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Original Paper

Osteopenia and Osteoporosis Assessed by Dual X Absorptiometry in Sickle Cell Anemia Adults Subjects

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Abstract

Background: *Sickle cell anemia is the most common genetic disease in sub-Saharan Africa. It is an inherited autosomal recessive disorder characterized by chronic hemolysis secondary to falciformation of red blood cells, also responsible of ischemia, bone infarction and accompanied by serious infections and organic lesions.*

Normal for weight at birth, Sickle cell anemia subjects have low pre puberty growth compared to normal children and also have compromised bone remodeling balance which results in decrease of bone mass and increase of bone fragility. Several studies have established that 37% to 50% of SCA patients were osteopenic or osteoporotic. This study aims to confirm the existence of bone remodeling disorders with osteoporotic translation and to compare the values found in Congolese sickle cell adults subjects to the general population.

Methods: *Spine and hip DXA were conducted on 270 SS homozygotes aged 18 to 50 years (121 men and 149 women) and 359 AA homozygotes as controls (138 men and 221 women), aged from 18 to 50 years old, who agreed to participate in the study, considered as a control group. AS heterozygotes were not included in the study.*

Results: *AA subjects shows higher density (BMD) and Bone mineral content (BMC) values. Both SCA and AA controls showed the characteristic curve with peak bone mass at the fourth decade of life, followed by a decay with age. The difference in BMD and BMC with the control population ranged from 7.94% to 26.34% (average of 16.02%) which means -0.8 to -2.7 standard deviations, whereas, compared to the T -score in the Congolese population, was 11.6% to 22.15% less (average of -17.5%) equivalent of -0.9 to -2 standard deviations.*

The overall decrease in bone mass rate for -2.5 DS of the T-score was: -28.4% and 33.2% for -2 DS of T-score.

Conclusion: *SCA subjects shows high rate of osteopenia and osteoporosis and are more likely at risk for fractures.*

Keywords

Bone mass, DXA, sickle cell anemia, osteopenia, osteoporosis, black, central Africa, adult

1. Introduction

Sickle cell anemia (SCA), the most common genetic disease in sub-Saharan Africa, is an inherited autosomal recessive disorder (Rees et al., 2010).

A mutation causes the replacement of hydrophilic glutamic acid by valine, which is hydrophobic, thereby explaining the fragility of the red blood cell in sickle cell patients under hypoxic conditions. Acute attacks (hematologic and vaso-occlusive) as well as chronic complications of this disease are the result of falciformation of red blood cells and chronic hemolysis, which are also responsible for ischemia, bone infarction and hyperplasia of the red marrow with a reduction in the trabecular component. SCA is furthermore accompanied by serious infections and organic lesions (Rees et al., 2010; Bookchin et al., 1996; Kazadi et al., 2017).

SCA patients have normal weights at birth but low pre-pubertal growth compared to normal children. Chronic anemia results in abnormalities in skeletal maturation (Kazadi et al., 2017; Piel et al., 2013; Henderson et al., 1994; Luban et al., 1982; Barden et al., 2000).

This feature is associated with osteomyelitis and repeated bone infarction, with a reduction in the rate of bone formation as a consequence of compromised bone remodeling balance (Henderson et al., 1994; Luban et al., 1982; Barden et al., 2000; Bennet et al., 1990; Meeuwes et al., 2013).

Great progress has been made in the management of this hemoglobinopathy, which permits the elderly patients with SCA to survive in developed countries.

However, the lack or absence of financial and sometimes human resources skills reduces access to quality care in low-income countries such as the DRC (Kazadi et al., 2017; Aloni et al., 2014; Williams et al., 2016; Chaturvedi et al., 2016; Matthie et al., 2015; Vanderjagt et al., 2002; Arlet et al., 2013; Emodi et al., 2001; Finkelstien et al., 1996).

In several studies, approximately half of the 35-year-old SCA patients have apophyseal necrosis, while others report stress fractures, vertebral collapse, sclerosis of the joint surfaces, and even orbital

compressions or problems that result from the decrease in bone mass and the increase in bone fragility and fracture risk (Arlet et al., 2013; Emodi et al., 2001; Finkelstien et al., 1996; Demirbas et al., 2004; Ganesh et al., 2001; Bahebeck et al., 2002).

Several studies have reported that 37 to 50% of SCA patients were osteopenic or osteoporotic which is associated with the foci of osteomyelitis and bone infarction and leads to an increased risk of fracture in SCA patients (Arlet et al., 2013; Bahebeck et al., 2002; Bennet et al., 1990; Meeuwes et al., 2013; Emodi et al., 2001; Demirbas et al., 2004; Finkelstien et al., 1996; Ganesh et al., 2001; Lal et al., 2006). The majority of these studies were conducted out of sub-Saharan Africa, and, despite a relatively different biological, genotypic and phenotypic profile, the Congolese SCA clinical profile reflects an equivalent impact of this hemoglobinopathy on the bone system, suggesting the presence of remodeling abnormalities in the setting of low bone mass (Kabeya et al., 2017; Kazadi et al., 2017; Mikobi et al., 2017; Mikobi et al., 2017; Tshilolo et al., 2012; Platt et al., 1984).

The aim of this study was to compare the values found in Congolese SCA subjects to those of a control group matched for age and sex and establish the existence of bone remodeling disorders with osteoporotic translation using DXA.

2. Material and Methods

2.1 Subjects

1862 respondents of a public media call for low cost checkup including DXA were examined by a physician and underwent clinical, biological and imaging investigations planned for the checkup.

This cross-sectional study included a total of 629 AA homozygotes (138 men and 221 women), aged from 18 to 50 years old, who agreed to participate in the study, considered as a control group and 270 SS homozygotes aged 18 to 50 years (121 men and 149 women) as subjects of the study.

AS heterozygotes were not included in the study.

Inclusion criteria:

-black Congolese bantu for origin.

-No vertebral fractures or other high or low energy fractures in the antecedents.

-be free of any disease or drug treatment known to affect bone metabolism for a period greater or equal to 3 months.

Inhalation steroids, smoking, physical inactivity and athleticism, although likely to influence bone metabolism, were not exclusion criteria.

2.2 Measurements

2.2.1 Anthropometric parameters (age, height and weight) were collected according to standardized procedures.

2.2.2 BMI was calculated by dividing weight in kilograms by height in square meters [BMI in kg / m ^{2}= w (kg) / T ^{2}(m)].

Patients BMI was quoted in 6 steps according to the system proposed by WHO (WHO, 2006).

2.2.3 DXA examinations were performed using a hologic densitometer: Densitometer Hologic QDR Discovery (Hologic, Inc., Bedford, Mass., USA)

The BMC and BMD of the patients was measured at the hip (total hip), at the lumbar spine (anteroposterior projection of L1 to L4), distal 1/3 of the forearm and carp.

2.3 Statistical Analysis

Statistical analyses were performed using commercially available software (SPSS version 21).

The student t test was performed to compare the means (averages).

The search for associated factors was done using linear regression.

The threshold for significance was set at 0.05.

2.4 Others Statements

The design of the study was approved by the local ethics Committee and the study was conducted in accordance with the Helsinki Declaration for Human Studies.

The authors declare that they have no conflicts of interest.

3. Results

3.1 Characteristics of the Subjects

Parameters measured in SCA subjects and in the control, group are shown in Table 1.

Table 1. General Characteristics of Subjects According to Type of Hemoglobin

Variables	all n=629	AA n=359	SS n=270	p
Age (years)	37,4 ±13,7	44,2 ±12,9	35,1 ±7,0	**<0,001**
BMI	27,6 ±5,8	28,6 ±5,8	26,1 ±6,6	**0,033**
Hydroxy vitamine D	32,3 ±9,4	31,0 ±9,3	37,1 ±8,2	**<0,001**
Calcium	9,7 ±0,7	9,6 ±0,6	10,0 ±0,6	**<0,001**
ALT/SGPT	21,0 ±4,2	21,1 ±7,2	20,3 ±2,1	0,807
fasting glucose	91,4 ±5,6	94,4 ±27,7	79,8 ±6,3	**<0,001**
iron	72,9 ±9,7	77,4 ±31,0	55,7 ±9,7	**<0,001**
TSH 3rd generation	2,5 ±0,7	2,8 ±0,6	1,5 ±0,1	0,195
Cholesterol	204,6 ±36,2	202,5 ±39,3	212,9 ±18,1	**0,032**
DXA L1-L4: BMC (g)	14,9 ±3,5	15,1 ±3,5	13,9 ±3,2	**<0,010**
DXA L1-L4: BMD (g/cm^2)	1,04 ±0,2	1,05 ±0,2	0,90 ±0,27	**<0,001**
DXA hip total BMC(g)	38,8 ±9,3	45,0 ±8,9	38,1 ±9,1	**<0,001**
DXA hip total BMD (g/cm^2)	12,1 ±9,7	21,1 ±2,5	15,5 ±5,2	**<0,001**
DXA carp: BMC(g)	3,4 ±0,7	3,6 ±0,7	2,8 ±0,5	**<0,001**
DXA carp: BMD (g/cm^2)	0,66 ±0,22	0,98 ±0,09	0,88 ±0,27	0,098
DXA forearm 1/3: BMC(g)	3,1 ±1,8	3,4 ±1,9	1,8 ±0,09	**<0,001**
DXA forearm 1/3: BMD (g/cm^2)	0,77 ±0,07	0,78 ±0,08	0,70 ±0,02	0,560

Comparison of the two groups showed a lower BMI among SCAs, although of moderate statistical significance ($p = 0.033$).

Blood levels of vitamin D, serum calcium and cholesterol were significantly higher in SCA than in the control, ($p = 0.032$ to $p < 0.001$) whereas serum iron was significantly lower in SCA ($p < 0.001$)).

Excluding carpal BMD and distal 1/3 of the forearm, which showed non-significant differences ($p = 0.098$ and $p = 0.56$), the others bone mass parameters (BMC and BMD) at total hip and lumbar vertebrae were significantly higher in AA homozygotes than in SCA ($p < 0.001$).

3.2 Age Related Evolution of Biometrical and Biological Parameters

Table 2 shows age- and sex -related evolution of the parameters measured in SCA subjects.

Table 2. Age- and Sex -related Evolution of Biometrical and Biological Parameters

	MEN			WOMEN		
Age (years)	18-30	31-40	41-50	18-30	31-40	41-50
Weight (Kg)	63,5 ±6,3	65,7 ±9,4	55,00	59,94 ±7,44	60,52 ±6,39	67,00 ±8,50
Height (m)	1,68 ±0,07	1,73 ±0,01	1,74	1,64 ±0,10	1,66 ±0,07	1,63 ±0,14
BMI (kg/m^2)	22,08 ±1,90	25,57 ±2,32	17,5	22,47 ±3,96	26,13 ±2,23	27,99 ±6,15
OH vit. D	39,00 ±10,49	42,71 ±0,95	42,00	35,21 ±7,13	35,36 ±9,05	39,36 ±8,12
Calcium	10,23 ±0,64	10,39 ±0,36	9,70	9,90 ±0,63	9,83 ±0,66	10,14 ±0,56
ALT/SGPT	20,50 ±1,27	20,36 ±1,60	19,00	20,56 ±1,14	19,55 ±3,17	21,50 ±2,57
Fast glucose	81,45 ±3,92	84,57 ±3,41	86,00	77,69 ±5,83	79,00 ±7,11	82,00 ±7,75
Pp glucose	89,15 ±2,98	90,29 ±3,40	89,00	88,50 ±4,33	88,32 ±4,19	82,14 ±21,18
Serum iron	50,15 ±8,97	49,43 ±4,83	54,00	58,50 ±7,27	57,47 ±13,21	55,07 ±6,87
TSH 3rd gen	1,40 ±0,05	1,42 ±0,06	1,32	1,47 ±0,12	1,48 ±0,14	1,53 ±0,10
Cholesterol	199,5 ±8,8	208,4 ±10,7	192,00	218,3 ±15,2	213,4 ±23,08	217,7 ±20,4

Men had a larger size at all ages.

Height has increased among men with the aging while it remained almost stationary in the female sex.

The BMI is stackable in both sexes except in the 40-49 years age group where men disclosed a lean type BMI while women in this category were overweight.

The other parameters do not show any significant gender or age differences.

3.3 BMD and BMC Comparative Data According to the Type of Hemoglobin versus T-score

Table 3 shows the differences in BMD and BMC between SCA, AA and T-score according to the type of hemoglobin.

Table 3. Differences/Gap in BMC and BMD in Percent According to Hemoglobin Type

Parameter	SCA	AA	Gap SCA Versus AA (%)	T-score	Gap SCA Versus T-score (%)
VERTEBRAL BMC (g)	13,6 ±3,2	15,1 ±3,5	7,9	15.98 ±2.81	16,26
VERTEBRAL BMD (g/cm^2)	0,90 ±0,27	1,05 ±0,2	14,28	1.14 ±0.14	22,15
HIP BMC (g)	3,81 ±0,91	4,50 ±0,89	15,34	4.31 ±0.80	11,6
HIP BMD(g/cm^2)	1,55 ±0,52	2,11 ±0,25	26,54	1.94 ±0.17	20,11

The difference in BMC and BMD between SCA and controls group ranged from 7.94 to 26.34% (average of 16.02%) with a standard deviation ranging from -0.8 to -2.7.

By contrast, compared to the T-score (Kabeya et al., 2017), the values were 11.6 to 22.15% less and average of -17.5%, with a SD ranging from -0.9 to -2.

The overall decrease in the bone mass rate for -2.5 DS of the T-score was -28.4%, and it was 33.2% for -2 DS of the T-score.

Table 4 and Figure 1 show Age- and sex-related variation in BMD according to type of hemoglobin.

Table 4. Age-and Sex-related Variation in SPINE BMD According to Type of Hemoglobin

Age Group (years)	< 31	31-40	41-50
BMD mean AA men (g/cm^2)	1,31	1,4121	1,1231
BMD mean AA women (g/cm^2)	1,07	1,11192	1,0831
BMD mean SS men (g/cm^2)	0,97	1.0412	0,9732
BMD mean SS women (g/cm^2)	0,85	0,926	0,752

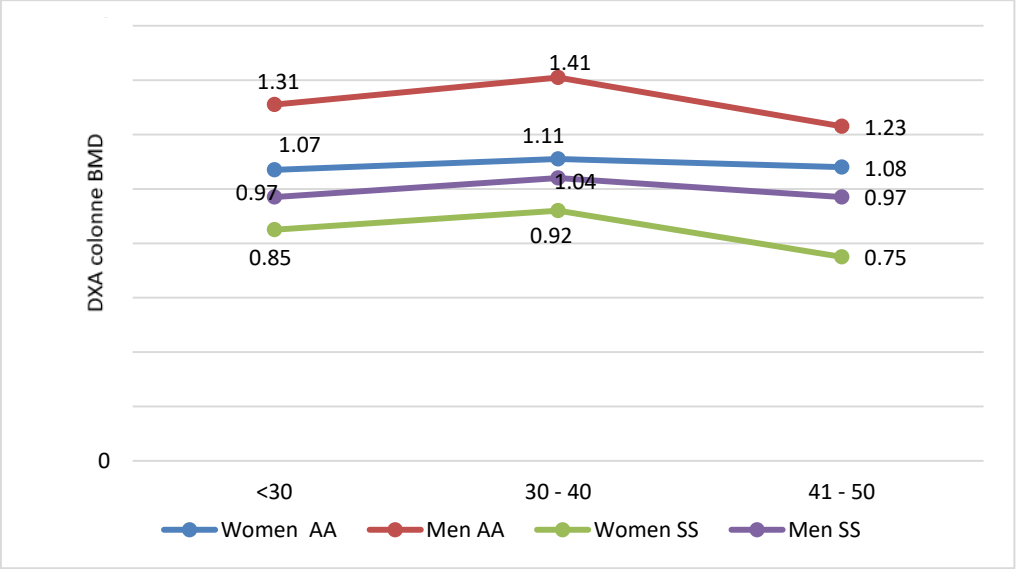

Figure 1. Age-and Sex-related Variation in SPINE BMD According to Type of Hemoglobin

Bone mineral density is higher in AA homozygotes at all ages. Females had lower rates than males of the same age.

Bone mineral density showed a peak of bone mass at the fourth decade of life in both SCA and AA controls followed by a decay with age.

3.4 Relationship between Parameters

The linear regression relationships between densitometric, biometric and biological parameters did not reveal significant relationships in SCA subjects.

Age showed a link, while vitamin D levels (Figures 2 and 3) showed no significant effects.

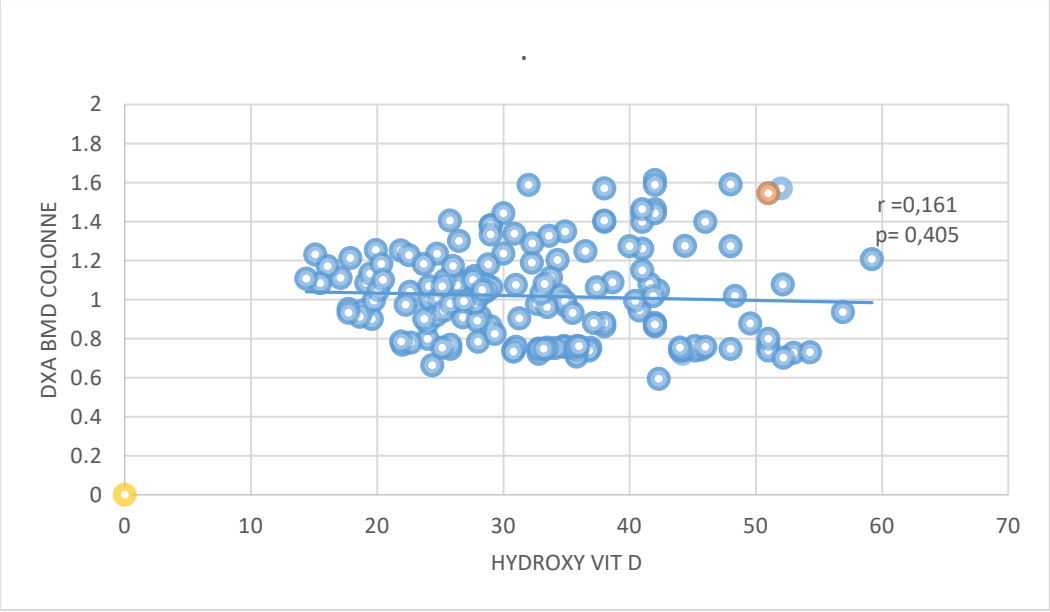

Figure 2. Regression of Lumbar Spine BMD by Vitamin D in SCA

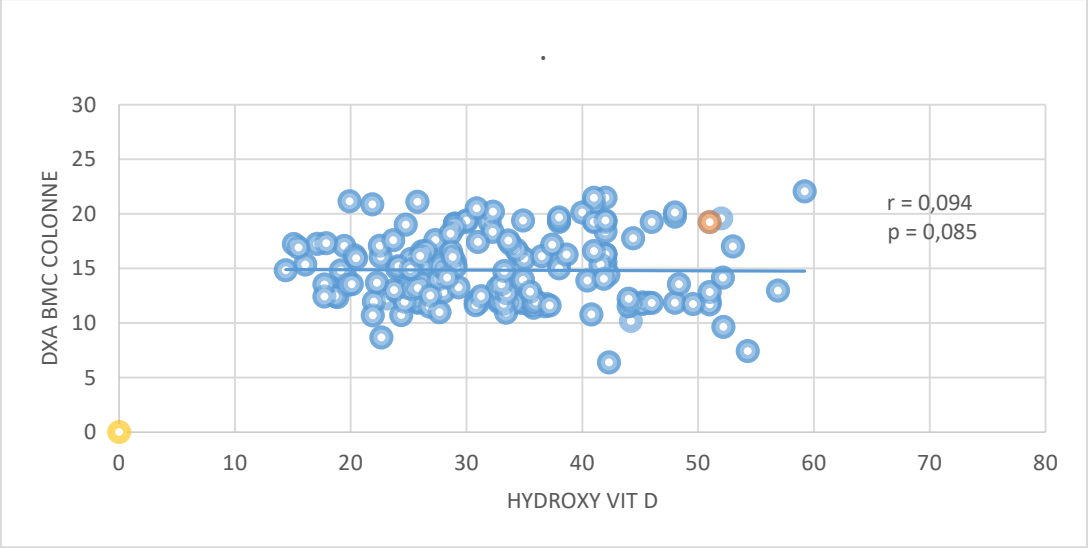

Figure 3. Regression of the BMC of the Lumbar Spine by Vitamin D in SCA

These figures expressed the absence of significant link between the parameters of the bone mass (BMC and BMD) at the spine with vitamin D levels.

4. Discussion

The aim of this study was to establish and confirm in Congolese SCA subjects, using DXA, the existence of bone remodeling disorders with osteoporotic translation and to compare the BMC and BMD values found in SCA Congolese subjects to those of a control population matched for age and sex.

Comparison of the two groups showed a miscellaneous difference between SCA subjects and controls (Table 1).

The BMI in SCA patients (Table 1) was lower than that of AA controls, although the data was of relatively moderate statistical significance ($p = 0.033$). This finding seems to be a phenomenon related to nutritional status, repeated infectious episodes and the metabolic status in SCA patients. A low BMI in SCA is richly documented in children and adults with SCA who have pre- and post-pubertal growth deficits and a weight at the 5th to 10th percentile of normal weight for age in some studies (Kazadi et al., 2017; Henderson et al., 1994; Aloni et al., 2014; Finkelstien et al., 1996).

Kazadi et al. (2017) and Platt et al. (1984) reported stunting, impaired body composition, delayed skeletal and sexual maturation, and chronic nutritional deficiencies in children with SCA resulting in errors when WHO or American population growth curves are used (Chawla et al., 2013; Kazadi et al., 2017; Muchanga et al., 2014; Reed et al., 1987; WHO, 2006).

In our study group (Table 1), the majority of subjects over 30 years old were nonetheless overweight.

Mikobi et al. (2017) links a near-overweight BMI to a common phenotypic type in the SCA population in Congo with a high average steady-state hemoglobin concentration and significantly higher rate of fetal hemoglobin (HbF). Overweight subjects was also found in a hight proportion in the Congolese population studied by DXA (Kabeya et al., 2017) and in the Congolese peri-menopausal by Muchanga et al. (2014).

Being overweight appeared to be a stigma in this population undergoing an epidemiologic transition in weights.

In this study (Table 2), unexplained higher blood levels of vitamin D ($p > 0.001$), serum calcium $p > 0.001$), and cholesterol ($p = 0.032$) were seen in SCA patients versus the controls.

Previous studies have reported that patients with SCA have more vitamin D deficiency than their counterparts who are supposedly in good health (Samim et al., 2013; Chapelon et al., 2009; Ross et al., 2011).

The role of the sun on the rate of vitamin D production cannot explain such a difference according to the type of hemoglobin (Buison et al., 2005).

Vitamin D is an important factor in bone formation. Nevertheless, previous studies on BMD in SCA patients including measurement of 25-hydroxyvitamin D levels, revealed a decrease in vitamin D in

almost all participants, but no significant association between vitamin D and BMD was noted in our subjects (Figures 3 and 4) as in the studies by Buison et al. (2005) as well as that of Samim-Özen et al. (2013).

It is known that vitamin D deficiency is a common, serious medical condition that significantly affects the health and well-being of older adults even in tropical countries and sunny climates. In addition, low vitamin D is linked osteoporosis (MacLaughlin et al., 1985).

In Europe, representative residents from the SENECA study of older Europeans aged 75-76 years old showed 36% of men and 47% of women were vitamin D deficient, most markedly in southern Europe, in a survey of 19 towns in 11 countries in the winter of 1988-1989 (Van der Wielen et al., 1995),

Furthermore, in the study of Bullamore et al. (1970), Calcium absorption was measured by plasma radioactivity after oral and malabsorption of calcium in the elderly were linked to vitamin-D deficiency, and plays a significant role in the pathogenesis of fractures in old people.

We don't have subjects nor control aged 50 and over.

BMC and BMD (Table 3) at the total hip and lumbar vertebrae were generally significantly higher in AA homozygotes than in SCA patients and varied with age and sex (Table 4).

Figure 3 showed curves of the same profile but under offset. The overall BMD rate below 2.5 SD was: 28.4% and it was 33.2% for -2 SD of T-score in this study.

The prevalence of low lumbar spine BMD (Z-score < -2 SD) varies from country to country.

Low lumbar spine BMD was 41% among Brazilian SCAs [9], 56% in the United States (Van der Wielen et al., 1995; Miller et al., 2006) and 19% in France (Ross et al., 2011).

The differences in the observed low BMD percentages can be explained by the difference in selection criteria, quality of care, difference in nutritional status, and size of samples among the various ethnicities. In USA (Miller et al., 2006; Lal et al., 2006) the patients recruited were heavily ill. In Brazil, the sample size was relatively small (Meeuwes et al., 2013) whereas our sample is made of ambulatory patients without, serious clinically problems.

With T-scores ranging from -0.9 to -2 standard deviations and Z-scores ranging from -0.8 to -2.7 standard deviations, the present study showed overall bone mass deficits superimposed on the Brazilian data which ranged from -0.8 to -1.81 for the T-score and an average of -2 SD for the Z-score, which appeared to be more deficient as the BMI was low (Meeuwes et al., 2013).

In the absence of normative size data for age (Kazadi et al., 2017) in our population, we could not verify the assertion regarding the significant relationships observed between BMD and low height for age, weight for age and BMI for age reported in several SCA studies (Henderson et al., 1994; Luban et al., 1982; Barden et al., 2000; Meeuwes et al., 2013; Bullamore et al., 1970; Lal et al., 2006; Miller et al., 2006; Baldanzi et al., 2011) but also between BMI and BMD in the general population (Kabeya et al., 2017).

Other studies have found no relationship between height or BMI and BMD (Chapelon et al., 2009; Lal A et al., 2006; Sarrai et al., 2006).

The present study did not seek to evaluate the quantity and the quality of the food intake of our subjects who are considered weak (Kazadi et al., 2017), Therefore, we can not determine the contributions of calories, calcium, microelements or vitamin D in the disclose of low BMD.

However, given that patients with SCA have high nutritional needs since they have a chronic hyper-metabolic state (Bookchin et al., 1996; Kazadi et al., 2017; Piel et al., 2013; Henderson et al., 1994; WHO, 2006; Chawla et al., 2013; Reed et al., 1987; Muchanga et al., 2014; Samim et al., 2013; Chapelon et al., 2009; Ross et al., 2011; Buison et al., 2005), low BMD is expected to result partly from inadequate nutritional intake.

The exact mechanism leading to low BMD in SCA patients is probably multifaceted.

Chronic kidney diseases related to sickle cell anemia may also serve as a factor. SCA patients are known to have progressive decline in kidney function associated with microalbuminuria (Aloni et al., 2017), and in adulthood, a decline in kidney function appears to be progressive from 40 years of age

Complications associated with SCA including bone infarction, osteonecrosis and osteomyelitis have a direct effect on bone structures. Infarcted areas of the bone are sites at high risk for osteomyelitis. In addition, repeated episodes of decreased blood flow and bone marrow hyperplasia can lead to loss of bone trabeculae, altering bone strength and increasing fracture risk.

This finding is due to the total bone strength being based on the combination of material properties (the mineral phase and the composition of the extracellular matrix), bone volume, and the micro and macro architecture.

5. Conclusion

Sickle Cell Anemia patients have low bone mass, osteopenia and osteoporosis, and greater susceptibility to fractures

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