DO AFRICAN CHILDREN WITH SLIPPED CAPITAL FEMORAL EPIPHYSIS HAVE METABOLIC BONE DISEASE ?

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A Dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Master of Medicine in Orthopaedic Surgery

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DECLARATION

I declare that this dissertation is my own, unaided work.
It is being submitted for the Degree of Master of Medicine (Orthopaedic Surgery)
in the University of the Witwatersrand, Johannesburg.
It has not been submitted before for any degree or examination
in any other University.

Josip N. Cakic

In Johannesburg, 14th day of March, ~~1999.~~ 2000.

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I would like to thank Professor C.M. Schnitzler for her endless support and enthusiasm, Professor M.B.E. Sweet for his advice, Mrs J.M. Mesquita for her assistance in the preparation of the histological specimens, Mr A. Webb for help with the illustrations and my wife Jasmine for her support and patience.

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ABSTRACT

Slipped femoral capital epiphysis (SCFE) is a disorder of puberty. The aetiology and pathophysiology of this growth plate disturbance remain unclear. African teenagers with SCFE not infrequently also have genu valgum (knock-knee). Because was previously demonstrated metabolic bone disease attributable to dietary calcium deficiency in black teenagers with genu valgum, we examined 29 black teenagers (15 male, 14 female) with SCFE for metabolic bone disease. Each patient had an iliac crest biopsy taken (after double tetracycline labelling) for routine histomorphometry, and blood and urine samples for bone biochemistry. Spinal bone mineral density was measured in 13 patients. Compared to reported data, we found our patients to be sexually more immature, older, at least as obese, and to have more severe and more frequently bilateral hip disease. Eighty percent of the children took dairy products only once or twice a week or less frequently and 37.9 % had genu valgum. Compared with race- and age-matched South Africans, bone biopsies in our patients showed lower bone volume (BV/TV, $p = 0.0003$), wall thickness ($p = 0.0002$), and trabecular thickness (Tb.Th, $p = 0.0002$), and a tendency to greater trabecular spacing (Tb.Sp, $P = 0.053$). Lower osteoid volume (OV/BV, $p = 0.0001$), osteoid surface (OS/BS, $P = 0.0001$), osteoid thickness (O.Th, $p = 0.0002$), double labelled surface (dLS/BS, $P = 0.29$), and bone formation rate (BFR/BS, $p = 0.037$) suggested poorer bone forming capacity in our patients. No evidence of hyperparathyroid bone disease or osteomalacia was found. Bone volume was below the reference range (14.2%) in 65.5% of cases; these patients had lower values for Tb.Th ($p = 0.037$) and Tb.N ($p = 0.0003$), greater Tb.Sp ($p = 0.0002$), a tendency to lower adjusted apposition rate (Aj.AR, $p = 0.057$), and had had less frequent intake of dairy products than those with normal BV/TV ($p = 0.024$). Furthermore, premenarchal status had an adverse effect on bone in that was associated with lower bone volume, thinner trabeculae, lower osteoid thickness, and tendency to lower adjusted apposition rate. Months since menarche correlated with histomorphometric variables BV/TV ($r = 0.667$, $p = 0.009$), Tb.Th ($r = 0.745$, $p = 0.002$), Tb.Sp ($r = - 0.549$, $p = 0.042$), O.Th ($r = 0.784$,

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INTRODUCTION

"Epiphysiolysis capitis femoris is not to be ranked among the fractures since its origin is presumed to be caused by a primary diminished solidity in the zone of growth." (Waldenstrom 1930).

Seventy years later we have not progressed beyond this statement. No one has conclusively demonstrated a primary defect in growth cartilage (Ponseti et al 1956, Ippolito et al 1981, Agamanolis et al 1985), nor has any investigator looked at the possibility whether bone - intricately interwoven with the slipping part of the physis – might be abnormal.

Slipped capital femoral epiphysis (SCFE) is a condition characterised by displacement of the capital femoral epiphysis from the femoral neck through the physeal plate (Figure 1).

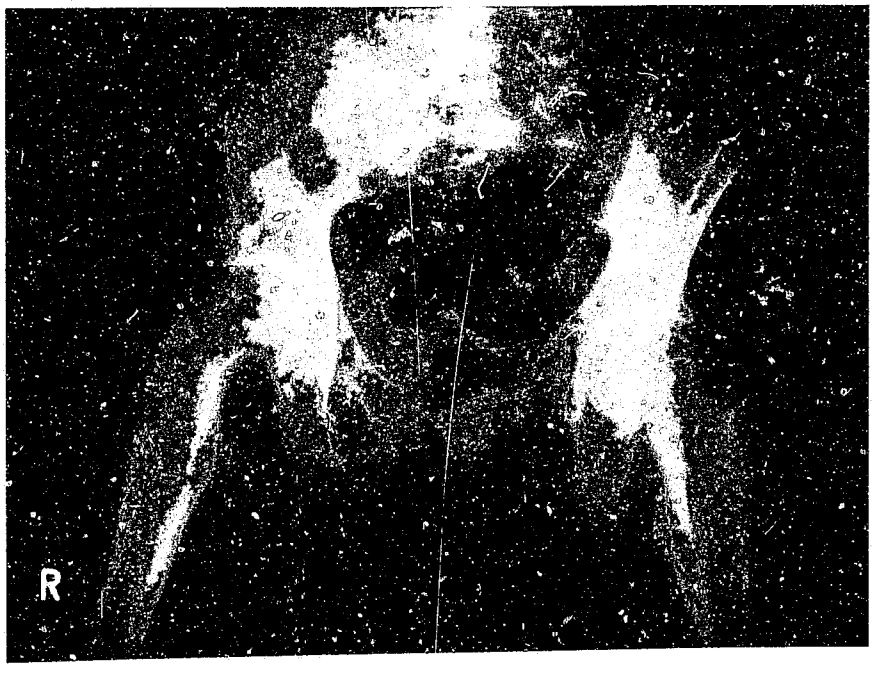

Figure I: *A-P radiograph of a pelvis with SCFE of the right hip*

The femoral shaft rolls into external rotation and the femoral neck is displaced forwards while the epiphysis remains seated in the acetabulum. Disruption occurs through the hyperthropic zone of the physis and, relatively speaking, the epiphysis slips posteriorly on the femoral neck. It has been shown that the displacement of the slipped capital femoral epiphysis occurs mainly in a posterior direction as the femoral head rotates around the axis of the femoral neck with a resultant apparent proximal femoral varus deformity secondary to optical illusion due to parallax, the femoral head being behind the femoral neck (Griffiths 1975). To date, the majority of the change has been demonstrated to occur in the hypertrophic zone of the physeal plate. The zone of hypertrophy normally constitutes 15% - 30% of the width of the normal physeal plate. In SCFE, this zone is claimed to increase to as much as 80% of the width of the physeal plate (Weinstein 1984, Ippolito et al 1981). Microscopically, the slip cleft is noted to traverse mainly the zone of hypertrophy (Ippolito et al 1981, Mickelson et al 1977, Ponseti et al 1956). The importance of slipped capital femoral epiphysis lies in the serious long-term crippling effects it has on the individual: pain, deformity, restriction of movement and a limp are expected to remain for life.

Slipped capital femoral epiphysis is related to puberty, as evidenced by 78 % of cases occurring during the adolescent growth phase (Sorenson 1968). The annual incidence of SCFE has been reported to average 2 cases per 100 000 in the general population. The age range at presentation in boys is most often between 10 and 16 years of age, and in girls between 10 and 14years of age (Henrickson 1969, Kelsey et al 1970). SCFE is more common in boys than in girls. This male predilection has been reported at 2.4 to 1, with the left hip being affected twice as often as the right (Wilson et al. 1965). Bilateral symptomatic involvement with slipped capital femoral epiphysis averages 25% during adolescence (Wilson et al 1965, Carney et al 1991, Loder et al 1993). Long-term follow-up studies, however, identify changes of bilateral involvement in as much as 60% to 80% of cases (Hagglund et al. 1988). The adolescents at greatest risk of SCFE are those who are skeletally immature and obese. The condition occurs more frequently in black than in white children (Kelsey 1970).

Obesity is definitely associated with the development of slipped capital femoral epiphysis. A child is considered obese if the weight is greater than the 95th percentile for that age (Kelsey et al 1972). Weight for age profiles over the 95th percentile were reported in 49% of affected children (Kelsey et al 1972), and weight for height profiles over the 90th percentile in 73 % of affected boys and in 52 % of affected girls. Clinically obese patients with SCFE also tend to present at a younger age (Loder et al 1993).

A delay in skeletal maturation is commonly seen in patients with slipped capital femoral epiphysis. Skeletal age has been found to be as much as 20 months behind chronological age in up to 70% of affected children (Sorenson 1968).

Slipped capital femoral epiphysis is still a disorder of uncertain aetiology. The theories advanced include trauma, mechanical factors, endocrine disorders, inflammatory reaction, nutritional factors, and irradiation therapy. These theories will be dealt with in greater detail in the Discussion.

It is unlikely that slipped capital femoral epiphysis is the result of a single factor but it is more likely secondary to multiple factors resulting in a weakened physeal plate that is loaded with a higher than normal shear stress resulting in failure of the proximal femoral physeal plate.

The outcome of the slip is related to the duration of symptoms before treatment, so that early diagnosis would improve the final results. The goals of treatment are stabilisation and prevention of additional slipping, the stimulation of early closure of the physis and prevention of the devastating disabilities as a result of complications, namely avascular necrosis of the femoral head, chondrolysis of the hip joint cartilage and osteoarthritis (Chung et al 1976). Black children have been reported not only to have a higher incidence of slipped capital femoral epiphysis (Kelsey et al 1970, Canale 1989, Loder et al 1993), but also to be at grater risk of having an unsatisfactory outcome

secondary to chondrolysis or avascular necrosis (Oroñno et al 1960, Tilema et al 1971, Kennedy et al 1990).

Clinical experience has shown that black teenagers with slipped capital femoral epiphysis not infrequently also have genu valgum (knock-knee). Since genu valgum in African black children is commonly associated with hyperparathyroid bone disease, osteomalacia or osteopenia, attributable in most cases to dietary calcium deficiency (Schnitzler et al 1994), the question arose whether our black patients with slipped capital femoral epiphysis might also have metabolic bone disease. Indeed, a high prevalence of biochemical abnormalities was found in a rural black community where 13.2 % of children were hypocalcaemic. It has been shown that bone deformities and biochemical abnormalities in rural black children are due to low dietary calcium intake (Pettifor et al 1979, Petttifor et al 1981).

The aim of this study is to investigate black patients with slipped capital femoral epiphysis for metabolic bone disease. To the best of my knowledge and after extensive search of the literature no scientific study has to date been carried out to examine slipped capital femoral epiphysis patients for metabolic bone disease using histomorphometry.

Bone histomorphometry includes the measurement of structural components, such as bone volume, trabecular thickness, trabecular number, trabecular spacing, and wall thickness of osteons. Bone histomorphometry can also measure erosion and osteoid variables reflecting static bone turnover, and kinetic bone turnover variables based on the use of double fluorescent labels, that are administered at timed intervals and incorporated into forming bone. The distance between such labels and their surface extent provide information about the rate of bone formation, about cellular activity, mineralization, and the duration of bone remodelling cycles. The incorporation of double tetracycline labels into bone as time-markers thus permits the dynamic description of current remodelling activity.

Bone densitometry, assays of biochemical markers of bone turnover in the serum, and calcium kinetics studies can only yield data on tissue or organ level activity, which therefore reflect a combination of individual cell activity and cell number. Histomorphometry, as quantitative bone histology is the only method by which alterations in cellular activity can be separated from changes in cell number.

The working hypothesis for this study was the assumption that metabolic bone disease could weaken methaphyseal bone adjacent to the physis and so predispose to more frequent and more severe slips of the femoral epiphysis than would be the case in the absence of bone disease.

PATIENTS AND METHODS

Patients

All patients included in this study were investigated and treated in the Department of Orthopaedic Surgery at Baragwanath Hospital. Laboratory investigations were carried out in the Biochemistry and Histomorphometry Laboratories of the MRC Mineral Metabolism Research Unit of the University of the Witwatersrand of Chris Hani - Baragwananth Hospital. In the period between October 1991 and August 1996, 29 black teenagers with slipped capital femoral epiphysis were included in the study: fifteen were boys and 14 girls, aged from 11 to 17 years. To be included in the study patients had to be healthy in all other respects (Table I).

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Table I: *List of anthropometric data of 29 black teenagers (15 boys, 14 girls) with Slipped capital femoral epiphysis (SCFE)*

No.	*Name*	*Sex*	*Age (yrs)*	*Weight (kg)*	*Height (cm)*
1	CT	F	15	87	172
2	NN	F	14	91.6	162
3	JM	M	17	78	162
4	PM	F	11	58	146
5	JK	M	16	48	174
6	IN	M	17	64	182
7	KM	M	16	65	164
8	HH	M	16	47.5	163
9	PM	F	15	52	166
10	SM	F	15	41	152
11	CS	F	14	53.5	144
12	CM	M	15	54	158
13	IM	F	14	52.5	146
14	TM	M	16	72.5	165
15	GM	M	15	51.5	152
16	BD	F	12	48.5	157
17	MK	M	15	42.5	155
18	NM	F	11	61.5	145
19	SM	M	16	40	158
20	ST	M	16	54.5	179
21	MJ	F	11	54	156
22	MS	M	16	80	166
23	PM	F	15	92	168
24	AM	M	13	51	150
25	SB	M	15	103	160
26	RP	M	14	44	149
27	KZ	F	14	53	141
28	PK	F	13	84	156
29	GM	F	12	67	150

In order to collect the necessary data, a questionnaire was drawn up. This was completed by the investigator at the time of the clinical examination. It consisted of general information related to place of residence, anthropometric measurements, history of complaints, and data related to clinical and laboratory examination performed during the clinical part of the research (Table II).

Table II: Sample of the questionnaire used in the study

SLIPPED CAPITAL FEMORAL EPIPHYSIS

Name: _____ Code No. _____

Hospital No. _____ Hospital: _____ Admission date: _____

Sex: _____ Age: _____ Race: _____ Date of biopsy: _____

Home address: (sticker): _____ Side of biopsy: R L

_____ Weight: _____ Kg

_____ Height: _____ cm

_____ Date of birth: _____

_____ Date bloods taken: _____

HISTORY:

When did hip/knee pain start? _____ Did the pain start by itself? Yes No

If No, How _____

Where did you live at: age 0-5 _____ age 5-10 _____

Where is your home now? _____ Do you go to school? Yes No Grade ____

How many rooms does your house have? _____ How many people sleep at your house ____

Does your father work? Yes No What work does he do? _____

Does your mother work? Yes No What work does she do? _____

Do you eat or drink dairy products? Yes No If yes, how often? Daily 2 x week 1 x week Never

GIRLS: Are you already menstruating? Yes No If yes, when was your first period? _____

EXAMINATION:

Non-orthopaedic abnormalities Yes No If yes, describe: _____

		F	ABD	ADD	ER	IR
Hips	Right	____to____	____to____	____to____	____to____	____to____
	Left	____to____	____to____	____to____	____to____	____to____

Knee valgus / varus angle (ASIS – patella – centre ankle) R _____ L _____

Other orthopaedic findings: _____

PUBERTY STAGES (1 – 5) **Boys:** Genital size _____ Pubic hair _____

Girls: Breasts _____ Pubic hair _____

X-RAYS (copied): Pelvis A-P _____ CT scan hips _____

BONE DENSITY: **DEXA lumbar spine:** BMC ____ BW ____ BMD ____

BLOODS (fasting): Ca ____ P ____ Alb ____ AP ____ 25D ____ Creat ____ PTH ____

URINE (fasting) Ca ____ Creatinine ____ Phosphorus ____

TETRACYCLINE

Preparation used _____ Dosage _____

First label from _____ to _____ Where did patient spend labelling interval?

Interval from _____ to _____ _____

Second label from _____ to _____

In the history we tried to obtain as much information as possible about the mechanism of injury, site of pain and timing of the injury. The next group of questions was related to family and living conditions: where the patient lived at a certain age, and where he/she is living now. The importance of this information relates to the fact that poorer nutritional status, including lower dietary calcium intake, had been found in children living in rural areas compared to those from urban centres (Pettifor et al 1979). The socio-economic status of the families studied was assessed by the size of the house, the number of persons living per room, and by employment status of the parents. Level of education was also used as an indicator of socio-economic status. The significance of the socio-economic status lay in its role as indicator of poverty which in turn would influence nutrition.

The next important questionnaire point was dietary calcium intake. Pettifor et al had (1979) previously shown, that the pathogenesis of biochemical abnormalities in rural children lay in low dietary intake of calcium. In the rural areas, milk and other dairy products are only ingested by families who keep cows, while in the urban areas milk is more readily available in the form of both fresh and powder milk. In the urban communities the amount of milk and thus calcium consumed is dependent on family income. Furthermore, a low level of dietary calcium is aggravated by the consumption of large quantities of the relatively inexpensive maize meal (corn) as staple food. Maize meal has a very low calcium content and is rich in phytates that bind calcium (Sly et al 1984). Dietary calcium intake was assessed by the frequency of intake of diary products and classified as daily, once or twice a week, or never.

In order to establish an association between slipped capital femoral epiphysis and metabolic bone disease it was essential to assess pubertal development because puberty increases bone mass. Pubertal development was rated according to Tanner staging (Tanner 1984) in the privacy of the hospital ward. All children were assessed by the same doctor. Using the Tanner stage pictures, boys were evaluated for genital size and pubic hair development. Girls were assessed for breast and pubic hair development.

Each individual was assigned the average value of the two criteria. Tanner stages are presented in Figure 2.

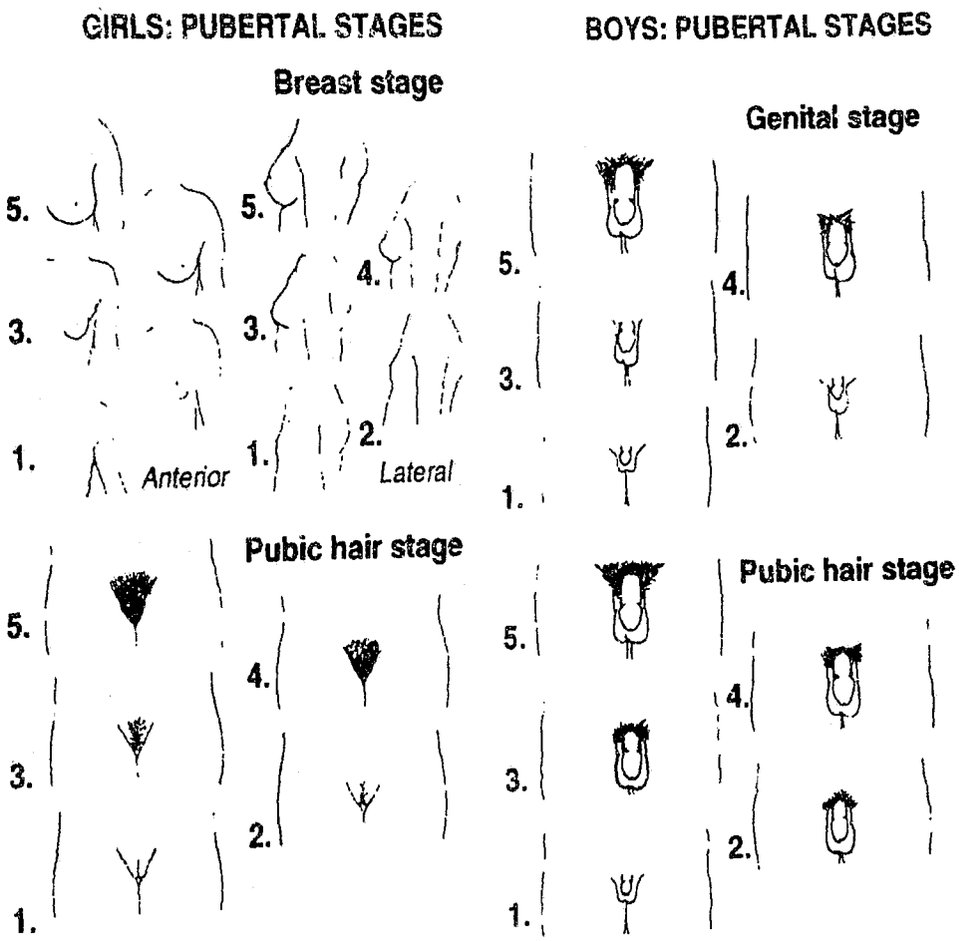


Figure 2: *Tanner's stages of pubertal development (From Buckler J.M.H., A reference manual of growth and development. In Lovel and Winter's Pediatric Orthopaedics.Ed.4, pp.92, Philadelphia, New York, Lippincot-Raven, 1996.*

Radiographs

In order to assess presence, bilaterality and severity of slipped capital femoral epiphysis, routine radiographs were taken. Several radiographic methods have been described in the assessment of slipped capital femoral epiphysis, as well as different radiographic classifications based on maximum anatomic displacement of the femoral head on the femoral neck.

The antero-posterior radiograph is usually diagnostic of SCFE with the possible exception of early presentation with minimal slipping. A crescent-shaped area of increased density frequently can be identified in the proximal portion of the femoral neck (blanch sign of Steel) (Steel 1986), as well as signs of physeal widening, irregularity and decreased epiphyseal height. The femoral metaphysis also appears to be more laterally displaced from the medial acetabular wall, compared with the unaffected side. On an A-P radiograph a positive Trethowan's or Klein's line sign can be identified. It is defined as a straight line drawn along the superior margin of the femoral neck, which normally intersects the lateral aspect of the epiphysis (Figure 3). However, in slipped capital femoral epiphysis this line passes lateral to the epiphysis.

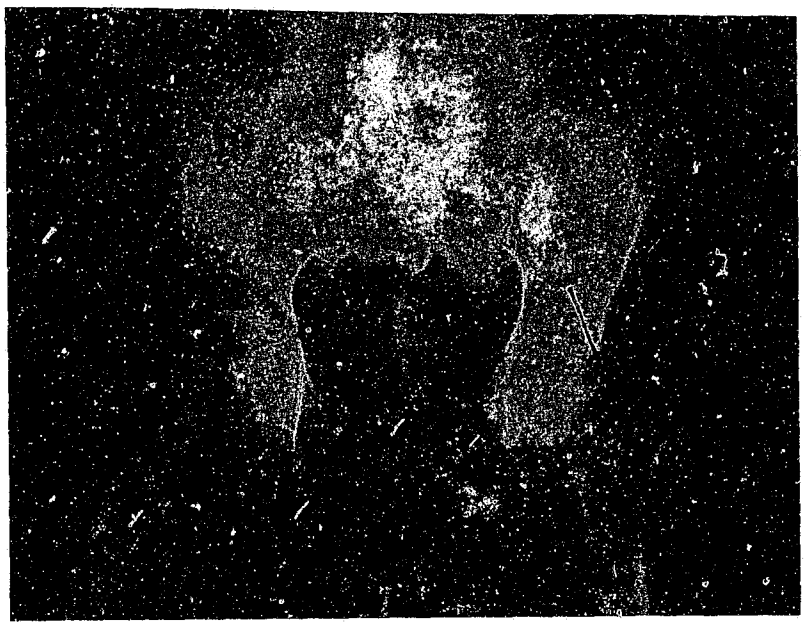


Figure 3: *Radiograph showing Trethowan's (Klein's) line: A line drawn along the superior aspect of the femoral neck should pass through the head of the femur, as in the left hip. The right hip shows the presentation in a case of SCFE.*

A true lateral or cross-table lateral radiograph of the affected hip defines the full extent of the posterior displacement of the femoral epiphysis. Capener's sign is described on this view, in which the head is tilted inferiorly out of the acetabulum (Figure 4). It is difficult to obtain this view in obese patients.

Figure 4: *Capener's sign: The head is seen to be tilted inferiorly out of the acetabulum*

The frog-leg lateral view should be avoided, especially in acute presentations because of the potential risk of increasing the physeal displacement during the positioning of the patient for the radiograph. The frog-leg lateral view requires the patient to flex the hip 45° and abduct the hip to 45°, which is a position extremely difficult to assume as movement is limited by pain. Nevertheless, Wilson et al (1965) described the percentage slip on the frog-leg lateral view: the amount of slip is measured as a percentage of the width of the femoral neck at the physis and classified as mild (33%), moderate (33-50%) and severe (>50%). Waldenstrom and Southwick described a measurement of the head-shaft angle on the frog-leg lateral view (Waldenstrom 1940, Southwick 1967)(Figure 5).

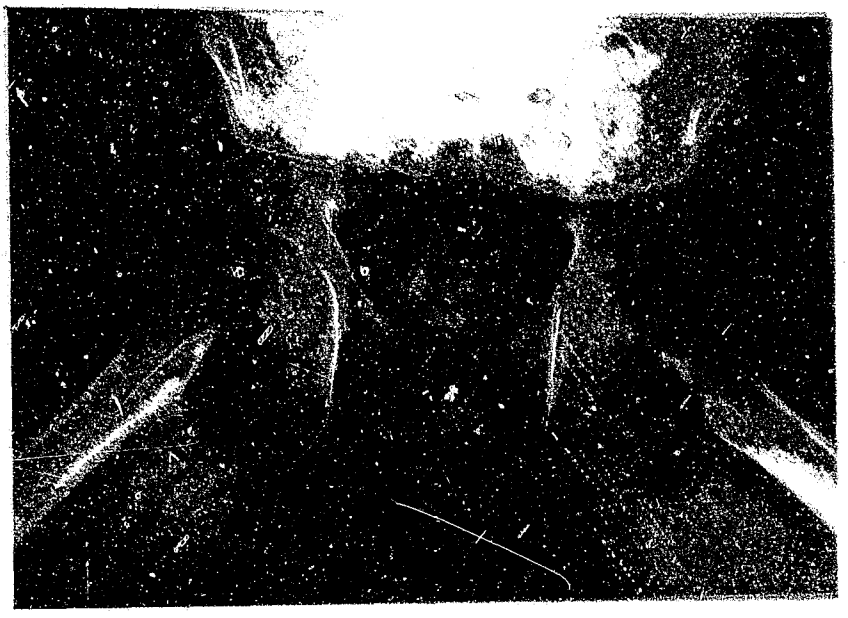


***Figure 5:** A frog-leg lateral radiograph of the hips showing a Southwick's head-shaft angle. Both hips are involved.*

Boyer proposed measurement of the maximum difference in the Southwick angles between the involved and uninvolved hip (Boyer et al 1981). He defined a mild slip as a head-shaft angle difference of $< 30^{0}$, moderate slip as a 30^{0}-50^{0}, and severe slip as a difference of $>50^{0}$. Loder proposed a new simplified classification system determined by the degree of physeal stability (Loder et al 1990). A slip is classified as unstable if the patient has such severe pain that walking is not possible even with crutches regardless of duration of symptoms. A slip is classified as stable if walking and weight bearing are still possible with or without crutches.

Jacobs described the head-neck angle on the Smith Petersen lateral view that offers a true lateral, reproducible position but the head of the femur is often very difficult to see because of obesity of the patients (Jacobs 1972).

The advent of the computed tomography scan (CT) has brought advances in diagnosis and treatment of SCFE. The CT scan can be used to confirm epiphyseal displacement and to accurately measure the amount of displacement. Cohen utilised the head-neck angle on the CT scan (Figure 6). He stated that "the computerised tomogram is a more accurate and reproducible method of assessing both posterior angulation and epiphyseal displacement" (Cohen et al 1986). It has also been shown to be of assistance in better evaluating the relation between the femoral head and neck, as well in assessing early physeal plate closure in severe slips.

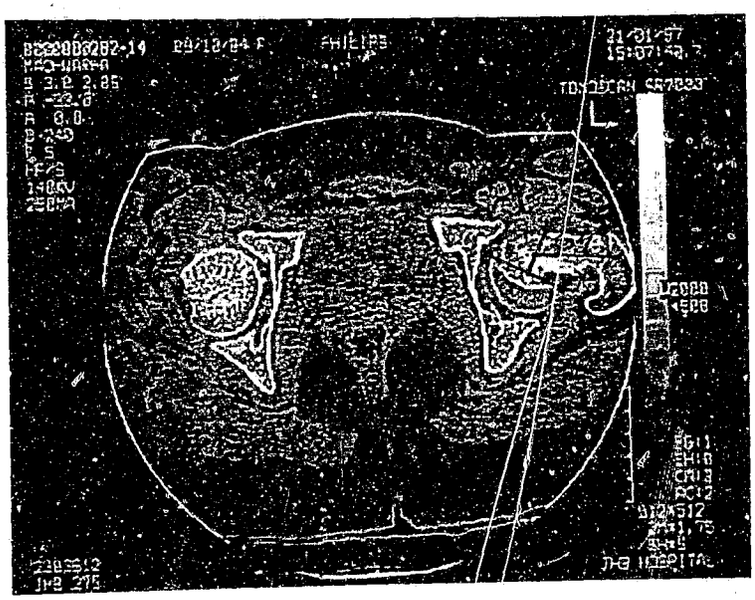


Figure 6: *CT scan of the pelvis through both hips. The left hip shows a SCFE and Cohen's angle of 64°.*

All of our patients have had an A-P radiograph of the pelvis and a CT scan of the hips taken. We did not perform lateral radiographs of the involved hips because of the potential of increasing the physeal displacement during positioning for the radiograph.

The severity of the physeal slip was assessed by the head-neck angle measured on the coronal CT scan view. In the present study we used the facilities of the Department of Radiology at Baragwanath Hospital. Computed tomography was carried out on a Philips helical Tomoscan SR 7000.

The radiographic classification of the severity of the slip was based on the maximum anatomic displacement of the femoral head on the femoral neck measured in degrees between a line through the base of the epiphysis and a line along the femoral neck axis (Cohen's angle). The angle by which the measurement differed from the normal 90° was the angle of displacement (Figure 6). The severity was defined as mild with a < 30° slip, moderate with a 30°-50° slip, or severe with a > 50° epiphyseal slip.

Bone biopsies

Bone biopsies are most frequently obtained from the anterior iliac crest region because this site has been shown to represent features of the skeleton as a whole. The standard site is two centimetres below the iliac crest and two centimetres behind the anterior superior iliac spine (Melsen et al 1981). A transcortical cylinder with a diameter of 6-8 mm is cut with a circular saw. This sample size provides adequate material for most histomorphometric analyses. The biopsy procedure itself is safe and can be performed under local anaesthesia. In our group each patient had a transiliac cylinder of bone 7.5 mm in diameter taken with a Mayo bone biopsy trephine (Zimmer USA, Warsaw, IN). All biopsies were performed in the operating theatre under fully sterile conditions as part of the surgical procedure carried out for stabilisation of the slipped capital epiphysis. In preparation for the bone biopsy, tetracycline double labelling was administered in all patients. Each patient received demethylchlortetracycline 300 mg for 2 days and again for 4 days, after a 10 days drug free-interval. The biopsies were taken between 3 and 10 days after the last tetracycline dose. The biopsy core was then fixed in 70% alcohol rather than in formalin to prevent elution of the mineralization front and with it tetracycline. The specimen was then sent to the laboratory for further processing. Bone histomorphometric

analysis requires undecalcified bone because of the need to assess mineralization. Our bone samples were therefore processed undecalcified, and embedded in methylmethacrylate. Methylmethacrylate is used as embedding medium because its hardness is similar to that of bone; this prevents shattering of bone during cutting. Four pairs of sections were cut at 7 microns on a Jung K heavy-duty microtome. One section of each pair was stained with Goldner's trichrome stain for examination of structural and static bone turnover variables and the other was left unstained for analysis of tetracycline – based dynamic bone turnover variables (Figure 7). Definitions of all variables are given in Table III (page 19).

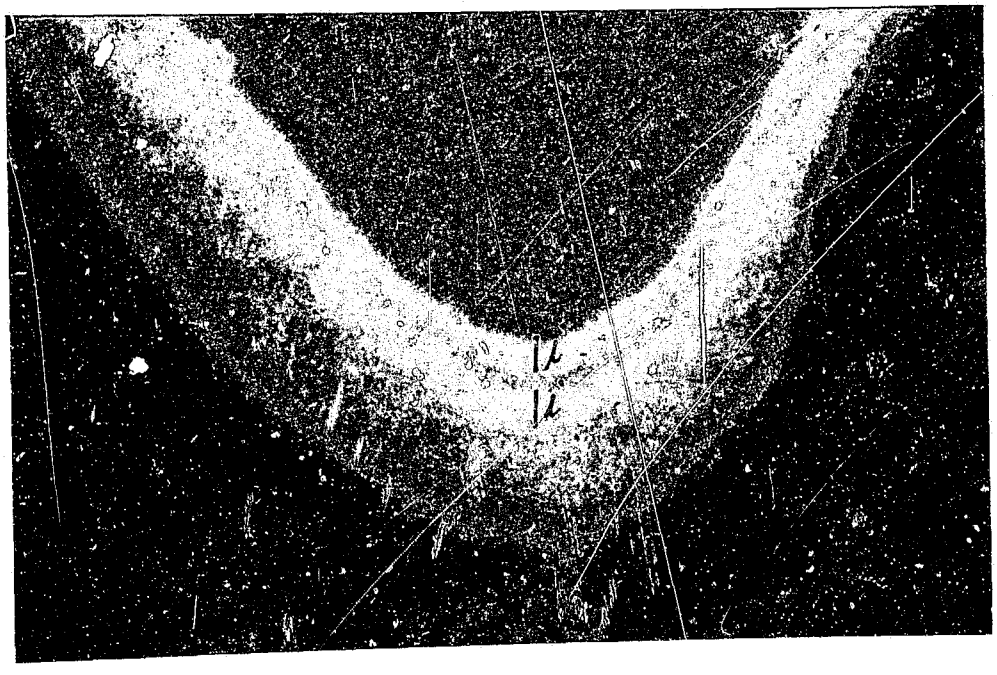


Figure 7: *Photomicrograph of a double tetracycline label under ultraviolet fluorescent light. Interlabel distance i divided by the number of days elapsed between the administration of the centre of each label gives the mineral apposition rate.*

It is important to perform the bone biopsy procedure and to prepare the bone samples and sections correctly since too small a sample or one that has been damaged during biopsy may substantially reduce the amount and quality of data obtainable.

For these reasons the following are minimum requirements for good quality biopsy samples and sections:

- Samples should have both cortices present and intact.
- Samples should not be compressed or twisted, and adequate material for complete analysis should be obtained for reasons of valid statistical analysis.
- In good quality sections, the trabecular structure is free of cracks and fractures.
- Marrow should be closely aligned with trabecular surfaces.
- Specimens should not be over - or understained. Understained specimens show poor cellular detail of bone. Overstained bone leads to misinterpretation of the bone-osteoid border.
- Tetracycline labels must be intact, not faded or washed out by water or acid.

Trabecular bone was examined by routine histomorphometry (Schnitzler et al 1990), using a Videoplan semiautomatic image analyser (Kantron, Munich, Germany) and the Osteoplan II program (Malluche et al 1982). The variables examined are given in Table III. Terminology and formulae used are those recommended by the American Society for Bone and Mineral Research (Parfitt et al 1987).

Table III: *Histomorphometric variables of iliac crest biopsies.*

ABBREVIATION	UNIT	DEFINITION
STRUCTURE		
BV/TV	%	Bone volume in tissue volume
Tb.Th	μm	Trabecular thickness
Tb.N	N/mm	Trabecular number per mm of a straight line
Tb.Sp	μm	Trabecular separation
W.Th	μm	Wall thickness of trabecular osteons
STATIC BONE TURNOVER		
OV/BV	%	Osteoid volume in bone volume
OS/BS	%	Osteoid-covered bone surface
O.Th	μm	Osteoid thickness
Ob.S/BS	%	Osteoblast covered bone surface
ES/BS	%	Eroded surface (with or without osteoclasts)
E.De	μm	Erosion depth (mean value)
Oc.S/BS	%	Osteoclast covered bone surface
DYNAMIC BONE TURNOVER		
MAR	μm/day	Mineral apposition rate
dLS/BS	%	Double labeled bone surface
sLS/BS	%	Single labeled bone surface
BFR/BS①	$\mu m^3/\mu m^2$/year	Bone formation rate per unit bone surface
Aj.AR②	μm/d	Adjusted apposition rate (averaged over all osteoid surfaces)
Mlt③	days	Mineralization lag time (time from deposition of osteoid to start of mineralization)

(①BFR/BS = MAR * (dLS/BS + ½ sLS/BS)

②Aj.AR = (BFR/BS) / OS/BS

③Mlt = O.Th / Aj.AR)

Control values for structural and static bone turnover variables were obtained from 18 black subjects. Twelve were males and six females, aged 10 to 21 years with a median of 13.5 years. Their mean age did not differ from that of our patients. Of these samples 12 had been taken from previously healthy black individuals who had died suddenly and had no demonstrable organic disease at autopsy. The other six samples were taken from healthy, ambulant black individuals during bone graft surgery. Control values for tetracycline-based variables were taken from five of these six individuals. Two were males and three females with a median age of 17 years.
Diagnostic histomorphometric criteria for osteomalacia were osteoid thickness in excess of 15 microns and mineralization lag time of more than 100 days (Parfitt 1990). We also looked for other features of osteomalacia, namely osteoid buried in the depth of mineralised bone and blurred tetracycline labels of low fluorescent light intensity (Malluche et al 1982).

Criteria for the diagnosis of histologic hyperparathyroid bone disease were elevated osteoid surface and eroded surface, peritrabecular marrow fibrosis (expressed as percentage trabecular bone surface covered by fibrosis) and normal osteoid thickness. All specimens were also examined for tunnel or hook erosions (erosion tunnels burrowing toward the trabecular core), which is a feature of excessive erosion activity in hyperparathyroidism.

Spinal Bone Mineral Density

For the measurement of bone mineral density (BMD) we used dual energy X-ray absorptiometry (DEXA). The technique analyses bone mineral content (BMC) by measuring the attenuation of an X-ray beam passed through the patient's body (Johnston et al 1995). The more bone a patient has, the more radiation energy is absorbed, and the weaker is the emerging beam which is measured in the detector. The X-ray source emits

two energy peaks (dual energy), one measures soft tissue density, and the other measures both, soft tissue and bone density. The computer subtracts the soft tissue value from that of soft tissue and bone, divides the resultant bone mineral content by the bone area scanned, and prints the resultant BMD values on a reference curve. Software is available for the spine (L1 to L4), proximal femur, forearm, and whole body. In all regions results are expressed as BMD = BMC / area in g/cm² (bone mineral density = bone mineral content / area scanned).

According to the World Health Organisation bone loss in adults is defined in the following categories (WHO Study Group 1994):

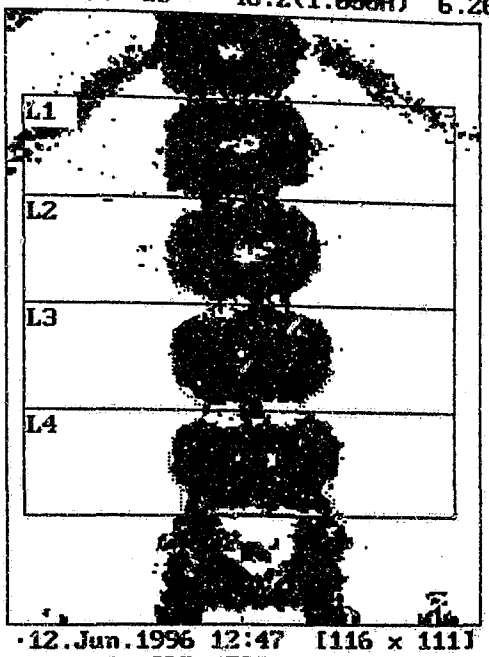
1. Normal bone: 0 –1.2 SD (standard deviation, or T-value)
   below the young (age 30) normal mean
2. Osteopenia: 1.2 – 2.5 SD below the young normal mean
3. Osteoporosis: 2.5 or more SD below the young normal mean
4. Severe osteoporosis: same as 3. with fragility fractures(c)

In the children the same number of SD's may be used for diagnosis but the SD's are those of the age-related mean (z-values).

Among our 29 patients, bone mineral content (BMC) and bone mineral density (BMD) were measured in 13 children (6 male, 7 female). A Hologic QDR 1000 scanner was used to measure vertebrae L1 trough L4 in postero-anterior projection. Hologic reference data for children were used for comparison (Figure 8, page 27) because we do not yet have reference data for black South African children. Hip bone density was not measured because hip pathology, potentially bilateral, would have affected bone mineral density. New bone formation could have increased and local disuse osteoporosis could have decreased BMD.

WITS MED SCHOOL

k = 1.131 d0 = 46.2(1.000H) 6.268



·12.Jun.1996 12:47 [116 x 111]
Hologic QDR-4500A (S/N 45233)
Lumbar Spine V8.16f:3

Y06129606 Wed 12.Jun.1996 12:36
Name: PETROS RAMAKWETSANE
Comment: BARA PAEDS
I.D.: GK230867 Sex: M
S.S.#: - - Ethnic: B
ZIPCode: Height: 150.00 cm
Operator: ABG Weight: 30.00 kg
BirthDate: 15.Apr.82 Age: 14
Physician: SCHNITZLER
Image not for diagnostic use

TOTAL BMD CV FOR L1 - L4 1.0%

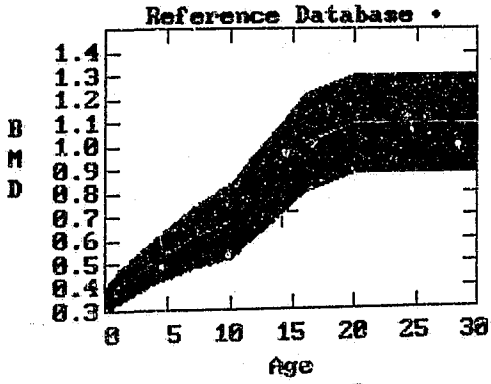
C.F. 1.030 0.999 1.000

Region	Est.Area (cm^2)	Est.BMC (grams)	BMD (gms/cm^2)
L1	7.98	5.03	0.631
L2	9.49	6.52	0.687
L3	10.54	7.93	0.752
L4	11.96	9.03	0.755
TOTAL	39.96	28.51	0.713

HOLOGIC

WITS MED SCHOOL

f Lumbar Spine
Reference Database •



BMD(L1-L4) = 0.713 g/cm^2

Region	BMD	T(30.0)		Z	
L1	0.631	-3.43	63%		
L2	0.687	-3.70	63%		
L3	0.752	-3.19	68%		
L4	0.755	-3.55	66%		
L1-L4	0.713	-3.43	65%	-1.85	79%

• Age and sex matched
T = peak bone mass

04 Nov 91

Y06129606 Wed 12.Jun.1996 12:36
Name: PETROS RAMAKWETSANE
Comment: BARA PAEDS
I.D.: GK230867 Sex: M
S.S.#: - - Ethnic: B
ZIPCode: Height: 150.00 cm
Operator: ABG Weight: 30.00 kg
BirthDate: 15.Apr.82 Age: 14
Physician: SCHNITZLER

HOLOGIC

Figure 8: Sample of results of measurement of bone mineral density with HOLOGIC equipment.

Biochemistry

All of our patients were tested for serum and urine biochemical variables relating to bone metabolism. Tested serum variables were creatinine, phosphorus, calcium, and alkaline phosphatase, and urine variables were 24 hour values for creatinine, phosphorus, and calcium. Alkaline phosphatase, serum and urine phosphorus and serum and urine creatinine were measured by routine Technicon II autoanalyser methods. Serum calcium and urine calcium concentrations were measured by atomic absorption spectrophotometry. Control values were used from previously published reports (Pettifor et al 1981). Serum total 25-hydroxyvitamin D levels were measured by the kidney cytosol receptor assay in nine patients, and parathyroid hormone concentration by immunoradiometric assay in ten patients. Table IV shows normal biochemical values for children.

Table IV: *Normal biochemical values for children*

Variable		**Normal range**
sCalcium	(mmol/l)	2.25 – 2.65
sAlkaline phosphatase	(units/l)	< 300
sPhosphorus	(mmol/l)	1.3 – 1.8
uCalcium	(mmol/24 hours)	2.5 – 7.5
25 – hydroxyvitamin D	(nmol/l)	10 – 50
Parathyroid hormone	(pg/ml)	10 - 55

Statistical analysis

All average values are given as median and the range of the lowest and highest values, unless indicated otherwise. Correlations between continuous variables were assessed by Pearson's correlation coefficient, and those involving semiquantitative variables by Spearman's rank correlation coefficient. Comparisons of continuous variables between patients and controls were made by the rank sum test. Differences between proportions were tested with the chi-square test, or where indicated by small numbers, by the Fisher-exact test.

Ethical consideration

The study was conducted with the permission of the Committee for Research on Human Subjects of the University of the Witwatersrand under Clearance Certificate No. 18/8/91.

All patients or their parents or guardians gave written informed consent to have an iliac crest bone biopsy taken at the time hip surgery.

RESULTS

Personal Data

In the period between October 1991 and August 1996, 29 black teenagers with slipped capital femoral epiphysis were included in the study. Fifteen were boys and fourteen girls, aged from 11 to 17 with a median value of 15 years. Boys were older than girls. Personal characteristics of 29 patients included in the study are presented in Table V.

Table V: *Anthropometric characteristics of 29 black children with slipped capital femoral epiphysis*

	BOYS N = 15		*GIRLS N = 14*		
	Median	**Range①**	**Median**	**Range①**	**P - values②**
Age (years)	16	13 - 17	14	11 - 15	0.0003
Weight (kg)	54	40 – 103	56	35 – 92	NS
Height (cm)	162	149 – 182	154	141 – 172	0.036
BMI③	22.6	19.1 – 24.7	24.2	21.0 – 26.9	NS
Pubertal development (Tanner stage)	2.5	1 – 4	2	1 – 4.5	NS

①Lowest to highest values; ②rank sum test; ③BMI, body mass index (weight/height^2)

Most of the children, in fact 86.2%, came from Soweto or similar urban areas where the socio-economic status tends to be better than in rural areas. It has previously been shown by Petiffor et al (1979) that the pathogenesis of biochemical abnormalities of bone metabolism in rural children is due to low dietary calcium intake. Judging by the

body mass index (BMI , weight/height^2) of our patients, the nutritional standard was more than adequate in most. The body mass index was above th 95th percentile in 55.2% of the patients (33% of boys, 78.6% of girls), and only three boys had a BMI below the 50th percentile. These comparisons were based on unpublished data by Noel Cameron, collected from healthy sub-Saharan African children. Investigation of socio-economic status showed that all of the families lived in single storey houses. Sixty-four percent of families lived in houses of four or more rooms with an average of 1.25 (0.6 – 4) persons living per room. Family size varied from 2 to 13 members. In 56% of cases the father was either unemployed or did not live with the family, 15% of fathers were artisans or professionals, and the remainder were working as labourers. Sixty percent of mothers were contributing to family income. Ninety-three percent of children were attending school and spent after-school hours outdoors where they were exposed to adequate sunlight because of the mild climate.

Dietary calcium intake was assessed by the frequency of intake of dairy products and classified as daily, once or twice a week, or less often. Calcium intake varied among the children. Only 20% of the children took dairy products daily, the majority, 52%, once or twice a week, and 28% less frequently or not at all. Thus, 80% of the children could be judged to have inadequate dietary intake of calcium.

Pubertal development was assessed according to Tanner staging. Using the Tanner stage pictures, boys were evaluated for genital size and pubic hair development, and girls were assessed for breast and pubic hair development. The average value of the two criteria was assigned to each individual. Taking all patients together, the average Tanner stage of pubertal development was 2.5 (1 – 4.5). Boys were slightly more mature than girls. Personal characteristics are given in Table V. Ten of 14 girls or 71.4% were premenarchal, and 4 of the girls (28.6%) had gone through menarche at the time of admission, namely, 1, 3, 20 and 23 months before presentation with slipped capital femoral epiphysis. In 3 of these 4 girls the onset of hip symptoms dated back to before the onset of manarche. Thus, only one of the 14 girls (7%) suffered a SCFE after menarche, namely 11 months later. The ages of the girls are given Table VI.

Table VI: *Comparison of age and of bone histomorphometric variables in pre- versus postmenarchal girls with SCFE.*

	Premenarchal N = 10		Postmenarchal N = 4		
	Median	**Range①**	**Median**	**Range①**	**P - value②**
Age (years)	13.5	11 – 15	14.5	12 –15	NS
BV/TV③ (%)	11.9	7.1 – 16.8	18.4	14.2 – 22.0	0 02
Tb.Th (μ)	88	70 – 102	114	95 – 123	0.009
Tb.N (N/mm)	1.378	0.784 – 1.928	1.645	1.401 – 1.849	NS
Tb.Sp (μm)	635	431 – 1186	512	422 – 591	0.056
W.Th (μm)	26.19	17 – 27.74	25.96	24.02 – 37.15	NS
OV/BV (%)	1.14	0.09 – 5.2	2.45	0.61 – 3.65	NS
OS/BS (%)	8.4	1.5 – 33.1	14.6	3.5 – 24.6	NS
O.Th (μm)	5.34	2.24 – 7.44	9.25	8.22 – 9.56	0.006
Ob.S/BS (%)	1.98	0.28 – 11.91	5.74	1.94 – 9.31	NS
ES/BS (%)	8.0	2.4 – 17.6	5.8	3.8 – 8.5	NS
E.De (μm)	6.81	4.29 – 11.48	7.44	6.72 – 7.80	NS
Oc.S/BS (%)	1.09	0 – 3.48	0.13	0.07 – 1.29	NS
MAR (μm/day)	0.630	0.165 – 1.063	0.878	0.782 – 0.986	NS
dLS/BS (%)	4.11	0.05 – 15.7	8.59	3.15 – 19.09	NS
sLS/BS (%)	1.49	0 – 5.12	1.96	1.23 – 3.32	NS
BFR/BS ($\mu m^3/\mu m^2$/year)	16.06	0.13 – 41.7	32.04	12.37 – 59.23	NS
Aj.AR (μm/day)	0.360	0.024 – 0.713	0.632	0.599 – 0.971	0.056
Mlt (days)	15.6	5.0 – 125.4	13.8	9.8 – 15.6	NS

①Lowest to highest values; ②Rank sum test; ③For definitions see Table III

Hip pathology

All 29 patients investigated in this study complained of hip pain which started on average 4 (0 to 36) months before presentation. Six patients who had had symptoms for less than a month, were classified as having acute slips. The onset of symptoms was spontaneous in 17 patients, or 59 %. The other 11 children could remember a specific traumatic episode prior to their hip symptoms. In one patient the mode of onset was not recorded. The causes of trauma were falls during play or sport in all children questioned. The condition was unilateral in 18 (62%) cases. The right hip was involved in 11 (38%) patients, and the left hip in 7 (24%). Bilateral involvement was present in 11 (38%) cases (Table VII). On clinical examination all patients had restriction of movement, pain and an antalgic gait with an externally rotated leg. Three of the patients who presented with an acute slip and a history of a traumatic event only 1-2 days before admissions were unable to weight-bear at all.

Table VII: *Classification of hip pathology*

Duration	Acute	Acute-on-chronic	Chronic
	6	10	13
Mechanism	Spontaneus	Traumatic	Unknown
	17 (59%)	11 (38%)	1 (3%)
Location	Bilateral	Unilateral	
	11 (38%)	18 (62%)	Right 11 (38%)
			Left 7 (24%)

Plain radiographs confirmed the slip in all cases. We did not perform lateral radiographs of the involved hips because of the potential of increasing of the physeal displacement during positioning for the radiograph. All patients had CT scans which revealed the severity of the slip: all femoral heads were retroverted by more than 50° measured by the Cohen head-neck angle. All slips were therefore classified as severe (angle > 50°). Associated orthopaedic conditions were genu valgum (knock-knee) in 11 (38%) patients, and scoliosis in one patient.

Bone biopsies

Sex differences were negligible: only the value for trabecular number was lower in boys. The values were 1.113 (0.783-1.884) for boys vs 1.409 (0.784-1.928) N/mm for girls, with p = 0.036. In view of there being no other sex differences, data from both sexes were analysed together.

Comparison of the patients' values with reference data (Table VIII) revealed that patients had lower bone volume (BV/TV) and wall thickness, thinner trabeculae (Tb.Th), and a tendency to greater trabecular spacing (Tb.Sp) than controls (Figures 9 and 10).

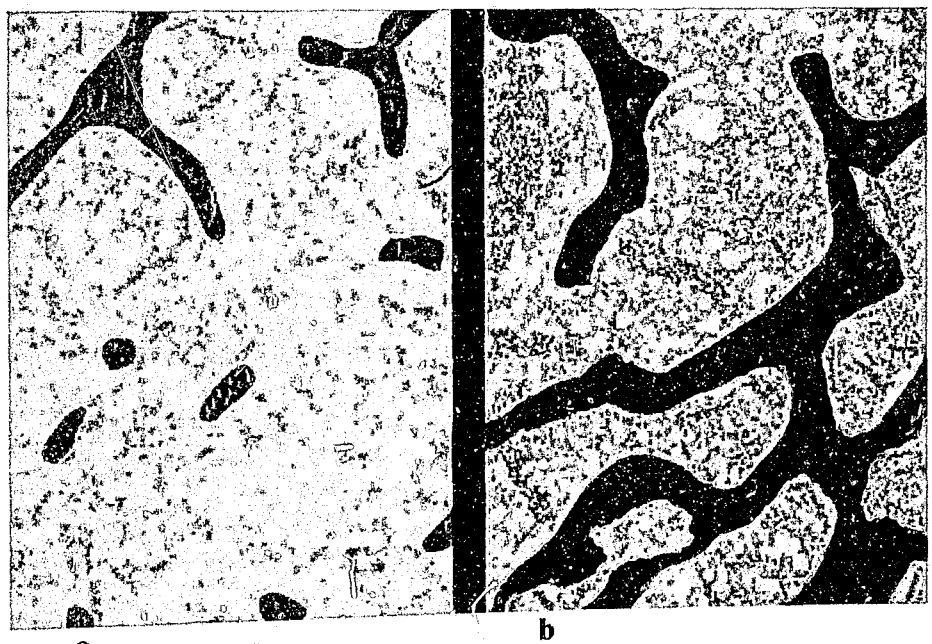


Figure 9: *Comparison of photomicrographs of iliac crest bone biopsies of a patient with SCFE (a) and that of a normal control (b)*

Table VIII: *Histomorphometric variables of iliac crest bone biopsies from 29 teenagers with SCFE and reference values.*

	Slipped capital femoral epiphysis		Reference values		
	Median	Range②	Median	95% CI③	p-value④
STRUCTURE	**N = 29**		**N = 18**		
BV/TV① (%)	12.3	6.8 – 22.2	20.0	14.2 – 26.8	0.0003
Tb.Th (μm)	92	62 – 176	148	122 – 161	0.0002
Tb.N (N/mm)	1.195	0.783 – 1.928	1.279	1.029 – 1.520	NS
Tb.Sp (μm)	728	413 – 1186	619	522 – 690	0.053
W.Th (μm)	26.56	17 – 37.15	36.53	25.67 – 42.89	0.0002
STATIC BONE TURNOVER	**N = 29**		**N = 18**		
OV/BV (%)	1.14	0.09 – 5.20	3.93	2.89 – 5.03	0.0001
OS/BS (%)	9.3	1.5 – 33.1	26.9	18.48 30.69	0.0001
O.Th (μm)	6.06	2.24 – 19.56	9.19	7.2 – 11.0	0.0002
ES/BS (%)	7.1	2.4 – 19.2	8.2	3.92 – 12.54	NS
E.De (μm)	7.15	4.29 – 14.56	7.85	6.63 – 8.69	NS
DYNAMIC BONE TURNOVER	**N = 29**		**N = 5**		
MAR (μm/day)	0.677	0.165 – 1.652	0.778	0.576 – 0.98	NS
dLS/BS (%)	3.12	0.05 – 19.52	12.68	4.9 – 26.47	0.029
sLS/BS (%)	1.26	0 – 5.12	1.84	1 – 3.8	NS
BFR/BS ($\mu m^3/\mu m^2$/year)	9.1	0.1 – 59.2	41.7	12.2 – 101.5	0.037
Aj.AR (μm/d)	0.374	0.024 – 1.276	0.397	0.172 – 0.755	NS
Mlt (days)	17.6	3.7 – 125.4	20.2	15.4 – 64.0	NS

①For definitions see Table III; ②Lowest and highest values; ③95% confidence interval; ④Rank sum test

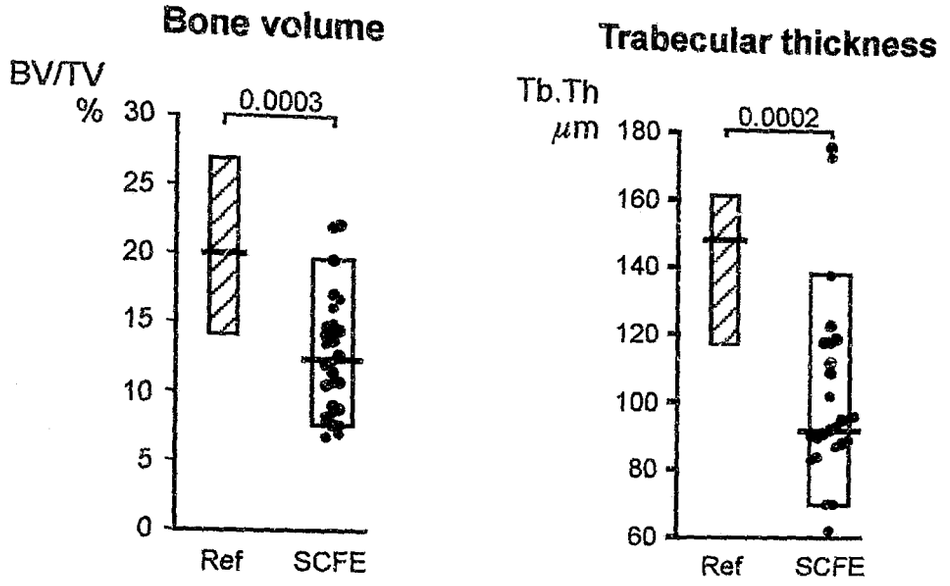


Figure 10: *Scattergram of bone volume and trabecular thickness in 29 patients with SCFE. The first bar represents the reference values of a control group and the second bar the values of patients with SCFE. Each dot represents one patient. Bar values for patients are given as median and 10^{th} and 90^{th} percentile. Both variables were significantly lower in the patient group with p values of 0.0003 and 0.0002, respectively.*

Patients also had lower average values for osteoid volume (OV/BV), osteoid surface (OS/BS), osteoid thickness (O.Th), double-labelled surface (dLS/BS), and bone formation rate (BFR/BS) than controls (Figures 11and 12). These findings suggest that bone formation was compromised in our patients with SCFE. No evidence of hyperparathyroid bone disease or osteomalacia was encountered.

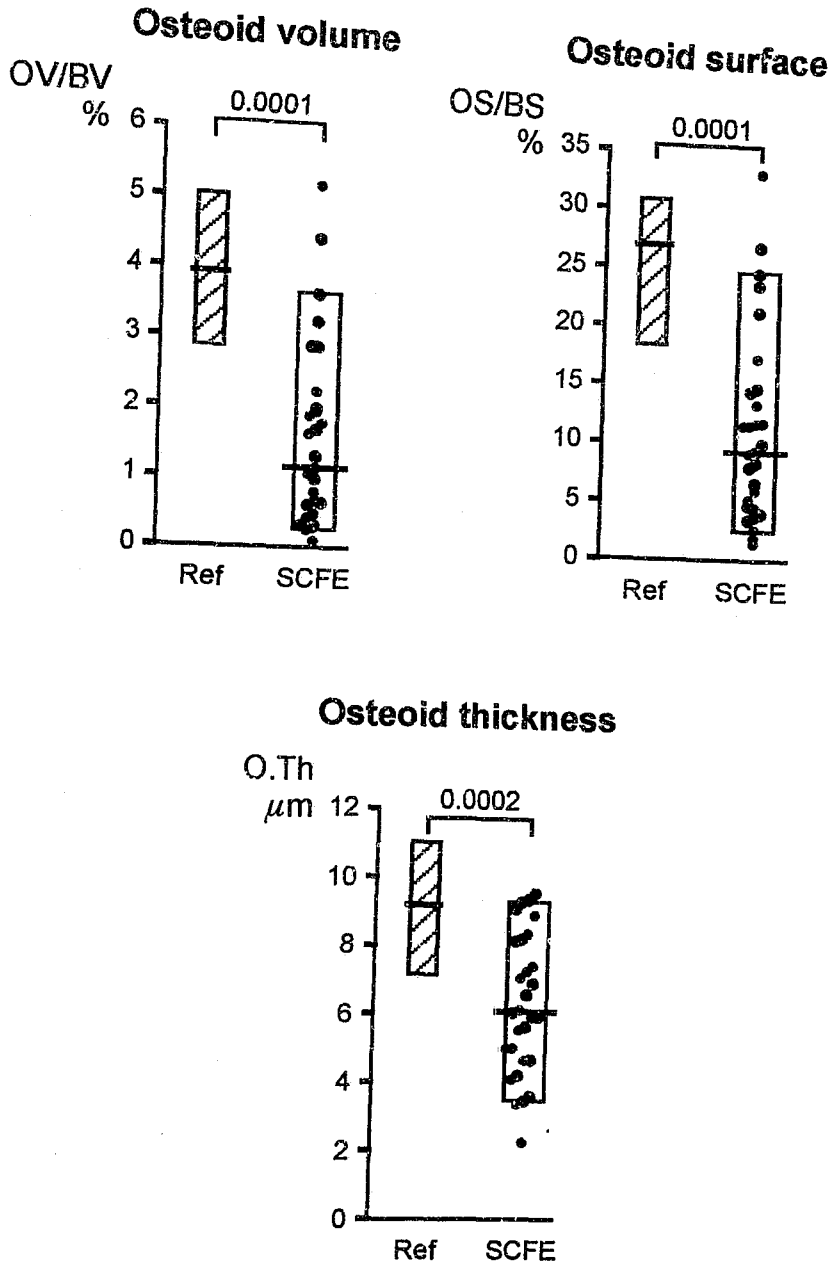


Figure 11: *Scattergram of osteoid volume, osteoid-covered bone surface and osteoid thickness in 29 patients with SCFE. The first bar represents the reference values of a control group and second bar the values of patients with SCFE. Each dot represents one patient. Bar values for patients are given as median and 10th and 90th percentile. All three evaluated variables were found to be significantly lower in the patients in comparison with the control group, with p values of 0.0001, 0.0001, and 0.0002, respectively.*

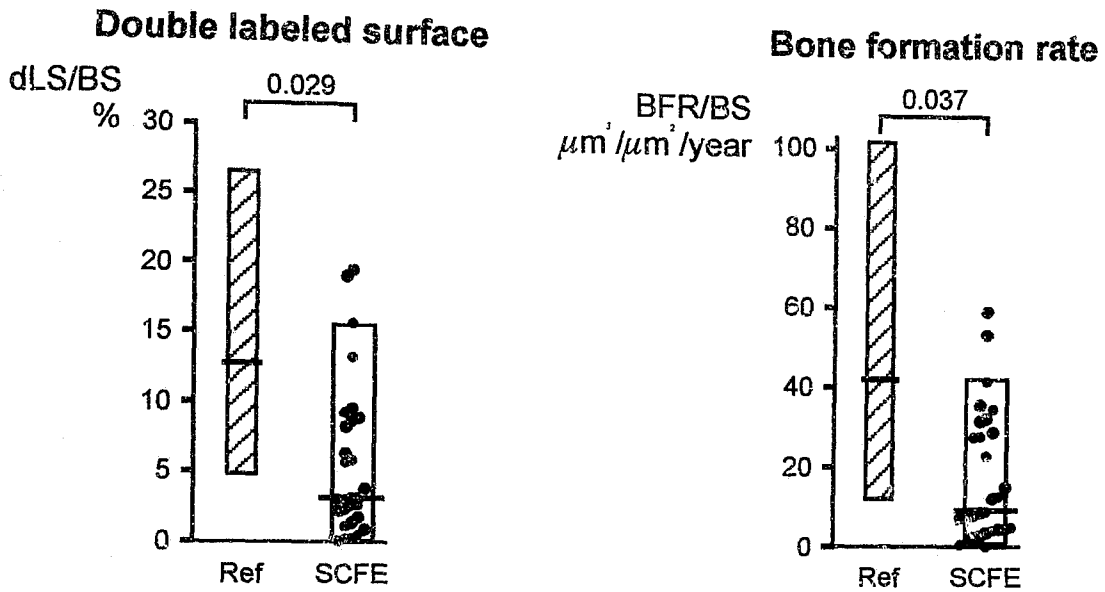


Figure 12: *Scattergram of double labelled bone surface (p=0.029) and bone formation rate (p=0.037) in 29 patients with SCFE as compared to reference values. The first bar represents the reference values of a control group and second bar the values of patients with SCFE. Each dot represents one patient. Bar values for patients are given as median and 10th and 90th percentile.*

Body mass index (BMI) and duration of symptoms had not affected histomorphometric variables. Biopsies were taken from the side of an affected hip in 18 patients, from the opposite side in 7, and in four patients the side of biopsy was not stated. Biopsies taken on the side of an affected hip had higher values for osteoid volume (OV/BV) and osteoblast surface (Ob. S/BS) than biopsies taken from the of an unaffected hip (Table IX).

Table IX: *Comparison of histomorphometric results with regards to the side of the biopsy.*

BIOPSY SITE	**Affected hip N=18**	**Opposite hip N=7**	**p-value①**
Osteoid volume % (OV/BV)	1.66 (0.32 – 5.2)	0.32 (0.09 – 2.24)	p = 0.027
Osteoblast surface % (Ob.S/BS)	3.29 (0.47 – 18.2)	0.65 (0 – 10.7)	p = 0.032

(①Rank sum test)

Bone volume (BV/TV) was below the reference range of 14.2% in 65.5% of cases. Compared with cases with normal bone volume these patients also had lower values for trabecular thickness (Tb.Th) (p = 0.037), and trabecular number (Tb.N) (p = 0.0002), and a tendency to lower adjusted apposition rate (Aj.AR) (p = 0.057). Most importantly, these patients had had less frequent intake of dairy products than those with normal bone volume (p = 0.024 , Fischer exact test).

As previously mentioned, 10 of our 14 female patients were premenarchal, and 4 girls had gone through menarche. Comparison of these two groups suggested that premenarchal status had an adverse effect on bone. Premenarchal status was associated with lower bone volume (BV/TV), thinner trabeculae (Tb.Th), lower osteoid thickness (O.Th) (Figure 13), and a tendency to lower adjusted apposition rate (Aj.AR). These data are shown in Table VI.

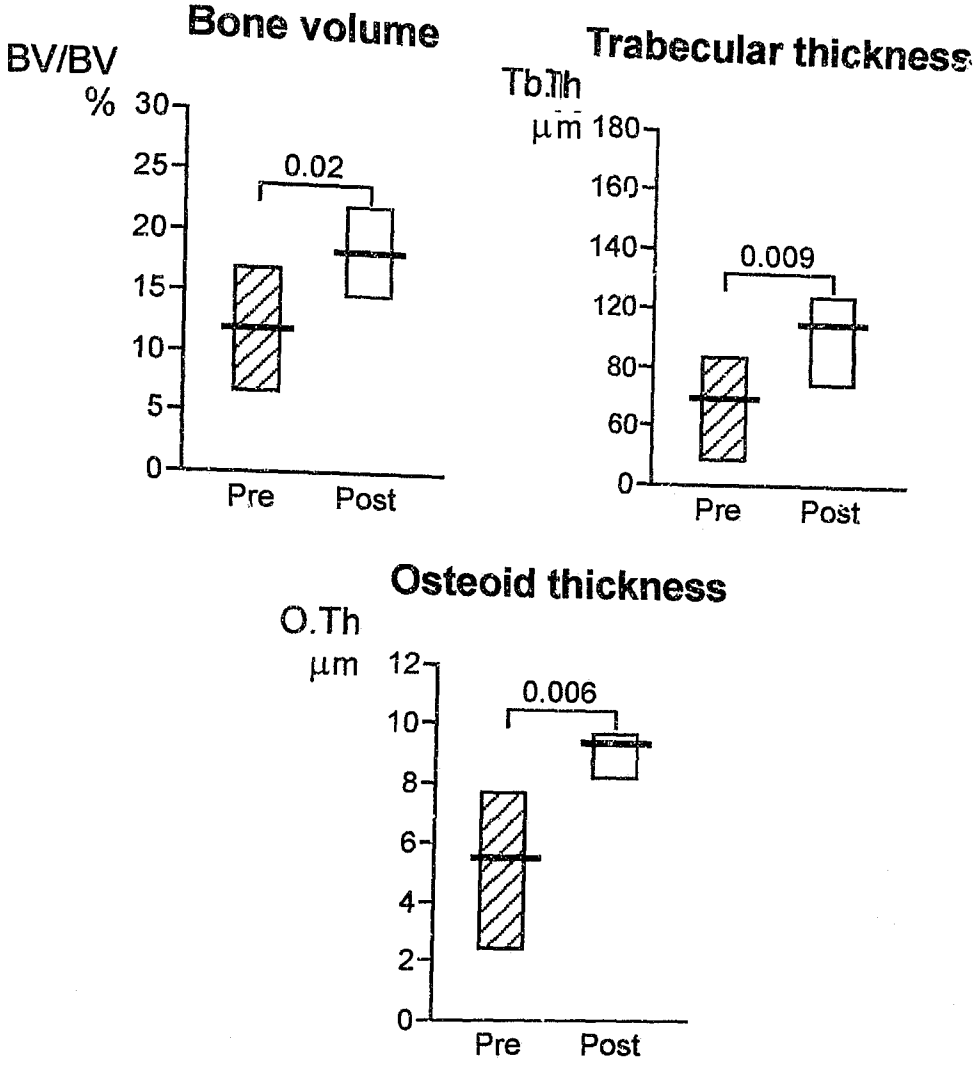


Figure 13: *Sattergram of bone volume, trabecular thickness and osteoid thickness in pre- versus postmenarchal girls with SCFE. The first bar represents the reference values of a control group and the second bar the values of patients with SCFE. Each dot represents one patient. Bar values are given as median and 10^{th} and 90^{th} percentile. All three variables showed significantly high values in post-menarchal girls.*

The beneficial influence of menarche on bone was also reflected in significant correlations between months since menarche and histomorphometric variables (Table X): BV/TV ($r = 0.667$, $p = 0.009$)

Tb.Th ($r = 0.745$, $p = 0.002$)

Tb.Sp ($r = -0.549$, $p = 0.042$)

O.Th ($r = 0.784$, $p = 0.0009$)

Aj.AR ($r = 0.549$, $p = 0.042$).

Significant correlations were found despite the fact that there were only four postmenarchal girls. Looking at Tanner staging in the female group of patients, pubertal development correlated positively with osteoid thickness (O.Th) ($r = 0.589$, $p = 0.027$). The correlation with trabecular thickness (Tb.Th) just failed to reach statistical significance ($r = 0.519$, $p = 0.057$).

Spinal bone mineral density

In 13 (6 males, 7 females) of the 29 patients, bone mineral content (BMC) and bone mineral density (BMD) were measured. A Hologic QDR 1000 scanner was used to measure vertebrae L1 to L4 in postero-anterior projection. Results were expressed in age-related z - values of normal reference data in order to take account of the effect of age on BMC and BMD. Seven of the 13 (54%) BMD values were more than 1 standard deviation (SD) below the age-related mean and therefore reflected osteopenia. A further three values fell between 0 and 1 SD below the mean (Figure 14) and could be rated normal.

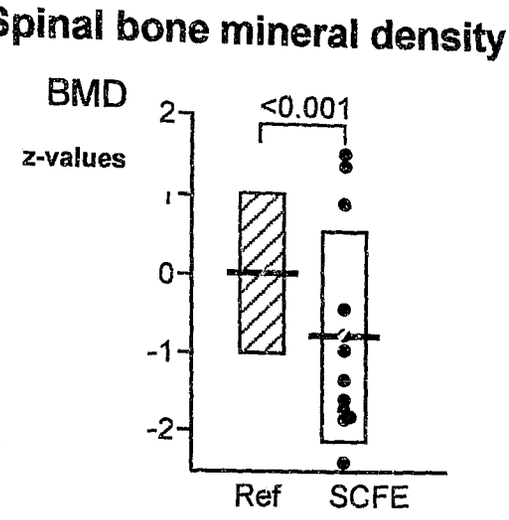


Figure 14: *Scattergram of spinal bone mineral density measured in 13 patients with SCFE. The first bar represents the reference values of a control group and the second bar the values of patients with SCFE. Each dot represents one patient. Bar values are given as median and 10^{th} and 90^{th} percentile. The patients had significantly lower values than the reference population.*

Chi-square testing revealed that a significantly greater proportion of SCFE patients than of a normal reference population had values below -1SD ($p = 0.001$). Spinal bone mineral content correlated with trabecular thickness (Table X) and Tanner stage ($r = 0.827$, $p = 0.0005$).

Table X: *Correlations between histomorphometric variables vs. months since menarche and Tanner stage in girls, and vs. biochemical variables and spinal BMC in boys and girls with SCFE*

Histovariables	**Months since menarche**	**Tanner stage**	**PTH**	**Serum phosphorus**	**Spinal BMC ③**
BV/TV (%) ①	0.667 ②				
	0.009				
Tb.Th (μm)	0.745	0.519			0.656
	0.002	0.057			0.015
Tb.Sp (μm)	-0.549				
	0.042				
O.Th (μm)	0.748	0.589			
	0.0009	0.027			
Aj.AR (μm/d)	0.549		0.661	-0.764	
	0.042		0.038	0.010	

①For definitions see Table III; ②r and p values; ③BMC, bone mineral content

Biochemistry

In all patients serum creatinine was within normal limits. The remaining results are given in Table XI. Median values for serum calcium, alkaline phosphatase and phosphorus were within normal limits.

Table XI: *Serum (s) and urine (u) biochemistry in black children with SCFE*

Variable	N	Median	Range①	Reference range
sCalcium mmol/l	26	2.43	2.13 – 2.84	2.25 – 2.65
sAlkaline phosphatase Units/l	26	243	106 – 1340	<300
sPhosphorus mmol/l	26	1.7	1.1 – 2.15	1.3 – 1.8
uCalcium mmol/24 hours	22	1.78	0.35 – 6.2	2.5 – 7.5
25-hydroxyvitamin D nmol/l	9	18.4	14.8 – 34.4	10 – 50
Parathyroid hormone Pg/ml	10	19.5	8 – 38	10 - 55

(①Lowest and highest values)

25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) levels were normal. The only significant correlation between biochemical and histomorphometric variables was a positive correlation between PTH and adjusted apposition rate, and a negative correlation between serum phosphorus and adjusted apposition rate. These correlations are shown in Table X.

Two boys, 15 and 16 years of age, had low serum calcium concentrations and low urine calcium levels. Their other biochemical values were normal but histomorphometric results showed low values for bone volume (BV/TV) and trabecular thickness (Tb.Th). The other histomorphometric variables were normal.

Two premenarchal girls, 13 and 14 years of age, had high serum calcium values. Their urine calcium and serum alkaline phosphatase levels were within normal limits. Apart from low bone volume (BV/TV) in one, and thin trabeculae (Tb.Th) in both girls, bone histomorphometry was normal.

DISCUSSION

"The Fracture of the thigh nigh to the Joint...Neither only such kind of Fractures, but also the separation of the appendix or head of this bone from its place, may induce one to think it is a dislocation: which thing hath sometimes deceived some heedless Surgeons, who have not dreamt of the divultion of separation of the appendix from the top of the thigh bone."

These words of Ambroise Paré, written in 1554, express disagreement among surgeons of his time concerning slipped capital femoral epiphysis (SCFE). To this day opinions about this condition differ among orthopaedic surgeons, and half a millennium later SCFE remains a condition of uncertain aetiology.

SCFE is often misdiagnosed, especially when patients present with a history of hip pain following an injury. Furthermore, the practitioner must be aware that knee pain in the adolescent may be the only symptom of hip pathology. This presentation is due to referred pain along the sensory distribution of the obturator nerve and is commonly seen in association with hip pathology. The intensity and duration of symptoms traditionally have been used to classify SCFE into four patterns of presentation: preslip, acute, chronic and acute-on-chronic. The true preslip or prodromal stage of SCFE theoretically occurs prior to any actual slippage through the physeal plate. The patient gives a history of an episodic limp and limb weakness associated with intermittent mild pain in the groin, medial thigh, or knee region, particularly with exertion. The accepted definition of an acute slip is where there is a sudden onset of symptoms of less than 3 weeks' duration in a patient who was previously asymptomatic (Fahey et al 1965). A chronic slip is one where the history is longer than 3 weeks in duration. The patient remains ambulatory but does show an antalgic gait. The radiological investigations also show signs of chronicity: there is evidence of bone resorption and new bone formation at the proximal femoral metaphysis. However, when the history is longer than 3 weeks in duration and there are no radiological signs of chronicity then the slip is

classified as being acute-on-chronic. This presentation is associated with an acute increase in slip severity from a previous milder chronic displacement.

Many theories have been advanced to try to explain this hip disorder of adolescence. Several authors have suggested that **mechanical factors** are important in the development of slipped capital femoral epiphysis (Speer 1982, Pritchett et al 1988). Laboratory experiments have demonstrated that the shear load to failure increases with age: Shear strength (kg/cm^2) = 6.56 + 0.55 (age in years), and shear failure load (kg) = shear strength x growth plate cross-sectional area (Chung et al 1976). The same authors also showed that shear force is directly related to the neck shaft angle. Reduction of this angle by 10 degrees reduces the forces necessary to produce a slipped epiphysis by approximately 17%. Although it was confirmed by several authors that shear stresses generated during gait are not likely to produce shear failure, this may change with higher levels of activity in which greater shear stresses are generated (Litchman et al 1984, Pritchett et al 1988).

Obesity has to be taken into consideration as an additional factor. A child is considered obese if the weight is greater than the 95^{th} percentile for age (Pritchett et al 1988). Compared with children of normal weight, obese children showed a significantly reduced angle of femoral anteversion which indicates that increased biomechanical forces generated across the hip joint of obese children lead to increased remodelling of the femoral neck (Galbraith et al 1987). This remodelling could influence the stability of the physis. It takes a load of six to ten times body weight to displace a capital femoral epiphysis in a normal child (Chung et al 1976). During single leg stance already up to three times body weight is borne on the femoral head of the weight-bearing leg (Frankel et al 1970). It is easy to reach slipping load if the child has abnormally increased body weight.

The occurrence of slipped capital femoral epiphysis during the adolescent growth spurt, a period of dramatic endocrine change, suggests that a **hormonal imbalance** may cause, or contribute to, this disorder. The fact that some of the patients

are obese and hypogonadal has led to the suggestion that an endocrine abnormality may play a role in the aetiology of the condition (Waldenstrom 1940, Harris 1950, Burrows 1957, Sorenson 1968, Ogden 1977, Brenkel et al 1989, Wells et al 1993).

Harris showed that an increase in **growth hormone** secretion led to an increase in the thickness of the hypertrophied (weakest) layer of the physis. He also suggested that **oestrogen**, by interfering with growth hormone release from the anterior pituitary, decreased the thickness of the hypertrophied layer. He therefore proposed that an increase in the ratio of growth hormone to oestrogen could lead to slipping of the capital femoral epiphysis (Harris 1950). Growth hormone acts via the intermediary hormone known as somatomedin (Phillips 1980, Underwood 1985). During puberty the plasma somatomedin-C concentration increases above adult values and this rise is related to the increasing levels of sex hormone (Rosenfield et al 1983).

Thyroxin is also important in the maturation of the skeletal system (Smeets et al 1983). The occurence of slipped capital femoral epiphysis in patients with primary hypothyroidism is well documented (Moorefield et al 1976, Crawford et al 1977, Hirano et al 1978, Puri et al 1985). However, there is no evidence of either sub-clinical or clinical hypothyroidism in patients with SCFE (Brenkel et al 1988, Mann et al 1988).

SCFE is also a recognised complication of chronic renal failure, and is in this instance likely due to secondary **hyperparathyroidism** (Shea et al. 1966, Krempien et al 1974, Mehls et al 1975, Nixon et al 1980). Although primary hyperparathyroidism is a rare condition in childhood, reports of this disorder in relation to SCFE have appeared (Rajasuja et al 1961, Chirrof et al 1963, Bone et al 1985). Hyperparathyroidism is thought to cause reso..ption of the metaphyseal bone, which predisposes to traumatic slippage through bone immediately adjacent to the provisional zone of calcification. From the evidence available, it does appear that excessive parathyroid hormone, either from the primary or the secondary disorder, has an adverse effect on the stability of the physeal/metaphyseal complex that can lead to epiphyseal displacement. Since PTH

primarily affects bone, this observation points to a role for bone disease in the mechanism of the slip.

Since **androgens** increase the strength of the physeal plate (Ogden et al 1977) low levels of androgens and delayed puberty may be expected to weaken the physeal plate, making it more susceptible to slip under shearing stresses. However, there is no evidence in the literature of a significant relationship between delay in the onset of puberty and SCFE (Brenkel et al 1989, Exner 1986).

Although no single hormonal abnormality can be directly implicated as the cause of SCFE, bone maturation is delayed in adolescent patients with certain endocrinopathies. It is currently believed that slipping is a multifactorial process influenced by hormonal imbalance of puberty coupled with biomechanical factors. This delicate hormonal imbalance, rather than absolute levels of particular hormones, cause a relative weakening of the epiphyseal plates (Wilcox et al 1988).

Inflammation presenting as synovitis of the hip joint raises the question of cause and effect. There may be an increase in the serum levels of IgA, IgM or IgG, which could represent local tissue alterations, but it is not certain whether this is related to the disease (Eisenstein et al 1976, Morrissy et al 1981).

The adverse effects of **irradiation** on the growing skeleton have long been recognised. The literature describes 20 cases of SCFE following radiotherapy (Barrett 1985). The mean age in postradiotherapy cases was lower, at 11 years, than the usual mean age of 13.5 years for boys and 11.5 years for girls. Whether the cause of the slip is directly attributable to radiotherapy alone or whether chemotherapy has a part to play remained uncertain. Because of the increasing number of long-term survivors of childhood cancer, SCFE should be considered a potential complication in any child whose radiation portal includes the femoral head and neck.

Little was known of the **epidemiology** of slipped capital femoral epiphysis until recently. In order to better understand this disease epidemiological studies were

undertaken. One of the areas of interest was the **seasonal variation** of the disorder (Loder et al 1990, 1996). In Michigan, slipped capital femoral epiphysis has a seasonal variation with a peak onset in mid June, possibly because of increased physical activity during the summer months (Loder et al 1990). Loder and 47 coinvestigators from all continents and 33 different Orthopaedic Centres carried out a large epidemiological study involving 1630 children with SCFE (Loder et al 1996). There was a significant seasonal variation of SCFE in North America and Europe, but not in Africa, Asia, Australia/New Zealand, or South America. The peak month of onset was late June in North America and late July in Europe. This phenomenon of slips occurring significantly more often in summer was only present when the children lived north of the 40° N latitude. The areas with less variable climates did not show a seasonal variation. This fact supports the hypothesis that attributes causation to the level of activity. Another study postulated that the increased incidence in the summer months in Sweden was attributable to an increased content of aminonitriles in cow's milk in summer (Andren et al. 1959). Lesions similar to slipped epiphyses have been shown to occur with increased exposure to aminonitriles in experimental animals. However, no food has been shown to contain aminonitriles to support this hypothesis.

Another possible cause for the seasonal variation of slipped capital epiphysis is **subclinical rickets**. One group of investigators documented subclinical rickets based on low vitamin D levels in winter in children with SCFE in the Detroit area. (Raines et al 1990). These low levels occurred in USA despite nationwide programs that supplement dietary milk and other foods with vitamin D. While inadequate exposure to sunlight can cause vitamin D deficiency rickets this was obviously not the case in our population since our children had adequate exposure to sunlight because of the mild and sunny climate.

Loder and coinvestigators also looked at the **ethnicity** of the 1630 children reviewed (Loder et al 1996). Kelsey previously noted that the average annual incidence of SCFE in Connecticut was 3.19 per 100 000 inhibitans for white children and 7.24 per 100 000 for black children. Thus, the incidence is 2.27 times greater in black than in white children (Kelsey 1971). These findings are very similar to the figures in Loder's

group where the ratio was 2.21, confirming the postulate that slipped capital femoral epiphysis is more common among black adolescents (Loder et al 1996).

To the best of my knowledge and after extensive search of the literature no scientific study has to date examined SCFE patients for **metabolic bone disease** using histomorphometry.

The present study of black teenagers with SCFE revealed that many patients were osteopenic as judged by low bone mass and thin trabeculae. This had likely come about through diminished bone formation that in turn led to reduced wall thickness of osteons and less bone. We considered contributory factors as possible causes of osteopenia. Prolonged symptomatology had been excluded since duration of symptoms had had no effect on histomorphometric values. Neither was local disuse due to ipsilateral hip disease found to be a causative factor, since iliac crest biopsies taken from the side of hip pathology were not different in bone volume and structure from biopsies taken on the side of a sound hip.

Although most children came from low income groups, poor socio-economic conditions were unlikely to be responsible for bone disease since the patients' nutritional status was good or excellent.

Contrary to the findings of Raines and coauthors (1990) who postulated subclinical rickets due to low vitamin D levels as possible cause for SCFE, vitamin D deficiency has been excluded as a cause for the bone disease in our cases, since 25- OHD levels were normal in the children tested and no evidence of osteomalacia was found on histomorphometry.

Despite the absence of current biochemical and histological evidence of hyperparathyroidism, past low dietary calcium intake may have had an adverse effect on bone since children with subnormal bone volume were found to have had the lowest

consumption of dairy products. The subnormal median values for urine calcium levels is in keeping with low dietary calcium intake.

The associated genu valgum deformity in 38% of the children may also have been the consequence of previous calcium deficiency-induced bone disease in view of previous findings in black teenagers with genu valgum of hyperparathyroid bone disease, with or without osteomalacia, due to dietary calcium deficiency, or of osteopenia (Schnitzler et al 1994). A frequent association of SCFE and genu valgum has also been noted by other workers who attributed the deformity to a possible upper tibial growth plate abnormality (Carlioz et al 1984). However, the authors showed no evidence of this.

Hypogonadism of delayed sexual maturation appears to have had a significant influence as a cause of the osteopenia in our cases since our premenarchal girls had significantly lower bone volume, thinner trabeculae, and evidence of less vigorous bone formation than the postmenarchal girls. Moreover, the average Tanner stage of pubertal development of patients in this study was only 2.5 (1 - 4.5). This is somewhat lower than the value of 2.64 in a study of British children with SCFE, particularly in view of the fact that patients in our study were approximately two years older than the British children: our boys were on average 16 years of age versus 14.3 years in the British boys, and our girls were 14 years versus 12.6 years in the British girls (Brenkel et al 1989). We concluded that our children were therefore sexually more immature than the British children with SCFE.

Chaning-Pearce and Solomon (1987) compared pubertal development in 2058 black and white Johannesburg girls. Their principal findings in this longitudinal survey was that height and weight increased more rapidly in white than in black children. We used these data to compare pubertal development in the girls with SCFE with that in normal black and white Johannesburg girls. This comparison confirmed that the girls with SCFE had delayed pubertal development. According to these published data, black girls reach menarche at age 13.9 years whereas white girls do so at age of 13.1 years, with the result that black girls have a prolonged pubertal growth spurt. Judging by these

data, by age 14 years, the average age of the girls in this study, 40% of our girls should have experienced menarche. However, only 28,6% had started menstruating by that age. This reflects relative hypogonadism, which has been shown to be associated with weakness at the physeal – metaphyseal junction (Harris 1950, Ogden et al 1977, Oka et al 1979, Brenkel et al 1989, Wells et al 1993). Harris presented support for an endocrine basis of SCFE already in 1950. He noted that growth hormone decreases the shear strength of the epiphyseal plate whereas sex hormone increase its strength by plate closure. Oka et al. showed physeal-metaphyseal weakness in an animal study of hypogonadal rats. They showed that the mechanical strength of the growth plate against shear forces is greater in intact female rats, than in ovariectomized female rats. Thus, they concluded that sex hormones, especially oestrogens, regulate the morphological, and biomechanical functions of the growth plate (Oka et al 1979).

Whatever caused the osteopenia in our patients appears to have operated through compromised bone formation with a resultant reduction in wall thickness, rather than through an increase in erosion surface or depth of erosion lacunae.

Our patients differed in several ways from SCFE patients reported in other studies. The average age of our patients at presentation was 2.5 years above that of boys and girls, both black and white, in reported series. Table XII presents epidemiological data from some of the reported studies of black and white children with SCFE, and from the present series. Comparison of our data with the biggest published demographic study by Loder et al., shows age differences. In our group the average age was 16 years for boys and 14 years for girls, whereas that of the 1630 children from Loder's study was 13.5 and 12 years, respectively (Loder et al 1996). These authors are the only investigators to have shown an age difference among different ethnic groups, where the youngest children were the Native Australian/Pacific children and the oldest were white and Indo-Mediterranean. The sex distribution in most of the published series was about twice as many boys as girls, Loder's figures being 41.2% girls and 58.8% boys. However, in our study the sex distribution was nearly equal. The large number of overweight girls in the present study may have contributed to the unusually high

proportion of girls. We used BMI (weight/height^2) rather than weight to assess obesity in order to take height into consideration because some of the girls were short in stature.

A large proportion of our patients, namely 38%, presented with **bilateral** hip involvement. The largest demographic series showed a figure of only 22.3% bilaterality (Loder et al 1996). However, two investigations of SCFE in blacks from the United States reported similarly high rates of bilateral involvement, namely 40% and 39.3% (Bishop et al 1978, Loder et al 1993). A review of the literature showed black children to have higher rates of bilateral involvement than white children. Bilaterality ranges from18% to 25% in white children, 31% to 51% in black children; it was only 19% in Japanese children (Loder et al 1996). It could be argued that the difference in bilaterality among racial groups merely reflects different surgical indications for prophylactic pinning of the uninvolved hip in various geographic areas. An uninvolved opposite hip, once pinned, will be protected against subsequent slippage. Nevertheless, demographic analysis of white, black and Amerindian children in Loder's study showed no statistically significant differences in the proportion of unilateral and bilateral involvement by continent for the white, black or Amerindian children. Thus, the differences in bilaterality by race are most likely real differences and not merely reflections of local orthopaedic practices or circumstances.

Table XII: *Epidemiologic data in black and white teenagers with SCFE: Literature review*

Author and source of patients	Race	N	Male:female	Age (years) M	Age (years) F	Unilateral Right : Left	Bilateral (%)	Severe slip (% patients)
Orofino et al 1960 Louisiana, USA	Blacks	95	-	-	-	-	33.6	45.3
Bishop et al 1978 Texas,USA	Blacks	50	1 :0.67	13.4		-	40	20
Kennedy, Weiner 1990 Ohio,USA	Blacks	44	1 : 0.26	13	10.9	1 : 1	20	4.5
Spero et al 1992 New York. USA	Blacks	29	1 : 0.45	13.6	12.3	1 : 0.87	27.5	5
Aronson, Loder 1992 Michigan, USA	Blacks	74	1 : 0.61	12.4	11.1	-	-	14.4
Loder et al 1993 Michigan, USA	Blacks	161	-	-	-	-	39.8	-
Loder et al 1993 Michigan, USA	Whites	62	-	-	-	-	29	-
Kelsey 1973 Connecticut/Texas, USA	Blacks Whites	431	Bl 1 : 0.86 Wh 1 : 0.35	13	11	-	-	-
Jackson Burrows, 1957 London, UK	Whites	100	1 : 0.67	15	12	M 1 : 2.3 F 1 : 1	M 11 F 12	-
Hägglund et al 1984 Sweden (1960-1969)	Whites	66	1 : 0.53	12.7	11.9	M 1 : 1.44 F 1 : 1	M 4.3 F 0	-
Henrickson 1969 Sweden	Whites	81	1 : 0.5	13.5	11.8	1 : 1	22.2	-
Loder et al 1996 An Internacional Multicenter Study	World	1630	1 : 0.7	13.5	12	1 : 1.48	22.3	-
Present series Johannesburg, South Africa	**Blacks**	**29**	**1 : 0.93**	**16**	**14**	**1 : 0.64**	**37.9**	**100**

Slipped capital femoral epiphysis due to generalised bone disorders such as primary hyperparathyroidism, renal osteodystrophy, and endocrinopathies have also been shown to have a higher than usual rate of bilateral hip involvement. Other than hypogonadism, endocrinopathies did not account for bilateral involvement in our study.

The proportion of our patients with a **severe** slip, which was defined as a slip with a head-neck angle of more than 50°, was greater than in any other study of black and white children with SCFE, including two reports, namely by Boyer et al (1981) (27.5%), and Carney et al (1991) (26%), which did not state the race of their patients. A high proportion of severe slips is therefore not specific to blacks in general but was a particular feature of our patients. Generalised disorders such as endocrinopathies have been shown to be associated with high rates of severe slip (Loder et al 1995). The osteopenia likely due to dietary calcium deficiency and late puberty in our patients may have been the generalised disorder predisposing to higher rates of severe and bilateral slips of the proximal femoral epiphysis.

A combination of all these factors, namely, delayed puberty, prolonged growth spurt, osteopenia, and obesity can be expected to have disastrous consequences for the proximal femoral region. At adolescent age the plane of the growth plate is not even but rather irregular and undulating (Chung et al 1976). As a result of this irregularity the cleavage plane of an epiphyseal separation is inconsistent. Bright and associates showed in their work on rats that in-substance horizontal cleavage tears develop in physeal cartilage when a moderate (50% failure load) bending force was applied to the physis (Bright et al 1974). If, however, a full load was applied failure-cracks developed not in the cartilage but through the junction of methaphyseal bone with hyperthrophic cartilage, and led to separation of the epiphysis. Photomicrographs taken of separated epiphyses showed that the plane of separation was situated at the junction of the metaphysis with hyperthrophic cartilage. Moreover, trabecular fragments were found on the separated epiphyses, which shows that the slip occurred partly through subphyseal bone and not only through the physis. Chung et al. were also supporting mechanical factors as a cause for slippage (Chung et al 1976). Their work gave further evidence that

physeal slips are going, at least partially, through bone. They loaded human cadaveric proximal femoral epiphyses from children aged 0 – 15 years and found that specimens from adolescents in particular developed the slip at the physeal-metaphyseal junction. They attributed slips at this site to diminishing thickness of the soft tissue sleeve surrounding and supporting the physeal region at this age. SCFE in children with other bone diseases such as primary and secondary hyperparathyroidism also takes place through abnormal subphyseal bone (Kirkwood et al 1972, Chiroff et al 1974). In these conditions the physis appears widened as erosions rarefy adjacent subphyseal bone. The epiphyseal slip, in fact, takes place through this eroded bone.

Light microscopic (Agamanolis et al II 1985) and ultrastructural studies (Agamanolis et al I 1985) have shown abnormalities in physeal cartilage in the biopsies of affected proximal femoral physes from patients with SCFE. Agamanolis and co-authors showed that slipped growth plates have diminished cellularity with an overall excess of matrix as well as severe disorientation and malalignment of chondrocytes. There was a deficiency in the supporting collagenous framework of slipped plates. Chondrocyte degeneration and death were seen at all levels of the proliferative and hyperthrophic zones, suggesting a disturbance in the life cycle of chondrocytes. However, the authors have not proven that these changes were the cause rather than the result of the slip. Furthermore, in another study by Jackson Burrows, no epiphyseal widening in an opposite uninvolved hip was found (Jackson Burrows 1957). This suggests that the physeal widening of a slipping epiphysis accompanies rather than precedes the slip.

Against the opinion of a generalised physeal cartilage abnormality is the failure by another group of investigators to demonstrate iliac crest growth plate abnormalities in patients with SCFE (Weiss et al 1990). They conclude that previously reported abnormalities may have been the result rather than the cause of the slip. These observations are in keeping with the finding that slips do not solely take place in cartilage but also pass through adjacent bone (Bright et al 1974, Chung et al 1976). Thus, generalised bone disease as in our patients can affect severity and bilaterality of slipped capital femoral epiphyses. Chung and coauthors in their study loaded human cadaveric

proximal femoral epiphysis from children aged 0 – 15 years and found that specimens from adolesents in particular developed the slip at the physeal-metaphyseal junction. A prolonged growth spurt at this particular time may further weaken this anatomical area because primary trabeculae, consisting of biomechanically weak woven bone (Baron et al 1996), continue to be deposited at a rapid rate adjacent to another weak structure, namely the hypertrophic layer of the physis. If secondary, i.e., lamellar trabecular bone is also suboptimal in quantity, microarchitecture, and bone forming capacity as in our patients, then the stage is set for a slip involving bone.

An increasing obliquity of the physis in adolescence and the concomitant powerful bending and shearing forces also enhance the risk of slipping. Moreover, rising body weight in a sexually immature individual raises the load placed on the physeal region and so further increases the risk of epiphyseal slipping. Thus, a child's bone has to carry an adult size body, which was of massive dimensions in some of our patients. As was mentioned above, it takes a load of six to ten times body weight to displace a capital femoral epiphysis. During single leg stance already up to 3 times body weight is borne on the femoral head of the weight-bearing leg. Several patients with more than double normal body weight in the present study reached the slipping load of six-fold normal body weight on the hip with practically every step.

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CONCLUSION

Slipped capital femoral epiphysis remains a disorder of uncertain aetiology. With the present study we add a new perspective to the understanding of the aetiology and pathogenesis of this adolescent hip disorder, namely that generalised bone pathology that weakens subphyseal bone may be a contributory factor for SCFE. This approach raises the question of whether SCFE is not a form of pathological fracture-separation of the capital femoral epiphysis of the Salter-Harris type I variety.

We conclude, that the combination of the adverse factors associated with delayed puberty, namely a prolonged growth spurt, obesity and the osteopenia of hypogonadism, aggravated by the osteopenia related to dietary calcium deficiency, placed the upper femoral physis and subjacent bone in our group of patients at particular risk of developing more severe and more often bilateral slips than in most other reported series.

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