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Vitamin D status in relation to systemic and intestinal inflammation in undernourished children, 6–59 months old: Design and rationale of a non-controlled open label trial

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ABSTRACT

Background: vitamin D deficiency is prevalent in undernourished children, even in countries with abundant sunshine. Child undernutrition is known to be associated with elevated markers of systemic and intestinal inflammation, which in turn have been related to vitamin D (vitD) status. Furthermore, vitD status has shown to be potentially associated with iron status because of shared inflammatory mechanisms. Considering the anti-inflammatory benefits of vitD, it is likely that the co-existence of high inflammation and poor iron status in undernourished children may be related to vitD status. Hence, supplementation of vitD may potentially reduce inflammation and improve the iron status of undernourished children. However, knowledge of this is limited.
Objectives and methods: to assess the (1) association of vitD status with systemic and intestinal inflammation and iron status in undernourished children, (2) effect of vitD supplementation on systemic and intestinal inflammation and iron status, and (3) predictors of vitD status. Undernourished (experimental) and non-undernourished (controls) children, 6–59 months, are recruited from clinics in the JB Marks Municipality, South Africa. At baseline participant's dietary vitD intake, sunshine exposure, anthropometry, medication and nutritional supplement history are assessed. 2 mL of venous blood is collected for 25(OH)D, inflammation and iron status assessment before and after the supplementation of three doses of 50,000 IU/week of vitD.
Anticipated results and conclusion: this trial will provide insights into the potential role of vitD in resolving inflammation and improving iron status in undernourished children, which will contribute to informing optimal strategies for advancing the treatment of child undernutrition.

1. Introduction

Vitamin D deficiency (VDD) is emerging as a common problem worldwide [1]. In Africa, a high prevalence of 60% has been reported for serum 25(OH)D concentration <30 ng/mL across 23 African countries [2]. Over the past few decades, several researchers have provided evidence of the extra-skeletal benefits of vitamin D (vitD) in optimising immune function, protecting against respiratory infections and improving growth and development in low birth weight and undernourished children [3–6]. Undernourished children have multiple micronutrient deficiencies, which alter optimal immune function and growth. Although vitD is not emphasised in the management of undernutrition in children, studies have shown the prevalence of its deficiency in these children in countries with abundant sunshine, and has been associated with underweight, wasting and stunting [7–10].

The topic of VDD in undernourished children is not new. A study in the early 1980s reported significantly lower concentrations of serum 25 (OH)D and the common incidence of rickets in undernourished compared to well-nourished children [11]. It is therefore surprising that the vitamin has not received more attention in the management of undernourished children over the years. This could be due to the popular assumption that VDD may not be an issue of concern in regions with

Abbreviations: AGP, alpha-1-acid glycoprotein; CRP, C-reactive protein; FGF21, fibroblast growth factor 21; HAZ, height-for-age z-score; Hb, Haemoglobin; IBD, inflammatory bowel disease; IFABP, intestinal fatty acid binding protein; IGF-1, insulin-like growth factor-1; IL, interleukin; MUAC, mid-upper arm circumference; sCD14, soluble cluster of differentiation 14; sTfR, soluble transferrin receptor; VDD, vitamin D deficiency; VitD, Vitamin D; WHZ, weight-for-height z-score; WAZ, weight-for-age z-score.

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abundant sunshine [2]. Recent literature has however shown that aside from sunlight exposure, other factors such as inflammation, poor nutrition, impaired intestinal absorption, and long-term use of certain medications largely influence vitD status [12–15].

Chronic systemic and intestinal inflammation and iron deficiency, which are prevalent in undernourished children, have been observed to be associated with VDD [12,16,17]. Elevated inflammation is conceived to be contributory to VDD by down regulating the conversion of vitD to 25(OH)D and increasing the depletion of 25(OH)D, leading to VDD [12, 18,19]. 25(OH)D is the most abundant vitD metabolite in serum and its concentration is a measure of vitD status. (*Additional information on vitD metabolism is provided in supplementary material*). On the contrary, VDD may contribute to heightened inflammation, as vitD is known to inhibit pro-inflammatory cytokines [20,21]. Furthermore, several studies have shown a reduction in the biomarkers of systemic and intestinal inflammation with vitD supplementation in inflammatory bowel disease (IBD) and tuberculosis, indicating that vitD plays a critical role in the inflammatory process, and its resolution [20–22]. Studies have also reported the immune-modulating benefits of vitD supplementation in preventing infections such as acute respiratory tract infections in children [4] and improvement of iron status through reduction of IL-6 and hepcidin in children with IBD [23]. Additionally, the beneficial role of vitD in improving the growth and development of undernourished and low birthweight children has been reported in earlier studies [5,6].

In undernourished children, elevated chronic systemic and intestinal inflammation caused by recurring infections due to compromised immune function and poor environmental sanitary conditions, is associated with impaired nutrient absorption, increased depletion of micronutrients, iron deficiency, growth hormone resistance, growth faltering and ultimately a continuous cycle of undernutrition [24–26]. Considering the anti-inflammatory and growth modulating benefits of vitD, it stands to reason that vitD status could be related to the systemic and intestinal inflammation and iron status of undernourished children. There is also the possibility of inflammation reduction and an improvement in iron status with vitD supplementation in undernourished children. This, however is unknown and worth investigating.

Apart from inflammation, the vitD status of undernourished children may be influenced by poor dietary intake and impaired vitD absorption in the gastrointestinal tract due to intestinal inflammation and reduced bile synthesis [27,28]. Furthermore, reduced exposure to sunlight due to weakness and limited mobility, may be contributory factors to VDD in undernourished children. Understanding the contribution of the different predictors of vitD status in undernourished children in the South African context will inform the right approach to the correction of vitD insufficiency/deficiency.

In view of the detrimental effect of elevated systemic and intestinal inflammation on child growth and its ability to undermine the impact of nutritional therapy, it is important to investigate and understand the potential benefit of vitD supplementation in reducing inflammation and improving the iron status of undernourished children. The conceptual framework of the hypothesised determinants of vitD status and the interrelationship between inflammation and vitD status in

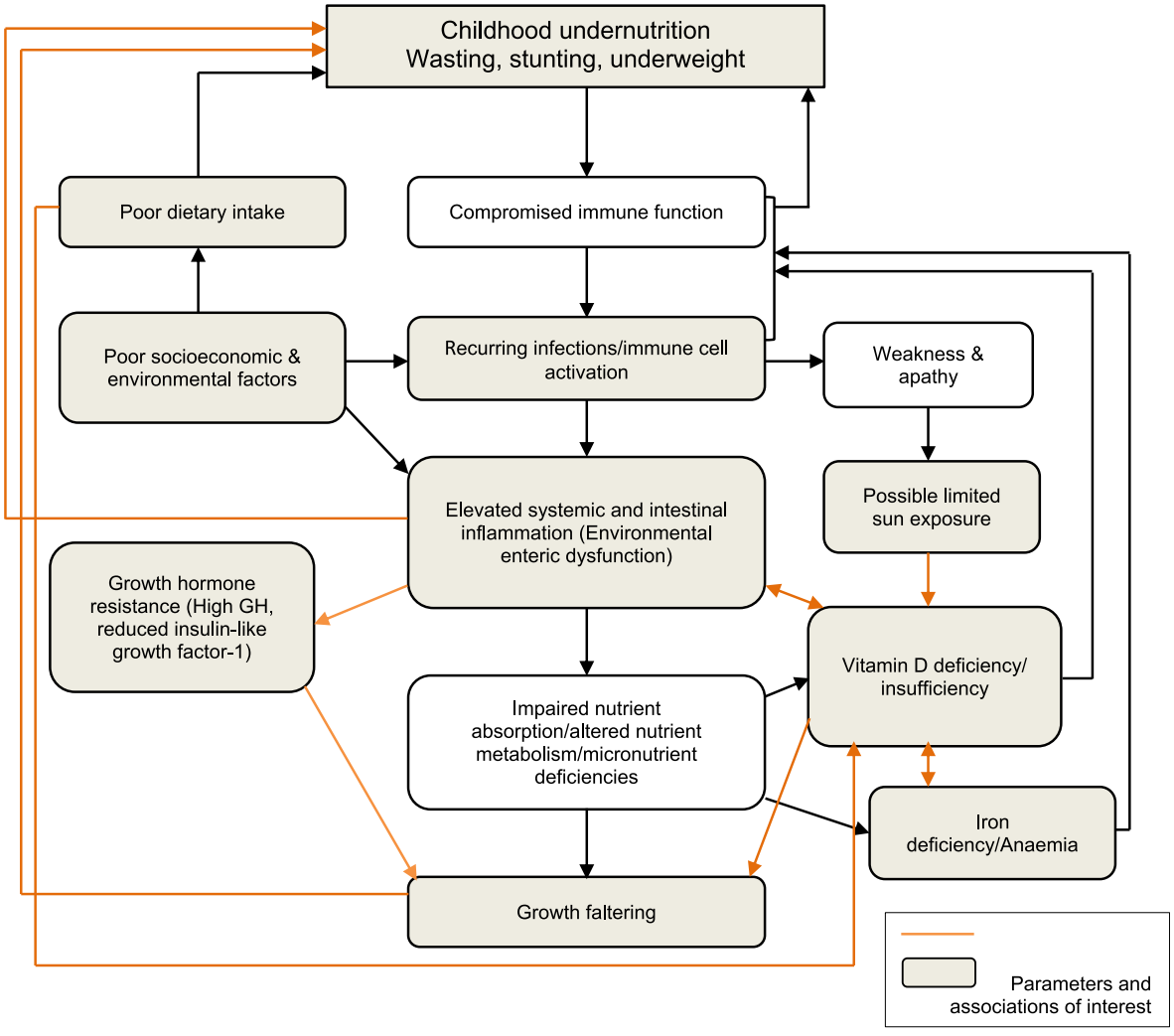


Fig. 1. Conceptual framework of study rationale and parameters of interest: predictors of vitamin D status in undernourished children.

undernourishment is illustrated in Fig. 1.

This trial will provide insights into the prevalence of VDD in undernourished children and how it associates with to systemic and intestinal inflammation and iron status, as well as the effect of vitD supplementation on inflammation and iron status.

1.1. Aims of the study

This study aims to, in undernourished compared to apparently healthy non-undernourished children, 6–59 months, (1) investigate the association of vitD status with systemic and intestinal inflammation (2) assess the effect of 3 doses of 50,000 IU/week of vitD on systemic and intestinal inflammation, iron status and anaemia in vitD insufficient children and (3) investigate the predictors of vitD status.

2. Methods

2.1. Study design and setting

This is a non-controlled open label experimental study which, includes children aged 6–59 months with moderate or severe undernutrition (wasting, underweight or stunting) (experimental group) and apparently healthy non-undernourished children (control group). The study involves two phases (Fig. 2).

Recruited participants are screened for wasting, underweight or stunting or non-undernutrition and comorbidities for inclusion and enrolment into phase 1 of the study. After enrolment, study questionnaires are administered, and a 2 mL venous blood sample is collected from participants for the analysis of 25(OH)D, markers of inflammation and iron status. Participants in both study groups who are vitD deficient (serum 25(OH)D $<$ 20 ng/mL) or insufficient (25(OH)D $<$ 30 ng/mL) are enrolled into phase 2 of the study, which is a single-arm pre-post supplementation trial to receive 3 doses of 50,000 IU/week of vitD. On day 21 after supplementation, a repeat venous blood sample is collected to investigate the effect of the supplement on vitD status, intestinal and systemic inflammation and iron status. Participants are given a $\pm$ 2-day window period for the weekly supplementation appointment and post-supplementation blood collection.

MUAC: Mid-upper arm circumference; WHZ: Weight-for-height z-score; WAZ: Weight-for-age z-score; HAZ: Height-for-age z-score; Hb: Haemoglobin; CRP: C-reactive protein; AGP: alpha-1-acid glycoprotein; IFABP: intestinal fatty acid binding protein; IGF-1: Insulin-like growth factor-1; sCD14: soluble cluster of differentiation 14; sTfR: soluble transferrin receptor; FGF21: fibroblast growth factor 21.

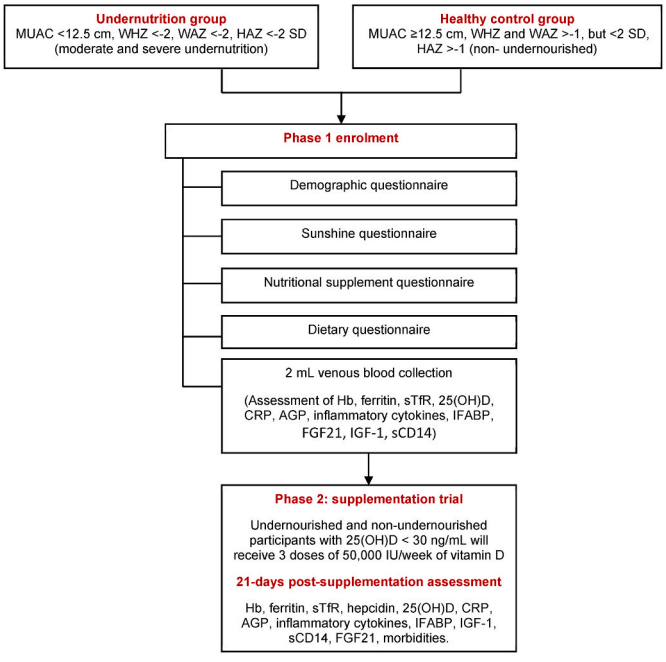


Fig. 2. Study design.

2.2. Study setting and population

The study is conducted in six primary healthcare community clinics in the JB Marks Municipality of the North-West Province, South Africa. These community healthcare facilities run maternal and child health clinics where children receive immunisations and growth monitoring. Potential study participants, i.e. all children aged 6–59 months reporting to the clinics for immunisation or growth monitoring, are screened for comorbidities and nutritional status after parental consent is obtained. All the research procedures are performed in a fully equipped mobile clinic which is stationed at the premises of the healthcare facilities to ensure privacy of participants.

2.3. Inclusion criteria

Undernutrition group: (i) age 6–59 months; (ii) mid-upper arm circumference (MUAC) $<$ 12.5 cm; and/or (iii) z-score of weight-for-height (WHZ), weight-for-age (WAZ) and height-for-age (HAZ) $<$ -2 SD (iv) and/or bilateral pitting oedema (+ or ++); (v) no medical complications. **Healthy group**: (i) age 6–59 months; (ii) MUAC $\geq$ 12.5 cm and (iii) WHZ and WAZ $>$ -1 SD but $<$ 2 SD and (iv) HAZ $>$ -1 SD.

2.4. Exclusion criteria

In both study groups, children are excluded if they have (i) fever (axillary temperature $>$ 38 °C); (ii) persistent cough in the past 2 weeks; (iii) persistent diarrhoea or vomiting in the past 3 days; (iv) intake of medications including anticonvulsants (phenobarbital, carbamazepine, phenytoin), antibiotics (rifampicin, isoniazid, etc.), antiretroviral medications (protease inhibitors and non-nucleoside reverse transcriptase inhibitors; e.g. efavirenz, darunavir and ritonavir; (v) medical record diagnosis of conditions associated with vitD hypersensitivity (i.e. sarcoidosis, primary hyperparathyroidism); (vi) children already receiving treatment for VDD; (vii) liver and kidney disease; (viii) blood transfusion in the last month.

2.5. Informed consent and recruitment

Consecutive sampling is used, hence all children visiting the clinics for growth monitoring or immunisation are invited to participate and recruited after informed consent is obtained. In the waiting area of the maternal and child health units, parents/guardians are verbally informed about the study by the field workers. Interested parents are then given the information leaflet of the study. Written consent is obtained from interested parents/guardians for screening their children for eligibility and enrolment into the study. The screening involves measurement of MUAC, weight and length/height, comorbidity assessment and the review of the participant's medical record for clinical history. Eligible children are enrolled into phase 1 of the study. 2 mL of venous blood is collected and study questionnaires administered. VitD deficient or insufficient participants are enrolled into phase 2 of the study for supplementation. Recruitment commenced in May 2022 and is expected to end by January 2023.

2.6. Data collection and study implementation

Measurements and time points of data collection are summarised in Table 1. Data are collected by qualified health professionals and trained field workers.

Table 1
Schedule of study activities.

Study procedure	Phase 1		Phase 2 (supplementation)			
	Recruitment and screening	Enrolment	Week 1 (1st dose)	Week 2 (2nd dose)	Week 3. (3rd dose)	Week 4 (post-supplementation)
Informed consent	X					
MUAC	X					
Weight	X					
Height/length	X					
Medical history	X					
Morbidity screening	X					X
Medication	X					X
Hb test		X				X
Socio-demographic information		X				
Sunshine exposure assessment		X				
Therapeutic nutrition/supplement intake data		X				X
Venous blood sample collection and aliquoting		X				X
50,000 IU Vitamin D supplementation in VDD children			X	X	X	
Biomarkers						
Hb		X				X
25(OH)D		X				X
IFABP		X				X
Ferritin, sTfR, hepcidin, CRP, AGP, cytokines, IGF-1, sCD14, FGF21		X				X

Hb: Haemoglobin; MUAC: Mid-upper arm circumference; IFABP: Intestinal fatty acid binding protein; CRP: C-reactive protein; AGP: Alpha-1-acid glycoprotein; IGF-1: Insulin-like growth factor-1; CD14: soluble cluster of differentiation 14; FGF21: fibroblast growth factor 21; sTfR: soluble transferrin receptor; VDD: Vitamin D deficiency.

2.6.1. Socio-demographic information

A structured questionnaire is used to collect information on the participants' date of birth and sex, as well as the educational level and household income of the parents/guardians and source of drinking water.

2.6.2. Anthropometric data

Weight, height/length and MUAC are measured according to the WHO, UNICEF 2019 recommendations for data collection, analysis and reporting on anthropometric indicators in children under 5 years old [29]. Weight is measured to the nearest 0.01 kg using a calibrated digital infant scale (Seca 727, Hamburg, Germany) for participants < 2 years and a digital weighing scale (Seca Robusta 813) for participants > 2 years who can stand. MUAC is measured with a standard non-stretchable colour–labelled tape to the nearest 0.1 cm. Recumbent length is measured to the nearest 0.1 cm using a length board (Seca model 416) in children < 2 years and those who cannot stand. Standing height is measured using a stadiometer (Seca 213 Stadiometer) in children > 2 years.

2.6.3. Medical history and morbidity data

Information on the medical history and morbidity symptoms present in the participants are collected from their medical records in addition to physical assessment by the study nurse. Morbidity symptoms assessed include fever, diarrhoea, cough and vomiting.

2.6.4. Medication and nutritional supplement data

Information on the medications, nutritional supplements and therapeutic foods (containing vitD) participants are taking is collected from their medical record by the study nurse during screening, phase 1 enrolment and post-supplementation.

2.6.5. Sunlight exposure

Information on the level and duration of exposure of participants to sunlight is collected using a structured sunlight exposure questionnaire in an interview with the parent. This questionnaire was adapted from the previously validated sunlight exposure questionnaires by Hanwel, 2010 and Alshahrani, 2014 [30,31]. The questionnaire assesses the duration of time spent outdoors each day ($<$ 15 min = 1; 15–30 min = 2; $\geq$ 30–60 min = 3; 1–2 h = 5 and $>$ 2 h = 5) and the level of skin exposure while outdoors (face and hands only = 1; face, hands and arms = 2; face, hands, arms and legs = 3; face, hands, arms, legs and upper body and thighs = 4). The number of days spent outdoors is also assessed as 1 day = 1; 2 days = 2; 3 days = 3; 4 days = 4 and $>$ 4 days = 5). A weekly sun exposure score is estimated as the product of time spent outdoors, level of skin exposure and the number of days spent outdoors in a week, with a maximum score of 100 and a minimum of 1. A weekly time in sun score is also estimated as the product of the time spent outdoors and the number of days in a week spent outdoors (maximum = 25; minimum = 1).

2.6.6. Dietary intake

Data on the dietary intake of vitD is assessed using a vitD-specific intake food frequency questionnaire (FFQ) adapted from two studies [32,33]. The adapted FFQ consists of fifteen (15) food items based on five food groups, namely fish and fish products, egg, milk and milk products, instant cereals and fat spreads. In addition to the 15 food items, the FFQ includes questions on the intake of multivitamins, cod liver oil, calcium and vitD supplements. The frequency of intake of vitD rich foods is ranked as daily (7x/week) = 7, 6–4x/week = 6, 3–2x/week = 5, 1x/week (4x/month) = 4, 3x/month = 3, 2x/month = 2, 1x/month = 1, and none = 0.

2.6.7. Venous blood sampling

A 2 mL venous blood sample is drawn from participants at phase-1 enrolment and post-supplementation into a serum-separating tube for biochemical analysis. The blood samples are centrifuged at 687 g for 10 min, and samples stored at 4 °C and transported within 4 h s to the Centre of Excellence for Nutrition (CEN) where the serum samples are aliquoted into 0.5 mL Eppendorf tubes and stored immediately at −80 °C until analysis.

2.7. Vitamin D supplement

In phase 2, participants in both groups receive 3 weekly doses of 50,000 IU of vitD3 in 1 mL of olive oil compounded by a registered pharmacist at Acupharm Retail and Compounding Pharmacy in Potchefstroom. One millilitre (50,000 IU) of the supplement is pre-packed in a

2 mL plastic syringe and stored at CEN under cool and dry conditions according to the manufacturer's instructions. The supplement is administered orally from the plastic syringe by the study nurse. Quality analyses of the supplement is performed during the study at Bio-industrial Services Laboratory Specialists to ensure that the concentration stays stable.

2.8. Outcome measurement and biochemical analysis

2.8.1. Vitamin D status

Pre- and post-supplementation vitD status (25(OH)D concentration) is measured in 350 μL of serum using chemiluminescence immunoassay standardised with the National Institute of Standards and Technology Standard Reference Materials 972a on Beckman DXI 800 [34,35].

2.8.2. Anaemia status

Haemoglobin (Hb) is measured on-site using a portable Hb 201+ HemoCue system (HemoCue Angelholm, Sweden) [36] at phase 1 enrolment and post-supplementation. Hb concentration will be adjusted for altitude, and anaemia will be defined as Hb $<$ 110 g/L [37].

2.8.3. Systemic and intestinal inflammation

Pre- and post-supplementation intestinal fatty acid binding protein (IFABP); an indirect marker of intestinal inflammation, C-reactive protein (CRP), alpha-1-acid glycoprotein (AGP), insulin-like growth factor (IGF-1), fibroblast growth factor (FGF) 21 and soluble cluster of differentiation (sCD) 14 will be measured in 5 μL of serum using the Q-Plex™ Human Environmental Enteric Dysfunction (11-Plex) kit from Quansys Biosciences (Logan, US) [38]. CRP and AGP are acute-phase proteins that serve as markers of inflammation or infection, although AGP is a better indicator of chronic inflammation [39]. Inflammation will be defined as CRP $>$ 5 mg/L and AGP $>$ 1 g/L [39]. IFABP is a marker of small intestine epithelial damage that has been associated with stunting and future risk of growth faltering [26]. sCD14 is an early marker of gut infection and serves as a measure of gut barrier dysfunction [40]. IGF-1 is a hormone which binds to growth hormone (GH) to promote tissue and bone growth. In undernutrition, there is GH resistance, characterized by elevated GH and lower IGF-1 levels. FGF21 is an endocrine hormone that is indicative of GH resistance due to a reduced protein intake [41,42]. Serum cytokine (interleukin (IL) -1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, interferon-γ, tumour necrosis factor-α) will be analysed using Human Cytokine–Inflammation (9-Plex) from Quansys Bioscience (Logan, US) in 25 μL of serum [43].

2.8.4. Iron status

Ferritin and soluble transferrin receptor (sTfR) will be measured in 5 μL of serum using Q-Plex Human Environmental Enteric Dysfunction (11-Plex) kit [44]. Ferritin concentrations corrected for inflammation $<$12 μg/L will be defined as an indication of low iron stores and iron deficiency (ID) [45,46]. Ferritin, an intracellular protein that stores iron, is also affected by inflammation. Hence, ferritin concentration will be adjusted for inflammation using the BRINDA method, taking into account CRP $>$ 5 mg/L and AGP $>$ 1 g/L [47]. sTfR, is a carrier protein for transferrin and is needed for the import of iron into the cells. sTfR increases in ID and reflects the intensity of erythropoiesis and the demand for iron [45]. sTfR is less affected by inflammation but will also be adjusted for inflammation using the BRINDA method [47]. sTfR $>$ 8.3 mg/L will be defined as ID erythropoiesis [48]. Hb $<$ 110 g/L together with adjusted ferritin $<$ 12 μg/L or sTfR $>$ 8.3 mg/L will be an indication of ID anaemia [37]. Hepcidin will be measured using DRG Hepcidin 25 ELISA in 20 μL of serum [23].

2.9. Data management and analysis

2.9.1. Sample size calculation

The sample size was calculated for both phases of the study using G*power 3.1.9.2. The sample size for the cross-sectional analysis was based on two different primary outcomes; IL-8 and IL-6. Firstly, a significant inverse relationship between IL-8 and 25(OH)D reported in the literature, with a correlation coefficient of −0.24 was used [49]. The calculation was based on correlation (bivariate normal model), 5% probability of error and a power of 80% and an effect size between 0.1 and 0.3, according to the aforementioned literature. Considering an effect size of 0.21, a total of 175 participants will be required. The second calculation was performed considering two tailed t-tests (difference between two independent means), an effect size of 0.5 [49], a 5% probability of error, 80% power, 0.5 effect size, and an allocation ratio of 2.5. A total sample size of 156 (111 in group 1 and 45 in group 2) will be required. Considering both calculations, a sample size of at least 175 participants with 125 in the undernutrition and 50 in the control group, will be required to have statistical power to detect an association between IL-8/IL-6 and vitD status. The sample size for the supplementation trial was calculated based on the change in 25(OH)D after supplementation of 3 times 50,000 IU over a 3-week period, with an effect size of 2.5 from literature [49]. Since the number of participants enrolled into the trial will be dependent on the number of vitD insufficient children obtained from the phase-1, this analysis was explorative. The calculation was based on Wilcoxon signed rank test (matched pairs) and 5% probability of error, 80% power and an effect size of 0.8. A minimum of 15 participants will be required. Hence, a minimum of 20 participants must be included in the trial to account for a 30% dropout rate.

2.9.2. Data management

Data is managed by an assigned data manager. Raw data is captured electronically into Microsoft Access and password-protected and backed up daily. All data, both electronic and hard copies, are anonymised. Documents linking the identity of participants to their unique participant number are detached and kept separately by the principal investigator. To ensure the quality and reliability of data, all data, are cross-checked for possible errors.

2.9.3. Data analysis

The electronic data will be checked for outliers and mistakes corrected where possible by referring to the original hard copies. Participant characteristics will be described using position and dispersion measures according to the test of normality assessed by the Kolmogorov-Smirnov test, the QQ plot and histogram plot visual inspection. Normality will be attempted with transformation applied to continuous non-normally distributed variables before analysis [50]. Multiple linear and logistic regression will be used to describe the association between exposure variables and 25(OH)D in the cross-sectional study. 25(OH)D and markers of inflammation and iron status will be compared between groups using one-way ANCOVA, adjusting for potential covariates such as age, sex and vitD intake. Prospective analyses to compare pre-vs post-supplementation biomarkers will be done using dependent t-tests if data are normal or Wilcoxon matched-pairs signed rank tests if data are skew. Statistical analyses will be conducted with SPSS version 27 and SAS version 9.4. Type-I error rate will be set to 5% ($\alpha = 0.05$).

2.10. Ethical considerations

The study was approved by the North-West University Health Research Ethics Committee (NWU-00253-21-S1, NWU-00253-21-A1) and the National and North-West Department of Health of South Africa. Permission was obtained from the managers of all the clinics involved. The principles of the 2013 World Medical Association Declaration of Helsinki [51] are meticulously upheld in this study. As such, all data is anonymised and collected in confidence, ensuring the privacy of participants. No child is recruited without written informed consent from the parent/guardian. This trial is registered with the Pan African Clinical Trial Registry (PACTR202110646172601).

3. Anticipated results

Outcomes of this study will add valuable knowledge to the body of science and more importantly, provide an understanding of the association of vitD status with systemic and intestinal inflammation, iron status and growth faltering in undernourished children. The supplementation trial will provide insights into the potential role of vitD in resolving elevated inflammation and anaemia in undernourished children, which will contribute to informing optimal strategies for the improvement of undernutrition management in children. This study will further provide information on the prevalence of VDD in undernourished and healthy under-five children in the South African context. Additionally, knowledge gathered from this study will serve as foundational data for the implementation of a vitD intervention trial in children with complicated severe acute malnutrition.

4. Discussion

Child undernutrition continues to be a global health challenge, as 144, 85.2 and 47 million children under-five years are stunted, underweight and wasted, respectively, worldwide [52,53]. The greatest proportion of these children are found in Asia and Africa [54]. In sub-Saharan Africa, it is estimated that 12.1 million children are wasted while 57 million are stunted [52]. Child undernutrition results from inadequate intake or absorption of nutrients (both macro- and micronutrient), as well as increased nutrient utilisation due to frequent infections and chronic systemic inflammation caused by poor household and environmental hygienic conditions and weakened immune function [55,56]. It is also associated with chronic sub-clinical intestinal inflammation and altered gut structure and function; nutrient malabsorption; elevated systemic inflammation; micronutrient deficiencies including iron deficiency anaemia; and growth faltering (a condition termed as environmental enteric dysfunction) [27,57–61]. Furthermore, undernutrition results in developmental and cognitive delay and an increased risk of mortality in children [61,62].

VitD has shown some promise of improving the growth, motor and cognitive development of undernourished children and those born with low birth weight [5,6], augmenting iron homeostasis [23], improving immune function [63] and restoring intestinal integrity and systemic inflammation [20,64]. However, the potential benefit of vitD in the management of undernutrition has not been explored in Africa despite the prevalence of VDD among undernourished children on the continent. In a Tanzanian study, a 30.6% prevalence of VDD (i.e. serum 25 (OH)D $<$ 20 ng/mL) was observed among undernourished children. Among the children with severe wasting and marasmic-kwashiorkor, VDD prevalence was 41.9% and 16.2%, respectively [9]. Similar observations have been reported in Kenya and Uganda [8,10]. Considering the potential benefits of vitD, its deficiency could be related to elevated inflammation in undernourished children. It is also anticipated that undernourished children may benefit from the anti-inflammatory and growth-modulating properties of vitD. Currently, there is no information in this regard.

4.1. Limitations

This study has some limitations. This study includes undernourished children who are not sick, hence, the prevalence of VDD in the cohort of undernourished children who have additional medical complications or illnesses will be missed. Additionally, participants who are eligible for supplementation are invited for enrolment into phase 2 of the study on a later date. This arrangement could result in self-selection bias. Nonetheless, the study will provide information on the prevalence of VDD and insufficiency in undernourished and healthy non-undernourished under-five children in South Africa and help provide an understanding of the potential benefit of vitD to the undernourished child, which will inform the optimal intervention needed for improving the management of undernourished children. Furthermore, the study is not a randomised controlled trial, hence, we cannot measure the direct effect of the supplementation compared to a placebo or no supplementation. The long-term benefit of this study will be the provision of knowledge and evidence that will influence policy to improve the treatment and outcomes of children with undernutrition.

5. Conclusion

VDD may be associated with inflammation and iron status of undernourished children. VitD supplementation may be beneficial for inflammation resolution and improvement of iron status in these children.

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Roles and responsibilities of authors

JAC: conceptualised, designed, planned, developed trial methodology and implementing trial, and is responsible for the day to day management of the trial, writing - original draft, LM: conceptualisation, planning and development of the trial methods, writing - review and editing, MJL: conceptualisation, planning and development of the trial methods, writing - review and editing, RCD: conceptualisation, planning and development of the trial methods, writing - review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hnm.2022.200181.

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