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Immobilization and hypercalciuria in children

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Abstract Intermediate-term immobilization may lead to an increase in serum and urinary calcium. In order to test this hypothesis, we evaluated 46 children, 21 with Legg–Calvé–Perthes disease (LCP; 7.2 ± 1.8 years old) and 25 with developmental dysplasia of the hip joint (DDH; 10 ± 5 months of age), submitted to immobilization for up to 16 weeks. These two conditions require intermediate-term immobilization as treatment modality, and no studies evaluating calcium metabolism in these groups of patients have been conducted. In LCP patients, blood and 24-h urine samples were obtained before the beginning of treatment and after 1, 6, 8, 14 and 16 weeks of immobilization, while in DDH patients, blood and spot urine samples were collected before treatment and after 6 and 14 weeks of treatment. Urinary calcium, creatinine, potassium and sodium as well as serum calcium, phosphorus, parathyroid hormone, creatinine and alkaline phosphatase were determined in those samples. Renal ultrasound was performed before and after treatment. A mean increase of 2.3 times baseline values of urinary

calcium was observed in 40% of previously normocalciuric LCP patients after only 1 week of immobilization. Among the DDH children, who had never previously ambulated, there was no significant variation in the urinary calcium excretion. None of the serum parameters changed in either group throughout the study. Urinary stones were not evidenced by renal ultrasound. Therefore, the present data suggested that intermediate-term immobilization led to a transient increase in urinary calcium in 40% of LCP patients. Complications such as urinary stones were not observed. In conclusion, this modality of treatment does not impose an increased risk of urinary stone formation in LCP and DDH patients.

Keywords Immobilization · Bone · Legg–Perthes disease · Hip dislocation, congenital · Calcium · Calcium metabolism disorders

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Introduction

The calcium concentration in the extracellular fluid, which plays a role in various physiologic processes, is balanced by the gastrointestinal tract, bone and kidneys. Hypercalcemia occurs when the calcium input into the blood compartment is higher than the output [1]. Orthopedic immobilization leads to increased bone resorption, causing both serum and urine calcium levels to rise, increasing the risk of stone formation [2–4]. Individuals with high bone turnover levels, such as children, are especially sensitive to such effects [3–6]. Intermediate-term immobilization in children is mandatory in Legg–Calvé–Perthes disease (LCP) and developmental dysplasia of the hip joint (DDH).

Interruption of blood supply to the bones is an important etiological factor of bone diseases. LCP is a typical form of avascular necrosis of the femoral epiphysis ossification center which occurs more often among boys (4:1 to 5:1) between 2 and 12 years old [7]. Treatment consists of keeping the epiphysis in the acetabulum until re-ossification is complete. This is achieved with bilateral orthosis, holding the hips abducted 45° and internally rotated ($5\text{--}10^\circ$) [7].

After 6 weeks of immobilization, the orthosis is removed but the patient remains in bed for 2 weeks. Depending on the results of radiological evaluation, a new 6-week period of immobilization is initiated and the process is repeated until maturation of bone epiphysis [7].

DDH is a condition of abnormal development of the hip, resulting in hip joint instability and potential dislocation. This condition often develops over the first few weeks, months, or years of life. The purpose of the treatment is to replace the head of the femur into the acetabulum and, by applying constant pressure, to enlarge and deepen the socket. Immobilization is maintained for 14 weeks, but usually the knees are freed after 6–8 weeks, [8].

In view of the potential risk of developing immobilization-induced hypercalcemia and/or hypercalciuria due to bone resorption, the aim of the present study was to evaluate the effects of intermediate-term immobilization on calcium metabolism in LCP children, who were weight bearing prior to their immobilization, as opposed to DDH children, who were not.

Patients and methods

Forty-six children were included in the study, 21 with LCP (all male, 7.2±1.8 years old, range 4–11 years) and 25 with DDH (6 male, 19 female, age 10±5 months, range 4–17 months).

Blood and urine samples from LCP patients were obtained before the commencement of treatment and after 1, 6, 8, 14 and 16 weeks of immobilization (all patients were ambulating before immobilization). In DDH patients, samples were obtained before treatment, after 6–8 weeks of immobilization and again at 14 weeks. Twenty-four-hour

urine samples were obtained from LCP patients, and morning fasting spot urine samples from DDH patients for determination of calcium (UCa), creatinine (UCr), potassium (UK) and sodium (UNa). Samples not properly collected were discarded. Blood was drawn between 8.00 and 11.00 a.m. for determination of calcium (Ca), phosphate (P), parathormone (PTH), creatinine (Cr) and alkaline phosphatase (AP).

Intact serum PTH was determined by a immuno-radio-metric assay [9]. Calcium was determined by a colorimetric method (o-cresolphthalein complexone method) and expressed per kilograms of body weight (BW) in 24-h urine samples, or corrected by urinary creatinine in spot urine samples according to the literature [10–12].

In DDH children, the normal upper limit for UCa/UCr in spot urine samples was considered to be 0.81 mg/mg for children 4–12 months of age and 0.56 mg/mg for children 1–2 years old [10]. In LCP children, the diagnosis of hypercalciuria was established when urinary 24-h excretion of calcium by BW was higher than 4 mg/kg/24 h [13, 14].

Statistical analysis was performed by means of a two-tailed paired *t*-test (vs baseline values) and a *p* value <0.05 was considered significant.

Renal ultrasound was performed before immobilization in 35 patients and after the treatment in 27 patients.

The institutional medical ethics committee approved the study and all parents signed the informed consent form.

Results

In LCP patients, mean UCa/kg/24 h levels were not statistically significantly different from baseline at any time after immobilization (Table 1). Among the 21 LCP

Table 1 Parameters in LCP children

Parameter		Basal	1 week	6 weeks	8 weeks	14 weeks	16 weeks
UCa/kg/24 h (mg/kg/day)	Mean±SE	3.8±0.6	4.0±0.9	3.0±0.8	3.2±0.9	2.7±0.6	2.1±0.5
	Median	3.5	4.1	2.2	2.6	3.0	1.8
	<i>n</i>	(21)	(16)	(16)	(17)	(14)	(17)
Ca (mg/dl)	Mean±SE	9.7±0.2	9.6±0.1	9.4±0.2	9.7±0.2	9.8±0.2	9.6±0.2
	Median	9.7	9.6	9.4	9.8	9.7	9.6
	<i>n</i>	(19)	(19)	(19)	(18)	(15)	(17)
P (mg/dl)	Mean±SE	5.0±0.3	5.6±0.2	4.6±0.1	4.8±0.2	5.0±0.2	4.6±0.1
	Median	5.3	5.6	4.7	4.7	5.0	4.4
	<i>n</i>	(20)	(19)	(19)	(18)	(15)	(17)
Cr (mg/dl)	Mean±SE	0.7±0.1	0.7±0.1	0.6±0.1	0.7±0.1	0.7±0.1	0.7±0.1
	Median	0.7	0.8	0.6	0.6	0.7	0.6
	<i>n</i>	(19)	(18)	(20)	(18)	(14)	(17)
PTH (pg/ml)	Mean±SE	13.3±1.5	16.0±1.3	13.0±1.5	15.5±1.5	19.2±2.6	21.2±1.2*
	Median	12.3	16.4	13.0	14.0	16.3	20.5
	<i>n</i>	(10)	(8)	(14)	(14)	(16)	(16)
AP (U/l)	Mean±SE	429±32	395±23	396±23	422±22	440±29	451±41
	Median	388	402	385	422	421	429
	<i>n</i>	(19)	(17)	(20)	(18)	(15)	(15)

SE, standard error; *n*, number of samples

**p*<0.05

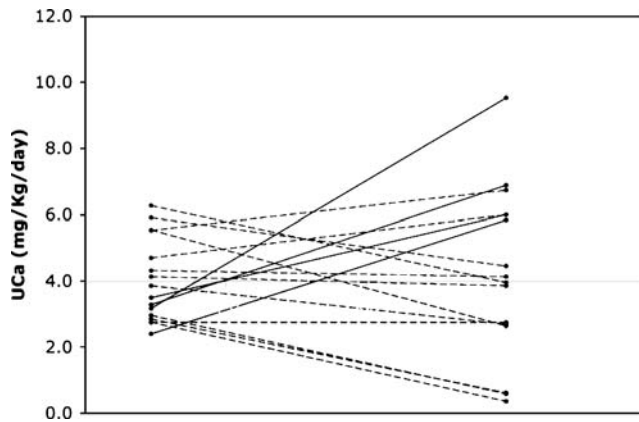


Fig. 1 UCa in LCP children at baseline and after 1 week of immobilization ($n=17$; 7 hypercalciuric and 10 normocalciuric at baseline)

patients, 7 were already hypercalciuric at baseline and 14 were not (data not shown in tables). From these 14 normocalciuric patients at baseline only 10 had collected properly the 24-h urine sample after the first week. We observed an increase in urinary calcium after the first week in 4 out of these 10 normocalciuric patients (Fig. 1, continuous lines). Urinary calcium returned to normal levels in the subsequent samples in the latter group. Conversely, five of the hypercalciuric patients remained with high urinary calcium levels in the majority of the subsequent urine collections.

The mean values of serum parameters (Ca, P, Cr, PTH, AP) and other urinary parameters (UNa, UK, UCr) did not change throughout the study.

In DDH children, no significant variations were found in the mean serum or urinary parameters evaluated (Table 2). None of the patients became hypercalciuric during the immobilization period.

Renal calculi were not detected in any patient at baseline (35 examinations performed). At the end of the study, from

a total of 27 ultrasound scans performed (15 for LCP and 12 for DDH children), no calculi had been detected.

Discussion

On the basis of studies in immobilized subjects [15, 16] and experimental in-flight studies [17], the existence of an imbalance between bone formation and resorption may induce a loss of skeletal mass, leading to osteoporosis, hypercalcemia, and hypercalciuria, with the attendant risk of nephrolithiasis.

Hypercalciuria after long-term immobilization is a well-reported event [4–6, 15, 16, 18–21], but to the best of our knowledge, no studies analyzing children with DDH or LCP with regard to calcium metabolism have been conducted.

In the majority of the studies, calcium urinary output rises after 1 week of immobilization and reaches its zenith at 6 weeks. After this period, calciuria usually decreases [16, 19, 22]. In the present study, a similar pattern of urinary calcium increase was observed in four previously normocalciuric LCP patients (40%) after 1 week of immobilization, with urinary calcium excretion returning to baseline values after 6 weeks and remaining normal until the end of the study. Although it is known that hypercalciuria may develop in 10% of the normal population [18], the existence of hypercalciuria at baseline in some of the LCP patients remains to be clarified. In any case, it is noteworthy that most of these patients remained hypercalciuric. Therefore, despite the fact that none of these hypercalciuric patients developed renal stones during the period of study, these children must be monitored long after the end of immobilization because of the potential risk.

Conversely, no significant variation has been detected in calcium excretion among DDH patients. Some factors may have contributed to the lack of a transient increase in calciuria in this group. First, as opposed to the LCP children, on grounds of age the DDH had never ambulated

Table 2 Parameters in DDH children

Parameter		Basal	6–8 weeks	14 weeks
UCa / UCr (mg/mg)	Mean±SE (n)	0.25±0.08 (15)	0.16±0.03 (7)	0.15±0.03 (6)
	Median	0.2	0.1	0.2
Ca (mg/dl)	Mean±SE (n)	10.0±0.2 (21)	10.1±0.2 (11)	10.3±0.2 (10)
	Median	10.1	10.2	10.35
P (mg/dl)	Mean±SE (n)	6.4±0.4 (21)	5.5±0.2 (12)	5.5±0.4 (9)
	Median	6	5.5	5.5
Cr (mg/dl)	Mean±SE (n)	0.8±0.2 (21)	0.5±0.0 (13)	0.6±0.0 (10)
	Median	0.5	0.5	0.6
PTH (pg/ml)	Mean±SE (n)	18.1±1.9 (16)	17.4±1.7 (9)	19.3±2.3 (6)
	Median	15.78	15.81	19.92
AP (U/l)	Mean±SE (n)	476±23 (21)	461±21 (13)	450±21 (9)
	Median	456	434	449

SE, standard error; n, number of samples

* $p<0.05$

before immobilization. Since they had never been under the effect of impact load, it is possible to speculate that immobilization-induced bone resorption did not provoke a higher calcium output sufficient to produce an increase in calciuria. This phenomenon has been described among paraplegics [23]. Second, hypercalciuria may have been missed due to the fact that the first urine sample was obtained only after 6 weeks of immobilization, when the need for orthopedic treatment control dictated the return of the patients. We are aware that the gold standard to evaluate hypercalciuria is a 24-h urine sample, but the young age of these children rendered this method difficult.

In the present series, none of the patients presented hypercalcemia. This is in accordance with other authors' findings, demonstrating that in previously healthy subjects immobilization-induced hypercalcemia is not a common event [15], as opposed to the observations in critically ill subjects [24, 25]. Hypercalcemia may ensue also when renal excretion of calcium is impaired by renal dysfunction [4, 26], which was not the case in the present study.

Parathyroid-1,25-dihydroxyvitamin D axis is usually suppressed in patients with immobilization-induced hypercalciuria, as would be predicted by a model of resorptive hypercalciuria [15]. Accordingly, we did not find abnormal levels of PTH or serum P in our children after immobilization. In a study conducted by Zerwekh et al. [16], serum biochemical markers of bone formation such as alkaline phosphatase (bone-specific) did not change significantly, while all resorption markers exhibited significant increases. In the present study, no significant variations in AP levels were observed, and despite the fact that resorption markers were not evaluated, the lack of sustained increase in calciuria suggest that bone resorption might not have been of an important magnitude in LCP patients.

As hypercalciuria was not present in all children and was not long-lasting in some of the LCP children, no calculi were observed in the present series, in accordance with the study of Andrews et al. [3] in immobilized children due to fractures. Renal function was also not affected during the period of our observation.

In conclusion, the present study seems to show that therapeutic immobilization leads to a transient increase in urinary calcium after the first week in some of previously normocalciuric LCP patients but not in DDH patients. Serum calcium values remained unchanged and no renal complications due to intermediate-term immobilization were observed, rendering this treatment modality safe with respect to the consequences on calcium metabolism.

References

- Bushinsky DA, Monk RD (1998) Electrolyte quintet: calcium. *Lancet* 352:306–311
- Pak CY (1991) Etiology and treatment of urolithiasis. *Am J Kidney Dis* 18:624–637
- Andrews PI, Rosenberg AR (1990) Renal consequences of immobilisation in children with fractured femurs. *Acta Paediatr Scand* 79:311–315
- Muller CE, Bianchetti M, Kaiser G (1994) Immobilization, a risk factor for urinary tract stones in children. A case report. *Eur J Pediatr Surg* 4:201–204
- Rosen JF, Wolin DA, Finberg L (1978) Immobilization hypercalcemia after single limb fractures in children and adolescents. *Am J Dis Child* 132:560–564
- Bergstrom WH (1978) Hypercalciuria and hypercalcemia complicating immobilization. *Am J Dis Child* 132:553–554
- Wang L, Bowen JR, Puniak MA, Guille JT, Glutting J (1995) An evaluation of various methods of treatment for Legg-Calve-Perthes disease. *Clin Orthop Relat Res* 225–233
- Wenger DR, Bomar JD (2003) Human hip dysplasia: evolution of current treatment concepts. *J Orthop Sci* 8:264–271
- Vieira JG, Nishida SK, Kasamatsu TS, Amarante EC, Kunii IS (1994) Development and clinical application of an immuno-fluorometric assay for intact parathyroid hormone. *Braz J Med Biol Res* 27:2379–2382
- Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP (1997) Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. *J Pediatr* 131:252–257
- Perrone HC, dos Santos DR, Santos MV, Pinheiro ME, Toporovski J, Ramos OL, Schor N (1992) Urolithiasis in childhood: metabolic evaluation. *Pediatr Nephrol* 6:54–56
- Cillo AC, Cattini H, Boim MA, Schor N (2001) Evaluation of lithogenic elements in urine of healthy newborns. *Pediatr Nephrol* 16:1080–1083
- Perrone HC, Ajzen H, Toporovski J, Schor N (1991) Metabolic disturbance as a cause of recurrent hematuria in children. *Kidney Int* 39:707–710
- Stapleton FB, McKay CP, Noe HN (1987) Urolithiasis in children: the role of hypercalciuria. *Pediatr Ann* 16:980–981, 984–992
- Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE (1982) Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. *N Engl J Med* 306:1136–1140
- Zerwekh JE, Ruml LA, Gottschalk F, Pak CY (1998) The effects of twelve weeks of bed rest on bone histology, biochemical markers of bone turnover, and calcium homeostasis in eleven normal subjects. *J Bone Miner Res* 13:1594–1601
- Collet P, Uebelhart D, Vico L, Moro L, Hartmann D, Roth M, Alexandre C (1997) Effects of 1- and 6-month spaceflight on bone mass and biochemistry in two humans. *Bone* 20:547–551
- Heilberg IP (2004) Hypercalciuria. In: Martini L (ed): *encyclopedia of endocrine diseases*, vol 2. Academic Press, San Diego, CA, pp 530–536
- Donaldson CL, Hulley SB, Vogel JM, Hattner RS, Bayers JH, McMillan DE (1970) Effect of prolonged bed rest on bone mineral. *Metabolism* 19:1071–1084
- Uthoff HK, Jaworski ZF (1978) Bone loss in response to long-term immobilisation. *J Bone Joint Surg Br* 60-B:420–429
- Winters JL, Kleinschmidt AG Jr, Frensilli JJ, Sutton M (1966) Hypercalcemia complicating immobilization in the treatment of fractures. A case report. *J Bone Joint Surg Am* 48:1182–1184
- Stark H, Barnett HL, Edelmann CM Jr (1965) Renal effects of hypercalciuria in immobilized children. *Proc Soc Exp Biol Med* 118:870–872
- Elias AN, Gwinup G (1992) Immobilization osteoporosis in paraplegia. *J Am Paraplegia Soc* 15:163–170
- Uran Moreno M, Alonso Riofrio R, Moliner Robredo C, Pons Morales S, Lopez-Herce Cid J (2001) Hypercalcemia due to immobilization in critically ill children: calcitonin treatment. *An Esp Pediatr* 54:555–558
- Clouston WM, Lloyd HM (1987) Immobilization-induced hypercalcemia and regional osteoporosis. *Clin Orthop Relat Res* 247–252
- Prince RL, Eisman JA, Simpson RW (1983) Hypercalcaemia in association with renal failure: the role of immobilisation. *Aust N Z J Med* 13:8–10