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Effect of nutritional supplementation on bone mineral density in children with sickle cell disease: protocol for an open-label, randomised controlled clinical trial

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ABSTRACT

Introduction Children with sickle cell disease show a significant decrease in bone mineral density, an increase in resting energy expenditure of more than 15%, a decrease in fat and lean mass as well as a significant increase in protein turnover, particularly in bone tissue. This study aims to evaluate the effectiveness of an increase in food intake on bone mineral density and the clinical and biological complications of paediatric sickle cell disease.

Methods and analysis The study is designed as an open-label randomised controlled clinical trial conducted in the Paediatrics Unit of the Orléans University Hospital Centre. Participants aged 3–16 years will be randomly divided into two groups: the intervention group will receive oral nutritional supplements (pharmacological nutritional hypercaloric products) while the control group will receive age-appropriate and gender-appropriate nutritional intake during 12 months. Total body less head bone mineral density will be measured at the beginning and the end of the trial. A rigorous nutritional follow-up by weekly 24 hours recall dietary assessment and planned contacts every 6 weeks will be carried out throughout the study. A school absenteeism questionnaire, intended to reflect the patient's school productivity, will be completed by participants and parents every 3 months. Blood samples of each patient of both groups will be stocked at the beginning and at the end of the trial, for future biological trial. Clinical and biological complications will be regularly monitored.

Ethics and dissemination The protocol has been approved by the French ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer 2, Toulouse; approval no: 2-20-092 id9534). Children and their parents will give informed consent to participate in the study before taking part. Results will be disseminated through peer-reviewed journals or international academic conferences.

Trial registration number NCT04754711.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective, interventional, randomised controlled trial on sickle cell anaemia children is performed to evaluate the effect of nutritional supplementation on bone mineral density and disease complications.
⇒ Blinding is not applicated due to technical logistic reasons to manufacture a genuine placebo.
⇒ Compliance in the consumption of the oral nutritional supplements is ensured by specialised dieticians, with previously planned modalities of contacts and meetings with participants.
⇒ Stratified statistical analysis of homogeneous groups in terms of age, gender, disease severity is planned.

INTRODUCTION

Sickle cell disease (SCD) is the most prevalent inherited haemoglobinopathy exhibiting an annual incidence estimate of 300 000 births.[1 2] More than half of these cases stem from Africa, with additional occurrences in India, the Mediterranean region and the Middle East.[2] During the past five decades, SCD has emerged as the predominant rare disease in France, with a patient count surpassing 30 000, half of them living in the Paris area.[3] This establishes France as the European nation harbouring the highest number of affected individuals.

SCD results from a point mutation, which involves the substitution of glutamic acid with valine at position 6 on the beta subunit of haemoglobin, leading to the formation of haemoglobin S (HbS).[4] While homozygous HbSS patients experience symptomatic manifestations, HbAS heterozygotes are asymptomatic carriers. Variant forms of SCD manifest when mutations associated with other defective haemoglobins (C or E) or beta-thalassaemia combine with HbS, resulting in genotypes SC, SE, Sbeta+ or Sbeta0. Among these, the most severe presentations are SS and Sbeta0.[5] Under hypoxic conditions, HbS undergoes polymerisation, leading to the

formation of fragile 'sickle' red blood cells (RBCs) characterised by a shortened lifespan. These RBCs contribute to microvascular occlusions by triggering an inflammatory cascade, platelet activation, increased adhesion of RBCs to the vascular endothelium and perturbed nitric oxide (NO) metabolism.[5] For unknown reasons, the bone is the primary target for acute complications in SCD.[6 7]

The comprehensive spectrum of symptoms encompassing SCD entails acute painful crises called vaso-occlusive crises (VOC), chronic pain, acute and chronic anaemia, infections and multiorgan involvement.[2] This results in a significant decline in both the quality of life and life expectancy of patients.[1 2 8] Neonatal screening, penicillin prophylaxis, pneumococcal conjugate vaccination, transfusion exchange programmes and hydroxyurea (since 2017) have improved prognosis in these high-risk patients.[9] Haematopoietic stem cell transplant is the only curative treatment, strongly limited by the rarity of matched sibling donors.[10 11]

The rationale of our study is based on the observation that a general follow-up programme[12] lacks explicit nutritional recommendations and systematic monitoring of bone mineral density (BMD) for children with SCD, even in Western countries. However, those patients exhibit:

- An increased resting energy expenditure of 15%–20% (quantified via indirect calorimetry).[13–16]
- Diminished fat and lean mass.[15 17 18]
- A marked increase in protein turnover, particularly affecting bone tissue.[13]
- A frequent decrease in BMD, ranging between 19% and 56%[17–22] (table 1).
- A statistically significant association between reduced BMD and lower body mass index (BMI),[17–22] although not with vitamin D deficiency.

The objective of this study is to assess the impact of increased oral caloric nutritional intake on BMD in children with SCD, over a 12-month period.

METHODS AND ANALYSIS

Design

This is an open-label, investigator-initiated, randomised, controlled, superiority interventional trial conducted within the Paediatrics Unit of the University Hospital Centre of Orléans, France. Our main hypothesis is that increased oral nutritional caloric intake may improve BMD in children with SCD. Seventy paediatric patients are to be randomised in two parallel groups.

Primary objective

This study is designed to assess the impact of additional 20% oral caloric food intake through oral nutritional supplement (ONS) on change of BMD in children with SCD.

Secondary objectives

We also seek to explore the potential influence of this nutritional intervention on various secondary outcomes. These encompass alterations in body composition (fat/lean body mass), changes in growth parameters (height and weight), frequency of complications related to SCD, school absenteeism (online supplemental file 1), cardiac function, brain vasculopathy and routine biological parameters.

An ancillary objective is the establishment of a blood samples collection for future biological research (inflammation, hypoxia, bone metabolism).

Table 1 Decrease of bone mineral density (BMD) in SCD children and adolescent

Publication	Paediatric SCD participants	Healthy control group	DXA site	Gender	Age (years)	Country	Low BMD (<–1SDs)
Meeuwes *et al* 2013[21]	27	None	Lumbar spine (LS)	12 F–15 M	14.9 (7–28)	Brazil	41%
Gupta *et al* 2010[22]	28	24	LS, femoral neck (FN)	14 F–14 M	9.7±3.4	Koweit	18% vs 13% on LS; 4% vs 0% on FN (p>0.05)
Chapelon *et al* 2009[19]	53	None	LS, FM, whole body excluding scull (WBES)	27 F–26 M	12.8±2.4 (9–19)	France	67% (F) on LS; similar FM, WBES 45% (M) on LS; similar FM, WBES
Fung *et al* 2008[18]	46	None	Whole body	23 F–23 M	11 (4 à 19)	USA	32%
Lal *et al* 2008[20]	25	None	Proximal femur, LS	13 F–12 M	12.8 (10.2–19.8)	USA	56%
Buison *et al* 2005[17]	90	198	Whole body mineral content	44 F–46 M	4 à 19	USA	32%

DXA, dual energy X-ray absorptiometry; F, female; M, male; SCD, sickle cell disease.

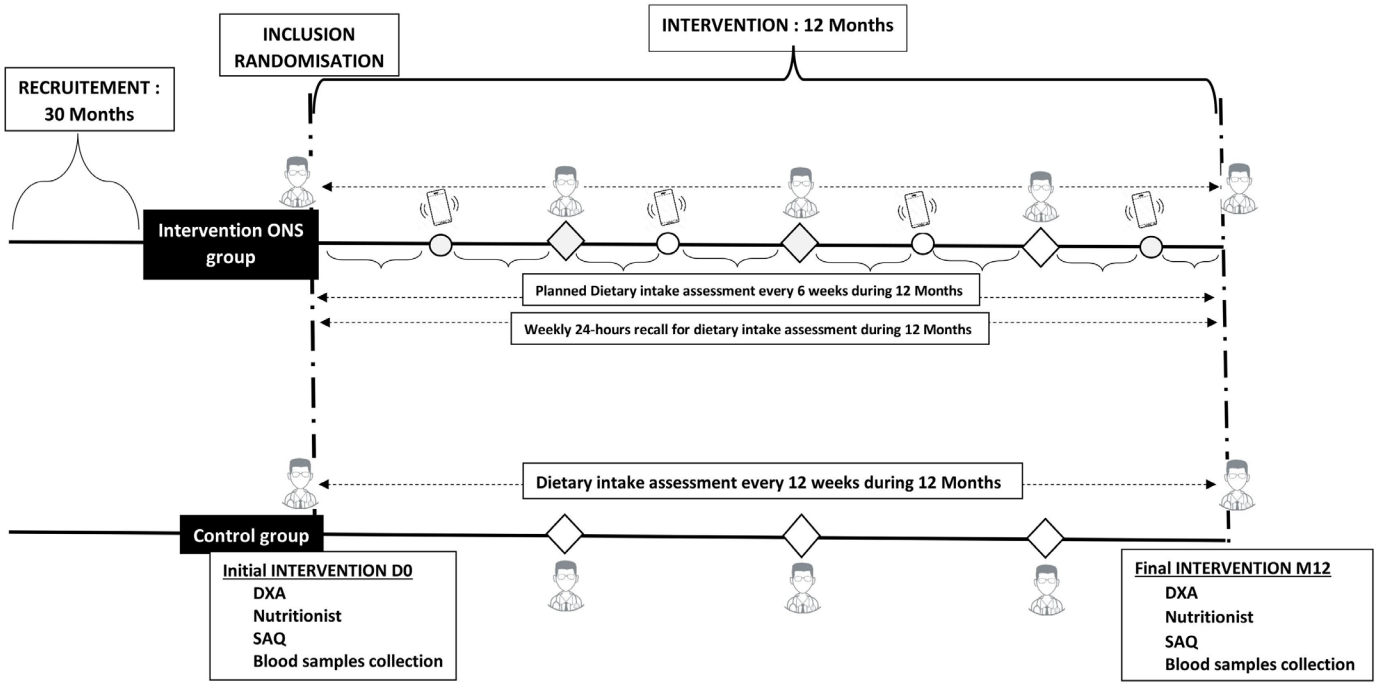

Figure 1 Flow chart of the sickle cell disease nutritional intervention project. DXA, dual energy X-ray absorptiometry; ONS, oral nutritional supplements; SAQ, School Absenteeism Questionnaire.

Study setting and time points

The trial is carried out in the University Hospital Centre of Orléans, France. The total study duration is 42 months, including 30 months of recruitment: starting date 23 September 2021, expected end recruitment date 23 March 2024 (initially 18 months was planned but it was subsequently extended for an additional year), and 12 months of follow-up. Two keys assessments are scheduled at enrolment and at the end of the follow-up. Minor assessments will be performed every 6 weeks. A 24-hour recall dietary intake will done once weekly. Figure 1 illustrates the overall study design.

Definitions

- Severe form of SCD: No paediatric severity score has been formally validated for SCD. We will use the following clinical criteria to define severity (the first two being suggested by Lal *et al*[20]):
  - Three or more hospitalisations per year in the 5 years prior to inclusion.
  - Two or more transfusions of packed RBCs per year in the 5 years preceding inclusion.
  - A history of acute chest syndrome in the 5 years prior to inclusion.
- Acute anaemia is defined as a 2 g/dL drop in haemoglobin concentration compared with the initial/usual value.
- Cerebral vasculopathy assessed by transcranial Doppler: time-averaged mean maximum velocity ≥170 cm/second in the supraclinoid internal carotid artery and/or middle cerebral artery.[23]

Patient and public involvement

The conception of the study was not influenced by patients or other public experiences or preferences. The investigators designed the study and recruited participants solely on the basis of predefined criteria and without any patient or public pressure.

Recruitment, informed consent and study time points

Children, adolescents and their parents will be approached either during a consultation with a paediatrician for routine follow-up of SCD, or during a hospitalisation, whatever the cause. Oral and written information will be given to the patient and his/her parents during this initial contact (online supplemental file 2). They will consider proposal to take part in the trial and ask any questions until the next consultation, during which the patient will be included if he/she consents and his/her parents give written consent. Date and time of randomisation determine the beginning of the intervention period.

Parents of included patients have the right to withdraw their consent and discontinue their participation at any time for any reasons.

Blinding

The decision was made not to pursue a double-blind study due to logistical, time and financial constraints. Additionally, we anticipated technical challenges in manufacturing a genuine placebo for the oral supplement for various reasons (eg, the supplement would unavoidably increase the volume of the food bolus, it would increase the intake of dietary fibres and/or inert materials that could

potentially affect intestinal transit and/or the absorption of micronutrients).

Inclusion criteria

- Children between 3 and 16 years old.
- Following SCD genotypes: SS, SC, SE, Sbeta+ and Sbeta0.

Exclusion criteria

- Children who are overweight: BMI ≥97th percentile.
- Children refusing, or for whom one of the two parents refuses the participation in the study.

In the case of siblings, only one child will be selected at random from all the children of the sibling group. The others will receive (free of charge), ONSs, if they so wish and if this is the group assigned to the selected children.

Randomisation

The randomisation by sealed envelopes will be done in two parallel arms by physician and/or nutritionist, with an allocation ratio of 1:1, with permutation blocks, the size of which will be unknown to the investigators. It will be stratified on three variables:

- Age: ≤or>8 years old.
- Gender.
- Severe or mild form of SCD.

Intervention

Each enrolled and randomised child will undergo key interventions as part of his/her annual routine general check-up conducted in a day hospital setting:

Nutritional assessment by a nutritionist

After randomisation, dietary intake assessment and anthropometric measures for all subjects, paediatric nutritionist will define the daily quantity of ONS to take for each subject of the intervention group. Detailed ONS composition is furnished in online supplemental file 3. ONS (provided to subjects as part of the study) will be distributed every 3 months during consultation, for the following 3 months. Intervention group participants will receive instructions for caloric increase with an ONS on the basis of his/her BMI: for BMI<50th percentile: increase in intake to reach or surpass the 50th percentile, and an additional 20% caloric intake in the form of ONS; for BMI>50th and <97th percentile, an additional 20% caloric intake in the form of ONS. If a child becomes overweight (BMI>97th) during the study, he/she will be excluded but will be rigorously followed by a dietician and physician until normalisation. The daily quantity of ONS will depend on one hand on the results of the dietary intake carried out beforehand for each patient included, and on the other hand—on the gustative interest of the child for this or that product. The intake of proteins, carbohydrates and lipids will be adapted so that it does not exceed the recommended daily intake.[24] The quantity of ONS consumed per day will in no case exceed 400 mL. Nutritionist will explain to patients/parents that the purpose of ONS is not a replacement of a usual meal but an addition to it in order to reach a caloric increase of 20% over the age-appropriate caloric recommendations. Different aromas and forms of ONS will be proposed, possibility to change ONS during the trial, possibility to contact dietician at any time (email, phone), planned contact with participants every 6 weeks. Moreover, we will collect empty ONS packaging. Nutritionist will assess dietary intake by a 24-hour recall. Evaluation of food intake will be performed 1 day per week in written form. Concerning the six other days of the week parents will be questioned about any changes of food habits of their child. If the child has eaten differently on one or more of the other 6 days of the week, this will be considered in the caloric calculation. During some special periods (holidays, hospitalisations) dietary assessment will be adapted to food intake changes. If illiterate parents, nutritionist will use photographs of the meals and estimate calories using professional nutritional guide such as https://dietcie.com/wp-content/uploads/2021/02/Guide-des-portions-pdf-compresse.pdf. Therefore, if necessary, change of caloric intake will be performed each week during the trial.

Nutritional status of subjects of control group will also be assessed by the nutritionist in order to correct, if necessary, caloric food intake to age-appropriate caloric recommendations.

- Total body less head (TBLH) BMD for all subjects will be measured by two experienced operators in the anterior–posterior direction by dual energy X-ray absorptiometry (DXA) using a Hologic Horizon system (Hologic, Waltham, Massachusetts, USA). As SCD is a chronic condition associated with malnutrition and with muscle deficits, soft tissue measures, that is, lean and fat body mass (%), will also be performed at baseline and at the end of the study. Considering the wide age range of children and adolescents who are to be recruited, the description of the study population in terms of BMD will use BMD values adjusted for individual body height, sex and age as recommended.[25]
- School absenteeism questionnaire for all subjects (in number of days, online supplemental file 1), intended to indirectly reflect the patient's school productivity. This will be filled in by the patient him/herself and his/her parents. This questionnaire will be checked for completion at each medical consultation planned at 3-month intervals during the study (figure 1).
- Collection of blood samples for future research trials for all subjects.

Evaluation and outcomes

The primary outcome is the change in mean TBLH BMD of the two randomised groups (in g/cm^2) during the time frame month 12 (M12)–baseline (first day of inclusion).

The secondary outcomes include:

- Change in body composition expressed by lean body mass (%), fat mass (%), bone mass, by region of the body and overall, during the time frame M12–baseline.

- Rate of participants with change of height (cm, percentile according WHO curves)[26] and weight (kg, percentile according WHO curves)[26] during the time frame month 12–baseline (day 1 of inclusion).
- Assessment of school absenteeism questionnaire at baseline, months 3, 6, 9 and 12.
- Frequency of complications of SCD during the study period (M12): VOC, chronic pain, acute anaemia, infections.
- Presence or not of impaired cardiac function and/or cardiac anatomy related to SCD determined by echocardiography, at baseline and M12.
- Presence of cerebral vasculopathy assessed by transcranial Doppler at baseline and M12.
- Value change of haemoglobin F-S-C, lactate-dehydrogenase (LDH) concentration iron and ferritin, serum folate, C reactive protein and 25 OH vitamin D at baseline and month 12.

Sample size

Based on the literature,[17–22] we hypothesise an increase in BMD in the intervention group corresponding to an effect size of 0.75 (the difference in the mean of BMD between the two groups will be 0.75 times the SD of the total population of the two groups). This reflects a strong effect of ONSs on BMD compared with control group, with a significant difference in the mean of BMD between the two groups. To show such a difference with a power of 80% and an α risk of 5%, the inclusion of 70 patients (35 patients in each group) is necessary if it is estimated that 20% will be lost to follow-up.

General management

The care and follow-up of children will comply with the management usually recommended[12]: (1) Medical consultation with clinical examination every 3 months including anthropometric parameters (weight, height, BMI, growth curve) and classification as prepubescent (girls P1/S1, boys G1/P1 according to Tanner's classification) or pubescent (girls P2–P5/S2–S5, boys G2–G5/P2–P5 according to Tanner's classification); (2) Biological monitoring every 3 months on the same day of the consultation: total haemoglobin, haemoglobin F-S-C, serum LDH, serum iron, ferritin, folate, CRP, vitamin D and (3) Echocardiography and transcranial Doppler every year.

Study safety, monitoring and data management

As this trial is associated with minimal risks according to French Law, we did not plan to set up an independent data safety and monitoring board. No adverse effects have been reported since the beginning of March 2021. Nevertheless, the study can be suspended or prematurely interrupted in case of unexpected serious adverse events, requiring the examination of the evolution of all the patients already included. University Hospital of Orléans reserves the right to interrupt the study at any time if the inclusion objectives are not reached. The investigator can definitively or temporarily stop the patient's participation for any reason which would better serve the patient's interests, and especially in case of serious adverse effects. In this case, these reasons are collected, assessed and reported.

A paper clinical report form (CRF) will be filled in by the investigators and the nutritionist at each visit or phone call. Clinical study technicians assigned by the sponsor will regularly check the CRFs to ensure that the data are complete and accurate, and that they correspond to the source data.

Data management is performed by the Direction de la Recherche, University Hospital Centre of Orléans. Research assistants regularly monitor collected data to check adherence to protocol and accuracy of collected information.

Statistical analysis

The variation in TBLH BMD between inclusion and 1 year will be compared between the two groups of randomisations by using a linear mixed model. We assumed that patients would have a random intercept. The randomisation group and the stratification variables will be handled as independent variables with a fixed effect. The differences in BMD and its variation between the two groups of randomisations will also be presented for the subgroups used to stratify the population, whether or not there is interaction between strata and treatment. Results will also be presented for different age groups ((3–5), (5–7), (7–9), (9–11), (11–13), (13–16 years)), as well as in prepubescent and pubescent children separately. Finally, the change in TLBH BMD of the two groups of randomisations (and by stratification variables) will also be described (1) using the reference population implemented in the DXA machine and (2) after adjustment of the TLBH BMD value for height-adjusted Z-scores of each category of age and gender.[25]

The secondary endpoints will be described at the different follow-up times of the study.

Subgroup description will be provided for each stratification variable (age, gender, severity), with appropriate graphic representations. Missing or aberrant data will be replaced by multiple imputation by chained equations (Function 'mice' of the R package 'mice') by generating 50 complete imputed populations; and 'pooled' analyses on these 50 populations.

ETHICS AND DISSEMINATION

Ethics approval

This paediatric study protocol was approved by the institutional review board of Orléans' Hospital, as well as by the French ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre-Mer 2, Toulouse; approval no: 2-20-092 id9534) on 5 November 2020 and was registered in ClinicalTrials.gov (NCT04754711).

The study is conducted in accordance with the current revision of the Declaration of Helsinki, 1996, International

Conference on Harmonisation Note for Guidance on Good Clinical Practice (ICH GCP) and the applicable French regulatory requirements.

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Contributors GD, EL and TB designed the study. GD, MC, TB and EL wrote the study protocol. TB determined the sample size. TB and MW planned statistical analysis and data interpretation. GD is the coordinating investigator. MC and DA include patients. All authors reviewed and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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