A commentary by Mark J. Adamczyk, MD, is linked to the online version of this article at jbjs.org.

Leptin Elevation as a Risk Factor for Slipped Capital Femoral Epiphysis Independent of Obesity Status

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Background: Slipped capital femoral epiphysis (SCFE) is strongly associated with childhood obesity, yet the prevalence of obesity is orders of magnitude greater than the prevalence of SCFE. Therefore, it is hypothesized that obesity is not, by itself, a sufficient condition for SCFE, but rather one component of a multifactorial process requiring preexisting physeal pathology. Leptin elevation is seen to varying degrees in patients with obesity, and as leptin has been shown to cause physeal pathology similar to the changes seen in SCFE, we propose that leptin may be a factor distinguishing between patients with SCFE and equally obese children without hip abnormalities.

Methods: Serum leptin levels were obtained from 40 patients with SCFE and 30 control patients with approximate body mass index (BMI) matching. BMI percentiles were calculated according to Centers for Disease Control and Prevention population data by patient age and sex. Patients were compared by demographic characteristics, leptin levels, odds of leptin elevation, and odds of SCFE.

Results: The odds of developing SCFE was increased by an odds ratio of 4.9 (95% confidence interval [CI], 1.31 to 18.48; $p < 0.02$) in patients with elevated leptin levels, regardless of obesity status, sex, and race. When grouping patients by their obesity status, non-obese patients with SCFE showed elevated median leptin levels at 5.8 ng/mL compared with non-obese controls at 1.7 ng/mL ($p = 0.006$). Similarly, obese patients with SCFE showed elevated median leptin levels at 17.9 ng/mL compared with equally obese controls at 10.5 ng/mL ($p = 0.039$). Serum leptin levels increased in association with obesity ($p < 0.001$), with an increase in leptin of 0.17 ng/mL (95% CI, 0.07 to 0.27 ng/mL) per BMI percentile point.

Conclusions: To our knowledge, this study is the first to clinically demonstrate an association between elevated serum leptin levels and SCFE, regardless of BMI. This adds to existing literature suggesting that SCFE is a multifactorial process and that leptin levels may have profound physiological effects on the development of various disease states. Despite a strong association with adiposity, leptin levels vary between patients of equal BMI and may be a vital resource in prognostication of future obesity-related comorbidities.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

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Slipped capital femoral epiphysis (SCFE) is classified as either atypical or idiopathic[1]. Atypical cases are associated with endocrinopathies such as hypothyroidism or hypogonadism, metabolic abnormalities such as renal osteodystrophy, or external causes such as radiation or chemotherapy[2]. A majority of SCFE cases are idiopathic, which present in the

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TABLE I Comparison of Demographic Characteristics Between the Control Group and the SCFE Group

	Control Group (N = 30)	SCFE Group (N = 40)	P Value
Age* *(yr)*	13.4 ± 2.6	12.8 ± 2.5	0.225
Sex†			0.668
Male	18	26	
Female	12	14	
Race†			0.457
Black	8	14	
White	22	26	
BMI percentile*† *(%)*	76.5 ± 28.6	90.7 ± 14.5	0.018

*The values are given as the mean and the standard deviation. †The values are given as the number of patients. ‡The SCFE group had a significantly higher BMI percentile than the control group at $p < 0.05$; no other demographic comparisons showed significant differences.

absence of another preexisting diagnosis, and have been shown to be strongly associated with childhood obesity[3-7]. The accepted pathogenesis presumes that increased biomechanical forces exceed the structural capacity of the physis, causing the epiphysis to translate, or slip, from its initial position, typically posteroinferiorly. As of 2012, 31.8% of American youth were overweight or obese[8], yet the prevalence of SCFE is far less, ranging between 0.33 and 24.58 per 100,000 adolescents[9,10]. This discrepancy between the prevalence of obesity and the prevalence of SCFE suggests that obesity is not, by itself, a sufficient condition for the development of idiopathic SCFE, but rather it is one component of a multifactorial process. The increased forces from obesity can only lead to a slip in the setting of preexisting physeal pathology.

This multifactorial theory is not new[11-13], yet in the absence of the above-mentioned atypical causes, clinical exploration for other factors that may have weakened the physis are rarely pursued. Histologic evaluation of physes in patients with SCFE show substantial distortion and widening in the columnar architecture of the zone of hypertrophy and zone of proliferation, with decreased cellularity, clustered degenerated chondrocytes, and irregular orientation and degradation of collagen fibers[13-19]. The hormone leptin, which is secreted by adipose cells and primarily provides negative feedback at the hypothalamus to signal satiety, has been shown to cause similar physeal pathology when present in elevated levels in animal models[20-22]. Obesity has been linked to leptin resistance, in which serum leptin levels must exceed the normal levels in non-obese peers to provide adequate satiety feedback, secondarily resulting in greater signaling at other sites of action[21,23]. Leptin receptors have been identified on articular and physeal chondrocytes in animal and human studies[22,24-26]. Animal studies have shown that, through these physeal receptors, leptin stimulates chondrocyte hypertrophy and proliferation, with alterations in leptin levels leading to an elongated physis, disturbed columnar structure, cellular apoptosis, and decreased expression and organization of the type-II and type-X collagen typically found throughout the hypertrophic zone[22,27-30].

TABLE II Comparison of Subgroup Demographic Characteristics Between the Control Group and the SCFE Group by Obesity Status*

	Control Group	SCFE Group	P Value
Age† *(yr)*			
Non-obese	13.3 ± 2.6	13.6 ± 2.7	0.701
Obese	14.1 ± 1.9	12.1 ± 2.5	0.133
Sex‡			
Non-obese			0.358
Male	10	10	
Female	8	4	
Obese			0.761
Male	8	16	
Female	4	10	
Race†§			
Non-obese			0.040#
Black	7	1	
White	11	13	
Obese			0.013#
Black	1	13	
White	11	13	
BMI percentile† *(%)*			
Non-obese	62.1 ± 29.1	76.8 ± 17.5	0.110
Obese	98.0 ± 1.4	98.2 ± 1.1	0.890

*There were 18 patients in the non-obese control group, 14 patients in the non-obese SCFE group, 12 patients in the obese control group, and 26 patients in the obese SCFE group. †The values are given as the mean and the standard deviation. ‡The values are given as the number of patients. §The non-obese control group and the obese SCFE group had significantly higher proportions of black patients than their comparison groups; no other demographic comparisons showed significant differences. #Significant.

Given the histologic similarities between physes affected by SCFE and hyperleptinemic physes, as well as the link between elevated leptin and body mass index (BMI)[31-33], we propose that leptin may be the source of physeal pathology necessary for the development of SCFE. This link has previously been suggested by in vitro work by Kishida et al., but, to our knowledge, no clinical studies have investigated the association between leptin and SCFE[27]. The purpose of this study was to evaluate the role of leptin as a distinguishing factor between obese children who develop SCFE and equally obese children without hip abnormalities.

Materials and Methods

Study Population

All patients presenting to the orthopaedic service at Monroe Carell Jr. Children's Hospital at Vanderbilt Medical Center, Nashville, Tennessee, between January 26, 2015, and January 26, 2016, with a new or previous diagnosis of SCFE were consecutively approached for study enrollment. Control patients were prospectively identified over the same time period on presentation to our service for elective non-obesity-related issues or from a pediatric weight management clinic after being identified as matching the age and approximate BMI percentile of an enrolled case patient. Parental consent and prospective enrollment were obtained for 40 patients with SCFE (age, 5 to 18 years) and 30 control patients (age, 8 to 18 years) in this institutional review board-approved, case-control study. Exclusion criteria were non-English speaking, preexisting systemic illness other than obesity, preexisting syndromic diagnosis, known atypical cause for SCFE, and inability to obtain serum leptin levels or demographic information.

Data Collection

Serum leptin levels were obtained between 8:00 A.M. and 4:00 P.M. for all patients. Demographic information was recorded, with BMI percentile defined using age and sex-adjusted values[34]. Per the Centers for Disease Control and Prevention (CDC) definition, obesity was defined as a BMI of ≥95th percentile for children of the same age and sex[35]. Using this definition, patients were placed into 4 groups: the non-obese control group, the non-obese SCFE group, the obese control group, and the obese SCFE group.

Statistical Analysis

Univariate linear regression was used to identify how patient demographic characteristics were associated with serum leptin. The association of demographic characteristics with the presence of elevated serum leptin was further evaluated through multivariate logistic regression. Assessment of how the presence of demographic factors affects the odds of developing SCFE was performed via logistic regression. As variation exists in published normal leptin values, we used our institutional laboratory definition of leptin elevation as values of >12.7 ng/mL[36]. Demographic characteristics and leptin values were assessed for normality by the Shapiro-Wilk test, with only leptin shown to be nonparametric. To assess the appropriateness of matching, comparison of demographic characteristics between groups was performed by the Mann-Whitney test. Leptin levels were compared within subgroups via the Mann-Whitney test and across all subgroups via the Dunn multiple comparison test for nonparametric data. Significance was set at $p < 0.05$. All statistics were calculated using R (version 3.2.5; R Foundation for Statistical Computing).

Results

Demographic Characteristics

Comparisons of patient age, sex, race, and BMI percentile between groups are shown in Table I, with subgroup comparisons by obesity status shown in Table II. Although the racial breakdown among all cases was similar to that among all controls, there was a lower percentage of black patients in the non-obese SCFE group compared with the non-obese control group ($p = 0.04$), and a higher percentage in the obese SCFE group compared with the obese control group ($p = 0.01$). The remaining demographic categories were similar between groups, suggesting that matching was adequate between cases and controls.

Role of Demographic Characteristics in Leptin Elevation

Across all patients, linear regression showed that serum leptin levels increased in the setting of obesity, as expected. Patients with a BMI in the ≥95th percentile were shown to have an expected serum leptin level 9.86 ng/mL (95% confidence interval [CI], 5.69 to 14.03 ng/mL; $p < 0.001$) higher than their non-obese counterparts, with expected increases per BMI percentile point of 0.17 ng/mL (95% CI, 0.07 to 0.27 ng/mL; $p < 0.001$) when controlling for race and sex. The association between demographic characteristics and serum leptin elevation was assessed via a multivariate logistic odds model, showing that the odds of having elevated leptin was 10.32 times greater in obese patients than non-obese patients, and 3.56 times greater in female patients than in male patients, but race showed no significant association ($p = 0.868$) (Table III). Bilateral slipped capital femoral epiphysis was present in 10 patients, with 5 in both the obese and non-obese groups. There were no significant differences ($p > 0.05$) between patients with bilateral SCFE and those

TABLE III Likelihood of Having Elevated Leptin

Factor	OR*	P Value
Sex (female vs. male)	3.56 (1.02 to 12.40)	0.046†
Race (white vs. black)	0.90 (0.26 to 3.13)	0.868‡
Obesity	10.32 (2.75 to 38.77)	0.001†

*The values are given as the OR, with the 95% CI in parentheses. †Increased odds of elevated leptin ($p < 0.05$) were shown with female sex and obesity. ‡Race showed no significant association.

TABLE IV Likelihood of Developing SCFE

Factor	OR*	P Value
Sex (female vs. male)	0.49 (0.15 to 1.59)	0.238†
Race (white vs. black)	0.71 (0.22 to 2.26)	0.556†
Obesity	1.50 (0.49 to 4.57)	0.472†
Elevated leptin	4.93 (1.31 to 18.48)	0.018‡

*The values are given as the OR, with the 95% CI in parentheses. †There was no significant association between the odds of SCFE and obesity, sex, or race. ‡The increased odds of SCFE diagnosis were shown to be significant only with leptin elevation when incorporating all variables into the model.

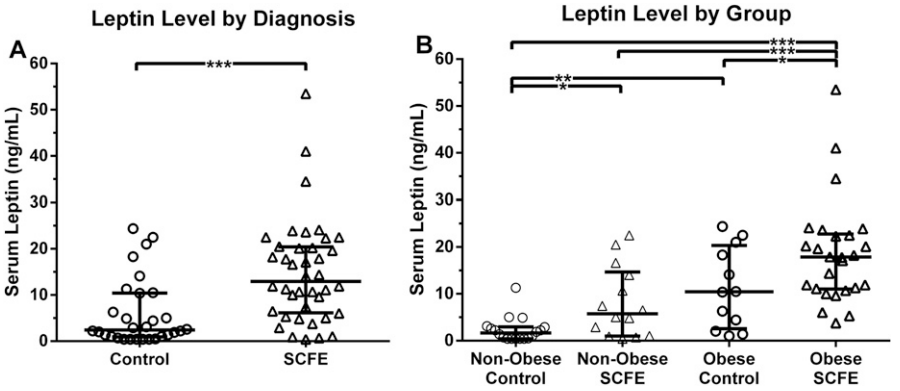

Fig. 1

Serum leptin levels compared according to diagnosis (**Fig. 1-A**) and obesity status and diagnosis (**Fig. 1-B**). The median values with IQRs are shown via bar-and-whisker plots for all groups. The SCFE group showed a significantly higher median leptin level ($p < 0.001$) at 13.0 ng/mL (IQR, 6.3 to 20.4 ng/mL) when compared with the control group at 2.4 ng/mL (IQR, 1.0 to 10.4 ng/mL). When grouped by obesity status, the non-obese SCFE group showed significantly higher median leptin levels ($p = 0.006$) at 5.8 ng/mL (IQR, 1.0 to 14.0 ng/mL) than the non-obese control group at 1.7 ng/mL (IQR, 0.4 to 2.9 ng/mL). There were similar findings ($p = 0.039$) between the obese SCFE group at 10.5 ng/mL (IQR, 3.2 to 19.7 ng/mL) and the obese control group at 17.9 ng/mL (IQR, 11.1 to 22.5 ng/mL). A single asterisk indicates significance at $p < 0.05$, a double asterisk indicates significance at $p < 0.01$, and a triple asterisk indicates significance at $p < 0.001$.

with unilateral SCFE with regard to BMI or leptin levels, although results of this analysis may be limited by the small number of patients with bilateral SCFE and the variable duration of patient follow-up, potentially missing the development of bilateral disease in patients previously treated unilaterally.

Factors Predictive of SCFE

Univariate logistic regression comparing SCFE diagnosis with leptin elevation, obesity status, race, and sex showed a significant increase in the odds of SCFE diagnosis for obese patients (odds ratio [OR], 2.79 [95% CI, 1.05 to 7.40]; $p = 0.04$) and those with

TABLE V Serum Leptin Levels by Group*

Serum Leptin Values	Control Group (N = 30)	SCFE Group (N = 40)	P Value
Mean†	5.9 ± 7.3 (0.4 to 24.4)	14.9 ± 11.1 (0.4 to 53.5)	<0.001
Median‡	2.4 (1.0 to 10.4)	13.0 (6.3 to 20.4)	<0.001

*Patients with SCFE were shown to have higher mean and median serum leptin levels compared with control patients. †The values are given as the mean and the standard deviation, with the range in parentheses, in nanograms per milliliter. ‡The values are given as the median, with the IQR in parentheses, in nanograms per milliliter. As leptin data were nonparametric, the median and the IQR are the preferred descriptors (the mean leptin level was included for completeness).

TABLE VI Serum Leptin Levels by Obesity Subgroup

	Control Group	SCFE Group	P Value
Non-obese subgroup*	18	14	
Mean†	2.3 ± 2.7 (0.4 to 11.3)	8.1 ± 7.5 (0.4 to 22.5)	0.002
Median‡	1.7 (0.4 to 2.9)	5.8 (1.0 to 14.0)	0.006
Obese subgroup*	12	26	
Mean†	11.4 ± 8.6 (1.0 to 24.4)	18.6 ± 11.1 (3.8 to 53.5)	0.028
Median‡	10.5 (3.2 to 19.7)	17.9 (11.1 to 22.5)	0.039

*The values are given as the number of patients. †The values are given as the mean and the standard deviation, with the range in parentheses, in nanograms per milliliter. Patients with SCFE were shown to have higher mean and median serum leptin levels compared with control patients when grouped by obesity status. ‡The values are given as the median, with the IQR in parentheses, in nanograms per milliliter. As leptin data were nonparametric, the median and the IQR are the preferred descriptors (the mean leptin was included for completeness).

elevated leptin (OR, 5.00 [95% CI, 1.60 to 15.68]; $p < 0.001$). Race and sex showed no significant association ($p > 0.05$). All factors were then combined in a multivariate logistic regression, in which leptin elevation remained the only patient factor associated with a significantly increased odds of developing SCFE (OR, 4.93 [95% CI, 1.31 to 18.48]; $p < 0.02$), with obesity, sex, and race not contributing to the likelihood of developing SCFE (Table IV).

Leptin Elevations Among Patients with SCFE

A comparison of serum leptin levels between the SCFE group and the control group is shown in Figure 1-A and Table V, with the subgroup comparison by obesity status shown in Figure 1-B and Table VI. The median serum leptin levels were significantly higher ($p < 0.001$) in the SCFE group at 13.0 ng/mL (interquartile range [IQR], 6.3 to 20.4 ng/mL) than the control group at 2.4 ng/mL (IQR, 1.0 to 10.4 ng/mL). In a subgroup comparison, the non-obese SCFE group showed elevated median leptin levels at 5.8 ng/mL (IQR, 1.0 to 14.0 ng/mL) compared with the non-obese control group at 1.7 ng/mL (IQR, 0.4 to 2.9 ng/mL) ($p = 0.006$); the obese SCFE group also showed elevated levels at 17.9 ng/mL (IQR, 11.1 to 22.5 ng/mL) compared with the obese control group at 10.5 ng/mL (IQR, 3.2 to 19.7 ng/mL) ($p = 0.039$). The mean serum leptin of our non-obese control group is similar to previously published values, as shown in the Appendix, which serves to ensure that our control group is in concert with the existing literature[37-42]. Similar data for obese controls were not included because of a lack of consistent obesity definitions preventing accurate comparison with the obese groups in our study[42-45]. When comparing leptin levels between all subgroups via the Dunn multiple comparison test, all comparisons between the 4 groups were significant ($p < 0.05$), with the exception of the comparison of the non-obese SCFE with the obese control group ($p = 0.16$).

Discussion

Our work highlights a previously unrecognized clinical link between elevated leptin levels and the development of SCFE, regardless of obesity status. When incorporating serum leptin into factors known to be associated with SCFE (race, sex, and BMI percentile), only serum leptin maintained a significant association with the development of SCFE, with hyperleptinemic patients showing an increased odds of SCFE at 4.93 times greater than patients with normal leptin levels.

With regard to the association between demographic characteristics and our outcomes, female sex was associated with greater odds of leptin elevation compared with male sex by a factor of 3.6, which parallels but exceeds the previously published increased leptin levels in girls compared with boys[46,47], but did not translate into increased odds of SCFE. This is consistent with reported male predominance of SCFE[48], which has been linked to the anabolic effects of testosterone during puberty in males causing an elongated, weaker physis compared with female patients, where estrogen directly induces growth plate closure and therefore stability[11]. Race did not alter leptin levels, consistent with the majority of previous research[49-51], although discrepant race associations with leptin have been reported[52,53]. Race also did not affect SCFE prevalence in our cohort, which differs from reported relative SCFE frequencies ranging from 2.2 to 4.6 times greater in black patients compared with white patients[9,10,48,54].

Of particular interest to highlight are the 14 patients with idiopathic SCFE despite not meeting criteria for obesity. Although their mean BMI percentile of 76.8 is still elevated compared with a theoretical perfect non-obese control population with a BMI percentile of 50.0, it was not significantly different from the non-obese control group mean BMI percentile of 62.1. Additionally, despite being elevated, the mean BMI percentile for this group does not even meet CDC criteria for overweight (BMI of the ≥85th percentile for age and sex)[35]. This non-obese SCFE group did not show a significant difference in leptin levels from obese patients without SCFE, which is in concert with our findings that although obesity was shown to be strongly associated with an increase in leptin, the diagnosis of SCFE shows that same association regardless of BMI. Of these non-obese patients with SCFE, the most interesting were the 2 with the highest leptin levels, a 12-year-old white female patient with a BMI percentile of 83 and a leptin level of 22.5 ng/mL, and a 13-year-old white male patient with a BMI percentile of 81 and a leptin level of 20.5 ng/mL. Both patients, although close to reaching overweight criteria, had elevated leptin levels far exceeding what is expected from increased adiposity alone.

To our knowledge, we are among the first to describe patients with abnormally elevated leptin levels in the absence of obesity or a known additional diagnosis. A comprehensive literature search showed that among non-obese patients, differences in leptin levels have been shown with multiple other endocrine conditions (decreased in hypothyroidism[55] and elevated in precocious puberty[56,57], hyperinsulinemia[57], elevation of thyroid autoantibodies[58], idiopathic intracranial hypertension[59], and hypothalamic dysfunction[60]), pulmonary conditions (decreased in smokers[32,61] and elevated in asthmatics[62], adults with impaired lung function[63], obesity hypoventilation syndrome[64], and obstructive sleep apnea[65]), and multiple myeloma[66] and in the setting of elevated uric acid[67]. Despite this extensive list, the magnitude of difference in leptin levels between cases and unaffected controls in these studies was usually only a few nanograms per milliliter, far smaller than the variations we have presented herein.

Although in our study the mean patient age at the time of SCFE diagnosis fits published norms, the age range of our patients with SCFE at the time of laboratory acquisition, from 5 to 18 years of age, exceeded the typically reported range of 12 to 15 years at idiopathic SCFE presentation[48] and deserves further discussion. Of note, limiting our analysis to only patients who were 12 to 15 years of age did not alter the significance of our results. The single patient with SCFE who was older than the standard range was 18 years of age at the time of enrollment and acquisition of serum leptin levels, but had been diagnosed with SCFE at the age of 15 years, fitting the expected age of idiopathic SCFE. The 2 patients with idiopathic SCFE who were younger than the expected range were particularly notable, as they presented at the surprisingly young ages of 5 and 9 years, both with BMI of >95th percentile by age. Given the recommendation of evaluation for endocrine and metabolic aberrations for patients with SCFE who were younger than 10 years (for girls) or 12 years (for boys)[12], thorough serology

work-up was performed and both patients were shown to have no atypical sources for SCFE. Despite their expected serum leptin levels based on their age and sex being <5 ng/mL, both patients had leptin levels of >20 ng/mL. Notably, both patients eventually developed bilateral SCFE, with the 9-year-old patient initially presenting after the second side became symptomatic, and the 5-year-old patient developing a contralateral unstable slip 2 years after fixation of the initial side, which at that point had already progressed to osteonecrosis.

The limitations to our study included the lack of exact 1:1 matching by age, sex, race, and obesity status, although demographic information showed significant differences between the groups only when looking at race. The disproportionate racial distribution of our cohort may explain why our findings regarding the role of race on leptin levels and SCFE risk do not match previous reports. The only races represented in our study were white and black, leaving several racial groups unrepresented. Additionally, with the exception of patients whose age alone prompted laboratory evaluation for atypical causes of SCFE, no formal investigations beyond history and physical examination were pursued to evaluate for other medical conditions that could alter leptin levels or put patients at risk for SCFE. Of note, history and physical examination did adequately identify 5 patients with previously undiagnosed endocrinopathies, prompting exclusion from the study. Lastly, the study was from a single institution, with enrollment of cases after SCFE had already occurred. With regard to inter-laboratory measurement issues, although the use of leptin values from a single institution avoids the reported variability of leptin reference ranges between institutions, this variability is a recognized limitation itself when combining our results with those from an earlier study[36].

Despite the diurnal profile of serum leptin levels[68], we do not believe that the lack of standardization in the timing of blood draws is a limitation. All values were obtained between 8:00 A.M. and 4:00 P.M., and although serum leptin does spike between midnight and 8:00 A.M. to roughly 25% greater than the 8:00 A.M. value, it shows a relatively constant level from 8:00 A.M. to midnight, with <10% deviation, which is far less than the intergroup differences that we identified[68]. Although non-obese patients have a higher proportional change in this diurnal profile, the reported differences of <2 ng/mL between morning and evening values do not explain our findings[69]. Additionally, some patients had laboratory values obtained in clinic without a nil per os (NPO) period, but this should not alter our results as food intake yields no acute alteration in serum leptin levels[70]. Lastly, the age at laboratory evaluation was as much as 3 years after the initial diagnosis of SCFE, as was the case of the 18-year-old patient discussed above. Although serum leptin does change somewhat throughout youth and adulthood[71], the expected changes in youth are based on the progression of puberty, with negligible differences within a single pubertal stage. Of several studies showing normal serum leptin levels throughout puberty[33,40,46,47], the greatest reported difference between prepuberty and postpuberty is a drop of 2.9 ng/mL in boys[47] and a rise of 3.7 ng/mL in girls[46], with much smaller differences between adjacent puberty stages. Accordingly, we believe that the time between SCFE diagnosis and laboratory acquisition does not detract from our findings. To ensure that a change in obesity between these 2 time points did not alter our results, patients with delay between SCFE and laboratory acquisition underwent post hoc comparison of BMI at both time points, without any significant changes identified.

Our results support the multifactorial pathogenesis of SCFE, while acknowledging its clear connection with obesity. The development of SCFE requires preexisting physeal pathology to weaken the physis, allowing the increased biomechanical forces from obesity to cause a slip. For patients diagnosed with atypical SCFE, the cause of their physeal pathology has been recognized as an endocrinopathy or other existing diagnosis. We propose that idiopathic SCFE similarly requires another diagnosis to explain the physeal pathology and that diagnosis very well may be hyperleptinemia, regardless of obesity status or severity. Recognition of this abnormality in orthopaedic patients and referral for early management of associated comorbidities may be vital to prevent subsequent orthopaedic and non-orthopaedic complications. Elevated leptin has been shown to be a marker for the risk of future cardiovascular disease in non-obese healthy children and is associated with future obesity[72]. Additionally, leptin has been repeatedly shown to be a key mediator in the pathophysiology of hypertension[73-77], which our group has previously shown to cause abnormal physeal changes similar to those in SCFE, and patients with SCFE have a significantly increased prevalence of undiagnosed hypertension compared with equally obese control patients[78].

In conclusion, the findings of this study demonstrate an association between elevated serum leptin levels and SCFE, regardless of BMI. This adds to existing literature suggesting that SCFE is a multifactorial process, leptin elevation has variations between patients regardless of obesity status, and leptin levels may have profound physiological effects on the development of various disease states. Clinically, recognition of this link may lead to improved patient prognostication for detrimental orthopaedic and non-orthopaedic conditions in patients found to have elevated serum leptin levels.

Appendix

eA A table showing serum leptin levels among healthy non-obese controls from prior studies is available with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/C862). ■

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References

1. Loder RT, Greenfield ML. Clinical characteristics of children with atypical and idiopathic slipped capital femoral epiphysis: description of the age-weight test and implications for further diagnostic investigation. J Pediatr Orthop. 2001 Jul-Aug;21 (4):481-7.

2. McAfee PC, Cady RB. Endocrinologic and metabolic factors in atypical presentations of slipped capital femoral epiphysis. Report of four cases and review of the literature. Clin Orthop Relat Res. 1983 Nov;180:188-97.

3. Kelsey JL, Acheson RM, Keggi KJ. The body build of patients with slipped capital femoral epiphysis. Am J Dis Child. 1972 Aug;124(2):276-81.

4. Poussa M, Schlenzka D, Yrjönen T. Body mass index and slipped capital femoral epiphysis. J Pediatr Orthop B. 2003 Nov;12(6):369-71.

5. Manoff EM, Banffy MB, Winell JJ. Relationship between body mass index and slipped capital femoral epiphysis. J Pediatr Orthop. 2005 Nov-Dec;25(6):744-6.

6. Bhatia NN, Pirpiris M, Otsuka NY. Body mass index in patients with slipped capital femoral epiphysis. J Pediatr Orthop. 2006 Mar-Apr;26(2):197-9.

7. Aversano MW, Moazzaz P, Scaduto AA, Otsuka NY. Association between body mass index-for-age and slipped capital femoral epiphysis: the long-term risk for subsequent slip in patients followed until physeal closure. J Child Orthop. 2016 Jun;10(3):209-13. Epub 2016 Apr 19.

8. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014 Feb 26;311(8):806-14.

9. Loder RT, Skopelja EN. The epidemiology and demographics of slipped capital femoral epiphysis. ISRN Orthop. 2011 Sep 21;2011:486512.

10. Lehmann CL, Arons RR, Loder RT, Vitale MG. The epidemiology of slipped capital femoral epiphysis: an update. J Pediatr Orthop. 2006 May-Jun;26(3):286-90.

11. Weiner D. Pathogenesis of slipped capital femoral epiphysis: current concepts. J Pediatr Orthop B. 1996 Spring;5(2):67-73.

12. Witbreuk M, van Kemenade FJ, van der Sluijs JA, Jansma EP, Rotteveel J, van Royen BJ. Slipped capital femoral epiphysis and its association with endocrine, metabolic and chronic diseases: a systematic review of the literature. J Child Orthop. 2013 Jun;7(3):213-23. Epub 2013 Mar 30.

13. Scharschmidt T, Jacquet R, Weiner D, Lowder E, Schrickel T, Landis WJ. Gene expression in slipped capital femoral epiphysis. Evaluation with laser capture microdissection and quantitative reverse transcription-polymerase chain reaction. J Bone Joint Surg Am. 2009 Feb;91(2):366-77.

14. Agamanolis DP, Weiner DS, Lloyd JK. Slipped capital femoral epiphysis: a pathological study. I. A light microscopic and histochemical study of 21 cases. J Pediatr Orthop. 1985 Jan-Feb;5(1):40-6.

15. Agamanolis DP, Weiner DS, Lloyd JK. Slipped capital femoral epiphysis: a pathological study. II. An ultrastructural study of 23 cases. J Pediatr Orthop. 1985 Jan-Feb;5(1):47-58.

16. Guzzanti V, Falciglia F, Stanitski CL, Stanitski DF. Slipped capital femoral epiphysis: physeal histologic features before and after fixation. J Pediatr Orthop. 2003 Sep-Oct;23(5):571-7.

17. Adamczyk MJ, Weiner DS, Nugent A, McBurney D, Horton WE Jr. Increased chondrocyte apoptosis in growth plates from children with slipped capital femoral epiphysis. J Pediatr Orthop. 2005 Jul-Aug;25(4):440-4.

18. Carter JR, Leeson MC, Thompson GH, Kalamchi A, Kelly CM, Makley JT. Late-onset tibia vara: a histopathologic analysis. A comparative evaluation with infantile tibia vara and slipped capital femoral epiphysis. J Pediatr Orthop. 1988 Mar-Apr;8 (2):187-95.

19. Kirsch T, von der Mark K. Remodelling of collagen types I, II and X and calcification of human fetal cartilage. Bone Miner. 1992 Aug;18(2):107-17.

20. Cinti S, Frederich RC, Zingaretti MC, De Matteis R, Flier JS, Lowell BB. Immunohistochemical localization of leptin and uncoupling protein in white and brown adipose tissue. Endocrinology. 1997 Feb;138(2):797-804.

21. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998 Oct 22;395(6704):763-70.

22. Maor G, Rochwerger M, Segev Y, Phillip M. Leptin acts as a growth factor on the chondrocytes of skeletal growth centers. J Bone Miner Res. 2002 Jun;17(6):1034-43.

23. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metab. 2010 Nov;21(11):643-51. Epub 2010 Sep 16.

24. Figenschau Y, Knutsen G, Shahazeydi S, Johansen O, Sveinbjörnsson B. Human articular chondrocytes express functional leptin receptors. Biochem Biophys Res Commun. 2001 Sep 14;287(1):190-7.

25. Nakajima R, Inada H, Koike T, Yamano T. Effects of leptin to cultured growth plate chondrocytes. Horm Res. 2003;60(2):91-8.

26. Steppan CM, Crawford DT, Chidsey-Frink KL, Ke H, Swick AG. Leptin is a potent stimulator of bone growth in ob/ob mice. Regul Pept. 2000 Aug 25;92(1-3):73-8.

27. Kishida Y, Hirao M, Tamai N, Nampei A, Fujimoto T, Nakase T, Shimizu N, Yoshikawa H, Myoui A. Leptin regulates chondrocyte differentiation and matrix maturation during endochondral ossification. Bone. 2005 Nov;37(5):607-21. Epub 2005 Jul 20.

28. Kalra SP, Dube MG, Iwaniec UT. Leptin increases osteoblast-specific osteocalcin release through a hypothalamic relay. Peptides. 2009 May;30(5):967-73. Epub 2009 Feb 7.

29. Li XF, Wang SJ, Jiang LS, Dai LY. Stage specific effect of leptin on the expressions of estrogen receptor and extracellular matrix in a model of chondrocyte differentiation. Cytokine. 2013 Mar;61(3):876-84. Epub 2013 Jan 26.

30. Gat-Yablonski G, Phillip M. Leptin and regulation of linear growth. Curr Opin Clin Nutr Metab Care. 2008 May;11(3):303-8.

31. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL, Caro JF. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996 Feb 1;334(5):292-5.

32. Papaioannou HI, Stakos DA, Tziakas DN, Chalikias G, Tsigalou C, Kartali S, Mantadakis E, Chatzimichael A. Plasma leptin and adiponectin concentrations in healthy, non-obese children. J Pediatr Endocrinol Metab. 2011;24(5-6):313-8.

33. Dencker M, Thorsson O, Karlsson MK, Lindén C, Wollmer P, Ahrén B. Leptin is closely related to body fat in prepubertal children aged 8-11 years. Acta Paediatr. 2006 Aug;95(8):975-9.

34. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. CDC growth charts: percentile data files with LMS values. 2009 Aug 4. https://www.cdc.gov/growthcharts/percentile_data_files.htm. Accessed 2016 Dec 15.

35. Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007 Dec;120(Suppl 4):S164-92.

36. Venner AA, Doyle-Baker PK, Lyon ME, Fung TS. A meta-analysis of leptin reference ranges in the healthy paediatric prepubertal population. Ann Clin Biochem. 2009 Jan;46(Pt 1):65-72.

37. Büyükgebiz B, Oztürk Y, Yilmaz S, Arslan N. Serum leptin concentrations in children with mild-to-moderate protein-energy malnutrition. Pediatr Int. 2003 Oct;45 (5):550-4.

38. Bjarnason R, Boguszewski M, Dahlgren J, Gelander L, Kriström B, Rosberg S, Carlsson B, Albertsson-Wikland K, Carlsson LM. Leptin levels are strongly correlated with those of GH-binding protein in prepubertal children. Eur J Endocrinol. 1997 Jul;137(1):68-73.

39. Charmandari E, Weise M, Bornstein SR, Eisenhofer G, Keil MF, Chrousos GP, Merke DP. Children with classic congenital adrenal hyperplasia have elevated serum leptin concentrations and insulin resistance: potential clinical implications. J Clin Endocrinol Metab. 2002 May;87(5):2114-20.

40. Garcia-Mayor RV, Andrade MA, Rios M, Lage M, Dieguez C, Casanueva FF. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. J Clin Endocrinol Metab. 1997 Sep;82(9):2849-55.

41. Moore SE, Goldblatt D, Bates CJ, Prentice AM. Impact of nutritional status on antibody responses to different vaccines in undernourished Gambian children. Acta Paediatr. 2003;92(2):170-6.

42. Valle M, Martos R, Gascón F, Cañete R, Zafra MA, Morales R. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. Diabetes Metab. 2005 Feb;31(1):55-62.

43. Kiess W, Englaro P, Hanitsch S, Rascher W, Attanasio A, Blum WF. High leptin concentrations in serum of very obese children are further stimulated by dexamethasone. Horm Metab Res. 1996 Dec;28(12):708-10.

44. Wabitsch M, Blum WF, Muche R, Braun M, Hube F, Rascher W, Heinze E, Teller W, Hauner H. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. J Clin Invest. 1997 Aug 15;100(4):808-13.

45. Hassink SG, Sheslow DV, de Lancey E, Opentanova I, Considine RV, Caro JF. Serum leptin in children with obesity: relationship to gender and development. Pediatrics. 1996 Aug;98(2 Pt 1):201-3.

46. Blum WF, Englaro P, Hanitsch S, Juul A, Hertel NT, Müller J, Skakkebaek NE, Heiman ML, Birkett M, Attanasio AM, Kiess W, Rascher W. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocrinol Metab. 1997 Sep;82 (9):2904-10.

47. Brandão CM, Lombardi MT, Nishida SK, Hauache OM, Vieira JG. Serum leptin concentration during puberty in healthy nonobese adolescents. Braz J Med Biol Res. 2003 Oct;36(10):1293-6. Epub 2003 Sep 16.

48. Loder RT. The demographics of slipped capital femoral epiphysis. An international multicenter study. Clin Orthop Relat Res. 1996 Jan;322:8-27.

49. Lee S, Bacha F, Gungor N, Arslanian SA. Racial differences in adiponectin in youth: relationship to visceral fat and insulin sensitivity. Diabetes Care. 2006 Jan;29 (1):51-6.

50. Johnson MS, Huang TTK, Figueroa-Colon R, Dwyer JH, Goran MI. Influence of leptin on changes in body fat during growth in African American and white children. Obes Res. 2001 Oct;9(10):593-8.

51. Danadian K, Suprasongsin C, Janosky JE, Arslanian S. Leptin in African-American children. J Pediatr Endocrinol Metab. 1999 Sep-Oct;12(5):639-44.

52. Wong WW, Nicolson M, Stuff JE, Butte NF, Ellis KJ, Hergenroeder AC, Hill RB, Smith EO. Serum leptin concentrations in Caucasian and African-American girls. J Clin Endocrinol Metab. 1998 Oct;83(10):3574-7.

53. Ambrosius WT, Compton JA, Bowsher RR, Pratt JH. Relation of race, age, and sex hormone differences to serum leptin concentrations in children and adolescents. Horm Res. 1998;49(5):240-6.

54. Benson EC, Miller M, Bosch P, Szalay EA. A new look at the incidence of slipped capital femoral epiphysis in New Mexico. J Pediatr Orthop. 2008 Jul-Aug;28 (5):529-33.

55. Yoshida T, Momotani N, Hayashi M, Monkawa T, Ito K, Saruta T. Serum leptin concentrations in patients with thyroid disorders. Clin Endocrinol (Oxf). 1998 Mar;48 (3):299-302.

56. Çatlı G, Anık A, Küme T, Çalan ÖG, Dündar BN, Böber E, Abacı A. Serum nesfatin-1 and leptin levels in non-obese girls with premature thelarche. J Endocrinol Invest. 2015 Aug;38(8):909-13. Epub 2015 Apr 2.

57. Ibáñez L, Potau N, Ong K, Dunger DB, De Zegher F. Increased bone mineral density and serum leptin in non-obese girls with precocious pubarche: relation to low birthweight and hyperinsulinism. Horm Res. 2000;54(4):192-7.

58. MacIver NJ, Thomas SM, Green CL, Worley G. Increased leptin levels correlate with thyroid autoantibodies in nonobese males. Clin Endocrinol (Oxf). 2016 Jul;85 (1):116-21. Epub 2015 Nov 16.

59. Lampl Y, Eshel Y, Kessler A, Fux A, Gilad R, Boaz M, Matas Z, Sadeh M. Serum leptin level in women with idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2002 May;72(5):642-3.

60. Patel L, Cooper CD, Quinton ND, Butler GE, Gill MS, Jefferson IG, Kibirige MS, Price DA, Shalet SM, Wales JK, Ross RJ, Clayton PE; Northern Paediatric Endocrine Group, UK. Serum leptin and leptin binding activity in children and adolescents with hypothalamic dysfunction. J Pediatr Endocrinol Metab. 2002 Jul-Aug;15(7):963-71.

61. Koc B, Bulucu F, Karadurmus N, Sahin M. Lower leptin levels in young non-obese male smokers than non-smokers. Ups J Med Sci. 2009;114(3):165-9.

62. Lessard A, St-Laurent J, Turcotte H, Boulet LP. Leptin and adiponectin in obese and non-obese subjects with asthma. Biomarkers. 2011 May;16(3):271-3. Epub 2011 Jan 20.

63. Sin DD, Man SF. Impaired lung function and serum leptin in men and women with normal body weight: a population based study. Thorax. 2003 Aug;58(8):695-8.

64. Phipps PR, Starritt E, Caterson I, Grunstein RR. Association of serum leptin with hypoventilation in human obesity. Thorax. 2002 Jan;57(1):75-6.

65. De Santis S, Cambi J, Tatti P, Bellussi L, Passali D. Changes in ghrelin, leptin and pro-inflammatory cytokines after therapy in obstructive sleep apnea syndrome (OSAS) patients. Otolaryngol Pol. 2015;69(2):1-8.

66. Esheba NE, Shahba A, El Shora O. Assessment of leptin and resistin levels in non-obese multiple myeloma patients and their relation with Ig level and disease stage. J Egypt Natl Canc Inst. 2014 Jun;26(2):61-6. Epub 2014 Mar 14.

67. Ogura T, Matsuura K, Otsuka F, Imai A, Tsukamoto C, Mimura Y, Iwasaki Y, Tobe K. Serum leptin correlates with serum uric acid but not serum testosterone in non-obese male adolescents. Res Commun Mol Pathol Pharmacol. 2000;107 (1-2):55-64.

68. Elimam A, Marcus C. Meal timing, fasting and glucocorticoids interplay in serum leptin concentrations and diurnal profile. Eur J Endocrinol. 2002 Aug;147(2):181-8.

69. Radić R, Nikolić V, Karner I, Kosović P, Kurbel S, Selthofer R, Curković M. Circadian rhythm of blood leptin level in obese and non-obese people. Coll Antropol. 2003 Dec;27(2):555-61.

70. Sinha MK, Ohannesian JP, Heiman ML, Kriauciunas A, Stephens TW, Magosin S, Marco C, Caro JF. Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. J Clin Invest. 1996 Mar 1;97(5):1344-7.

71. Carraro R, Ruiz-Torres A. Relationship of serum leptin concentration with age, gender, and biomedical parameters in healthy, non-obese subjects. Arch Gerontol Geriatr. 2006 Nov-Dec;43(3):301-12. Epub 2006 Jan 31.

72. Stakos DA, Papaioannou HI, Angelidou I, Mantadakis E, Paraskakis E, Tsigalou C, Chatzimichael A. Plasma leptin and adiponectin concentrations correlate with cardiometabolic risk and systemic inflammation in healthy, non-obese children. J Pediatr Endocrinol Metab. 2014 Mar;27(3-4):221-8.

73. Xue B, Yu Y, Zhang Z, Guo F, Beltz TG, Thunhorst RL, Felder RB, Johnson AK. Leptin mediates high-fat diet sensitization of angiotensin II-elicited hypertension by upregulating the brain renin-angiotensin system and inflammation. Hypertension. 2016 May;67(5):970-6. Epub 2016 Mar 28.

74. Rahmouni K. Obesity-associated hypertension: recent progress in deciphering the pathogenesis. Hypertension. 2014 Aug;64(2):215-21.

75. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015 Mar 13;116(6):991-1006.

76. Simonds SEE, Simonds SE, Pryor JT, Ravussin E, Greenway FL, Dileone R, Allen AM, Bassi J, Elmquist JK, Keogh JM, Henning E, Myers MG Jr, Licinio J, Brown RD, Enriori PJ, O'Rahilly S, Sternson SM, Grove KL, Spanswick DC, Farooqi IS, Cowley MA. Leptin mediates the increase in blood pressure associated with obesity. Cell. 2014 Dec 4;159(6):1404-16.

77. Huby AC, Otvos L Jr, Belin de Chantemèle EJ. Leptin induces hypertension and endothelial dysfunction via aldosterone-dependent mechanisms in obese female mice. Hypertension. 2016 May;67(5):1020-8. Epub 2016 Mar 7.

78. Taussig MD, Powell KP, Cole HA, Nwosu SK, Hunley T, Romine SE, Iwinski H Jr, Talwalkar V, Warhoover T, Lovejoy SA, Mencio GA, Martus JE, Walker J, Milbrandt T, Schoenecker JG. Prevalence of hypertension in pediatric tibia vara and slipped capital femoral epiphysis. J Pediatr Orthop. 2016 Dec;36(8):877-83.