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Calcium acetate versus calcium carbonate as oral phosphate binder in pediatric and adolescent hemodialysis patients

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Abstract. Calcium carbonate is widely used as an oral phosphorus binder to control hyperphosphatemia in children on maintenance hemodialysis. Intestinal calcium absorption may induce hypercalcemia, particularly if calcitriol is given simultaneously. In adults, calcium acetate binds phosphorus more effectively than calcium carbonate, while reducing the frequency of hypercalcemic events. We therefore compared calcium acetate with calcium carbonate in nine pediatric patients on long-term maintenance hemodialysis. Following a 1-week withdrawal of phosphorus binders, calcium carbonate was administered for 7 weeks; after a second withdrawal, calcium acetate was given for another 7 weeks. All patients received calcitriol regularly. Both agents lowered the serum phosphorus concentration significantly (calcium carbonate 5.7 ± 1.4 vs. 7.7 ± 2.1 mg/dl, $P < 0.005$; calcium acetate 5.8 ± 1.4 vs. 7.8 ± 2.0 mg/dl, $P < 0.005$). Significantly less elementary calcium was ingested with calcium acetate than with calcium carbonate: 750 (375–1,500) vs. 1,200 (0–3,000) mg calcium/day, $P < 0.0001$. With calcium carbonate serum calcium increased significantly. The number of episodes of hyperphosphatemia or hypercalcemia did not differ between treatments. Intact plasma parathyroid hormone (PTH) decreased significantly with both phosphate binders, and serum 25-hydroxyvitamin D_3 increased. There was a close relationship between serum phosphorus and PTH in prepubertal but not in pubertal patients. We conclude that hyperphosphatemia can be controlled effectively by both calcium acetate and calcium carbonate in pediatric hemodialysis patients. The oral load of elementary calcium is reduced significantly by binding phosphorus with calcium acetate instead of calcium carbonate; nevertheless, hypercalcemic episodes remain equally frequent with both phosphate binders.

Key words: Calcium acetate – Calcium carbonate – Pediatric hemodialysis – Hypercalcemia – Phosphate binder – Parathyroid hormone – Hyperparathyroidism

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Introduction

Secondary hyperparathyroidism in patients with chronic renal failure is partly due to phosphate accumulation in body fluids [1–5]; as a consequence of renal bone disease, growth will be stunted [5, 6]. Pediatric patients on maintenance hemodialysis usually have to ingest large amounts of oral phosphate-binding agents such as calcium carbonate to control hyperphosphatemia [7–11]. About 30% of the calcium ingested is absorbed [12, 13], often leading to hypercalcemia, especially under concomitant therapy with 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] [7–9, 14–17].

Calcium acetate is able to bind phosphate in vitro and in vivo (healthy volunteers) more effectively than calcium carbonate [13, 18]. Clinical studies in adult hemodialysis patients have shown calcium acetate to be more potent than calcium carbonate [12, 18–28] and the oral dose of elementary calcium could be reduced by 50% [12, 19–26, 29]. Results concerning reduction of the incidence of hypercalcemia have been conflicting. In children on maintenance hemodialysis, there has been no study to date of calcium acetate use as an oral phosphate binder. Consequently, we studied the effectiveness and side effects of calcium acetate versus calcium carbonate in pediatric hemodialysis patients.

Patients and methods

Twelve patients entered the study; three of them had to be excluded because of renal transplantation (2) or noncompliance with the treatment protocol (a deaf, mentally handicapped boy who took the same dosage of phosphate binder throughout the study despite repeated instruction of his family). Nine patients completed the study (Table 1). Four were in a prepubertal stage and five in a pubertal stage according to Tanner [30]. All patients were treated by maintenance hemodialysis three times a week using a standard bicarbonate dialysis fluid containing 1.75 mmol/l calcium. All patients were clinically well. Serum phosphorus concentration before the study had been controlled by oral calcium carbonate in the majority of patients and by calcium acetate in the remainder; none of the patients had been treated with phosphate binders containing aluminum. All patients received an oral medication

Table 1. Patient characteristics

Patient no.	Sex	Age (years)	Weight (kg)	Signs of puberty[a]	Underlying disease	Duration of dialysis (months)
1	M	18.0	42.0	Yes	Urinary tract obstruction	15.0
2	M	17.0	37.0	Yes	Alport syndrome	65.0
3	F	9.0	24.0	No	Nephronophthisis	16.0
4	M	19.0	74.5	Yes	Urinary tract obstruction	44.0
5	F	13.0	28.5	Yes	FMF	11.0
6	M	14.0	36.0	No	Nephronophthisis	19.0
7	M	11.0	41.5	No	Urinary tract obstruction	37.0
8	M	12.0	31.0	No	FSGS	14.0
9	F	14.0	31.0	Yes	Urinary tract obstruction	12.0
Mean		14.1	38.6			25.9
± SD		3.2	14.1			18.7

FMF, Familial Mediterranean fever; FSGS, focal segmental glomerulosclerosis

[a] According to Tanner; no, Tanner stage 1; yes, Tanner stage 2–5

of $1,25(OH)_2D_3$ (calcitriol) two or three times a week, which had been started at least 1 month before entry into the study; during the study, two patients had to be switched to daily calcitriol. Six patients took an additional daily vitamin D_3 supplement that had been initiated several months before the beginning of the study, and for a seventh patient vitamin D_3 was administered from the 8th week of the study.

The study lasted for 16 weeks. At the onset, phosphate binders were discontinued for a week ("wash-out 1") and then calcium carbonate was given orally for 7 weeks. This was followed by a second wash-out period of 1 week ("wash-out 2"). During the subsequent 7 weeks calcium acetate was prescribed. Blinding was not done as the two drugs could be distinguished easily by their taste. Randomizing was considered but not undertaken for the following reasons: we knew that most patients' phosphorus level was hard to control with an everyday dialysis routine; hence, in the first part of the study we determined the degree of serum phosphorus lowering that could be achieved using a fixed protocol of adjusting the phosphate binder the patients were familiar with, i.e., calcium carbonate; individual patients' problems could thus be recognized. With calcium acetate, phosphorus levels were maintained in the established range and no further lowering was attempted. Rather than reducing phosphorus levels maximally, we tried to achieve similar levels with both binders for better comparison of the incidence of hypercalcemia. Furthermore, in our dialysis unit with very close patient-to-patient contact previous experience told us that compliance – especially if the medication tastes unpleasant – is easier achieved if the group as a whole takes the same medication at the same time.

Blood samples were drawn weekly for analysis of serum calcium and phosphorus. $1,25(OH)_2D_3$, $25(OH)D_3$, intact parathyroid hormone, (PTH) and alkaline phosphatase were measured at the end of the first wash-out period and after each test period. The dose of phosphate binders was adjusted weekly to the actual predialysis serum phosphate and serum calcium concentration. Target serum phosphorus levels of 4.0–6.0 mg/dl and calcium levels between 9.5 and 11.0 mg/dl were considered acceptable. Levels above the upper limit of the target range were referred to as hyperphosphatemia and hypercalcemia, respectively. In the case of hypercalcemia, phosphate binders were not usually increased.

Phosphate binders were provided in tablet form (Sertürner, Gütersloh). A tablet of calcium carbonate contains 200 mg of elementary calcium, a tablet of calcium acetate 126 mg. The initial dosage was two tablets three times a day with meals, corresponding to 1,200 and 756 mg elementary calcium, respectively. Compliance was checked at each dialysis session.

The serum concentration of total calcium and phosphorus was measured before the first dialysis session of each week, i.e., after an interdialytic interval of 2 days. Calcium, phosphorus, and alkaline phosphatase activity were determined according to automated standard methods (Beckman analyser). Intact PTH was measured with a commercial kit (Nichols, USA, normal range 1.2–6 pmol/l), $1,25(OH)_2D_3$ by high-performance liquid chromatography and radioimmunoassay, and $25(OH)D_3$ by acetonitrile extraction and radioimmunoassay (Schmidt-Gayk, Heidelberg, Germany) [31].

Unless otherwise indicated, only data from defined study weeks were analyzed: 0, 2, 4, 6 or 7, 8, 10, 12, 14 or 15. The incidence of hypercalcemia and hyperphosphatemia was calculated from weekly calcium and phosphorus measurements. Calcium and phosphorus values were normalized using reciprocal transformation and are presented as mean plus or minus standard deviation. All other data are given as median and range. To assess differences between groups, *t*-tests and Wilcoxon tests were used. Differences were considered statistically significant when the *P* value was less than 0.05.

Results

Generally both calcium carbonate and calcium acetate were tolerated well, although some patients complained of calcium acetate being unpleasant to taste and causing gastrointestinal discomfort. There were some problems throughout the study; most patients were somewhat reluctant to

Table 2. Calcium and phosphorus metabolism in nine children on hemodialysis without oral phosphate binder (wash-out), with calcium carbonate, or with calcium acetate[a]

	Wash-out 1	Calcium carbonate	Wash-out 2	Calcium acetate
Serum phosphorus (mg/dl)	7.7±2.1	5.7±1.4*2	7.8±2.0	5.8±1.4*2
Serum calcium (mg/dl)	9.7±0.6	10.2±0.9	10.2±1.0	10.3±1.1
Calcium intake (mg/day)	–	1,200 (0 –3,000)	–	750 (375 –1,500)*5
Alkaline phosphatase (U/l)	184 (86 –526)	179 (69 – 556)	193 (76–489)	216 (36 – 418)
PTH (intact) (pmol/l)	16.0 (1.3 – 75.0)	6.1 (1.0– 20.0)*1	ND	4.3 (1.0– 17.0)*1
1,25-Dihydroxyvitamin D_3(ng/l)	48 (34 – 63)	46 (21 – 73)	ND	48 (36 – 78)
25-Hydroxyvitamin D_3 (nmol/l)	292 (190 –544)	715 (268 – 800)*4	ND	338 (229 – 800)*3

ND, not determined; PTH, parathyroid hormone

*1 $P < 0.05$ vs. wash-out 1; *2 $P < 0.005$ vs. preceding wash-out; *3 $P < 0.05$ vs. calcium carbonate; *4 $P < 0.001$ vs. wash-out 1; *5 $P < 0.0001$ vs. calcium carbonate

[a] Data are median and range except calcium and phosphorus values, which are mean ± SD

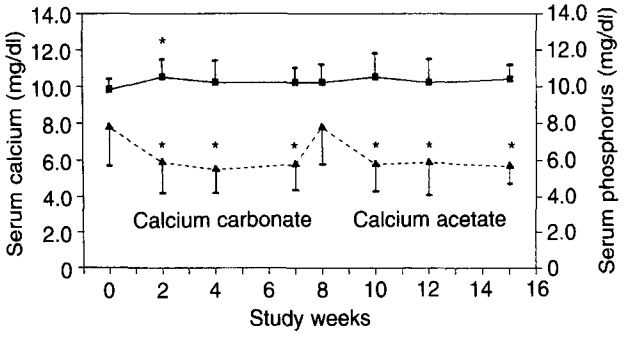

Fig. 1. Serum phosphorus (▲) and calcium (■) concentrations (mean and standard deviation) in nine children on regular hemodialysis with no oral phosphate binder (week 0 and 8 wash-out), with oral calcium carbonate (week 1–7), and with oral calcium acetate (week 9–15). With both phosphate binders serum phosphorus decreased significantly compared with the preceding wash-out period. * $P<0.05$

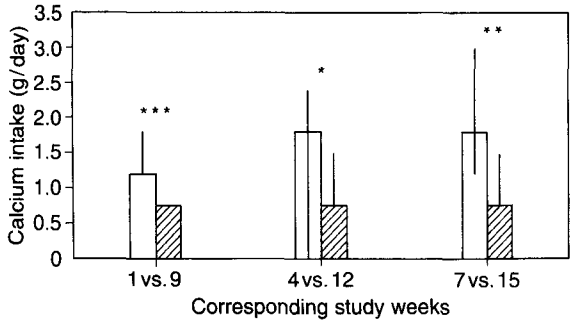

Fig. 2. Daily oral calcium intake (median and range) in the corresponding weeks of treatment with calcium carbonate (*open bars*) and calcium acetate (*hatched bars*) in nine children on regular hemodialysis . * $P<0.01$, ** $P<0.005$, *** $P<0.0001$

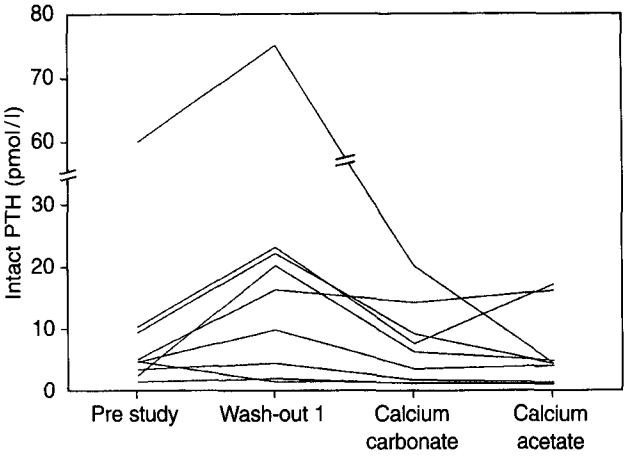

Fig. 3. Individual courses of serum intact parathyroid hormone (*PTH*) in nine children on regular hemodialysis before the study (prestudy), after withdrawal of oral phosphate binder (wash-out 1), with oral calcium carbonate and with oral calcium acetate. Both phosphate binders led to a significant decrease of mean intact PTH compared with the wash-out period

ingest more than their familiar dose of phosphate binder, but regular interviews and tablet countings did not reveal any obvious non-compliance in most patients, and there were no group differences in compliance. The few patients known to be only partially compliant in the past continued to be so during both study periods. At the end of both wash-out periods, the serum phosphorus concentration was elevated to similar mean values of 7.7 ± 2.1 mg/dl and 7.8 ± 2.0 mg/dl respectively, whereas mean serum calcium levels were in the normal range and did not differ from each other (Table 2). Both calcium carbonate and calcium acetate intake led to a significant and successful reduction of serum phosphorus: 5.7 ± 1.4 mg/dl versus 5.8 ± 1.4 mg/dl ($P<0.005$). The serum calcium concentration rose significantly to a high normal range during the 1st week of calcium carbonate medication (9.7 ± 0.6 mg/dl vs. 10.4 ± 0.9 mg/dl, $P<0.05$) (Fig. 1 for comparison of study weeks).

The prescription of phosphate binders in terms of milligrams of elementary calcium necessary to achieve an acceptable and comparable decrease in serum phosphorus levels was significantly less with calcium acetate than with calcium carbonate: 750 mg/day (375–1,500) versus 1,200 mg/day (0–3000), $P<0.0001$, corresponding to 20.5 mg/kg per day (10.0–36.2) versus 39.0 mg/kg per day (0–84.2) (Fig. 2 for comparison of corresponding study weeks). The frequency of hyperphosphatemic episodes per patient was similar in both groups: 2 (0–7). There was no significant difference in the incidence of hypercalcemic episodes between calcium acetate and calcium carbonate medication: 1 (0–4) versus 0 (0–4).

Plasma concentrations of intact PTH, which were in the desired range before the onset of the study (with one exception), rose during the wash-out period and fell significantly both with calcium carbonate and calcium acetate treatment (Fig. 3, Table 2). In three patients (nos. 5, 6, 8) individual values remained very low throughout the whole study period; one was a girl in puberty with familial Mediterranean fever who had very poor control of serum phosphorus and frequent episodes of hypercalcemia. The other two were prepubertal boys; one had frequent episodes of hypercalcemia, whereas in the other calcium and phosphorus were well controlled.

Serum levels of $25(OH)D_3$ increased during calcium carbonate treatment ($P<0.001$) and decreased with calcium acetate ($P<0.05$); the increase was also evident after exclusion of patients who had had their $1,25(OH)_2D_3$ or vitamin D_3 medication changed during the study. $1,25(OH)_2D_3$ and alkaline phosphatase levels did not change significantly throughout the study (Table 2).

In order to identify patients at risk for hypercalcemia, we compared data of patients with a low incidence of hypercalcemia (0 or 1 episode throughout the study, $n=4$) with those with a high incidence (2 or more episodes, $n=5$) during treatment with calcium carbonate or calcium acetate (Table 3). Patients at high risk for hypercalcemia shared several characteristics: younger age, higher serum phosphorus levels and more episodes of hyperphosphatemia, lower serum levels of alkaline phosphatase and $25(OH)D_3$ (all statistically significant). PTH, $1,25(OH)_2D_3$, and daily oral calcium intake (absolute and per kilogram body weight) were not different. As the patients were at different pubertal stages, the different ages of patients prone to hypercalcemia and patients with normal serum calcium level

Table 3. Comparison of patients with low and high frequency of hypercalcemia (median and range)

Parameter	Low frequency of hypercalcemia (n = 4)	High frequency of hypercalcemia (n = 5)	P
Age (years)	15.5 (12–18)	13.0 (9–19)	<0.05
Weight (kg)	34.2 (30.0–43.0)	36.5 (23.5–75.0)	NS
Serum phosphorus (mg/dl)	5.1 (3.0–6.8)	6.2 (3.7–9.1)	<0.01
Serum calcium (mg/dl)	9.5 (8.8–10.8)	11.0 (7.8–13.0)	<0.01
Calcium intake (mg/day)	1,125 (0–2,400)	1,200 (375–3,000)	NS
Alkaline phosphatase (U/l)	296 (216–556)	133 (36–338)	<0.01
PTH (intact) (pmol/l)	6.6 (1.0–20.0)	3.7 (1.1–17.0)	NS
1,25-Dihydroxyvitamin D_3 (ng/l)	58.5 (42–69)	43.5 (21–78)	NS
25-Hydroxyvitamin D_3 (nmol/l)	656 (412–800)	325 (229–800)	<0.01

Table 4. Comparison of pubertal and prepubertal patients (median and range)

Parameter	Pubertal patients (n = 5)	Prepubertal patients (n = 4)	P
Age (years)	17.0 (13–19)	11.5 (9–14)	<0.01
Weight (kg)	37.2 (28.5–75.0)	33.2 (23.5–42.5)	<0.05
Serum phosphorus (mg/dl)	5.8 (3.0–9.1)	5.4 (3.7–8.8)	NS
Serum calcium (mg/dl)	9.8 (8.8–12.8)	10.6 (7.8–13.0)	<0.05
Calcium intake (mg/day)	1,200.0 (0–3,000)	1,162.5 (375–2,400)	NS
Alkaline phosphatase (U/l)	296.0 (69–556)	148.5 (36–253)	<0.05
PTH (intact) (pmol/l)	8.2 (1.1–20.0)	2.5 (1.0–6.1)	<0.05
1,25-Dihydroxyvitamin D_3 (ng/l)	45.5 (21–69)	49.0 (36–78)	NS
25-Hydroxyvitamin D_3 (nmol/l)	484 (229–800)	476 (229–800)	NS

may reflect the different, age-related pubertal stages with concomitant metabolic influences on bone and calcium/phosphorus metabolism. Prepubertal children displayed significantly higher serum calcium concentrations and significantly lower PTH values than pubertal patients (Table 4), but did not show any difference in the number of episodes of hypercalcemia or hyperphosphatemia (data not shown). There was a close linear relationship between serum phosphorus and PTH in prepubertal patients, but not in pubertal patients, regardless of study phase: prepubertal children without phosphate-binding agent $r=0.668$ ($P<0.05$) and with phosphate binder $r=0.981$ ($P<0.01$); pubertal children without phosphate-binding agent $r=-0.228$ and with phosphate binder $r=-0.2182$ (not significant).

Discussion

Several studies in adult patients on chronic hemodialysis have shown calcium acetate to be superior to calcium carbonate in its ability to control hyperphosphatemia [12, 19–28]. The amount of orally ingested calcium taken as calcium acetate needed to bind phosphorus effectively is between 49% and 83% of that ingested with calcium carbonate [19, 21, 29]. Data on the reduction of the incidence of hypercalcemia are conflicting.

In this study we demonstrated that both calcium salts are effective in binding intestinal phosphorus and preventing hyperparathyroidism in pediatric patients on regular hemodialysis. With calcium acetate the mean calcium intake was reduced by 47% compared with calcium carbonate, while the control of serum phosphorus levels was similar. The significant decrease in PTH with both agents shows that there was an efficient reduction of serum phosphorus, although the mean serum phosphorus was only slightly below the upper limit of the target range. Undetected noncompliance may be one explanation for high serum phosphorus levels. But more importantly, in each study phase the phosphate binder dosage could not be increased repeatedly due to hypercalcemia. Finally, as a consequence of our study design phosphorus levels with acetate were expected to be similar to those with carbonate.

Individual PTH courses were variable, mostly showing a prompt increase after withdrawal of phosphate binder, followed by a decrease of the same magnitude after its resumption. Some patients with low normal PTH levels displayed very little change. Their parathyroid was possibly oversuppressed, and they may have suffered from adynamic bone disease [32]. We have no explanation for the high 25(OH)D_3 levels with calcium carbonate.

Our data confirm the efficiency of lowering serum phosphorus found in healthy volunteers [13] and in chronic renal failure patients [12] using the lavage technique. There is no doubt that a given dose of calcium ingested orally as calcium acetate binds more phosphorus in the intestine than the same dose ingested as calcium carbonate. This may be due to the better solubility of calcium acetate regardless of pH [13]. In addition, the elevated binding capacity of calcium acetate for phosphorus seems to be linked with reduced gastrointestinal calcium absorption [13]. It is likely that a larger amount of calcium is bound to alimentary phosphorus with calcium acetate than with calcium carbonate, thus leaving less calcium available for enteral absorption. Thus calcium acetate should be able to control serum phosphorus without producing hypercalcemia.

Results of different calcium acetate studies in adults are not conclusive, demonstrating both a significant decrease [20] and increase [19, 21, 28] or even no change [24] in the incidence of hypercalcemia. Different medication with vitamin D metabolites may in part account for these differences. Caravaca et al. [21] and Pflanz et al. [27] prescribed

no vitamin D metabolites at all, Moriniere et al. [19] prescribed 74 μg/week $25(OH)D_3$, and Schaefer et al. [20] investigated three groups with no $1,25(OH)_2D_3$, with 0.5 μg/day, or 4 μg twice a week. Furthermore, the definition of hypercalcemia varied between the studies: >2.7 mmol/l [24, 27, 28], >2.75 mmol/l [19, 29], >2.86 mmol/l [21], and >3 mmol/l [20]. There was a tendency towards a higher incidence of hypercalcemia in studies using vitamin D metabolites.

In the present study the incidence of hypercalcemic episodes was not different with calcium acetate and calcium carbonate. Under both regimens mean serum calcium levels were not pathologically high. Several explanations may be offered: (1) In contrast to the results of short-term studies with the lavage technique, the better solubility of calcium acetate in the intestinal environment may lead to increased absorption of calcium in the long term, especially if the patients are treated concomitantly with $1,25(OH)_2D_3$. (2) The appetite of the organism for calcium driven by the parathyroid glands may actively counterbalance the changing intestinal calcium supply. With regard to studies reporting an altered (i.e., higher) set-point of serum calcium for supression of PTH secretion in hyperparathyroidism [33], it might be reasonable to accept calcium values up to 12 mg/dl in selected patients if good serum phosphorus control is achieved. (3) Patients with a relatively low bone turnover rate may be prone to hypercalcemia as calcium is not deposited in the bone matrix [11, 32]. In the present study, a high incidence of hypercalcemia was in fact associated with indirect biochemical signs of a low bone turnover rate, e.g., a relatively low alkaline phosphatase. As no bone biopsies were performed and direct markers of bone turnover were not studied, we can only speculate that these signs may have reflected adynamic bone disease. Conversely, biochemical signs of active bone metabolism associated with relatively low serum calcium levels were found in the subgroup of pubertal children, a phenomenon possibly brought about by the endocrine changes at puberty, more osteitis fibrosa-like type of bone disease, and unknown factors that might also explain the lack of correlation between serum phosphorus and PTH in these patients.

Although calcium acetate is effective, it is very unpleasant to taste. There is a problem of gas production in the stomach with a bitter taste ascending, even some hours after ingestion. The ideal phosphate binder for children with renal failure is not yet available. It would be desirable for a stronger preparation of calcium acetate to be available, e.g., containing 250 mg of elementary calcium per tablet. The number of tablets to be taken by the patient could thus be reduced, which would assist compliance.

In conclusion, calcium acetate is a potent oral phosphate-binding agent and useful in children on chronic hemodialysis. The oral calcium intake can be reduced by about 50% (compared with calcium carbonate) without losing any phosphate-binding capacity; nevertheless the problem of hypercalcemia remains. It is speculated that an increased risk of hypercalcemia is related to a low bone turnover rate. Further studies should be undertaken to clarify the role of different types of renal bone disease and the possible hormonal effects at different stages of puberty in the pathogenesis of hypercalcemia under oral phosphate-binding agents and vitamin D analogues in children on chronic hemodialysis.

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Literature abstract

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Smooth muscle tumors associated with X-linked Alport syndrome: carrier detection in females

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X-linked Alport syndrome (AS) associated with diffuse esophageal leiomyomatosis (DL) has been reported to be due to deletions removing the 5′ ends of both the COL4A5 and COL4A6 genes, encoding the α5 and α6 chains of type IV collagen, respectively, whereas a variety of mutations in COL4A5 has been identified in patients with AS alone. Here we report three additional DL-AS patients who also display deletions removing the 5′ ends of both COL4A5 and COL4A6 genes. Furthermore, we tracked the mutation in 15 females belonging to six DL-AS families by gene copy number determination. We found that, like AS, DL is transmitted as an X-linked dominant trait but, contrary to AS, DL is fully penetrant and completely expressed in females. These results are in agreement with our previous work suggesting that DL could be due to a dominant effect of an abnormal α6(IV) collagen chain. Finally, we have detected a similar deletion of the COL4A5 and COL4A6 genes in a DL affected female who showed no sign of nephropathy, demonstrating the AS carrier status of this DL patient. These results emphasize the importance of molecular analysis of female DL patients for genetic counseling.