Growth and bone health in paediatric patients with Crohn's disease receiving subcutaneous tumor necrosis factor antibody

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AIM: To study whether adalimumab (ADA) was associated with improvement in growth, bone mineral density (BMD) and bone metabolism.

METHODS: In children with Crohn’s disease (CD) there is a high prevalence of growth failure and reduced BMD. Treatment with infliximab is associated with an improvement in growth. Anthropometry, paediatric CD activity index (PCDAI), bone markers and BMD was measured in 18 patients (72% females) one year before and after start of ADA with a median age of 14.4 years (range: 5-19 years) at treatment start. Outcomes were indicators of growth with treatment as well as interval growth.

RESULTS: Eleven (61%) children experienced catch-up growth after ADA. PCDAI significantly decreased from 52.1 ± 16 to 30.4 ± 23 (P ≤ 0.001). Post ADA, body mass index (BMI) standard deviation score (SDS) was significantly higher compared to those with moderate to severe inflammation. The main predictors for growth were 25-hydroxycholecalciferol and for bone mineralisation weight and height SDS. ADA had no significant influence on bone markers and BMD.

CONCLUSION: Next to improvement of PCDAI, half of the children achieved a positive catch-up growth. A better nutritional status with improvement in BMI and weight is positive predictor for improved growth and bone mineralisation.

Key words: Crohn’s disease; Adalimumab; Growth; Bone health; Paediatrics

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Core tip: This cohort study describes the effect of adalimumab (ADA) on growth and bone health by...
measuring bone density. ADA induced and maintained remission in children with Crohn’s disease that do not respond to infliximab. Next to improvement of paediatric Crohn’s disease activity index, half of the children achieved a positive catch-up growth. A better nutritional status is positive predictor for improved growth and bone mineralisation.

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INTRODUCTION
The primary aim of treatment for inflammatory bowel disease (IBD) is to achieve and maintain remission and additional growth. Growth retardation (GR) has been reported in up to 40% of children with Crohn’s disease (CD)\[1-5\]. Peak bone mass attained during adolescence was found to be a most important determinant of lifelong skeletal health\[1,3,4\]. Bone mass has been shown to be decreased in children with IBD\[1,4\].

There is an altered secretion and action of growth promoting hormones and the direct effects of proinflammatory cytokines\[1-5\]. Persisting treatment failures of steroids have led to the development of a new class of drugs such as biological that have been used to target specific cytokines and receptors thought to be pivotal in the perpetuation of intestinal inflammation. Most target the proinflammatory cytokine tumor necrosis factor-α (TNF-α)\[1,5\].

TNF-α is elevated in CD and appears to play a pivotal role in cytokine-mediated growth retardation, affecting growth via multiple pathways. These include anorexia, loss of skeletal muscle and cachexia, and a direct effect on the growth plate dependent and independent of insulin-like-growth factor-1\[1,5-7\]. The monoclonal anti-TNF-α chimeric antibody infliximab (IFX, Remicade®) has been reported to have a significant beneficial effect on growth and bone metabolism in children with IBD\[1,8,9\], with an additional effect on bone mineral density in adults\[1,10,11\].

Loss of IFX effect can be effectively treated with an additional released humanised anti TNF-α agent, adalimumab (ADA, Humira®). Studies in adults have been shown that ADA is efficacious as induction and maintenance therapy in CD\[12-15\]. ADA is currently not licenced for the use of paediatric IBD patients, however ADA has also shown its efficacy as a second-line anti TNF-α in a small series of paediatric CD\[16-29\]. The effect of ADA on growth and bone health is still unknown.

The study aim was: (1) to investigate growth and bone metabolism in children with CD receiving ADA; (2) to identify related factors associated with growth retardation and osteoporosis; and (3) to assess bone markers one year before and after the introduction of ADA.

MATERIALS AND METHODS
Study design and population
This retrospective case series was performed at a tertiary care children hospital in Vienna, Austria. All eighteen paediatric patients who received ADA between 2007 and 2011 were identified and their medical records reviewed. The indication for ADA was in seventeen severe CD, refractory to previous treatment including IFX, and in one case an allergic reaction to IFX. The diagnosis was made by using defined and classified standard guidelines for Crohn’s disease\[30-32\].

Adalimumab
ADA was started with subcutaneous administration every other week in all patients.

Loading and maintenance doses of ADA was calculated according to body weight: 160 and 80 mg every two weeks with body weight ≥ 40 kg, and 80 and 40 mg in these children with body weight < 40 kg.

Study methods
The following demographics were obtained: gender, age at diagnosis and start of ADA, primary diagnosis and location of inflammation in the gut.

At three time points data were assessed: (1) Pre ADA, one year before ADA initiation; (2) time of ADA start; and (3) Post ADA, one year after start. Change in variables was defined (delta or Δ) before and after ADA.

Concomitant medication was coded (absent/present) including immunosuppression, previous IFX administration and vitamin D and calcium supplementation. The calcium/vitamin D supplementation contained usually 600 mg calcium and 400 IU cholecalciferol (vitamin D3).

All doses of corticoids were noted and converted to prednisone equivalents. Corticosteroid exposure was summarized as cumulative cortisol dose and as daily cortisol ingestion.

Paediatric Crohn’s disease activity index
Disease activity was assessed at each visit using paediatric Crohn’s disease activity index (PCDAI)\[1,33\]. An improvement in PCDAI categorization was defined as “responder” to ADA. The outcome of PCDAI was assessed as the difference between PCDAI at the different time points (baseline to start of ADA and start to end of ADA)\[1\].

Anthropometry and assessment of bone health
Weight, height and BMI were converted to and analysed as standard deviation scores (SDS), based on reference data\[1,34\]. SDS < -2 was considered as low.
Children underwent bone densitometry as part of the annual nutritional assessments. Bone mineral density of the lumbar spine (LS; L2-L4) was investigated using dual energy X-ray absorptiometry (DXA; GE Lunar Prodigy) before and after the initiation of ADA. The scans provided measurements of LS bone mineral content (BMC; g), bone area (cm²), areal bone mineral density (BMD; g/cm²), and the machine-derived age and sex-adjusted BMD SDS. To adjust for body size, which is well recognised to significantly influence areal bone mass measurements, bone mineral apparent density (BMAD) as BMC/BA (g/cm³) and derived BMAD SDS for age, sex and ethnic group using UK DXA reference data was calculated. BMD or BMAD SDS < -2 was defined low.

Biochemical measures of bone metabolism
Data were collected if available before and after ADA start. Indices of calcium homeostasis were albumin adjusted calcium, phosphate, 25-hydroxycholecalciferol (25-OHD), 1,25-dihydroxycholecalciferol (1.25-OHD) and parathyroid hormone (PTH). Serum 25-OHD concentrations < 25 ng/mL has been used to define vitamin D insufficiency. Markers of bone formation used were bone alkaline phosphatase (BAP) and osteocalcin, and for bone resorption C-telopeptide.

Ethics
The study protocol was approved by the institutional Ethics Committee of the University Clinics Vienna.

Statistical analysis
Statistical analyses were performed with SPSS Software. Variables are presented as mean, standard deviation, median, range and categorical data as absolute frequencies and proportions. The \( \chi^2 \)-test, paired t-test, t-test and ANOVA were used for comparisons between time points or disease activity groups. Multivariate analyses used were linear regression. Effects are reported as coefficient and 95% CIs. \( P < 0.05 \) was considered to indicate statistical significance.

RESULTS

Patients characteristics
The case series consisted of 18 patients (13% or 72% female). Demographic variables at start of ADA are presented in Table 1. The underlying diagnosis was in all children Crohn’s disease. The age at diagnosis of CD and age ADA initiation was median 7.8 years (range: 2.9-15.3 years) and 14.4 years (range: 5.3-19.1 years). In all, 17 patients completed 52 wk of ADA and one only 40 wk due to loss of efficacy. Anthropometry and puberty status at ADA initiation are shown in Table 2. Two children showed height SDS < -2 at commencement of treatment.

Effect of ADA on inflammatory marker
After ADA start, disease activity fell significantly with PCDAI scores decreasing from mean 52.1 ± 16 to 30.4 ± 23 (\( P \leq 0.001 \)). In all, 6 (33%) of the 18 patients entered remission (PCDAI < 10), 4 (22%) had mild and 8 (45%) had on-going moderate to severe disease activity. A steroid sparing effect was found for...
Effects of ADA on anthropology

In regards of changes in anthropology, there was a no significant improvement in Δheight, Δheight and ΔBMI SDS post ADA (for all P > 0.05, Table 3). Eleven (61%) children experienced a positive catch-up growth after start of ADA. Weight and height SDS at start (P = 0.03 and P = 0.04) and weight and height SDS post ADA (P = 0.03 and P = 0.02) were significantly lower compared to reference data (Table 2). Post ADA, BMI SDS and ΔBMI SDS in children in remission were significantly higher compared to those with moderate to severe inflammation (P = 0.04 and P = 0.01). The effects of ADA on anthropology of PCDAI responder and non-responder are presented in Table 4.

Effects of ADA on bone density

BMC, BMD SDS and BMAD SDS remained static after the start of ADA (Table 3). In all, 4/18 (22%) paediatric CD patients had a BMD SDS < -2 after ADA start, compared to 3/18 (17%) children before (P > 0.05). Post ADA, BMD SDS in PCDAI non-responder significantly decreased (P = 0.02, Table 4). Using other univariate models there was no significant differences in low BMD < -2 and the use of vitamin D and calcium supplementation, steroids, the presence of 25-OHD deficiency, inflammation in the gut and low anthropometry.

Effect of ADA on bone metabolism

In our study population, ADA had no significant influence on calcium homeostasis, bone metabolism and bone resorption. Table 3 gives an overview of the effect of ADA on bone health including data on calcium homeostasis and bone markers pre and post ADA. There was not significant improvement in the number of children with 25-OHD insufficiency, 6 (37%) pre ADA vs 5 (29%), P > 0.05). The number of children receiving calcium or vitamin D supplements at initiation of ADA and 12 mo after were similar (4 (22%) paediatric patients at start and at end, P > 0.05).

PCDAI responder had significantly lower PTH levels at start of ADA (P = 0.03) and higher BAP levels at end (P = 0.03) compared to PCDAI non-responder (Table 4).

Predictors for improvement in growth and bone mineralisation

Linear regression analysis was performed to assess simultaneously the effect of several potential predictors of growth and bone health after treatment with ADA (Table 5). There was a strong association between Δheight SDS post ADA and 25-OHD levels. Higher 25-OHD levels were positive predictors for better growth with the use of ADA. When bone health was analysed using ΔBMD SDS, PCDAI at start was the only significant predictor for bone mineralisation. With a lower disease activity it is more likely to have a better bone mineralisation.

DISCUSSION

This is the first study that presents the effect of ADA on growth and bone metabolism measuring bone density in children with CD.

Hyams et al[28] could observe a significant improvement in height velocity SDS from baseline to weeks 26 and 52 in 129 children with IBD under treatment with ADA, independent if a high or low ADA dose was given. Malik et al[29] reported in a cohort of 36 children with CD that 42% showed catch-up growth in children 6 mo after the initiation of ADA. Impro
growth was more likely in patients entering remission and on imunosuppression but not solely due to a steroid sparing effect. This was in line with our previous studies. The children had significantly reduced BMD and BMAD, and a positive catch-up growth following the treatment was more likely in patients entering remission. Nevertheless, we could not find any association in children with improved linear growth; the small sample size could be the reason.

We could demonstrate that inflammation has an impact on growth since children in remission showed significantly better weight and height SDS compared to those with mild or moderate to severe disease activity, similar as already found in children under IFX.

Growth was influenced by disease related factors such as weight and BMI SDS at start and serum 25-OHD. The improvement of nutritional status, hence improved weight and BMI, could be partly explained by the positive effect of ADA on the intestinal mucosa similar to IFX with reduction of excessive loss of nutrients from the inflamed gut, since previous studies have demonstrated mucosal healing next to the anti-inflammatory impact of IFX. In histology results performed before and after the introduction of ADA, an improvement in inflammation infiltrate in the gut mucosa could be seen.

Pagnanelli et al. described 7/10 children with CD on maintenance therapy with IFX having significantly higher BMAD compared to those never receiving IFX. The children had significantly reduced BMD and BMAD, but remained stable after ADA initiation. Disease related factors influencing bone health were number of IFX infusion prior to start of ADA and improvement of nutritional status, hence improved weight and BMI SDS at start and serum 25-OHD. The improvement of nutritional status, hence improved weight and BMI, could be partly explained by the positive effect of ADA on the intestinal mucosa similar to IFX with reduction of excessive loss of nutrients from the inflamed gut, since previous studies have demonstrated mucosal healing next to the anti-inflammatory impact of IFX. In histology results performed before and after the introduction of ADA, an improvement in inflammation infiltrate in the gut mucosa could be seen.

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| Factors | Coefficient | 95%CI | P value |
|---------|-------------|-------|--------|
| ΔHeight SDS | 0.0 | 0.04 | 0.048 |
| ΔBMD SDS | 0.8 | 0.09-0.6 | 0.02 |
| Weight SDS | 0.7 | 0.04-0.5 | 0.03 |
| ΔMAH SDS | -0.1 | -0.02-(-0.002) | 0.02 |

SDS: Standard deviation score; 25-OHD: 25-hydroxycholecalciferol; IFX: Infliximab; BMD: Bone mineralisation density; BMAD: Bone mineral apparent density; PCDAI: Paediatric Crohn’s disease activity index.
a reduction of growth hormone secretion and its action[5,6] and are known to have effects on calcium and bone metabolism[44]. Although we found a trend in reduction, however not significantly, of daily and cumulative steroid dose, we could not find any association with improved growth or bone health in our limited number of patients. In line with this, also other clinical studies of the role of steroids in IBD and growth retardation have reported conflicting data[6].

The skeleton of the children treated with ADA did not mineralize at the expected rate over the one-year period however did not deteriorate further with static BMD SDS similar to IFX[1]. Sylvester et al[3] already described that mineralization rates in children with CD did not improve over a 2-year period in newly diagnosed paediatric IBD patients. This might be partly explained by persisting low-grade mucosal inflammation, even in clinical remission similar to IFX[1]. Our patients suffered from CD since years with a moderate to severe disease activity at start of ADA. Delay in "mineralisation catch-up" could be similar explained by the persistent low-grade inflammation (undetected) although a significant improvement in PCDAI scores could be achieved, in line with our previous findings[1]. Bone mineralisation can be negatively affected by low vitamin D intake[4,45,46]. Only two children had 25-OHD deficiency at start of ADA, accompanied with low BMD < -2. We could not replicate that ADA modulates bone metabolism in patients with active intestinal inflammation, either in bone formation or bone resorption[10,11,18,19].

There are several limitations in the study. We had incomplete data on observation of bone age and estimated midparental target height that would have brought helpful additional information on growth outcome. We could not demonstrate a significant improvement in overall anthropometry after treatment with ADA. There are several explanations that might influence these findings. Firstly, all children were not naïve to TNF-blockers. Before starting ADA, the mean duration of IFX was around one year. Secondly, our paediatric patients had a long history of CD with the majority having a severe disease activity at ADA start. Although PCDAI scores have significantly improved, there might be a delay in catch-up growth although a significant improvement in PCDAI scores could be achieved. Thirdly, in the majority of indication for the switch to ADA, was loss of efficacy to IFX. The majority of children were started on ADA because of medically refractory CD and in one case of an allergic reaction to IFX. This is a cohort of patients were ADA was used as rescue therapy with previous treatment failure to IFX or other immunomodulators. Children with refractory CD are one of the sickest children where poor disease control may compromises growth, and this can lead to long-term adverse outcome such as impaired adult height.

Another limitation is that the sample size of the study was too small to draw a final conclusion on bone mineralisation and ADA. In addition, with such a limited number of patients statistical analyses are difficult to interpret.

In conclusion, next to improvement of PCDAI, eleven or 61% children achieved a positive catch-up growth. For the whole cohort, weight SDS, height SDS, BMI SDS and bone density remained static with treatment. Treatment with ADA was not associated with changes in bone markers. In a small cohort of patients endoscopy results revealed even a mucosal healing effect. Prospective studies are required to investigate cytokines, markers of bone formation and resorption, mucosal healing and BMD under treatment to fully understand the effect of ADA on bone health.

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