useful indices of fluoride status.

KEY WORDS: Fluorosis; Ionic fluoride; Nonionic fluoride; Serum fluoride; Total fluoride.

Introduction

It has been demonstrated that there are two forms of fluoride in human serum: ionic fluoride (F⁻) and nonionic fluoride (NF) (bound or organic fluoride). The latter constitutes 80-90% of total fluoride (TF) (1-4).

Results of many studies suggest that serum F⁻ is directly correlated with water fluoride concentration (5-7) or previous intake (8). Serum F⁻ tends to increase with age. However, no sex-related difference has been found (9).

Singer et al. reported that the mean total fluoride concentrations in plasma of individuals who had consumed water containing 0.15-2.5 mg/L fluoride for at least 5 years were similar; concentrations in plasma were only slightly higher when the water supply contained 5.6 mg/L (10). In a similar study, Guy et al. reported that bound fluoride of plasma samples from residents of five cities, whose water supplies contained 0.1-5.6 mg of fluoride per liter, averaged 1.35 μmol/L; it was not related to the fluoride concentration in drinking water (11).

Regarding the relationship between F⁻ and NF or IF, Li et al., who studied the ratio of F⁻/TF, found that both serum F⁻ and F⁻/TF of fluorosis patients was significantly higher than that of normal subjects. The results suggest that F⁻/TF is a useful index on fluoride and health (3). The following presents further study on serum F⁻, TF, NF, and their ratios in healthy adults and in fluorosis patients.

Materials and Methods

Specimens: Blood was collected from each of 97 healthy adults (age 20-44) and fluorosis patients (age 26-62) living in the Tianjin Yangliuqing area where drinking water contains 3.8-4.8 μg/mL of fluoride. The serum obtained by centrifugation was stored frozen until analyzed.

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Analysis: Serum ionic fluoride was determined with an ion selective electrode (Orion 94-09). Total fluoride was determined by measuring the molecular absorption intensity of AlF₃ with an atomic absorption spectrophotometer (3,4). Serum nonionic fluoride was calculated as the difference between total and ionic fluoride concentrations of serum.

Statistics: Means were compared statistically by the Student's t-test.

Results

Sex and Fluoride of Healthy Adults: There are no significant differences in serum F⁻ concentrations and the ratios of F⁻/NF and F⁻/TF for healthy males and females (Table 1). Serum NF and TF concentrations of males were slightly lower, but not significantly (p > 0.05), than those of females. The results indicate that the metabolism of fluoride did not differ for males and females. It is clear from Table 1 that F⁻/NF or F⁻/TF consisted of both F⁻ and NF (or TF), so they are useful indices of fluoride status.

Healthy Adults and Fluorosis Patients: The serum F⁻ concentration of fluorosis patients was statistically higher than that of healthy adults (p < 0.001, Table 2, Figures 1 and 2). Their serum NF concentrations were slightly lower than those of healthy adults (p > 0.05).

| Table 1 |
| Serum F⁻, NF, TF Concentrations and Their Ratios for Healthy Males and Females Residing in the Tianjin Yangliuqing Area. |
|----------|----------|----------|----------|----------|
| F⁻ µg/mL | NF µg/mL | TF µg/mL | F⁻/NF | F⁻/TF |
| Male (n = 46) | 0.046 ±0.011 | 0.298 ±0.097 | 0.344 ±0.097 | 0.173 ±0.068 | 0.143 ±0.047 |
| 0.048 ±0.012 | 0.319 ±0.097 | 0.367 ±0.096 | 0.171 ±0.080 | 0.142 ±0.055 |
| Significance | p = 0.05 | p = 0.05 | p = 0.05 | p = 0.05 | p = 0.05 |
| Values are Mean ±S.D. |

| Table 2 |
| Serum F⁻, NF, TF and Their Ratios in Healthy Adults and Fluorosis Patients Residing in the Tianjin Yangliuqing Area. |
|----------|----------|----------|----------|----------|
| F⁻ µg/mL | NF µg/mL | TF µg/mL | F⁻/NF | F⁻/TF |
| Healthy Adults (n = 97) | 0.047 ±0.011 | 0.309 ±0.098 | 0.357 ±0.097 | 0.174 ±0.075 | 0.144 ±0.052 |
| 0.118 ±0.017 | 0.283 ±0.094 | 0.402 ±0.101 | 0.473 ±0.206 | 0.311 ±0.083 |
| Significance | p < 0.001 | p = 0.05 | p = 0.05 | p < 0.001 | p < 0.001 |
| Values are Mean ±S.D. |

Fluoride
Figure 1
Comparisons of Serum F⁻, NF and TF between Healthy Adults (□, n = 97) and Fluorosis Patients (■, n = 13) in the Tianjin Yangliuqing Area.

Figure 2
Comparison of Serum F⁻/NF and F⁻/TF between Healthy Adults (□, n = 97) and Fluorosis Patients (■, n = 13) in the Tianjin Yangliuqing Area.
The ratios of serum $F^-$/NF and $F^-$/TF of fluorosis patients were significantly higher than those of healthy adults. For example, the ratio $F^-$/NF was 1:5.7 for healthy adults and 1:2.1 for fluorosis patients. The variation of $F^-$/NF in fluorosis patients was perhaps related to the degree of fluorosis.

**Frequency Distribution of Serum $F^-$/NF for both healthy adults and fluorosis patients** was plotted to examine the correlation of, and the differences in, values of $F^-$/NF of both groups (Figures 3 and 4). Since that of $F^-$/TF was the same it was omitted.

In healthy adults, the serum $F^-$/NF of 85.6% of total adults was less than 0.250; 12.4% were within 0.250-0.340; only 2% were within 0.400-0.430, which were distributed inconsistently. The lowest value of serum $F^-$/NF in

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**Figure 3**
Frequency Distribution of Serum $F^-$/NF of Healthy Adults in the Tianjin Yangliuqing Area ($n = 97$).

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**Figure 4**
Frequency Distribution of Serum $F^-$/NF of Fluorosis Patients in the Tianjin Yangliuqing Area ($n = 13$).
fluorosis patients was 0.316. The majority ranged from 0.3 to 0.4; the highest value was 0.913. The variations were due to the degree of fluorosis. The ratios in "healthy adults" residing in the Yangliuqing area where the water supply contains 3.8-4.8 μg/mL of fluoride had a relative meaning. The possibility that some of these persons had a condition of subfluorosis could not be excluded. Two adults with F⁻/NF of 0.400-0.4300 were most likely in a state of subfluorosis. However, in other respects the healthy adults were comparable with fluorosis patients. Only 13 patients were investigated, therefore further study on the frequency distribution of F⁻/NF in fluorosis patients is needed.

Discussion

Serum ionic fluoride constituted 15% of total fluoride for healthy adults, which agreed with other reports (1,3), and 31% for adults with fluorosis. The value of F⁻/NF is larger than that of F⁻/TF because TF is the addition of F⁻ and NF (Table 2).

This study shows that both F⁻/NF and F⁻/TF contain more information than single F⁻ and are useful indices of fluoride status. The value of F⁻/NF or F⁻/TF reflected the damage to normal equilibrium of different forms of fluoride in fluorosis patients. The F⁻/NF or F⁻/TF ratio increases when fluoride intake and/or retention by the body increases, whereas it decreases when intake decreases and/or excretion increases. Thus F⁻/NF or F⁻/TF is helpful for understanding the fluoride status of the body and the changes between different forms of fluoride.

Singer et al. (12) and Ekstrand et al. (13) failed to find the fluoride bound with large molecules and with protein, respectively. Guy et al. isolated a perfluorinated C₈ compound from plasma samples of patients in the United States, the fluorine part of which is not exchangeable with radioactive fluoride (11). However, Venkateswarlu et al. observed that some of the serum NF was ionizable under certain conditions (14). Such problems as the components of, the metabolism of, and the necessity of NF are not completely known.

There may be two sources of serum NF:

1. Some serum component(s) possibly bind(s) F⁻ in order to buffer the harmfulness of high F⁻ and saturate(s) easily at high fluoride intake. NF releases F⁻ for excretion when intake decreases. This mechanism was clearly demonstrated in rats by Ophaug and Singer (15). Whether it exists in humans is unknown. However, Li et al. found that serum NF in monkeys with skeletal fluorosis decreased when osteoarthritis became severe (4). The same occurred in fluorosis patients in this study.

2. Serum NF comes directly from food, air, anesthetics etc. Guy et al. reported that fluoride of plasma was not related to fluoride concentration in drinking water. Serum NF concentrations of rhesus monkeys and male rats were increased after administration of perfluorooctanoic acid (16). Singer and Ophaug analyzed each of the twelve composites of the Food and Drug Administration's young male "Market Basket" food collections and found that nonionic fluoride, as a percent of the total fluoride, ranged from 5% (beverages) to 66% (dairy products) (16). How much serum NF comes from food is also unknown.
Reports on the effect of high NF intake on serum F⁻ and the danger of fluorosis are sparse. Ubel et al. reported that serum NF concentrations of workers exposed to fluoro-chemicals at one plant, which produces ammonium perfluorooctanoate, were 1-71 ppm, and the serum F⁻ concentrations were in the normal range (0.01-0.09 ppm). Upon medical examination of exposed workers, they concluded that no ill health effects were attributable to fluoro-chemical exposure (16). However, Tatiana Davidkova et al. reported that the concentrations of serum ionic fluoride and organic fluoride of 18 ASA physical status 1 or 2 patients increased significantly after the onset of inhalation of isoflurane (17). The difference between the two reports may be due to the different forms of nonionic fluoride ingested. Adequate explanation requires further research.

Conclusion

The metabolism of fluoride was not different for males and females. Serum F⁻, F⁻/NF and F⁻/TF ratios of fluorosis patients were significantly higher than those of healthy adults. Both F⁻/NF and F⁻/TF are good indices of fluoride status.

References


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