ORIGINAL ARTICLE

SERUM CALCIUM-TO-MAGNESIUM RATIO AND MINERAL DYSREGULATION IN SICKLE CELL ANAEMIA: A COMPARATIVE STUDY IN ZARIA, NIGERIA

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Abstract

Context:

Sickle cell anaemia (SCA) is a genetic disorder characterised by chronic haemolysis, vaso-occlusion, and systemic complications. Mineral dysregulation, particularly involving calcium and magnesium, has been implicated in the pathophysiology of SCA, with potential impacts on vascular function, oxidative stress, and bone health.

Aim:

This study evaluated serum calcium, magnesium, and their ratio in SCA patients during steady state and vaso-occlusive crisis, compared to healthy controls, and

explored the clinical implications of these alterations.

Settings and Designs:

One hundred and eighty adult participants were recruited, comprising 60 SCA patients in steady state, 60 during vaso-occlusive crisis, and 60 age- and sex-matched apparently healthy HbAA controls in a cross-sectional comparative study.

Methods and materials:

Demographic and clinical data, as well as blood samples, were collected after participants met the study's inclusion criteria. This was after informed consent for inclusion in the study was obtained from all participants, following a full explanation of the study in the language best understood by them. Serum calcium and magnesium levels were determined using a Selectra Chemistry Auto-analyser. The calcium-to-magnesium ratio was calculated.

Statistical Analysis Used:

Data were analysed using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 25. One-way ANOVA was used to compare the biochemical parameters among the study groups, while correlations between the variables were done using Pearson's correlation analysis. The ROC curve was used to assess the discriminatory power of the biochemical markers.

Results:

The study revealed significantly lower serum calcium and magnesium levels in SCA patients compared to controls, with the lowest values observed during vaso-occlusive crises ($p < 0.001$). The calcium-to-magnesium ratio was significantly elevated in patients during crises, suggesting an imbalance that may exacerbate disease pathology ($p < 0.001$). Furthermore, the ratio demonstrated potential as a discriminatory biomarker for identifying vaso-occlusive crisis in SCA. (AUC = 0.691).

Conclusion:

This study highlights the role of mineral homeostasis in SCA and its potential contribution to disease severity. The calcium-to-magnesium ratio emerged as a clinically relevant marker, warranting further investigation for its diagnostic and therapeutic applications.

Introduction

Sickle cell anaemia (SCA) is the most prevalent and severe form of sickle cell disease (SCD), a group of autosomal recessive genetic disorders characterised by the production of abnormal sickle haemoglobin (HbS).[1] The underlying defect is a point mutation in the β-globin gene (GAG→GTG), substituting glutamic acid with valine at position six. This single amino acid change alters the physicochemical properties of haemoglobin, leading to polymerisation under deoxygenated conditions, deformation of red blood cells into sickle shapes, and subsequent microvascular occlusion.[2,3] These pathophysiological changes cause chronic haemolysis, recurrent vaso-occlusive crisis (VOC), and cumulative multi-organ damage.[4]

Globally, SCA is a significant public health concern, but its burden is disproportionately high in sub-Saharan Africa. Nigeria alone contributes an estimated 150,000 newborns annually with SCA, more than half of the global total.[5,6] Without adequate intervention, many affected children die before the age of five, while survivors endure lifelong complications including anaemia, stroke, acute chest syndrome, osteonecrosis, chronic pain, and renal impairment.[4,7] The chronic nature of the disease often impacts educational attainment, employment opportunities, and quality of life.[8]

Beyond the haematological and vascular manifestations, SCA is associated with profound metabolic and nutritional disturbances.[9] Alterations in mineral metabolism are of particular concern because of their potential to worsen disease

outcomes. Calcium and magnesium are essential macro-minerals with interdependent physiological roles. Calcium is indispensable for skeletal mineralisation, cardiac contractility, blood clotting, and nerve conduction.[10] Magnesium is required for over 300 enzymatic reactions, including those involved in ATP production, nucleic acid synthesis, and the regulation of muscle and nerve function.[11] The two minerals act synergistically in many physiological processes, and an optimal calcium-to-magnesium (Ca: Mg) ratio is necessary to maintain homeostasis.[12]

In SCA, chronic inflammation, oxidative stress, and renal tubular dysfunction can lead to impaired intestinal absorption, increased urinary losses, and redistribution of calcium and magnesium.[13,14] These imbalances may exacerbate complications such as osteoporosis, pathological fractures, arrhythmias, vascular dysfunction, and neuromuscular instability.[15,16] While most previous studies have focused on calcium or magnesium levels independently, emerging evidence suggests that the Ca: Mg ratio may be more clinically relevant, as it reflects the interplay between these two minerals rather than their isolated values.[12,17] A deranged ratio has been linked to conditions such as vascular calcification, coronary artery disease, cardiac arrhythmias, and bone fragility—pathologies also encountered in SCA.[17,18]

Despite this, there is limited research on the Ca: Mg ratio in African SCA populations, particularly in resource-limited settings where environmental, genetic, and dietary factors may uniquely influence mineral balance.[19] Zaria, a major city in Northwestern Nigeria, provides a distinct context for investigating this relationship. The region has one of the highest SCA prevalence rates in the country due to the high carrier frequency of the sickle cell gene.[20] Dietary habits are based mainly on cereals (millet, sorghum) and legumes that are high in phytates, which bind divalent

cations and reduce the intestinal absorption of calcium and magnesium.[21] Furthermore, low dietary diversity, limited intake of dairy products, and seasonal food scarcity may exacerbate mineral deficiencies.[22]

Environmental and socioeconomic factors further compound these risks. High ambient temperatures and low humidity contribute to recurrent dehydration, which can increase mineral loss and precipitate vaso-occlusive crises.[23] Access to specialist haematology services is limited, and healthcare costs are borne mainly out-of-pocket, leading to delayed presentation and suboptimal crisis management.[24] Infectious diseases, particularly malaria and bacterial infections, remain prevalent and can accelerate haemolysis and metabolic stress.[25] Collectively, these factors create a unique milieu in Zaria that may influence the Ca: Mg ratio in SCA patients, making local data essential for guiding nutritional and therapeutic interventions.

Therefore, this study aimed to evaluate serum calcium, magnesium, and their ratio in adult SCA patients during steady state and vaso-occlusive crises compared with healthy controls. By exploring the relationship between mineral balance and disease state in this population, the study seeks to determine whether the Ca: Mg ratio could serve as a valuable biomarker for VOC and inform targeted interventions to improve patient outcomes in Northwestern Nigeria and similar settings.

Materials and Methods

This was a comparative cross-sectional study conducted between January and June 2023 at the Day Care Unit, Weekly Clinic of the Department of Haematology and Accident and Emergency Unit of Ahmadu Bello University (ABUTH), Zaria.

The study population for the cases consisted of SCA patients admitted into the Department of Haematology with a diagnosis of VOC. The first group of controls were SCA patients attending the

Routine Haematology Clinic in steady states. In contrast, the second group of controls were apparently healthy Haemoglobin AA (HbAA) individuals who were staff and students of the institution, as well as friends and family. Both control groups were age- and sex-matched participants.

Exclusion criteria were renal disease as defined by eGFR of 60 mL/min/1.73m^2 and below, using the CKD-EPI creatinine equation below, as well as apparent bone abnormalities like deformity and swelling.

A sample size of 180 participants was determined by the Power formula [26] for calculating the minimum required sample size comprising 60 SCA patients in VOC, 60 SCA in steady state, and 60 apparently healthy HbAA controls. They were recruited consecutively by purposive, non-probability sampling.

Steady state in SCA was defined as a period with no history of acute painful episodes requiring hospitalization for the past 4 weeks, no history of blood transfusion in the previous 3 months, no history of intercurrent illness such as infection in the past 4 weeks, and no history of treatment with medications such as antibiotics that may affect the blood counts during the previous 3 weeks.[27]

All participants had haemoglobin electrophoresis results from the department of Haematology confirming their haemoglobin status.

Approval for the study was obtained from the Health Research Ethical Committee of Ahmadu Bello University Teaching Hospital, with reference number ABUTHZ/HREC/F43/2023 (12th January 2023-12th January 2024. The study was conducted according to the World Medical Association's Helsinki Declaration.

Patients who satisfied the inclusion criteria were approached, counselled, and informed consent was obtained. A pre-tested questionnaire was administered to the patient by the investigator or assistants who

had received appropriate training on the study protocol. Information was collected on the sociodemographic data. Anthropometrics were measured. Blood pressure was measured using a mercury sphygmomanometer, using the standard protocol.[28]

Five millilitres (5 mL) of venous blood were collected in plain bottles from all participants. Sera were obtained following centrifugation and were stored at -80 ˚C. Analysis for serum magnesium, total calcium, and albumin (for possible correction of calcium) was done in batches using the Selectra automated Clinical Chemistry Analyser. However, the serum total calcium was not corrected since all serum albumin levels were within the reference values.[29] Thereafter, the calcium-to-magnesium ratio was calculated.

Data obtained from the study were analysed using Statistical Package for the Social Sciences 25.0 (SPSS 25.0) for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2016. Qualitative values were summarised as percentages, frequencies, and tables. The distributions of quantitative variables were assessed using the Kolmogorov-Smirnov test. Data were normally distributed. The mean concentrations of magnesium, total calcium, albumin, and the calculated calcium-to-magnesium ratio among the three study groups were compared using the One-Way ANOVA test. Correlations between the variables were done using Pearson's correlation analysis. The ROC curve was used to assess the discriminatory power of the biochemical markers for the presence or absence of VOC. A p-value of equal to or less than 0.05 ($p \leq 0.05$) was considered statistically significant.

Results

Socio-demographic and clinical characteristics

The age and gender distributions were comparable across the three groups, minimising demographic bias. Most

participants were single, a pattern more pronounced in the SCA groups, possibly reflecting the socioeconomic impact of SCA. Educational attainment was highest among HbAA controls, whereas secondary education predominated in SCA participants, likely due to illness-related interruptions.

BMI differed significantly ($p < 0.001$), with HbAA participants showing higher values and a greater prevalence of overweight/obesity. In contrast, most SCA participants were of normal weight, with a higher proportion underweight, reflecting the metabolic demands and nutritional challenges of SCA. Blood pressure was significantly lower in both SCA groups compared to HbAA controls ($p < 0.001$). Table I

Biochemical Parameters

Serum calcium levels differed significantly across the groups ($p < 0.001$). Participants in the SCA in crisis group had the lowest mean calcium levels (2.38 ± 0.34 mmol/L), while those in the HbAA group had the highest (2.55 ± 0.24 mmol/L). Serum albumin levels followed a similar trend, with the lowest levels observed in the SCA in crisis group (38.28 ± 4.38 mmol/L) and the highest in the HbAA group (44.55 ± 4.51 mmol/L). Serum magnesium levels were significantly reduced in the SCA in crisis group (0.69 ± 0.03 mmol/L) compared to the other groups, which showed progressively higher levels ($p < 0.001$). The calcium-to-magnesium ratio was highest in the SCA in crisis group (3.42 ± 0.42) and decreased across the groups, with the HbAA group showing the lowest ratio (3.12 ± 0.19, $p < 0.001$)—Table II.

Correlations Between Age, BMI, and Biochemical Analytes

No significant correlations were identified between age or BMI and serum calcium, magnesium, or the calcium-to-magnesium ratio in participants with SCA in crisis. All p-values exceeded 0.05, suggesting no strong relationship between these variables in this subgroup—Table III.

Biochemical Differences by Gender in the SCA in Crisis Group

Gender-based comparisons in the SCA crisis group revealed no significant differences in serum calcium and magnesium levels between males and females ($p = 0.058$ and $p = 0.059$, respectively). Similarly, the calcium-to-magnesium ratio showed a higher mean in females (3.49 ± 0.35) compared to males (3.32 ± 0.49), but this difference was not statistically significant ($p = 0.109$). Table V

Discriminatory Power of Biochemical Markers

The receiver operating characteristic (ROC) curve analysis evaluated the ability of serum calcium, magnesium, and the calcium-to-magnesium ratio to distinguish between the presence and absence of vaso-occlusive crises (VOC) in participants with sickle cell anaemia. Serum magnesium demonstrated feeble discriminatory power (AUC = 0.249), while serum total calcium showed moderate discriminatory capacity (AUC = 0.319). The calcium-to-magnesium ratio exhibited the most substantial discriminatory potential (AUC = 0.691), suggesting its potential usefulness as a biomarker for identifying VOC. Figure I.

Table 1: Socio-demographic and clinical characteristics

Variable	SCA in Crisis n = 60	SCA in Steady State n = 60	HbAA n = 60	p-value
Age (Mean ± SD)	25.3 ± 7.87	24.7 ± 7.21	24.83±4.83	0.878
Gender				
Male	24 (40.0)	24 (40.0)	24 (40.0)	
Female	36 (60.0)	36 (60.0)	36 (60.0)	
Marital status				
Married	11 (18.3)	9 (15.0)	14 (23.3)	
Single	49 (81.7)	51 (85.0)	46 (76.7)	

Highest level of education				
None	2 (3.3)	0 (0.0)	0 (0.0)	
Primary	6 (10.0)	4 (6.7)	0 (0.0)	
Secondary	37 (61.7)	37 (61.7)	28 (46.7)	
Tertiary	15 (25.0)	19 (31.7)	32 (53.3)	
BMI (mean±SD)	20.01 ±2.34	20.07 ± 2.04	23.34 ±4.75	**<0.001**
BMI categories				
Underweight	13 (21.7%)	13 (21.7%)	7 (11.7%)	
Normal weight	44 (73.3%)	46 (76.7%)	35 (58.3%)	
Pre-obesity	3 (5.0%)	1 (1.6%)	14 (23.3%)	
Obesity	0(0.0%)	0(0.0%)	4(6.7%)	
BP (mmHg) mean (±SD)				
Systolic	109.9 ± 13.1	106.1 ± 9.1	112.5 ± 15.6	**<0.001**
Diastolic	69.1 ± 8.3	66.5 ± 6.0	70.4 ± 9.4	**<0.001**

Table 2: Biochemical parameters of the study population

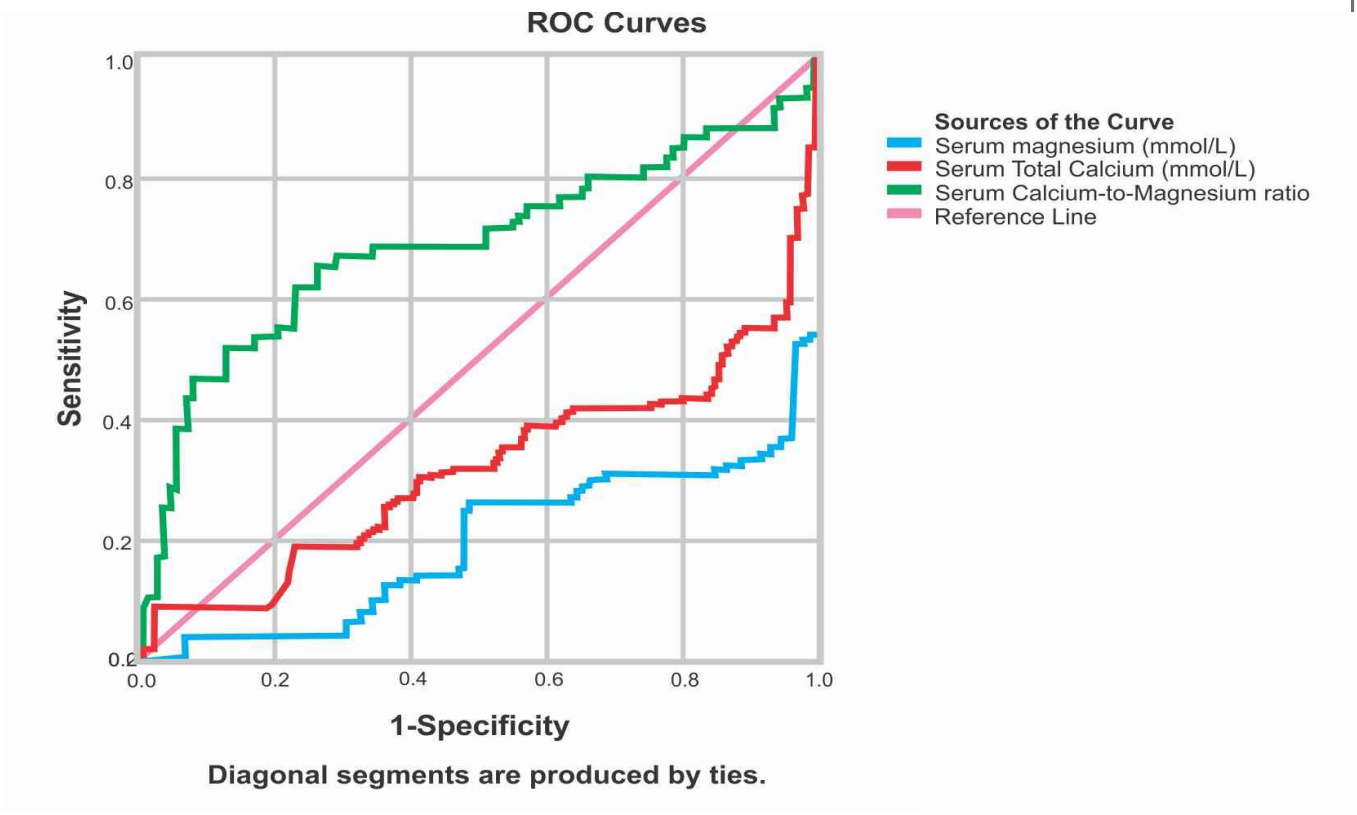
Variable	**SCA in Crisis n = 60**	**SCA in Steady State n = 60**	**HbAA n = 60**	**p-value**
Serum total calcium (mmol/L)- Mean ± SD	2.38 ± 0.34	2.54 ± 0.19	2.55 ± 0.24	**<0.001**
Serum albumin (mmol/L) – Mean ± SD	38.28 ± 4.38	41.43 ±.3.62	44.55 ± 4.51	**<0.001**
Serum magnesium (mmol/L) – Mean ± SD	0.69 ± 0.03	0.77 ± 0.04	0.82 ± 0.06	**<0.001**
Calcium-to-Magnesium Ratio - Mean ± SD	3.42 ± 0.42	3.32 ± 0.23	3.12 ± 0.19	**<0.001**

Table 3: Correlation between age and BMI of SCA patients in Crises with the serum biochemical analytes

Biochemical analyte	**r – value**	**P – value**
Age		
Serum total Calcium	- 0.050	0.704
Serum Magnesium	0.044	0.741
Calcium : Magnesium ratio	-0.073	0.580
BMI		
Serum total Calcium	0.063	0.634
Serum Magnesium	0.068	0.606
Calcium : Magnesium ratio	0.053	0.688

Table 4: Serum total calcium, magnesium and calcium-to-magnesium ratio among sickle cell anaemia participants in crises by sex.

Variable	**Male** **n = 24**	**Female** **n = 36**	***p-value***
Serum total calcium (mmol/L)- Mean ± SD	2.28 ± 0.39	2.45 ± 0.29	0.058
Serum magnesium (mmol/L) – Mean ± SD	0.69 ± 0.03	0.70 ± 0.03	0.059
Calcium-to-Magnesium Ratio - Mean ± SD	3.32 ± 0.49	3.49 ± 0.35	0.109



Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Serum magnesium	.249	.037	.003	.186	.336
Serum calcium	.319	.047	.000	.227	.411
Calcium_Magnesium_Ratio	.691	.047	.000	.598	.783

The test result variable(s): Serum magnesium, Serum Total calcium, Calcium-to-Magnesium_Ratio has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1: Comparing the ability of serum calcium, magnesium, and calcium-to-magnesium ratio to discriminate between the presence or absence of VOC in sickle cell anaemia participants using ROC curve

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Discussion

The results of this study highlight significant and non-significant differences in socio-demographic, clinical, and biochemical parameters among participants with SCA in crisis, SCA in steady state, and HbAA. These findings reflect the complex interplay of physiological, genetic, and environmental factors in the health status of individuals with SCA.

The similarity in age distribution across the three groups was expected, as participants were matched in this regard to minimise confounding effects. The mean age of the study population was 25.3+7.9 years. This was similar to findings obtained by Ghaleb *et al*[30] in Saudi Arabia, where the average ages of sickle cell patients in similar research were 26 and 25 years, respectively. Also, the mean age of SCA in some research in the southern part of Nigeria by Asafa M.A *et al*[31] revealed lower age groups than those obtained in this study. These similarities and lower age findings might be a result of increasing awareness of early presentation to health facilities, and also an increasing prevalence of sickle cell anaemia. The rising prevalence might be a result of some cultural and religious beliefs and practices, eg, consanguineous marriage. Contrary to the findings in this research work, Nouraie *et al*[32] in the United States recorded an average age of 38 years. This might probably be a result of the reduced prevalence of sickle cell anaemia in this environment, as well as a lower sample size when compared with this study. This study found a female (60%) preponderance over males, similar to findings in the Southern part of Nigeria.[31] The predominance of single participants, particularly in the SCA groups, may be attributable to the chronic nature of SCA, which can impair social and economic development, delaying marriage and other life milestones. [4] Furthermore, the higher proportion of tertiary-educated individuals in the HbAA group could reflect better

health, enabling sustained academic progression, whereas SCA individuals, especially those in crisis, might experience interruptions in education due to frequent hospitalizations and complications. [8]

The significant differences in BMI between the groups ($p < 0.001$) can be attributed to the metabolic demands of SCA. SCA participants, particularly during crises, often experience chronic inflammation, hypermetabolism, and reduced nutrient absorption, leading to lower BMI compared to HbAA individuals.[33] The HbAA group's higher prevalence of overweight and obesity reflects the absence of these stressors and possibly higher socio-economic stability, allowing for better nutrition and lifestyle choices.[34] Blood pressure findings further support the systemic impact of SCA. The significantly lower systolic and diastolic BP in the SCA groups aligns with previous studies indicating autonomic dysfunction and reduced vascular resistance in SCA.[35] HbAA participants, with standard haemodynamic profiles, naturally exhibited higher blood pressure.

This study demonstrated significantly lower serum calcium, magnesium, and albumin levels in SCA patients compared with HbAA controls, with the most marked reductions during vaso-occlusive crises. Conversely, the calcium-to-magnesium ratio was highest during crises, intermediate in steady state, and lowest among controls. These findings indicate substantial mineral dysregulation in SCA, which appears to intensify with acute disease activity.

The reduced calcium levels in SCA patients, particularly during crises, likely result from the combined effects of chronic haemolysis, bone infarctions, renal tubular dysfunction, and inflammation-related suppression of vitamin D metabolism.[13,15] Additionally, increased influx of Ca^{2+} through cation channels—known to be upregulated in SCD erythrocytes—may further disrupt calcium homeostasis. [20] Similarly, reduced magnesium levels in our

cohort align with evidence that oxidative stress and recurrent haemolysis increase urinary magnesium loss and impair its cellular retention.[14,16] The elevated calcium-to-magnesium ratio seen in crises thus reflects both absolute reductions in magnesium and a shift in mineral balance, potentially exacerbating vascular and neuromuscular dysfunction.[12,17,18]

No significant correlations were found between BMI or gender and mineral parameters in the crisis group. This suggests that these imbalances are primarily driven by disease-specific mechanisms—such as oxidative stress, haemolysis, and ion transport abnormalities—rather than by differences in body composition or sex hormones. While low BMI is typical in SCA due to hypermetabolism and nutrient malabsorption, our results indicate that mineral dysregulation persists independently of body habitus. Similarly, the absence of a gender effect mirrors findings from Ghana[8] and the United States, [36] suggesting that mineral metabolism in SCA is not significantly influenced by sex, even in diverse populations.

Our results are consistent with studies from sub-Saharan Africa, such as Antwi-Boasiako et al. in Ghana[16] and Manu et al. in Northwestern Nigeria, [9] both of which reported lower calcium and magnesium in SCA. In Saudi Arabia, Ghaleb et al. [30] reported reduced bone mineral density in adult SCA patients, a likely downstream effect of chronic mineral imbalance. In high-income countries, such as the United States, Zehtabchi et al.[12] reported less severe mineral depletion, possibly reflecting better nutrition, supplementation, and comprehensive care. These differences highlight the role of environmental, dietary, and healthcare factors in influencing mineral status.

Several nutritional and environmental factors unique to Northern Nigeria may explain the degree of imbalance observed in our cohort. Diets in this region are dominated by cereals and legumes with

high phytate content, which binds divalent cations and reduces their intestinal absorption.[21,22] Limited intake of dairy products and green leafy vegetables further restricts the availability of calcium and magnesium. Environmental stressors such as high ambient temperatures and recurrent dehydration can increase renal mineral loss, while infectious diseases like malaria and bacterial infections add metabolic stress, further disrupting homeostasis.[23,24,25] Limited access to specialist haematology services and reliance on out-of-pocket healthcare costs can delay crisis intervention, prolonging periods of imbalance.[24]

The ROC analysis in this study identified the calcium-to-magnesium ratio as a potentially useful biomarker for differentiating disease states in SCA, with greater discriminatory power than either mineral alone. This finding is clinically relevant given the interplay between calcium and magnesium in vascular tone regulation, neuromuscular stability, and bone health.[17,18] Incorporating this ratio into clinical monitoring could help identify patients at higher risk of complications, particularly in resource-limited settings.

Overall, these findings emphasise the need to address both nutritional and pathophysiological contributors to mineral dysregulation in SCA. Interventions combining dietary diversification, targeted supplementation, and timely crisis management may help restore mineral balance and improve patient outcomes. Future research should investigate whether correcting the calcium-to-magnesium ratio can lead to measurable improvements in vascular function, bone integrity, and quality of life in SCA patients in Northern Nigeria and similar environments.

Conclusion

This study identified significant disturbances in mineral homeostasis among adults with SCA in Zaria, characterised by reduced serum calcium, magnesium, and albumin levels, and an elevated calcium-to-magnesium ratio, especially during vaso-

occlusive crises. These alterations were not influenced by BMI or gender, suggesting a disease-driven mechanism rather than demographic or anthropometric determinants. The calcium-to-magnesium ratio demonstrated moderate discriminatory potential for distinguishing crisis from steady state, indicating its promise as a supplementary biomarker in SCA management. These findings highlight the relevance of monitoring combined mineral indices, rather than isolated levels, in the assessment of disease severity in this population.

Limitations

This study has some limitations that should be considered when interpreting the findings. Its cross-sectional design limits the ability to establish a causal relationship between mineral disturbances and clinical outcomes in SCA. Dietary calcium and magnesium intakes were not assessed, which makes it difficult to attribute the observed serum changes to nutritional status directly. Furthermore, the research was conducted in a single tertiary healthcare centre in Northwestern Nigeria, and this may affect the generalisability of the results to other regions with different dietary patterns, healthcare access, and environmental conditions. The study measured total calcium and magnesium rather than ionised fractions, which might have provided a more accurate reflection of physiologically active mineral levels. Additionally, temporal changes in mineral status before, during, and after vaso-occlusive crises were not explored, preventing an assessment of short-term fluctuations associated with disease episodes.

Recommendation

Based on the findings, future research should adopt longitudinal designs to monitor calcium, magnesium, and their ratio over time, particularly across different phases of the disease, to understand temporal dynamics better. Including dietary assessments would help clarify the extent to which nutritional intake contributes to

mineral imbalances in SCA. Multicentre studies involving diverse geographical and socio-economic settings within Nigeria and across sub-Saharan Africa are encouraged to enhance the external validity of the results. Future work should also consider measuring ionised calcium and magnesium to provide more clinically relevant information on mineral bioavailability. Interventional studies assessing the impact of targeted calcium and magnesium supplementation on crisis frequency, bone health, and vascular outcomes in SCA would be valuable. Finally, incorporating the calcium-to-magnesium ratio into routine laboratory evaluation could aid in the early identification of patients at risk for complications, allowing for timely nutritional or therapeutic interventions.

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