Review Paper

Investigating Legg-calve-perthes Disease: A Comprehensive Review of Diagnosis, Management and Current Treatment Options

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ABSTRACT

Background: Legg-calve-perthes disease (LCPD) is an idiopathic condition affecting children's hip joints, causing bone tissue death and deformity. Typically, occurring between ages 2 to 15 years, LCPD is influenced by genetic and environmental factors. The disease progresses through distinct stages including necrosis, fragmentation, re-ossification, and remodeling.

Objectives: This study aims to perform a a comprehensive review of diagnosis, management and current treatment options of LCPD.

Methods: A literature review focusing on the etiology, diagnosis and treatment of LCPD was conducted. The inclusion criteria were studies reporting clinical or preclinical findings. The research team performed a refined search on PubMed to gather relevant information.

Results: This article highlights key aspects of LCPD management, encompassing etiology, diagnostic modalities, and various treatment strategies. The primary goals of treatment are to preserve normal hip joint function, prevent deformities and mitigate the risk of long-term complications. The Steinberg classification system categorizes LCPD into six stages based on size, morphology, and gross changes. Diagnosis and staging are typically performed using conventional radiography, with magnetic resonance imaging playing a crucial role in early prognosis.

Conclusions: The study evaluates various diagnostic and therapeutic approaches, encompassing both non-surgical interventions and surgical procedures. Treatment methods are compared based on patient-specific factors, such as physical condition, age, and timing of intervention to provide a comprehensive understanding of the strengths and limitations of each approach.

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Introduction

Legg-calve-perthes disease (LCPD) is an idiopathic condition affecting children's hip joints. The characteristic feature of LCPD is the cutting off of the blood supply to the femoral head epiphysis, which ultimately results in the death of bone tissue (aseptic osteonecrosis) and the deformity of the femoral head (FH). LCPD typically manifests clinically between the ages of 2 and 15 years, with males afflicted five times more often than females [1].

Initial symptoms of LCPD may be subtle, such as mild discomfort or limping, which may intensify with physical activity (primarily in the anterior hip and midthigh) [1]. As the disease progresses, limited hip range of motion, atrophy of the thigh muscles, decreased internal rotation, hip abduction, and Trendelenburg gait can occur [2, 3].

The pathogenesis of LCPD is characterized by various stages as follows: 1) Necrosis phase, 2) Fragmentation and 3) Re-ossification and remodeling. In the early phases of LCPD, x-rays are frequently used to determine the disease's stage, FH position and FH involvement. However, in cases where radiographic findings are not diagnostic, magnetic resonance imaging (MRI) is recommended [3, 4].

The therapy of LCPD is determined in part by several parameters, including the age and disability of the patient at the time of diagnosis, the lateral pillar classification and the stage of the disease. Conservative treatments, such as rest, physical therapy, and braces or casts can be combined with surgical procedures, such as osteotomy to preserve the hip joint. Treatment maintains normal hip joint function, prevents deformity, and decreases the likelihood of long-term complications [5, 6].

Despite advances in knowledge and treatment options, managing LCPD remains complicated. These may result from the disease's varied manifestations, the inability to predict outcomes precisely and the lack of consensus regarding the most effective treatment strategies. Hence, this paper is based on recent data in the literature to review the etiology, imaging, and treatment of LCPD.

Clinical manifestations and physical examination

Patients in the early stages of the disease experience mild and nonspecific symptoms, such as pain or limping [3, 7]. Due to stimulation of the sensory branch of the obturator nerve, the patient often localizes the pain in the thigh or knee. The patient's examination revealed a reduction in internal rotation and abduction of the hip, an occasional antalgic gait, and a reduction in the range of motion of the hip joint, all of which are caused by muscle spasm, joint effusion and FH collapse [2, 3, 8]. Significant FH collapse can result in a leg length discrepancy and Trendelenburg gait in patients. In addition, shortening of the ipsilateral gluteal musculature can exacerbate the patient's limping [1, 2, 8].

Etiology

Despite numerous hypotheses, the exact cause of LCPD is still uncertain. A disruption in the blood supply to the developing FH is the hallmark of LCPD resulting in ischemic necrosis and subsequent structural alterations in the developing FH. Genetic and environmental factors contribute to the condition's development. Genetic factors may influence susceptibility to interruption of blood supply to the FH. LCPD has been linked to mutations of the *COL2A1* gene on the 12q13 chromosome and the *COL1A1* gene, which is associated with osteogenesis imperfecta [9, 10]. In contrast, environmental factors, such as repetitive trauma or mechanical excess, increased blood viscosity [11] and coagulation disorders may initiate the disease. In addition, passive smoking exposure, and high-dose and long-term glucocorticoids have been linked to an increased risk of LCPD [12, 13]. Furthermore, sickle-cell anemia, thalassemia, trichorhinophalangeal syndrome, and hemophilia can be a risk factor for LCPD [6]. Sickle-cell anemia patients with osteonecrosis had substantially higher hospitalization rates (mostly due to vaso-occlusive crisis) compared to subjects without osteonecrosis, according to Adekile [14]. Meanwhile, according to Leandro et al. polymorphisms in the *BMP6*, *Klotho* and *ANXA2* genes may be related to LCPD in sickle-cell anemia patients [15].

Pathogenesis

The progression of LCPD consists of various stages: 1) In the initial phase, the FH's blood supply (the subchondral cortical bone mostly) is cut off, resulting in bone and cartilage death (necrosis phase); 2) In the revascularization stage, new blood vessels form, and new bone gradually supplants necrotic bone (fragmentation); 3) During this phase, osteoblasts reactivate, resulting in remodeling, which might be malformed or asymmetrical, leading to adult-onset degenerative osteoarthritis (re-ossification and remodeling).

Table 1. Stages of LCPD

Stage	Findings
0	No symptoms Normal radiograph MRI non-specific Mild pain in the affected hip or pain with internal rotation
1	Normal radiograph Abnormal bone scan and/or MRI changes suggestive of early disease Worsening or persistent pain
2	Increased sclerosis or cysts in the FH
3	Subchondral collapse without flattening (crescent sign)
4	Flattening of the FH
5	Narrowing of the joint space with/without FH involvement
6	Advanced degenerative changes

MRI: Magnetic resonance imaging; FH: Femoral head.

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The pathological progression of LCPD affects multiple parts of the FH, including the articular cartilage, epiphysis, physis, and metaphysis, leading to the destruction of trabecular bone microarchitecture and necrosis in the bone marrow. The disruption of blood supply can result in growth cessation of the epiphysis, necrosis of the deep layer of articular cartilage, an increase in vascular endothelial growth factor (VEGF), a rise in vascularization, and deformity. In addition, serum VEGF may serve as a useful disease follow-up marker [16, 17].

Following revascularization, the primary reparative response is osteoclastic bone resorption which causes the normal tissue of the FH to be replaced by fibrovascular tissue. The inability of the growth plate that surrounds the osseous epiphysis to continue forming is another factor that leads to the degeneration of the FH. VEGF and bone morphogenetic protein (BMP)-2 are involved in this process due to their respective roles in angiogenesis and endochondral ossification [18].

The blood supply to the FH depends on several number of anastomoses that contribute to its vascularization. Several anastomoses contribute to the FH's blood supply: 1) The anastomosis between the medial and lateral circumflex branches of the profunda femoris is the most essential; 2) Cruciate anastomosis of the inferior gluteal artery to the medial circumflex femoral artery; 3) An anastomosis between the superior gluteal artery and the medial/lateral circumflex femoral arteries at the trochanter. In addition, the foveal artery, which passes through the ligamentum teres, supplies blood to the FH, which is especially significant in children. Due to insuf-

ficient collateral circulation in the FH, ischemia and necrosis may develop, if the blood supply is cut off.

Neutrophils and macrophages are the most prevalent inflammatory cells involved in the pathogenesis of osteonecrosis, resulting in macroscopic subchondral collapse and subsequent joint deterioration. Disruption in blood supply causes ischemia of the covering cartilage and flattening of the head articulates with the acetabulum, which causes secondary osteoarthritis [19-21].

Classification

LCPD is classified into the following stages based on symptoms, as well as plain radiographs, bone scans and MRI findings (Table 1) [22].

Imaging

The majority of LCPD diagnosis and staging is performed using conventional radiography as the imaging modality. The epiphyseal involvement and the height of the lateral pillar are associated with FH deformity and can be used to assist in classification, prognostic evaluation, and surveillance of disease progression on conventional radiographs [6, 23]. If the FH involvement is not evident on standard x-rays, lateral x-rays may be necessary to detect alterations in the anterolateral aspect of the FH [4].

In cases where hip radiographs are normal or inconclusive, the MRI is essential for diagnosing LCPD (Figure 1). For effective joint preservation treatments to be initiated, early diagnosis is essential. Hence, using non-enhanced and contrast-enhanced imaging sequences,

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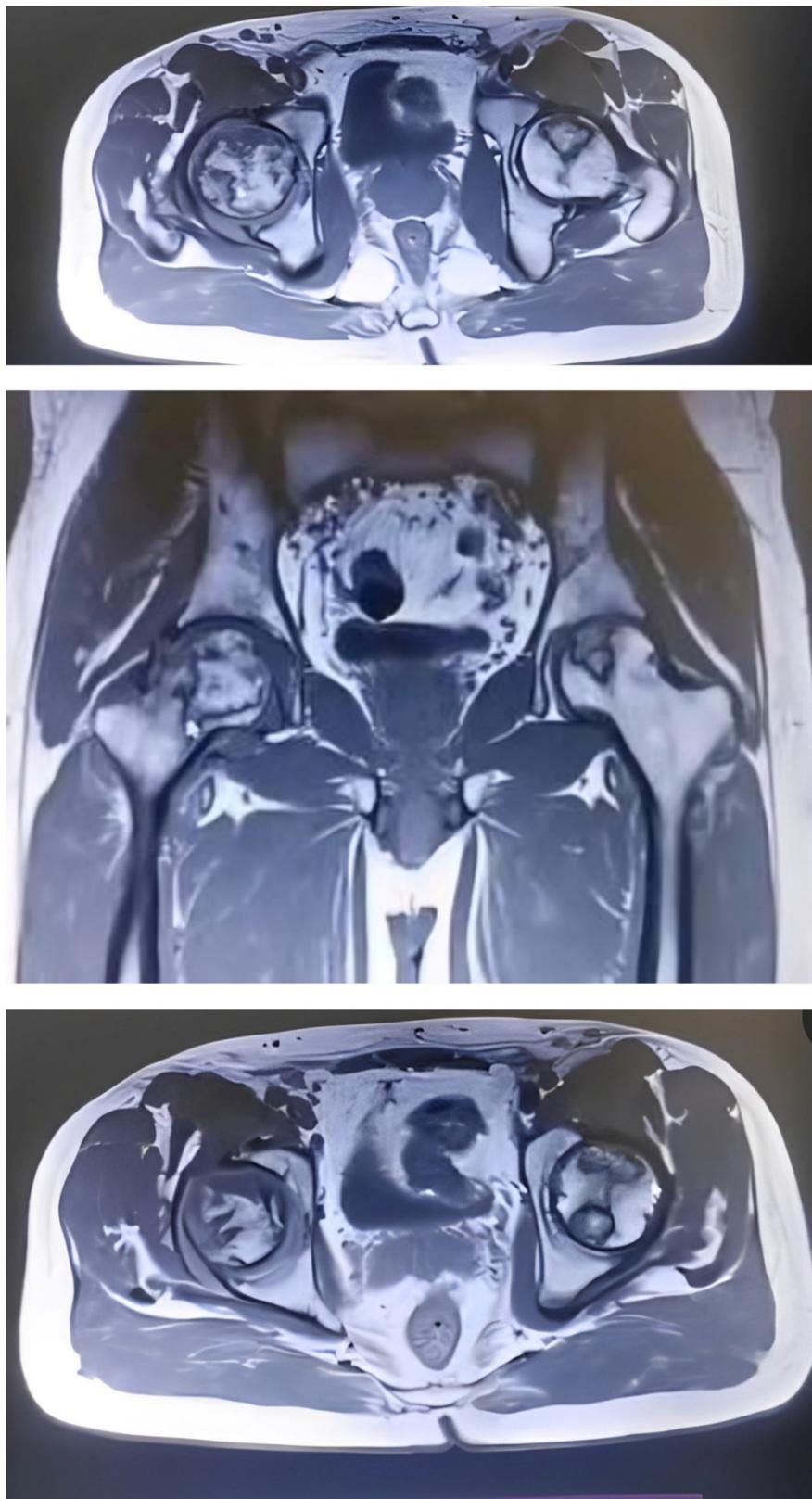
Figure 1. The non-contrast hip magnetic resonance imaging, reconstructed in axial and coronal views *Journal of Pediatrics Review*

Notes: Using the T1 sequence, the image reveals areas of low signal intensity, suggesting edema. These regions are marked by a hyperintense line, indicating the presence of blood products. In T2 sequences, a second hyperintense inner line becomes apparent between the normal marrow and ischemic marrow. This distinctive feature, known as the ''double-line sign,'' is highly specific for hip osteonecrosis.

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MRI can confidently diagnose LCPD and facilitate the initiation of appropriate therapies. Contrast-enhanced MRI using gadolinium has proved to be superior to radiography and can detect FH perfusion early at an early stage and aid in early prognostication [3]. Hypoperfusion is one of the early alterations visible in LCPD and can be demonstrated on T1-weighted fat-suppressed imaging performed 2–5 min after contrast administration [24]. Furthermore, bone scintigraphy and diffusion-weighted MRI can be employed to evaluate the severity of perfusion abnormalities in LCPD may be a significant prognostic factor [23]. Dynamic contrast-enhanced subtraction MRI has demonstrated high sensitivity, excellent correlation with bone scintigraphy, and the ability to provide specific information about blood flow to the FH, thereby facilitating the early detection of ischemia [24].

MRI is also beneficial for accurate disease early staging, assessing associated complications, and distinguishing LCPD from other epiphyseal lesions [25]. It allows for the differentiation of LCPD from multiple epiphyseal dysplasia, spondyloepiphyseal dysplasia and Meyer dysplasia. In the early phases of LCPD, contrast-enhanced MRI better defines the extent of FH necrosis than non-contrast MRI. Radiographic measurements of FH deformity correlate strongly with perfusion measurements obtained from contrast-enhanced subtraction MRI, specifically the MRI perfusion index, after at least two years of follow-up [26].

Treatment

The objective of LCPD treatment is to achieve a spherical FH contour with excellent congruency during the disease process [27]. Depending on the onset age, disease stage, and severity of FH involvement LCPD is treated differently. Current LCPD treatment emphasizes protecting the FH mechanically to prevent future hip deformity and degeneration [1]. The following treatment options and factors can be considered.

Conservative treatment

LCPD can be treated conservatively with non-weight bearing casts, abduction casts, orthotics, and rehabilitation, and are better suited to younger patients (Table 2). The goal is to decrease deformity, promote revascularization and resorption of the infarcted epiphysis, and increase the range of motion. However, the effectiveness of conservative treatment has been contested, and results can vary. Those who are younger than 6 years at the time of diagnosis or who have necrosis of less than

50% of the FH should be treated symptomatically, according to Wiig et al. [28].

Observation

The observation method may be advised in children aged 2 to 3 years and permits the FH to recuperate naturally and endure remodeling without intervention [28].

Non-weight bearing

In the treatment of LCPD, the non-weight bearing has demonstrated contradictory results. Several studies indicate that early weight-bearing restrictions can reduce FH deformity and facilitate revascularization and healing. It could be considered a treatment option for patients who are unable or unwilling to undergo surgery. According to Peck et al., prolonged non-weight-bearing should be regarded as a treatment option for patients unwilling to undergo operative treatment in early-stage LCPD with significant hypoperfusion [29]. Protective weight bearing improved collapse ratings. Protective weight-bearing helps most pre-collapse and post-collapse patients delay total hip arthroplasty or hip-preserving surgery [30].

Bisphosphonate therapy

Due to the lack of consistent patient groups and pharmacological protocols, the clinical evidence for bisphosphonate therapy to reduce FH deformity in LCPD is inconclusive. Studies suggest that bisphosphonate therapy (systemic and local) can prevent deformity of the infarcted FH in LCPD and preserve FH morphology. This strategy targets the pathological processes that contribute to FH collapse, particularly the imbalance of osteoclast resorption and the delay in new bone formation [31]. Some authors reported that bisphosphonate can reduce discomfort, improve mobility, and prevent articular collapse [32].

FH deformation can be prevented or greatly reduced when BMP2 is administered locally [33]. In a pig model of ischemic osteonecrosis, administration of BMP-2 decreased bone resorption and increased new bone formation in an animal study [34]. According to Vandermeer et al. in an immature animal model of ischemic osteonecrosis, the combination of ibandronate and BMP-2 reduced FH deformity and stimulated bone formation [35].

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Table 2. Type of conservative treatment method in LCPD

Type of Conservative Treatment Method	Target Group	Advantages
Observation	Children 2 to 3 years old	Allowing FH to recuperate naturally, endure remodeling without intervention
Non-weight bearing	Patients who are unable or unwilling to undergo surgery	Reduce FH deformity, facilitate revascularization and healing
Bisphosphonate therapy		Prevent deformity of the infarcted FH, preserve FH morphology, reduction in discomfort, improvement in mobility, prevention of articular collapse

FH: Femoral head.

Bisphosphonate dose may depend on therapy timing. Preventing deformity may require starting therapy early. Anabolic stimulation is needed to facilitate healing and new bone formation, even if bisphosphonates and other anti-resorptive medicines can preserve FH's spherical shape. Weight loss and activity modifications may be required during recovery due to the necrotic FH's impaired mechanical characteristics [36].

Surgical treatment

In certain cases of LCPD, surgery may be considered a treatment option (Table 3). Typically, the decision to conduct surgery is influenced by age, the extent of FH involvement (Catterall classification), and prognosis. In patients with 6 years of age or higher with FH necrosis exceeding 50%, surgical intervention should be considered [28]. In surgical procedures, femoral osteotomy, salter osteotomy, lateral shelf acetabuloplasty, and so on may be performed. Surgical treatment in patients older than 6 years has outstanding outcomes for Herring B and B/C hips and poor outcomes for Herring C hips, with a modest advantage for patients aged 6 to 8 years [37].

A-frame orthoses

According to Rich et al. restoring and sustaining a hip range of motion in conjunction with the use of an A-frame orthosis led to a high proportion of spherically congruent hips in patients of all ages and disease severity. This method has proven effective for preserving joint function and improving hip congruency [38].

Arthrodiastasis

Arthodiastasis is a relatively new method of treating LCPD. Using an external fixator, an articulated distraction is conducted on the hip joint. The purpose of the procedure is to restore joint function, make room for the FH, alleviate physical pressure, and maintain synovial fluid circulation. In several studies, improvements in range of motion and joint congruence have been observed [39]. Aguado-Maestro et al. asserted that arthrodiastasis is a minimally invasive treatment for late-onset LCPD and, early application enhances clinical outcomes and maintains cephalic shape. However, complications can occur in as many as eight out of ten patients who undergo the procedure [40].

Rotational open-wedge osteotomy

Rotational open-wedge osteotomy is performed to correct the FH deformity and enhance the alignment of the hip joint. The surgical process entails making a carefully controlled incision in the femur and rotating the FH to achieve a more favorable position within the hip socket.

The aims of rotational open-wedge osteotomy in LCPD encompass the following items: 1) Improving the position of the FH within the hip socket by rotating it and achieving realignment; 2) Realignment of the FH; 3) Prevention of long-term complications, including the development of hip joint arthritis and degenerative changes. Nakamura discovered that combining rotational open-wedge osteotomy with non-weight-bearing treatment produced superior results in elder children with severe LCPD than in non-weight bearing treatment alone [41].

The salter or innominate osteotomy

The salter or innominate osteotomy surgical method is a form of femoral osteotomy that is frequently used to treat LCPD. This osteotomy's primary advantage is its influence on FH remodeling during remaining growth. This osteotomy also moves the acetabulum one to one and a half centimeters to the medial side, which results in a reduction in the number of biomechanical compression pressures across the hip joint [42]. Kitakoji et al. asserted that salter innominate osteotomy is the superior treatment for patients with LCPD to reduce residual complications, such as coxa vara, trochanteric prominence, inadequate acetabular coverage and surgi-

cal incision [43]. Kacki et al. hypothesized that surgical treatment with salter osteotomy could facilitate spherical FH reconstruction, and patients in Catterall categories III and IV may benefit from this surgical procedure [44]. The salter pelvic osteotomy is an effective surgical treatment for LCPD in children aged 6 to 8 years [45]. salter osteotomy can be used to treat older patients who manifest with lateral pillar stages B, B/C and C [46].

The primary benefit of the salter osteotomy is its ability to ensure adequate coverage of the FH by the acetabulum, which is crucial for maintaining joint stability and preventing further deformity [47]. The procedure restores the normal contour and alignment of the FH, leading to improved long-term outcomes for LCPD patients.

The results of a salter osteotomy are permanent and independent of the length of follow-up. This indicates that the positive effects of the surgery are anticipated to be maintained throughout the patient's life without the need for further interventions related to the LCPD condition. This operation seeks to restore proper alignment and improve the condition of the FH [1].

Femoral varus osteotomy

Femoral varus osteotomy is a common surgical procedure used to treat LCPD. The primary goal of surgical procedures, such as femoral varus osteotomy is to prevent the deformation of the FH and the subsequent onset of hip osteoarthritis. This procedure involves repositioning the femur to enhance hip joint alignment and correct deformities. It alleviates symptoms, enhances joint function, and encourages healthy joint development.

During the procedure, a controlled incision is made in the femur bone, typically near the hip joint. By meticulously repositioning the bone fragments, the surgeon seeks to center the FH within the acetabulum and correct any flexion and rotational deformities that may be present. The hip joint must have an adequate range of motion, congruency, and the capacity to contain the FH during abduction.

Studies have shown that femoral varus osteotomy provides greater benefits than non-operative interventions for adolescents older than 6 years. This procedure provides for hip joint realignment, joint congruity restoration, reduction of femoroacetabular impingement, correct deformities, and prevent the onset of hip osteoarthritis.

Without any FH deformity and flatness, proximal femoral varus osteotomy produces satisfactory outcomes in children aged 6–10 years, especially with adequate containment in abduction [48]. According to Kim et al., when performing proximal femoral varus osteotomy on hips with early stages of LCPD, it is recommended to achieve 10° to 15° of varus correction. This is because greater varus angulation does not necessarily produce better preservation of the FH following the procedure [49].

Triple innominate osteotomy

Triple innominate osteotomy is an additional containment method for LCPD. In severe instances, salter osteotomy may not provide sufficient acetabular rotation to encompass the FH, leading to iatrogenic hinge abduction. For more severe cases, sophisticated containment techniques, such as triple innominate osteotomy, have been devised due to the limitations of these two procedures. Multiple studies indicate that advanced age and extensive involvement of the FH are risk factors for inferior outcomes. Prior research revealed unsatisfactory surgical outcomes for patients older than 10 years at onset. It is anticipated that triple innominate osteotomy will accomplish greater FH containment than salter osteotomy alone and prevent the leg length disparity induced by femoral varus osteotomy. In all circumstances, this is one of the most effective methods for FH containment. However, excessive coverage may cause pincer impingement. It is not recommended to correct the enter-edge angle further than 44° to prevent pincer impingement. As expected, triple innominate osteotomy appears to be more effective in younger patients with less severe disease, but favorable outcomes are not wholly dependent on the stage of disease in LCPD when triple innominate osteotomy is used for containment [50]. Rosello et al. asserted that triple pelvic osteotomy provided superior radiologic and clinical outcomes in comparison to Chiari osteotomy, particularly in terms of the final Stulberg classification [51].

Triple pelvic osteotomy

The triple pelvic osteotomy surgery is typically used in older adolescents in whom hip containment is difficult to achieve with salter pelvic osteotomy. This procedure is at end-stage disease, when a large, inadequately covered FH remained, necessitating surgical coverage by those who rejected other types of osteotomies. Bernese triple pelvic osteotomy (a modified anterior Smith-Peterson technique) is an alternative treatment for LCPD in skeletally underdeveloped older children. In

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Table 3. Type of surgical treatment in LCPD

Type of Surgical Treatment	Target Group	Advantages
A-frame orthoses	Patients of all ages and disease severity	Preserving joint function Improving hip congruency
Arthrodiastasis	Late-onset LCPD patients	Restore joint function Make room for the FH Alleviate physical pressure Maintain synovial fluid circulation
Rotational open-wedge osteotomy	Elder children with severe LCPD	Improving the position of the FH within the hip socket Realignment of the femoral head Prevention of long-term complications
The Salter or innominate osteotomy	Patients in Catterall categories III and IV Older patients who manifest with lateral pillar stages B, B/C and C	Reduction in residual complications, such as coxa vara, trochanteric prominence, inadequate acetabular coverage, and surgical incision
Femoral varus osteotomy	Adolescents older than six	Prevent deformation of the FH and the subsequent onset of hip osteoarthritis Enhance hip joint alignment Correct deformities Alleviate symptoms Enhance joint function Encourage healthy joint development
Triple innominate osteotomy	Severe cases of LCPD Advanced age (patients older than 10 years at onset) Extensive involvement of the FH	Accomplish greater FH containment than Salter osteotomy alone Prevent the leg length disparity induced by femoral varus osteotomy
Triple pelvic osteotomy	Older adolescents in whom hip containment is difficult to achieve with Salter pelvic osteotomy End-stage disease, when a large, inadequately covered FH remained, necessitating surgical coverage Those who rejected other types of osteotomies	Provide a substantial acetabular correction Accomplish biomechanical stability
Lateral shelf acetabuloplasty	Severe cases of LCPD in patients older than 8 years	Enhance the coverage of the FH Improve joint stability Facilitate the remodeling process during the healing of LCPD disease

LCPD: Legg-calve-perthes disease; FH: Femoral head.

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addition to providing a substantial acetabular correction, it also accomplishes biomechanical stability [52]. Jishuitan (another simplified approach for triple pelvic osteotomy) is a safe, more effective method that can achieve satisfactory correction [53].

Lateral shelf acetabuloplasty

When hip subluxation is reduced with shelf acetabuloplasty, the FH is better able to undergo biological remodeling inside the acetabulum [54]. In severe cases of LCPD in patients older than 8 years, the surgical results of combined shelf acetabuloplasty with femoral varus osteotomy are on par with those of other cutting-edge techniques [55].

The primary goals of lateral shelf acetabuloplasty are as follows: 1) Enhance coverage of the FH by creating a shelf on the outer side of the acetabulum, thereby increasing the supportive surface area available; 2) Improve joint stability by reshaping the acetabulum, promoting better alignment and reducing the chances of hip subluxation or dislocation; and 3) Facilitate the remodeling process during the healing of LCPD disease by providing a more favorable environment through the reshaping of the acetabulum [56].

Total hip arthroplasty

The incidence of total hip arthroplasty among LCPD patients was relatively low. According to Zhi et al. the incidence of THA increased with age at disease onset and duration of follow-up, but the Stulberg classification was not explicitly associated with the incidence of total hip arthroplasty [57]. According to the findings of Froberg and colleagues, people who have LCPD have a higher risk of developing radiographic hip osteoarthritis than a control group does. Those who are classified as Class III/IV/V appear to be at a greater risk of developing total hip arthroplasty and osteoarthritis compared to individuals who have FH classified as Class I/II [58].

Conclusion

The outcomes of this review underscore the significance of enhancing the knowledge of physicians and healthcare professionals regarding LCPD. This condition arises from a combination of genetic and environmental factors impacting the hip joints of children, leading to deformities and morbidity. While conventional radiography serves as the primary imaging modality for this disease, MRI contributes to enhanced diagnostic accuracy, particularly in the initial phases, thereby optimizing patient prognoses. Treatment strategies for affected individuals encompass conservative and surgical interventions aimed at preserving joint functionality, averting deformities and mitigating long-term complications.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

All authors contributed equally to preparing all parts of the research.

Conflicts of interest

The author declared no conflict of interest.

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