Impact of an exercise program in children with inflammatory bowel disease in remission

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BACKGROUND: The aim of our study was to investigate the impact of a structured exercise program on bone mineral density (BMD) and body composition parameters in children and adolescents with IBD in remission.

METHODS: Patients were recruited to participate in a 6-month exercise program. Total body less head (TLBH) dual energy X-ray absorptiometry (DXA) was used to measure BMD. The same method was used to assess fat mass (FM) and lean body mass (LBM) at baseline and at the completion of the program.

RESULTS: Based on the baseline and endpoint TBLH DXA measurements, a total of 42 study participants (25 boys; aged 15.3 ± 2.08 years) experienced an increase in BMD (from 0.959 ± 0.023 g/cm² to 0.988 ± 0.025 g/cm², p < 0.001) and LBM (from 37.12 ± 1.43 kg to 38.75 ± 1.61 kg, p = 0.012). Age- and sex-based BMD Z-score increased significantly (from −0.35 ± 0.15 to −0.28 ± 0.17, p = 0.020), whilst LBM Z-score did not significantly change (from −1.78 ± 0.23 to −1.71 ± 1.49, p = 0.908).

CONCLUSIONS: There was a significant improvement in BMD, age- and sex-based BMD Z-score, and LBM amongst study participants. Subgroup analysis showed that patients with CD and male study participants experienced significant improvement in all parameters, whilst patients with UC and IBD-U and female patients experienced improvement solely in BMD.

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IMPACT STATEMENT:

- Children and adolescents with IBD, regardless of disease activity, are under increased risk of secondary osteoporosis and lean body mass deficits.
- A 6-month home-based structured exercise program leads to a significant improvement in bone mineral density and lean body mass.
- Exercise therapy should be explored as a potentially adjacent to standard treatment modalities.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic, relapsing and remitting inflammatory disorders of the alimentary tract, comprising of Crohn’s disease (CD), ulcerative colitis (UC) and IBD-unclassified (IBD-U). The incidence of pediatric IBD around the world has been steadily rising for the last two decades. The affected children and adolescents are at an increased risk of developing secondary osteoporosis, a systemic disorder characterized by low bone mass and deterioration of bone microarchitecture, with consequent increased risk of fractures throughout their lifetime. Currently, the prevalence of low bone mineral density (BMD) in children and adolescents with IBD is estimated between 8% and 65%5-7. Moreover, a recent systematic review and meta-analysis demonstrated that 93.6% of patients with CD and 47.7% of patients with UC have deficits in lean body mass (LBM) compared to healthy controls, regardless of disease activity5. The impaired digestive and absorptive function of the gastrointestinal tract, chronic systemic inflammation, glucocorticoids used to treat relapses, poor dietary intake, as well as, the lack of physical activity, are all thought to play a role in the impairment of bone health and body composition8-10. Physical activity (PA), defined as any bodily movement produced by the skeletal muscle that results in energy expenditure9, improves physical fitness through an increase in cardiorespiratory efficiency, muscle mass accrual, increased muscular strength and endurance, thus leading to improved bone strength9.

We have previously described, in cross-sectional study, a strong positive correlation between the time spent in moderate-to-vigorous PA (MVPA) and BMD and LBM; with an increase in time spent in MVPA associated with an increase in BMD10. Puberty is generally deemed as a critical period of muscle and bone growth, with 90% of peak bone mass attained by late adolescence11. No studies have yet evaluated the effects of an exercise intervention on musculoskeletal outcomes in pediatric IBD. The aim of the study was to evaluate the impact of a home-based, structured exercise program on BMD and body composition in children and adolescents with IBD in clinical remission.
MATERIALS AND METHODS

Participants and study design

A single-center pre-post interventional study was conducted from March 2019 to December 2020. Pediatric patients with IBD in stable clinical remission, aged 10 to 18 years old, were invited to participate in the study. The IBD diagnosis was made according to the Porto criteria and disease localization was determined based on the Paris classification at the time of study enrollment. Stable remission was defined as weighted pediatric CD activity index (wPCDAI) < 12.5 or pediatric UC activity index (PUCAI) < 10 and lasting for a minimum of one month prior to enrollment. Exclusion criteria were any acute or other chronic disease associated with a decrease in PA and a recent (within 1 month) and/or scheduled (within upcoming 6 months) surgical procedure. Patients who were already physically active, engaging in competitive sports for more than 180 minutes per week, and those receiving glucocorticosteroid therapy at the time of potential inclusion were not invited into the study. The study was approved by the Institutional Review Board at the Children's Hospital Zagreb. Written consent was obtained from both the patient and one of their parents or caregivers.

Baseline and endpoint measurements

Clinical and laboratory assessment, anthropometry and body composition measurements, dietary intake analysis, physical activity assessment (previously described in detail elsewhere), as well as muscular strength and endurance assessment were done in all included patients at the time of enrollment and following the completion of the exercise program. Dietary intake was assessed using three-day food diaries. Prodi 6.1 expert software package (Nutri-Science GmbH, Freiburg, Germany) was used to analyze collected data. Daily energy, macronutrient, vitamin D, calcium and phosphorus intake were expressed as a percentage of the daily recommended intake for healthy children of same age and sex. Resting energy expenditure was determined using the Schofield equation and multiplied by an appropriate activity factor for observed physical activity level to determine estimated energy requirements (EER).

Physical activity

Fitness Charge 2 (Fitbit Inc., San Francisco, California), a consumer-marketed triaxial accelerometer, was used to measure PA in free-living conditions. Subjects were asked to wear it on the non-dominant wrist, for 5 consecutive days before and after the intervention period. The device was initialized using complementary software with the subject's characteristics in mind and synchronized daily with the mobile phone application. At the end of the wear period, data were downloaded from a secure website and examined. Valid wear time was defined as ≥22 hours/day for 5 days. Total PA was analyzed as light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA).

Muscular strength and endurance

The five-task battery was designed to provide a swift and comprehensive assessment of muscle strength and endurance of the six large skeletal muscle groups. Prior to testing, each participant was instructed on the correct technique and form to ensure optimal task execution and to minimize the risk of injury. During a series of 30-second intervals, participants were asked to do the maximum possible number of repetitions of sit-ups, push-ups, back extensions and squats. The last, fifth exercise, was a plank hold, during which the participants were asked to remain in the standard plank position for as long as possible whilst maintaining the correct form.

Intervention

Following the initial multifaceted assessment, the patient and their parent or caregiver were introduced to a personalized, home-based structured exercise program lasting for a total of six months. The kinesiologist provided each participant with video materials demonstrating each exercise and its possible modifications based on the individual’s fitness level. Participants were also provided with a weekly exercise schedule and a diary to log in each training session. The exercises were divided into six 4-week-long sections and the intensity of exercises was gradually increased throughout the program. Adherence was assessed using the activity logs and via weekly telephone calls conducted with participants and their parents. Appropriate adherence to the program was defined as the performance of default exercises (for the predetermined number of repetitions) at least three times a week, with a minimum of 12 sessions per month, during the 26-week-long intervention period.

Outcomes

The primary outcome was to assess the changes in whole-body BMD, LBM and FM, expressed as absolute values and as age-, sex-, and height-based Z-scores at baseline and after the intervention. The primary outcome was also to compare changes among patients with CD, UC and IBD-U, male and female study participants, and prepubertal and early pubertal children (defined as stages I to III according to Tanner and Whitehouse) with those with more advanced pubertal status (defined as stages IV and V). Secondary outcomes were to assess the changes in laboratory parameters pertaining to disease activity status, dietary intake, muscular strength, endurance and PA engagement at the baseline and following the intervention period. Lastly, the study aimed to explore the relationship between improvement of BMD and LBM and variables such as age at diagnosis, duration of the disease and different treatment modalities and to record possible adverse events during the intervention period.

Statistical analysis

The differences between categorical variables were assessed by chi-square test, whilst the differences for non-categorical variables were assessed by ANCOVA analysis and corrected for age and sex or disease. Binary logistic regression was performed; dependent values were increased in BMD and LBM Z score (expressed as binary values) and proposed predicted factors included age at diagnosis, disease duration, pubertal stage, use of biological therapy, exclusive enteral nutrition, glucocorticosteroid dose, surgical treatment. All statistical tests were done at the two-tailed a level of 0.05. Statistical analysis was performed using SPSS 24.0 (IBM Corporation, Chicago, Illinois) statistical software.

RESULTS

Patient characteristics

Overall, 42 children (25 boys, 56%) with IBD in stable clinical remission were included. Of those, 22 (52%) were affected by CD, 18 (43%) with UC and 2 (1%) with IBD-U. Their baseline characteristics are summarized in Table 1. Amongst patients with CD, 17 (77%) had non-stricturing non-penetrating disease, whilst 5 (23%) had stricturing disease. Perianal disease was recorded in 11 (50%) patients with CD. On average, patients were recruited into the study 45 months after their diagnosis, and disease duration did not differ significantly between patients with CD and patients with UC and IBD-U. Same can be said for age and sex corrected values for BW Z-score, BH Z-score and BMI Z-score at

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and FM Z-score increased significantly (from 37.12 ± 1.43 kg to 38.75 ± 1.61 kg, p < 0.001), LBM (p < 0.001), FM (p = 0.017) and BMD Z-score (p = 0.017), LBM (p < 0.001), FM (p = 0.002) and FM Z-score (p = 0.030), but not in height-adjusted BMD Z-score (p = 0.103). Patients with UC and IBD-U significantly improved only their BMD (p < 0.001). Similarly, male patients experienced an improvement in BMD (p < 0.001), BMD Z-score (p = 0.043), LBM (p < 0.001) and FM (p = 0.006), without a statistically significant change in height-adjusted BMD Z-score (0.192), LBM Z-score (p = 0.126) and FM Z-score (p = 0.079). Female patients improved only in the BMD (p = 0.046) and FM (p = 0.026), while the increase in BMD Z-score, height-adjusted BMD Z-score, LBM, LBM Z-score and FM Z-score was not statistically significant (p = 0.269, p = 0.185, p = 0.708, p = 0.225 and p = 0.317, respectively). BMD and body composition were also compared amongst prepubertal and early pubertal baseline. Laboratory findings were normal, except for elevated fecal calprotectin levels.

**Primary outcomes**

As shown in Table 2, a significant increase in both BW Z-score (p = 0.017) and BH Z-score (p = 0.049) has been observed throughout the duration of the study, without a statistically significant increase in BMI Z-score (p = 0.120). Moreover, based on the baseline and endpoint TBLH DXA measurements, study participants experienced an increase in total body mass from 53.21 ± 11.13 kg to 56.24 ± 12.27 kg (p < 0.001), with an increase in BMD (from 0.959 ± 0.023 g/cm² to 0.988 ± 0.025 g/cm², p < 0.001), FM (from 16.05 ± 1.18 kg to 17.25 ± 1.19 kg, p < 0.001) and LBM (from 37.12 ± 1.43 kg to 38.75 ± 1.61 kg, p = 0.012). BMD Z-score and FM Z-score increased significantly (from −0.35 ± 0.15 to −0.28 ± 0.17, p = 0.020 and from −0.44 ± 0.18 to −0.29 ± 0.16, p = 0.044), whilst LBM Z-score did not significantly change (from −1.78 ± 0.23 to −1.71 ± 1.49, p = 0.908). However, when BMD Z-score was corrected for height, the difference was not significant anymore.

Subgroup analysis of observed BMD and body composition changes is detailed in Table 3. Patients with CD experienced a significant increase in BMD (p < 0.001), BMD Z-score (p = 0.017), LBM (p < 0.001), FM (p = 0.002) and FM Z-score (p = 0.030), but not in height-adjusted BMD Z-score (p = 0.103). Patients with UC and IBD-U significantly improved only their BMD (p < 0.001). Similarly, male patients experienced an improvement in BMD (p < 0.001), BMD Z-score (p = 0.043), LBM (p < 0.001) and FM (p = 0.006), without a statistically significant change in height-adjusted BMD Z-score (0.192), LBM Z-score (p = 0.126) and FM Z-score (p = 0.079). Female patients improved only in the BMD (p = 0.046) and FM (p = 0.026), while the increase in BMD Z-score, height-adjusted BMD Z-score, LBM, LBM Z-score and FM Z-score was not statistically significant (p = 0.269, p = 0.185, p = 0.708, p = 0.225 and p = 0.317, respectively). BMD and body composition were also compared amongst prepubertal and early pubertal
children and those with more advanced pubertal status. The first group experienced a statistically significant increase in BMD, BMD Z-score and LBM (p < 0.001, p = 0.020 and p < 0.001 respectively), but not height-adjusted BMD Z-score (p = 0.286), whilst the later group experienced a statistically significant increase in BMD, FM and FM Z-score (p = 0.001, p = 0.002 and p = 0.019 respectively), without a significant increase in BMD Z-score, height-adjusted Z-score, LBM and LBM Z-score (p = 0.096, p = 0.092, p = 0.667 and p = 0.519 respectively).

**Secondary outcomes**

All study participants remained in stable clinical remission throughout their participation in the study and no significant changes in laboratory findings were detected. Furthermore, participants consumed on average 1993 ± 704 kcal/day at the time of enrollment and 1946 ± 503 kcal/day at the end of intervention period, without any statistical change in daily caloric intake detected (p = 0.995). Similarly, daily protein, calcium and phosphorus intake did not change significantly during the study period (p = 0.309, p = 0.851 and p = 0.206 respectively). On the contrary, whilst serum levels of vitamin D increased slightly, from 51.9 ± 20.2 nmol/L to 55.6 ± 18.1 nmol/L (p = 0.096), daily vitamin D intake significantly decreased from 22.5 ± 28.7 μg/day to 15.2 ± 21.7 μg/day (p = 0.02). Patients significantly increased their fitness level by the end of the study (Table 2). We have not observed any significant changes in the daily PA patterns of study participants before and after the completion of the structured exercise program; no statistically significant changes in total time spent in PA, time spent in LPA and time spent in MVPA were detected (p = 0.402, p = 0.437 and p = 0.866 respectively).

Regression models found that none of the predicted prepared factors (age at diagnosis, disease duration, pubertal stage, use of biological therapy, EEN, glucocorticosteroid dose and surgical treatment) was associated with an increase in BMD and LBM Z-scores.

Adherence to the program was defined as exercising at least three times a week during the 26-week-long intervention period and 36 (86%) study participants completed more than 75% of the expected training sessions. Only one participant withdrew from the study, citing increased stress levels due to the COVID-19 pandemic and the Zagreb earthquake in March 2020 as the reason for withdrawal. No adverse events were noted.

**DISCUSSION**

To the best of our knowledge, this is the first interventional study evaluating the impact of a personalized, home-based structured exercise program on BMD and bone composition in children and adolescents with IBD in clinical remission. Study participants experienced significant improvements in BMD and age- and sex-based BMD Z-score, as well as in LBM. Subgroup analysis showed that only patients with CD and male study participants experienced significant improvement in all parameters, whilst patients with UC and IBD-U and female patients experienced solely improvement in BMD.

Only a handful of clinical trials regarding the impact of structural exercise programs on BMD and body composition have been conducted in adults with IBD, the first one dating back to 199721. A total of 117 patients with CD were included in a year-long study evaluating the effects of a low-impact exercise program. Although the intervention group experienced a greater increase in BMD compared to the control group, the difference did not reach a statistical significance21. More recently, 20 adult patients with IBD in clinical remission were randomized in a cross-over trial involving eight weeks of moderate intensity aerobic and resistance training. Significant improvement in body composition was noted in the intervention group compared to the control group, with a median decrease of 2.1% body fat and a median increase of 1.59 kg of LBM, as estimated by DXA22. Finally, a study conducted amongst 47 adults with stable CD assessing the effects of 6 months of combined impact and resistance training on BMD and muscle function, concluded that the intervention led to a significantly improved BMD and muscle function amongst study subjects.23

Our earlier findings show that children and adolescents with IBD in remission spent on average 45 minutes daily engaging in MVPA, with multivariate analysis showing positive correlation between time spent in MVPA and BMD.20 During resistance training, repeated muscle contractions provide effective strain on bone, leading to bone remodeling and an increased bone mass
Table 3. Subgroup analysis of the impact of the high-impact bodyweight exercise program on bone mineral density and body composition.

| CD (n = 22)** | UC and IBD-U (n = 20)** |
|---------------|--------------------------|
|               | Baseline | Endpoint | p-value | Baseline | Endpoint | p-value |
| BMD (g/cm²)   | 0.945 ± 0.114 | 1.028 ± 0.124 | <0.001 | 0.950 ± 0.158 | 0.967 ± 0.165 | 0.001 |
| BMD Z-score   | −0.35 ± 0.91  | 0.50 ± 1.04  | 0.017  | −0.32 ± 0.86  | −0.31 ± 0.94  | 0.641 |
| Height-adjusted BMD Z-score | −0.58 ± 0.85 | −0.4 ± 1.04 | 0.103 | −0.64 ± 0.20 | −0.60 ± 0.19 | 0.613 |
| LBM (kg)      | 38.35 ± 7.09  | 43.48 ± 8.16  | <0.001 | 35.30 ± 9.80  | 35.52 ± 11.39 | 0.801 |
| LBM Z-score   | −1.45 ± 1.23  | −0.44 ± 1.26  | 0.083  | −1.98 ± 1.26  | −2.12 ± 1.63  | 0.199 |
| FM (kg)       | 17.37 ± 7.43  | 19.03 ± 7.49  | 0.002  | 15.11 ± 6.66  | 15.71 ± 6.73  | 0.072 |
| FM Z-score    | −0.21 ± 1.10  | −0.12 ± 0.98  | 0.030  | −0.55 ± 0.97  | −0.50 ± 0.95  | 0.570 |
| **Boys (n = 25)** |           |           |          |           |           |          |
|               | Baseline | Endpoint | p-value | Baseline | Endpoint | p-value |
| BMD (g/cm²)   | 0.968 ± 0.141 | 1.016 ± 0.140 | <0.001 | 0.917 ± 0.123 | 0.935 ± 0.141 | 0.046 |
| BMD Z-score   | −0.28 ± 0.75  | −0.17 ± 0.86  | 0.043  | −0.42 ± 1.05  | −0.39 ± 1.14  | 0.269 |
| Height-adjusted BMD Z-score | −0.46 ± 0.13 | −0.32 ± 0.15 | 0.192 | −0.83 ± 0.26 | −0.73 ± 0.28 | 0.185 |
| LBM (kg)      | 39.71 ± 9.07  | 42.76 ± 9.53  | <0.001 | 32.77 ± 5.70  | 32.39 ± 7.82  | 0.708 |
| LBM Z-score   | −1.63 ± 0.96  | −1.54 ± 0.96  | 0.126  | −1.80 ± 1.64  | −1.96 ± 2.04  | 0.225 |
| FM (kg)       | 14.66 ± 7.79  | 15.93 ± 7.87  | 0.006  | 18.54 ± 5.30  | 19.49 ± 5.83  | 0.026 |
| FM Z-score    | −0.42 ± 1.17  | −0.24 ± 1.08  | 0.079  | −0.32 ± 0.86  | −0.27 ± 0.87  | 0.317 |
| **Girls (n = 17)** |           |           |          |           |           |          |
|               | Baseline | Endpoint | p-value | Baseline | Endpoint | p-value |
| BMD (g/cm²)   | 0.854 ± 0.141 | 1.056 ± 0.141 | <0.001 | 0.895 ± 0.123 | 0.953 ± 0.141 | 0.003 |
| BMD Z-score   | −0.38 ± 0.75  | −0.17 ± 0.86  | 0.043  | −0.42 ± 1.05  | −0.39 ± 1.14  | 0.269 |
| Height-adjusted BMD Z-score | −0.56 ± 0.13 | −0.32 ± 0.15 | 0.192 | −0.85 ± 0.25 | −0.73 ± 0.28 | 0.185 |
| LBM (kg)      | 39.36 ± 9.07  | 42.58 ± 9.53  | <0.001 | 32.50 ± 5.70  | 32.39 ± 7.82  | 0.708 |
| LBM Z-score   | −1.62 ± 0.96  | −1.54 ± 0.96  | 0.126  | −1.80 ± 1.64  | −1.96 ± 2.04  | 0.225 |
| FM (kg)       | 14.66 ± 7.79  | 15.93 ± 7.87  | 0.006  | 18.54 ± 5.30  | 19.49 ± 5.83  | 0.026 |
| FM Z-score    | −0.42 ± 1.17  | −0.24 ± 1.08  | 0.079  | −0.32 ± 0.86  | −0.27 ± 0.87  | 0.317 |

Values are expressed as mean ± SD, corrected for age* and sex**. P-values were calculated from the paired sample t-test.

BMD: bone mineral density, CD: Crohn’s disease, IBD-U: inflammatory bowel disease-unclassified, LBM: lean body mass, UC: ulcerative colitis.
different exercise modalities, with contrasting exercise types, variable training duration and frequency, on BMD and body composition in children and adolescents with IBD, in order to improve future guidelines on the topic.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafting and revising the manuscript and have approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Written consent was obtained from both the patient and one of their parents or caregivers in the case of all 42 study participants.

ADDITIONAL INFORMATION

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