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Original Article

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The pathogenetic influence of I-parathyroid hormone on slipped capital femoral epiphysis. Towards a new etiologic approach?

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Abstract

The displacement of the femoral head along the upper femoral physis that occurs during adolescence or slipped capital femoral epiphysis (SCFE) is not a very common traumatic entity. Ever since Müller[1] first described it in 1888, its symptoms, clinical manifestations, diagnosis, treatment and complications have been thoroughly described and studied. Nevertheless little progress has been accomplished as far as its etiology is concerned. In order to assess the potential pathologic influence of any parathyroid hormone (PTH) disturbances on the development of SCFE, we conducted a prospective clinical study with 14 patients, 7 boys and 7 girls (16 hips), suffering from SCFE (Group A). Another 5 patients who had been treated for SCFE a few years before the study, were used as a control group (Group B). We measured the level of I-PTH along with serum calcium (Ca) and phosphorus (P) levels. Furthermore, we checked all the necessary anthropometric characteristics of the patients (i.e., age, height, weight and sexual maturation). Each patient of Group A was categorized from grade I to grade V according to the progress of the slipping. The results showed an increased incidence of serum PTH level abnormalities (both decrease and increase) in Group A while Group B patients had normal results. The detected I-PTH serum level abnormalities were not in any pattern related to the Ca and P serum levels. We believe that a temporary parathyroid hormone disorder during the early years of adolescence may play a potentially significant role (along with other etiologic factors) in the development of SCFE.

Keywords: Parathyroid Hormone, Slipped Capital Femoral Epiphysis, Epiphysiolysis, Injury of the Hip, Childhood

Introduction

The displacement of the femoral head along the upper femoral physis that occurs in adolescence during a period of rapid growth, is called "epiphysiolysis of the upper femoral epiphysis" or "slipped capital femoral epiphysis" (SCFE). The weakened upper femoral physis, under the shearing stress which is forced by the continuously increasing body weight, is fractured and displaced posteriorly and inferiorly. The SCFE is a type I fracture according to the Salter & Harris classification[2].

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The incidence of slipped capital femoral epiphysis varies from 0.71 to 3.41 cases per 100,000[3,4] adolescents and differs among races, sex[1] (it occurs more often in boys than girls with a ratio of almost 2.5:1) and geographic location[1]. The male patients that suffer from SCFE are 13 to 15 years old, while the female patients are usually younger (11 to 13 years old). The typical pattern of a SCFE patient is either an obese, relatively short and sexually underdeveloped young boy or a tall and thin girl. The left hip is more often involved, nevertheless in almost 25% of all cases bilateral SCFE is reported. SCFE is classified according to the time elapsed since the onset of problems as acute or chronic. Another classification (from Grade I to Grade V) exists according to the severity of the slipping.

The most common symptom of SCFE is pain (dull and vague) in the groin region that radiates to the anteromedial aspect of the thigh and knee. The onset of pain may take sev-

Patient	Sex M=Male F=Female	Age in years	Height in cm	Centennial height position	Weight in kg	Centennial weight position
A1	F	12	153	50th	39	0
A2	M	10	158	99th	45	85th
A3	M	14	168	50th	70	88th
A4	M	14	163	35th	80	99th
A5	M	13.5	162	67th	70	93th
A6	M	12.5	154	60th	62	90th
A7	F	12	150	32nd	44	46th
A8	M	12	160	81st	75	100th+
A9	F	13	158	57th	50	50th
A10	F	11.5	165	99th	60	97th
A11	F	12	155	50th	50	65th
A12	F	11	149	55th	62	98th
A13	F	11	150	58th	55	87th
A14	M	13	153	22nd	65	89th
B15	M	16.5	185	97th	73	78th
B16	M	16	168	22nd	56	18th
B17	M	16	175	60th	100	100th+
B18	F	13	170	99th	63	99th
B19	M	13	165	85th	75	100th

Table 1. The anthropometric data of our patients. A1 to A14 are the patients that form Group A, while B15 to B19 patients form Group B. The patients are classified in a centennial scale, as far as their height and weight are concerned, according to their age.

eral weeks or months and is sometimes related to a minor or major injury of the region. The limitation of range of motions of the hip joint and the typical radiographic appearance of the slipping in the anteroposterior and lateral projection confirm the diagnosis.

The actual cause (or causes) of slipped capital femoral epiphysis remains a mysterious puzzle. Many factors may predispose to its development, namely (1) increased width of the upper femoral physis due to hormonal[5-8] or other influence, (2) changes in the geometry of capital physis (inclination angle[1], planarity[9] and femoral anteversion[10-13]), (3) obesity that exerts increased shearing stress on the growth plate[9] and (4) insufficiency of the tensile and hydrostatic components of the growth plate[14]. It is necessary to emphasize that it is not essential or necessary that all these factors simultaneously exist for the slip to occur.

The effects and influence of parathyroid hormone (PTH) on bone have been well known and scientifically documented. Its direct action on osteoblasts' (and secondarily on osteoclasts') activity and on calcium (Ca) and phosphorus (P) serum concentrations have also been studied and understood. All these actions have established PTH as one of the most important hormones of bone metabolism. The relatively recent discovery of PTH (and other hormonal) receptors in growth plate chondrocytes (the actual place where SCFE occurs) reinforced its role in bone homeostasis and subsequently re-animated the theory that there may be some hormonal intervention in the development of SCFE. All these data intrigued us into further investigation of the possible 'missing' link between the development of SCFE and the actions exerted by parathyroid hormone on growth plate chondrocytes.

Materials and methods

Nineteen patients in total were included in this study. All of them were treated surgically with *in situ* internal fixation with the use of Steinmann pins. Fourteen of them (7 boys and 7 girls) formed Group A. They were the patients who were admitted to the 2nd Orthopaedic Department of the Medical School of the Aristotle University of Thessaloniki for acute SCFE during the year 1999. Their ages ranged from 10 to 14 years in boys (mean 12.8 years) while the girls were a little younger (11 to 12.5 years, mean 11.6 years). The remaining 5 formed Group B. They were the patients that had been treated for acute SCFE in the past (1 to 6 years before the onset of this study). Four of them were boys (age ranging from 13 to 16.5 years, mean: 15.4) and one girl (13 years old). The number of Group B patients is relatively small as we focused on the research of any potential hormonal abnormalities during the actual slipping of the upper femoral epiphysis. Due to these parameters (small number of patients and SCFE treated surgically long before the onset of this study) we do not consider the Group B patients to serve as a control group.

All patients' height (cm) and weight (kg) were measured upon admittance. In order to eliminate the influence of height and age on Group A patients' weight, we projected all data on the National Height-Weight-Age Development Board. All patients were categorized in a one hundred degrees anthropometric scale according to their results. The higher the rank of the patient, the more obese or the taller he is according to his age. The boys' weight results ranged from the 85th to the 100th centennial position (mean 92 position) while the girls were much thinner (ranging from 0 to the 97th centennial position, mean 63rd position). The boys' height results ranged from the 22nd to the 99th centennial position (mean 59th) while the girls' results were much the same, ranging from the 32nd to the 99th centennial position (mean 58th). A brief analysis of these results shows that almost all our Group A members (mainly the boys) tend to fit the obese and short patient pattern. Group B weight and height results are of no particular interest as they cannot be categorized due to the small number of patients. Nevertheless, with the exception of patient B16, all the others seem to be taller and fatter than expected in relation to their age. All our patients' anthropometric and clinical data are shown in Table 1.

In Group A patients, the left hip was involved in 8 cases (6 boys and 2 girls) while the right hip was involved in 4 cases (1 boy and 3 girls). Two girls had bilateral SCFE. The majority of all Group A slippings was categorized as 2nd grade (9 cases; 6 boys and 3 girls). Third degree SCFE occurred in another 2 girls while the remaining 5 cases were 1st grade slippings (1 boy and 4 girls). All our Group B patients developed a 2nd degree SCFE in their left hip. (Table 2).

In order to assess the sexual maturation of our patients we conducted the Tanner et al.[15] Classification of the Secondary Sexual Characteristics. Tanner et al.[15] described a simple method of assessment of the sexual maturation of adolescents that depends on the size of testis (male) and breast (female) along with their pubic hair development. All three characteristics (testis = T, breast = B and pubic hair = P) range from 1 (small size of testis and breast, no pubic hair) to 5 (adult testis, breast and pubic hair). The results (as presented in Table 3) showed that all Group A patients developed SCFE during the earlier stages of their adolescence and sexual maturation. The majority of the boys (4 cases) were categorized as T1, two of them as T2, while only 1 reached T3 stage. Two girls were categorized as B1, three as B2 and the remaining 2 as B3. As far as pubic hair development is concerned, eight patients (6 boys and 2 girls) were found to be in stage P1, another 5 (1 boy and 4 girls) were in P2 and 1 girl was P4. Group B patients' sexual maturation more or less had been accomplished at the time that our study was conducted.

We used the ELISA-PTH kit (produced by CIS Bio International) for the quantitative immunoradiometric determination of I-PTH or 1-84-PTH (biologically active PTH) in human serum or plasma (EDTA). We also used the regular laboratory kits for the quantitative determination of the calcium and phosphorus serum levels.

Patient	Hip L=Left R=Right	SCFE grade	Years since onset
A1	L&R	L:3rd, R:1st	
A2	L	2nd	
A3	R	2nd	
A4	L	2nd	
A5	L	2nd	
A6	L	2nd	
A7	R	1st	
A8	L	2nd	
A9	L	3rd	
A10	L	2nd	
A11	L&R	L:2nd,R:1st	
A12	R	2nd	
A13	R	1st	
A14	L	1st	
B15	L		6
B16	L		1
B17	L		3
B18	L		2
B19	L		1

Table 2. The location and the degree of slipping of Group A patients and the location and the years that passed since the onset of slipping of Group B patients. The majority of all Group A slippings was categorized as 2nd grade. All Group B's patients developed a 2nd degree SCFE in their left hip. SCFE = slipped capital femoral epiphysis.

Results

The I-PTH results of Group A patients ranged from 2 pg/ml to 103 pg/ml (Group A mean value 22.13 pg/ml, mean value of boys' results 10.31 pg/ml and girls' 33.95 pg/ml). The normal values of I-PTH, as supplied by the manufacturer, were between 11 and 62 pg/ml. Group A girls' mean serum I-PTH values (33.95 pg/ml) were triple those of the same group's boys' mean values (10.31 pg/ml). Nine out of the 14 patients in Group A had abnormal I-PTH serum levels. Seven of them (5 boys and 2 girls) had decreased values while 2 girls had elevated I-PTH values. Another girl had an I-PTH value very close to the lowest normal (Table 4).

The serum calcium (Ca) values of Group A ranged from 9.02 mg/dl to 11.05 mg/dl (mean value 10.39 mg/dl, mean boys' value 10.39 mg/dl, mean girls' value 10.38 mg/dl). The normal Ca results as provided by the manufacturer range from 8.08-10.40 mg/dl. The serum phosphorus (P) values of Group A ranged from 3.2 mg/dl to 5.95 mg/dl (mean value 5.12 mg/dl, mean boys' value 5.31 mg/dl, mean girls' value 4.94 mg/dl). The normal serum P values, according to the kit's manufacturer was 2.7-4.5 mg/dl.

What is very interesting is that serum I-PTH abnormalities in Group A patients do not co-exist with the normally expected

Patient	Testis size (T)	Breast size (B)	Pubic hair (P)
A1		B 2	P 2
A2	T 1		P 1
A3	T 1		P 1
A4	T 3		P 2
A5	T 2		P 1
A6	T 1		P 1
A7		B 1	P 1
A8	T 1		P 1
A9		B 2	P 4
A10		B 3	P 2
A11		B 3	P 2
A12		B 2	P 1
A13		B 1	P 2
A14	T 2		P 1
B15	T 5		P 5
B16	T 5		P 5
B17	T 4		P 5
B18		B 5	P 5
B19	T 4		P 5

Table 3. The patients' sexual maturation classification according to Tanner et al[15]. All Group A patients developed slipped capital femoral epiphysis during the earlier stages of their adolescence and sexual maturation.

calcium and phosphorus increase or a decrease (i.e., a decrease in serum I-PTH levels is combined with a decrease in serum calcium levels and an increase in serum phosphorus levels, while an increase in serum I-PTH levels is usually manifested with an increase in serum calcium and a decrease in serum phosphorus levels), which is found in hyper- or hypoparathyroidism. Five out of the seven patients with decreased I-PTH values had, contrary to what we expected, increased serum Ca levels (Table 4). The remaining 2 had normal values. As far as serum phosphorus is concerned, 5 had increased values while in 2, serum phosphorus was normal. One of the 2 patients with increased I-PTH values also had increased serum Ca and P values, while the other had only an increase in serum P value. Neither the 7 patients with decreased serum I-PTH value had any other clinical manifestation or laboratory finding of hypoparathyroidism, nor were the 2 with I-PTH increase known to suffer from hyperparathyroidism.

In Group B patients, the serum level of I-PTH was surprisingly normal in all five cases, ranging from 12.87 pg/ml to 53.41 pg/ml (mean value of Group B 23.48 pg/ml, mean boys' value 24.93 pg/ml) while the serum Ca levels ranged from 9.5-11.81 mg/dl (mean 10.41 mg/dl) and the serum P levels ranged from 4.4-5.57 mg/dl (mean 4.69 mg/dl), being normal or very close to normal.

Discussion

The discovery of hormonal receptors in growth plate chondrocytes was a breakthrough in the understanding of all the physiologic and biochemical parameters involved in the epiphyseal fusion process. Parathyroid hormone receptors have been identified in the resting[16], growth[16], temporary calcification[17] and hypertrophied cells'[18,19]growth plate's zones. Crabb et al.[19] and Barling et al.[18] claim that PTH receptors are found in large numbers in the hypertrophied cells zone. This is the same zone where the slipping of the upper femoral epiphysis occurs. Even though it seems that the existence of other biochemical mediators (i.e., insulin-like growth factor-1[20], c-AMP[16] and parathyroid hormone-related peptide[21]) is necessary in order for PTH to exert its action on growth plate's chondrocytes, the latter is undoubted[19,22-24]. Kawashima et al.[25] have recently proved that PTH plays a significant pivotal role in the induction of various metalloproteinases in ossifying cartilage by controlling the cartilage-matrix degradation during endochondral bone formation.

It is not yet certain, but quite possible, that the action of PTH on growth plate's chondrocytes, through its mediators and metalloproteinases, may be deranged due to any hormonal imbalance (increase or decrease of PTH), resulting in the abnormal mineralization of the cartilage, that may elongate the time needed for the epiphysis fusion to complete. This elongated period, when the cartilage cells remain uncalcified, may be at least one of the actual causes that provokes the development of SCFE. It is well known that during the early years of adolescence, the increasing body weight along with the changes in growth plate's planarity, exert an extremely powerful shearing stress on the upper femoral epiphysis. We believe that a hormonal imbalance may trigger the whole procedure by exposing the growth plate in the destabilizing effects of all the other contributing factors (i.e., body weight, growth plate planarity, increased femoral retroversion, increased physical activity, injury, insufficiency of the tensile and hydrostatic components of the growth plate) for a prolonged period of time.

There are numerous case reports of patients with SCFE who were found to have serum parathyroid hormones levels higher than normal[26-31] and few with lower than normal PTH values[32,33]. Jingushi et al.[32] have reported decreased serum M-PTH values in 13 patients with SCFE. What is interesting is that these same 13 patients were found to have normal serum I-PTH values and this result seems to be in confrontation with ours. We believe that there might be some possible explanations for this differentiation. Guillemant et al.[34] consider the measurement of 'intact' I-PTH to be more reliable than the measurement of the intermediate fragment of the hormone. Furthermore, the complete pathogenic mechanism of SCFE is not fully understood. What is widely accepted is that the combined and simultaneous action of many etiologic factors (i.e., increased body weight, growth plate planarity and height, other hormonal disorders, trauma, femoral anteversion angle, perichondrium stability etc.) is necessary in order for the slipping

Patient	PTH Level (pg/ml)	Ca Level (mg/dl)	P Level (mg/dl)
A1	17.03	10.04	5.2
A2	2.89	11.05	5.95
A3	9.64	10.58	5.41
A4	7.38	10.73	5.11
A5	8.96	10.34	5.62
A6	2	9.2	5.2
A7	18	10.42	6.55
A8	11	10.6	5.12
A9	8.68	10.88	3.2
A10	6.75	10.58	3.85
A11	11.2	10.36	4.3
A12	73	9.73	5.7
A13	103	10.69	5.8
A14	30.3	10.27	4.79
B15	53.41	9.5	4.4
B16	12.87	11.81	5.57
B17	16.7	10.38	4.4
B18	17.66	10.55	4.03
B19	16.77	9.85	5.09

Table 4. Serum PTH, Ca and P levels. The results of our patients. Nine of the 14 patients in Group A had abnormal serum PTH values. The serum Ca and P values of these patients did not increase or decrease as expected according to the PTH imbalance and none of them showed any other clinical signs of hyper- or hypoparathyroidism. PTH = Parathyroid Hormone, Ca = Calcium, P = Phosphorus.

to occur. The actual extent of the contribution of the PTH (I-PTH or M-PTH or any other PTH fragments) remains to be further and thoroughly investigated. That is probably the reason why there are studies[35] that fail to attribute the occurrence of SCFE to any disorder or imbalance of PTH.

Our results show that 9 out of 14 patients with SCFE (Group A) had abnormal serum I-PTH values (7 patients had decreased I-PTH and 2 had increased I-PTH) at the time that they were surgically treated. None of the seven patients manifested any clinical sign of hyper- or hypoparathyroidism, and none had serum calcium and phosphorus values as expected according to the parathyroid hormone imbalance pattern. It is interesting to mention at this point that the manufacturer of the I-PTH quantitative determination kit provided no data concerning abnormal or even different from usual values of I-PTH manifested in either adolescents or furthermore adolescents or adults with fractures. Our further investigations, through Medline, of any relative published data, failed to reveal anything that correlates the occurrence of fractures with serum I-PTH abnormalities. There is, however, a publication, which moves towards the "opposite" direction. Dubin et al.[36] have reported an increase in measured serum PTH (and calcium) levels one year after hip fractures in postmenopausal women. We believe that this is an interesting finding which needs further investigation. Nevertheless, it probably cannot be related to our results as we are dealing with completely different age groups (adolescents experiencing rapid hormonal changes, compared with approximately 80-year-old postmenopausal women) and completely different types of fractures (epiphysiolisis versus osteoporotic fracture, slowly progressing versus acute trauma, developing versus aged skeleton). Furthermore, the majority of our patients' pathologic serum PTH values (7 out of 9) were lower than normal and not connected to the expected in hyperparathyroidism and hypoparathyroidism calcium and phosphorus increase/decrease pattern.

On the contrary, there are numerous studies that correlate the increased incidence of pathological fractures in patients with PTH imbalances[37-41]. Khosla et al.[36,37] have reported an overall fracture increase in adult patients suffering from primary hyperparathyroidism, while Bennett et al.[38] presented a case report of a pathologic fracture of the femoral neck that occurred in an adolescent with parathyroid adenoma. Coco and Rush[39] have published an interesting study that describes an increased possibility, for dialysis patients with low serum PTH, to sustain a hip fracture compared with the patients with higher PTH levels. Although the patients suffering from SCFE are not similar to the ones previously described, it is quite interesting that PTH is more and more often "related" to the development of fractures (pathological or not). The possible contribution of PTH to the development of all these fractures still remains unknown. It is possible that an inhibition or stimulation of PTH release or production, or/with the PTH action on bone and growth plate cartilage with/or (even) a temporary imbalance of calcium receptors to sense extracellular Ca++ level, may trigger the whole procedure.

None of the 5 patients (Group B) that had been treated in the past for SCFE had any I-PTH abnormalities detected. The number of these patients (Group B) is relatively small, but it enables us to begin to understand some of the possible facts about SCFE. Although we do not yet have sufficient data to prove and support our theory, we believe that a temporary, transient and probably self-redeemed PTH imbalance which exerts a (more or less) unknown action, may also (together with other pathogenic contributing factors) predispose to the development of SCFE by delaying the fusion rate of the upper femoral epiphysis.

Conclusions

All the pre-mentioned can possibly lead us to the conclusion that a temporary self-redeemed (?) hormonal imbalance of PTH is one (at least) of the actual causes of the upper femoral epiphysis slipping. The increased and decreased values of PTH and not hyper- or hypoparathyroidism are what may trigger the slipping procedure. The combined action of hormonal imbalance together with other etiologic factors or the prolonged exposure of the upper femoral physis to the pre-mentioned destabilizing factors due to this hormonal imbalance may lead to the development of the SCFE.

References

1. Tachdjian MO. Slipped capital femoral epiphysis. In: Pediatric orthopedics Vol. 2, 2nd ed. WB Saunders, Philadelphia; 1990:1016-1081.
2. Nguyen D, Morrissy RT. Slipped capital femoral epiphysis: rationale for the technique of percutaneous *in situ* fixation. J Pediatr Orthop 1990; 10:341-346.
3. Jacobs B. Diagnosis and natural history of slipped capital femoral epiphysis. Instr Course Lect 1972; 21:224.
4. Kelsey JL. An epidemiological study of slipped capital femoral epiphysis. Yale University, Ph.D. Thesis; 1969.
5. Burch WM, Lebovitz HE. Triiodothyronine stimulates maturation of porcine growth-plate cartilage *in vitro.* J Clin Invest 1982; 70:496-504.
6. Burch WM, Van Wyk JJ. Triiodothyronine stimulates cartilage growth and maturation by different mechanisms. Am J Physiol 1987; 252:E176-182 .
7. Lewinson D, Harel Z, Shenzer P, Silbermann M, Hochberg Z. Effect of thyroid hormone and growth hormone on recovery from hypothyroidism of epiphyseal growth plate cartilage and its adjacent bone. Endocrinology 1989; 124:937-945.
8. Werther GA, Haynes K, Edmonson S, Oakes S, Buchanan CJ, Herington AC, Waters MJ. Identification of growth hormone receptors on human growth plate chondrocytes. Acta Paediatr Suppl 1993; 391(Suppl.82):50-53.
9. Gelbermann RH, Cohen MS, Shaw BA, Kasser JR, Griffin PP, Wilkinson RH. The association of femoral retroversion with slipped capital femoral epiphysis. J Bone Joint Surg Am 1986; 68:1000-1007.
10. Humphrey GM. The angle of the neck with the shaft of the femur at different periods of life and under different circumstances. J Anat Physiol 1889; 23:273.
11. lanz T von, Mayet A. The human hip joint in the progressive phase of its round-about development. Z Anat 1953; 117:317.
12. Shands AR, Steele MK. Torsion of the femur. J Bone Joint Surg Br 1961; 43:518.
13. Watanabe RS. Embryology of the human hip. Clin Orthop 1974; 98:8-26.
14. Stanley M, Chung K. Hip disorders in infants and children. Lea & Febiger, Philadelphia; 1981:1-29.
15. Ross GT. Disorders of the ovary and female reproductive tract. In: Wilson JD, Foster DW (eds) Textbook of endocrinology, 7th ed. WB Saunders, Philadelphia; 1985:206-258.
16. Schwartz Z, Semba S, Graves D, Dean DD, Sylvia VL, Boyan BD. Rapid and long-term effects of PTH (1-34) on growth plate chondrocytes are mediated through two different pathways in a cell-maturation-dependent manner. Bone 1997; 21:249-259.
17. Loveys LS, Gelb D, Hurwitz SR, Puzas JE, Rosier RN. Effects of parathyroid hormone-related peptide on chick growth plate chondrocytes. J Orthop Res 1993; 11:884-891.
18. Barling PM, Bibby NJ. Study of the localization of [3H] bovine parathyroid hormone in bone by light microscope autoradiography. Calcif Tissue Int 1985; 37:441-446.
19. Crabb ID, O'Keefe RJ, Puzas JE, Rosier RN. Differential effects of parathyroid hormone on chick growth plate and articular chondrocytes. Calcif Tissue Int 1992; 50:61-66.
20. Rihani-Bisharat S, Maor G, Lewinson D. *In vivo* anabolic effects of parathyroid hormone (PTH) 28-48 and N-terminal fragments of PTH and PTH-related protein on neonatal mouse bones. Endocrinology 1998; 139:974-981.
21. Lee K , Lanske B , Karaplis AC , Deeds JD , Kohno H, Nissenson RA, Kronenberg HM, Segre GV. Parathyroid hormone-related peptide delays terminal differentation of chondrocytes during endochondral bone development. Endocrinology 1996; 137:5109-5118.
22. Klaus G, von Eichel B, May T, Hugel U, Mayer H, Ritz E, Mehls O. Synergistic effects of parathyroid hormone and 1,25-dihydroxyvitamin D3 on proliferation and vitamin D receptor expression of rat growth cartilage cells. Endocrinology 1994; 135:1307-1315.
23. Pines M, Hurwitz S. The effect of parathyroid hormone and atrial natriuretic peptide on cyclic nucleotides production and proliferation of avian epiphyseal growth plate chondroprogenitor cells. Endocrinology 1988; 123:360-365.
24. Spagnoli A, Rosenfeld RG. The mechanisms by which growth hormone brings about growth. The relative contributions of growth hormone and insulin-like growth factors. Endocrinol Metab Clin North Am 1996; 25:615-631.
25. Kawashima-Ohya Y, Satakeda H, Kuruta Y, Kawamoto T, Yan W, Akagawa Y, Hayakawa T, Noshiro M, Okada Y, Nakamura S, Kato Y. Effects of parathyroid hormone (PTH) and PTH-related peptide on expression of matrix metalloproteinase-2, -3, and -9 in growth plate chondrocyte cultures. Endocrinology 1998; 139:2120-2127.
26. Chiroff RT, Sears KA, Slaughter WH III. Slipped capital femoral epiphyses and parathyroid adenoma. J Bone Joint Surg Am 1974; 56:1063-1067.
27. Kinoshita J, Kaneda K, Matsuno T, Hosokawa Y, Nagashio R. Slipped capital femoral epiphysis associated with hyperparathyroidism. A case report. Int Orthop 1995; 19:245-247.
28. Krempien B, Mehls O, Ritz E. Morphological studies on pathogenesis of epiphyseal slipping in uremic children. Virchows Arch A Pathol Anat Histol 1974; 362:129-143.
29. Mehls O, Ritz E, Krempien B, Gilli G, Link K, Willich E, Scharer K. Slipped epiphyses in renal osteodystrophy. Arch Dis Child 1975; 50:545-554.
30. Rutskii AV, Romanchak MN, Livshits IB. Hormonal disorders in patients with spontaneous epiphysiolysis. Ortop Travmatol Protez 1983; 4:41-43.
31. Shea D, Mankin HJ. Slipped capital femoral epiphysis in renal rickets. Report of three cases. J Bone Joint Surg Am 1966; 48:349-355.

32. Jingushi S, Hara T, Sugioka Y. Deficiency of a parathyroid fragment containing the midportion and 1,25-dihydroxyvitamin D in serum of patients with slipped capital femoral epiphysis. J Pediatr Orthop 1997; 17:216-219.
33. Schmidt H, Kunhle U. Epiphysiolysis capitis femoris as a possible complication of hypoparathyroidism in partial Di George syndrome. Klin Paediatr 1993; 205:116-118.
34. Guillemant S, Guillemant J, Oberlin F, Dairou F, Camus JP. Primary hyperparathyroidism: value of 'intact parathormone' assay (PTH 1-84). Presse Med 1989; 18:1509-1512.
35. Schnitzler CM, Daniels ED, Mesquita JM, Moodley GP, Zachen D, Cakic J, Pettifor JM. Bone disease in African children with slipped capital femoral epiphysis: histomorphometry of iliac crest biopsies. Bone 1998; 22:259-265.
36. Dubin NH, Monahan LK, Yu-Yahiro JA, Fox KS, Sachs M, Michael RH, Zimmerman SI, Magaziner J. Changes in plasma steroids, parathyroid hormone (PTH) and calcitonin (CAL) during the year following hip fracture in postmenopausal women. Fertil Steril 1997; 68(S1):S228-S229.
37. Khosla S, Melton LJ III, Wermers RA, Criwson CS, O'Fallon W, Riggs B. Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res 1999; 14:1700-1707.
38. Khosla S, Melton LJ III. Fracture risk in primary hyperparathyroidism. J Bone Miner Res 2002; 17 (Suppl.2): N103-107.
39. Bennett JT, Alexander HH, Morrissy RT. Parathyroid adenoma presenting as a pathologic fracture of the femoral neck in an adolescent. J Pediatr Orthop 1986; 6:473-476.
40. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis 2000; 36:1115-1121.
41. Fournier A, Oprisiu R, Mazouz H, Moriniere P, El Esper N, Choukroun G. Low parathyroid hormone levels and higher risk of hip fractures and mortality. Am J Kidney Dis 2001; 38:222-224.