Decreased bone mineral density in children receiving long-term anticoagulation is associated with pubertal development

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Background

Children with chronic diseases have significantly improved outcomes due to advanced medical and surgical treatment. However, due to an increased thrombosis risk many of these patients require long-term anticoagulation (LTA). Additionally, several chronic diseases as well as medication comprise a relevant risk for secondary osteoporosis. In adults, LTA including Vitamin K antagonist (VKA) treatment has been associated with osteoporosis and hip fractures(1). Despite pediatric approval of new direct oral anticoagulants (DOACs), there will remain indications for VKA.

Vitamin K derivates are protective against osteoporosis, demonstrated by significantly reduced fractures by Vitamin K supplementation in adults. Conversely, inhibition of vitamin K reductase and vitamin K epoxide reductase results in vitamin K deficiency. Undercarboxylated osteocalcin has been shown a predictor of osteoporosis and hip fracture (2). Data on children are sparse (3,4), and the role of LTA on bone metabolism during the vulnerable phase of linear bone growth in children remain poorly understood.

This study aimed to assess bone mineral density (BMD) and bone metabolic parameter to characterize risk factors for impaired skeletal health in children with chronic CD receiving LTA.

Patients and Methods

In this prospective cross-sectional cohort study, consecutive children aged 12 months to 18 years with chronic medical conditions treated at the Children's Hospital, University of Vienna (MUW) were eligible for the study. Inclusion criteria were chronic diseases, such as congenital heart disease, vascular diseases (Kawasaki syndrome), thrombophilia (e.g. antithrombin-or protein c deficiency, systemic lupus erythematodes) under e.g. VKA, DOACs, corticosteroids **(Table 1).**

Bone densitometry was assessed using Hologic QDR 4500 Elite densitometer (Hologic, Bedford, MA). BMD was corrected according to height, weight, pubertal stage and bone age, and results reported as SD or Z-score.

	mean	SD
Age (years)	11.56	4.59
Body length SDS	-0.56	1.45
BMI SDS	0.01	1.82
Body proportions SDS	0.03	1.68
	n	**%**
Tanner => 2	27	69.2
Female	12	30.8
Fractures	9	23.1
Diagnostic groups	**n**	**%**
Cardiologic	27	69.2
Cerebral	5	12.8
Arterial disorder	5	12.8
Venous disorder	1	2.6
Thrombophilia	11	28.2
Autoimmune	5	12.8

Therapy	**n**	**%**
Cumarin	31	79.5
DOAK	8	20.5
Duration 3-6m	4	10.3
Duration 6-12m	5	12.8
Duration >12m	30	76.9
Complications	7	17.9
	mean	**SD**
INR target	2.61	
Cumarins (m)	60.41	49.23

References

1) Signorelli, S.S et al Anticoagulants and Osteoporosis. Int. J. Mol. Sci. 2019, 20, 5275
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3) Avila ML, et al. Timing of low bone mineral density and predictors of bone mineral density trajectory in children on long-term warfarin: a longitudinal study. Osteoporos Int 2016; 27: 1547-5
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Results

39 children (age 4-18 years) were included, 31 (79%) on VKA and 8 (21%) on DOACs. Included patients revealed a reduced body height in comparison to an age matched Austrian reference population. Standardized BMI and body proportions were at the precise average of healthy Austrian children and adolescents.

Mean BMD was below average for lumbar spine (LS) -0.7 +/- 0.9; total body less head (TBLH)-1.32 +/- 0.98). Pubertal stage was significantly associated with alterations of TBLH (R2 0.28; Early - vs Prepubertal: 0.01; Early vs. late pubertal p=0.04).

Lower bone density is associated with specific stages of pubertal development

Lumbar spine DXA revealed a different pattern (R2=0.13; Prepubertal vs. late pubertal p=0.04). Patients with VKA and DOACs showed similar patterns in TBLH and lumbar spine DXA throughout pubertal development as indicated.

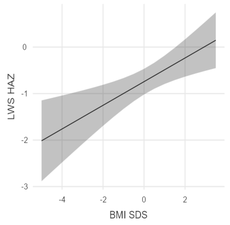


Fig. 2: Linear correlation of LS-HAZ with BMI-SDS

Low body mass index (BMI) correlated significantly with reduced lumbar spine BMD

(R^2 0.24; p=0.003) (Fig 2). This effect was less pronounced for TBLH-BMD. Neither LTA type, intensity nor treatment duration were associated with BMD alterations (data not shown).

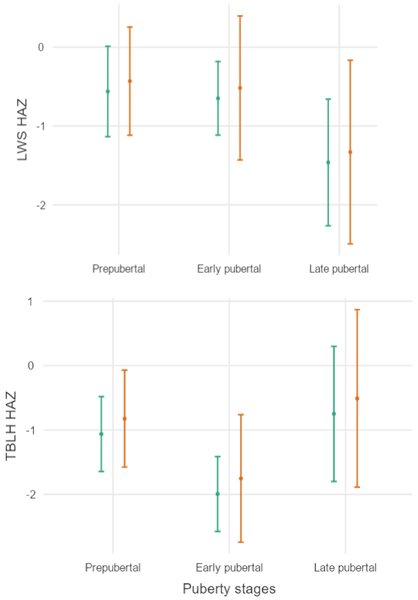


Fig. 1: BMD-HAZ according to clinical pubertal development (Tanner 1- prepubertal, Tanner2-3 early pubertal, Tanner 4-5 later pubertal). Mean +/-SD shown for patients with cumarin (green) and DOAK treatment (orange).

Carboxylation of osteocalcin is highly age-dependent

The undercarboxylated osteocalcin fraction strongly correlated with patients' age (R^2 0.28; p<0.001) but not with BMD. Vitamin D deficiency was detected in 26% of patients with significantly lower values after onset of puberty (-34.5%; p=0.03).

Whereas the undercarboxylated fraction of OC remained relatively stable over the observed age period (R2 0.04), the carboxylated fraction decreased significantly with age (p=0.007, R2=0.22) resulting in a highly significant association of ratio between ucOC and cOC (p=0.001, R2 0.29). All regression models have been corrected for sex differences

Undercarboxylated MGP are dependent on pubertal stage

Lower values occurred in prepuberty as compared to early and late pubertal children (R^2=0.4, p<0.001, Fig 3d). BMI was negatively correlated with ucMGP independently (Estimate -23, p=0.03), while sex, disorder or parameters associated with anticoagulative treatment did not correlate with ucMGP levels (data not shown).

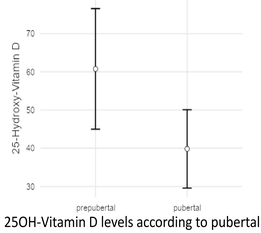


Fig. 4: 25OH-Vitamin D levels according to pubertal stage

Vitamin D insufficiency is common among anticoagulated patients

10 children revealed 25-OH Vitamin D deficiency, 12 insufficiency and 14 a sufficient 25-OHD serum level >50nmol/L. Pubertal patients revealed a significantly lower values as compared to prepubertal children (p=0.03, Fig 4)

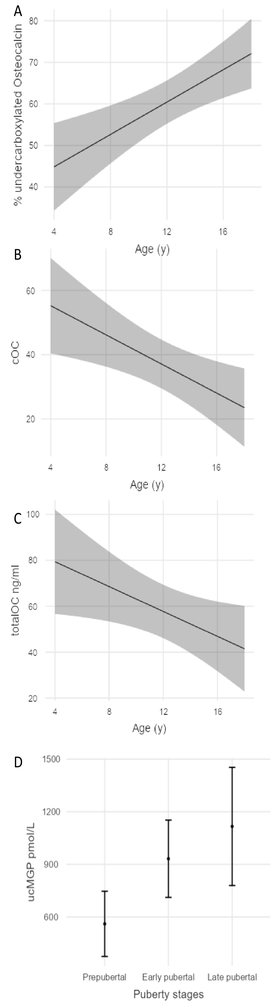
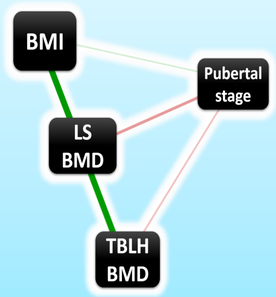


Fig. 3: Linear correlation of age with total osteocalcin (3a), caboxylated osteoclacin (3b) and percentage of undercarboxylated osteocalcin (3c). ucMGP according to pubertal stage (3d)

Conclusions



- Pediatric patients under oral anticoagulation therapy reveal a **markedly reduced BMD**.
- Whilst choice, duration and intensity of anticoagulation was not associated with BMD alterations, low **BMI** and **delayed progression of puberty** represent important risk factors.
- Awareness of this potential treatment options especially in pubertal patients could substantially contribute to improve bone health in this vulnerable patient group.

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