Article published online: 2022-07-02

Zinc, Magnesium, and Copper Levels in Patients with Sickle Cell Disease: A Systematic Review and Meta-analysis

Ibrahim H. Elkhidir[1] Shahd S. Ali[1] Waad K. Ali[1] Hind R. Madani[1] Rawya A. Basheir[1] Rayan M. Altayeb[1] Rayan H. S. Shazali[1] Safaa Fadlelmoula[1] Wisal M. Eltayeb[1] Zeina I. Omar[1] Mahmoud Elnil[1] Sagad O.O. Mohamed[1]

[1] Department of Pathology, Faculty of Medicine, University of Khartoum, Khartoum, Sudan

Avicenna J Med 2022;12:45–53.

Address for correspondence Ibrahim H. Elkhidir, MD, Faculty of Medicine, University of Khartoum, Alqasr Avenue, P.O. Box 102, Khartoum 11111, Sudan (e-mail: ibrahim_hassan12@yahoo.com).

Abstract

Background Sickle cell disease (SCD) is associated with oxidative stress due to an imbalance between production and elimination of the reactive oxygen species. It has been reported that SCD patients are at risk of multiple micronutrients' deficiencies, including several trace elements involved in the antioxidation mechanisms. We aimed to assess the status of these micronutrients in SCD patients.

Methods This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The databases of MedLine, Embase, and PsycInfo were used for the systematic search from time the databases existed until April 2021. A total of 36 studies fulfilled the eligibility criteria. We calculated the pooled standardized mean difference (SMD) of serum zinc, magnesium, or copper levels among patients with SCD and their healthy controls.

Results SCD patients had significantly lower zinc (SMD= −1.27 [95% CI: 1.67−0.87, p 0.001]) and magnesium levels (SMD= −0.53 [95% CI: 1.0−0.06, p 0.026]) than their controls. Copper level was found to be significantly higher in SCD patients, with SMD =0.68 (95% CI: 0.05−1.32, p 0.004).

Conclusion This review showed that SCD patients may potentially prompt to have lower zinc and magnesium levels and higher copper levels compared with those without the disease. Future research need to be directed to investigate clinical outcome of nutritional difficiencies in patients with SCD, as well as the possibility of implementing nutritional supplement programs which may help minimizing the harmful effects of the disease on human body.

Keywords

- sickle cell
- SCD
- zinc
- magnesium
- copper

published online
July 2, 2022

DOI https://doi.org/10.1055/s-0042-1749612.
ISSN 2231-0770.

© 2022. Syrian American Medical Society. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

Sickle cell disease (SCD) is an inherited red blood cell disorder that leads to forming the mutated hemoglobin S, resulting in a wide range of signs and symptoms, including chronic hemolytic anemia, sequestration crisis, susceptibility to repeated infections, and periodic episodes of pain mostly due to vasoocclusive phenomena.[1–3] SCD also presents with long-term effects such as cerebrovascular accidents, sickle nephropathy, pulmonary complications, renal impairment, cardiomyopathy, delayed puberty, and reduced growth.[1–7]

The sickling and ischemic reperfusion injury associated with SCD lead to a state of oxidative stress due to an imbalance between production and elimination of the reactive oxygen species.[8,9] Furthermore, hemoglobin S has a high autoxidation rate which contributes to the oxidative stress in SCD patients.[8,9] As a result of the high-energy expenditure associated with the high rate of red cell turnover, SCD patients are at risk of multiple micronutrients deficiencies that could have an impact on SCD severity.[8–11] It has been reported that the concentrations of multiple micronutrients and trace elements tend to be low in patients with SCD.[8–11]

Many of these micronutrients are involved in antioxidation mechanisms which are further compromised as a result of high oxidative stress in the sickled erythrocytes.[8,9] Of these trace elements, zinc, copper, and magnesium and their roles have been widely described in the literature.[8,9] Zinc and copper are essential cofactors for the optimal performance of superoxide dismutase, a scavengering enzyme responsible for detoxifying anion superoxide to hydrogen peroxide. However, copper could act as a prooxidant and promotes free radicals when it presents in high concentration in the state of impaired zinc bioavailability, a condition that has been previously described in various diseases, including SCD.[8,9,12,13] Also, magnesium has a role in the modulation of endothelial inflammation, besides its roles in regulating heart rhythm, immune system functions, and bone metabolism.[14]

Several studies provided data on the status of these micronutrients in SCD but these data require further summary and analyses for better accuracy. This review aimed to provide a quantitative, comprehensive view of the status and extent of zinc, copper, and magnesium levels and deficiencies in SCD patients.

Methods

Search Strategy and Eligibility Criteria

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[15,16] A systematic search was performed in April 2021 through Medline, Embase, and PsycInfo databases from data of inception up to specified databases up to April 2021. Databases were queried for the terms ((zinc or magnesium or copper) AND (Sickle cell or Sickler)). Duplicate records were removed subsequently. We included studies reported sufficient data on the mean levels of zinc, magnesium, or copper among patients with SCD and their healthy controls for evidence synthesis. Neither age restriction nor specific population criteria were implemented. Studies with insufficient data, case reports, conference presentations, editorials, proposals, and abstracts were excluded.

The titles and abstracts of retrieved articles were screened by two independent reviewers for potential inclusion. Any discrepancy between the reviewers was resolved by consensus with a third reviewer. Full-text screening was done by two independent reviewers and any discrepancy between the reviewers was resolved by consensus with a third reviewer. Appraisal of individual study quality was performed by two independent reviewers using the Newcastle–Ottawa scale, a tool that determines the quality based on the selection of the study group, comparability of groups, and ascertainment of the exposure and outcomes.[17] Data extraction was done with a data collection sheet made in a Microsoft Excel Spreadsheet. When data were presented in medians and interquartile range, we transformed them into means and standard deviations.[18]

Statistical Analysis

The standardized mean difference (SMD) was selected as a measurement tool to estimate the difference in serum levels of the targeted micronutrients. SMD was chosen as the included studies reported the results using different tools and measures. Statistical analysis was performed using R language v.4, using the "meta" and "metafor" packages, through the MARVIS app (Elkhidir, Ibrahim (2022): MARVIS. Figshare software).[19–22] Random effects models were used to pool the individual estimates and to accommodate for the heterogeneity in the reported pooled effect sizes. The effect size selected for statistical computation is the pooled SMD. Statistical heterogeneity was estimated using I^2 statistics and further assessed using subgroup analysis and metaregression. Publication bias was evaluated by both the Egger test and funnel plot visual analysis.

Result

Studies Characteristics

The search yielded a total of 986 records. After eliminating duplicate data, 696 studies were included for the title and abstract screening of which 599 were excluded due to irrelevance. Full texts of the remaining 97 records were screened with a subsequent exclusion of 54 records. A total of 36 studies published from 1974 to 2019 met the eligibility criteria and were further included for evidence synthesis; 15 from Africa, 9 from the United States, 8 from Asia, and 4 from Europe.[8,9,12,23–60] Details of the selection process are summarized in (►Fig. 1).

Zinc

Discriptive summary of data for zinc in ►Table 1. The pooled SMD of serum zinc across all included studies was −1.27 (95% confidence interval [CI]: −1.67 to −0.87, $p < 0.001$) with a prediction interval of (−3.44; 0.90; ►Fig. 2). A substantial heterogeneity across studies was noted ($I^2 = 95\%$, $p < 0.001$).

 © 2022. Syrian American Medical Society. All rights reserved.

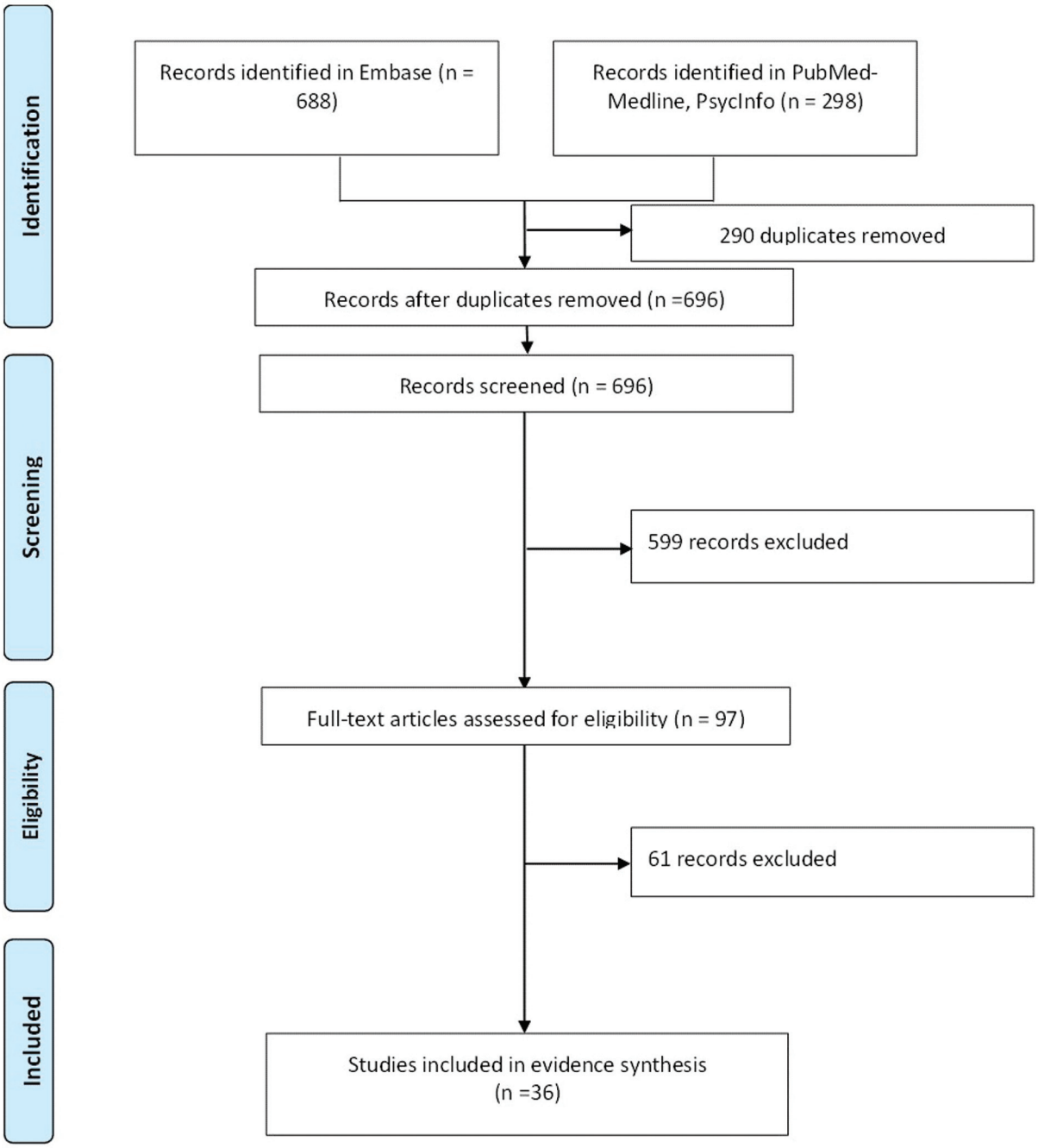

Fig. 1 The flow diagram for the process of study selection.

A potential risk for publication bias was noted on visual examination of funnel plot and the Egger's test = −2.14; $p = 0.042$. Subgroup analysis by study location as a grouping variable revealed that the Asian (−1.65), African (−1.63), and American (−0.71) studies have statistically significant SMD, unlike the European studies (−0.82). Year of publication explained approximately 10.34% (R^2) of the total heterogeneity.

Magnesium

Discriptive summary of data for magnesium in ►**Table 2**. The pooled SMD of serum magnesium across all included studies was −0.53 (95% CI: −1.0 to −0.06, $p < 0.026$) with a prediction interval of (−1.0; 1.25; ►**Fig. 3**). A substantial heterogeneity across studies was noted ($I^2 = 92\%$, $p < 0.01$). No potential risk for publication bias was noted visual examination of the funnel plot and the Egger's test was 0.964, $p = 0.36$. Subgroup analysis by study location as a grouping variable revealed that SMD was only significant among American studies. Both location and year explained 17.20% (R^2) of the total heterogeneity. Testing for residual heterogeneity was significant (QE [df = 6] = 98.3528, $p < 0.001$), indicating that there are other factors not included in the model that significantly contributing to the high heterogeneity.

 © 2022. Syrian American Medical Society. All rights reserved.

Table 1 Data of zinc between sickle cell disease patient(s) and non–sickle cell disease patient(s)

Study	Location	Design	Sickle cell disease patient(s)			Non–sickle cell disease patient(s)		
			Mean	SD	*n*	Mean	SD	*n*
Akinkugbe and Ette (1987)[37]	Africa	Cross-sectional	53.45	25.19	40	79	61.6	20
Alayash et al (1987)[49]	Asia	Cross-sectional	113	35.9	57	117.43	34.1	45
Al-Naama et al (2016)[51]	Asia	Cross-sectional	62.2	12.6	42	94.2	12.5	50
Antwi-Boasiako et al (2019)	Africa	Cross-sectional	66.5	5.8	34	101.4	9.4	50
Bashir (1995)[55]	Asia	Cross-sectional	85.6	10.3	15	107.2	11.7	25
Canellas et al (2012)[43]	The United States	Cross-sectional	60	10	43	80	20	60
Emokpae et al (2019)[59]	Africa	Case control	46.26	1.986	74	54.6	1.237	50
Hasanato et al (2019)[9]	Asia	Cross-sectional	65.5	22.5926	33	94	13.75	33
Karayalcin et al (1979)[23]	The United States	Cross-sectional	114.9	22.2	46	133.63	24.36	46
Karayalcin-zinc et al (1974)[24]	The United States	Cross-sectional	116	33	50	177	49	50
Kehinde et al (2011)[25]	Africa	Cross-sectional	70	6	20	70	7	20
Kilinç et al (1991)[28]	Europe	Case control	58	18.6529	20	96.4	22.8	20
Kudirat et al (2019)[30]	Africa	Descriptive longitidual	23.4	7.4	70	48.9	14.4	70
Kuvibidila et al (2006)[31]	The United States	Case control	96.1	20.5	90	95.1	46.1	82
Olaniyi et al (2010)[36]	Africa	Case control	1320	230	59	1170	200	35
Oliveira et al (2001)[56]	The United States	Case control	85.15	32.18	34	108.45	22.89	20
Onukwuli et al (2018)[39]	Africa	Cross-sectional, case control	58.01	10.58	81	68.37	8.67	81
Oztas et al (2012)[40]	Europe	Case control	158.3	13.8	15	154.1	22.4	10
Phebus et al (1988)[41]	The United States	Case control	76.3	8.9	56	82.2	9.8	44
Prasad et al (1976)	The United States	Case control	104	10.5	84	113	13.6	70
Smith et al (2019)[42]	Africa	Cross-sectional	101	13.4683	80	105.7	11.5	80
Wasnik et al (2017)[44]	Asia	Cross-sectional	83.09	9.26	33	104.06	6.27	33
Yousif et al (2018)[45]	Asia	Case control	67.25	17.78	87	90.34	16.38	90
Yuzbasiyan et al (1989)[46]	The United States	Case control	87	17	7	83	17	8
Arinola et al (2008)[50]	Africa	Case control	11.2545	5.66609	44	15.94	5.51066	50
Arcasoy et al (2001)[48]	Europe	Case control	77.3	15.74	10	90.04	13.83	20
Durosinmi et al (1993)[57]	Africa	Case control	2.89	0.73	18	5.21	1.97	27
Sungu et al (2018)[8]	Africa	Case control	0.27	0.58	76	1.64	0.14	76

Copper

Discriptive summary of data for copper in ►**Table 3**. The pooled SMD of serum copper across all included studies was 0.68 (95% CI: 0.05–1.32, $p < 0.004$), with a prediction interval of (−2.29; 3.66; ►**Fig. 4**). A substantial heterogeneity across studies was noted ($I^2 = 97\%$, $p < 0.001$). On visual examination of funnel plot, no potential risk for publication bias was noted and the Egger's test statistics was 0.561, $p = 0.58$. Subgroup analysis by study location as a grouping variable, revealed that SMD was only significant among Asian studies. Between group difference is significant ($Q = 12.01865$, df = 3, $p = 0.007$). Mixed model of study location and year of publication explained approximately 21.77% (R^2) of the total heterogeneity. Testing for residual heterogeneity was significant (QE [df = 5] = 242.2145, $p < 0.001$), indicating that there are other factors not included in the model that significantly contributing to the high heterogeneity.

Discussion

This review aimed to provide an overarching resource about the status of zinc, magnesium, and copper in SCD patients. Most of the studies (28 out of 36) focused on zinc serum level among patients with SCD. The analyses showed that both zinc and magnesium levels were lower in SCD patients, whereas copper level was higher among them. These findings coincide with the known nature of the chronic inflammatory process occurring in SCD associated with ischemia-

 © 2022. Syrian American Medical Society. All rights reserved.

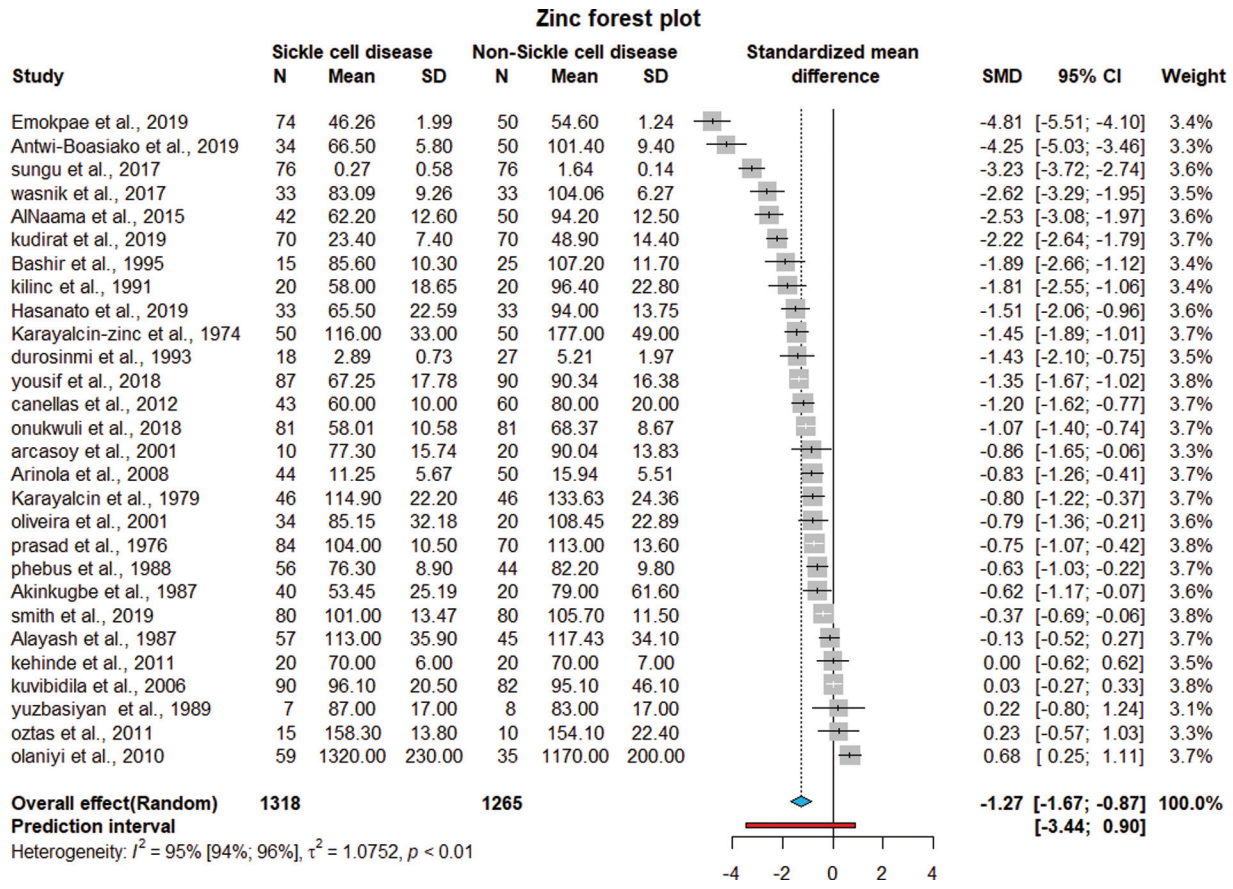

Fig. 2 Pooled SMD of zinc levels among patients with SCD. CI, confidence interval; SCD, sickle cell disease; SD, standard deviation; SMD, standardadized mean difference.

Table 2 Data of magnesium between sickle cell disease patient(s) and non–sickle cell disease patient(s)

Study	Location	Design	Sickle cell disease patient(s)			Non–sickle cell disease patient(s)		
			Mean	SD	*n*	Mean	SD	*n*
Antwi-Boasiako et al (2019)	Africa	Case control	0.79	0.25	79	0.90	0.11	48
Elshal et al (2012)[58]	Asia	Case control	0.79	0.13	60	0.85	0.17	20
Khan (2003)[27]	Asia	Case control	0.84	0.09	51	0.78	0.05	29
Kontessis et al (1992)[29]	Europe	Case control	0.77	0.10	8	0.85	0.10	14
Olaniyi et al (2010)[36]	Africa	Case control	0.39	0.09	59	0.38	0.08	35
Olukoga et al (1993)[38]	Africa	Case control	0.76	0.10	25	0.83	0.15	25
Prasad et al (1976)	The United States	Case control	0.78	0.10	29	0.82	0.08	38
Sungu et al (2018)[8]	Africa	Case control	0.13	0.02	76	0.42	0.21	76
Yousif et al (2018)[45]	Asia	Case control	0.55	0.19	87	0.77	0.11	90
Zehtabchi et al (2004)	The United States	Case control	0.79	0.09	74	0.81	0.07	32

reperfusion injury, excessive production of free radicals like superoxide, and hydrogen peroxide.[61,62] Additionally, due to the norable heterogeneity in SMD meta-anaylsis, subgroup analysis was done, and the Asian and African descent had significanly lower values than both American and European. This stress on the importance of race and ethnicity on the clinical outcome in SCD patients which is well established in the literature.[63] The high copper values in these patients may be attributed to the chronic hemolysis state and aggravated by the coexisting zinc deficieny. In two studies by Antwi-Boasiako et al and Osredkar and Sustar et al, they discovered that serum copper is influenced by zinc bioavailability, as they observe that zinc deficiency significantly enhance copper absorption from the gut.[12,64]

 © 2022. Syrian American Medical Society. All rights reserved.

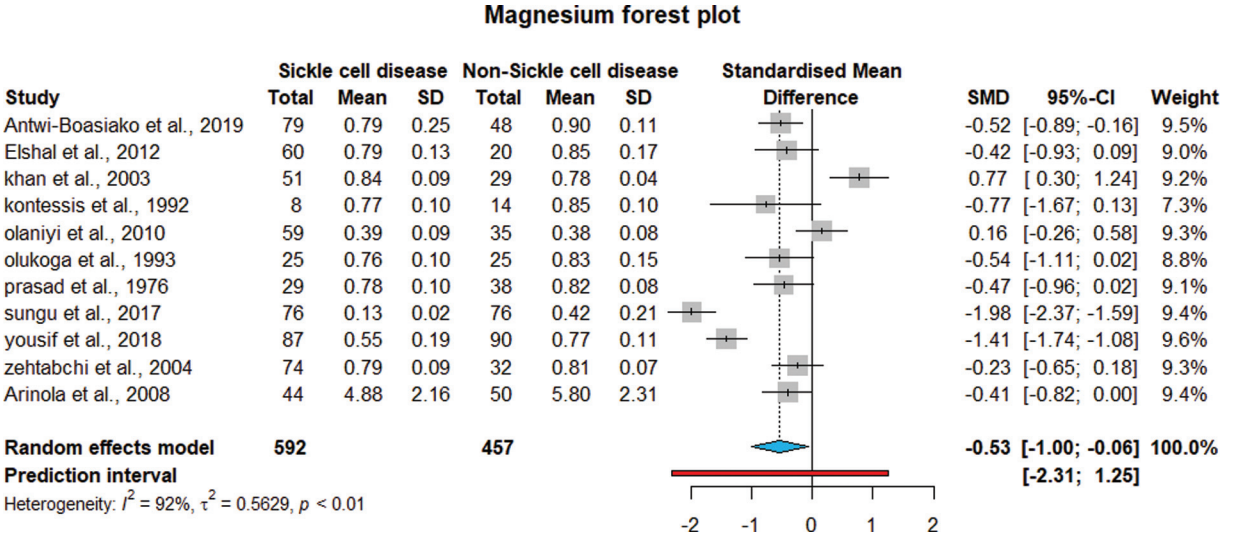

Fig. 3 Pooled SMD of magnesium levels among patients with SCD. CI, confidence interval; SCD, sickle cell disease; SD, standard deviation; SMD, standardadized mean difference.

Table 3 Data of copper between sickle cell disease patient(s) and non–sickle cell disease patient(s)

Study	Location	Design	Sickle cell disease patient(s)			Non–sickle cell disease patient(s)		
			Mean	SD	*n*	Mean.c	SD	*n*
Akinkugbe and Ette (1987)[37]	Africa	Cross-sectional	70.40	42.62	40	89.30	61.30	20
Alayash et al (1987)[49]	Asia	Cross-sectional	144.93	44.09	57	148.40	44.40	45
Al-Naama et al, (2016)[51]	Asia	Cross-sectional	145.50	14.30	42	100.90	13.50	50
Antwi-Boasiako et al, 2019	Africa	Cross-sectional	220.90	27.80	34	114.00	16.30	50
Bashir (1995)[55]	Asia	Cross-sectional	131.30	11.50	15	109.00	15.10	25
Canellas et al (2012)[43]	The United States	Cross-sectional	120.00	10.00	43	100.00	10.00	60
Emokpae et al (2019)[59]	Africa	Case control	105.80	2.46	74	102.60	1.59	50
Erhabor et al (2019)[60]	Africa	Case control	40.40	9.66	45	75.60	6.50	25
Hasanato et al (2019)[9]	Asia	Cross-sectional	131.67	15.56	33	88.00	10.50	33
kehinde et al (2011)[25]	Africa	Cross-sectional	6.00	2.00	20	7.00	3.00	20
Kilinç et al (1991)[28]	Europe	Case control	133.80	64.67	20	168.70	39.30	20
Mukuku et al (2018)[33]	Africa	Case control	172.00	15.00	76	189.00	20.00	76
Olaniyi et al (2010)[36]	Africa	Case control	67.00	10.10	59	68.50	10.00	35
Oztas et al (2012)[40]	Europe	Case control	95.90	9.90	15	96.30	9.10	10
Prasad et al, 1976	The United States	Case control	126.00	25.00	41	116.00	19.00	60
Smith et al (2019)[42]	Africa	Cross-sectional	144.00	17.09	80	116.00	27.70	80
Yousif et al (2018)[45]	Asia	Case control	142.35	49.92	87	109.66	24.42	90

Additionally, high copper may promote a prooxidant state as illustrated by Chirico and Pialoux.[65] Although there is noted heterogenity using I^2 statistics, most of included studies for zinc and magnesium had a pattern of consistency across them that nearly 22 studies out of 28 fall below SMD of 0 for zinc, and 10 out of 12 studies for magnesium that fell below a SMD of 0 which, in fact, explained by Borenstein et al which concluded that not to miss such patterns in expense of high heterogeneity.[66]

The differences noted in these trace elements levels between SCD patients and others could be attributed to several peculiar characteristics of SCD such as increased physiological demands due to the fast rate of erythrocytosis and red blood cells turnover in SCD, impact of suboptimal renal function, glomerular injury in SCD, and impaired absorption by the damaged intestinal mucosa as a complication of SCD.[8,42,67] There are implications to the reported findings. From a clinical perspective, the SCD patients might

 © 2022. Syrian American Medical Society. All rights reserved.

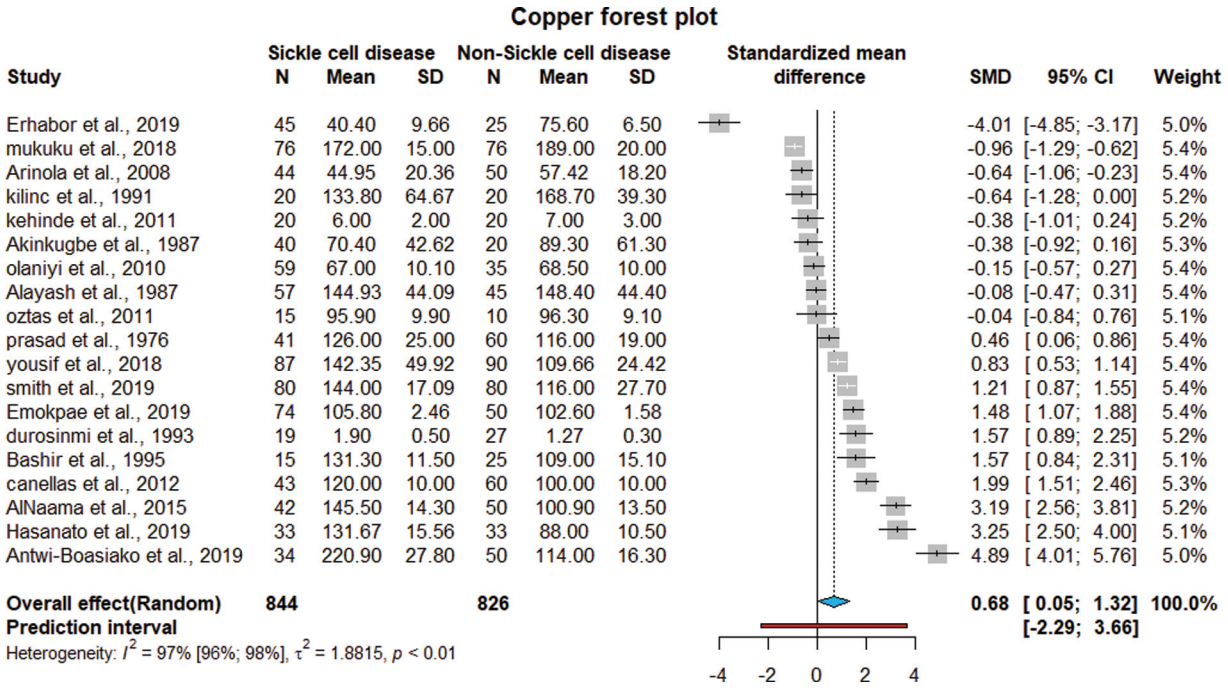

Fig. 4 Pooled SMD of copper levels among patients with SCD. CI, confidence interval; SCD, sickle cell disease; SD, standard deviation; SMD, standardadized mean difference.

have benefited from nutritional supplementations with these elements, as it has been reported by previous studies[13,68] but nutritional guidelines concerning the performance of these micronutrients in SCD patients are still not broadly available.[13]

From a research perspective, the paucity of data on clinical outcomes of trace elements deficiencies needs to be addressed and could benefit from further studies to give a better understanding of the exact pathogenesis and effects of such deficiencies.

Limitations

The results of this review need to be considered in the context of some limitations. The protocol of the study was not registered in PROSPERO which is a well-known review registry portal.[69] The inclusion of observational studies published only in English which might compromise representativeness, as well as the notable heterogeneity among studies, which was partially explained by some demographic variables. In addition, despite the paucity of data on the clinical outcomes associated with these trace element deficiencies, it does not mean that the laboratory findings cannot have implications on clinical significance, but the included studies used different tools making using the raw mean difference difficult to implement.

Conclusion

This review showed that SCD patients may potentially prompt to have lower zinc and magnesium levels and higher copper levels compared with those without the disease. Future research needs to be directed to investigate clinical outcome of nutritional difficiencies in patients with SCD, as well as the possibility of implementing nutritional supplements programs which may help minimizing the harmful effects of the disease on human body.

Funding
None.

Conflict of Interest
None declared.

Availability of Data and Material
The dataset generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions'
S.O.O.M. and I.H.E. conceptualized the research idea and designed the study; R.H.S.S., W.M.E., H.R.M., and R.A.B. undertook articles searching, articles assessment, and review; and S.S.A. and W.K.A.) undertook data extraction and analysis. All authors interpreted the results and drafted the manuscript. All authors revised and approved the final manuscript.

References

1 Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. Arch Dis Child 2015;100(01):48–53
2 Brousse V, Makani J, Rees DC. Management of sickle cell disease in the community. BMJ 2014;348:g1765
3 Wastnedge E, Waters D, Patel S, et al. The global burden of sickle cell disease in children under five years of age: a systematic review and meta-analysis. J Glob Health 2018;8(02):021103

 © 2022. Syrian American Medical Society. All rights reserved.

4 Farooq S, Testai FD. Neurologic complications of sickle cell disease. Curr Neurol Neurosci Rep 2019;19(04):17
5 Pinto VM, Balocco M, Quintino S, Forni GL. Sickle cell disease: a review for the internist. Intern Emerg Med. 2019;14(07):1051–1064
6 Kosaraju V, Harwani A, Partovi S, et al. Imaging of musculoskeletal manifestations in sickle cell disease patients. Br J Radiol 2017;90 (1073):20160130
7 Barden EM, Kawchak DA, Ohene-Frempong K, Stallings VA, Zemel BS. Body composition in children with sickle cell disease. Am J Clin Nutr 2002;76(01):218–225
8 Sungu JK, Mukuku O, Mutombo AM, Mawaw P, Aloni MN, Luboya ON. Trace elements in children suffering from sickle cell anemia: a case-control study. J Clin Lab Anal 2018;32(01):e22160
9 Hasanato R. Alterations in serum levels of copper, zinc, and selenium among children with sickle cell anemia. Turk J Med Sci 2019;49(05):1287–1291
10 Mandese V, Marotti F, Bedetti L, Bigi E, Palazzi G, Iughetti L. Effects of nutritional intake on disease severity in children with sickle cell disease. Nutr J 2016;15(01):46
11 Mohamed SOO, Mohamed Elmugadam FAA, Awadalla HFM, et al. A meta-analysis on vitamin D deficiency in patients with sickle cell disease. Med J 2020;2(03):95–100
12 Antwi-Boasiako C, Dankwah GB, Aryee R, et al. Serum iron levels and copper-to-zinc ratio in sickle cell disease. Medicina (Kaunas) 2019;55(05):1–7
13 Delesderrier E, Curioni C, Omena J, Macedo CR, Cople-Rodrigues C, Citelli M. Antioxidant nutrients and hemolysis in sickle cell disease. Clin Chim Acta
14 Than NN, Soe HHK, Palaniappan SK, Abas ABL, De Franceschi L. Magnesium for treating sickle cell disease. Cochrane Database Syst Rev 2017;4(04):CD011358
15 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700
16 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535
17 Wells G, Shea B, O'Connell D, Peterson J. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed April 21, 2022 at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
18 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5(01):13
19 Viechtbauer W. Conducting meta-analyses in {R} with the {metafor} package. J Stat Softw 2010;36(03):1–48
20 R Core Team. R: a language and environment for statistical computing. Accessed April 21, 2022 at: https://www.r-project.org/
21 Metaprop: meta-analysis of single proportions. In meta: general package for meta-analysis. Accessed June 18, 2020 at: https://rdrr.io/cran/meta/man/metaprop.html
22 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22(04):153–160
23 Karayalcin G, Lanzkowsky P, Kazi AB. Zinc deficiency in children with sickle cell disease. Am J Pediatr Hematol Oncol 1979;1(03): 283–284
24 Karayalcin G, Rosner F, Kim KY, Chandra P. Letter: plasma-zinc in sickle cell-anaemia. Lancet 1974;1(7850):217
25 Kehinde MO, Jaja SI, Adewumi OM, Adeniyi IM, Nezianya MO, Ayinla EO. Liver enzymes and trace elements in the acute phase of sickle cell anaemia. West Afr J Med 2010;29(04):244–248
26 Abshire TC, English JL, Githens JH, Hambidge M. Zinc status in children and young adults with sickle cell disease. Am J Dis Child 1988;142(12):1356–1359
27 Khan JAJ. Vitamin D status and serum level of some elements in children with sickle cell disease in Jeddah, Saudi Arabia. Pak J Med Sci 2003;19(04):295–299
28 Kilinç Y, Kümi M, Yilmaz B, Tanyeli A. A comparative study of zinc and copper values in serum, erythrocytes and urine in sickle cell homozygotes and heterozygotes. Acta Paediatr Scand 1991;80(8-9):873–874
29 Kontessis P, Mayopoulou-Symvoulidis D, Symvoulidis A, Kontopoulou-Griva I. Renal involvement in sickle cell-beta thalassemia. Nephron 1992;61(01):10–15
30 Kudirat AA, Shehu UA, Kolade E, Ibrahim M. Serum zinc level during and after acute painful episodes in children with sickle cell anemia at the aminu kano teaching hospital, Kano, Northern Nigeria. Niger J Clin Pract 2019;22(01):16–23
31 Kuvibidila SR, Sandoval M, Lao J, et al. Plasma zinc levels inversely correlate with vascular cell adhesion molecule-1 concentration in children with sickle cell disease. J Natl Med Assoc 2006;98(08): 1263–1272
32 Leonard MB, Zemel BS, Kawchak DA, Ohene-Frempong K, Stallings VA. Plasma zinc status, growth, and maturation in children with sickle cell disease. J Pediatr 1998;132(3 Pt 1):467–471
33 Mukuku O, Sungu JK, Mutombo AM, et al. Albumin, copper, manganese and cobalt levels in children suffering from sickle cell anemia at Kasumbalesa, in Democratic Republic of Congo. BMC Hematol 2018;18(01):23
34 Niell HB, Leach BE, Kraus AP. Zinc metabolism in sickle cell anemia. JAMA 1979;242(24):2686–2687
35 Oladipo OO, Temiye EO, Ezeaka VC, Obomanu P. Serum magnesium, phosphate and calcium in Nigerian children with sickle cell disease. West Afr J Med 2005;24(02):120–123
36 Olaniyi JA, Arinola OG. Nitric oxide and trace metals in relation to haemoglobin F concentration in Nigerian sickle cell disease patients. Turk J Med Sci 2010;40(01):109–113
37 Akinkugbe FM, Ette SI. Role of zinc, copper, and ascorbic acid in some common clinical paediatric problems. J Trop Pediatr 1987; 33(06):337–342
38 Olukoga AO, Adewoye HO, Erasmus RT, Adedoyin MA. Urinary magnesium excretion in steady-state sickle cell anaemia. Acta Haematol 1993;90(03):136–138
39 Onukwuli VO, Chinawa J, Eke CB, Nwokocha AR, Emodi IJ, Ikefuna AN. Impact of zinc on sexual maturation of female sickle cell anemia (SCA) children in Enugu, Southeast Nigeria. Pediatr Hematol Oncol 2018;35(02):145–155
40 Oztas Y, Durukan I, Unal S, Ozgunes N. Plasma protein oxidation is correlated positively with plasma iron levels and negatively with hemolysate zinc levels in sickle-cell anemia patients. Int J Lab Hematol 2012;34(02):129–135
41 Phebus CK, Maciak BJ, Gloninger MF, Paul HS. Zinc status of children with sickle cell disease: relationship to poor growth. Am J Hematol 1988;29(02):67–73
42 Smith OS, Ajose OA, Adegoke SA, et al. Plasma level of antioxidants is related to frequency of vaso-occlusive crises in children with sickle cell anaemia in steady state in Nigeria. Pediatr Hematol Oncol J 2019;4(01):17–22
43 Canellas CGL, Carvalho SMF, Anjos MJ, Lopes RT. Determination of Cu/Zn and Fe in human serum of patients with sickle cell anemia using radiation synchrotron. Appl Radiat Isot 2012;70(07): 1277–1280
44 Wasnik RR, Akarte NR. Evaluation of serum zinc and antioxidant vitamins in adolescent homozygous sickle cell patients in Wardha, district of central India. J Clin Diagn Res 2017;11(08): BC01–BC03
45 Yousif OO, Hassan MK, Al-Naama LM. Red blood cell and serum magnesium levels among children and adolescents with sickle cell anemia. Biol Trace Elem Res 2018;186(02):295–304
46 Yuzbasiyan-Gurkan VA, Brewer GJ, Vander AJ, Guenther MJ, Prasad AS. Net renal tubular reabsorption of zinc in healthy

 © 2022. Syrian American Medical Society. All rights reserved.

man and impaired handling in sickle cell anemia. Am J Hematol 1989;31(02):87–90
47 Zehtabchi S, Sinert R, Rinnert S, et al. Serum ionized magnesium levels and ionized calcium-to-magnesium ratios in adult patients with sickle cell anemia. Am J Hematol 2004;77(03):215–222
48 Arcasoy A, Canata D, Sinav B, Kutlay L, Oğuz N, Şen M. Serum zinc levels and zinc binding capacity in thalassemia. J Trace Elem Med Biol 2001;15(2-3):85–87
49 Alayash AI, Dafallah A, Al-Quorain A, Omer AH, Wilson MT. Zinc and copper status in patients with sickle cell anemia. Acta Haematol 1987;77(02):87–89
50 Arinola OG, Olaniyi JA, Akiibinu MO. Evaluation of antioxidant levels and trace element status in Nigerian sickle cell disease patients with plasmodium parasitaemia. Pak J Nutr 2008;7(06):766–769
51 Al-Naama LM, Hassan MK, Mehdi JK. Association of erythrocytes antioxidant enzymes and their cofactors with markers of oxidative stress in patients with sickle cell anemia. Qatar Med J 2016; 2015(02):14
52 Aloni MN, Lecerf P, Lê P-Q, et al. Is Pica under-reported in children with sickle cell disease? A pilot study in a Belgian cohort. Hematology 2015;20(07):429–432
53 Antwi-Boasiako C, Kusi-Mensah YA, Hayfron-Benjamin C, et al. Total serum magnesium levels and calcium-to-magnesium ratio in sickle cell disease. Medicina (Kaunas) 2019;55(09):1–8
54 Claster S, Wood JC, Noetzli L, et al. Nutritional deficiencies in iron overloaded patients with hemoglobinopathies. Am J Hematol 2009;84(06):344–348
55 Bashir NA. Serum zinc and copper levels in sickle cell anaemia and β-thalassaemia in North Jordan. Ann Trop Paediatr 1995;15(04): 291–293
56 Oliveira PM, Póvoa LC, Oliveira MHCF, Pfeiffer WC. Study of zinc and growth hormone in sickle cell disease. J Pediatr Endocrinol Metab 2001;14(06):773–779
57 Durosinmi MA, Ojo JO, Oluwole AF, Akanle OA, Arshed W, Spyrou NM. Trace elements in sickle cell disease. J Radioanal Nucl Chem Article 1993;168(01):233–242
58 Elshal MF, Bernawi AE, Al-Ghamdy MA, Jalal JA. The association of bone mineral density and parathyroid hormone with serum magnesium in adult patients with sickle-cell anaemia. Arch Med Sci 2012;8(02):270–276
59 Emokpae MA, Fatimehin EB, Obazelu PA. Serum levels of copper, zinc and disease severity scores in sickle cell disease patients in Benin City, Nigeria. Afr Health Sci 2019;19(03): 2798–2805
60 Erhabor O, Ogar K, Erhabor T, Dangana A. Some haematological parameters, copper and selenium level among children of African descent with sickle cell disease in Specialist Hospital Sokoto, Nigeria. Hum Antibodies 2019;27(03):143–154
61 Ansari J, Gavins FNE. Ischemia-reperfusion injury in sickle cell disease: from basics to therapeutics. Am J Pathol 2019;189(04): 706–718
62 Granger DN, Kvietys PR. Reperfusion injury and reactive oxygen species: the evolution of a concept. Redox Biol 2015; 6:524–551
63 Reinier K, Rusinaru C, Chugh SS. Race, ethnicity, and the risk of sudden death. Trends Cardiovasc Med 2019;29(02):120–126
64 Osredkar J, Sustar N. Copper and zinc, biological role and significance of copper/zinc imbalance. J Clin Toxicol 2011; S3:001
65 Chirico EN, Pialoux V. Role of oxidative stress in the pathogenesis of sickle cell disease. IUBMB Life 2012;64(01):72–80
66 Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to meta-analysis. Statistics and Data Science 2009. Doi: 10.1002/9780470743386
67 Emokpae M, Tijani A. The impact of proteinuria on serum levels of trace elements in sickle cell disease patients. J Med Biomed Sci 2015;3(03):16–20
68 Zemel BS, Kawchak DA, Fung EB, Ohene-Frempong K, Stallings VA. Effect of zinc supplementation on growth and body composition in children with sickle cell disease. Am J Clin Nutr 2002;75(02): 300–307
69 PROSPERO is fast-tracking registration of protocols related to COVID-19. Accessed February 28, 2022 at: https://www.crd.york.ac.uk/prospero/
70 Prasad AS, Ortega J, Brewer GJ, Oberleas D, Schoomaker EB. Trace elements in sickle cell disease. JAMA 1976;235(22):2396–2398

 © 2022. Syrian American Medical Society. All rights reserved.