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Bone Density in Children with Single Ventricle Physiology

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Abstract

Background—Children with chronic diseases are at risk for low bone mineral density (BMD). There are no studies of BMD in children with congenital heart disease and particularly SV. Children with this defect are often treated with warfarin, suspected to negatively impact BMD in adults. We assessed BMD in patients with single ventricle (SV) physiology and compared the BMD of subjects taking warfarin to those who were not.

Methods—Subjects 5-12 years with SV were included. BMD z-scores by dual-energy X-ray absorptiometry (DXA) of the spine and total body less head (TBLH) were obtained. Calcium intake, activity level, height, and Tanner stage were assessed. Linear regression models and t-tests were used to investigate differences between participants and normative data as well as between subjects' subgroups.

Results—Twenty six subjects were included; 16 took warfarin. Mean BMD z-score at the spine was significantly lower than expected at -1.0±0.2 ($p<0.0001$), as was the BMD z-score for TBLH at - 0.8±0.2 ($p<0.0001$). Those results remained significant after adjusting for height. Subjects who were on warfarin tended to have lower BMD at both the spine and TBLH than those who were not, with a z-score difference of 0.6±0.46 at the spine ($p=0.106$) and a difference of 0.4±0.34 at TBLH ($p=0.132$).

Conclusions—BMD is significantly reduced in children with SV. Warfarin appears to lower BMD but the effect is less conclusive. Continued evaluation is recommended for these patients at risk for reduced bone density. Evaluation of other cardiac patients on warfarin therapy should also be considered.

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Keywords

congenital heart disease/defects; bone mineral density; bone health; child health status; anticoagulation

Introduction

Since inception of the Fontan procedure in 1971 to treat single ventricle patients,[1] early mortality has decreased substantially, and delineating and avoiding associated long-term morbidities have become of great interest. Described morbidities include dysrhythmia, systemic ventricular dysfunction, protein-losing enteropathy, and thromboembolic complications.[2-4] With increasing number of patients surviving the Fontan operation well into adulthood anthropometric patterns have been well described in such patients.[5-8] However, no study has looked at the bone mineral density (BMD) in such a population although these patients are, theoretically, at a greater risk of having low BMD because of the chronicity of their condition.[9-10]

Thrombolic events (TE) in Fontan patients occur at the venous and arterial level. Venous TE have been described in 3 to 16% of patients post-Fontan, and arterial emboli occur in 3 to 19% of patients.[11-17] However, the time course at which TE occur is not well elucidated: While some authors report TE most commonly in the first year with a second peak 10 years after surgery,[12] others observed the initial risk and a continued risk thereafter,[18] or no association with time after surgery.[11]

Because of the possibility of thrombosis, anticoagulation has been used for patients after Fontan completion. Retrospective studies have shown anticoagulation to reduce the risk of TE.[19-20] However, multiple other studies have found that prophylactic anticoagulation is not routinely required in all children after Fontan completion.[21-25] More recently, a multicenter prospective study in which patients post Fontan were randomized to receive warfarin or aspirin failed to show any difference between aspirin and warfarin as primary thromboprophylaxis in the first 2 years after Fontan surgery.[26] Hence, the necessity, optimal duration, and best means of anticoagulation for Fontan patients remain controversial leading to different practices among cardiologists ranging from no anticoagulation to chronic warfarin +/- aspirin treatment.[21-22]

Recently, there has been mounting concern that warfarin might worsen bone mineral accrual and maintenance and may lead to osteoporosis in adult.[27-30] There are only two published studies that examine the effect of warfarin in children.[31-32]

The aim of our study was, therefore, to describe results of BMD assessments performed on subjects with the same medical condition (SV) and within a narrow age range to study the effect of warfarin on BMD. We hypothesized that children with single ventricle (SV) physiology would have lower BMD compared to the normal population. We also hypothesized that, within our SV group, subjects who were on warfarin would have lower BMD compared to those who were not.

Materials and Methods

We included children between 5 and 12 years of age with SV physiology, without known bone disease or oral steroid intake. By starting at age 5, we incorporated the lowest age for which normative densitometry data for BMD were available. By limiting the upper age to 12 years, we tried to eliminate puberty as a confounding variable. There are also fewer discrepancies in diet and exercise within this age group.

Between March 2010 and March 2011, we enrolled patients satisfying our criteria. The project was approved by the Indiana University Institutional Review Board. Consent from parents or guardians as well as assent from children older than 7 years of age were obtained. Questionnaires to assess for calcium intake, physical activity, and Tanner staging were also completed.

BMD of the total body less head (TBLH), lumbar spine (L1-L4), and hip were assessed using dual energy x-ray absorptiometry (DXA) (Lunar Prodigy). Results were expressed as z scores based upon reference manufacturer data.

Calcium intake was assessed using a questionnaire based on the criteria by Musgrave et. al. [33] The questionnaire allows estimations of calcium intake in mg/day. History of fractures in our cohort was obtained from a questionnaire that guardians filled out about their children prior to the DXA scan.

Physical activity was assessed using the *Physical Activity Questionnaire for Older Children (PAQ-C)*.[34] This questionnaire measures general physical activity over the previous 7 days. It consists of nine items; each has a 5-point response scale ranging from low “1” to high activity “5”. A total PAQ-C summary score, which can range from 1 (low activity) to 5 (high-activity), is calculated by dividing the total scores for the nine items by the number of items. The Physical Activity Questionnaire has been shown to have acceptable validity for research purposes: one week test ± retest reliability was $r = 0.75$ for boys and 0.82 for girls. [34] Tanner staging was self-reported by patients and their guardians.[35]

Clinical, surgical, catheterization and echocardiography data were collected on patients enrolled. Patients were considered to have been on long-term warfarin therapy if they had been prescribed the anticoagulant for longer than 18 months. Compliance was confirmed by reviewing the patients' international normalized ratio (INR) values. Except for the presence of a mechanical valve where a target INR of 2.5 and above was sought, an INR between 1.5 and 2.5 is considered therapeutic in our SV patients.

Oxygen saturation data were collected from clinic notes; a cutoff of 92% for the oxygen saturation determined by pulse oximetry was selected to differentiate between patients with low and high saturation.

All analyses were performed using the standardized BMD measured from the spine, the standardized BMD for the TBLH, and the bone mineral content (BMC) which represents the bone mass. The one sample *t* tests were used to test for differences between the study participants and the normal population. To test for differences among patients who had

different functional SV and among those who were on warfarin, pooled *t* tests were used. Regression models were fit in order to investigate the difference among these patients while controlling for potential confounding variables. The response variable for these models was the standardized BMD or BMC while the main factor of interest was warfarin or functional single ventricle. Other covariates included in the models were Fontan type, activity level, oxygen saturation by pulse oximetry, and height. Results are given below and are reported as "mean ± standard error" along with a one-sided p-value. The one-sided p-value is reported since there is prior indication that those patients on warfarin and with single right ventricle were predisposed to having lower BMD.

Results

Seventy subjects were identified who fit our inclusion criteria. Thirty seven were contacted prior to their appointments. Of those, 9 patients refused enrollment and 2 had scheduling difficulties. The remaining 26 constituted our cohort. (Table 1)

Thirteen (50%) were male. All but three were white. Median age at time of the DXA was 8.6 years (range 5.6 - 11.5). Median z-score for height was -1.08 (range -3.82 to 0.94). Median BMI z-score was -0.03 (range -2.96 to 1.83). All subjects were prepubertal except for one 11.5 year old-girl, who was Tanner III. The calcium and activity questionnaire was completed by 24 participants. Median calcium intake was 1100 mg daily (range 360 – 2600) with 19 patients reporting intakes of more than 1000 mg/day. The median score on the PAQ-C was 2.5 (1 – 4.1) indicating mild to moderate activity levels.

Four subjects reported a history of bone fracture. All of them were in the group receiving warfarin. Three were females and 1 was male. One subject had an arm broken at age 2 years; one had a thumb broken at age 2 years; one sustained a leg fracture as a baby, and the fourth one had both her elbows broken at age 8 years while playing soccer. The first three subjects sustained their fractures prior to the initiation of the warfarin therapy. The last subject had been on warfarin when her fracture occurred; the z-score for her BMD spine was -1.8 and the z-score for the TBLH BMD was -1.7. Because of the small number of subjects, especially since only one of them was on warfarin at the time the fracture occurred, no statistical analysis was conducted to evaluate the effect of warfarin intake on bone fracture in our cohort.

Eighteen (69%) patients had a single right ventricular physiology. The remaining 8 (31%) had either single left or mixed ventricular morphology.

Twenty five patients had had the Fontan procedures prior to the time of their DXA. One patient was at the hemi-Fontan stage. Of the twenty five patients who had their palliation completed, 7 had an extracardiac type repair while 18 had a lateral caval (LC) Fontan. All but one patient with a LC palliation had a fenestration at the time of the Fontan ranging from 2.5 – 4 mm in size. Sixteen patients were found to have O2 saturation ≥ 92% by pulse oximetry. Sixteen patients had received warfarin for more than 18 months. At the time of DXA, 14 subjects were still on warfarin. Although use of warfarin was at the cardiologist's discretion, the most common indication for warfarin was the presence of a fenestration (n =

11). All were on aspirin 81 mg daily. Table 2 compares the patients who are on warfarin and those who are not, taking into account various parameters. There was a trend toward a difference between groups in age (p=0.059), and significant differences between groups in z-scores for weight and BMI.

A spine DXA was obtained on all subjects. DXA of the TBLH was done on 24 patients. The mean z-score for BMD spine in all our SV patients was -1.0 ± 0.2 (p<0.0001). (Figure 1) This result was also significant when adjusting for height: the mean z-score for BMD spine was -0.8 ± 0.3 (p=0.004). Similarly the mean z-score for TBLH BMD in all our SV patients was -0.8 ± 0.2 (p<0.0001). This result was also significant when adjusting for height with the mean z-score for BMD TBLH -0.5 ± 0.2 (p=0.004).

Subjects on warfarin tended to have lower BMD at both the spine and TBLH than those who were not, with a z-score difference of 0.6 ± 0.5 at the spine (p = 0.106) and a difference of 0.4 ± 0.3 for TBLH (p = 0.132). (Figure 2) After adjusting for activity level, Fontan type, oxygen saturation, and height, we still found spine BMD tended to be lower (z-score differences of 0.5 ± 0.4, 0.5 ± 0.4, 0.7 ± 0.4, 0.5 ± 0.5, respectively) among patients receiving warfarin compared to those who were not on warfarin, although not statistically significant (p = 0.134, p = 0.142, p = 0.072, p = 0.132, respectively). (Table 3)

Because of the differences found in table 2, we compared the z- score for BMD spine and the z-score for BMD TBLH in patients on and off warfarin, sequentially adjusting for weight, z-score of weight, BMI, z-score of BMI and age. Adjustment for these variables did not significantly change the trends seen in the above models.

When comparing BMD of patients based on their functional single ventricle, we found that patients with single right ventricle also tended to have lower BMD than those patients with single left or mixed ventricular morphology. The mean difference in z-score for BMD TBLH was 0.6 ± 0.4 (p = 0.055). After adjusting for warfarin, activity level, Fontan type, oxygen saturation, and height in these patients we found similar trends with mean z-score differences of 0.6 ± 0.4, 0.6 ± 0.4, 0.4 ± 0.4, 0.5 ± 0.5, 0.4 ± 0.3, respectively (p = 0.064, p = 0.055, p = 0.122, p = 0.158, p = 0.152, respectively). (Table 3)

Discussion

Oral anticoagulants exert their effect by inhibiting vitamin K reductase and vitamin K epoxide reductase in the liver and bones, leading to vitamin K deficiency in these organ systems. Vitamin K is an essential cofactor for the vitamin K-dependent carboxylase. In the bone, through the effect of the vitamin K-dependent carboxylase, vitamin K is responsible for the posttranslational modification of three bone matrix components: osteocalcin, matrix Gla protein, and protein-S.[36] Matrix Gla protein has been shown to promote endochondral calcification. Vitamin K is also important for osteoblast differentiation. Hence by causing vitamin K deficiency, warfarin leads to decreased bone mineralization.

Many studies suggest that long-term oral anticoagulation therapy with vitamin K antagonists might be associated with a modest increase in osteoporotic fracture risk.[30] This may be due to decreases in bone formation. Childhood is a critical period of bone mineral

acquisition. Adequate accrual of bone mass is important for preventing fractures in children and osteoporosis in adults.[37-38] Therefore, therapies that adversely affect bone mineral accrual will have particularly severe effects in pediatric populations. Studies that examine the effects of warfarin on BMD in children are very limited. One study enrolled 23 children between 5 and 18 years of age who were on warfarin for various reasons, cardiac and noncardiac. The conclusion was that long-term use of warfarin may cause low BMD for age and sex.[31] A second report of seventeen patients with a mean age 14.7 years (range 8.6 to 18.8 years) with various cardiac diseases on warfarin for a mean of 8.2 years (range 1-14 years) showed a reduction in lumbar spine bone mineral apparent density and z-scores compared to controls.[32] Of note, however, the children in the treated group, although height- and weight-equivalent to the controls, were older and no attempt was made to control for puberty, which greatly influences BMD at these ages. In addition neither study compared BMD of patients on warfarin with a specific medical condition to patients with the same condition but who are not taking warfarin. Rather the comparison was done to normative data for BMD; hence it is difficult to conclude whether the effect seen is related to the warfarin or to the medical condition for which these patients are on warfarin.

Our study demonstrates that children with SV have decreased BMD compared to the normal population even after palliative repair of their congenital heart disease. Because patients post Fontan surgery are shorter and BMD is height-dependent,[8] we adjusted our data to height and the results were very similar. To our knowledge, this is the first report that highlights this important finding.

Another interesting finding is that subjects with single left or mixed ventricular morphology tend to have a higher BMD than those patients with single right ventricle even after adjusting for variables including warfarin intake. It is difficult to give a clear explanation for our finding. However, patients with left single ventricle fare better than patients with a single right ventricle as the left ventricle can better sustain the systemic pressure than the right ventricle and hence, is less likely to fail.[39] Our speculation is that it is the fact that these patients do better in general that leads to better BMD.

As survival after the Fontan procedure continues to improve and the Fontan population continues to grow older, recognizing low bone mass early on and initiating early therapy when necessary will minimize the risk of subsequent bone fractures. In our center, we referred patients who were found to have a BMD z-score below -2 to pediatric endocrinology for evaluation. Therapy was instituted in the form of lifestyle and dietary changes by encouraging exercise and increasing vitamin D and calcium intake. Because of their young age and the potential for bone growth during puberty, no medications were started. These patients will be followed up by the endocrinologists yearly and repeat DXA scan will be performed at their discretion.

As the efficacy of warfarin in reducing TE after the Fontan procedure continues to be controversial,[19-26] avoiding potential side effects of this medication might be a decisive factor in limiting its use. Significant risk of bleeding is well established in Fontan patients on warfarin.[22,26,40] In our study, the effects of warfarin on BMD were not conclusive. However, although not statistically significant, our results show a trend for decrease BMD in

patients who are on chronic warfarin even after adjusting for activity level, Fontan type, oxygen saturation and height.

Interpretation of our results is subject to certain limitations. Because of the small number of patients that could be enrolled in one year, our finding that warfarin decreases BMD did not reach statistical significance. Furthermore therapy with either warfarin and aspirin or aspirin alone was not randomized but rather left at the cardiologist's discretion. Except for the presence of a fenestration, we did not find any other indication to start warfarin. Therefore the two groups of patients, the one taking warfarin and the one not taking should be very similar except for a slight difference in O2 saturation. This was not shown to have any effect on BMD when we adjusted our results for O2 saturation.

In conclusion, our study is the first to show that BMD is significantly reduced in patients with SV compared to age and sex matched norms. It is also the first in the pediatric age group to compare the effect of warfarin on BMD within a very similar patient population particularly, and most importantly, in regards to the medical condition for which warfarin is prescribed. Warfarin appears to lower BMD but the effect is less conclusive. Having a functional single right ventricle also appears to predispose these patients to decreased BMD compared to having a functional left ventricle. Based on our data, we recommend performing DXA scan in patients with SV, and particularly those on warfarin and/or single right ventricle, at some point before puberty to identify patients with low BMD and hence avoid a potential risk of bone fracture in early adulthood. Continued enrollment and further study are recommended to better elucidate the effects of warfarin on BMD. Finally, the evaluation of other cardiac patients in general and those taking warfarin in particular should also be considered.

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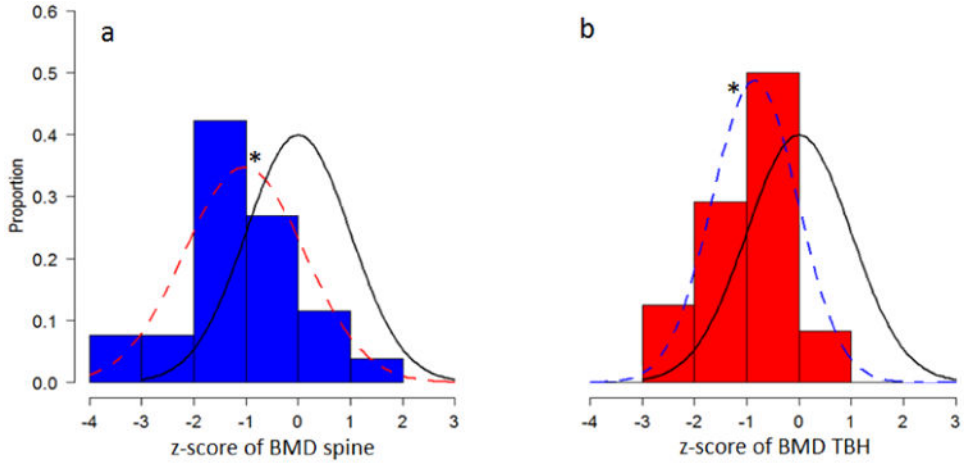

Fig. 1.

Comparison of mean z-score BMD in SV patients and normal population.

a. The mean z-score for BMD spine in SV patients was -1.0 ± 0.2; b. the mean z-score for BMD TBLH in the same population was -0.8 ± 0.2. The broken, lines on both diagrams represent the mean z-score BMD in our population compared to the mean in the normal population in full, black, line. *P < 0.0001

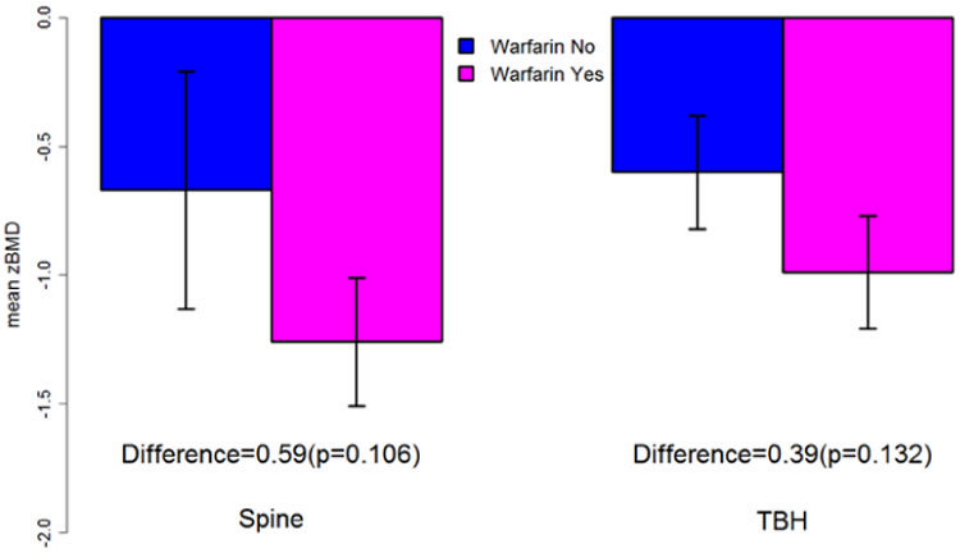

Fig 2.

Comparison of mean z-score BMD for patients who were on warfarin and those who were not.

Subjects on warfarin tended to have lower BMD at both the spine and TBLH than those who were not with a z-score difference of 0.6 ± 0.5 at the spine (p = 0.106) and a difference of 0.4 ± 0.3 for TBLH (p = 0.132). The purple bar refers to warfarin treatment whereas the blue bar indicates no warfarin treatment. Data are presented as mean ± SD

Table 1

Demographic and cardiac characteristics of the cohort

Demographic/Cardiac Characteristics	Sample size *n* (%)
No. of participants	26
Gender	
Male	13 (50%)
Female	13 (50%)
Ethnicity	
Caucasian	23 (88%)
African American	2 (8%)
Chinese	1 (4%)
Cardiac anatomy	
RV	18 (69%)
LV	8 (31%)
Surgical palliation stage and type	
Fontan	25 (96%)
Extracardiac	7 (28%)
Lateral caval	18 (72%)
Fenestrated	17 (94%)
Non fenestrated	1 (6%)
Hemi-Fontan	1 (4%)
Warfarin	
Yes	16 (62%)
No	10 (38%)
Aspirin	
Yes	26 (100%)
No	0 (0%)
O2 saturation	
> 92%	16 (62%)
< 92%	10 (38%)

Table 2

Comparison of the patients who were on warfarin and those who were not.

	Warfarin (16 pts)	No warfarin (10 pts)	p value
Male *n* (%)	7 (44%)	6 (60%)	NS
Caucasian *n* (%)	14 (88%)	8 (80%)	NS
Feeding problems *n* (%)	3 (19%)	1 (10%)	NS
HLHS *n* (%)	11 (69%)	7 (70)	NS
Lateral caval Fontan *n* (%)	11 (69%)	8 (80%)	NS
Fenestration *n* (%)	11 (69%)	7 (70%)	NS
Oxygen saturation (%)	92.3	92.8	NS
Age at time of DXA (years)	8.9	7.5	0.059
Height at time of DXA (cm)	126	120	NS
Z-score height	-1.17	-0.83	NS
Weight at time of DXA (kg)	26.1	24.9	NS
Z-score weight	-1.16	-0.06	0.0146
BMI (kg/m^2)	15.9	17.2	NS
Z-score BMI	-0.52	0.6	0.0045
Calcium intake (mg)	1188	1476	NS
Activity (activity units)	2.5	2.5	NS

BMI = body mass index; DXA = dual energy x-ray absorptiometry; HLHS = hypoplastic left heart syndrome; NS = nonsignificant; Pts = patients.

Table 3

Comparison of mean z-score BMD between patients on warfarin and those who were not and between patients with LV and those with RV. Patients who were on warfarin and patients with RV had decreased BMD compared to their counterparts adjusting for various variables.

	Total	Adjusting for warfarin intake	Adjusting for activity level	Adjusting for Fontan type	Adjusting for oxygen saturation	Adjusting for height
BMD spine z-score difference between patients not on warfarin and those who are	0.6 ± 0.5 (p = 0.106)		0.5 ± 0.4 (p = 0.134)	0.5 ± 0.4 (p = 0.142)	0.7 ± 0.4 (p = 0.072)	0.5 ± 0.5 (p = 0.132)
BMD TBH z-score difference between patients with LV and those with RV	0.6 ± 0.4 (p = 0.055)	0.6 ± 0.4 (p = 0.064)	0.6 ± 0.4 (p = 0.055)	0.4 ± 0.4 (p = 0.122)	0.5 ± 0.5 (p = 0.158)	0.4 ± 0.3 (p = 0.152)

BMD = bone mineral density; LV = single left or mixed ventricle physiology; RV: single right ventricle physiology; TBH: total body minus head.