Potential influence of hormones in the development of slipped capital femoral epiphysis: a preliminary study

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The potential influence of hormonal imbalance on the development of slipped capital femoral epiphysis was assessed through a prospective clinical study. The serum levels of T_3, T_4, thyroid-stimulating hormone, testosterone, estradiol, dehydroepiandrosterone-sulfate, follicle-stimulating hormone, luteinizing hormone, human growth hormone, adrenal cortex hormone and cortisol were evaluated in seven boys and seven girls. Forty-three out of 154 hormonal determinations (27.9%) were abnormal. The results showed increased incidence of pathological values mainly in the levels of follicle-stimulating-hormone, luteinizing-hormone and testosterone. No patient had clinical findings of endocrinopathy. A (possibly) temporary hormonal disorder may play a potentially significant role in the development of slipped capital femoral epiphysis.

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Introduction

Slipped capital femoral epiphysis (SCFE) is a rather rare type of fracture. Its incidence ranges from 0.71 to 3.41 cases per 100 000 adolescents [1]. Microscopically SCFE is manifested in the growth plate's 'hypertrophied cells' zone. The relatively recent discovery of hormonal receptors in exactly this zone, intrigued us into further investigating the possibly 'missing link' between the development of SCFE and the actions exerted by several different hormones on the growth plate's chondrocytes.

After reporting the influence of I-parathyroid hormone on the development of SCFE [2], we decided to further assess the impact of several other hormones as well. The hormones that were evaluated, and the reasons for assessing them, are the following:

1. *3.5.3'-Triiodothyronine (T_3)*, *thyroxine (T_4)* and *thyroid-stimulating hormone (TSH)*. Receptors for both T_3 and T_4 exist in growth plate chondrocytes.
2. *Testosterone*, *estradiol*, *follicle-stimulating hormone* (*FSH*), *luteinizing hormone* (*LH*) and dehydroepiandrosterone-sulfate (*DHEA-S*). These hormones are directly related to the sexual development and maturation procedures.
3. *Human growth hormone* (*hGH*). Its action on a growth plate's chondrocytes is important and its potential influence on the development of SCFE has been discussed since 1950.
4. *Cortisol* receptors have also been identified in a growth plate's chondrocytes.
5. *Adrenal cortex hormone* (or *ACTH*). It controls the secretion of the androgens and the glucocorticoids that are produced in the adrenal cortex and it induces the secretion of hGH.

Materials and methods

This prospective cohort study was approved by the Hospital's Scientific Research Board and it was conducted in accordance with the World Medical Association Declaration of Helsinki of 1975 as revised in 1983. Seven boys and seven girls (16 hips in total) suffering from SCFE were included in this study. Their parents were fully informed about the participation of their children in this study and a signed parental consent form was obtained in all cases. Patients suffering from any other known disease (apart from SCFE) were excluded from this study.

All patients were treated surgically (in-situ internal fixation with the use of two or three smooth Steinmann pins). The boys' mean age was 12.8 years (range: 10–14 years). The girls were a little younger (mean age: 11.6 years, range: 11–12.5 years). In order to assess the sexual maturation of our patients, we used the Tanner [3] classification (Table 1).

The serum levels of the following hormones were evaluated: T_3, T_4, TSH, testosterone, estradiol, FSH, LH, DHEA-S, hGH, cortisol and ACTH. All patients had been fasting for 12 h before the collection of blood

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samples and in all cases it was performed by the first author at exactly 0800 h.

The hormonal determinations in the patients' serum were evaluated according to the range of normal values provided by the reagent manufacturers. As the normal value provided by the manufacturer depended on the menstrual cycle phase (estradiol, FSH and LH) and because we were unable to determine accurately in which phase every female patient exactly was, we considered as below normal any detected value that was below the lowest of all three phases, and as above normal any detected value that was above the highest of all three phases. Similarly, when examining the results obtained from the measurement of serum DHEA-S and hGH (that depend on the patient's sexual maturation), we used the Tanner [3] classification in order to determine whether or not a patient could be categorized into a preadolescence stage of development.

Results

The results showed that all patients developed SCFE during the earlier stages of adolescence (Table 1). An increased incidence of abnormal hormonal values (both increases and decreases), but not necessarily endocrinopathies, was noticed. Forty-three out of a total of 154 hormonal determinations (27.9%) were found to be out of normal range (Tables 2 and 3).

The evaluation of the patients' thyroid hormones revealed a typical case of hyperthyroidism (increased T_3 and T_4, decreased TSH in patient no. 1). Another two abnormal values (T_3: 1, T_4: 1) were also detected.

Five boys and four girls had decreased serum FSH values. Eight patients (five boys and three girls) had also decreased serum LH values. As far as serum estradiol values were concerned, two boys had increased and two girls had decreased values. Testosterone serum level was lower than expected in six boys.

The serum level of DHEA-S in patient nos. 2, 3, 6, 7 and 8 (who were in a preadolescence stage of development) was above normal.

Serum hGH level was increased in three patients (two boys and one girl). Serum cortisol levels were normal in all but one patient. ACTH level was normal in all but two patients (one boy and one girl).

Discussion

The actual cause of SCFE remains, more or less, unknown. Several theories exist on the pathogenesis of SCFE [1], but none of them managed to explain adequately the reason why SCFE occurs in adolescents who share so few common characteristics and have so many differences. The identification of hormonal receptors in a growth plate's chondrocytes has been a tremendous breakthrough that re-animated the theory of hormonal intervention in the development of SCFE.

Table 1 Age, location (left, right or bilateral), grade of the slipping and the patients' sexual maturation according to the Tanner [3] classification

					Tanner classification		
Patient	Sex	Age (years)	Hip	SCFE grade	Testis size (T)	Breast size (B)	Pubic hair (P)
1	F	12	L and R	L: 3rd, R: 1st		B2	P2
2	M	10	L	2nd	T1		P1
3	M	14	R	2nd	T1		P1
4	M	14	L	2nd	T3		P2
5	M	13.5	L	2nd	T2		P1
6	M	12.5	L	2nd	T1		P1
7	F	12	R	1st		B1	P1
8	M	12	L	2nd	T1		P1
9	F	13	L	3rd		B2	P4
10	F	11.5	L	2nd		B3	P2
11	F	12	L and R	L: 2nd, R: 1st		B3	P2
12	F	11	R	2nd		B2	P1
13	F	11	R	1st		B1	P2
14	M	13	L	1st	T2		P1

SCFE, slipped capital femoral epiphysis; M, male; F, female; L, left; R, right.

Table 2 Serum hormone values of the male patients

Parameter	2	3	4	5	6	8	14	Expected value
T_3 (ng/ml)	1.03	1.48	1.39	1.31	0.53	0.89	1.17	0.51–1.65
T_4 (mg/dl)	12.8	8.1	8.51	9.6	10.6	7.96	7.2	4.5–12
TSH (mIU/ml)	1.02	2.58	1.3	1.8	1.67	3.24	1.77	0.4–5
hGH (ng/ml)	0.37	0.22	0.39	0.14	5.5	4.4	1.7	Preadolescence: 0–2.0, adolescence: 0–15
Testosterone (mmol/l)	1.94	1.23	6.89	0.55	0.53	1.1	0.53	4.6–28.2
DHEA-S (ng/ml)	112	100	167	175	225.3	589.1	148.5	Preadolescence: 2–43, 17–50 years: 281–605
Estradiol (pmol/l)	188.4	169.2	318.9	295.9	104.8	115	72.2	20–242
ACTH (pg/ml)	54.48	93.87	11.76	27.21	6.7	45.8	10.1	<70
FSH (mIU/ml)	5.2	1.16	3.17	1.44	0.95	1.54	1.25	1.6–9.7
LH (mIU/ml)	4.9	1.19	1.75	0.17	0.18	0.55	0.07	1.3–10.5
Cortisol (mmol/l)	343	323	261	386	395	790	389	123–626

TSH, thyroid-stimulating hormone; hGH, human growth hormone; DHEA-S, dehydroepiandrosterone-sulfate; ACTH, adrenal cortex hormone; FSH, follicle-stimulating-hormone; LH, luteinizing hormone.

Table 3 Serum hormone values of the female patients

Parameter	1	7	9	10	11	12	13	Expected value
T_3 (ng/ml)	1.94	1.51	1.11	1.76	0.95	1.4	1.39	0.51–1.65
T_4 (mg/dl)	17.28	6.9	10.66	7.26	8	8.6	9	4.5–12
TSH (mIU/ml)	0.08	1.55	1.36	2.03	2.1	2.02	2.45	0.4–5
h-GH (ng/ml)	12.17	0.5	2.4	3.7	0.2	1.2	1.1	Preadolescence: 0–2.0, adolescence: 0–5
Testosterone (mmol/l)	0.79	0.3	0.8	0.5	0.54	0.24	0.35	0.2–2.7
DHEA-S (ng/ml)	85	77.9	295.5	115.5	177.2	17.6	264.8	Preadolescence: 19–63, 17–50 years: 195–507
Estradiol (pmol/l)	390.4	77.9	145	38	357	145	386	follicular: 98–592, luteinic: 120–738, mid-circle: 684–1404
ACTH (pg/ml)	18.6	128	11.09	13.4	14.8	24.6	22.1	<70
FSH (mIU/ml)	7.7	1.06	1.2	2.34	3.44	0.37	0.9	follicular: 2–11.6, luteinic: 1.4–9.6, mid-circle: 9–23
LH (mIU/ml)	5.05	0.7	0.8	1.79	0.925	0.5	0.54	follicular: 2.6–12.1, luteinic: 0.8–15.5, mid-circle: 27–97
Cortisol (mmol/l)	356	351	343	392	355	548	146	123–626

TSH, thyroid-stimulating hormone; hGH, human growth hormone; DHEA-S, dehydroepiandrosterone-sulfate; ACTH, adrenal cortex hormone; FSH, follicle-stimulating-hormone; LH, luteinizing hormone.

Thyroid gland-related hormones

The action that T_3 exerts on growth plate chondrocytes is probably double. It stimulates the proliferation of chondrocytes (by reinforcing the action of insulin growth factor-1 or IGF-1) and it accelerates the differentiation of chondrocytes towards their hypertrophied form [4]. The influence of T_3 on a growth plate is exerted directly on the hypertrophied cells zone [5], the same zone where SCFE occurs. The action exerted by T_4 on a growth plate is considered to be essential for its homeostasis and especially for the normal development of the hypertrophied cells zone [6]. Externally administered thyroxine acts in a way somewhat similar to that of T_3. It increases the number of chondrocytes in the growth zone and it induces (when administered together with hGH) mitotic activity in both growth and hypertrophied cell zones, resulting in the enlargement of the width of the growth plate [7].

The destabilizing action of T_3 and T_4 on growth plate seems to be exerted through their intervention on the maturation process of the chondrocytes. Both thyroid hormones target the prehypertrophied cells and induce their maturation procedure towards a more 'developed' stage (hypertrophied cell). This intervention is absolutely necessary for the normal mineralization (and consequently fusion) procedure of the growth plate [8]. Nevertheless, the dose-related intervention of both thyroid hormones may lead to an increased number of hypertrophied cells, thus increasing the growth plate's width. The latter, if it happens during the rapid body development period that occurs in adolescence, may expose the proximal femoral growth plate to other destabilizing factors and may lead to the development of SCFE.

There are several reports that correlate the development of SCFE with alterations of the serum values of T_3 or T_4 [1,9–13]. Burrow *et al.* [9] believe that the preliminary test for a possible endocrine abnormality in patients suffering from SCFE should necessarily include the measurement of free thyroxine and TSH. This seems to be validated by our results as well. Three of our patients had abnormally increased serum T_3 or/and T_4 value and one of them suffered from hyperthyroidism.

Sex hormones

Estradiol receptors are abundant in a growth plate's proliferating and hypertrophic chondrocytes. Estradiol action is believed to be mainly stabilizing [14,15], as it induces chondrocyte proliferation and mineralization (and therefore keeps the growth plate's width within normal limits), inhibits bone resorption and osteoblast activity and alters the release of cytokines. As a result, oophorectomy results in wider proliferative and hypertrophic zones as a consequence of osteogenesis arrest [4]. Therefore, we have reasons to believe that estradiol deficiency (or simply decreased values) may lead (or contribute) to the instability of growth plate and consequently to the development of SCFE.

Estradiol and other estrogens exert the major skeletal actions of sex steroids in both sexes [5]. Nevertheless, while some of the androgenic effects of testosterone may be induced through aromatization into oestrogen, the direct action of androgens on the activity of growth plate chondrocytes is undoubted [14], as bone cells and epiphyseal chondrocytes also express androgen receptors and respond to androgen both *in vitro* and *in vivo*. The administration of androgens during puberty has a positive effect on mineralization [4]; thus it stabilizes the growth plate. All these facts lead to the possibility that testosterone stabilizes the growth plate via (i) its direct action and (ii) its aromatization into estrogen (which also plays a stabilizing role). Therefore,

testosterone-decreased values may act against growth plate stability, leading also to the development of SCFE.

The increased incidence of sex-hormone abnormalities in our patients, may be of some (not clear at the moment) significance. The lower serum levels of estradiol may be responsible for the development of SCFE in two girls. The vast majority of boys (six out of seven) had decreased testosterone values.

The role of adrenal androgens (such as dehydroepiandrosterone-sulfate) is less well defined. Some of their effects may be indirect through their exerted 'control' over the action of oestrogen on the hGH-IGF-1 axis [4]. Adrenal androgens are known to act directly on both the cartilage and the bone [4]. Unfortunately, to the best of our knowledge, there is insufficient bibliographic data as far as DHEA-S involvement in a growth plate's maturation procedures is concerned. Furthermore, our results were limited to only five patients and they cannot be evaluated and further analyzed (even though all measurements were pathological and above normal).

FSH and LH seem to exert their action on the growth plate (and consequently on the development of SCFE) through their control on the secretion of estradiol and testosterone. The increased incidence of abnormal FSH and LH serum values (17 out of 28 measurements) cannot be overlooked, as it is probably directly related to the sexual development and growth plate maturation procedures that may trigger and initiate the development of SCFE.

Growth hormone

One of the major systemic hormones that regulate linear growth during childhood is the hGH [5]. Its receptors have also been identified in hypertrophic chondrocytes [11]. In-vivo injections of growth hormone (GH) stimulate growth plate chondrocytes at all stages of differentiation and induce the longitudinal orientation of hypertrophic cells, thereby adding substantially to bone length. Monsonego *et al.* [16] have proved that GH inhibits differentiation in avian growth-plate chondrocytes. As a result, the latter remain in a proliferative status for a longer period, and this may act in a destabilizing way as far as the development of SCFE is concerned. Our results probably agree with this remark, as three patients had increased serum GH values that might have led to the development of SCFE.

Cortisol

The actual action of corticosteroids on endochondral bone formation is not so clear at the moment and little information is available regarding their skeletal effects. It is believed though [4], that long-term glucocorticoid excess causes growth retardation through its interference with osteoblast function and decrease of new bone formation. Glucocorticoid excess also suppresses the synthesis of cartilage extracellular matrix collagen and the mineralization procedures [4]. Hence, the role of glucocorticoids (when in excess) is destabilizing for the growth plate and may possibly lead to the development of SCFE. Nevertheless, our results are not in complete agreement with this theory, as only one patient had elevated serum cortisol value.

Adrenal cortex hormone

ACTH induces the secretion of hGH and controls the secretion of the sex-steroid hormones and the glucocorticoids that are produced in the adrenal cortex. All these hormones are known for their direct or indirect action on the development and homeostasis of the growth plate [4]. Therefore, it is possible to assume that ACTH could (potentially) exert an indirect role in the stability/instability of the growth plate. Although this theory seems quite interesting, it has not been proved (yet) and furthermore, it cannot be verified and validated by our results. The hormonal imbalance of sex steroid hormones (and cortisol) that was noted in our results was probably not induced by ACTH fluctuations and the actual extent (if any) of ACTH involvement in the development of SCFE is doubted and remains to be further investigated.

Given the rarity of SCFE [1], it is extremely difficult to gather a large number of patients in order to accurately detect any possibly existing hormonal alterations in the patient's sera. Larger, multicentric, prospective studies that will include larger number of patients are probably needed in order to draw stronger conclusions.

It is our belief that SCFE's etiology is probably multifactorial. Hormone imbalance seems to play an interesting, important and potentially etiological role in the development of SCFE. Our results may suggest that SCFE occurs when some kind of (temporary or/and self-restricted?) hormonal imbalance coexists with other etiological factors such as obesity, minor or major trauma, growth plate planarity and inclination angle, insufficiency of hydrostatic and tensile growth plate components. The hormonal imbalance that may trigger the development of SCFE during puberty is usually subtle and does not necessarily lead to the development of a typical hormonal disorder with clinical findings. The most important hormones that may contribute to the development of SCFE are the thyroid hormones (T_3 and T_4), the sex hormones (mainly estradiol, testosterone, FSH and LH) and GH. Parathyroid hormone seems to play a potential destabilizing role too [2].

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