A VITAMIN D INTERVENTION IN CHILDREN WITH SICKLE CELL DISEASE: A PILOT RANDOMISED CONTROLLED TRIAL

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INTRODUCTION

Sickle cell disease (SCD) is an inherited blood disorder affecting predominantly individuals of African descent and caused by a mutation in the gene encoding the β-globin protein, thereby resulting in its abnormal structure and hence dysfunctional red blood cells. Ultimately, such alterations lead to multi-system vaso-occlusion, for which the most common clinical manifestation is recurrent painful episodes. Moreover, patients with SCD cope with other complications including poor bone health, chronic systemic inflammation and impaired cell-mediated immunity, for which vitamin D deficiency is known as a potential contributing or exacerbating factor.

Vitamin D deficiency is particularly prevalent in children with SCD

Vitamin D deficiency is now recognized as one of the most common nutritional conditions among individuals with SCD with prevalences ranging from 56 to 96.4%[1]. The high prevalence of vitamin D deficiency is attributed to several factors impeding vitamin D endogenous production, intake or metabolism. Indeed, most SCD patients are dark skinned, which limits their cutaneous synthesis of vitamin D. Lactose intolerance, highly prevalent in African Americans, as well as damage to the intestinal mucosa may reduce dietary intake of vitamin D and interfere with its absorption. Finally, comorbidities such as liver or renal impairment may affect the conversion of vitamin D to its circulating and bioactive form respectively.

Since SCD patients have high nutritional demands due to the constant production of red blood cells, alterations in micronutrient intake, supply or metabolism are of concern. Furthermore, we showed that, despite three-monthly follow-ups, use of and compliance to vitamin D supplementation are particularly low in this population[2]. In light of these findings, it is reasonable to postulate that optimizing vitamin D nutrition of SCD children, using a dosage regimen that favours compliance, may prevent or lessen SCD-related complications. While the role of vitamin D deficiency as a contributing factor in SCD complications is not yet proven, vitamin D deficiency could be reliably and inexpensively treated, making it a prime intervention to potentially improve health outcomes among those with SCD.

The overarching aim of this pilot randomised controlled trial (RCT) is to assess the feasibility of recruitment and intervention, and obtain pilot safety data of a single oral bolus of vitamin D3 to inform the design of a larger-scale RCT. Secondarily, we aim to: 1) observe if a single oral bolus of vitamin D3 effectively raises serum 25-hydroxyvitamin D (25OHD), the marker of vitamin D status, to levels considered sufficient for potential extra-skeletal benefits (≥75 nmol/L) in children with SCD; and 2) determine if this intervention is associated with improvements in outcomes clinically relevant to SCD children.

STATE OF KNOWLEDGE AND PRELIMINARY DATA IN SUPPORT OF THIS PROPOSAL

A large proportion of SCD children followed up at Sainte-Justine University Hospital Center exhibit vitamin D deficiency/insufficiency

We previously conducted a cross-sectional assessment of vitamin D status, intakes and compliance to supplementation in a cohort of children with SCD (n=116), representative of the population of SCD patients followed up at Sainte-Justine UHC (total population is 307)[2]. We measured 25OHD levels in summer and fall in order to capture, not only the contribution of dietary and supplemental vitamin D to vitamin D status, but also of sun exposure. With this approach, we portrayed more accurately the highest vitamin D status these individuals managed to get to. Nevertheless, despite a significant time spent outdoors in summer (108±58 min/day), two-third of children (66%) had suboptimal vitamin D status (<50 nmol/L) while 33% were deficient (<30 nmol/L), thereby confirming that vitamin D synthesis through sun exposure is limited in these children in our latitude during summer. The situation was even worse in fall whereby 77% and 55% of children were vitamin D insufficient (<50 nmol/L) and deficient (<30 nmol/L) respectively. Regardless of season, only 6% of children had vitamin D sufficiency (≥75 nmol/L) with a maximum value of 99 nmol/L. Serum 25OHD levels did not vary according to genotypes (the most severe SS: 41.0±20.4 nmol/L; SC: 45.7±17.9 nmol/L; and β-thal: 40.4±15.9 nmol/L; p=0.767). Vitamin D intakes (353±234 IU) were below recommendations (600IU/day) in 72% of children and came mostly from foods (292±128 IU). Moreover, our data revealed that only 8 children (out of 46 questioned; 17%) took vitamin D supplement and only 50% of these children (n=4 out of 8) reported taking it at least 4 days a week. The high proportion of SCD children with impaired vitamin D status combined to the low proportion of subjects consuming supplements, their poor compliance, their northern geographical location and their limited ability to produce vitamin D from sunlight led us to propose an intervention strategy to overcome these issues.

Vitamin D is important for SCD children

Beyond its effects on bone, vitamin D deficiency has been linked to multiple health conditions including cardiovascular disease, inflammatory disorders, asthma, nephropathy, and chronic musculoskeletal pain, all of which are also complications of SCD. Our preliminary data revealed that SCD children with vitamin D deficiency (25OHD<30 nmol/L; n=36) had lower haematological values (total hemoglobin and erythrocyte counts) and higher level of the pro-resorptive parathyroid hormone (PTH) compared to those with 25OHD>30nmol/L (n=72)[2]. In support of our data, others have found pathological association between 25OHD levels and acute or chronic pain, markers of hemolysis as well as low bone mineral density[3-6]. Based on these findings, we postulate that an impaired vitamin D status contributes to multi-system functional impairments in SCD children, which in turn, leads to the onset or progression of SCD complications and deterioration of quality of life. These results provide a clinical rationale for the correction of vitamin D insufficiency in these children.

Very few vitamin D intervention studies have been conducted in SCD children

Only six studies aimed at documenting the effects of vitamin D supplementation on vitamin D status and clinical outcomes (e.g. chronic pain, haematology and inflammation) in SCD children have been published thus far[7-12], among which only one has reported the effects of a vitamin D bolus[7]. In the most well-designed study, Dougherty et al. randomized 44 African-Americans aged 5 to 20 years with (n=21) and without (n=23) SCS-SS to daily 4,000 or 7,000 IU vitamin D_3 (no placebo) for a period of 12 weeks[11]. While 57% of children had suboptimal status (<50 nmol/L) at baseline, it decreased to 5% after 12 weeks of supplementation with a significant reduction in PTH levels, which may benefit bone health by attenuating bone resorption. Modest improvements in hematology and inflammatory outcomes were also reported but an adherence rate of 73% may have confounded the clinical effects of the intervention. Although 4000 to 7000 IU vitamin D_3/day appears effective to correct suboptimal vitamin D status in this population, compliance remains an issue and an intervention strategy aimed at improving this aspect is warranted. In their pilot study, Osunkwo et al. randomized 39 SCD children and adolescents (7-21 years) to a vitamin D3 bolus dosed according to weight (i.e. 240,000-600,000 IU) and given over 6 weeks (note: frequency of bolus administration is unclear) with monitoring extended to 6 months[7]. In addition, subjects received daily 200 IU vitamin D_3 and there were no placebo group. Safety data were not provided but clinically, the authors found a notable reduction in the number of pain days and evidence of improved physical functioning with a rise in serum 25OHD with the peak effect occurring when serum 25OHD > 75nmol/L. These effects were not influenced by baseline vitamin D status suggesting that vitamin D therapy may benefit all SCD patients, not only deficient patients. This study also highlights the need for pulsed dosing to achieve serum 25OHD>75nmol/L combined to a daily supplementation required to maintain and further increase the gain in serum 25OHD. Finally, most intervention trials have been conducted among African-Americans or children of unspecified ethnicity while none has been specifically carried out in children of predominantly sub-Saharan African and Haitian origin, which represents 90% of our population (vs. 1% of African-Americans). In addition, vitamin D status of Canadian SCD children, a group characterized by limited sun exposure during winter, has been documented in only one study, along with other micronutrient deficiencies[13]. Our study will therefore advance the knowledge on the efficacy and safety of vitamin D among SCD children of ethnicities and geographical location that have been underrepresented in previous studies.

RATIONALE

The rationale for the proposed trial is summarized below:

1. **More than two-third** of SCD children followed up at Sainte-Justine UHC are either vitamin D deficient or insufficient during summer and fall and may therefore clinically benefit from improving their vitamin D status.
2. Given the low dietary and supplemental intakes of vitamin D of SCD children, their poor compliance to vitamin D supplementation, their compromised cutaneous synthesis of vitamin D, the presence of other potential contributing factors (e.g. impaired vitamin D metabolism, increased

nutritional demands, lactose intolerance) and the poor adherence to the CanHaem clinical practice guidelines[14] regarding vitamin D, a vitamin D nutritional intervention is clinically and ethically desirable.

3. The fact that conditions associated with vitamin D deficiency/insufficiency are similar to SCD-related complications suggests that correcting vitamin D nutrition of these children may potentially result in clinical improvements and ultimately a better quality of life.

4. Very few SCD children in our cohort had serum 25OHD levels > 75 nmol/L (i.e. 6%), the suggested target level for the extra-skeletal effects of vitamin D. Given that some clinical benefits have been demonstrated in SCD children when serum 25OHD exceeds 75 nmol/L, an effective intervention strategy aimed at normalizing vitamin D status while ensuring reasonable compliance is warranted.

HYPOTHESIS

We hypothesize that administration of a single oral bolus of 300,000 IU of vitamin D_3 to children with SCD represents a safe, acceptable and clinically feasible regimen that will result in the attainment of vitamin D sufficiency (25OHD levels >75 nmol/L) in 80% of participants and in mild improvements in some clinical outcome measures after 3 months.

RESEARCH OBJECTIVES

Primary objectives:

- To assess the feasibility of recruitment and intervention (vitamin D_3 bolus)
- To assess the acceptability of the intervention by patients and parents
- To assess the safety of the vitamin D_3 bolus (serum and urinary calcium levels, serum 25OHD)

Secondary objectives:

- To observe the mean change in total serum 25OHD from baseline to 3 months. At 3 months, a raise of the 25OHD level to 75nmol/L or more is expected.
- To observe the effects of the vitamin D_3 bolus intervention in improving growth (height, weight and BMI), haematological (fetal hemoglobin), inflammatory (TNF and IL-6), bone health (PTH, biochemical markers of bone formation and resorption, musculoskeletal pain) and quality of life.

DESCRIPTION OF THE POPULATION

The children who will participate in this study are the ones who are followed at the Sainte-Justine UHC SCD clinic. Inclusion criteria: Children aged 5 to 17 years regardless of SCD genotypes (e.g. HbSS, HbSC, HbS/β-thalassemia, others). We purposely choose to include all genotypes since our preliminary data showed that they did not differ much in terms of vitamin D status and should therefore all benefit from optimizing vitamin D nutrition. Exclusion criteria include: conditions or

use of medications known to interfere with calcium or vitamin D absorption or metabolism, known hypercalcemia, conditions characterized by a hypersensitivity to vitamin D (e.g. granulomatous disorders), patients clinically diagnosed with rickets or other conditions requiring vitamin D therapy, history or presence of urolithiasis, anticipated difficult follow up, patients already enrolled in other investigational studies, recent hospitalization for severe pain crisis or acute sickle complication in the past 2 weeks and unresolved pain issues.

PARTICIPANTS APPROACH

Children attending the Sainte-Justine UHC SCD clinic will be screened for enrollment by a research trainee. Eligible children and parents will be approached at their next follow up appointment at the clinic by the collaborating haematologists. The children and parents interested to participate in the study will then meet the research trainee for a more in depth description of the study and to answer any questions they could have. The consent form will be signed in the presence of the research trainee the same day or during the patient's next appointment at the clinic.

METHODOLOGY

Design: We propose to carry out a pilot double-blind RCT in children aged 5-17 years followed up at the SCD clinic of Sainte-Justine UHC.

Randomisation and allocation concealment: Using a computer-generated random list, children will be randomly allocated to placebo or intervention, using random permuted blocks. The Applied Clinical Research Unit of Sainte-Justine UHC will generate the randomisation scheme. Group allocation codes will be held in a secure location with a restricted access by the Central pharmacy (Sainte-Justine UHC). All participants and research personnel, including the nurse, research trainee and research team will be blinded to group assignment.

Interventions: Experimental group: a single liquid bolus of 300,000 IU oral vitamin D_3, which corresponds roughly to 3,333 IU/day; Control group: placebo identical in taste and appearance. The proposed dose of bolus vitamin D_3 is based upon a previous report showing that 4,000 to 7,000 IU/day administered to SCD children over 12 weeks was effective to correct vitamin D insufficiency in more than 95% of their cohort and led to some clinical improvements[11].

Co-interventions: In addition, all subjects will be provided with a 3-month prescription of vitamin D3 tablets (1,000 IU/tablet) to comply with the CanHaem guidelines[14] and instructed to take 1 pill per day. The research trainee will assess calcium intake and if deemed too low, participants will also receive a prescription for calcium supplements in order to ensure adequate daily calcium intake. The reason for such a co-intervention is to prevent symptoms of hypocalcemia in those who take supplemental vitamin D but have a low calcium intake.

Overall, participants in the experimental group will be taking 4,333 IU/day + dietary vitamin D intake, which falls within the range of 4000 to 7000 IU/day previously found to correct suboptimal status of SCD children[11]. Placebo group will be taking 1,000IU/day in addition to dietary vitamin D intake. Previously, the evaluation of dietary vitamin D intakes of a sample of children attending the SCD clinic at UHC Sainte-Justine (n = 46) revealed that the children took, on average, 292 +/- 128 IU of vitamin D per day[2]. Therefore, by taking into account dietary vitamin D intakes similar to what we have previously found, the participants in the experimental group will take 4, 625 IU of vitamin D per day in total (supplement + dietary intakes) while participants in the placebo group will take 1, 292 IU per day.

Observation period duration: The duration of the observation period will be of 3 months +/- 2 weeks, which corresponds to the time between the first appointment at the clinic during which the participants will take the vitamin D bolus and the second appointment. Because this study is a project which is realised in the context of a master's degree, we chose this duration for the observation period so the data could be collected in the proposed sample of patients in the time that we have for that type of study. Although 3 months is a short duration to obtain meaningful clinical improvements, the primary objectives of this study are to evaluate the feasibility, the acceptability and the security of the proposed intervention.

Supplement preparation: The supplier Euro-Pharm will provide the placebo and vitamin D_3 preparations (50,000 IU/mL) in coded bottles. Pharmacy will obtain the allocated treatment through a web-based randomisation system and will prepare the 6-mL bolus in coded syringes.

Supplement administration: Upon randomisation, the research nurse will administer the syringe to the participants and provide the prescription for the daily dose. Participants will be requested to return pillboxes at the end of the study period, coinciding with their next follow-up visit to the clinic (i.e. 3 months +/- 2 week-window).

Compliance assessment: Compliance of bolus retention will be visually assessed by the nurse while compliance to daily regimen will be assessed through pill counts. To maximize compliance, the research trainee will make weekly phone calls in order to gather information on compliance to daily regimen. In addition, pharmacies will be contacted to check if the prescription has been filled.

Sample size: Based on our preliminary data, only 6% of SCD children had vitamin D sufficiency (≥75nmol/L). One of our objectives is to bring this proportion to 80%. To detect such an increase with a power of 0.90 and a α=0.05 by 2-tailed testing, we need 30 patients per group. Taking into account an attrition rate of 20%, we aim to recruit a total of 72 participants (36 per group).

Outcomes:

1. *Feasibility and acceptability*: Information pertaining to: i) identification and number needed to screen to identify eligible candidates; ii) willingness of patients and parents to participate in the study and of clinicians to recruit; iii) reasons and rates of refusal, recruitment and attrition, and burden of

participation; iv) response rates to questionnaires and compliance to the interventions will be gathered throughout the trial by the research trainee.

2. *Safety*: Urine will be collected by the research nurse at baseline and 3 months and calcium/creatinine ratio measured using automated methods (Clinical Biochemistry Service, Sainte-Justine). At baseline, participants will be provided with a container to collect urine on day 7 (± 3days) post-bolus along with the team endocrinologist's prescription for the assessment of urine calcium and creatinine. They will be instructed to bring the urine to the nearest medical clinic for measurement. Results will be communicated to the team endocrinologist for evaluation and management. Serum calcium will be measured if deemed necessary by the endocrinologist. Code breaking will be done only if required for patient management. The proportion of children with episodes of hypercalciuria, hypercalcemia or serum 25OHD levels > 250nmol/L as well as any other adverse health effects will be documented at endpoint while weekly follow-up phone calls will be made by the research trainee to inquire about adverse events.

3. *Dietary intakes and sun exposure*: The research trainee will assess calcium and vitamin D intakes at baseline and endpoint by means of a validated food frequency questionnaire[15]. Analysis of the FFQ will be based on values from the Canadian Nutrient File version 2010 and the US Department of Agriculture National Nutrient Database for Standard Reference as done previously[16]. Sun exposure will be evaluated with a non-validated questionnaire at both timepoints.

4. *Mean change of 25OHD levels*: To measure this outcome, blood will be collected at baseline and 3 months post bolus by the research nurse. Serum 25OHD will be measured in batches by tandem mass spectrometry at the Clinical Biochemistry Service of Sainte-Justine UHC.

5. *Clinical outcomes*:

Those outcomes will be either collected or measured at baseline and endpoint:

(i) Growth: weight, height and BMI will be retrieved from medical records.
(ii) Haematological: complete blood count, lactate deshydrogenase (as index of hemolysis), bilirubin and creatinine. These assessments are routinely performed in these children and will be extracted from medical records.
(iii) Inflammatory: serum TNF and IL-6 will be measured by ELISA kits in Dr Mailhot's lab.
(iv) Bone health and musculoskeletal pain: serum PTH and biochemical markers of bone formation (P1NP) and resorption (C-telopeptides (CTX)) will be measured by standard methods in the Clinical Biochemistry Service, Sainte-Justine or using ELISA kits in Dr Mailhot's lab. Musculoskeletal pain will be assessed with the Brief Pain Inventory (BPI) [17]. This questionnaire provides information on the variability of pain intensity as well as on the quality of the pain felt by patients. It takes approximately 10 minutes to complete and will be administered by the research trainee to the participants or their parents (in case of young children).
(v) SCD-related complications: Other complications affecting bone (e.g. fractures, avascular necrosis, osteomyelitis, bone infarct), the kidneys (e.g. nephrocalcinosis, microalbuminuria), the retina (e.g. retinopathy), blood vessels (e.g. stroke, thrombosis), the heart (cardiomegaly, tachycardia), the lungs

(e.g. asthma, pulmonary hypertension), the spleen (splenomegaly, spleen sequestration crisis), the liver and gallbladder (e.g. hepatomegaly, hepatic cytolysis, cholelithiasis, cholecystitis) will be noted. (vi) Quality of life: Health-related quality of life will be assessed through the Pediatric Quality of life inventory (PedQL). This 23-item validated questionnaire[18] covers four domains: physical, emotional, social and school functioning, takes less than 4 minutes to complete and will be administered by the research trainee separately to the children and their parents.

General characteristics of the participants, such as age, sex, genotype in regards of SCD, ethnicity and drugs taken by the participants will also be collected from medical records.

Data collection will be entirely performed by the research trainee and supervised by the two principal investigators.

Feasibility: Preliminary data showed that we already have access to a large cohort of patients (n=307) through our ongoing collaboration with two SCD expert haematologists. Infrastructure is already in place since we have previously performed data collection in more than a third of the SCD population (n=116) followed up at the clinic. Study is not invasive as those children have their blood drawn at each follow-up visits. Although a certain level of involvement is required from participants and their parents, we believe that a nutritional intervention will be perceived as more acceptable than a pharmacological treatment. For all these reasons, we anticipate few recruitment issues. Supplements (both boluses (placebo and vitamin D_3) will be provided by Euro-pharm at no cost for the study. Ethics approval will be sought and a no-objection letter will be requested from Health Canada, pending results of this review. The no-objection letter is required given that the proposed total amount of vitamin D_3 exceeds the upper intake level (UL) of vitamin D recommended for otherwise healthy children aged 4-8 years (i.e. 3,000 IU) and 9 and older (i.e. 4,000 IU).

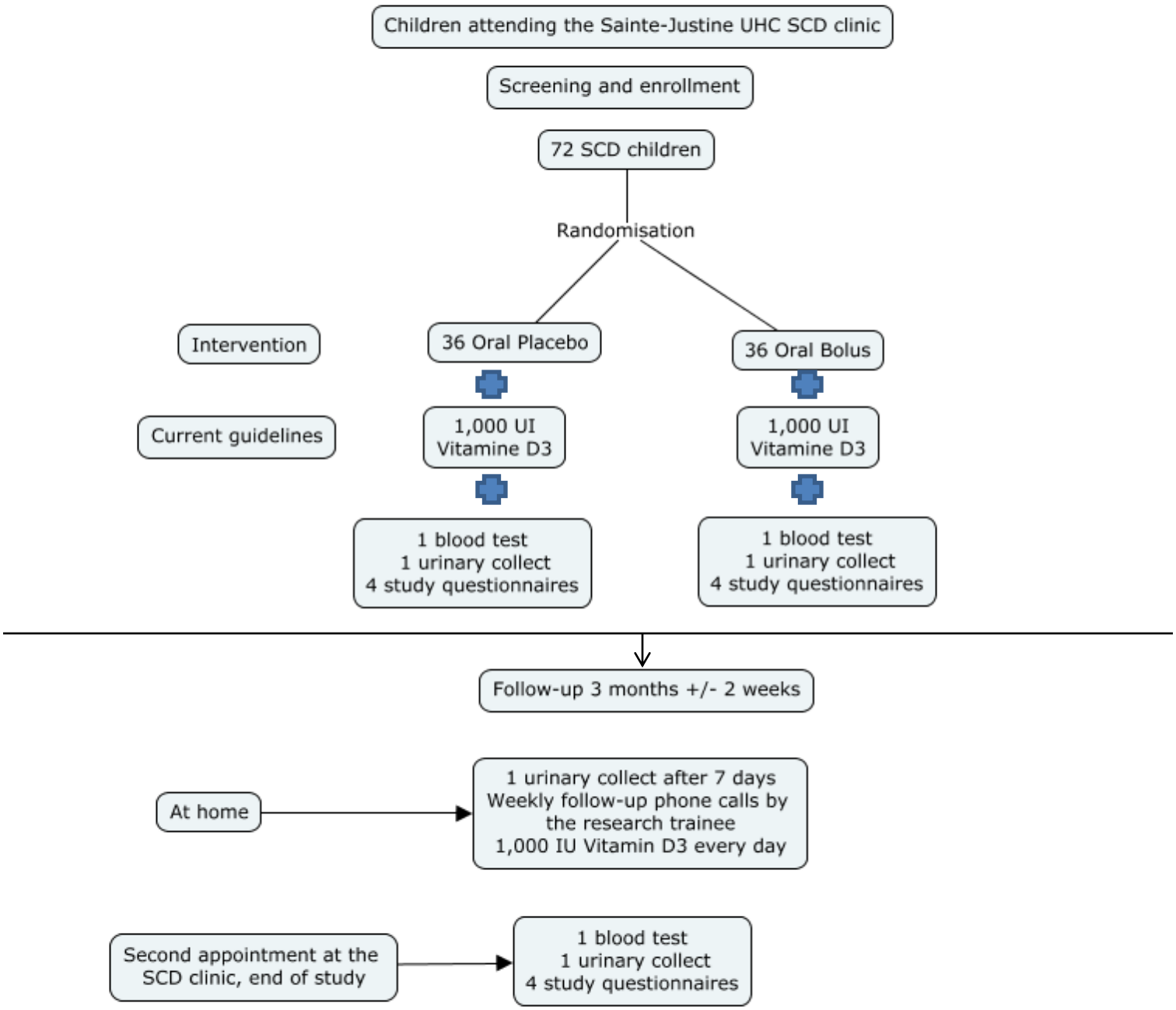

Fig.1 Experimental design

STATISTICAL ANALYSIS

The analyses will be made using the intention-to-treat model where all subjects are included regardless of their adherence to the study protocol. Differences in outcomes between experimental groups at baseline and endpoint will be assessed using parametric Student's t test or non-parametric

Mann Whitney U test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. Intragroup differences will be assessed using paired Student's t test with Bonferroni adjustment. Analyses will be performed under allocation concealment with unblinding occurring after trial completion and analysis of primary outcomes. Given the pilot nature of our study, subanalyses will be undertaken on variables that may potentially influence the response to vitamin D such as genotype, season of the year or baseline vitamin D status. However, these analyzes remain exploratory.

CLINICAL SIGINIFICANCE

By implementing this pragmatic and highly acceptable intervention and achieving a compliance of 100% with the administration of the vitamin D bolus, we expect to: 1) correct vitamin D insufficiency in SCD children; 2) avoid monitoring their 25OHD levels on a regular basis; and 3) ultimately demonstrate improvements in clinical outcomes.

The participation of 2 expert hematologists of the SCD clinic in this project is a great asset, because their implication will facilitate the knowledge translation brought by the research to the clinical practice. Furthermore, the eventual benefits of the study are of high clinical importance because they are easily implantable to the clinical practice and could lead to improvement in the nutritional status of these patients. Therefore, these patients could benefit from the intervention rapidly and could see their quality of life improved. Finally, our study is still at an early stage, because it is first and foremost an acceptability and feasibility study. The results of this study will give us the necessary data to inform a RCT at much bigger scale so it could benefit more children. The results of this study will also allow us to evaluate the incidence on the quality of life of the patients and on the onset of SCD related complications.

ETHICAL ISSUES

In this study, there will be an intervention, which is a vitamin D supplementation, regular and direct contacts with the participants by the administration of questionnaires at baseline and endpoint, and phone calls during the period of observation. The inform consent of the patients will be obtained before performing any intervention related to the study. Moreover, medical charts will be consulted at the beginning of the study to identify eligible patients for the study. The authorisation of the Medical and University Affairs Directorate will also be asked to consult the medical records. Finally, the project will be registered at Health Canada and a no-objection letter will be sought for the vitamin D_3 bolus. The project will also be registered at clinicaltrials.gov.

Risk of toxicity: The vitamin D supplementation that will be given to the children puts them at risk of toxicity given the high dose and the nature of the vitamin (fat-soluble vitamin, which can accumulate in the organism). However, we anticipate the risk of overdosing children with normal

baseline 25OHD levels to be minimal for the following reasons. First, a very small proportion of our cohort (i.e. 6%) had normal 25OHD levels (>75 nmol/L)[2]. Second, vitamin D toxicity is associated with high chronic intake and serum 25OHD levels > 250 nmol/L[19]. However, using a more conservative approach, the report on Dietary reference intakes (DRI) for calcium and vitamin D stated that 25OHD levels above 125 nmol/L may be associated with risks[20]. In our cohort, none displayed serum 25OHD considered toxic whereby the maximum 25OHD concentration achieved was 99 nmol/L, which is well below toxic levels[2]. Furthermore, the majority of blood draw were made in spring and in summer, 2 seasons in which we expect 25OHD serum levels to be higher due to sun exposure. Third, vitamin D bolus administration has not been associated with reports of toxicity in both non-SCD children (bolus of 300,000 and 600,000 IU) [21] and SCD patients (bolus of 240,000 IU) [9]. Thus, most of our participants are vitamin D deficient or insufficient and will likely benefit from raising their 25OHD levels. Finally, given that the study includes only one vitamin D bolus and lasts only 3 months, the risk of toxicity for the patients is minimal.

Use of a placebo: The use of a placebo in this study is justified by the fact that both groups (experimental and placebo) will received, in addition to the study intervention, a prescription for a supplementation of vitamin D_3 of 1,000 IU per day, which corresponds to the current guidelines. Therefore, the children in the placebo group will not be exposed to higher risks of vitamin D deficiency. The difference of vitamin D received by experimental group (4, 625 IU) and the placebo group (1, 292 IU) should allow us to discriminate enough the effect of the intervention compared to the placebo.

No pre-selection of children based on their baseline vitamin D status or season: All eligible SCD children will be asked to participate in this study regardless of their baseline vitamin D status or season of the year. The absence of pre-screening is justified by our preliminary data, which showed that a large proportion of SCD children are either vitamin D deficient or insufficient during summertime (insufficiency 33% and deficiency 66%) [2]. Moreover, serum 25OHD levels of these children declined seasonally (45.6±19.5 nmol/L in summer vs. 33.9±15.9 nmol/L in fall, p=0.01). From these observations, we anticipate that nearly all SCD children would benefit from such an intervention. Although it is suggested that serum 25OHD > 75nmol/L is likely associated with extra-skeletal benefits, the optimal target serum 25OHD is still unknown. Hence, by restricting the intervention to children with baseline vitamin D deficiency/insufficiency, we would exclude children that may benefit. The absence of pre-selection will also allow us to study the impact of the baseline status on the efficacy of the intervention in addition to facilitate the implementation of the intervention in clinic.

TEAM INFORMATION

Principal investigator:

Genevieve Mailhot, PhD, RD

Associate professor, Department of Nutrition, Université de Montreal Researcher, CHU Sainte-Justine Research Center

Areas of expertise: vitamin D, calcium, bone health, inflammation, rare diseases, chronic diseases

Roles: The PI is a PhD registered dietitian with specific training in vitamin D whereby she has accumulated more than two decades of experience. The PI will oversee study logistics along with her research trainee, supervise data collection, and lead the data analysis, manuscript writing, team meetings and knowledge dissemination. Her lab personnel will process the blood samples and perform measurements using ELISA kits.

Nathalie Alos, MD
Endocrinology Division
Department of pediatrics
CHU Sainte-Justine
Researcher, CHU Sainte-Justine Research Centre

Areas of expertise: vitamin D, bone health, metabolic bone diseases

Roles: Dr Alos is a pediatric endocrinologist and the director of the Pediatric Bone Health Unit at the CHU Sainte-Justine. She will prescribe the daily vitamin D and calcium supplements and oversee all safety aspects of the intervention. She has collaborated to the design of the research protocol and will be involved in data analysis and interpretation, manuscript editing, and knowledge dissemination.

Co-investigators:

Sylvie LeMay, PhD, RN
Professor
Faculty of nursing
Université de Montréal
Researcher, CHU Sainte-Justine Research Centre

Areas of expertise: musculoskeletal pain, pain measurement

Roles: Dr Le May is a PhD registered nurse who will provide expertise regarding pain issues, measurement and analyses, as well as review drafts of the manuscript following completion of the study.

Yves Pastore, MD

Hemato-oncology Division

Department of pediatrics

CHU Sainte-Justine

Areas of expertise: hematology, sickle cell disease

Roles: Dr Pastore is one of the haematologists who will be responsible for enrolling the patients. He has collaborated to the design of the research protocol and will be involved in data analysis and interpretation, manuscript editing, and knowledge dissemination.

Nancy Robitaille, MD

Hemato-oncology Division
Department of pediatrics
CHU Sainte-Justine

Areas of expertise: hematology, sickle cell disease

Roles: Dr Robitaille is the other haematologist involved in patient's recruitment. She has also collaborated to the design of the research protocol and will be involved in data analysis and interpretation, manuscript editing, and knowledge dissemination as well.

Research trainee

Pascale Grégoire-Pelchat is a registered dietitian who performed the cross-sectional study (Vitamin D status in a Canadian cohort of children with SCD, manuscript submitted) as a research internship project. The proposed project will be the topic of her master studies scheduled to begin in September 2017. She will oversee all study logistics in collaboration with the PI. She will be responsible for ethics submission, screening participants for enrollment, assisting the haematologists for recruitment, meeting with the parents to administer the food frequency, sun exposure, the Brief Pain Inventory and PedQL questionnaires, retrieving laboratory results and data from medical records, performing data analysis and dissemination, and drafting the manuscript.

Other collaborator

Euro-Pharm: Euro-Pharm is a pharmaceutical company, which manufactures and distributes vitamin D oral preparations for children. They will supply the vitamin D and identical placebo oral supplement for the proposed number of patients and will provide all documentation required to fulfill Health Canada requirements. They will have no input on the design and the conduct of the study as well as on the analysis and interpretation of the data.

TIMELINE

We plan to carry out this project over a 2-year period. Timeline will be divided into three major segments:

i) Ethics application and approval, and study set-up: October 2017-April 2018 (5 months)
ii) Patient recruitment, data collection, sample processing and analysis: May 2018-March 2019 (11 months)
iii) Data analysis, manuscript drafting and dissemination: March 2019-July 2019 (5 months)

BUDGET

This is a research project that is not subsidised. The vitamin D bolus and placebo will be provided at no cost by Euro-Pharm. The research trainee will be paid by two grants that she received ($9,500 total + $1,000 from her director) and by her part time job (2 days per week) as a dietician which will fill the difference for the minimum intake required for master's students. The other expanses will be covered by the research fund of the two principal investigators.

KNOWLEDGE TRANSLATION

Our key knowledge transfer goals are to increase knowledge and awareness to ultimately move research evidence into practice, improve patient's nutritional management and the role of dietitian in that respect, and inform future research priorities. The CanHaem existing guidelines are based on minimal data, collected in individuals of different ethnic backgrounds. Our study will thus provide additional evidence in a Canadian context that may prompt a change in clinical practice guidelines. To achieve the knowledge transfer goals, we will reach out to our target audiences via 1) presentations at international (e.g. American Society of Pediatric Hematology/Oncology (ASPHO)), national (e.g. Canadian Nutrition Society) and local conferences or to national/local groups and 2) peer and non-peer review publications in disciplines such as nutrition and hematology. Upon completion of the study, we will invite the study participants (parents and children) to a "Scientific Café" in order to present and discuss the results and gather their input and thoughts on the study and future participation. Finally, the study results will also be presented at the annual Symposium for Sickle cell disease, which is an event intended for SCD patients and their family.

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