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OSTEONECROSIS OF THE FEMORAL HEAD IN SICKLE CELL DISEASE: PREVALENCE AND COMORBIDITIES IN SAUDI ARABIA

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Abstract

Background: Osteonecrosis is one of the most common musculoskeletal complications in sickle cell anaemia. Osteonecrosis of the femoral head (ONFH) is a prevalent and particularly debilitating alteration, with the frequency ranging from 9% to approximately 37%. Patients with ONFH suffer from the impact of subchondral bone collapse, producing pain and reduction in the functional capacity of the hip, school performance and health-related quality of life.

Objectives: The study aimed to assess the prevalence and comorbidities of osteonecrosis of the femoral head in sickle cell disease among male and female patients of all ages in Saudi Arabia.

Methods: This was a cross-sectional study, carried out from August 2023 to September 2024. By using the qualtrics calculator, our sample size was 384. Structured questionnaire was used as study tool. This tool developed after consulting relevant studies conducted in Saudi Arabia. Analysis of data was entered into the computer using the 'Microsoft Office Excel Software' program 2016 for windows. The data was transferred to the Statical Package for the Social Sciences (SPSS) software program.

Results: As regard the prevalence of SCD symptoms among our study participants, most respondents, 93.5% out of 261 participants, reported experiencing symptoms of the disease with 38.9% experienced pelvic problems and 89.3% out of them were due to non-traumatic causes, indicating a high prevalence of symptomatic cases within the surveyed population. In term of associated comorbidities, 83.5% of participants reported hospitalization due to the disease, with a considerable proportion experiencing multiple hospitalizations per year. The prevalence of acute chest syndrome and pelvic problems among respondents was notable, with 51.7% and 39.8% respectively. As regard, relation between experiencing pelvic diseases and sociodemographic characteristics, we have found a statistically significant relation to age (p value=0.018), marital status (p value=0.0001), weight (p value=0.0001), and height (p value=0.0001). It also shows statistically insignificant relation to gender and region of residence.

Conclusion: the study highlighted the high prevalence of symptomatic cases of sickle cell disease among patients in Saudi Arabia, with a significant proportion experiencing symptoms of osteonecrosis

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of the femoral head. The findings underscore the need for increased awareness and management of this debilitating condition, particularly in light of the associated complications and hospitalizations reported by the participants. Furthermore, the study revealed important sociodemographic factors that may influence the development of pelvic problems in patients with sickle cell disease.

Keywords: Prevalence, sickle cell disease, osteonecrosis, femoral head.

Introduction:

High rates of mortality and morbidity are linked to the inheritable illness known as sickle cell anemia, which is marked by the formation of defective hemoglobin [1]. Sickle cell anemia can cause a serious vaso-occlusive crisis that affects many body organs [2]. individuals with severe forms of this disease (HbSS or HbSB) have a high risk of developing bone ischemia [3]. Bone ischemia (osteonecrosis), particularly of the head of the femur, is a common medical problem among sickle cell anemia patients [4,5]. It can be provoked by facing of multiple risk factors such as: cold weather, dehydration, infection and stress [6]. Sickle cell disease was first discovered by James Herrick in 1910[7]. In the 1960s, the initial cases of Sickle Cell Disease (SCD) were documented in Saudi Arabia's Eastern province. Despite a decline in the occurrence of sickle cell disease (SCD) across all regions of Saudi Arabia, the prevalence of the condition continues to exceed that of other countries.

The prevalence rate in the Eastern province is significantly higher at 145 cases per 10,000 population compared to the lower rates observed in the southern region (24 cases per 10,000 population) , western region (12 cases per 10,000 population) , and central region (6 cases/10,000 population)[8]. In a cohort study conducted in California by Adesina et al., it was found that osteonecrosis of the femoral head has a high prevalence rate in individuals with sickle cell disease (SCD) [4]. The study revealed that approximately 23% of SCD patients developed osteonecrosis of the femoral head and subsequently required total hip arthroplasty (THA) to address the condition. The median age at which these patients underwent THA was 36 years [9]. A study investigating the natural progression of untreated symptomatic osteonecrosis (ON) of the femoral head in adults with sickle cell disease (SCD) found that approximately 87% of patients experienced the development of subchondral collapse and end-stage arthritis within five years of diagnosis [10]. Due to a severe lack of research related to our topic in Saudi Arabia, an accurate prevalence is unknown, and the sample size is small. Previous research suggests that the high occurrence of femoral head avascular necrosis in Saudi populations mainly results from symptomatic selection in a referral center. While the prevalence among a broader Saudi sickle cell patient sample remains unclear, previous research suggests differing risk factors compared to other regions.

Objective:

This study aims to assess the prevalence and comorbidities of osteonecrosis of the femoral head in sickle cell disease among patients of all ages in Saudi Arabia.

Methodology:

Study design:

This is an observational descriptive cross-sectional study conducted in Saudi Arabia from August 2023 until September 2024.The study's population includes all genders diagnosed with sickle cell disease across all age groups in Saudi Arabia. Participants were recruited during 2023 from receiving the questionnaire.

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Sample size:
by using the Qualtrics calculator and a 95% degree of confidence, the size of the sample was estimated, So the minimum sample size was 384.
The Sample size was estimated by using this formula:
n= P (1-P) * Zα 2 / d 2 with a confidence level of 95%.
n: Calculated sample size
Z: The z-value for the selected level of confidence (1- a) = 1.96. P: An estimated knowledge
Q: (1 – 0.50) = 50%, i.e., 0.50
D: The maximum acceptable error = 0.05.
So, the calculated minimum sample size was:
n = (1.96)2 X 0.50 X 0.50/ (0.05) 2 = 384.

Inclusion and Exclusion criteria:
Inclusion criteria:
All individuals of any age, whether male or female, including pregnant women and children, who have a confirmed diagnosis of sickle cell disease and belong to the Saudi population, should possess the ability to provide informed consent and comply with research procedures.
Exclusion criteria:
Patient presence of substantial underlying medical conditions that might distort study results, such as severe cardiovascular disorders or ongoing infections, a history of bone marrow or organ transplantation, an inability to understand study requirements or provide informed consent, participation in another conflicting clinical trial within the past 30 days, a known history of drug abuse, previous occurrences of malignant tumors, or ongoing cancer therapy.

Method for data collection:
Structured questionnaire was used as study tool. This tool was developed after consulting relevant studies conducted in Saudi Arabia and elsewhere the final version of the questionnaire consisted of 24 classifieds into main three sections. Section one contained personal information characteristics questions. The second section includes information about sickle cell disease like age of the diagnostic. The third part asked questions on type of osteonecrosis and comorbidities.

Analyzes and entry method:
The data was entered into the computer using the "Microsoft Office Excel Software" program (2016) for Windows. Subsequently, the data was transferred to the Statistical Package for the Social Sciences (SPSS) software program, specifically version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.), for statistical analysis.

Results:

Table (1) shows several demographic statistics for a group of participants having a total of 261. The distribution of participants across different parameters reveals interesting insights into the sample population. In terms of age, the mean age of the participants is 27.7 years with a standard deviation of 10.4. Most participants fall within the age range of 25 to 30, comprising 26.4% of the sample, followed by those aged less than 22 at 23.4%. Gender distribution shows a slight predominance of females, accounting for 56.3% of the participants. All participants reside in Saudi Arabia, with the highest representation from the Eastern region at 43.7%. Education level varies among participants, with the

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majority holding a bachelor's degree (46.0%), followed by those with a secondary school education (31.0%). The marital status of participants indicates that a significant portion is single (66.3%). Additionally, the data includes information on weight and height distribution, with mean values of 53.7 kg and 153.6 cm, respectively. Interestingly, all participants affirm being affected by Sickle Cell Disease, highlighting a crucial aspect of health within the sample group. This data provides a foundation for further analysis and insights into the sociodemographic composition of the participants.

Table (1): Sociodemographic characteristics of participants (n=261)

Parameter		***No.***	***Percent (%)***
Age (Mean:27.7, STD:10.4)	less than 22	61	23.4
	22 to 25	49	18.8
	25 to 30	69	26.4
	30 to 40	51	19.5
	more than 40	31	11.9
Gender	Female	147	56.3
	Male	114	43.7
Do you live in Saudi Arabia?	No	0	0
	Yes	261	100.0
Region of residence	Southern region	61	23.4
	Central region	1	.4
	Eastern region	114	43.7
	Western region	85	32.6
Education level	Primary school	23	8.8
	Middle school	18	6.9
	Secondary school	81	31.0
	Diploma	13	5.0
	Bachelor's degree	120	46.0
	College	5	1.9
	Uneducated	1	.4
Marital status	Single	173	66.3
	Married	88	33.7
Weight (Mean:53.7, STD:16.5)	Less than 50 kg	104	39.8
	50 to 60 kg	75	28.7
	60 to 70 kg	56	21.5
	more than 70 kg	26	10.0
Height (Mean:153.6, STD:29.2)	Less than 150 cm	49	18.8
	151 to 160 cm	109	41.8
	161 to 170 cm	67	25.7
	more than 170 cm	36	13.8
Are you affected by Sickle Cell Disease?	No	0	0
	Yes	261	100.0

As shown in figure 1, it is evident that a total of 261 individuals were surveyed regarding their experience of symptoms associated with a particular disease. Out of this sample, 244 respondents

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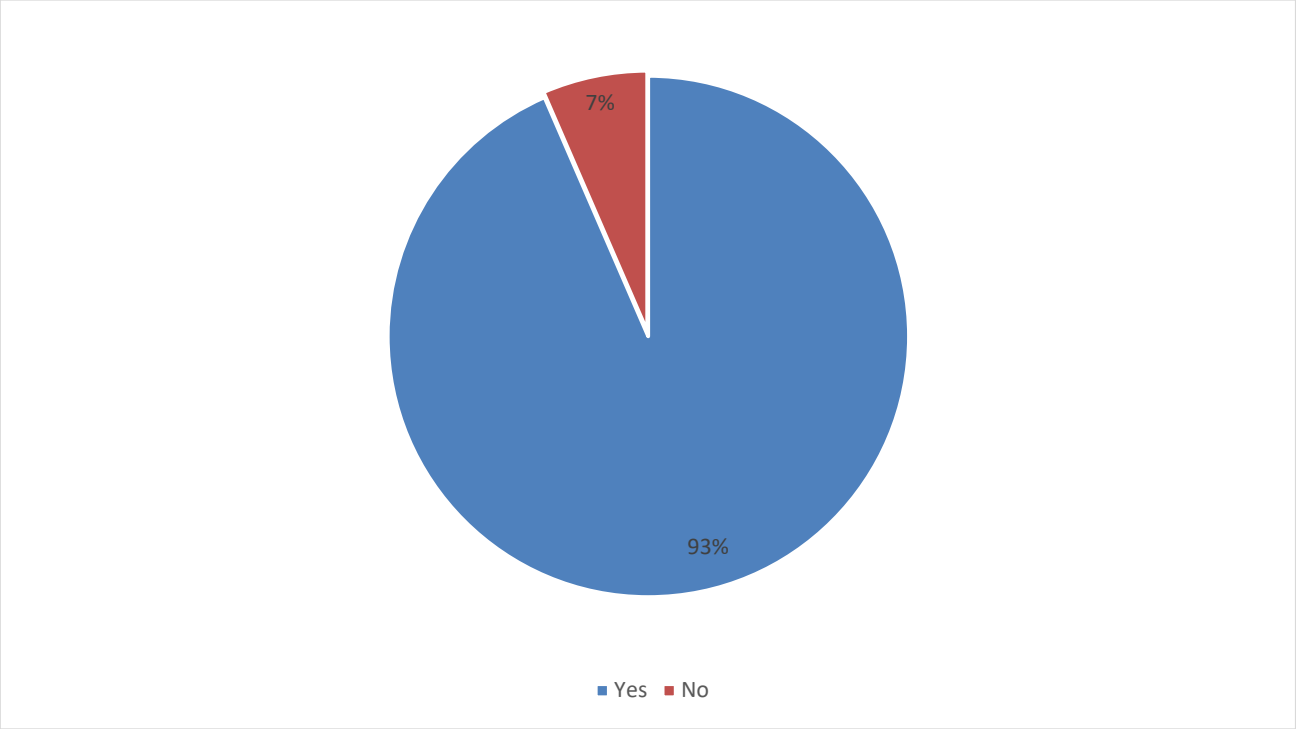
indicated that they do experience symptoms of the disease, while only 17 individuals reported not experiencing any symptoms. The stark contrast between the number of individuals affirming the presence of symptoms compared to those denying it raises significant implications for further investigation and analysis. The overwhelming majority of respondents acknowledging the presence of symptoms may suggest a prevalent issue within the population under study, warranting a closer examination of the disease's prevalence, risk factors, and potential interventions. Moreover, the disparity in responses between those affirming and denying symptoms underscores the importance of understanding the factors influencing individuals' experiences with the disease, as well as the need for targeted healthcare strategies to address these varying needs effectively.

Figure (1): Illustrates if participants are experiencing symptoms of sickle cell disease.



As illustrated in table (2), Most respondents, 93.5%, reported experiencing symptoms of the disease, indicating a high prevalence of symptomatic cases within the surveyed population. Interestingly, a significant portion of individuals, 27.6%, were diagnosed with the disease since birth, while an equal percentage received their diagnosis when symptoms first appeared. This suggests a varying timeline of disease identification among patients. Furthermore, the data indicates that 14.6% of respondents are smokers, potentially highlighting a risk factor for the development or progression of the condition. Hospitalization due to the disease was reported by 83.5% of participants, with a considerable proportion experiencing multiple hospitalizations per year. The prevalence of acute chest syndrome and pelvic problems among respondents was notable, with 51.7% reporting the former and 39.8% experiencing the latter. The age distribution of pelvic problems onset revealed a higher incidence among individuals aged 15 years or less, underscoring the impact of the disease at a younger age. Additionally, the use of painkillers was widespread, with various medications such as Morphine, Brufen (ibuprofen), and Paracetamol (Panadol) being commonly reported. The data provides a comprehensive overview of the experiences and management strategies of individuals with Osteonecrosis of the femoral head in sickle

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cell disease, shedding light on the complexities of the condition and highlighting areas for further research and intervention.

Table (2): Parameters related to knowledge of sickle cell disease among participants (n=261).

Parameter		***No.***	***Percent (%)***
When were you diagnosed with the disease?	Since birth	72	27.6
	In your early years	117	44.8
	When symptoms appeared	72	27.6
Are you a smoker?	Yes	38	14.6
	No	223	85.4
Have you been hospitalized due to the disease?	Yes	218	83.5
	No	43	16.5
If your answer is yes, how many times per year? (n=218)	1-2 times a year	111	50.9
	3-4 times a year	41	18.8
	More than 4 times	66	30.3
Have you ever experienced acute chest syndrome due to the illness?	Yes	135	51.7
	No	126	48.3
Have you ever experienced pelvic problems?	Yes	104	39.8
	No	157	60.2
If your answer is yes, at what age did these problems appear?	15 years or less	139	53.3
	15 to 30 years	81	31.0
	More than 30 years	41	15.7
Was it due to an injury in the pelvis?	Yes	28	10.7
	No	233	89.3
Do you take any painkiller? What is it? * (n=234)	Morphine	134	57.3
	Brufen (ibuprofen)	145	62.0
	Paracetamol (Panadol)	190	80.9
	Aspirin	1	0.4
	Tramadol	2	0.8
	Ketamine	12	5.1
	Diclofenac sodium	76	32.5
	Oxy Contin	1	0.4
	Fentanyl	16	6.8

****Results may overlap***

Upon reviewing figure (2), it is evident that the data presented pertains to the inquiry of whether the problems discussed necessitated surgical intervention. The figure illustrates a clear distinction between the responses, with 28 indicating that surgical intervention was required, while a significantly larger proportion, specifically 233, suggests that surgical intervention was not necessary. This disparity in responses raises intriguing questions regarding the nature of the problems discussed and the decision-making process surrounding the need for surgical intervention. Further analysis of the underlying factors influencing these responses could offer valuable insights into the management of such issues and the considerations involved in determining the appropriate course of action.

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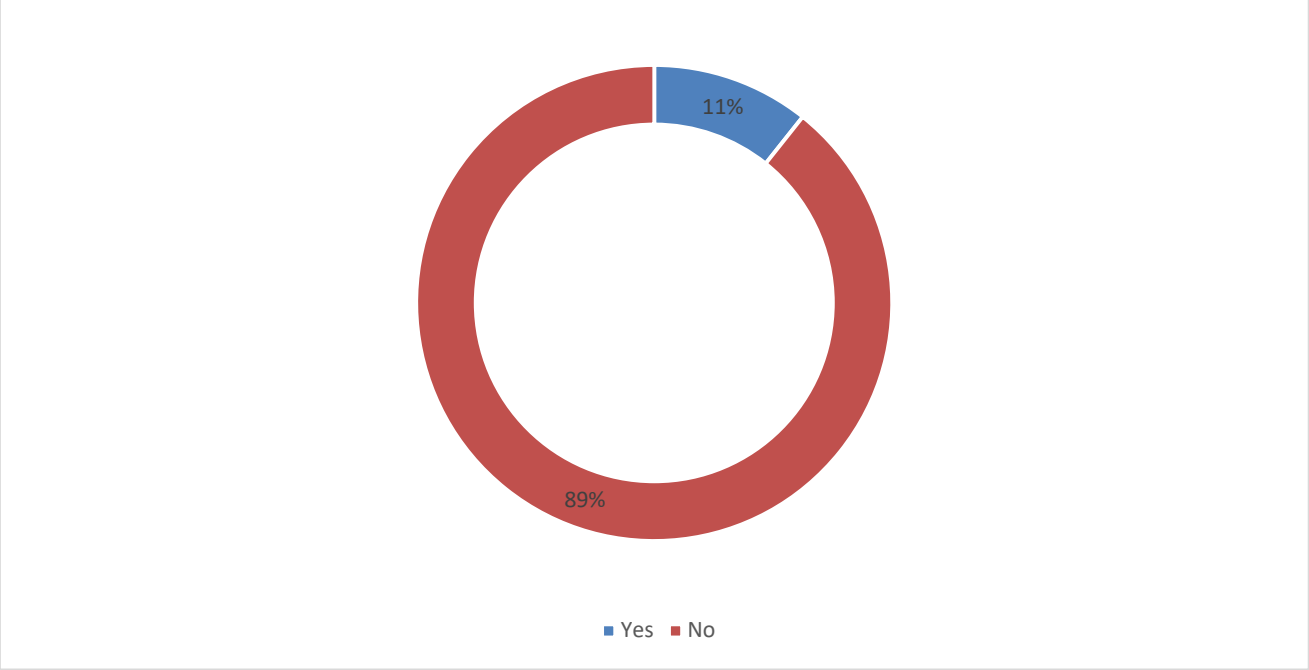
Figure (2): Illustrates if participants require surgical intervention for their pelvic complaint.



In analyzing the data presented in Table (3) regarding participants' awareness about Osteonecrosis of the femoral head in sickle cell disease, several key insights can be gleaned. Among the 261 participants surveyed on whether the problems necessitated surgical intervention, 10.7% indicated that they did require such intervention, while the majority (89.3%) did not. For those who underwent surgery (n=38), the types of surgical procedures performed included Complete replacement of the hip joint (28.9%), Partial replacement (28.9%), and Joint reconstruction (42.1%). Furthermore, a significant portion of participants (61.3%) reported needing a blood transfusion, with varying units of blood required: One unit (38.2%), Two units (14.65%), and more than two units (47.1%). Post-surgery, a small percentage (7.3%) experienced complications, while the majority did not (92.7%). Additionally, a substantial number of participants (75.5%) reported other complications attributed to the illness, with a lower percentage (24.5%) indicating no other complications. Interestingly, a significant portion of participants (50.6%) reported that other family members exhibited similar symptoms, highlighting a potential genetic or familial predisposition to the condition. Overall, the data underscores the complex interplay between sickle cell disease, Osteonecrosis of the femoral head, surgical interventions, blood transfusions, post-operative complications, and familial patterns of illness manifestation, warranting further investigation and tailored management strategies.

Table (3): Patients' knowledge of osteonecrosis of the femoral head in sickle cell disease (n=261).

Parameter		***No.***	***Percent (%)***
Did the problems require surgical intervention?	Yes	28	10.7
	No	233	89.3
If your answer is yes, what type of surgical procedure was performed? (n=38)	Complete replacement of the hip joint	11	28.9

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	Partial replacement	11	28.9
	Joint reconstruction	16	42.1
Did you need a blood transfusion?	Yes	160	61.3
	No	101	38.7
If your answer is yes, how many units of blood were required? (n=157)	One unit	60	38.2
	Two units	23	14.65
	More than two units	74	47.1
Have you had any complications after the surgery?	Yes	19	7.3
	No	242	92.7
Are there any other complications due to the illness?	Yes	197	75.5
	No	64	24.5
Does any other family member have the same symptoms?	Yes	132	50.6
	No	129	49.4

Table (4) shows that sickle cell patients experiencing pelvic diseases has statistically significant relation to age (p value=0.018), marital status (p value=0.0001), weight (p value=0.0001), and height (p value=0.0001). It also shows statistically insignificant relation to gender and region of residence.

Table (4): Relation between experiencing pelvic diseases and sociodemographic characteristics.

Parameters		***Have you ever experienced pelvic diseases?***		***Total (N=261)***	***P value****
		Yes	**no**		
Gender	Female	51	96	147	0.054
		49.0%	61.1%	56.3%	
	Male	53	61	114	
		51.0%	38.9%	43.7%	
Age	less than 22	17	44	61	0.018
		16.3%	28.0%	23.4%	
	22 to 25	20	29	49	
		19.2%	18.5%	18.8%	
	25 to 30	38	31	69	
		36.5%	19.7%	26.4%	
	30 to 40	20	31	51	
		19.2%	19.7%	19.5%	
	more than 40	9	22	31	
		8.7%	14.0%	11.9%	
Marital status	Single	55	118	173	0.0001
		52.9%	75.2%	66.3%	
	Married	49	39	88	
		47.1%	24.8%	33.7%	

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Region of residence	Southern region	33	28	61	0.057
		31.7%	17.8%	23.4%	
	Central region	0	1	1	
		0.0%	0.6%	0.4%	
	Eastern region	39	75	114	
		37.5%	47.8%	43.7%	
	Western region	32	53	85	
		30.8%	33.8%	32.6%	
Education level	Primary school	0	23	23	N/A
		0.0%	14.6%	8.8%	
	Middle school	0	18	18	
		0.0%	11.5%	6.9%	
	Secondary school	33	48	81	
		31.7%	30.6%	31.0%	
	Diploma	0	13	13	
		0.0%	8.3%	5.0%	
	Bachelor's degree	67	53	120	
		64.4%	33.8%	46.0%	
	College	3	2	5	
		2.9%	1.3%	1.9%	
	Uneducated	1	0	1	
		1.0%	0.0%	0.4%	
Weight	Less than 50 kg	22	82	104	0.0001
		21.2%	52.2%	39.8%	
	50 to 60 kg	48	27	75	
		46.2%	17.2%	28.7%	
	60 to 70 kg	26	30	56	
		25.0%	19.1%	21.5%	
	more than 70 kg	8	18	26	
		7.7%	11.5%	10.0%	
Height	Less than 150 cm	3	46	49	0.0001
		2.9%	29.3%	18.8%	
	151 to 160 cm	45	64	109	
		43.3%	40.8%	41.8%	
	161 to 170 cm	40	27	67	
		38.5%	17.2%	25.7%	
	more than 170 cm	16	20	36	
		15.4%	12.7%	13.8%	

P value was considered significant if ≤ 0.05.

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Discussion:

Sickle cell disease (SCD) is a prevalent blood disorder that impacts millions worldwide, stemming from a genetic mutation that leads to irregular hemoglobin production. This condition can cause persistent complications affecting various body organs [11]. The disease is marked by deformed red blood cells due to oxygen deprivation, which can lead to hemolysis both internally and externally. This significant alteration in physiology may initiate a series of consequences, including the release of inflammatory cytokines, which can contribute to hemolysis in microvessels and cause obstructions [12]. Osteonecrosis of the femoral head (ONFH) is a frequent complication associated with SCD, thought to arise when rigid and abnormally adhesive red blood cells impair blood circulation to susceptible joint surfaces, leading to bone death and early onset of arthritis [13]. Although osteonecrosis can affect multiple joints simultaneously in individuals with SCD, the femoral head is most commonly impacted due to its lack of collateral blood circulation, making it particularly prone to vascular damage. Additionally, its occurrence has been reported in a range of 10% to 30% in studies conducted at single institutions and through collaborative research efforts [14]. Thus, we aimed in this study to assess the prevalence and comorbidities of osteonecrosis of the femoral head in sickle cell disease among male and female patients of all ages in Saudi Arabia.

In light of our study findings, it is essential to contextualize and compare them with previous literature on (ONFH) among (SCD) patients, thereby enriching our understanding of the prevalence and outcomes associated with this condition. Matos et al. reported a relatively low ONFH prevalence of 11% among SCD subjects under 21 years old [15]. In contrast, our study indicates a significantly higher prevalence of symptomatic presentations, suggesting a more severe or widespread occurrence in our cohort. Supporting this notion, Milner et al., [16] noted that about 10% of participants in a robust Cooperative Study of Sickle Cell Disease displayed radiographic evidence of ONFH at entry, highlighting a potential underestimation of symptomatic cases outside specialized settings, further corroborated by our high hospitalization rates at 83.5%. Moreover, Adesina et al., [17] found that 22% of the study population developed ONFH at a median age of 27, with notable implications for those with a history of acute chest syndrome (ACS), where the cumulative incidence reached 24%. Our findings align with this link, as we reported significant associations between comorbidities like acute chest syndrome and pelvic issues, particularly noticeable in younger demographics. Moreover, our study's observation that 61.3% required blood transfusions aligns with existing research emphasizing the interplay of severe disease manifestations and the incidence of ONFH. Additionally, Worrall et al., [18]conducted a nuanced investigation revealing an ONFH prevalence of approximately 9% in children with SCD, with the highest prevalence observed in patients with SBeta0 thalassemia but no significant correlation with sociodemographic variables such as height or body mass index. This contrasts with our findings, which emphasize various sociodemographic factors, including age and marital status, as significant correlates of pelvic disease, indicating a potential variance in disease expression and impact across populations or study samples. Another study revealed that adults with SCD and symptomatic ONFH of the hip, progression to femoral head collapse is near inevitable with 87% of precollapse hips progressing to collapse within 5 years and a mean time to collapse of 42 and 30 months for Steinberg Stage I and II disease [19]. Additionally, the risk factor concerning systolic blood pressure outlined by Worrall et al.[20] and the relationship of high hemoglobin levels to ONFH as theorized by Mukisi-Mukaza et al., [21] warrant attention and call for further investigation into standardized care approaches that could mitigate these risks.

Conclusion:

In conclusion, this study highlighted the high prevalence of symptomatic cases of sickle cell disease

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among patients in Saudi Arabia, with a significant proportion experiencing symptoms of osteonecrosis of the femoral head. The findings underscore the need for increased awareness and management of this debilitating condition, particularly in light of the associated complications and hospitalizations reported by the participants. Furthermore, the study revealed important sociodemographic factors that may influence the development of pelvic problems in patients with sickle cell disease. Future research and healthcare interventions should focus on addressing these factors to improve the quality of life and outcomes for individuals affected by sickle cell disease in Saudi Arabia.

Acknowledgement:

We thank the participants who all contributed samples to the study.

Ethical approval

An informed consent was obtained from each participant after explaining the study in full and clarifying that participation is voluntary. Data collected were securely saved and used for research purposes only.

Funding

The study did not receive any external funding.

Conflict of interests

The authors declare that there are no conflicts of interest.

Informed consent:

Written informed consent was obtained from all individual participants included in the study.

Data and materials availability:

All data associated with this study are present in the paper.

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