FLUORIDE METABOLISM AND RENAL OSTEODYSTROPHY IN REGULAR DIALYSIS TREATMENT

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Summary

Fluoride in plasma, urine and bone tissue ash were estimated using a fluoride-ion electrode in 20 control persons (CP), 32 patients with compensated chronic renal failure (CRFP) and 59 patients in RDT (RDTP). The increase in plasma fluoride (CP: 2.4 ± 1.4, CRFP: 6.5 ± 2.2, RDTP: 12.3 ± 4.5μmol/L) and bone fluoride (CP: 55.1 ± 31, CRFP: 99.9 ± 31.2, RDTP: 339.1 ± 150.6μmol/g) significantly correlated with the decrease of residual glomerular filtration rate (RGFR), in RDT with the number of haemodialyses, so that the maximum increase in fluoride was found in completely anuric patients (379.7 ± 153μmol/g). The increase in fluoride retention was intensified by body retention of considerable amounts of fluoride each dialysis (the fluoridated dialysate increased the post-dialysis plasma fluoride by 195%). Development of bone fluorose known to develop with a bone fluoride greater than 180μmol/g was not found in any of 40 iliac crest trephine bone biopsy specimens. No correlation was found between laboratory and histological findings of renal osteodystrophy and plasma or bone fluoride. No patient developed spontaneous fractures even after 11 years of using fluoridated dialysate. In conclusion, this report indicates that fluoride might have a protective effect against the progression of renal osteodystrophy in patients with high retention values. The longer the exposure of RDT patients to the fluoridated dialysate, the greater the bone fluoride concentration.

Introduction

Uraemic patients on maintenance RDT employing fluoridated water for dialysate preparation absorb and retain considerable amounts of fluoride each dialysis with subsequent long-term storage in bone tissue [1–3]. The incorporation of fluoride in bone results in the formation of fluorapatite with improved mineral
crystallisation leading to reduced chemical reactivity and reduced solubility of the bone mineral [4] following reduction in calcium. The hypocalcaemia results in secondary hyperparathyroidism [5,6] associated with the development of osteomalacia because of poor mineralisation [7], in which increased bone resorption is blocked and only the stimulation of new bone formation is manifest [4]. The high fluoride accumulation in bone induces the activated osteoblasts to produce excessive osteoid in which the collagen fibrils are disarrayed [8]. A somewhat analogous activating effect on the osteoblasts occurs also in chronic renal failure itself.

We have studied 91 chronic renal failure patients before and during RDT to determine quantitatively the bone uptake of fluoride and its influence on bone changes in patients maintained for many years on RDT.

Methods

Twenty control persons and ninety-one uraemic patients aged 21–54 years (48 males and 43 females) were included in this study. The mean duration of RDT was between two (patients with RGFR) and five (patients with anuria) years but in some patients the duration exceeded even 11 years. Forty patients had chronic glomerulonephritis, 21 chronic pyelonephritis, 12 polycystic kidney disease, and 18 other causes of CRF. All patients were receiving aluminium hydroxide when serum phosphate exceeded 2.5mmol/L and/or Ca:P product was over six; oral calcium and/or dihydrotachysterol when serum calcium fell below 2.2mmol/L. Dialysis schedules were individually adapted to maintain a stable clinical status and pre-dialysis blood values below 30mmol/L for urea. On average the patients dialysed three times weekly for six hours. The preparation of the dialysate was performed by means of special decalcification-cation-exchange filter. The dialysate calcium concentration was 1.75mmol/L.

The biochemical determinations were performed by commonly used methods. Parathormone (PTH) was measured by RIA. Fluoride in plasma, urine and bone tissue was estimated using fluoride-selective-electrode [9]. The double iliac crest trephine bone biopsy specimens were obtained from 40 patients with CRF who were dialysed with fluoridated dialysate (14 with RGFR:RDTDP, 26 with anuria:RDTAP), 15 patients waiting for RDT (:CRFT) and 20 control orthopaedic patients (CP) in order: a) to determine tissue fluoride concentration in the bone ash after burning in 400°C and b) to establish the histological criteria of renal osteodystrophy. Biopsies were classified as normal or as showing hyperparathyroid bone disease, osteomalacia, or combined disease. The following parameters were evaluated in four stages in trabecular bone: total bone volume, relative osteoid surfaces and volume, mean width of osteoid seams, trabecular osteoclastic resorption surface, mean size of perosteocytic lacunae, osteoblastic surface, and area of fibrosis.

Results and discussion

Absorbed fluoride is quickly distributed through body fluids. The amount of fluoride in the plasma is determined mainly by the rate of absorption from the
gut, excretion by the kidney and the uptake by calcified tissue [4]. Regulation of plasma fluoride content is effected mainly by the skeletal uptake of fluoride. The skeletal regulation of the body fluoride is faster and quantitatively more significant than the excretion of fluoride by the kidney [10]. These homeostatic mechanisms may be overwhelmed by very large fluoride uptake occurring when patients are dialysed with fluoridated dialysate. Excessive osteoid may be produced and severe osteomalacia may develop [8].

The fluoride concentration of fluoridated tap water and also of our dialysate fluctuated between 20–50 μmol/L. The influence of single haemodialyses on the plasma fluoride of dialysed patients was studied in 22 patients. Mean ± SEM values were 12.9 ± 5.1 μmol/L before and 38.1 ± 5.7 μmol/L after haemodialysis (p<0.0001), i.e. a 195 per cent increase in plasma fluoride after dialysis.

Table I demonstrates mean ± SEM values of fluorides in single patient groups with significant differences between plasma concentrations of CP and CRFP, RDTDP and RDTAP, and between bone tissue ash concentrations of all groups of patients.

TABLE I. Fluoride concentration in plasma and in bone tissue ash in single groups of patients: control persons (CP), patients waiting for RDT in chronic compensated renal failure (CRFP), RDT patients with RGFR (RDTDP), and RDT patients with anuria (RDTAP)

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>n</th>
<th>Plasma fluoride in μmol/L: ‘t’ test</th>
<th>p&lt;</th>
<th>n</th>
<th>Bone tissue fluoride μmol/g: ‘t’ test</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CP</td>
<td>20</td>
<td>2.40 ± 1.40</td>
<td>4.91</td>
<td>0.001</td>
<td>20</td>
<td>55.1 ± 31.0</td>
</tr>
<tr>
<td>CRF</td>
<td>32</td>
<td>6.47 ± 2.2</td>
<td></td>
<td></td>
<td>15</td>
<td>99.9 ± 31.2</td>
</tr>
<tr>
<td>RDTDP</td>
<td>34</td>
<td>10.8 ± 4.5</td>
<td>4.25</td>
<td>0.001</td>
<td>14</td>
<td>263.5 ± 117.54</td>
</tr>
<tr>
<td>RDTAP</td>
<td>25</td>
<td>15.6 ± 2.99</td>
<td></td>
<td></td>
<td>26</td>
<td>379.7 ± 153</td>
</tr>
</tbody>
</table>

Figure 1 shows a significant correlation between fluoride and creatinine clearance in 31 RDTDP (r=0.868, p<0.0001), but a non-significant correlation was found in 28 CRFP (r=0.275, p>0.05). The fluoridated drinking water and/or fluoridated dialysate influence body fluoride concentration of all persons depending on their RGFR. Fluoride absorption from the alimentary tract depends on the solubility of the compound and/or dietary factors, i.e. dietary fat increases their skeletal storage. The fluoride intake from domestic water supplies is too small in comparison with the intake from the fluoridated dialysate during haemodialysis. It seems that when plasma fluoride concentrations are low they are influenced mainly by bone clearance [10] and when in high concentrations by renal clearance. A significant correlation between the fluoride in plasma and in bone tissue in 55 renal insufficiency patients (r=0.97, p<0.05) suggests that the bone flow is the major determinant of fluoride transfer from blood to bone where the fluoride is stored.
Figure 1. Correlation between fluoride clearance ($K_F$) and RGFR (creatinine clearance) in RDT patients.

Fluoride storage in the bone depends on the duration of RDT. Significant correlations between bone fluoride concentration and the number of haemodialyses in RDT ($n=40$, $r=0.75$, $p<0.01$), or the number of RDT-months ($r=0.81$, $p<0.01$), indicate that the longer the exposure of RDT patients to the fluoridated dialysate, the greater bone fluoride storage. The influence of the exposure to uraemia and RDT with fluoridated dialysate play their own part. There are close morphological resemblances between uraemic osteodystrophy and chronic skeletal fluorosis [4], but this most probably is a measure of the involvement of the parathyroid glands in fluorosis. The histological features in bone biopsies are similar in hyperparathyroidism and in osteoporotic patients treated with fluoride [6]. The demonstrable hyperactivity of the parathyroid glands, may be a compensatory phenomenon maintaining the serum calcium at a constant value [1] in fluorosis and also in chronic renal failure. Our results demonstrate a non-significant correlation between plasma and/or bone fluoride and alkaline phosphatase ($r=0.32$), bone isoenzyme of alkaline phosphatase ($r=0.01$), serum calcium ($r=-0.06$), serum PTH ($r=0.162$), and histological and radiological evidence of renal osteodystrophy. We have never found any spontaneous fractures during RDT for as long as 11 years using fluoridated dialysate, but there is a borderline significant correlation between bone fluoride and histological stages of secondary hyperparathyroidism ($r=0.39$, $p<0.05$).

In conclusion, our results show that 1) dialysate fluoridation was not associated with the development of osteodystrophy of the advanced degree found in fluorosis, 2) the longer the exposure of RDT patients to the fluoridated dialysate, the higher is the bone fluoride storage concentration, 3) plasma fluoride is influenced by bone clearance (fluoride sequestration) in low concentrations and largely by RGFR at higher concentrations, 4) our results suggest a certain protective effect of bone fluoride storage against the progression of renal osteodystrophy. It remains to be established whether there exists an upper limit of bone fluoride concentration beyond which the bone would be damaged rather than strengthened.
Acknowledgment

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References

2. Taves D, Freeman RB, Tamm DE et al. Trans ASAIO 1968; 14: 412