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

Adalbert Raimann,1,4 Janina Patsch,1,2 Michael Weber,1 Florentina Haufler,1,2 Christiane Peet,2 Christoph Male,4 Katharina Thom,4 Gabriele Haueisen,1,2

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 derivatives 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 parameters 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-III deficiency, systemic lupus erythematosus)), and anticoagulated patients (e.g. VKA, DOACs, corticosteroids (Table 1)). Bone densitometry was assessed using Hologic QDR 4500 Elite densitometers (Hologic, Bedford, MA). BMD was corrected according to height, weight, pubertal stage and bone age, and results reported as SD or Z score.

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): 1.3 ± 0.98. Pubertal stage was significantly associated with alterations of TBLH (R2; 0.28; Early vs Prepubertal: 0.91; Early vs late pubertal p=0.04).

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.

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.

References
1. Medical University of Vienna, Division of Pediatric Pulmonology - Allergy and Endocrinology, Department of Pediatrics and Adolescent Medicine, Vienna, Austria.
2. Vienna Bone and Growth Center, Vienna, Austria.
3. Medical University of Vienna, Department of Biomedical Imaging and Image-Guided Therapy, Vienna, Austria.
4. Medical University of Vienna, Division of Pediatric Cardiology and Haematology, Vienna, Austria.

Fig. 1: Linear correlation of total osteocalcin levels with DOACs.

Fig. 2: Lower bone density is associated with specific stages of pubertal development.

Fig. 3: Undercarboxylated MGP is dependent on pubertal stage.

Fig. 4: Vitamin D insufficiency is common among anticoagulated patients.

The undercarboxylated osteocalcin fraction strongly correlated with patients’ age (R1; p=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.