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Priapism in the Context of Sickle Cell Disease: State of the Art and Perspectives

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ABSTRACT

Priapism is a frequent complication in patients with sickle cell disease, putting their sexual and reproductive health at risk. This systematic review aims to analyze existing studies on priapism in this context comprehensively. The results show that priapism, particularly the ischaemic type, is prevalent in men with sickle cell disease, especially those carrying HbSS genotypes. Risk factors include vaso-occlusive crises, severe anemia, infections, and dehydration. Pathophysiological mechanisms involve endothelial dysfunction, vasoconstriction, local hypoxia, and inflammation. Diagnosis is based on clinical assessment and investigations such as penile Doppler ultrasound. Treatments include conservative measures, aspiration of the corpora cavernosa, intracavernous injections of vasoconstrictors, and surgical shunts. Prevention involves specific management of sickle cell anemia, with regular monitoring and raising awareness among the general public. This review highlights the clinical challenges of priapism in sickle cell disease and underlines the importance of a multidisciplinary approach to improve care and quality of life for affected patients.

Keywords: Sickle Cell Disease, Priapism, Emergency, Epidemiology, Mechanism, Diagnosis, Treatment.

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1. INTRODUCTION

Priapism, an often painful and disabling complication, is a frequent manifestation in patients with sickle cell disease that puts their sexuality and reproductive health at risk. It is defined as a prolonged erection lasting more than four hours, regardless of sexual stimulation [1].
Sickle cell anemia is the most common structural hemoglobinopathy and the leading genetic disease in black Africa. It results from a mutation affecting the gene on the beta chain of hemoglobin, causing normal hemoglobin A to be replaced by an abnormal form, hemoglobin S. Haemoglobin S has the particularity of polymerizing under the influence of various factors such as acidosis, hypoxia, fever, and dehydration [2].
The disease is widespread in sub-Saharan Africa, the Middle East, India, and the Mediterranean region [3,4]. The disease is inherited in an autosomal recessive fashion and is characterized by a defective hemoglobin, hemoglobin S, leading to deformation of the red blood cells, which is responsible for various clinical manifestations[5,6].
These include neuroandrogenic complications, including priapism of all types and modes, but most often chronic, reported in 32%–40% of people with sickle cell disease [7,8], with a cumulative incidence of 60% by the age of 40 [9]. It is a medical emergency that must be rapidly recognized and treated.
This systematic review aims to comprehensively analyze existing studies on priapism in the context of sickle cell disease, examining pathophysiological mechanisms, risk factors, diagnostic methods, and available treatment options. Understanding these aspects is crucial for improving the clinical management and quality of life of patients affected by this debilitating complication.

2. METHODS

Literature search: A systematic literature search was performed in relevant medical databases, including PubMed, MEDLINE, Cochrane Library, and Google Scholar, using specific search terms related to priapism and sickle cell disease. All studies published between 1997 and 2024 were selected.

Inclusion criteria: The following articles were included: observational studies, clinical trials, systematic reviews, and meta-analyses published between 1997 and 2024 dealing with priapism in sickle-cell patients.

Exclusion criteria: Clinical cases, editorials, letters to the editor, and irrelevant articles were excluded.

Data analysis: The extracted data were analyzed and synthesized to provide a comprehensive overview of the subject.

3. RESULTS

In total, 50 articles were identified from electronic databases. After eliminating duplicates and applying the pre-established selection criteria, 30 studies were retained for the final analysis. Of the 30 included studies, one was a clinical trial, two guidelines (European and American), 16 were systematic reviews, and the remainder were observational studies.

4. DISCUSSION

Through an in-depth analysis of the white literature, several important results were observed:

A- Epidemiology and Risk Factors:

Prior studies revealed that priapism is quite common in men with sickle cell disease, particularly in those carrying genotypes (HbSS) associated with greater disease severity.

The risk factors identified include the presence of vaso-occlusive crises, the severity of the anemia, infections, fever, and dehydration [2]. Research conducted at Brazzaville University Hospital also shows the role of sleep in the onset of priapism in sickle cell patients through a reduction in the partial pressure of oxygen in the blood and an increase in the partial pressure of carbon dioxide [10].

With regard to age, we note that the patients are young, as shown in Table 1.

Table 1: The prevalence, mean ages, and risk factors found in the various series.

Authors	Prevalence (%)	Mean age (years)	Risk factors
O. Gaye, Sénégal, 2023[11]	41.5 (219)	27.1	Genotype (HbSS), history of priapism, unknown priapism
Kano, Nigéria, 2021[12]	32 (353)	15	Anxiety and depression
Rimtebaye, Tchad, 2021[2]	77 (13)	26.3 (17–34)	Ethnicity (Arabic), low educational and socioeconomic level, severe anemia
Okoko, Congo, 2013[13]	34 (202)	10.4 (5–19)	Infections, fever, vaso-occlusive bone crisis
Habou, Niger, 2017[14]	62 (29)	19 (5–43)	Genotype (HbSS), self-medication, use of traditional plants

B- Pathophysiological mechanisms and types of priapism:

Priapism can be classified into two categories: ischemic and nonischemic. Ischemic priapism occurs in >95% of cases[1]. In ischaemic priapism, the erection is painful, with little or no arterial flow to the corpora cavernosa and little venous return. It can be compared to compartment syndrome, with impaired cavernous flow and complications that may be irreversible, such as cavernous tissue necrosis, cavernous fibrosis, and permanent erectile dysfunction. The duration of priapism is an essential predictor of the development of the above complications[15].

The main aetiological factors in ischaemic priapism are hematological diseases, including sickle cell anemia, neoplastic syndromes, and the use of specific pharmacological agents (intracavernosal prostaglandinE1 (PGE1), second-generation antipsychotics, alpha-adrenergic antagonists). Nearly 33% of men with sickle cell anemia have experienced priapism at least once in their lives [16].

Research has identified endothelial dysfunction, vasoconstriction, local hypoxia, and inflammation as the main mechanisms underlying priapism in sickle cell disease. These

processes interact in a complex way, leading to blood stasis and ischemia in the corpora cavernosa, thus contributing to the onset and persistence of priapism.
More recently, a team of researchers highlighted the role of heme in increasing renal and cardiac blood flow in patients with sickle cell disease. Sickle cell patients with high levels of heme oxygenase were found to be more likely to develop priapism. By promoting the accumulation of intracellular heme, hemolysis plays a crucial role in activating smooth muscle relaxation mechanisms, leading to an uncontrolled increase in blood flow to the corpora cavernosa [17].
A subtype of ischemic priapism is intermittent priapism, recurrent or chronic, defined by recurrent, painful episodes of ischaemic priapism, usually self-limiting and of shorter duration than the classic ischemic priapism described above. This type of priapism is more common in patients with sickle cell disease. Patients with acute ischaemic priapism lasting more than four hours are at risk of developing intermittent priapism at a later stage[15].
Rarely, sickle cell disease can induce nonischemic priapism characterized by unregulated arterial flow to the corpora cavernosa as long as the venous return is still functional and uncompromised. There is no local ischemia [15].

C- Diagnosis and Assessment:
Clinical trials and systematic reviews emphasized the importance of careful assessment to differentiate ischemic from nonischemic priapism. Diagnostic investigations, such as penile Doppler ultrasound, are essential to guide clinical management and assess the severity of the condition.
A thorough and specific anamnestic investigation and a clinical examination can enable a precise classification of the type of priapism. It is essential to ask questions about various aspects such as the quality and duration of the erection, the presence of pain, a history of perineal or genital trauma, previous episodes of priapism, medical comorbidities including familial hematological disorders (notably sickle cell disease, hemoglobinopathies, coagulation disorders, and vasculitis), and the use of medication, particularly proerectile drugs. Ischaemic priapism is characterized by intense, progressive pain accompanied by a rigid erection, whereas in nonischemic priapism, the erection is partially rigid and painless. Doppler ultrasound can also help differentiate the type of priapism. This should be carried out before any blood is drawn from the corpora cavernosa and without injecting any intra-cavernosal treatment, which can distort the results. In ischaemic priapism, there is virtually no cavernous arterial vascularization [15]. However, it is not necessary in cases of typical painful ischaemic priapism.
A complete blood count (CBC), including platelet and reticulocyte counts, and hemoglobin electrophoresis (or sickle cell smear test for rapid diagnosis of sickle cell disease) should be performed in the absence of an apparent cause. However, treatment should be done without waiting for the results[18].
Magnetic resonance imaging (MRI) may be performed in cases of ischemic priapism to assess the degree of fibrosis of the penis and the viability of the corpora cavernosa. It is beneficial in the context of refractory priapism or priapism lasting >48 h, as it allows the viability of smooth muscle tissue to be assessed indirectly and, therefore, provides information on the potential recovery of erection [15].

Table 2: The differences between ischaemic and nonischemic priapism [15].

	Ischemic priapism	**Nonischemic priapism**
Medical history	Progressive pain, possible hematological abnormalities	Painless, history of local trauma possible
Clinical examination	Rigid erection, penis tender to palpation	The penis swollen but not rigid, which is a possible sign of past trauma
Blood appearance	Dark blood	Bright red blood
Gasometry	pH acide (<7.25), pO_2 <30 mmhg, pCO_2 > 60 mmHg	pH normal (7.40), pO_2 >90 mmHg, pCO_2 <40 mmHg
US Doppler	Absence of flow in the cavernous arteries	Fistula or flow velocity can be visualized
Other imaging	MRI to assess the degree of fibrosis	Selective arteriography for fistula embolization
mmHg: millimeter of mercury; **US**: ultrasound; **MRI**: magnetic resonance imaging		

D- Prevention:

During a sickle cell crisis, the recommended treatment approach involves a combination of analgesics, intravenous hydration, oxygenation, addressing triggering factors, and potential transfusion therapy. Patients may benefit from iso-group, iso-rhesus blood transfusions in cases of severe anemia. This not only corrects anemia but also helps dilute sickle red blood cells, which can obstruct capillaries and contribute to conditions like sickle cell priapism, as suggested by Bagayogo and Dodo [19,20].

Various studies investigated pharmacological interventions for preventing priapism in sickle cell patients. These include hydroxyurea, which plays a role in preventing hemolysis, alpha-stimulants like oral etilefrine alone or in combination with self-administered CIIs, and PDE5 inhibitors. However, additional research is necessary to evaluate their long-term effectiveness and safety in this patient population [4, 8, 9,11].

Other preventive strategies described for men with recurrent ischemic priapism associated with sickle cell disease include cyproterone acetate, 5-α-reductase inhibitors, and ketoconazole, which act by modulating circulating testosterone levels to suppress the action of androgens on penile erection. Although these treatments have high success rates, they are also associated with significant drop-out rates due to their side effects [21,22].

Regular medical monitoring is crucial for sickle cell patients to assess their overall health, including erectile function and the potential onset of priapism symptoms.

Increasing public awareness about sickle cell disease can facilitate early recognition of symptoms in affected individuals, leading to prompt diagnosis and proper management of complications.

E- Therapeutic options:

Therapeutic options for priapism in the context of sickle cell disease have evolved over time, with a better understanding of the underlying pathophysiology and the results of recent clinical studies. Recent scientific articles evaluated various approaches to the management of priapism in patients with sickle cell disease, taking into account both the clinical efficacy and safety of treatments. Treatment strategies include conservative medical interventions and surgical techniques, ranging from minimally invasive to more complex procedures.

Conservative interventions are often preferred as first-line treatment, particularly in patients with non-ischaemic priapism or short erection duration. These include measures such as cold compresses, exercise, adequate hydration, using analgesic drugs to relieve associated pain, and administering oxygen to promote vasodilation and improve tissue oxygenation.

According to the guidelines of the European Association of Urology (EAU) and the American Urological Association (AUA), conservative therapies are generally ineffective and should not delay definitive interventions. In patients with sickle cell disease, conservative measures such as using ice packs or cold baths can exacerbate the condition by inducing vasoconstriction and intravascular sickling [21,22].

Aspiration of the corpora cavernosa is a technique commonly used to treat ischaemic priapism. This procedure involves removing stagnant blood from the corpora cavernosa using a needle or catheter, restoring normal blood flow, and relieving prolonged erection. Studies have demonstrated its effectiveness in rapidly reducing the symptoms of ischaemic priapism. Concurrent irrigation of the corpora cavernosa with a 0.9% NaCl solution can be performed. One study shows that optimal irrigation is achieved with NaCl at 10°C [23].

Intracavernosal injections (ICI) of vasoconstrictors such as phenylephrine are often used to induce vasoconstriction of the corpora cavernosa and promote the return of blood flow. This approach can be effective in treating ischaemic priapism refractory to other treatment modalities. However, it is crucial to closely monitor potential side effects such as systemic hypertension, tachycardia, and headache.

Phenylephrine is the adrenergic agonist drug of choice due to its high selectivity for the α1-adrenergic receptor and fewer side effects [21]. Compared to all other agents combined (epinephrine and ethylephrine), phenylephrine demonstrated a 28% higher rate of detumescence, while the other agents were comparable to aspiration alone [22].

A recent study in France recommends combining alpha-stimulant CIIs with cavernous blood drainage, which gives good results and fewer failures [15]. Cautious reinjection of alpha stimulant is possible every 10–15 minutes for at least an hour before taking a surgical decision[24].

In cases of severe or recurrent ischaemic priapism, a surgical cavernospongiosus shunt may be considered. This procedure aims to create a shunt between the corpus cavernosum and the venous system to allow adequate blood drainage. Although this option can be effective, it is associated with a risk of surgical complications and should be reserved for selected cases. There are several surgical techniques for creating a shunt. This can be done between

the tunica albuginea and the glans penis, the corpus spongiosum, or a vein. A distal shunt, which is less invasive and associated with less risk of erectile dysfunction, is often preferred over a proximal shunt [15]. The Al-Ghorab and Quackels techniques are the most commonly used [14]. Postoperative anticoagulation is recommended to avoid thrombosis of the corpora cavernosa, help resolve priapism, and prevent recurrence[25].

Refractory acute ischemic priapism, resistant to treatment or lasting more than 48 hours, usually leads to complete erectile dysfunction and can result in significant long-term penile deformity. In such cases, immediate surgical intervention for penile prosthesis implantation is recommended [26–28].

The optimal time for penile prosthesis implantation is within the first three weeks following the priapism episode [29,30]. If bypass surgery has been performed, implantation may be delayed to allow for the reduction of edema, wound healing, and the reduction of the risk of prosthetic infection.

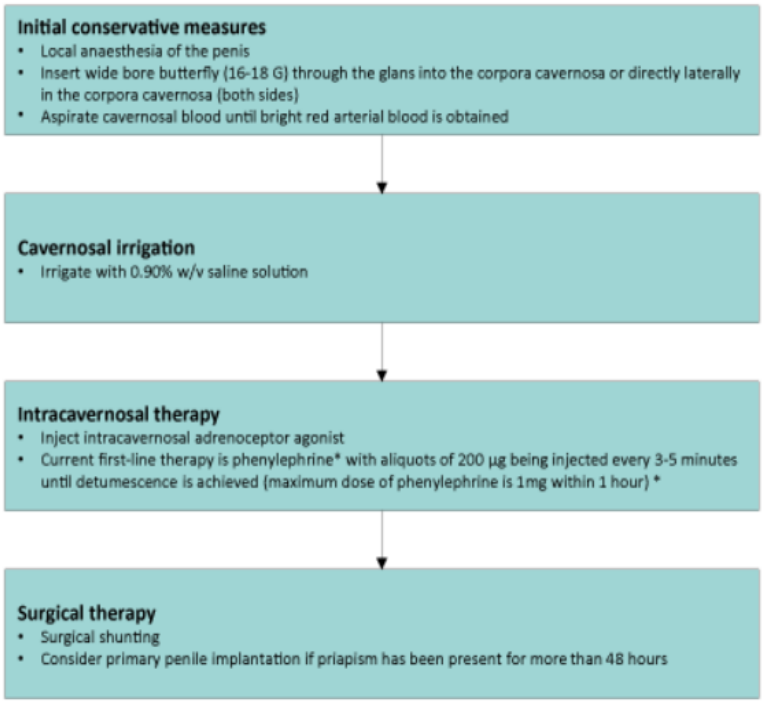

Figure 2: Management work-up of ischemic priapism [21].

F- Prognosis-Complications [15, 31, 32]

Priapism, a serious complication of sickle cell disease, can lead to various complications such as recurrence, ischemia of the corpora cavernosa, necrosis of cavernous smooth muscle tissue, penile deformity, and erectile dysfunction.

The duration of priapism is a crucial factor in the prognosis of postoperative erectile function, with a high incidence of erectile dysfunction for episodes lasting 36–48 hours. Shunting procedures can relieve pain but do not restore normal erectile function.

Penile fibrosis resulting from priapism can lead to long-term complications such as irreversible penile deformity and severe erectile dysfunction. Implantation of a penile prosthesis can correct these complications, with recommendations suggesting its use in cases of priapism lasting more than 48 hours, cases refractory to conservative or shunting treatments, and those with confirmed smooth muscle necrosis of the corpora cavernosa.

Clinical management must be prompt to avoid permanent complications and to inform patients of potential risks, particularly with regard to erectile dysfunction treatments that could trigger a new episode of priapism. Interventions must be carefully discussed with patients to balance risks and benefits.

G- Recommendations and New Therapeutic Approaches:

Current research is investigating innovative strategies for the prevention and treatment of sickle cell priapism. Burnett and Bivalacqua[32] emphasize the need for therapies that specifically address the underlying pathophysiological mechanisms of priapism. Future treatments should focus on preventing complications and preserving erectile function, with promising approaches including the molecular targeting of phosphodiesterase type 5 (PDE5) and antifibrotic therapies. These methods aim to effectively manage priapism, particularly in sickle cell patients who are at high risk of recurrent episodes.

The guidelines from the American Urological Association (AUA) and the Sexual Medicine Society of North America (SMSNA) [22] outline critical areas for future research to enhance the management of priapism, especially in sickle cell patients. They advocate for basic research to identify effective therapeutic targets and develop preventive medical and interventional strategies. While penile prostheses can be a viable option for acute ischemic priapism, their implementation requires a comprehensive risk-benefit analysis. Additionally, antithrombotic therapies and early surgical interventions show promise for the prevention and treatment of priapism.

Similarly, the European Association of Urology (EAU)[21] recommends a multidisciplinary approach to managing sickle cell priapism, integrating pharmacological and mechanical interventions. They suggest the use of drugs such as vasoactive agents and intracellular signaling modulators to prevent priapism episodes. The guidelines also stress the importance of ongoing research to rigorously evaluate the efficacy of these new approaches through clinical trials.

5-CONCLUSION

Sickle cell priapism is a serious and recurrent complication in individuals with sickle cell disease, manifested by prolonged and painful erections. Risk factors include vaso-occlusive crises, severe anemia, and infections, highlighting the importance of proactive management. Primarily ischaemic in origin, it results from endothelial dysfunction, vasoconstriction, and local hypoxia. Early diagnosis is of paramount importance, facilitated by tools such as penile Doppler ultrasound.

Management strategies encompass both conservative and interventional approaches, pivotal in addressing priapism in sickle cell disease patients. Interventions such as cavernous body aspiration and intracavernous vasoconstrictor injections have demonstrated efficacy in symptom relief and restoring normal blood flow. In cases of greater severity or recurrence, surgical cavernospongiosus shunting may be considered, albeit with a heightened risk of complications necessitating careful patient selection.

Prevention hinges on proactive management of vaso-occlusive episodes and heightened public awareness. Pharmacological avenues, including hydroxyurea and alpha-stimulants, present promising avenues, yet further investigation into their long-term effectiveness is required. Future research endeavors aim to deepen our understanding of underlying mechanisms and devise more efficacious interventions to preempt and treat this incapacitating complication.

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