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Impaired Bone Health in Pediatric Survivors of Retinoblastoma after early in life Chemotherapy treatment

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Introduction

Impairment of bone health in survivors of childhood cancer occurs frequently. Retinoblastoma (RB) is a malignant eye tumor developing in very young children. Treatment can include chemotherapy as an adjuvant or eye sparing treatment attempt. We conducted a cross sectional study to assess bone health in a pediatric cohort of survivors of who had received treatment with chemotherapy at an especially young age (mean age 0.76 ± 0.67 years).

Patients and Methods

The study (DRKS00003636) was approved by the local ethics committee. Thirty-eight survivors (14/38 female) were recruited at regular visits to the Children's Hospital Essen. Of these, 14 patients had unilateral, 23 bilateral and one patient trilateral RB.
Datasets of 33 patients, who underwent polychemotherapy combined with local therapies, were available for statistical evaluation. Patients were evaluated at a mean age of 4.4 ± 3.9 (0.7 – 15.8) years. Polychemotherapy typically consisted of cyclophosphamide (4800 mg/m^2), etoposide (1800 mg/m^2), vincristine (9mg/m^2) and carboplatin (1200mg/m^2).
Clinical and biochemical parameters of growth, pubertal development and bone health were obtained. The history of fractures and bone pain was assessed.

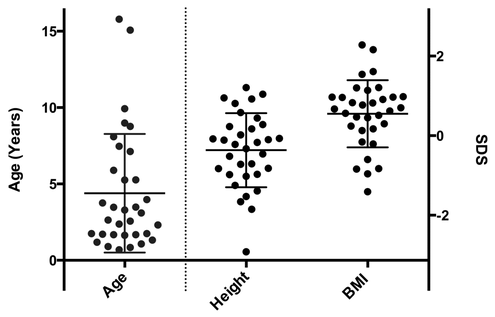

Figure 1 Patient characteristics: *Age at study (years) is represented on the left side of the graph. The right side shows the height and BMI SDS-values (n=33). The mean and SD are indicated.*

	Mean	+/- SD	Range	N
Female/male				12/21
Age (years)	4.4	3.9	0.7 - 15.8	33
Age at diagnosis (years)	0.76	0.67	0.01 - 2.95	33
Time since initial diagnosis (years)	3.63	3.81	0.51 - 14.8	33
Height SDS	-0.37	0.93	-2.92 - 1.21	33
BMI SDS	0.55	0.85	-1.41 - 2.28	33
Delta bone age to biological age	-0.36	0.55	-3.0 - 0.36	10
PH SDS	-0.06	0.32	-0.99 - 0.00	25
TV/BR SDS	0	0.4	-1.29 - 1.41	24
25-OH VD (ng/ml)	23.2	13.6	8.0 - 73.8	29
1,25-$(OH)_2$ VD (pg/ml)	49.5	11.8	29 - 81	27
PTH (pg/ml)	35.1	18.9	14.5 - 85.4	26
Ca:Crea (mg/mg)	0.14	0.15	0.01 - 0.62	24
Osteocalcin (ng/ml)	87.6	34.9	53.6 - 200.1	23
Leptin SDS	-0.71	1.62	-5.07 - 2.77	26
IGF-1 SDS	-0.31	0.92	-1.94 - 1.25	32
Vitamin D intake (U/d)	131.2	102.8	2.4 - 471.0	32
Calcium intake (mg/d)	928.7	465.4	22.6 - 2085	32

Table I Descriptive statistics: *Mean, SD, range and the number of patients examined are displayed for the following parameters: height SDS, body mass index SDS (BMI SDS), pubic hair stage SDS (PH SDS), testicular volume/breast development stage SDS (TV/BR SDS), serum 25-OH vitamin D (25-OH VD), serum 1,25-$(OH)_2$ vitamin D (1,25-OH VD), plasma parathyroid hormone (PTH),urinary calcium to creatinine ratio (Ca:Crea), plasma osteocalcin, leptin SDS, insulin-like growth factor-1 SDS (IGF-1 SDS) and nutritional vitamin D and calcium intake.*

Results

	Number of patients affected	Percentage (%)
Calcium Metabolism:		
Vitamin D deficiency	15/29	51.7
Severe vitamin D deficiency	4/29	13.7
Decreased calcium excretion in urine	9/25	36
Bone Metabolism:		
Bone resorption:		
Elevated NTX or DPD in urine	4/23	17.4
Elevated PTH	4/27	14.8
Bone formation:		
Elevated Osteocalcin	4/23	17.4
Elevated BSAP or TSAP	14/33	42
Bone strength:		
Knee pain (exercise)	2/32	6.3
Recurrent back pain	1/31	3.2
Fractures of long bones	3/32	9.4

Table II Prevalence of bone morbidity: *Number and percentage of patients affected by altered parameters of calcium metabolism, bone metabolism or bone strength are displayed.*

We found no difference in bone health between children with bilateral and unilateral disease, or between irradiated vs. non irradiated children.

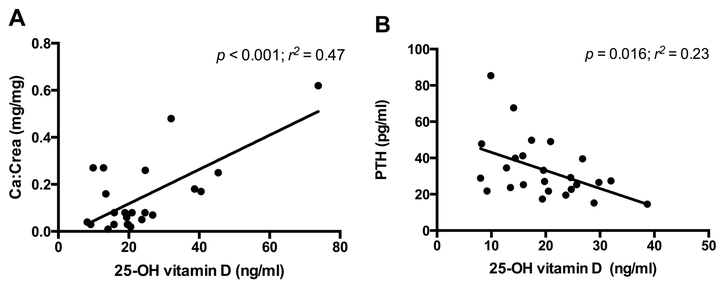

Figure 2 25-OH Vitamin D and calcium metabolism*: A) Positive association between 25-OH vitamin D levels in serum and the urinary calcium to creatinine ratio (n=23). B) 25-OH vitamin D and PTH levels are inversely correlated (n=25). The predicted values based on bivariate regression analysis are indicated as a solid line.*

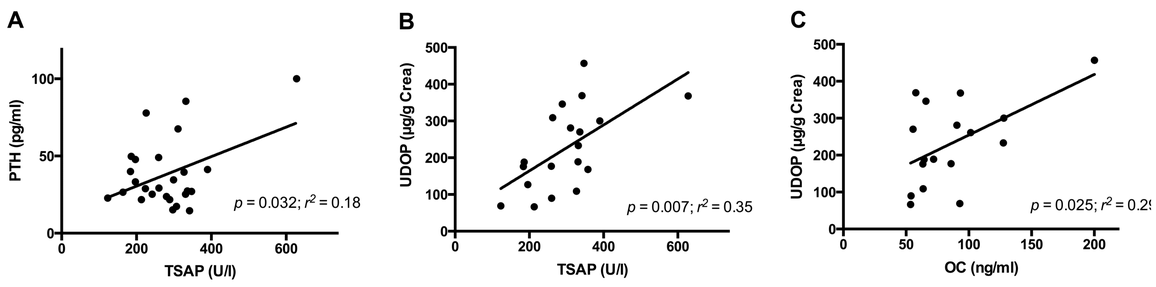

Figure 3 Parameters of bone metabolism: *A) Parathyroid hormone (PTH) plotted against total serum alkaline phosphatase (TSAP, n=26). B) Urinary deoxypyridinoline (UDOP) plotted against TSAP (n=19). C) UDOP plotted against osteocalcin (OC, n=17). The predicted values based on bivariate regression are indicated as solid lines.*

Conclusion

In addition to a vitamin D deficiency, around 20 % of the survivors after early in life chemotherapy presented with bone pain and altered parameters of bone health. These are the children who might be at risk to develop bone health complications. Since identification of children at risk is difficult, we recommend long term monitoring and supplementation of vitamin D.

The authors have nothing to disclose.