

Review

Slipped Capital Femoral Epiphysis Pathogenesis and Its Relation to Obesity—Where Do We Stand? A Narrative Review

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Abstract: Slipped capital femoral epiphysis (SCFE) is the most common adolescent hip disorder in children 9–15 years old with an incidence that ranges from 0.33:100,000 to 24.58:100,000. Idiopathic SCFE is strongly associated with obesity, while atypical SCFE is associated with endocrinopathies, metabolic and renal disease, radiation therapy, and chemotherapy. In this review, we summarized the current data regarding the pathogenesis of SCFE and its association to obesity. In the last years, there have been increasing evidence regarding the implication of obesity in the pathogenesis of SCFE, but no definitive mechanism has been proven. The etiology is probably multifactorial, with both mechanical and metabolic factors contributing to the disease, with the later gaining more ground, especially in obese patients. Understanding what causes the disease will help paediatricians and orthopaedists develop more efficient strategies for treating patients and diminishing complication rates.

Keywords: slipped capital femoral epiphysis; obesity; children



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1. Introduction

Slipped capital femoral epiphysis (SCFE) is a common condition among adolescents, primarily affecting children between the ages of 9 and 15 years old [1,2].

It is defined as displacement of the proximal femoral epiphysis from the metaphysis through the proximal femoral growth plate. It is a condition that is often not detected early, because the primary clinical characteristic is subtle pain in the knee or thigh, that goes on for weeks or months, causing confusion among patients and clinicians alike. Delay in diagnosis is even more frequent when the primary complaint at presentation is knee pain, which can be misleading for physicians [3,4]. SCFE can be classified as stable or unstable, with the latter being more severe and preventing the patient from ambulating even with the aid of crutches [5]. No pathognomonic clinical sign exists, but limited internal rotation of the hip and passive hip flexion are the most common findings. Diagnosis is made with standard biplanar radiographic examination of the hips, where the supine anteroposterior pelvis and Lauenstein (frog) lateral view present the classical anterior displacement of the anterior femoral neck, with relative posterior displacement of the capital femoral epiphysis, while in the pre-slip, slight widening of the physis may be depicted [6].

The natural history of untreated SCFE seems to cause a low level of disability particularly in mild cases according to the reports of Orderberg et al. [7] and Carney and Weinstein et al. [8], but activity level and patient expectations may have changed since the early 20th century and operative treatment has been established as the gold standard [9]. The long-term sequelae of SCFE may lead to avascular necrosis of the femoral head, femoroacetabular impingement, permanent hip deformity, and the need for early hip arthroplasty due to degenerative arthritis [10]. The most common cause for an early total hip replacement in patients with SCFE is avascular necrosis of the femoral head, which occurs in 15–50% of patients with acute, unstable slips. Although the greatest risk to the

femoral head may be avascular necrosis, we must not neglect that to the child, the greatest risk is undoubtedly the associated medical comorbidities and sequelae of obesity [9].

In addition to discussing the risk factors associated with obesity and SCFE, this study will also highlight the importance of early detection and proper management of the condition. Timely diagnosis and treatment can prevent long-term complications, such as avascular necrosis, hip deformity, and early hip arthroplasty. Furthermore, understanding the underlying mechanisms of SCFE can lead to the development of more effective prevention and treatment strategies. Overall, this study aims to provide a comprehensive overview of SCFE, with a focus on the relationship between obesity and the disease.

2. Epidemiology

The overall current incidence of SCFE ranges from 0.33 in 100,000 in Korean to 24.58 in 100,000 in African-American children 8–15 years and in the US-based population, it is 10.8/100,000 [11]. There is variation in the disease prevalence depending upon ethnicity, gender, season, geographical location, and place of residence [1,12,13]. In the US, the highest prevalence is seen in the Northeast regions while the lowest in the Midwest [2]. In the last century, a gradual decline in age of onset had been seen, but this trend has now stopped [11,14]. Currently, the average age of onset reported is 12.0 years for boys and 11.2 years for girls [15]. There are also variations regarding the male to female ratio, with reports from 1.1:1 in the Maori population, up to 4.1:1 in the Singapore population, but the difference has gradually leveled out with time [1,11,16]. Loder et al. [11] reported that the relative racial frequency (RRF) of SCFE relative to Caucasians is 5.6 for Polynesians, 3.9 for Africans, and 2.5 for Hispanics. The percentage is higher at 5.6 for Maori and at 4.2 for other Pacific Islanders. In Singapore, the RRFs, relative to Chinese, is 9.6 for Indo-Mediterraneans, 2.8 for Indo-Malay, and 3.0 for mixed Eurasians. The native Maori population is affected the most, while the Asian population demonstrates low incidence (Table 1). Epidemiologic studies suggest that obesity is prevalent among adolescents with SCFE, with >50% being over the 95th percentile weight for age and presenting with the condition in a younger age [11].

Table 1. Epidemiologic studies on SCFE.

Author	Study Years	Region	Incidence per 100.000	Age Range (in Years)
Larson et al.	1965–2005	Midwest USA	8.3	9–16
Herngren et al.	2007–2013	Sweden	44 females 57 males	11.7 * females 13 * males
Witbreuk et al.	1998–2010	Netherlands	11.6	5–19
Murray and Wilson	1981–2000	Scotland	9.66	11.6 * females 12.6 * males
Benson et al.	1995–2006	New Mexico	5.99	8–17
Lehmann et al.	1997, 2000	USA	10.8	9–16
Kwang-Soon Song et al.	1989- 2003	Korea	0.499 males 0.142 females	10–14
Perry et al.	2016–2017	Great Britain	3.34	6–18
Noguchi et al.	1997–1999	Japan	2.22 males 0.76 females	10–14
Ravinsky et al.	2002–2011	Ontario, Canada	5.68	9–16
Phadnis et al.	2000–2010	Maori/ New Zealand	81 Maori 11.3 New Zealand	5–14
Fedorak et al.	2005–2014	American Samoa	53.1	5–14
Longo et al.	2001–2015	Italy	2.9	10–14
Beharry et al.	2008–2018	North Trinidad	2.2	
Nguyen et al.	1988–2007	South Australia	8.2	10–19

* Mean. SCFE: Slipped capital femoral epiphysis [1–3,17–28].

3. Slipped Capital Femoral Epiphysis and Obesity

Slipped capital femoral epiphysis has either idiopathic or atypical etiology [29]. Idiopathic SCFE is strongly associated with obesity, which consists almost 80% of the total population at risk [30], while atypical is associated with endocrinopathies, metabolic and renal disease, radiation therapy, and chemotherapy [31].

Most of the children presenting with SCFE are obese, with more than 50% of children being in the >95th percentile weight for the age [11]. A large cohort study that used data from health screening examinations at primary school entry (597,017 children 5–6 years old) in Scotland and a further screening examination at primary school exit (39,468 children 11–12 years old), linked to a nationwide hospital admissions database, from Perry et al. [32], found that children with the lowest BMI at 5 to 6 years old had an almost insignificant lifetime risk of SCFE, those with a normal BMI had an estimated lifetime risk of 1:2500, those overweight had an estimated risk of 1:1750, those with mild or moderate obesity had a risk of 1:650, and those with severe obesity had a lifetime risk of 1:450. For children 11–12 years old, which is the age where obesity has the strongest association with SCFE, the lifetime risk among those with severe obesity is 1:250. One of the most critical public health issues of the twenty-first century is childhood obesity. Rising obesity rates among children and adolescents aged 5 to 19 have been observed in practically all countries, even those where the issue was not very concerning 40 years ago. In the WHO European Region, one child out of three is overweight or obese [33]. According to WHO report of 9 June 2021 [34], the prevalence of overweight and obese children and adolescents aged 5–19 has risen dramatically, from just 4% in 1975 to just over 18% in 2016. The rise has occurred similarly among boys and girls: in 2016, 18% of girls and 19% of boys were overweight. In a retrospective study in the US that was conducted to investigate long-term patient-reported outcomes of a cohort of 64 patients with SCFE (91 affected hips) with a 20-year follow up, and to determine whether the slip angle was associated with poorer health outcomes, the self-reported health was poorer than the average population, with higher rates of diabetes, hypertension, and obesity observed [35]. In a case-control study of 51 patients treated for SCFE and 62 healthy adolescents without SCFE, mean HbA1c levels were significantly higher than in obese patients without the condition, but there were no differences in the lipid profile, pointing out that patients diagnosed with SCFE should be considered as potential future type 2 diabetes mellitus patients. As a result, follow-up after surgical treatment of SCFE patients should include not only orthopedic outcomes but evaluation of risk factors for diabetes mellitus as well [36]. Although association between childhood obesity and SCFE has not yet been definitively proven, the increase in its prevalence along with the increase in incidence of SCFE is alarming.

4. Pathogenesis

The pathogenesis of the disease is not yet thoroughly ascertained, with SCFE being most frequently the outcome of a multifactorial event [11]. Understanding SCFE's pathogenesis precisely is crucial for both interpretation of the disease, the potential development of a rational therapeutic plan, as well as prevention strategies [37]. There are several etiological factors that can lead to SCFE, and which can act both separately or collectively. These include mechanical and anatomic factors [38,39], hormonal and endocrine factors [40,41], obesity [42,43], and immunological abnormalities [30].

Most cases of SCFE are idiopathic, presenting without any other underlying condition. However, a strong relation with childhood obesity has been demonstrated [19]. Obesity is recognized as a global health issue, particularly in Western industrialized nations [32–34], and is a well-established risk factor for SCFE. Three key elements in the pathophysiology of SCFE include an increase in body mass, the maintenance of the perichondrial ring, and high levels of activity [39]. In the presence of preexisting physeal pathology, the additional forces induced by obesity could result in a slip [43].

Obesity has been linked to leptin resistance, primarily by providing adequate satiety feedback and secondarily resulting in greater signaling at other sites of action [42]. This

is achieved when the serum leptin levels exceed the normal ones in non-obese individuals. Leptin levels are elevated in children with obesity. As observed in SCFE, leptin has the potential to enhance the proliferative zone's width. Leptin stimulates chondrocyte hypertrophy and proliferation; variations in leptin levels result in an extended physis, disrupted columnar structure, cellular apoptosis, and diminished expression and organization of the type-II and type-X collagen, normally observed throughout the hypertrophic zone [44]. Regarding the histologic similarities between SCFE-affected physes and hyperleptinemic physes, in addition to the connection between increased leptin and body mass index (BMI), we can suspect that leptin may be the cause of physal pathology necessary for the emergence of SCFE [44,45]. In tissues obtained from biopsies in SCFE, alterations in the longitudinal orientation of the physal cartilage cells, which are typically parallel to the axis of the bone, are observed. The columnar organization and the extracellular matrix composition of the physis in SCFE differ significantly histologically from those of a healthy physis (Figure 1). Although all the above changes are performed in sequence and in response, their role is still unknown. It remains a question as to whether they are of causal or adaptive reason. Additionally, some of these modifications can be present in endocrine or metabolic disorders [40].

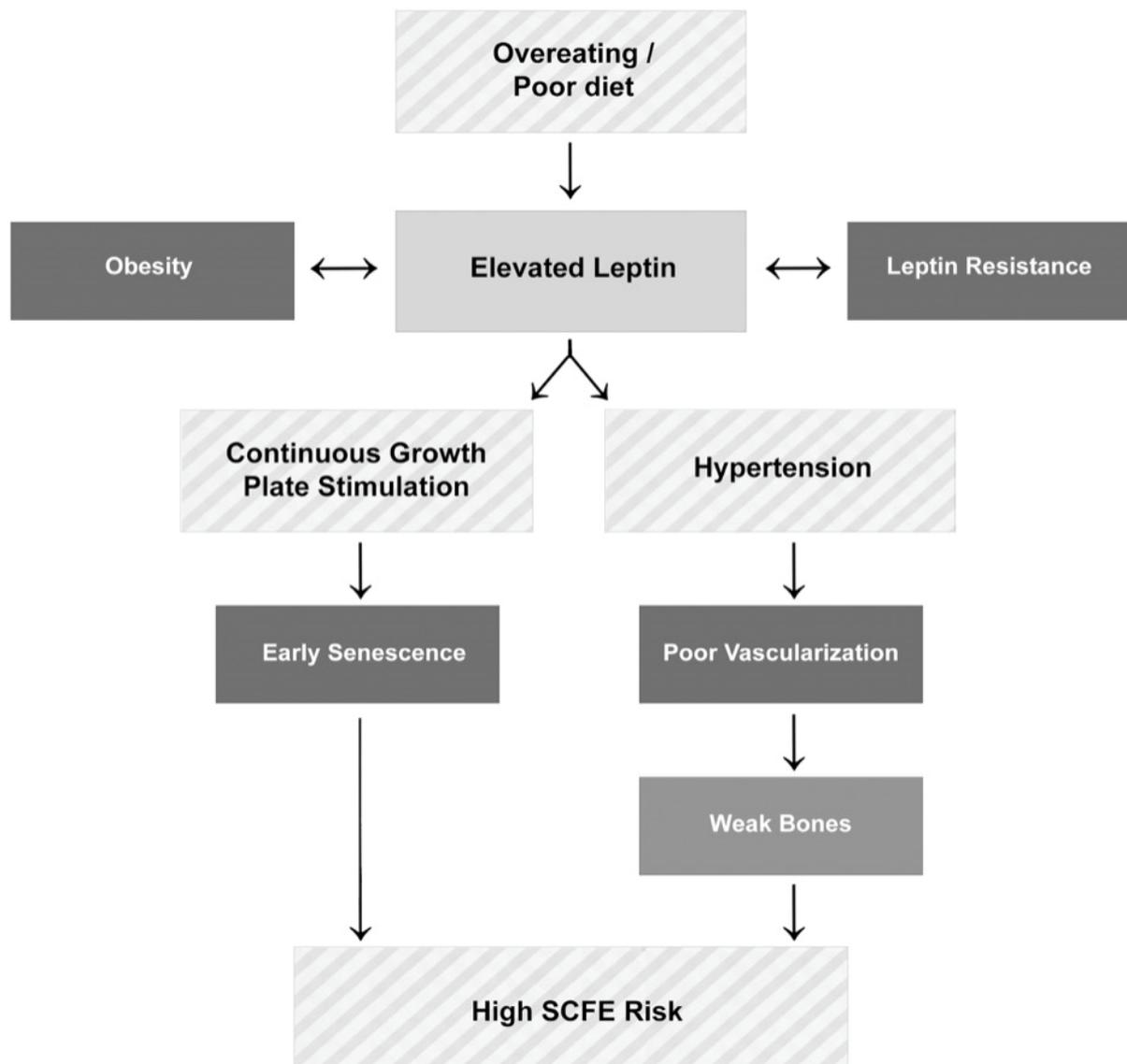


Figure 1. The effect of leptin on the pathophysiology of slipped capital femoral epiphysis.

Obesity causes accelerated growth earlier in the prepubescent stage, advancing puberty in females and delaying it in males [46,47]. The positive effect of insulin and insulin like growth factor 1 (IGF-1) in the proliferation and hypertrophy of differentiated chondrocytes of the physis has been well demonstrated [48–50]. Wu et al. [51], using a mice model, demonstrated that mice fed with a high fat diet developed greater body and tibial growth and higher serum insulin levels. Montanez-Alvarez et al. [41], in a case-control study of 14 children with SCFE compared to 23 age and BMI matched obese children without the disease conducted in Mexico, found elevated serum insulin, triglycerides, and very low density lipoprotein levels in the first group. Hyperinsulinemia impairs normal apoptosis of chondrocytes, which is necessary in the transition from physis to bone, therefore contributing in the broadening and weakening of the physis [49,52]. In a histologic study of the proximal femoral growth plate of eight core biopsies of the proximal femoral growth plate during in situ epiphysiodesis in patients with SCFE in the pre-slipping stage in two cases and at the mild slipping stage (Southwick angle $< 30^\circ$) in six cases, there were significant structural changes. Chondrocytes were smaller, elongated, and arranged in clusters rather than columns, with thinner collagen fibrils and impaired physal architecture [53], events suggesting that there are probably hormonal and metabolic factors rather than mechanical that cause the physis to deteriorate before the slip occurs.

Patients with SCFE frequently have delayed sexual maturation, which could indicate a delay in physal closure. This produces an extended period of weakness, resulting in a physis prone to the impacts of augmented load, mainly in the pre-existence of obesity. This interruption is implicated in the slip. Children with obesity are most commonly diagnosed with the above-mentioned condition [40].

It is fundamental to consider that atypical SCFE manifests with distinct clinical and radiological features, as well as different complications from idiopathic SCFE. Atypical SCFE is linked to endocrine abnormalities, neoplastic or metabolic disorders, including renal osteodystrophy, chemotherapy, or radiation therapy on the pelvic region [54].

Both biomechanical and biochemical alterations developing during puberty are generally established etiologies [55].

4.1. Endocrine Factors

Hypogonadal diseases, hypothyroidism, as well as growth hormone (GH) supplementation that constitute systemic or endocrine abnormalities deteriorate the physis. SCFE is prevalent among pediatric patients diagnosed with apparent endocrinopathies, which include hypopituitarism, hyperparathyroidism, and hypogonadal states but also hypo- and hyperthyroidism. Thyroid hormone via signaling of the Indian hedgehog/parathyroid hormone-related protein (IHH-PTHrH) pathway affects the physis both directly and indirectly [40].

Thyroid hormone facilitates growth, development, and maturation of the skeleton by stimulating chondrocyte proliferation, inducing differentiation of bone progenitor cells, mineralization, and angiogenesis. Moreover, it facilitates pituitary GH secretion and GH-dependent IGF-1 production in the bone, which both have regulatory effects on the activity of GH [56]. The epiphyseal plate becomes hypoplastic and endochondral and intramembranous ossification are delayed in children with thyroid hormone insufficiency. The growth hormone/insulin-like growth factor axis is rendered inactive by thyroid hormone deprivation. Recent animal studies have shown that hypothyroid swine displays much lower aggrecan and type X collagen gene expression, demonstrating the effect of hypothyroidism on the development plate [57]. Such modifications probably reduce the overall strength and resilience of the epiphysis, which may provide insight on the diseases of the human orthopedic growth plate. In patients with SCFE with atypical presentation, such as children younger than the age of 10 or older than 16 years old, those who have bilateral SCFE, or those whose height is less than 10% of the normal range for their age and sex, suggested thyroid function screening is suggested [58,59].

A rare pediatric condition, known as pseudohypoparathyroidism (PHP) type 1b, is marked by renal resistance to the parathyroid hormone (PTH), which results in biochemical hypoparathyroidism with skeletal sensitivity to PTH. Despite otherwise normal renal function, PHP is characterized by renal resistance to PTH, which leads to hypocalcemia and hyperphosphatemia and increased PTH concentrations. Since there is osseous sensitivity to PTH, bone resorption occurs [60].

In pediatric patients, long-lasting ailments provoke growth deficiency through altered mechanisms, which manifest on the GH/IGF-1 axis [61].

Physéal disorders mimic those developed in SCFE, mostly in young children with chronic renal failure that have higher risk of developing renal osteodystrophy. High and long-lasting concentrations of glucocorticoids decrease growth, directly and indirectly. Nevertheless, there is no clear evidence indicating the relation between glucocorticoids and SCFE [40].

In patients with malignancies, the survival rates have significantly improved, leading to the hypothesis of atypical SCFE as a late complication of radiotherapy and chemotherapy due to the systemic effects on the physis. Although physéal chondrocyte radiosensitivity, radiation's indirect endocrine effects, and chemotherapeutic radiosensitization have all been proposed as potential reasons, the exact mechanisms are still unknown. The fact that the majority of studies to date have not particularly addressed the clinical and radiologic characteristics of atypical SCFE is likely related to the relatively small number of subjects. Chemotherapy as a systemic treatment for pediatric malignancies may be the cause of atypical SCFE associated with a secondary endocrine dysfunction. Up to date, there is lack of evidence about an immediate association between chemotherapy and SCFE [54].

4.2. Immunological/Biochemical Factors

In their study, Eisenstein and Rothschild [62] investigated the biochemical abnormalities associated with SCFE and chondrolysis. They found that patients with SCFE had elevated levels of serum immunoglobulins, particularly IgA, as well as an elevated C3 component of complement. Interestingly, IgA had the highest values despite other laboratory tests being normal. Additionally, urinary glycosaminoglycan levels were elevated and increased with the severity of the illness. The authors speculated that these findings could suggest either that slipping of the epiphysis generates an antigen that triggers an autoimmune response, or that slipping is a localized manifestation of a generalized process replicating a connective tissue disorder or an inflammatory state. They also noted that while no other biochemical abnormalities were detected in patients with chondrolysis, the IgM fraction was significantly increased. These preliminary findings suggest that SCFE may be associated with underlying immunological and connective tissue disorders. Furthermore, it is possible that a subset of patients with SCFE may be genetically predisposed to chondrolysis. However, further research is needed to confirm these hypotheses and to fully understand the underlying mechanisms of SCFE and its associated complications. Overall, the study by Eisenstein and Rothschild sheds light on the complex pathophysiology of SCFE and provides important insights into potential underlying mechanisms. Further studies are needed to confirm and expand upon these findings, which may ultimately lead to more effective prevention and treatment strategies for this condition.

4.3. Mechanical Factors

Mechanical factors are categorized as contributing factors in the pathogenesis of SCFE. Direct or indirect injuries are fairly uncommon, in most cases, mild and rarely of decisive importance [39]. The proximal femoral physis' mechanical insufficiency is assumed to be part of the pathogenesis of SCFE. The slip can be caused either due to an abnormally high load across a normal physis or due to a physiological load across an abnormally weak physis, or a combination of both. Obesity, femoral and acetabular retroversion, the persistence of the perichondrial ring, epiphyseal tubercle height and location, and physéal cupping [63,64] are part of the mechanical factors contributing to the

disease [39,65]. The accepted etiology postulates that as biomechanical forces increase, they eventually exceed the physis' structural capacity, causing the epiphysis to slip or translate from its starting position, usually posteroinferiorly [44]. Many children during their growth expose their hip joints to high mechanical loads during both normal as well as strenuous sports activities [40]. Results indicate that during physical activity, the growth plate may undergo an abnormal escalation in tension when subjected to an impact loading. Even under physiological conditions, this could cause the plate to deteriorate and subsequently fracture [66]. Despite being obese and rapidly growing, the majority of adolescents with SCFE do not have hormonal metabolic or chronic disorders. However, it seems unlikely that mechanical overload of the proximal femur epiphysis caused, for instance, by excessive body weight alone, can result in a slip. The aforementioned theory is further supported by the results of Winston et al. [38]. In their research, they measured using computerized tomography, epiphyseal tubercle height, width, and volume, physeal diameter, cupping height, acetabular inclination and rotation, and metaphyseal bone density in 31 obese children and 31 age- and gender-matched children with normal weight. Their results indicate that obesity does not cause morphologic changes in the proximal femoral physis, but there is high metaphyseal metabolic activity, as demonstrated by lower bone mineral density in the metaphysis of obese children [38]. In a finite element 3-dimensional model of the adolescent hip, the combined effect of physeal thickness, physeal-diaphysis angle, body weight, physical activity, and the presence of the perichondrial ring were studied for their combined effect. Their results indicate that the most influential factors that contribute to the stresses along the physis are body mass, the presence of the perichondrial ring, and physical activity. In fact, the presence of the perichondrial ring decreased the stress along the physis by 2.53 MPa and high impact activity, such as jumping, had a double mean stress value than toe-off. Slipping angles between 49.9–51.9 had mean stress value 1.36 times greater than angles 41.9–47.9 [39], therefore indicating that increased obliquity is a stress riser of the physis. A detailed diagram of the factors contributing to the pathophysiology of SCFE is shown in Figure 2.

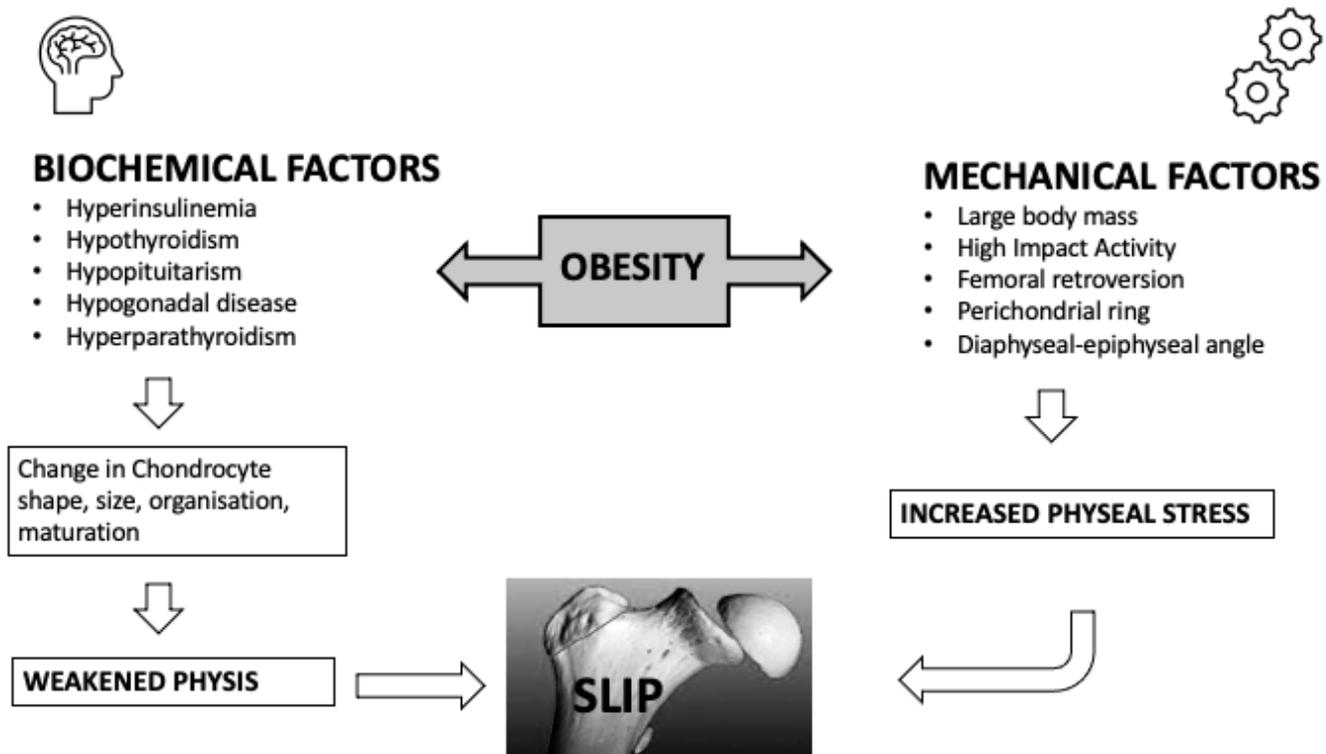


Figure 2. Pathogenesis of slipped capital femoral epiphysis.

5. Summary

Although the exact mechanisms through which obesity predisposes adolescents to the disease are not yet fully understood, evidence linking obesity with idiopathic SCFE have been provided through observational studies [67,68], case series [69,70], mathematical models [39,71,72], and population-based epidemiologic cohorts [1,14,32], where a strong association has been demonstrated. Non-obese children presenting with the disease are more likely to suffer an atypical, unstable, and more severe slip [30]. For idiopathic cases, the lifetime risk for adolescents with severe obesity is 17 times higher than those with normal weight, who have almost negligible risk, as shown by Perry et al. [32]. The mechanisms through which obesity predisposes adolescents to the disease are based on metabolic and mechanistic theories, with no clear superiority of one over the other. On one hand, the excess adipose tissue of obese children causes earlier onset of the prepubertal period, delayed physeal closure, morphologic changes in the zones of the physis, and changes in the shape, size, alignment, and apoptosis of the physeal chondrocytes [46,47,49–53]. Elevated insulin levels observed in obese children contribute to the proliferation, hypertrophy, and delayed chondrocyte apoptosis, thus contributing to the proximal femoral growth plate widening and delayed ossification [51,52]. Other studies have suggested that obesity can lead to mechanical factors that increase stress on the proximal femoral physis [39,73,74]. Physeal thickness has been proposed as a contributing factor to the forces exerted across the proximal femoral physis, which is influenced by metabolic changes. As Castro et al. [39] showed, when physeal thickness exceeded 2.1 mm, there were significant changes in stress through the physis. In a retrospective study, the hip morphology of 31 obese and non-obese adolescents was documented using computerized tomography. Physeal diameter, tubercle height, width, and volume, cupping height, acetabular inclination and rotation, and bone density were measured. Obese children were found to have non-significant morphologic changes of the aforementioned parameters compared to non-obese children, with the exception of lower metaphyseal bone density [38]. On the other hand, another study demonstrated that children between 9–12 years old tend to have a more vertical proximal femoral orientation [73], which increases stress to the physis. The perichondrial ring, which is stronger and more important in early childhood, and the epiphyseal tubercle and metaphyseal fossa, are structures important to the stability of the capital epiphysis and resistance to shear forces. Damage to those elements may predispose the proximal femoral physis to failure under excess stress [39,65,74]. Children with increased body mass and high impact activities place their femurs in higher mechanical stress [39]. All the aforementioned factors, when combined, may lead to physeal fracture and a clinical slip. In the last years, there have been increasing evidence regarding the implication of obesity in the pathogenesis of SCFE, but no definitive mechanism has been proven. The etiology is probably multifactorial, with both mechanical and metabolic factors contributing to the disease, with the later gaining more ground, especially in obese patients.

Developing effective strategies for preventing, diagnosing, and managing SCFE is essential for improving the prognosis and reducing the morbidity and mortality associated with this condition. Given the established link between obesity and idiopathic SCFE, interventions that focus on reducing obesity may be a critical component of primary prevention efforts. Efforts should also be directed towards screening high-risk individuals, including overweight and obese children, for early detection and timely management of the disease. Treatment approaches for SCFE include surgical and non-surgical interventions, with the former being the preferred treatment option for severe slips. In addition, early diagnosis and treatment can help prevent complications, such as chondrolysis and avascular necrosis. Clinicians should also be aware of potential risk factors for the disease and provide appropriate counseling to patients and families regarding lifestyle modifications and weight management. Overall, a better understanding of the etiology of SCFE can lead to the development of more effective prevention and treatment strategies, ultimately improving the outcomes for children with this condition.

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