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Progressive loss of bone mass in children with Fontan circulation

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Abstract

Objective: We investigated bone mineral density (BMD) at different ages after the Fontan completion, and we evaluated the relationship between BMD, vitamin D levels, and pertinent patient variables.

Methods: A cross-sectional sample of 64 patients was examined with dual-energy X-ray absorptiometry (DXA) scans to determine BMD. Of these patients, 24 were also examined with BoneXpert software to determine bone *mass* density (BMX), expressed as the bone health index (BHI). Blood samples from all patients were analyzed. Patients were divided into three different age groups; A: 4-9 years old (n = 22), B: 10-15 years old (n = 21), and C: 16-18 years old (n = 21).

Results: Overall, BMD z scores were (mean ± SD): −1.0 ± 1.3 for the lumbar spine and −0.2 ± 1.2 for the total body. Groups B and C had significantly lower z score values compared to group A. Of patients in group C, 35% had z score values ≤−2 SD of the mean of the healthy population. There was no difference related to systemic ventricular anatomy (left or right); however, patients with lateral tunnels had lower BMD than patients with extra cardiac conduits. Overall, the BHI z score was (mean ± SD): −1.2 ± 0.9, but low BMX did not correlate with low BMD. The 25-hydroxy vitamin D level was 58 ± 30 nmol/L. Vitamin D levels decreased with age: in group C, 33.3% of patients exhibited vitamin D deficiencies. Vitamin D levels were not correlated with bone mineral densities.

Conclusion: BMD levels decreased with age in patients with Fontan circulation. Different bone components were involved. Vitamin D levels also decreased with age, but they were not consistently associated with bone mineral densities. The single factor most predictive of low BMD was a lateral tunnel Fontan, compared to an extra cardiac Fontan.

KEYWORDS

bone mineral density, extra cardiac conduit, Fontan, lateral tunnel, univentricular heart, vitamin D

1 | INTRODUCTION

Survival rates of children with univentricular heart defects have improved dramatically, since the introduction of the palliative Fontan procedure. This stepwise surgical treatment leaves children with only one functioning heart chamber that supplies the systemic circulation. When completed, at around 3 years of age, the entire systemic venous return is rerouted past the heart; instead, it drains directly into the pulmonary arteries, advancing without the energy supplied by the right heart chamber.

In addition to improve the outcomes in these patients, focus has increased on late morbidity. Recently, we have come close to fully appreciate the notion that Fontan circulation inevitably leads to multi-organ disease.[1-4]

Our previous clinical observation that vitamin D deficiencies occurred frequently in adolescents with Fontan circulation raised concern regarding a potentially unrecognized failure in bone mineralization.[5] Awareness of bone health is highly relevant, because throughout life, this patient group encounters factors that favor bone resorption, rather than acquisition, such as physical inactivity[6] and long-term steroid treatments.[7]

The present study aimed to investigate bone mineral density (BMD) at different ages after the Fontan completion and to evaluate the relationship between BMD, vitamin D levels, and pertinent patient variables.

2 | MATERIALS AND METHODS

2.1 | Study population

The study participants were recruited from Oslo University Hospital, which is the only surgical center that treats patients with congenital heart disease (CHD) in Norway. From our patient database, which stores records of all children with surgically treated CHD, we identified 64 children living with a Fontan circulation. The younger participants (group A: 5-9 years and group B: 10-15 years) were recruited from all patients with Fontan circulation that were living within 150 km approximately from our center. Families with eligible patients were approached, either during routine outpatient visits or by telephone. The older, adolescent participants (group C; 16-18 years) were recruited during a comprehensive routine work-up, before transition to adult care. The only exclusion criterion was any metabolic disorder other than diabetes.

We reviewed patient medical records to extract variables of cardiac anatomy, the date and type of Fontan operation, duration of pleural effusion after TCPC, and a clinical history of protein losing enteropathy (PLE). We interviewed patients to gain data on fracture histories, medications, and participation in recreational activities. A clinically significant fracture history was defined as either two long bone fractures that occurred by 10 years of age, three long bone fractures that occurred at any age, up to 19 years or 1 vertebral fracture.[8] Participation in organized recreational physical activities (competitive or non-competitive) was defined as weekly attendance (yes or no).

2.2 | Bone mineral density measurement

BMDs were measured at the lumbar (L2-L4) spine and over the entire body. Measurements were acquired with a narrow fan beam, dual-energy X-ray absorptiometer (DXA; GE Healthcare Lunar Prodigy densitometer, Lunar Corp., Madison, WI, USA) and analyzed with the accompanying software (version 16 [SP2]) according to a standard protocol.[9] The *z* score was estimated by comparing measured BMDs to those in the Lunar reference database, incorporated in the software. The Lunar database included BMD reference data from healthy youth of similar ages, sexes, and ethnicities.[10] Absolute BMD values were expressed as the amount of mineral per square centimeter (g/cm^2). BMD *z* scores were adjusted for bone age, based on radiograph, when possible. A *z* score below −2 standard deviations (SD) from the healthy population mean was labeled "low." We defined osteoporosis as the presence of a clinically significant fracture history, accompanied by a low BMD *z* score (≤−2 SD).[8]

2.3 | Hand radiograph

Among the 64 patients included, 27 underwent radiographs of the left hand to measure bone growth. This value was used to investigate potential confounding deviations in bone age. Bone age was determined with the BoneXpert, a digital, automated method for assessing bone age.[11,12] Delayed or accelerated growth was defined as an estimated bone age that deviated at least ±2 SD from the mean bone age expected at the corresponding chronological age.[13] Furthermore, the BoneXpert method provided an automated estimation of bone mass density (BMX), based on radiogrammetry. The cortical thicknesses of the metacarpals were measured and compared to their lengths and widths. The results were corrected for bone age and expressed as the Bone Health Index (BHI). The BHI SD score was defined as *z* score of the mean BHI. This automated method for estimating BMX has been validated in a healthy pediatric population for several diseases.[14,15]

2.4 | Laboratory studies

Blood samples were drawn, and serum vitamin D (25(OH)-D) levels were quantified with liquid chromatography in tandem with mass spectrometry at the Hormone Laboratory, Oslo University Hospital, Oslo, Norway. Vitamin D results were categorized according to current recommendations.[16] A vitamin D deficiency was defined as a serum 25(OH)-D level ≤30 nmol/L (12 ng/mL). A vitamin D insufficiency was defined as a 25(OH)-D level between 30 and 50 nmol/L (20 ng/mL). Vitamin D sufficiency was defined as a 25(OH)-D level above 50.0 nmol/L. When 25(OH)-D levels were <12 nmol/L, we used 12 nmol/L as the value in calculations, which likely contributed to slight overestimations of the mean group levels. When evaluating vitamin D levels, we used the 25(OH)-D levels recorded at the time of inclusion. However, for some patients, there was a time delay between the initial vitamin D measurement and the DXA measurement. When the time

interval exceeded 90 days, the vitamin D measurement was repeated, and the new value was used in correlation and regression analyses.

This study was approved by the Institutional Review Board at Oslo University Hospital and by the Regional Ethics Committee. The study was conducted according to the Declaration of Helsinki II. Depending on patient age, written informed consent was obtained from patients and/or caregivers.

2.5 | Statistics

Categorical variables are expressed as frequencies and proportions. Continuous variables are presented as the mean ± SD, when normally distributed, and as the median and interquartile range (IQR), otherwise. Between-group comparisons were performed with the Student's *t* test, ANOVA, or rank sum test, as appropriate. Bivariate correlations are expressed as the Pearson's correlation coefficient. Crude and adjusted linear regression analyses between independent factors and the BMD were performed for the whole body or for the spine only. In the multivariable model, we adjusted for factors that might potentially influence the dependent variable. Results are presented as the beta coefficient and 95% confidence interval (95% CI). The amount of explained variance is expressed as the R^2 value. Two-tailed *P* values ≤ .05 were considered significant.

We performed all statistical analyses and graphic displays with SPSS Statistics 25 (IBM Corp., Chicago, IL, USA) and SigmaPlot 12.5 (Systat Software Inc., San Jose, CA, USA).

3 | RESULTS

3.1 | Study population

A total of 64 patients (*n* = 26 females: 40.6%) were included and assigned to the following groups: group A: *n* = 22; group B: *n* = 21; group C: *n* = 21. Hypoplastic left heart syndrome represented the

TABLE 1 Patient demographics and basic characteristics

Characteristics	Group A: 5-9 years *n* = 22	Group B: 10-15 years *n* = 21	Group C: 16-18 years *n* = 21	Total *n* = 64
Demographics				
Gender (female:male)	11:11	8:13	7:14	26:38
Age at TCPC (years)	3.9 (1.07)	2.1 (1.10)	1.5 (1.45)	2.5 (2.32)
Time since TCPC (years)	3.3 (3.27)	11.4 (2.40)	15.5 (1.41)	11.2 (9.68)
Body mass index (kg/m^2)	15.8 (1.77)	19.1 (3.97)	21.7 (2.88)	19.1 (5.51)
Ventricular morphology				
Right ventricle	10	12	13	35
Left ventricle	11	9	7	27
Indeterminate/mixed	1	0	1	2
Type of Fontan				
Extra cardiac conduit	21	16	13	50
Lateral tunnel	0	4	7	11
Other	1	1	1	3
Pleural effusion				
Duration after TCPC (days)				
Clinical history of PLE				
	0	3	2	5
Current Medication				
Acetylsalicylic acid	20	17	18	55
Warfarin	1	4	2	7
Beta blocker	1	3	1	5
Angiotensin-enzyme-inhibitor	0	8	1	9
Diuretic	0	2	2	4
Corticosteroids	0	0	1	1
Sildenafil	1	2	2	5
Bosentan	0	1	1	2
Recreational activity				
	10 (45.5%)	5 (23.8%)	4 (19.0%)	19 (29.7%)

Abbreviations: PLE, protein losing enteropathy; TCPC, total cavopulmonary connection.

most frequent diagnosis, followed by right heart obstructions (pulmonary atresia and tricuspid atresia), and atrioventricular septal defects. The majority of patients (54.7%) had a morphologic right systemic ventricle. The mean age at the completion of the Fontan circulation was 2.8 ± 1.4 years; the widest range of ages at Fontan completion (1.0-6.2 years) was observed in the oldest cohort. Patient demographics and characteristics are summarized in Table 1.

3.2 | Bone mineral density

Overall BMD *z* scores for the lumbar spine and the total body were −1.0 ± 1.3 and −0.2 ± 1.2, respectively. There was a negative linear relationship between the time of performing the total cavopulmonary connection (TCPC) and the BMD measurements (whole body, $\beta = -0.49$, $P < .001$, $R^2 = .24$, spine, $\beta = -0.41$, $P = .001$, $R^2 = .17$). For group A, the BMD *z* scores for the spine and the total body were −0.3 ± 1.0 and 0.6 ± 0.8, respectively (Figure 1). A *z* score value below −2 SD of the healthy mean was observed only in the spine BMD of one patient. In group B, the BMDs for the spine and the total body were −1.3 ± 1.4 and −0.4 ± 1.1, respectively. *z* score values below −2 SD of the healthy mean were observed in five patients (24%). Among these patients, the spine was affected in all five patients, and the total body was affected in only one patient. In group C, the BMDs for the spine and the total body were −1.5 ± 1.1 and −0.7 ± 1.1, respectively. *z* scores below −2 SD of the healthy mean were observed in seven patients (35%); the spine was affected in 29% and the total body was affected in 14% of patients.

One patient was taking steroid hormones at the time of inclusion, and two additional patients had been treated with steroids previously. All three of these patients had markedly reduced BMDs, with *z* scores for the total body below −3 SD of the healthy mean.

3.3 | Hand radiograph

Hand radiographs and BoneXpert software analyses were performed for 24 of the 64 patients (37.5%). Seven (29.2%) of the examined patients exhibited abnormal skeletal maturation. Five patients exhibited delayed bone age, and two patients exhibited accelerated bone age. BHI estimates of BMX were determined for 23 patients, with a mean of 4.3 ± 0.6. The overall BHI *z* score was −1.2 ± 0.9. Five patients (21.7%) had BHI *z* scores below −2 SD of the healthy mean, but only two had a concomitant low BMD based on DXA.

To correct for bone size,[17,18] we reanalyzed the DXA values in the seven patients with abnormal skeletal maturation. For the five patients that showed growth delays, reanalyzing DXA based on bone age increased the individual BMD *z* scores, for both spine and total body. For the two patients that showed growth accelerations, reanalyzing DXA based on bone age decreased the individual BMD *z* scores, for both spine and total body. Two patients with pathological BMD *z* scores based on chronological age had normal BMD *z* scores based on bone age. For the entire group of 24, the mean initial BMD *z* scores for the spine and total body were −0.6 ± 1.2 and 0.0 ± 0.9, respectively. After correcting for abnormal bone age, the BMD *z* scores for the spine and total body were −0.5 ± 1.0 and 0.2 ± 0.7.

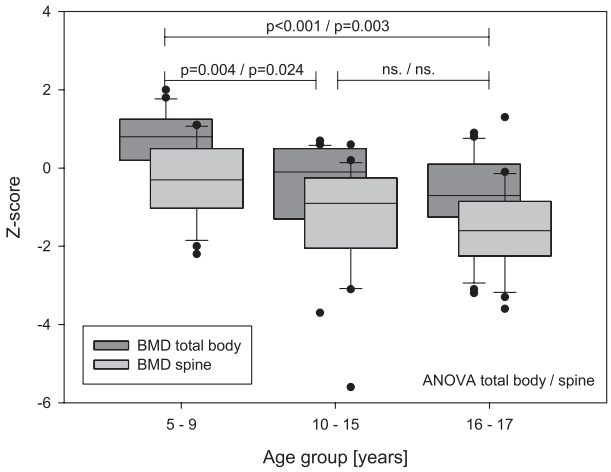

FIGURE 1 Group-wise *z* scores (mean 2 SD) for bone mineral density (BMD) of the spine and the total body. Light gray: spine *z* scores; dark gray: total body *z* scores

3.4 | Fracture history and physical activity

The medical histories revealed that 11 patients (17.2 % of patients) had sustained at least one fracture (1 patient in group A, 6 patients in group B, and 4 patients in group C). No patients had a significant fracture history consistent with osteoporosis. Overall, 30% of patients participated in recreational activities; the highest proportion was in the youngest cohort (Table 1).

3.5 | Vitamin D

The vitamin D analysis showed an overall mean 25-(OH)-D level of 58 ± 30 nmol/L. For group A, the mean vitamin D level was 71 ± 31 nmol/L. In this group, vitamin D was insufficient or deficient in 31.8% of patients, and it was deficient in 9.1% of patients. In group B, the mean vitamin D level was 64 ± 28 nmol/L. Vitamin D was insufficient or deficient in 28.5% of patients, and it was deficient in 19.0%. In group C, the mean vitamin D level was 38 ± 18 nmol/L. Vitamin D was insufficient or deficient in 71.4%, and it was deficient in 33.3% of patients. Two patients (9.5%) in group C had vitamin D levels <12 nmol/L. We observed an age-related decline in vitamin D levels. There was a significant difference between the oldest age group and the two youngest groups (ANOVA overall $P < .001$; A vs. C: $P = .001$, B vs. C: $P = .008$; Figure 2). When vitamin D levels were compared between blood samples taken in winter/spring and summer/fall, we found a non-significant trend toward higher values in summer/fall (56.9 ± 23.3 nmol/L vs. 65.9 ± 29.6 nmol/L, respectively; $P = .09$).

3.6 | BMD relationship with vitamin D and other associated factors

The overall mean values of both BMD *z* scores and vitamin D levels were within normal limits. A group-wise comparison showed

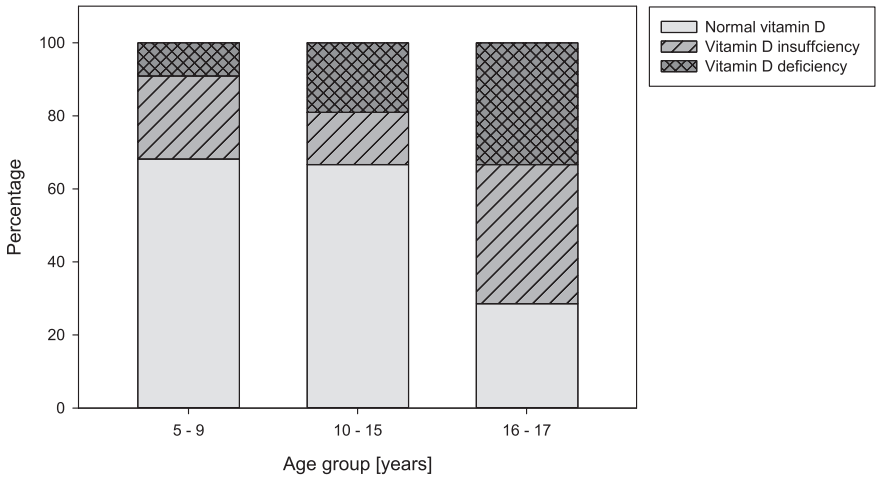

FIGURE 2 Group-wise distribution of vitamin D statuses. Gray: normal vitamin D level, diagonal lines: vitamin D insufficiency; cross-hatching: vitamin D deficiency

that the values of both parameters gradually decreased with increasing age (Figure 1 and 2). Comparison of individual vitamin D levels and BMD *z* scores in all study participants is shown in Figure 3. Vitamin D was correlated with total body BMD (r = .156, P = .036), but not with spine BMD. For the analysis of the association with cardiac characteristics, indeterminate ventricular morphologies and surgical solutions, other than lateral tunnel, and extra cardiac conduit, were excluded (n = 59). Patients with lateral tunnel type Fontan had lower total body BMDs, but not spine BMDs, compared to patients with extra cardiac-type Fontan (BMD total body: −1.5 ± 1.3/−0.3 ± 0.9; P = .034 and BMD spine: −2.0 ± 1.2/−1.2 ± 1.1; P = .178). This finding was consistent when analyzing the oldest patients only (group C) and still adjusting for time since TCPC. The different systemic ventricular morphologies did not show differences in BMDs (left/right ventricle: *z* scores for spine BMD: −0.8 ± 1.1/−1.1 ± 1.4; P = .36; *z* scores for total body BMD: 0.1 ± 1.0/−0.4 ± 1.3, P = .12). In multivariable regression analyses, the type of Fontan circulation was the only factor associated with BMDs in both the total body (beta: −0.492, P < .001; overall model fit: R^2 = .411) and in the spine (beta: −0.373, P = .006; overall model fit: R^2 = .295). In contrast, the vitamin D level, the ventricular morphology, the elapsed time since TCPC, and duration of pleural effusion were not associated with BMDs. Table 2 compares the characteristics of Fontan patients operated with lateral tunnel versus extra cardiac conduit.

4 | DISCUSSION

We have demonstrated that BMD was progressively impaired throughout childhood in patients with Fontan circulation. We found that the decline in BMD was accompanied, but not explained by a vitamin D deficiency or insufficiency, which increased with age, and hence, with the time since the Fontan completion. The lateral tunnel Fontan type, compared to extra cardiac Fontan type, was the only predictive factor associated with lower BMD values, even after correcting for the surgical era and the time since Fontan completion.

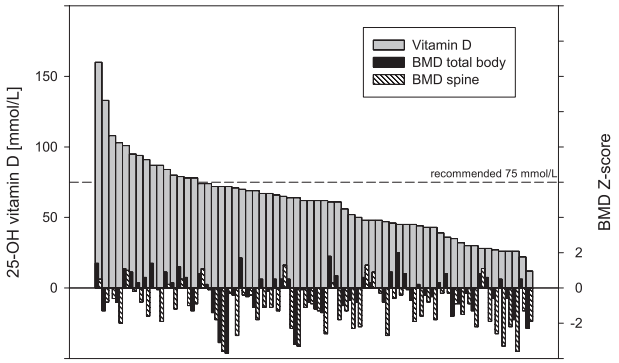

FIGURE 3 Comparison of individual vitamin D levels and bone mineral density (BMD) *z* scores in all study participants (n = 64). Dotted line indicates recommended vitamin D level for pediatric patients with chronic disease

4.1 | Physiologic aspects

In healthy individuals, the increased muscle mass during puberty and growth imparts a positive modeling effect on bone mass and strength. However, in chronically ill patients, the functional bone-muscle unit is often negatively affected by immobilization, hospitalization, and steroid treatment.[19] Previous studies have shown that patients with Fontan circulation are less active compared to healthy adolescents.[6] The reduction in mechanical load compromises bone acquisition and modeling. Prolonged hospital stays may lead to a vitamin D deficiency.[20] Vitamin D deficiency causes a decreased intestinal absorption of calcium followed by a rise in parathyroid hormone levels and a potential increase in bone turnover.[21,22] Moreover, patients with Fontan circulation and PLE often require glucocorticoid therapy. Glucocorticoids directly affects bone cells and induce a negative calcium balance which indirectly affects bone metabolism. The result is an overall negative effect on bone tissue development and maturation. However, in several pediatric chronic diseases characterized by inflammation, the intrinsic rise in cytokines might be more important than glucocorticoid treatment in causing secondary osteoporosis.[7,23]

Adolescence is a critical period for gaining bone mass.[24] Failure to achieve a normal peak bone mass can have implications on bone

TABLE 2 Comparison of characteristics of patients with Fontan circulation operated with lateral tunnel versus extra cardiac conduit

Characteristic	Lateral tunnel (total numbers and groupwise A/B/C) *n* = 10 (0/4/5)	Extra cardiac (total numbers and groupwise A/B/C) *n* = 49 (20/16/13)
Anthropometrics and demographics		
Gender (female: male)	4:6	20:29
Age (years)	16.8	12.0
Time since TCPC (years)	15.2	9.1
Height (cm)	168	147
Weight (kg)	59.4	43.1
Body mass index (kg/m^2)	21.1	18.8
Fenestration		
At time of TCPC (yes:no)	6:3	20:28
Pleural effusion		
Duration after TCPC (days)	27	23
Clinical history of PLE		
	3	1
BMD		
Total body	−1.6	0.1
Spine	−2.3	−0.7
Vitamin D		
At time of inclusion (nmol/L)	55	59

Abbreviations: PLE, protein losing enteropathy; TCPC, total cavopulmonary connection.

health throughout life. A reduced mineral content increases bone fragility and the risk of osteoporosis. In children and adolescents, osteoporosis is diagnosed, based on clinically significant fractures.

4.2 | Bone mineral density

DXA is considered the gold standard for BMD measurements. DXA has the advantage of minimal irradiation, and there are established reference values for the pediatric population.[25] Overall, our study population had below average BMD levels and *z* scores decreased with increasing age. In a previous study, Goldberg et al found reduced BMD measured with DXA in 12 patients with Fontan circulation and PLE.[26] However, half of their study group had received chronic glucocorticoid therapy. Our study demonstrated that low BMD *z* scores occurred in patients with Fontan circulation that did not have PLE or take steroids. Our findings were consistent with those of Avitabile et al, who reported that that the mean *z* scores for the volumetric BMD of trabecular and cortical structures were significantly lower in 43 participants with Fontan compared to reference participants, measured in the tibia with peripheral quantitative computed tomography.[27] However, they did not report whether the findings correlated with age or whether there were any individual differences in cortical versus trabecular effects.

We found low mean *z* scores for the cortical BMX (expressed as BHI) in the group examined with BoneXpert. However, at the individual level, a single patient rarely had both low BMD, measured with DXA, and a low BMX. The lack of correlation has been shown in other pediatric populations[28,29] and might be explained by several factors. First, the two assessment methods measured different parts of the skeleton and different components of bone. DXA measures both trabecular bone (which predominates in the lumbar spine) and cortical bone (which predominates in the total body); in contrast, BHI measures only cortical bone in the peripheral skeleton. Trabecular and cortical bone are affected differently by some stimuli, like chronic inflammation, glucocorticoid treatment, and physical activity.[28,30] Second, the *z* scores for the two methods were established on different reference data; age, sex, and ethnicity for DXA and bone age for BHI.

4.3 | BMD findings related to Fontan type

In lateral tunnel Fontan, venous blood from the lower part of the body is rerouted through a tunnel within the atrial complex. In extra cardiac conduit Fontan, the blood is rerouted through a Gore-Tex conduit outside the heart. Several studies have compared the results of these two types. The most consistent difference was that lateral tunnel Fontan was associated with a higher incidence of arrhythmias, compared to extra cardiac conduit Fontan.[31,32] Our study suggested that, beyond any cardiovascular differences, the two types of Fontan surgery had different effects on bone health. Moreover, total body and spine BMDs were linearly related to patient age, which warranted an awareness of bone health with increasing age. Our findings could be weakened by low number. However, autoimmune processes appear to play a role in Fontan complications and differences in the levels of relevant cytokines could be important.[33,34]

4.4 | BMD findings related to growth

A high proportion (29.2%) of examined patients had abnormal skeletal maturation. Both delayed and accelerated bone age were observed. In the individual patient, a bone growth assessment is important, because it affects the interpretation of BMD measured with DXA.[10,17,18] Two of our patients with growth delay and pathological BMD *z* scores, based on chronological age, had normal BMD *z* scores based on bone age.

4.5 | Evidence of osteoporosis

Despite the high incidence of reduced BMDs, no patients fulfilled the clinical criteria of osteoporosis. The positive fracture history found in 17.2% of our patients was considered low compared to the general population. A study conducted in Sweden, where weather conditions and physical activities among children are comparable to those in Norway, showed that the cumulative risk of sustaining a fracture before 17 years of age was 34%.[35] A potential explanation for the low fracture history observed in our study could be that patients with Fontan are less physically active than healthy children and teenagers.[36] Based on our data, participation in recreational activities was highest among younger patients.

4.6 | Vitamin D

We found a high overall prevalence of vitamin D insufficiency[37] with no significant seasonal variation in vitamin D levels. The prevalence and severity of vitamin D deficiency was associated with older age and increased time after the Fontan completion. These findings contrasted with those from a similar study by Holler et al, who retrospectively assessed 28 patients, aged 2.0-22.0 years.[38] They observed an overall prevalence of vitamin D insufficiency, with levels below 50 nmol/L (20 ng/mL) in 70.3% of patients with Fontan circulation. However, they found no significant difference in the age or time after the Fontan completion between patients with vitamin D levels above or below 10 ng/mL. Nevertheless, a large UK study, conducted in 2011, suggested that a third of children in the general population had serum 25(OH)-D levels <50 nmol/L, with a mean value of 59.4 nmol/L for children living at a latitude of 53°-59° (hence, comparable to the geographic location of the region of Oslo at 59°).[39] That study also showed a continuous decrease in vitamin D levels with age, but apparently, not as pronounced as that found in the present study.

4.7 | Correlation between BMD and vitamin D

We did not find a consistent association between vitamin D and BMD levels. This finding was in accordance with current studies, which have provided conflicting results on whether a low level of vitamin D was a risk factor for low BMD or frequent fractures during growth.[40-42] A potential explanation for the conflicting results might be that laboratory measurements of vitamin D levels represent instant values and do not reflect long-term status. Moreover, in patients with Fontan, there might be several risk factors contributing to both low BMX and low vitamin D level without any causative association.

4.8 | Limitations

The primary limitations of this study were related to patient inclusion, the number of patients examined with a hand radiograph, and the lack of a control group for the vitamin D analysis. Patients in group C were recruited from the entire country, but patients in groups A and B were recruited only from the South-Eastern part of Norway. Therefore, environmental differences in nutritional status and activity levels could potentially have influenced the BMD and vitamin D statuses of these groups. The number of patients examined with a hand radiograph and the BoneXpert analysis was relatively small, particularly in group C; thus, the reliability of this part of the study could be limited. Lastly, we did not have a control group for the vitamin D analysis. To assess the clinical significance of low vitamin D levels, we measured parathyroid hormone levels. However, due to inconsistent clinical routines, the data lacked reliability.

5 | CONCLUSION

This study supported the notion that patients with Fontan circulation have impaired bone health. Importantly, we found that BMD levels deteriorated with age. Different skeletal parts and components appeared to be involved, which could be explained by several stimuli that had uneven effects on bone. The single most predictive factor of a low BMD was the presence of a lateral tunnel-type Fontan, instead of an extra cardiac Fontan. Vitamin D deficiencies gradually decreased with age, but this decline was not associated with the decline in BMD. Further studies are needed to identify causal mechanisms of impaired bone health in this patient group.

CONFLICTS OF INTEREST

The authors have no financial relationships relevant to this article to disclose. None of the authors have conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conceptualized and designed the study, collected patient data, carried out analysis, drafted the initial manuscript, and reviewed and revised the manuscript: Diab

Collected patient data, contributed in drafting the methods section and reviewed and revised the manuscript: Godang

Carried out hand radiographs and BoneXpert analysis, reviewed and revised the manuscript: Müller

Contributed to study design and reviewed and revised the manuscript: Almaas

Carried out hand radiograph analysis and reviewed the manuscript: de Lange

Contributed in interpretation of data, reviewed and revised the manuscript: Brunvand

Collected patient data, reviewed and revised the manuscript: Hansen, Bollerslev

Contributed to study design, reviewed and revised the manuscript: Myhre, Døhlen

Contributed to study design, reviewed and revised the manuscript: Thaulow

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