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Review Article

Role of Vitamin D on Endothelial Function and Erythropoiesis: Implications for Sickle Cell

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Received date: November 16, 2023; Accepted date: December 21, 2023; Published date: January 08, 2024

Citation: Tarimoboere Agbalalah, Peter Ella-Tongwiis (2024), Role of Vitamin D on Endothelial Function and Erythropoiesis: Implications for Sickle Cell, *J. Nutrition and Food Processing*, 7(1); **DOI:10.31579/2637-8914/178**

Abstract:

Endothelial dysfunction and chronic anaemia are key features of sickle cell disease (SCD), which significantly increases the risk of vaso-occlusive crises, pulmonary hypertension and stroke in affected individuals. Evidence indicates that vitamin D (VD), known for bone health, is linked to better endothelial function by increasing nitric oxide (NO) bioavailability, and promoting antioxidant and anti-inflammatory activities. It also regulates erythropoiesis by enhancing and prolonging red blood cell production and lifespan. VD deficiency is common in individuals affected by SCD, intensifying the already poor cardiovascular health. Up to date, only one study have investigated the effect of VD supplementation, and endothelial function outcome measures in SCD. The potential benefits of maintaining adequate circulating VD concentration in improving endothelial dysfunction and chronic anaemia would be of immense significance to affected individuals living in sub-Saharan Africa, who bear the greatest burden of the disease, with a substantial impact on morbidity and mortality. There is a lack of clinical data investigating the effect of VD on erythropoiesis in SCD. Therefore, this review aims to examine the current evidence regarding the influence of VD on both endothelial function and erythropoiesis and the clinical implications of enhancing endothelial function and erythropoiesis through VD supplementation in this at-risk group. A thorough search of databases, including PubMed, MEDLINE, and Google Scholar, was performed to gather relevant articles exploring the interplay between VD, endothelial function and erythropoiesis in SCD. Robust clinical evidence is warranted to show the impact of VD supplementation on improving endothelial function and erythropoiesis in SCD.

Key words: sickle cell disease; vitamin d; endothelial function; erythropoiesis; inflammation

Introduction

Sickle cell disease (SCD) is a general term for haemoglobinopathies consisting of at least one haemoglobin (Hb) S allele expressed as homozygous (HbS/S, most common and fatal), heterozygous (HbS/C, which is less severe), two phenotypes of sickle beta (β) thalassemia (HbS/β+ thalassemia and HbS/βo_thalassemia) and other rare forms such as HbS/D, HbS/O and HbS/E (Serjeant&Vichinsky, 2018). SCD is the most common monogenic and autosomal recessive disorder, impacting millions of people worldwide (Kato et al., 2018). While its global prevalence is uncertain, over 75% of Africans are affected, with the highest burden occurring in sub-Saharan Africa. It also affects individuals of Hispanic, Middle Eastern, and Mediterranean descent (Piel et al., 2013; Ware et al., 2017). Furthermore, SCD prevalence is rising steadily in Europe, USA, the UK, and other regions mainly due to migration (Roberts & Montalembert, 2007).

SCD results from a missense point mutation in the β-globin gene on chromosome 11, leading to a defective Hb structure resulting in the formation of sickle-shaped red blood cells (RBCs) (Serjeant & Vichinsky, 2018). Sickle RBCs undergo haemolysis, causing vaso-occlusion, reduced oxygen delivery, and increased inflammation, worsening complications (Reiter et al., 2002; Sundd et al., 2019). Low oxygen concentration cause abnormal HbS polymerisation, leading to increased haemolysis, free Hb and iron release, as well as reactive oxygen species (ROS) generation (Hebbel et al., 2004). Depleted nitric oxide (NO) due to released Hb disrupts vascular function, causing ischaemic reperfusion injury and increased ROS (Hebbel et al., 2020). Vaso-occlusion, inflammation, antioxidants reduction, and endothelial dysfunction contribute to vaso-occlusive crises, pain, renal dysfunction, acute chest syndrome, pulmonary hypertension, and stroke in SCD (Kassim & DeBaun, 2013; Meremikwu & Okomo, 2016). Managing inflammation,

endothelial dysfunction, and oxidative stress is crucial to alleviate SCD complications and improve quality of life despite limited access to comprehensive care due to high treatment costs.

Continuous erythropoiesis to compensate for frequent haemolysis and chronic inflammation in SCD leads to nutrient deficiencies (Hibbert et al., 2006; Claster et al., 2009), including vitamin D (VD) deficiency, which disrupts normal endothelial function (Brown et al., 2020) and erythropoiesis (Wu et al., 2005) regardless of age. Adequate VD may indirectly impact endothelial function through immune system modulation (Renke et al., 2023). Moreover, optimal circulating VD concentration may influence erythropoiesis by downregulating hepcidin (a peptide that regulates systemic iron levels, reducing iron absorption and release during times of iron sufficiency) and pro-inflammatory cytokines (Smith & Tangpricha, 2015). Thus, optimal VD may prevent and manage complications related to anaemia, endothelial dysfunction, inflammation, and oxidative stress in SCD individuals. Due to the high prevalence of VD deficiency in this population, it is crucial to understand its influence on endothelial function and erythropoiesis. Exploring the clinical implications of enhancing endothelial function and erythropoiesis through VD supplementation in this at-risk group is of significant importance.

Literature search

A comprehensive search of PubMed, MEDLINE, and Google Scholar databases, was conducted to gather relevant articles exploring the role of vitamin D on endothelial function and erythropoiesis in SCD. Several search terms were employed, including "vitamin D3," vitamin D2 "SCD," "global prevalence of SCD," Impact of SCD on Erythropoiesis and endothelial dysfunction." Additionally, specific searches were conducted to investigate vitamin D deficiency in SCD and the influence of vitamin D on erythropoiesis. The search did not impose any restrictions on publication dates, and only articles written in English were included in the search results.

Impact of SCD on erythropoiesis

In SCD, RBC production (erythropoiesis) is disrupted, leading to a shorter lifespan and premature rupture of sickle-shaped RBCs (haemolysis) compared to healthy RBCs (Zheng et al., 2021). This constant breakdown causes chronic anaemia, resulting in fatigue and weakness (Zheng et al., 2021). The body compensates by releasing erythropoietin, a hormone released by the kidneys in response to low oxygen levels in the blood, but the process becomes inefficient, leading to bone marrow hyperplasia, bone pain, and complications (Wu et al., 2016) (Fig.1). Sickle-shaped RBCs block small blood vessels, further stressing the bone marrow, and triggering tissue hypoxia (Wu et al., 2016). Infections or triggers can suppress erythropoiesis temporarily, leading to an aplastic crisis and worsening anaemia (Hankins et al., 2016). In response, the bone marrow releases less functional reticulocytes into the bloodstream, contributing to higher circulating levels of reticulocytes (Gallivan et al., 2023). Understanding these disruptions in RBC production helps manage the complications of SCD.

Impact of SCD on Endothelial function

Endothelium

The vascular endothelium acts as an endocrine, paracrine, and autocrine system (Lu et al., 2021). It is composed of a single layer of cells, lining the inner surface of blood vessels, including arteries, veins, and capillaries (Wang et al., 2022). The endothelium serves as both a structural and functional barrier between blood and the vessel wall, playing an essential role in maintaining vascular health through various physiological processes (Marti et al., 2012). The endothelium regulates vascular tone and blood pressure while ensuring adequate perfusion to tissues and organs by releasing vasoactive substances like NO, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF) (Dalan et al., 2016). It inhibits platelet activation and aggregation, preventing blood clot formation, and maintains blood fluidity through the production of plasminogen activator, that possess anticoagulant and fibrinolytic properties (Gorog et al., 2022). The endothelium possesses anti-inflammatory and anti-oxidant properties, protecting blood vessel walls from damage and maintaining vascular function. Additionally, it plays a role in angiogenesis, essential for tissue repair and wound healing (Rajendran et al., 2013).

Endothelial dysfunction in SCD

Endothelial cells are implicated in the development and progression of atherosclerosis, as endothelial dysfunction is the initial abnormality observed in the arterial wall (Kassi et al., 2013). Endothelial dysfunction is characterised by changes in endothelial cells that result in reduced NO generation, increased ROS production, and high pro-inflammatory and prothrombotic states (Kassi et al., 2013). This dysfunction impairs the ability of endothelial cells' to prevent clotting, leading to increased production of tissue factor and plasminogen activator inhibitor-1, both associated with a higher risk of thrombosis and atherosclerosis (Brewer et al., 2011).

Endothelial dysfunction is critical to the pathogenesis of SCD. It impairs capillary function, compromising tissue oxygenation and nutrient supply, leading to complications that promote organ damage (Hebbel et al., 2020). It also leads to reduced NO availability, contributing to platelet aggregation and vasoconstriction (Park & Park, 2015), while also triggering the release of inflammatory mediators and increasing oxidative stress, promoting atherosclerosis and other vascular complications (Mohammed et al., 2010). It significantly heightens the risk of stroke, acute chest syndrome and pulmonary hypertension which are highly prevalent in SCD Fig.1 (Abdullahi et al., 2022; Potoka & Gladwin, 2015). This dysfunction is observed in SCD both during crisis (Jutant et al., 2021), and in steady-state conditions (Ayoola et al., 2020). This dysfunction has been demonstrated in both children and adolescents (Teixeira et al., 2017), and in adults with SCD (Ayoola et al., 2020). Implementing nutritional strategies aimed at reducing inflammation, mitigating oxidative stress, and modulating adhesion molecule expression, while also enhancing NO bioavailability, holds promise in improving endothelial function and overall outcomes in SCD. This approach has the potential to alleviate endothelial dysfunction and its associated complications in SCD, leading to improved overall health and well-being for affected individuals.

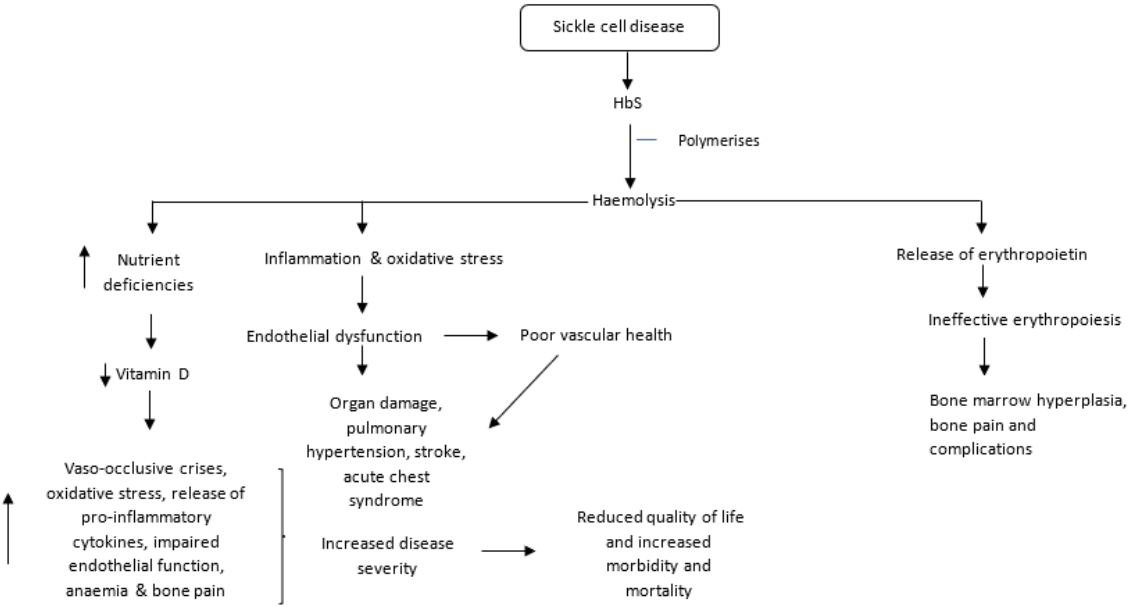

Figure 1. Role of sickle cell disease (SCD) on endothelial function and erythropoiesis. SCD leads to endothelial dysfunction, chronic anaemia and reduced circulating vitamin D levels. This leads to vaso-occlusive crises, oxidative stress, inflammation, bone pain and organ damage, resulting in increased morbidity and mortality, and reduced quality of life. Complications include pulmonary hypertension, stroke, and acute chest syndrome. Addressing endothelial dysfunction is crucial for better outcomes.

Vitamin D

VD is a fat-soluble hormone obtained from sun exposure, diet, and supplements. It is converted to 25-hydroxyvitamin D (25OHD) in the liver and then to its active form, calcitriol (1, 25 (OH) 2D), in kidney cells (Bahrami et al., 2018; Holick, 2010). VD maintains calcium and phosphorus homeostasis. It also has non-skeletal functions due to VD receptors (VDR) present in various tissues and cells, including bone marrow, endothelial and erythroid cells, suggesting potential direct effects on vascular health and erythropoiesis (Lumme, 2022).

Vitamin D deficiency in SCD

VD deficiency is common in SCD children and adults (Sahu et al., 2022). The results of a meta-analysis of 26 studies revealed that the global prevalence of VD deficiency in SCD is 60% (Sahu et al., 2022). This deficiency could arise from multiple factors in this population, one being, diminished nutrient absorption caused by intestinal mucosa damage (Mandese et al., 2019). Additionally, SCD patients experience lower nitrogen economy and heightened protein turnover due to increased demands for erythropoiesis. This can lead to kidney failure and a high risk of developing VD deficiency (Borel et al., 1998; Cordovil et al., 2022). Moreover, levels of VD binding protein could be decreased in SCD (Hama et al., 2021; Mandese et al., 2019). Studies have reported an association between VD deficiency and higher incidence of vaso-occlusive crises and disease severity in SCD (Brown et al., 2020; McCaskill et al., 2018). Thus, adequate levels of VD is essential for this at risk population.

Potential mechanisms by which VD impacts endothelial function

VD possesses a range of vaso-protective effects that impact vascular health. These effects include, improving NO release, inhibiting vascular smooth muscle cell proliferation and migration, and down-regulating the inflammatory process Fig.2 (Witham et al., 2012). Additionally, it indirectly protects against atherosclerosis by reducing insulin resistance, improving lipid profiles, and regulating blood pressure parameters (Holt et al., 2022; Schmitt et al., 2023). By exerting these multifaceted effects, vitamin D plays a crucial role in maintaining vascular function and reducing the risk of cardiovascular complications.

Vitamin D Supplementation on endothelial function, inflammation and oxidative stress in SCD.

It is important to conduct research on the effects of VD supplementation on endothelial function in SCD. This will validate its potential in improving endothelial dysfunction, reducing the risk of stroke and pulmonary hypertension, and enhancing the quality of life for this population, considering its overall health benefits. However, limited studies currently exist on the impact of VD on endothelial function in SCD. Randomised controlled trials (RCTs) have reported positive effects of VD on endothelial function in different populations, including those with cardiovascular diseases (Harris et al., 2011; Witham et al., 2012). However, as of now, only one trial has been conducted in the SCD population (Lintel et al., 2015). In the pilot study by Lintel et al. (2015), SCD patients showed improved endothelial function after receiving 100,000 IU of VD2 weekly for 8 weeks. More research in this area is needed to further explore its potential benefits.

However, studies evaluating the effect of VD on inflammatory markers in SCD patients have been conducted. One RCT in 62 SCD children found that high-dose VD3 (100,000 IU/month) led to reductions in various pro-inflammatory markers (Lee et al., 2019). Another RCT in SCD children reported that 2000 IU/day of VD3 lowered pro-inflammatory cytokines and improved anti-inflammatory cytokines (Adegoke et al., 2017). By reducing inflammatory markers, VD may attenuate the systemic inflammation associated with SCD, which can positively impact endothelial function in this population. However, as of now, there is no RCT showing that VD supplementation improves oxidative stress markers in SCD. More RCTs are needed to investigate the impact of VD supplementation on oxidative stress in SCD. This research could provide

valuable insights into its role in managing oxidative stress and its implications for the overall health and well-being of SCD individuals.

Vitamin D and Erythropoiesis

There is evidence that VD may be protective against anaemia by stimulating erythropoiesis, due to the presence of its receptors in the bone marrow and on erythroid cells (Yoo & Cho, 2015). Observational studies have indicated an inverse association between circulating VD concentration and anaemia in adults (Lucisano et al., 2014; Yoo & Cho, 2015). VD deficiency has also been reported in children, adolescents, and adults with iron-deficiency anaemia (Suh et al., 2016). Additionally, a meta-analysis of observational studies, found VD deficiency to be associated with a 64% higher risk of developing anaemia compared to VD sufficient individuals (Liu et al., 2015).

These observational studies proposed that VD supplementation may improve Hb levels. A recent RCT found that administering 8000 IU VD3 daily for 12 weeks led to beneficial effects on erythropoiesis and iron availability in chronic kidney disease (CKD) patients with low baseline VD concentration compared to the placebo group (Pistis et al., 2023). However, a meta-analysis of RCTs, in which participants received 20 to 500,000 IU VD3 did not find a significant effect on Hb levels overall, but observed a significant effect on transferrin saturation and iron levels (Arabi et al., 2020). The RCTs reported in this meta-analysis may not have found a significant impact of different doses of VD on Hb and ferritin levels due to the high heterogeneity of the combined studies (Arabi et al., 2020). To the best of our knowledge, no RCT has been conducted in SCD population.

Potential mechanisms by which vitamin D impacts erythropoiesis

VD impacts erythropoiesis through various mechanisms. First, it downregulates hepcidin mRNA expression, reducing iron absorption and release during iron sufficiency (Smith & Tangpricha, 2015). Second, VD enhances burst-forming unit-erythroid proliferation, collaborating with erythropoietin to promote erythroid progenitor cell proliferation fig.2 (Aucella et al., 2003), and reduce erythropoiesis-stimulating agent (ESA) requirements in CKD patients (Kiss et al., 2011). Furthermore, VD may stimulate bone marrow function, maturation and proliferation of erythroid progenitor cells and increasing erythropoietin production (Borojević et al., 2022). Lastly, VD's anti-inflammatory effects, downregulate the release of pro-inflammatory cytokines, increasing iron availability for erythropoiesis (Zughaier et al., 2014).

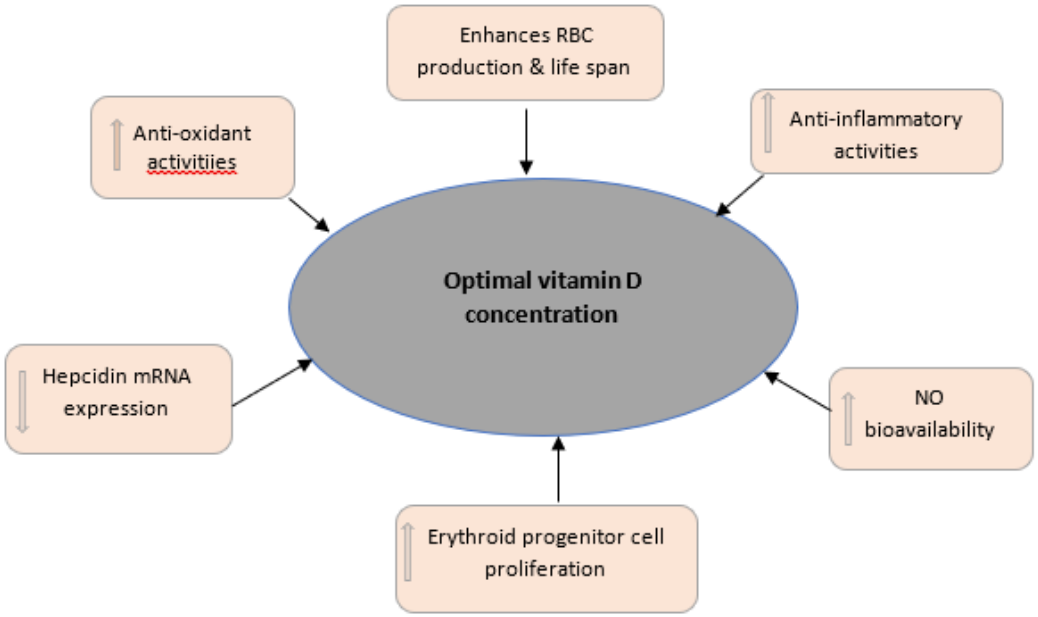

Figure 2: Optimal circulating vitamin D concentration positively impacts both endothelial function and erythropoiesis by improving NO bioavailability, anti-oxidant and anti-inflammatory activities; enhancing RBC production & life span, and increasing erythroid progenitor cell proliferation. Vitamin D also down regulates hepcidin mRNA expression.

What are the implications for SCD?

This review suggests that maintaining sufficient VD levels could be beneficial as a complementary therapy for managing endothelial dysfunction and anaemia in SCD. Future interventional trials should explore the clinical efficacy and safety of VD supplementation in SCD patients to enhance endothelial function, improve erythropoiesis, and reduce vaso-occlusive crises and related complications. Identifying and treating VD deficiency early on could provide a new approach to optimize vascular health and manage anaemia in SCD, ultimately leading to improved cardiovascular health and patient outcomes. As SCD is a heterogeneous disorder, genetic variations in genes related to endothelial function and inflammation could contribute to endothelial dysfunction in SCD. Polymorphisms in genes involved in NO production, adhesion molecules, and inflammation pathways may also influence the severity of endothelial dysfunction and the progression of the disease. Thus, understanding this polymorphisms in this population is important.

The potential benefits of maintaining optimal circulating VD concentrations in order to improve endothelial dysfunction in SCD are crucial, particularly for those living in sub-Saharan Africa, where the disease burden is highest. SCD significantly impacts morbidity and mortality in this region. Given the high prevalence of VD deficiency

among SCD individuals, it could further worsen the already compromised endothelial function. Understanding the potential role of VD in alleviating endothelial dysfunction, offers a cost-effective and accessible intervention that can be easily integrated into existing public health programs. By incorporating VD supplementation as part of standard care, this study can directly enhance the health outcomes and quality of life for SCD individuals in the region. This empowers affected individuals and healthcare providers in sub-Saharan Africa to combat the devastating effects of SCD more effectively.

VD's positive impact on endothelial function has significant implications for reducing the high risk of pulmonary hypertension and stroke in affected individuals. In SCD, chronic haemolysis and endothelial dysfunction increase the workload on the pulmonary vasculature, leading to pulmonary hypertension. By enhancing endothelial function, VD may improve NO production and vasodilation, mitigating the progression of pulmonary hypertension in SCD patients.

SCD individuals have an increased propensity for vaso-occlusive events, predisposing them to a high risk of stroke, resulting in ischaemia and infarction in the brain. Impaired endothelial function leads to reduced cerebral blood flow, increased platelet activation, and enhanced inflammation, all contributing to the occurrence of strokes. VD's potential anti-inflammatory and vasodilatory effects may attenuate the underlying mechanisms that lead to stroke, thereby reducing the frequency and severity of cerebrovascular events in SCD.

Considering the high prevalence of pulmonary hypertension and stroke in SCD, particularly in sub-Saharan Africa with limited access to specialised medical care, incorporating VD supplementation as an adjunct therapy could help reduce the burden of these life-threatening complications. By addressing endothelial dysfunction, VD intervention may lead to improved outcomes and enhanced quality of life for individuals affected by SCD in the region. However, further interventional trials and clinical studies are needed to fully substantiate these potential benefits and provide evidence-based guidelines for implementing VD supplementation as a preventive measure against pulmonary hypertension and stroke in SCD.

SCD, being a chronic haemolytic disorder, may benefit from the potential role of VD in regulating erythropoiesis. Optimal VD concentration may enhance and prolong RBC production and lifespan, indirectly influencing the frequency and severity of vaso-occlusive crises, and improving overall health. Moreover, VD's impact on erythropoiesis and RBC health might lead to better immune function and infection control in this population. However, evidence on the direct role of VD in erythropoiesis regulation and its clinical implications in SCD is lacking. Further research, including RCTs and longitudinal studies, are necessary to establish the specific clinical benefits and appropriate dosing regimens of VD supplementation for SCD patients. Until then, healthcare providers should consider individual patient needs and consult the latest clinical guidelines when considering VD supplementation as part of the management strategy for SCD patients.

Future Directions and Challenges

Despite potential benefits, more research is needed to establish the efficacy and safety of VD supplementation for SCD. Robust clinical evidence is lacking to directly show the impact of VD supplementation on improving endothelial function and clinical outcomes in SCD. Well-designed clinical trials are necessary to evaluate its efficacy in reducing crises and complications in SCD. Clinical trials are essential to determine the appropriate dosage, considering factors like age, body weight, baseline VD levels and clinical manifestation. It is also crucial to investigate the duration needed to achieve and maintain optimal VD concentration and its long-term effects on clinical outcomes. This would provide valuable insights into the specific effects of VD on endothelial function in SCD patients. This research could uncover underlying mechanisms, identify potential biomarkers, and clarify the pathways through which VD influences endothelial function in this population. Such knowledge is crucial for developing targeted interventions and improving SCD management.

Factors like different SCD phenotypes, individual variability, potential interactions between VD and SCD disease-modifying medications, and how underlying health conditions can influence VD absorption, metabolism, and utilisation in SCD individuals. A personalized approach, considering these factors, allows healthcare providers to tailor the dosage and minimize the risk of adverse effects. Overall, further research is crucial to improve clinical understanding, inform interventions, enhance patient care, and contribute to advancing knowledge and implementation of VD supplementation in managing endothelial dysfunction and improving outcomes.

The existing literature on SCD population is scarce, posing challenges in establishing strong research objectives. Several factors contribute to this lack of evidence: SCD is predominant in resource-poor sub-Saharan Africa, where limited healthcare resources, including providers, diagnostic tools, and medications, result in high treatment costs and complications. Political instability and conflict disrupt healthcare services, making consistent care difficult for SCD patients in the region. Conducting large-scale RCTs in sub-Saharan Africa may be challenging due to these obstacles. Additionally, the lack of dedicated funding for investigating the impact of VD on endothelial function in SCD patients may result in fewer studies being conducted in this area, exacerbating the dearth of evidence.

Conclusion

Endothelial dysfunction and ineffective erythropoiesis contributes to severe anaemia and vaso-occlusive crises, impaired blood flow, and increased risk of cardiovascular disease complications. VD has demonstrated anti-inflammatory and anti-oxidative properties, promotes NO production which may help mitigate anaemia and endothelial dysfunction in SCD. While preclinical and observational studies provide promising insights, there is a need for further research and personalised approaches to optimise clinical management for this population. These approaches should consider the heterogeneity of the disease, and tailor interventions to individual needs, incorporate predictive and prognostic markers, optimise supportive care, enable prevention and early intervention, and engage patients in shared decision-making. By embracing personalised strategies, healthcare providers can enhance outcomes, improve patient satisfaction, and pave the way for more effective and patient-centered care in SCD.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

None.

Author contribution

TA conceived the idea, conducted the literature search, designed the figures and produced the initial draft of the manuscript and. TA and PET

reviewed and edited the initial draft of the manuscript. All authors approved the final draft for submission.

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DOI:10.31579/2637-8914/178