Original Papers

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**Potential Effects of an Exoskeleton-Assisted Overground Walking Program for Individuals With Spinal Cord Injury Who Uses a Wheelchair on Imaging and Serum Markers of Bone Strength: Pre-Post Study**

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**Abstract**

**Background:** As many as 60% of individuals use a wheelchair long term after a spinal cord injury (SCI). This mode of locomotion leads to chronic decline in lower-extremity weight-bearing activities and contributes to the development of severe sublesional osteoporosis and high rates of fragility fracture. Overground exoskeleton-assisted walking programs provide a novel opportunity to increase lower-extremity weight bearing, with the potential to improve bone health.

**Objective:** The aim of the study is to measure the potential effects of an exoskeleton-assisted walking program on lower-extremity bone strength and bone remodeling biomarkers in individuals with chronic (≥18 months) SCI who use a wheelchair.

**Methods:** In total, 10 participants completed a 16-week exoskeleton-assisted walking program (34 individualized 1-hour sessions, progressing from 1 to 3 per week). Bone mineral density and bone strength markers (dual-energy x-ray absorptiometry: total body, left arm, leg, total hip, and femoral neck and peripheral quantitative computed tomography: 25% of left femur and 66% of left tibia) as well as bone remodeling biomarkers (formation=osteocalcin and resorption=C-telopeptide) were measured before and after intervention and compared using nonparametric tests. Changes were considered significant and meaningful if the following criteria were met: \( P<0.1 \), effect size \( \geq 0.5 \), and relative variation \( >5\% \).

**Results:** Significant and meaningful increases were observed at the femur (femoral neck bone mineral content, bone strength index, and stress-strain index) and tibia (cortical cross-sectional area and polar moment of inertia) after the intervention (all \( P<.10 \)). We also noted a decrease in estimated femoral cortical thickness. However, no changes in bone remodeling biomarkers were found.
Conclusions: These initial results suggest promising improvements in bone strength markers after a 16-week exoskeleton-assisted walking program in individuals with chronic SCI. Additional research with larger sample sizes, longer interventions (possibly of greater loading intensity), and combined modalities (eg, pharmacotherapy or functional electrical stimulation) are warranted to strengthen current evidence.

Trial Registration: ClinicalTrials.gov NCT03989752; https://clinicaltrials.gov/ct2/show/NCT03989752

International Registered Report Identifier (IRRID): RR2-10.2196/19251

KEYWORDS
assistive technology; bone architecture; bone turnover; osteoporosis; rehabilitation; spinal cord injuries; SCI; spinal cord injury; assistive device; wheelchair; exoskeleton device; locomotion; bone strength; risk; fracture

Introduction

Mechanical loading is a key factor influencing bone strength [1]. Indeed, osteocytes detect and respond to mechanical stimuli by triggering an anabolic state that stimulates bone formation and leads to adaptations in bone geometry (known as the “mechanostat principle”) [1]. Healthy bones are therefore well adapted to the habitual loads regularly encountered during daily function (ie, concept of specificity) [2]. However, after sustaining a spinal cord injury (SCI), up to 60% of individuals use a wheelchair as their primary mode of locomotion—leading to a chronic reduction in lower-extremity weight bearing and reduced mechanical loading [3]. As a result, these individuals experience an accelerated loss in lower-extremity bone mass, particularly if no mitigation strategies are implemented during the first 18 to 24 months following the SCI [4]. This complication, referred to as sublesional osteoporosis, is associated with an increased risk of fracture, notably at the distal femur and proximal tibia [5].

Bone strength is directly related to fracture risk and can be influenced by several characteristics, such as bone mineral density and content, as well as geometry [6]. Measuring areal bone mineral density by dual-energy x-ray absorptiometry (DEXA) remains widely recommended to assess fracture risk in this population [7]. Indeed, low areal bone mineral density has been associated with increased risks of lower-extremity fractures in individuals with SCI as well as in the general population [8]. However, solely relying on areal bone mineral density to assess bone strength can be misleading since DEXA images display 2D (ie, x- and y-axis) representations of 3D structures (ie, loss of the z-axis) [9]. DEXA condenses structures by superposing images, causing “deeper” bones to artificially appear denser (ie, increased bone mineral density) and may lead to misclassifying individuals with a lower risk of fracture [9]. As such, this limits the DEXA’s capability to inform on bone geometry (eg, cross-sectional areas and cortical thickness) [9,10]. Peripheral quantitative computed tomography (pQCT) aims to overcome this limitation by assessing volumetric bone mineral density based on 3D images [11]. Moreover, pQCT can provide additional advantages by analyzing both trabecular and cortical bone compartments separately (ie, bone geometry) and enable the estimation of mechanical properties of strength (ie, resistivity to compression, bending, and torsion).

Although imaging (DEXA and pQCT) can provide an instantaneous “snapshot” of estimated bone strength, it does not directly assess bone turnover (remodeling). Bone turnover rate can provide fundamental information as to whether bone formation or resorption is dominant at the time of measure. Indeed, serum bone biomarkers (eg, osteocalcin and C-telopeptide) may serve as a precursor indication of a positive therapeutic effect of an intervention, even before changes can be measured with DEXA or pQCT. Osteocalcin is secreted by osteoblasts, is a marker of anabolic bone activity, and has been used in previous studies with individuals with SCI [12]. C-telopeptide, which has also been studied previously in this population, is released during bone resorption and used to characterize catabolic bone activity [13]. Since vitamin D levels can impact bone metabolism, 25-hydroxyvitamin D levels should also be measured as a possible confounding factor when characterizing serum bone biomarkers [7].

Recently, the emergence of wearable robotic exoskeletons has led to new opportunities to develop interventions that can significantly increase lower-extremity weight bearing and mobilization. Among others, a goal of such interventions is to increase bone strength and ultimately mitigate fracture risks (and associated complications) in individuals with SCI. Pilot studies have previously demonstrated that exoskeleton-assisted walking programs are feasible in this population with high rates of satisfaction (95.2%), excellent attendance (ie, 229 completed training sessions out of 234 planned training sessions, 97.9%), and relatively low dropout rates (ie, 1 dropout out of 14 individuals recruited, 7.1%) [14,15]. In terms of learnability and ease of use, most individuals can stand and walk with walking aids and minimal assistance from a therapist by the end of the program (18 to 24 sessions) [15,16]. Walking parameters, including speed and distance, have also been shown to progress consistently and safely over the course of a walking program, especially when individualized progression strategies are used [13,15-19]. Increased walking speed and distance may provide a progressive stimulus for bone strength adaptations, equating to increased intensity and volume for these tissues. Body composition improvements have also been documented following exoskeleton-assisted walking programs, including a decrease in total and regional (ie, lower extremities) body fat and an increase in muscle mass [20]. Overall, these results are encouraging; however, the effects on bone have not been comprehensively evaluated to date.
Thus, the main objective of this paper was to measure the potential effects of a 16-week exoskeleton-assisted walking program on lower-extremity bone density and strength and serum bone turnover markers in individuals with SCI who use a wheelchair [21]. It was hypothesized that immediate positive and meaningful effects would be observed on bone mineral density, mineral content, geometry, and mechanical strength indexes in the lower extremities as well as serum markers of bone turnover (ie, increase in bone formation markers and decrease in bone resorption markers) following the intervention.

Methods

Ethical Considerations

Ethics approval for this study was received on March 14, 2019, from the Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal ethics committee (CRIR-1338-0518). The protocol has been published previously and was registered with the US National Library of Medicine on June 7, 2019 (ClinicalTrials.gov NCT03989752) [21].

Study Design and Participants

This prospective pre- and postinterventional study included adults (≥18 years of age) with chronic (ie, ≥18 months) complete or incomplete SCI. To be included, individuals needed to use a wheelchair as their primary mode of locomotion, understand French or English, and reside (or be able to arrange to reside) within 75 km of the main research site. Individuals were excluded if they had neurological impairments unrelated to the SCI (eg, multiple sclerosis); had a concomitant or secondary musculoskeletal impairment limiting their ability to safely ambulate (eg, hip heterotopic ossification); had a history of fragility fracture within the past year; or had any other condition that may preclude safe lower-extremity weight bearing, walking, or exercise tolerance (eg, unstable cardiovascular or autonomic system and renal insufficiency). Individuals also had to meet criteria specific to the wearable robotic exoskeleton (Ekso GT; Ekso Bionics) used in this study, including maximum anthropometric measures and minimal lower- and upper-extremity range of motion. Inclusion and exclusion criteria are described in greater detail in the published (open access) protocol [21].

Measurement Times and Intervention

Due to constraints imposed by the COVID-19 pandemic (Multimedia Appendix 1), the 4 measurement times in the published protocol were not possible. Measurement times were only possible before the intervention (2 measurements) and immediately after the intervention (1 measurement). A participant’s preintervention measurements represented the average value between measurements taken before 4 weeks and immediately before initiating the intervention. Postintervention measurements were solely taken immediately following the end of the intervention (ie, within 7 days).

Following preintervention measurements, individuals engaged in a wearable robotic exoskeleton–assisted overground walking program consisting of 34 sessions (60 minutes per session) over a 16-week period. A published algorithm was used to individualize training volume and progression based on osteoporotic profile determined by DEXA [19]. Individuals were classified in 1 of 3 profiles: osteoporosis, osteopenia, or preserved bone mineral density. The number of steps taken per training session was then modulated, starting at 300, 400, and 500, and progressed weekly by 10%, 15%, and 20%, respectively, according to the assigned profile. For all profiles, individuals began with 1 training session per week and progressed to 3 training sessions per week by the end of the program. To maintain a moderate to vigorous exercise intensity during the sessions, walking speed, resting time, assistive devices (ie, walker or crutches), and assistance provided by the therapist were modulated to ensure a rate of perceived exertion of ≥3/10. All training sessions were supervised by a certified physiotherapist, with the help of a second physiotherapist or a physiotherapy technician if necessary.

The exoskeleton-assisted walking program was performed using the Ekso GT exoskeleton. This ready-to-wear exoskeleton has motorized hip and knee joints and semirigid ankle orthoses. Several sensors integrated into the exoskeleton (accelerometers, gyroscopes, pressure sensors, etc) are used to detect weight transfers and movements. Front and lateral spatial targets are used to guide weight transfer with an audible sound emitted when targets are reached. Step initiation depends on the walking mode used. In “FirstStep” mode, front and lateral spatial targets must be reached, followed by the press of a confirmation button by the therapist for stepping movements to be initiated. In “ProStep” mode, stepping is automatically initiated once front and lateral spatial targets are reached (no confirmation button is pressed). In “ProStep+” mode, the lateral spatial target must be reached (no front target is necessary), and the participant must initiate a hip flexion moment to activate stepping. Additionally, the exoskeleton also provides different levels of assistance, from partial (the participant must generate some lower extremity force, and the exoskeleton assists as required) to maximal (the participant does not generate lower extremity force, and the exoskeleton realizes all movements).

Outcomes

DEXA Measurement

Total body, lumbar, and left hip mineral density and content were measured using DEXA (General Electric Lunar Prodigy; standard mode; version 12.30.008). Calibration was executed daily with a standard phantom prior to each test. Participants were asked to fast for at least 8 hours prior to the assessment. Participants were also asked to empty their bladder if they had not done so within the hour preceding the DEXA. Scans were taken following the standardized protocol recommended by the manufacturer. For all scans, participants lay supine, free of jewelry or any other metallic objects. Clothing worn was noted, and participants were asked to wear the same clothing for repeated scans. For lumbar scans, participants’ lower extremities rested on a block to maintain a flexed-hip position and reduce lumbar lordosis, as recommended by the Centers for Disease Control and Prevention [22]. For hip scans, a triangular bracing device attached to the feet maintained the lower extremity in slight internal rotation, as recommended by the Centers for Disease Control and Prevention [22]. Quantitative analysis was provided automatically by the manufacturer’s software. Total

https://rehab.jmir.org/2024/1/e53084
body, L4 lumbar vertebrae, left arm, left leg, left total hip, and left femoral neck bone mineral densities and contents were selected as outcomes of interest. Total body measurements provided an estimate of the whole skeletal system. Lumbar vertebrae and left arm measurements provided comparators for lower extremity measurements, as changes were not expected to occur at these sites. Left leg measurements provided an estimate of the overall response of the lower extremities, which complemented the more specific pQCT measurements (described hereafter). Total hip and femoral neck sites provided a comparator with the broader osteoporosis literature, as these remain standard measurements for all populations with osteoporosis. When applicable, the left side of the body was selected to match with the pQCT scan sites.

**pQCT Measurement**

All pQCT imaging was realized on the left distal femur and proximal tibia. A standardized scan protocol was developed based on previous recommendations [11]. Calibration was executed daily with a standard phantom prior to each test. For all scans, a voxel size of 0.5×0.5×0.5 mm was used, and the scan speed was set to 10 mm/s to optimize resolution for bone and soft tissues. The total length was measured manually for the femur from the lateral femoral condyle to the greater trochanter [11]. To ensure location consistency for repeated scans, scout scans were realized at the knee joint with a reference line placed at the distal limit of the lateral femoral condyle. Following the scout scan, the pQCT was programmed to take one 2-mm slice at 25% of the total bone length calculated from the reference line. For the tibia, the total length was measured manually from the medial malleolus to the medial plateau [11]. To ensure location consistency for repeated scans, scout scans were realized at the knee joint with a reference line placed at the most distal and flattest portion of the tibial plateau. Following the scout scan, the pQCT was programmed to take one 2-mm slice at 66% of the total length calculated from the distal limit of the bone (using the reference line in this study, this equates to 33% from the knee joint). Both sites were selected to optimize for the presence of both bone and soft tissues in the scans.

Prior to quantitative analysis, the quality of all pQCT images was independently assessed by 2 evaluators (AB and MG or JTATL) using a previously published 5-level visual inspection and quality scale, where an image score of 1 indicated high quality and an image score of 5 represented low quality [23]. To further standardize the assessment of image quality, the following criteria were agreed upon between evaluators: score 1, if the image was free of movement artifacts; score 2, if the image was only a few movement artifacts; score 3, if the image had several movement artifacts, but periosteum continuity was not affected; score 4, if the image had several movement artifacts, and periosteum continuity was affected; and score 5, if the image had movement artifacts leading to complete loss of bone continuity. A mean score was calculated for each image. Scans with a mean score greater than 3 were excluded, as such quality of the image has been proposed to be incompatible with quantitative analysis software [23]. Excluded images were treated as missing data, and measurements were computed following an intention-to-treat protocol.

Quantitative analysis of pQCT scans was realized using the manufacturer’s software (Stratec XCT-3000; version 6.20). For all scans, contour mode 3 with a threshold set to 130 mg/cm³, peel mode 2 set to 400 mg/cm³, and separation mode 4 with an outer threshold of 200 mg/cm³ and an inner threshold of 650 mg/cm³ were used [11]. Outcomes of interest were those related to bone mineral density (total, trabecular, and cortical), bone mineral content (total, trabecular, and cortical), bone geometry (cross-sectional areas and cortical thickness), and mechanical strength indexes (bone strength index, stress-strain index, and polar moment of inertia) [7,11]. The software provides 2 measurements for cortical thickness. The first (CRT_THK), referred hereafter as measured cortical thickness, is the mean cortical thickness based on an iterative algorithm that attempts to draw the endosteal and periosteal borders by consecutively comparing neighboring voxels (pixels). Due to occasional failure of the algorithm, particularly in individuals with severe cortical thinning and loss of cortical bone mineral density (ie, many individuals with chronic SCI), the software also provides a second measurement. This measurement (CRT_THK_C), referred hereafter as estimated cortical thickness, is based on a subtraction of endosteal radius from periosteal radius in a theoretical circular model, where total and trabecular cross-sectional areas match those measured. Since measured cortical thickness systematically failed in 2 participants, estimated cortical thickness is also reported in this study.

Estimations of mechanical strength indexes are based on material properties and are calculated as follows. The bone strength index is the product of total bone mineral density squared by total cross-sectional area (ie, bone strength index = total bone mineral density² × total cross-sectional area) and is indicative of resistance to compression [10,24]. The stress-strain index (resistivity to bending) is based on the calculation of the cross-sectional moment of inertia (ie, area moment of inertia or second moment of area) [10,24]. The cross-sectional moment of inertia considers the distance of cortical bone from the central axis of the bone. The greater the distance separating cortical bone from the central axis, the greater the resistivity. To calculate the stress-strain index, section modulus (Z) is computed from the cross-sectional moment of inertia in the transversal plane. Section modulus is then weighted against measured cortical bone mineral density. Thus, resistance to bending is influenced by cortical size, shape, and mineral density [10,24]. Polar moment of inertia is based on the calculation of the cross-sectional moment of inertia in the longitudinal plane [10,24]. Thus, resistance to torsion is influenced by cortical size and shape but not mineral density [10,24]. The pQCT-related variables of interest and their cross-relationships are summarized in Figure 1.
Blood Samples
Blood samples were drawn in the morning, following an 8-hour fast, by a licensed nurse into gold-top serum separator and lavender-top anticoagulant ethylenediaminetetraacetic acid tubes. Samples were immediately placed on ice and centrifuged within an hour. Serum (from gold-top serum separator tubes) and plasma (from lavender-top anticoagulant ethylenediaminetetraacetic acid tubes) were collected and stored at −80 °C until analysis. Blood samples were transported on dry ice to a university hospital laboratory at the McGill University Health Centre for analysis after the completion of the study. Serum was used to measure 25-hydroxyvitamin D, and plasma was used to measure osteocalcin and C-telopeptide.

Statistics
Descriptive statistics were used to characterize participants. Since the sample size was limited and some outcome measures
were not normally distributed, nonparametric tests (ie, Wilcoxon signed rank test) were used to compare pre- versus postintervention data. Standardized effect sizes (r) were calculated by dividing the \( z \) value by the square root of the number of observations and interpreted as being negligible (<0.1), small (≥0.1), medium (≥0.3), or large (≥0.5) [25]. Relative pre- versus postintervention median variations (%) were also computed for all outcomes. Given the explorative nature of this study, three criteria needed to be met to reach significance and meaningfulness: (1) the \( \alpha \) for statistical tests needed to be <.10 to balance the risk of false negatives due to an anticipated lack of statistical power, (2) calculated effect sizes needed to be large (ie, ≥0.5) for an outcome to be deemed potentially clinically relevant, and (3) relative variation needed to be greater than 5% to be considered as a change exceeding natural variability and potential measurement errors. This threshold has been used in previous work, as the least significant change reportedly varies between 2% and 5% for DEXA and pQCT depending on the location of the scan [12,26]. All statistical analyses were conducted using SPSS (version 28; IBM Corp).

**Results**

**Overview**

Characteristics of the participants are summarized in Table 1. Among the 10 participants, only 1 had a very minimal motor function in the lower extremities (lower-extremity motor score: 5 out of 50), although it was not sufficient for active participation of the lower extremities during the exoskeleton-assisted walking program. Therefore, the exoskeleton was programmed to detect body weight shifts and realize stepping movements without active participation of the lower extremities (“ProStep” mode with maximal assistance in the exoskeleton) for all participants.

Table 1. Description of the participants (N=10).

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Sex</th>
<th>Age (y)</th>
<th>BMD profile(^a)</th>
<th>Walking program progression</th>
<th>Neurological lesion level</th>
<th>AIS(^b)</th>
<th>LEMS(^c)</th>
<th>Exoskeleton mode (Ekso GT)</th>
<th>SCI(^d) duration (y)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BMI (kg/m(^2))</th>
<th>Total body fat (%)(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>41</td>
<td>Preserved</td>
<td>Fast</td>
<td>T8</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>9.6</td>
<td>66.7</td>
<td>1.71</td>
<td>22.8(^f)</td>
<td>34.1(^f)</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>36</td>
<td>Preserved</td>
<td>Fast</td>
<td>T6</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>11.6</td>
<td>99.7</td>
<td>1.92</td>
<td>27.0(^f)</td>
<td>39.5(^f)</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>67</td>
<td>Preserved</td>
<td>Fast</td>
<td>T10</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>12.0</td>
<td>92.3</td>
<td>1.88</td>
<td>26.1(^f)</td>
<td>37.8(^f)</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>60</td>
<td>Preserved</td>
<td>Fast</td>
<td>T11</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>3.3</td>
<td>90.6</td>
<td>1.74</td>
<td>29.9(^f)</td>
<td>38.7(^f)</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>35</td>
<td>Preserved</td>
<td>Fast</td>
<td>C3</td>
<td>C</td>
<td>0</td>
<td>ProStep</td>
<td>3.6</td>
<td>50.2</td>
<td>1.65</td>
<td>18.4</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>32</td>
<td>Osteopenia</td>
<td>Moderate</td>
<td>T3</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>8.6</td>
<td>73.5</td>
<td>1.75</td>
<td>24.0(^f)</td>
<td>24.6(^f)</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>48</td>
<td>Osteopenia</td>
<td>Moderate</td>
<td>T12</td>
<td>B</td>
<td>5</td>
<td>ProStep</td>
<td>45.5</td>
<td>62.4</td>
<td>1.60</td>
<td>24.4(^f)</td>
<td>51.8(^f)</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>42</td>
<td>Osteopenia</td>
<td>Moderate</td>
<td>T3</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>7.7</td>
<td>70.7</td>
<td>1.66</td>
<td>25.7(^f)</td>
<td>44.4(^f)</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>55</td>
<td>Osteoporosis</td>
<td>Slow</td>
<td>T4</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>7.8</td>
<td>61.2</td>
<td>1.66</td>
<td>22.2(^f)</td>
<td>43(^f)</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>47</td>
<td>Osteoporosis</td>
<td>Slow</td>
<td>C5</td>
<td>A</td>
<td>0</td>
<td>ProStep</td>
<td>18.3</td>
<td>81.3</td>
<td>1.86</td>
<td>23.5(^f)</td>
<td>42.7(^f)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>N/A(^g)</td>
<td>46.3 (10.9)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>12.8 (11.6)</td>
<td>74.9 (15.0)</td>
<td>1.70 (0.10)</td>
<td>24.4 (2.9)</td>
<td>38.5 (7.4)</td>
</tr>
</tbody>
</table>

\(^a\)BMD profile: preintervention bone mineral density profile of the left hip as measured by dual-energy x-ray absorptiometry (DEXA).

\(^b\)AIS: American Spinal Injury Association Impairment Scale.

\(^c\)LEMS: lower-extremity motor score on the AIS.

\(^d\)SCI: spinal cord injury.

\(^e\)Total body fat percentage as measured by DEXA.

\(^f\)Identifies obesity using criteria recommended by Paralyzed Veterans of America (BMI≥22 kg/m\(^2\) or body fat>22% in men and >35% in women) [27].

\(^g\)N/A: not applicable.

**DEXA Outcome Measures**

Outcome measures for DEXA are summarized in Table 2. Only the left femoral neck bone mineral content met all 3 criteria with a \( P= .08 \), a large effect size (0.55), and a relative increase of 6% postintervention.
Table 2. Summary of dual-energy x-ray absorptiometry outcome measures (N=10).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Preintervention, median (IQR)</th>
<th>Postintervention, median (IQR)</th>
<th>P value</th>
<th>Effect sizea</th>
<th>∆b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areal bone mineral densities (g/cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body bone mineral density</td>
<td>1.159 (1.060-1.277)</td>
<td>1.145 (1.082-1.267)</td>
<td>.80</td>
<td>0.08 (N)</td>
<td>−1.2</td>
</tr>
<tr>
<td>Left arm bone mineral density</td>
<td>1.046 (0.909-1.155)</td>
<td>1.073 (0.889-1.221)</td>
<td>.51</td>
<td>0.20 (S)</td>
<td>+2.6</td>
</tr>
<tr>
<td>Left leg bone mineral density</td>
<td>1.018 (0.613-0.898)</td>
<td>0.979 (0.442-0.902)</td>
<td>.45</td>
<td>0.24 (S)</td>
<td>−3.8</td>
</tr>
<tr>
<td>Left total hip bone mineral density</td>
<td>0.862 (0.756-0.992)</td>
<td>0.832 (0.755-0.989)</td>
<td>.68</td>
<td>0.13 (S)</td>
<td>−3.4</td>
</tr>
<tr>
<td>Left femoral neck bone mineral density</td>
<td>0.852 (0.765-0.992)</td>
<td>0.908 (0.770-0.947)</td>
<td>.11</td>
<td>0.50 (L)</td>
<td>+6.6</td>
</tr>
<tr>
<td>Bone mineral contents (g/cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body bone mineral content</td>
<td>2759 (2377-3499)</td>
<td>2757 (2365-3466)</td>
<td>.33</td>
<td>0.31 (M)</td>
<td>−0.1</td>
</tr>
<tr>
<td>Left arm bone mineral content</td>
<td>188 (174-236)</td>
<td>202 (173-241)</td>
<td>.65</td>
<td>0.15 (S)</td>
<td>+7.3</td>
</tr>
<tr>
<td>Left leg bone mineral content</td>
<td>393 (300-510)</td>
<td>370 (312-528)</td>
<td>.80</td>
<td>0.08 (N)</td>
<td>−5.9</td>
</tr>
<tr>
<td>Left total hip bone mineral content</td>
<td>28.3 (20.8-34.9)</td>
<td>32.1 (20.2-36.7)</td>
<td>.39</td>
<td>0.27 (S)</td>
<td>+13.5</td>
</tr>
<tr>
<td>Left femoral neck bone mineral content</td>
<td>4.5 (3.5-6.0)</td>
<td>4.8 (3.6-5.9)</td>
<td>.03d</td>
<td>0.55 (L)</td>
<td>+6</td>
</tr>
</tbody>
</table>

aStandardized effect sizes interpreted as N=negligible (<0.1), S=small (≥0.1), M=medium (≥0.3), or L=large (≥0.5).
b∆=relative variation between medians (positive indicates an increase in value from pre- to postmeasurement).
cItalics format indicates variables meeting the following 3 criteria: statistically significant difference, effect size ≥0.5, and relative median difference ≥5%.
dStatistically significant difference (P<.10) for Wilcoxon signed rank tests.

pQCT Outcome Measures

For the femur, outcome measures for pQCT are summarized in Table 3. Although 9 outcomes were statistically significant (P<.10), only 3 had large effect sizes and sufficient relative changes to be considered as intervention effects. Bone strength index (resistivity to compression; P=.09) and stress-strain index (resistivity to bending; P=.01) increased by 9.6% and 11%, respectively, whereas estimated cortical thickness (P=.01) decreased by 9.9%. Of note, scans at the femur were not possible for 1 participant (participant 10), as his weight and lack of core stability impeded his ability to safely take and maintain the crouched sitting position necessary to set up the femur into the pQCT.

For the tibia, outcome measures for pQCT are summarized in Table 4. Although 6 outcomes were statistically significant (P<.10), only 2 had large effect sizes and sufficient relative changes to be considered potential intervention effects. Cortical cross-sectional area (P=.06) and polar moment of inertia (P=.01) increased by 7.3% and 5.1%, respectively.
Table 3. Summary of peripheral quantitative computed tomography outcome measures at 25% of the left femur (n=9).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Preintervention, median (IQR)</th>
<th>Postintervention, median (IQR)</th>
<th>P value</th>
<th>Effect size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ&lt;sup&gt;b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Volumetric bone mineral densities (mg/cm&lt;sup&gt;3&lt;/sup&gt;)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bone mineral density</td>
<td>355.8 (334.2-470.5)</td>
<td>381.6 (330.8-442.6)</td>
<td>.51</td>
<td>0.22 (S)</td>
<td>+7.3</td>
</tr>
<tr>
<td>Trabecular bone mineral density</td>
<td>87.7 (80.5-113.0)</td>
<td>88.5 (83.6-110.0)</td>
<td>.15</td>
<td>0.22 (S)</td>
<td>+1</td>
</tr>
<tr>
<td>Cortical bone mineral density</td>
<td>905.9 (805.0-968.1)</td>
<td>938.2 (871.5-981.6)</td>
<td>.04&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.69 (L)</td>
<td>+3.6</td>
</tr>
<tr>
<td><strong>Bone mineral contents (mg/mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bone mineral content</td>
<td>346 (275-434)</td>
<td>341 (266-429)</td>
<td>.05&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.65 (L)</td>
<td>−1.5</td>
</tr>
<tr>
<td>Trabecular bone mineral content</td>
<td>46.6 (37.9-76.7)</td>
<td>48.0 (39.1-78.4)</td>
<td>.95</td>
<td>0.02 (N)</td>
<td>+3</td>
</tr>
<tr>
<td>Cortical bone mineral content</td>
<td>275 (224-350)</td>
<td>268 (217-343)</td>
<td>.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.89 (L)</td>
<td>−2.5</td>
</tr>
<tr>
<td><strong>Bone geometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cross-sectional area (mm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>822 (736-1066)</td>
<td>805 (770-1023)</td>
<td>.14</td>
<td>0.49 (L)</td>
<td>−2</td>
</tr>
<tr>
<td>Trabecular cross-sectional area (mm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>489 (418-700)</td>
<td>472 (435-659)</td>
<td>.46</td>
<td>0.25 (S)</td>
<td>−3.4</td>
</tr>
<tr>
<td>Cortical cross-sectional area (mm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>312 (233-394)</td>
<td>305 (221-354)</td>
<td>.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.89 (L)</td>
<td>−2.4</td>
</tr>
<tr>
<td>Measured cortical thickness (n=7; mm)</td>
<td>4.03 (3.56-4.28)</td>
<td>3.88 (3.31-4.23)</td>
<td>.03&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.83 (L)</td>
<td>−3.6</td>
</tr>
<tr>
<td>Estimated cortical thickness (mm&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>3.28 (2.89-3.44)</td>
<td>2.95 (2.95-3.35)</td>
<td>.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.85 (L)</td>
<td>−9.9</td>
</tr>
<tr>
<td><strong>Mechanical strength indexes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression: bone strength index (g/cm&lt;sup&gt;4&lt;/sup&gt;)</td>
<td>1.35 (1.16-1.60)</td>
<td>1.48 (0.94-1.51)</td>
<td>.09&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.57 (L)</td>
<td>+9.6</td>
</tr>
<tr>
<td>Bending: stress-strain index (mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>2240 (2047-2589)</td>
<td>2486 (2356-2706)</td>
<td>.01&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.89 (L)</td>
<td>+11</td>
</tr>
<tr>
<td>Torsion: polar moment of inertia (mm&lt;sup&gt;4&lt;/sup&gt;)</td>
<td>48,002 (43,337-72,759)</td>
<td>48,800 (42,470-71,304)</td>
<td>.02&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.77 (L)</td>
<td>+1.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Standardized effect sizes interpreted as N=negligible (<0.1), S=small (≥0.1), M=medium (≥0.3), or L=large (≥0.5).

<sup>b</sup>Δ=relative variation between medians (positive indicates an increase in value from pre- to postmeasurement).

<sup>c</sup>Statistically significant difference (P≤.10) for Wilcoxon signed rank tests.

<sup>d</sup>Italics format indicates variables meeting the following 3 criteria: statistically significant difference, effect size ≥0.5, and relative median difference ≥5%.
Table 4. Summary of peripheral quantitative computed tomography outcome measures at 66% of the left tibia (N=10).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Preintervention, median (IQR)</th>
<th>Postintervention, median (IQR)</th>
<th>P value</th>
<th>Effect size</th>
<th>Δ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volumetric bone mineral densities (mg/cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bone mineral density</td>
<td>666.0 (571.1-772.6)</td>
<td>669.2 (554.0-772.4)</td>
<td>.06c</td>
<td>0.60 (L)</td>
<td>+0.5</td>
</tr>
<tr>
<td>Trabecular bone mineral density</td>
<td>97.3 (86.0-105.9)</td>
<td>95.0 (81.3-109.5)</td>
<td>.14</td>
<td>0.47 (M)</td>
<td>−2.4</td>
</tr>
<tr>
<td>Cortical bone mineral density</td>
<td>984.9 (961.0-1007.9)</td>
<td>956.4 (898.2-1004.8)</td>
<td>.07c</td>
<td>0.56 (L)</td>
<td>−2.9</td>
</tr>
<tr>
<td>Bone mineral contents (mg/mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bone mineral content</td>
<td>326 (288-425)</td>
<td>333 (292-427)</td>
<td>.14</td>
<td>0.47 (M)</td>
<td>+2.3</td>
</tr>
<tr>
<td>Trabecular bone mineral content</td>
<td>20.1 (12.5-24.5)</td>
<td>18.0 (13.1-24.4)</td>
<td>.88</td>
<td>0.05 (N)</td>
<td>−10.1</td>
</tr>
<tr>
<td>Cortical bone mineral content</td>
<td>283 (264-394)</td>
<td>288 (270-398)</td>
<td>.09c</td>
<td>0.53 (L)</td>
<td>+1.9</td>
</tr>
<tr>
<td>Bone geometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cross-sectional area (mm²)</td>
<td>602 (425-621)</td>
<td>610 (423-660)</td>
<td>.06c</td>
<td>0.60 (L)</td>
<td>+1.4</td>
</tr>
<tr>
<td>Trabecular cross-sectional area (mm²)</td>
<td>224 (124-274)</td>
<td>217 (124-295)</td>
<td>.34</td>
<td>0.50 (L)</td>
<td>−3</td>
</tr>
<tr>
<td>Cortical cross-sectional area (mm²) d</td>
<td>294 (267-388)</td>
<td>315 (273-420)</td>
<td>.06c</td>
<td>0.60 (L)</td>
<td>+7.3</td>
</tr>
<tr>
<td>Measured cortical thickness (n=8; mm)</td>
<td>5.22 (4.74-5.67)</td>
<td>5.31 (4.86-5.53)</td>
<td>.12</td>
<td>0.54 (L)</td>
<td>+1.8</td>
</tr>
<tr>
<td>Estimated cortical thickness (mm)</td>
<td>4.80 (3.96-5.48)</td>
<td>4.70 (4.26-5.78)</td>
<td>.33</td>
<td>0.31 (M)</td>
<td>−2.1</td>
</tr>
<tr>
<td>Mechanical strength indexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression: bone strength index</td>
<td>2.06 (1.67-2.85)</td>
<td>2.03 (1.63-2.88)</td>
<td>.20</td>
<td>0.40 (M)</td>
<td>−1.5</td>
</tr>
<tr>
<td>Bending: stress-strain index (mm³)</td>
<td>1838 (1346-2294)</td>
<td>1828 (1300-2250)</td>
<td>.58</td>
<td>0.18 (S)</td>
<td>−0.5</td>
</tr>
<tr>
<td>Torsion: polar moment of inertia</td>
<td>35,706 (23,560-47,987)</td>
<td>37,539 (23,638-49,806)</td>
<td>.01c</td>
<td>0.79 (L)</td>
<td>+5.1</td>
</tr>
</tbody>
</table>

a Standardized effect sizes interpreted as N=negligible (<0.1), S=small (≥0.1), M=medium (≥0.3), or L=large (≥0.5).
b Δ=relative variation between medians (positive indicates an increase in value from pre- to postmeasurement).
c Statistically significant difference (P≤.10) for Wilcoxon signed rank tests.
d Italics format indicates variables meeting the following 3 criteria: statistically significant difference, effect size ≥0.5, and relative median difference ≥5%.

Serum Bone Turnover Biomarkers
Outcome measures for serum bone turnover biomarkers are summarized in Table 5. Only 25-hydroxyvitamin D met all 3 criteria with a P=.03, a large effect size, and a relative increase of 11.4% postintervention.
Table 5. Summary of serum bone turnover biomarkers (N=10).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Preintervention, median (IQR)</th>
<th>Postintervention, median (IQR)</th>
<th>P value</th>
<th>Effect sizea</th>
<th>Δb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone formation (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>18.3 (15.6-19.4)</td>
<td>21.0 (15.3-24.0)</td>
<td>.20</td>
<td>0.69 (L)</td>
<td>+15.1</td>
</tr>
<tr>
<td>Bone resorption (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-telopeptide</td>
<td>0.3 (0.2-0.4)</td>
<td>0.3 (0.2-0.4)</td>
<td>.17</td>
<td>0.43 (M)</td>
<td>−13.8</td>
</tr>
<tr>
<td>Others (nmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-Hydroxyvitamin D³</td>
<td>74.5 (62.4-111)</td>
<td>83.0 (66.3-129)</td>
<td>.03 d</td>
<td>0.69 (L)</td>
<td>+11.4</td>
</tr>
</tbody>
</table>

aStandardized effect sizes interpreted as N=negligible (<0.1), S=small (≥0.1), M=medium (≥0.3), or L=large (≥0.5).

bΔ=relative variation between medians (positive indicates an increase in value from pre- to postmeasurement).

cItalic font indicates variables meeting the following 3 criteria: statistically significant difference, effect size ≥0.5, and relative median difference ≥5%.

dStatistically significant difference (P<.10) for Wilcoxon signed rank tests.

Discussion

Principal Findings

Results of this preliminary study indicate that the completion of a progressive 16-week exoskeleton-assisted walking program may elicit some beneficial bone adaptations in individuals with chronic SCI who have limited-to-no motor function in their lower extremities and use a manual wheelchair as their primary mode of locomotion.

DEXA Revealed an Increase in Left Femoral Neck Bone Mineral Content, but No Changes in Bone Mineral Densities

Left femoral neck bone mineral content increased significantly and meaningfully following the intervention which is, to our knowledge, a novel and key finding partly supporting our hypotheses. Moreover, a similar trend (ie, P=.11) was also observed in left femoral neck bone mineral density (ie, +6.6% with a large effect size). Indeed, since bone mineral content and density are directly related (ie, bone mineral density = bone mineral content / area), it would be expected for both to change together. Directly comparing our results to the literature remains difficult due to the lack of previously published evidence. This is particularly true with regard to bone mineral content, as this outcome has not been reported in the limited available literature with regard to exoskeleton-assisted overground walking and treadmill-based interventions [12,20,28-32].

Nevertheless, with regard to exoskeleton-assisted overground walking, a pilot study conducted in our laboratory did not reveal any significant changes in total body and total leg areal bone mineral densities, which is consistent with this study [20]. To our knowledge, only 2 other studies have reported areal bone mineral density measurements following exoskeleton-assisted overground walking. First, in a pilot study, an upward trend in areal bone mineral density was reported following 8 weeks of training (1 hour per session, 2 sessions per week). However, the authors neither specify in what body region this occurred nor present data to support this claim [28]. Second, in a pilot randomized controlled trial, including 16 participants with SCI (≥2 years) who use a wheelchair, areal bone mineral density (total hip and femoral neck) decreased in the activity-based exercise training group (60 minutes per session, 3 sessions per week for 24 weeks), whereas it remained stable in the exoskeleton-assisted walking group (60 minutes per session, 3 sessions per week for 24 weeks). It was hypothesized that exoskeleton-assisted walking may provide a sufficient stimulus to maintain areal bone mineral density but perhaps not to augment it [29]. Since this study did not include a comparison group, it remains unclear whether the areal bone mineral densities measured in our participants would have decreased further over the course of the study had they not participated in the walking program. However, all participants in this study sustained their SCI at least 3 years before initiating the study and were deemed to have reached a stable state in terms of bone mineral density. To this effect, it is now well evidenced that bone loss is greatest within the first 18 to 24 months following the lesion and tends to slow considerably thereafter [4]. Although a true steady state in bone mass may never be reached, it would be premature to state that the intervention in this study had a protective effect on areal bone mineral density [33]. Such a hypothesis would be best tested by recruiting participants who recently sustained their SCI (ie, no more than 2 years prior) and including a comparison group.

The effects of treadmill-based walking programs have also been reported in the literature using robotic assistance (eg, Lokomat; Hocoma), functional electrical stimulation, or manual assistance [12,30,31]. To our knowledge, no study has reported bone mineral content, and no changes in areal bone mineral density have been previously found [12,30-32]. Since these programs imply the use of partial body weight support, the gravity-related mechanical effects decreased considerably in comparison to overground walking, which may impede the effectiveness of such programs. This is further highlighted by the fact that treadmill-based walking programs have also been tested in combination with pharmacotherapy (ie, teriparatide) and functional electrical stimulation, which should have optimized the potential effects on bone [12,30].

Overall, this study suggests that exoskeleton-assisted overground walking may elicit a beneficial bone response at the hip that can be detected by DEXA. A combination of pharmacotherapy...
(eg, teriparatide), functional electrical stimulation, and overground walking may be needed to provide an optimal anabolic stimulus to significantly increase areal bone mineral density, and this warrants consideration for future research.

**Potential Improvements in Bone Strength as Measured by pQCT**

A few pQCT outcomes changed significantly and meaningfully following the completion of the intervention. This result supports our hypotheses in part. Four such outcomes increased, suggesting positive bone strength adaptations: femoral bone strength index (compression), femoral stress-strain index (bending), tibial cortical cross-sectional area, and tibial polar moment of inertia (torsion).

With regard to the femur, to our knowledge, the increase in bone strength index is a novel finding [12,20,30-32,34]. However, an increase in stress-strain index has been previously reported in a case study following robotic-assisted treadmill training [34]. Yet, the amplitude of change reported in this previous case study (right femur=+2% and left femur=+0.5%) was much lower than in this study (ie, +11%), and may not have exceeded natural variability or measurement error. Nevertheless, these findings highlight the importance of including both femoral and tibial measurements with pQCT in this population.

Since bone is expected to respond in areas of greatest mechanical strain, certain biomechanical concepts may help partially explain the results in this study [33]. First, although the increase in bone strength index would be expected with increased weight-bearing, the design of the exoskeleton may also contribute to greater compression forces at the femur during heel strike. Indeed, the exoskeleton used in this study uses a brace at the proximal tibia, just below the knee, to counteract the forward velocity of the lower limb (and body) during heel strike. Since the individuals in this study had very little-to-no motoricity in the lower limbs, this forward velocity could not be absorbed to the same extent by musculotendinous structures (ie, through eccentric contraction of the quadriceps) and would therefore be mainly absorbed by the skeletal (ie, femur) and ligamentous structures [35]. Second, due to the oblique orientation of the femoral diaphysis, it is possible that the forces with heel strike and unilateral stance during walking provide greater strain (ie, bending force) to the femur than the tibia, which may have also contributed to the results in this study [36]. Overall, these hypotheses warrant further investigation.

With regard to the tibia, changes in cortical cross-sectional area and polar moment of inertia have been previously reported in 2 treadmill-based interventions [12,34]. However, the relatively small amplitudes of changes in these previous studies (ie, –1 to +1.4%) raise questions as to whether these changes can be attributed to more than natural measurement error. In fact, in one of these studies, comparisons with a control group yielded no significant difference for polar moment of inertia (cortical cross-sectional area was not reported in this study) [12]. Interestingly, we have previously hypothesized that the design of current exoskeletons may limit the automatic external rotation of the tibia on the femur (and consequently, the foot) during knee extension [37]. This may have led to increased torsion moments in the tibia, which would not occur during treadmill walking without robotic assistance (ie, knee extension in an open kinetic chain)—and could partially explain the difference in amplitude of change between studies.

**Uncertainties Remain Regarding pQCT Outcomes**

The fact that the estimated femoral cortical thickness decreased (–9.9%) in this study, which does not align with our hypotheses, could raise concerns regarding the possible negative effects of the walking program on bone strength. Indeed, cortical bone is largely believed to be the primary source of resistance and strength for long bones, such as the femur and tibia [9,10]. To our knowledge, these results have not been previously reported in the femur. In 1 treadmill-based trial, a statistically significant reduction of cortical thickness was reported in the tibia [12]. However, this reduction only occurred 8 months following the completion of the training program and was not statistically different than that of the control group [12]. Of interest, a statistically significant reduction in cortical cross-sectional was also observed in this study, which most likely is explained by natural variability or measurement error, considering the relatively small magnitude of change (–2.4%). Moreover, when compared to men without SCI, individuals with SCI show reductions in cortical cross-sectional area of approximately 34% [38]. Thus, the clinical significance of a 2.4% reduction in this parameter remains questionable. Nevertheless, reductions in cortical thickness and cross-sectional area may suggest that the analysis software assigned a larger proportion of bone as subcortical (identified in yellow in Figure 1), which could be related to changes in density (ie, increased porosity) at the endosteal border due to bone resorption. This possibility cannot be completely excluded from the results of this study, particularly when considering the small sample size and the limited statistical power. Future studies should pay special attention to the possible negative effects on cortical thickness and cross-sectional area at the femur.

**Serum Biomarkers Were Not Able to Contextualize pQCT Findings, but an Unexpected Increase in Levels of Serum Vitamin D Occurred**

Serum osteocalcin (bone formation) and C-telopeptide (bone resorption) did not change significantly between before and after the intervention. This provides further evidence with regard to the complexity of the interpretation of the pQCT findings, as it is not immediately obvious whether increased bone formation or resorption was occurring following the intervention. These results were not anticipated, as 4 months of treadmill walking combined with functional electrical stimulation has been shown to significantly increase osteocalcin (+6.4%) and reduce C-telopeptide (–7.7%) levels in individuals with chronic SCI [12]. The variations found in this study (ie, osteocalcin=+15.1% and C-telopeptide=–13.8%) present trends of similar direction and of greater amplitude when compared to those previously reported, although the statistical threshold was not reached.

Serum vitamin D (25-hydroxyvitamin D) increased significantly and meaningfully by 11.4% during the intervention. Although higher vitamin D levels have been associated with greater levels of physical activity, this is generally attributed to increased time exposed to the sun in more active individuals [39]. In this study,
all participants were educated regarding vitamin D supplementation recommendations by Osteoporosis Canada [40]. Participants who were not already taking vitamin D (4/10) were offered 1 year’s worth of oral supplementation. Only 1 participant began taking vitamin D supplementation during the 4-week period before initiating training. However, even when removing this participant, the data remained statistically significant ($P=.05$). A possible explanation for this finding is the fact that most training sessions were delivered during the transition from winter to summer months. It is well recognized that vitamin D levels tend to be lower during winter months in northern countries such as Canada, as individuals spend more time indoors [41]. Thus, it is possible that the timing of the study coincided with an expected increase in vitamin D levels seen in the general population during the transition from winter to summer [41]. Nevertheless, serum 25-hydroxyvitamin D levels remained within optimal ranges (ie, ≥75 nmol/L) throughout the duration of the study [42]. As such, bone turnover and metabolism are not expected to have been significantly affected. Moreover, vitamin D supplementation, on its own, has not been shown to effectively increase bone mineral density [43]. Therefore, it is not expected that the variations in bone markers in this study can be attributed to the measured changes in serum 25-hydroxyvitamin D levels.

**Limitations and Future Perspectives**

This study has limitations that warrant consideration when interpreting its results. First, the sample size was smaller than that initially planned due to numerous challenges associated with the COVID-19 pandemic. Consequently, this reduced statistical power and increased the chance of potential type 2 errors (ie, false negatives). Moreover, the relatively small sample size impeded the possibility of conducting additional subgroup analysis. For example, it was not possible to compare participants according to clinical characteristics (eg, gender, osteoporotic status, obesity status, and response to intervention). Unfortunately, this limits progress toward a more personalized approach for the proposed intervention. Second, the absence of bone mineral density–based inclusion or exclusion criteria led to the recruitment of 5 participants (50% of the sample size) with “preserved” bone mineral density. Hence, these participants were inherently less inclined to benefit from the walking program in terms of bone health. Third, this study did not have specific inclusion or exclusion criteria for concomitant bone health treatments. However, a complete list of medications was taken for each participant, and they were instructed to inform the research team if any changes in medications occurred during the project. Of note, none of the participants were receiving antosteoporosis agents at the time of the study. Participants were also asked to maintain their physical activity levels during the duration of the study, including their regular exercise regime. Fourth, this study did not have a control group, as such, results should be interpreted with caution as it is unknown to what extent the absence of (or relatively small) changes measured would differ from natural variability in time. Finally, the intensity and duration of the intervention may have been insufficient. Bone resorption typically lasts 30 to 40 days, whereas bone formation frequently requires an additional 150 days, for a total bone turnover cycle requiring up to 6 months [10]. Therefore, it is plausible that clinically significant changes in bone strength could take up to 6 months, indicating that the 4-month measurement period in this study may not have been sufficient. For instance, interventions of 6 or more months, with stationary cycling assisted by functional electrical stimulation, have measured positive effects on bone mass, whereas shorter interventions have not [44-50]. Moreover, despite being initially planned, no follow-up assessments were authorized due to the COVID-19 pandemic, and the beneficial changes that may have emerged later in relation to the temporality of bone adaptation were not captured.

Future research should focus on larger sample sizes, with a particular interest on individuals most likely to benefit from the intervention (ie, individuals with reduced bone mass). From a pragmatic perspective, large multicentric trials will be most likely required to have a sufficient sample size to detect a 5% change in femoral bone mineral density (pQCT) and compensate for large natural heterogeneity in this population. In fact, using the data in this study, this most likely entails the recruitment of roughly 200 participants based on Lehr equation (n=8$\delta/\beta^2$). Interventions should be of sufficient volume (ie, at least 3 times per week), possibly of greater intensity, and of medium- to long-term durations (ie, at least 6 months) to ensure adequate stimulus and time for complete bone turnover cycles. Follow-up assessments, after the completion of the intervention, are also warranted to assess possible latent adaptations. The addition of a control group also remains relevant to compensate for natural variability and measurement error related to bone imaging and serum sampling. Finally, combining pharmacological interventions (eg, teriparatide) or functional electrical stimulation or both with overground exoskeleton–assisted walking may also warrant consideration.

**Conclusions**

The results from this paper confirm that a 16-week exoskeleton-assisted walking program may elicit bone adaptations. On one hand, significant and meaningful increases were documented via DEXA and pQCT at both the femur (ie, femoral neck bone mineral content, bone strength index, and stress-strain index) and tibia (ie, cortical cross-sectional area and polar moment of inertia). On the other hand, possible significant and meaningful decreases (ie, femoral cortical thickness) raise concerns. Although positive bone adaptations are emerging, it remains unclear whether completing a 16-week exoskeleton-assisted walking program increases bone strength in individuals with chronic SCI. The need for stronger evidence warrants additional research with larger sample sizes that focus on longer interventions (possibly of greater loading intensity), and combining modalities should be considered (eg, pharmacotherapy or functional electrical stimulation). To do so, national or international collaborations will most likely be required.
Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Project timeline and effects of the COVID-19 pandemic.

References


Abbreviations

DXA: dual-energy x-ray absorptiometry
pQCT: peripheral quantitative computed tomography
SCI: spinal cord injury
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Results of Gensingen Bracing in Patients With Adolescent Idiopathic Scoliosis: Retrospective Cross-Sectional Feasibility Study

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Abstract

Background: Bracing is an essential part of scoliosis treatment. The standard of brace treatment for patients with scoliosis today is still very variable in terms of brace quality and outcome. The Gensingen brace is a further developed Chêneau brace derivative with individual design, which can be adapted through computer-aided design.

Objective: This study aims to generate a template to obtain a database for prospective multicenter studies study to analyze the results of high-corrective asymmetric Gensingen brace treatment for patients with adolescent idiopathic scoliosis (AIS).

Methods: A template for the database was created, which contains the patients' basic data (age, menarcheal status, Risser Sign, curve pattern, and daily brace wearing time), the Cobb angles of curvature, and the cosmetically relevant angles of trunk rotation (ATR). A retrospective review of medical records of patients with AIS, who met the Scoliosis Research Society’s inclusion criteria for brace studies, was performed to test the feasibility of the template. Template items were filled in by the researchers.

Results: Out of 115 patients between 2014 and 2018, the complete data of 33 patients followed up at least 3 months after complete Gensingen brace weaning could be analyzed. The mean age was 12 years, the mean Cobb angle was 33.6°, and the mean Risser value was 0.7 at the beginning of the treatment. The mean improvement in the Cobb angle on in-brace x-ray imaging was –26.1° (80% of in-brace correction). The Cobb angle of the major curvature changed as follows: curve stabilization was achieved in 7 (21.2%) cases, and curve improvement was achieved in 26 (78.8%) cases. None of the patients showed a curve progression. The Cobb angle was significantly reduced in the brace at the end of treatment and at follow-up evaluation (P<.001). ATR improved significantly for thoracic (P<.001) and lumbar curves (P<.001).

Conclusions: The database proved to be informative in the assessment of radiological and clinical outcome parameters. The example data set we have generated can be a helpful tool for professionals who work in clinics but do not store regular patient data. Especially with regard to different patient collectives worldwide, different results may be achieved with the same standards of care. In addition, the results of this study suggest that above-average correction effects with a full-time brace application lead to significant improvements in the Cobb angle after brace treatment has been completed.

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Introduction

3D spinal deformities, called scoliosis, can have different causes. What most forms of scoliosis have in common is that they tend to progress in curvature during periods of increased growth. In most cases (between 80% and 90%), scoliosis affects otherwise healthy individuals and first appears during the pubertal growth spurt [1-4].

Treatment of adolescent idiopathic scoliosis (AIS) consists of corrective exercise treatments, the application of various braces, and surgical treatment [5]. High-quality studies support the use of physical therapy measures [6-8] and brace application [9-13].

Scoliosis can progress rapidly, especially in adolescence—a period of rapid growth. Therefore, it is very important to apply evidence-based treatment approaches promptly. When patients are meaningfully “observed” rather than braced, a curve progression of 6° within a period of 6 months is between 20% and 40% more likely in growing children and adolescents [1]. Hence, it is crucial that patients with AIS receive conservative management treatments as soon as possible after their diagnosis, especially if they are premenarchal and still have significant growth potential [14].

Despite the existing evidence for treatment with braces, there is a significant variation in the success rates of different brace applications and even within individual brace families. Meanwhile, it is crystallizing that highly corrective asymmetric braces are superior to a more symmetrically compressive thoracolumbosacral orthosis. However, even with asymmetric brace applications, the quality of treatment is highly variable [15]. Therefore, to ensure patient safety, only computer-aided design (CAD) brace series should be used, which are subject to a quality management program and that use standardized adjustment algorithms corresponding to the curvature pattern [15-17].

One of these brace series is the Gensingen Brace (GBW) [18,19], used in our centers and other centers worldwide. Based on our clinical experience, we hypothesize that the progression of curvature in children with AIS treated with GBW can be stopped and that there would be improvements in curvature in a certain proportion of the cohort [19,20].

Although GBW efficacy has been demonstrated in previous studies published in the literature, follow-up studies after completion of treatment are limited [19,20].

The purpose of this study is to test the feasibility of a prospective multicenter study by generating a database, including radiological and clinical outcome parameters. For this purpose, the database has been tested with a retrospective review of medical records of patients from 1 center.

Methods

Ethical Considerations

This retrospective cross-sectional study was conducted in accordance with the tenets of the Declaration of Helsinki. Ethics approval for the study was obtained from the Ethics Committee of Bandirma University (2022/195). The parents of each child were informed of the study procedures, and written consent of the caregivers and participants was obtained which in accordance with the ethics committee’s guidelines. The data set did not contain any identifiable information.

Study Design

This paper reports the results of treatment with a GBW for AIS in a retrospective nonrandomized feasibility study.

Recruitment

Patients who were admitted to Nan Xiaofeng’s Spinal Orthopedic Workshop and Schroth Health Technology centers between 2014 and 2018 and were treated with a GBW and followed up at least 3 months after complete brace weaning were included in this study.

A template for the database to be tested was created, which contains the basic data of the patients and their Cobb curvature angles and the cosmetically relevant angles of trunk rotation (ATR). A retrospective review of medical records of patients with AIS, who met the Scoliosis Research Society’s (SRS’s) inclusion criteria for brace studies [20], was performed, and the investigators then filled in the template. These criteria were as follows: female patients with prescribed brace treatment for AIS, aged between 10 and 14 years, with a Cobb angle between 25° and 40° for at least 1 structural curve, during growth with a Risser stage between 0 and 2, premenarcheal or less than 1 year after menarche, and without previous treatment [21].

Patients with nonidiopathic scoliosis; other orthopedic, neuromuscular, or rheumatic diseases; mental or psychiatric problems; iliac crest ossification of Risser stage 3-5, or continuing treatment were excluded.

According to the current guidelines, it is recommended that patients with Risser stage 0-3 and a scoliosis progression risk of more than 60% according to the Lonstein and Carlson [22] formula should start bracing treatment. In this study, risk of progression was calculated and brace treatment was recommended to the patients. For brace treatment to be effective, full-time use was recommended [23].

All children in this study used the GBW (Figures 1-3).
Figure 1. A 12-year-old minor patient with a single lumbar curve of 32° treated with a short Gensingen brace (GBW) with full in-brace correction (middle picture). Final outcome 12 months after brace weaning with a curvature of 22° with a nicely recompensated clinical appearance (right).

Figure 2. A 12-year-old minor patient with a single thoracic curve of 48° treated with a functional 3-curve balanced with a minor and shorter lumbar countercurve and Gensingen brace (GBW) with full in-brace correction (middle picture). Final outcome 9 months after brace weaning with a curvature of 28° with a nicely recompensated clinical appearance (right).
A 12-year-old minor patient with a Lenke 6 combined curve of 45° (thoracic) and 40° (lumbar) treated with a functional 4-curve, double curvature and Lenke Gensingen brace (GBW) with good in-brace correction (middle picture). Final outcome 15 months after brace weaning and a curvature of 37° (thoracic) and 32° (lumbar) with a nicely recompensated clinical appearance (right). In particular, a Lenke 6 pattern is not as easy to correct with a brace like other curve patterns.

The GBW is a further developed Chêneau brace derivative with individual design, which can be adapted through CAD. Customization, accuracy, and quality control of scoliosis braces are significantly aided by CAD. By using this technology, braces can be generated specifically for each patient's particular spinal curve pattern, resulting in more effective and comfortable treatment. The individual production steps have already been described in the literature [18]. First, the patient is scanned, and patient data are collected and entered into the database together with the x-ray image. Based on these data, the basic model corresponding to the curvature pattern is first selected from the brace library.

The patient's scan is cropped and scaled. Then, the selected brace is inserted into the scene and adjusted in accordance with the individual's body shape. Then, the correction algorithms specified for the particular pattern and curvature strength (Cobb angle) are applied accordingly. The result is a brace model that reflects the respective curvature pattern and the individual entities of the patient [24].

The following brace weaning process was applied. For curves with an initial curve grade of ≤35, the brace wearing time was decreased by wearing the brace for 16 hours per day for 3 months, 12 hours per day for 3 months, and at night for 6 months. For curves above the initial grade of 35, brace treatment was terminated by wearing a brace for 16 hours per day for 12 months, 12 hours per day for 12 months, and 6 months at night.

Database Template

The template for the database contained the following: the patient's age (in years) before starting treatment and the menarchal status (in months) were recorded. Risser's sign and curvature pattern, according to the Augmented Lehnert-Schroth (ALS) classification, were evaluated on pretreatment x-ray imaging. The Cobb angle and ATR were evaluated as primary outcome measures. The progression factor was calculated with the Cobb angle, patient's age, and Risser's finding. Daily brace-wearing time was recorded by asking parents and patients.

Risser's sign determines bone maturity, growth rate, and progression risk of a patient with scoliosis. It has been reported to be reliable and sensitive in determining bone maturity. Risser grading was assessed on the anteroposterior radiograph. The epiphyseal plate starts becoming visible from the lateral edge of the anterior superior iliac spine, progresses medially, and finally fuses at the posterior superior iliac spine. Degree of completion was indicated as a percentage: grade 1: ≤25%; grade 2: between 26% and 50%; grade 3: between 51% and 75%; and grade 4: between 75% and 100%. When the epiphyseal plate is fully fused to the ilium, it is defined as being grade 5 [25].

Curve classification was performed in accordance with the ALS classification that was developed as an expansion of the Lehnert-Schroth classification and included eight different curvature types: (1) 3CH: functional 3-curve, with hip prominence; (2) 3CTL: functional 3-curve, thoracolumbar, which implies a functional 3-curve with hip prominence and a thoracolumbar apex at thoracic vertebra 12; (3) 3C: functional...
3-curve balanced with a minor and shorter lumbar countercurve; (4) 3CL: functional 3-curve lumbar with a long lumbar countercurve; (5) 4C: functional 4-curve, double curvature; (7) 4CL: functional 4-curve with major lumbar curvature; and (8) 4CTL: functional 4-curve with major thoracolumbar curvature (and an apex at lumbar vertebra 1) [26].

The Cobb method was used to measure the degree of curvature: vertical lines were drawn on the superior and inferior vertebral endplate lines of the neutral vertebrae on the anteroposterior x-ray image of the whole spine [27], and the angle of the 2 vertical lines was recorded. X-ray images were taken at four stages: (1) before treatment (baseline), (2) at 4 to 6 weeks after the brace was fitted (in-brace), (3) at the end of treatment, and (4) at follow-up assessment after brace weaning. All braceless x-ray images were taken at least 24 hours after removal to eliminate the brace effect. All x-ray measurements were taken independently by the same experienced orthopedist. The difference between the Cobb angle at follow-up and that before treatment were calculated. Based on this difference, 3 possible outcomes are distinguished in accordance with the International Society On Scoliosis Orthopaedic and Rehabilitation Treatment’s guidelines: curve correction (\(\leq -5^\circ\) Cobb angle), curve stabilization (\(-5^\circ <\) and \(<5^\circ\) Cobb angle), and curve progression (\(\geq 5^\circ\) Cobb angle) [23].

The ATR is the most commonly used method for clinical and cosmetic assessment of scoliosis. ATR of 86% repeatability is supposed to be a reliable measurement. A change of 2\(^\circ\) in interobserver measurements is considered significant [28]. ATR are measured using a special inclinometer called a scoliometer (according to Bunnel [28]). The patient was asked to bend forward with relaxed arms (Adam’s forward bend test). The scoliometer is placed on the back of the patients, and the maximum degree of each curve was recorded [28]. ATR measurements obtained before treatment and at follow-up assessment were analyzed.

The risk for progression of the Cobb angle was calculated using the progression factor formula in accordance with Lonstein and Carlson [22]:

\[
\text{Risk for Cobb angle progression} = \text{Cobb angle} - (3 \times \text{Risser stage}) / \text{chronological age (in years)}
\]

The International Society On Scoliosis Orthopaedic and Rehabilitation Treatment’s guidelines and the validated Schroth Best Practice Academy Guidelines suggest using this formula to decide treatment indications and avoid over- and undertreatment [29,30].

According to this formula, observation is recommended for cases with a risk factor of 1.4 and below (<40% incidence of progression), physiotherapy is recommended for cases with a risk factor of 1.4-1.6 (between 40% and 60% incidence of progression), and brace treatment is recommended for cases with a risk factor of 1.6 and above (>60% incidence of progression) [31].

**Statistical Analysis**

Data analysis was performed using SPSS (version 16; IBM Corp). The Shapiro-Wilk test was used to test the normality of each variable. \(P\) values less than .05 were considered statistically significant for a 2-tailed test. Mean (SD) values and minimum and maximum values were determined using descriptive statistics.

Repeated-measures ANOVA was used to compare Cobb angle values at baseline, in-brace, end of treatment, and follow-up, and a paired samples \(t\) test was used to compare ATR values at baseline and follow-up.

**Results**

Out of 115 patients from 2014 to 2018, complete data of 33 patients who could be followed up at least 3 months after complete brace weaning have been analyzed. The mean age was 12 years, the mean Cobb angle was 33.6\(^\circ\), and the mean Risser value was 0.7 at the beginning of the treatment (Table 1). Based on the ALS classification, most cases (45.5%) had a 3C scoliosis pattern (major thoracic curve). A total of 18 of the patients were premenarcheal, and menarche had started in 15 patients (mean 5.7 months).
Table 1. Baseline demographic and clinical characteristics of patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD; range)</td>
<td>12 (1.06; 10-14)</td>
</tr>
<tr>
<td>Risser value, mean (SD; range)</td>
<td>0.7 (0.8; 0-2)</td>
</tr>
<tr>
<td>Main Cobb angle (°), mean (SD; range)</td>
<td>33.6 (8.1; 22-50)</td>
</tr>
<tr>
<td>Angle of trunk rotation (°; thoracic), mean (SD; range)</td>
<td>9.4 (5.1; 2-21)</td>
</tr>
<tr>
<td>Angle of trunk rotation (°; lumbar), mean (SD; range)</td>
<td>5.5 (4.05; 0-15)</td>
</tr>
</tbody>
</table>

Main curve location, n (%)  
- Thoracic: 26 (78.8)  
- Lumbar: 7 (21.2)

Augmented Lehnert-Schroth curve classification, n (%)  
- 3CH\(^{a}\): 5 (15.2)  
- 3CL\(^{b}\): 15 (45.5)  
- 3CN\(^{c}\): 5 (15.2)  
- 4C\(^{d}\): 6 (18.2)  
- 4CTL\(^{e}\): 2 (6.1)

\(^{a}\)3CH: functional 3-curve, with hip prominence.  
\(^{b}\)3CL: functional 3-curve lumbar with a long lumbar countercurve.  
\(^{c}\)3CN: functional 3-curve, compensated.  
\(^{d}\)4C: functional 4-curve, double curvature.  
\(^{e}\)4CTL: functional 4-curve with major thoracolumbar curvature.

The mean treatment period with the brace was 33.6 (SD 10.1, range 15-51) months, and the mean follow-up duration was 12 (SD 6.1, range 3-35) months. Daily brace wearing time in the first year of the brace treatment was 21.3 (SD 1.2, range 16-22) hours. All patients reported wearing the brace for at least 20 hours each day, with the exception of 1 who only wore it for 16 hours.

The mean improvement in Cobb angle on x-ray imaging performed in the brace was –26.1° (SD 6.8°, range –43° to –12°; [Figure 4](#fig4)), which implies a correction effect in the brace of 80%. The difference in Cobb angle at baseline and follow-up was –11.7° (SD 6.8°, range –24° to 0°; a 35% improvement from the initial value). The change in ATR at baseline and follow-up was –4.5° (SD 4.5°, range –13° to –6°; a 49% improvement from the initial value), and the change in lumbar ATR was –3.2° (SD 4.2°, range –12° to –7°; a 62% improvement from the initial value). Changes in the Cobb angle and thoracic and lumbar ATR values at the end of treatment were significant (Table 2).

Figure 4. Changes in the main Cobb angle over time.
Table 2. Changes in the Cobb angle and angles of trunk rotation (ATR).

<table>
<thead>
<tr>
<th>Outcome measurements</th>
<th>Value, mean (SD; range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Cobb angle (°)</strong></td>
<td></td>
<td>&lt;.001a</td>
</tr>
<tr>
<td>Baseline</td>
<td>33.6 (8.1; 22 to 50)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>In-brace</td>
<td>7.4 (7.9; –11 to 25)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>End of treatment</td>
<td>19.7 (9.3; 2 to 42)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Follow-up</td>
<td>21.8 (9.2; 3 to 42)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td><strong>Thoracic ATR (°)</strong></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline</td>
<td>9.4 (5.1; 2 to 21)</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>4.4 (2.6; –2 to 12)</td>
<td></td>
</tr>
<tr>
<td><strong>Lumbar ATR (°)</strong></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.5 (4.05; 0 to 15)</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.3 (2.3; –3 to 8)</td>
<td></td>
</tr>
</tbody>
</table>

aRepea ted-measures ANOVA.
bPaired samples t test.

The mean progression risk factor was 2.6 (SD 0.7, range 1.43–4.55), which, in the case of untreated scoliosis, would correspond to a probability of progression of far more than 95% reported by Lonstein and Carlson [22]. According to the SRS’s criteria, curve stabilization was achieved in 7 (21.2%) cases, and curve improvement was achieved in 26 (78.8%) cases. None of the patients had a curve progression in this sample with a probability of progression of far more than 95% reported by Lonstein and Carlson [22].

The improvement in the Cobb angle achieved in the brace was negatively moderately correlated with the pretreatment Cobb angle ($r=–0.452$). There was a positive moderate correlation between the amount of change in Cobb angle obtained at the end of treatment and the amount of improvement obtained in the brace ($P<.001, r=0.593$).

Discussion

Principal Findings

Our study shows that the template generated can be used for future prospective multicenter studies. On analyzing the data we saved in the template, the results showed that the GBW, which provides a 3D correction, is effective in stopping curvature progression and reducing the angle of curvature in adolescents with idiopathic scoliosis who continue to experience vertebral growth and are at high risk of progression.

Brace treatment and scoliosis-specific exercise methods are the most widely used, accepted, and effective treatment methods for patients with AIS [6–11,31,32]. Extensive evidence in the literature shows the effectiveness of brace treatment [15,33,34]. Previous studies have reported that brace treatment stops progression, corrects moderate curves, and reduces the rate of surgical indication [33–35]. Our results show that besides stopping curvature progression with high-correction full-time bracing also potentially improves the Cobb angle and ATR.

After the onset of the initial deformity, it is generally accepted that AIS progresses with asymmetric vertebral growth that occurs during the growth spurt. Adolescence is one of the periods of rapid growth. It has been reported that children with a high risk for progression during the rapid growth period experience progression in their curvature when left untreated [31].

In this study, the risk of progression was >95%, according to the formula developed by Lonstein and Carlson [22]. However, when growth was complete and in subsequent evaluations, it was found that there was no progression at all. The Cobb angle did not increase by ≥5° in any patient.

The patient population included in this study does not differ significantly from the cohorts of previously published studies in terms of age, maturity, menarcheal status, Cobb angle, and curvature pattern distribution [18,19].

Weiss et al [19] assessed 28 patients with AIS with a mean age of 12.7 years and Cobb angle of 30.5° using the GBW. However, they carried out their final evaluation an average of 24 months after brace treatment was initiated. They reported that the in-brace correction in their sample was from 33.9° to 15.9°, indicating an average correction of 52.7%.

In another study, Weiss et al [18] observed 167 patients with AIS who were treated with a GBW over a period of at least 18 months. The authors reported a 47%–52% rate of correction of the Cobb angle of the main curve in the brace [18]. When we calculated the success rate in accordance with the Cobb angle obtained in the brace, the treatment success rate was 80% in our cases.

In previous studies [18,19], the success rate at the end of treatment was between 86% and 92% in different subcohorts, but in our study, progression in curvature was stopped and no longer observed in all children. Therefore, GBW’s success may be considered as 100% in this study. Since the brace design worldwide follows standardized CAD algorithms and the
material (high-density polyethylene) does not differ from that used in other studies, the specifics of the studied collective might play a role. The cohort studied is from mainland China, and it is possible that the patients included in this study take brace treatment more seriously than may be the case in other countries. Another factor may be that brace treatment in China has to be financed by the patients or their parents themselves, which may also improve their motivation to wear the brace.

The main curvature Cobb angle at first diagnosis was >40° in 8 children included in this study. Considering that the Risser grade is low and the growth potential of these children is high, it is predicted that the curvatures will most likely progress. However, children with a curvature of >40° completed their treatment with an average of 16.7° (range 2°-34°). Based on these results, the use of GBWs significantly reduces the need for surgical treatment in children with AIS.

In this study, a template prepared by the investigators was filled with the help of a retrospective review of medical records. Our study shows that it would be appropriate to use this template in future prospective studies and the data intended to be recorded in this template can indicate treatment effectiveness for brace treatment. An international multicenter study considering the SRS’s inclusion criteria for brace treatment studies seems feasible.

Our study supports the conclusions of other studies regarding the corrective effect of the brace [36,37] and confirms previous findings in this field, which show that above-average corrective effects with full-time brace application lead to significant improvements in the Cobb angle after completion of brace treatment [38,39].

Evaluation of the treatment outcomes with the Cobb angle, which is still accepted as the gold standard today, the establishment of the study sample group considering the SRS’s brace study criteria, and continuation of the follow-up of the children after the end of treatment can be considered as the strengths of the study.

**Limitations**

The study’s limitations include our inability to determine the changes specific to different curve patterns, the fact that the effectiveness of the brace was not evaluated at different daily wearing times, and the fact that daily brace wearing time was recorded in accordance with the participants’ families statement. We suggest investigating the effectiveness of brace treatment in different curvature patterns and different wearing times with larger sample groups in future studies.

**Conclusions**

The results of this study suggest that above-average correction effects with full-time brace application lead to significant improvements of the Cobb angle upon completion of brace treatment. The example data set we have generated can be a helpful tool for professionals who work in clinics but do not store regular patient data. Furthermore, prospective multicentral studies with large samples can be conducted by collecting the same data at different centers.

**Data Availability**

The data that support the findings of this study are available upon request from the authors.

**Authors' Contributions**

XN, HX, and LZ conceptualized the study. XN, TKC, and BA designed the study. TKC, BA, and MB supervised the study. XN, HX, LZ, and MB collected the data. TKC and BA carried out the analysis. HX, LZ, and MB conducted the literature review. XN, TKC, BA, HX, LZ, and MB drafted the manuscript. XN, TKC, and BA critically reviewed the manuscript. The manuscript has been read and approved by all named authors.

**Conflicts of Interest**

None declared.

**References**


Abbreviations

3C: functional 3-curve balanced with a minor and shorter lumbar countercurve
3CH: functional 3-curve, with hip prominence
3CL: functional 3-curve lumbar with a long lumbar countercurve
3CTL: functional 3-curve, thoracolumbar
4C: functional 4-curve, double curvature
4CL: functional 4-curve with major lumbar curvature
4CTL: functional 4-curve with major thoracolumbar curvature
AIS: adolescent idiopathic scoliosis
ALS: Augmented Lehnert-Schroth
ATR: angles of trunk rotation
CAD: computer-aided design
GBW: Gensingen Brace
SRS: Scoliosis Research Society

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Quality of Life in Children With Achondroplasia Undergoing Paired Limb Lengthening With an External Fixator and Modified Distraction Control: Observational Nonrandomized Study

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Abstract

Background: Transosseous distraction osteosynthesis is prioritized in orthopedic care for children with achondroplasia. However, difficulties encountered during treatment and rehabilitation directly impact patients’ quality of life. Using rod external fixators within a semicircular frame for osteosynthesis is less traumatic compared to spoke circular devices. Their straightforward assembly and mounting on the limb segment can help significantly reduce treatment duration, thereby improving children’s quality of life during treatment and rehabilitation.

Objective: This study aimed to conduct a comparative analysis of the quality of life (measured by postoperative pain syndrome, physical activity, and emotional state) among children with achondroplasia undergoing paired limb lengthening using either an external fixator with modified distraction control or a circular multiaxial system developed by the authors.

Methods: This was an observational, prospective, nonrandomized, and longitudinal study with historical control. The study group consisted of 14 patients ranging from 5 to 15 (mean 7.6, SD 2.3) years old with a genetically confirmed diagnosis of achondroplasia. All patients underwent paired limb lengthening with a rod external fixator and a modified distraction control developed by the authors. A total of 28 limb segments, among them 4 (14%) humeri, 8 (29%) femurs, and 16 (57%) tibias, were lengthened in 1 round. Unpublished data from the previous study served as the control group, comprising 9 patients (18 limb segments) of the same age group (mean age at surgery 8.6, SD 2.3 years), who underwent limb lengthening surgery using a circular multiaxial system—2 (11%) humeri, 6 (33%) femurs, and 10 (56%) tibias. The Wong-Baker Faces Rating Scale was used to measure pain symptoms, while the Russified Pediatric Quality of Life (PedsQL) v4.0 questionnaire assessed quality of life.

Results: During the latent phase (7 to 10 days after surgery), a more pronounced decrease in the indicators of physical activity and emotional state on the PedsQL v4.0 questionnaire was noted in the control group (mean 52.4, SD 4.8 versus mean 52.8, SD 5.5 points according to children’s responses and their parents’ responses, respectively) compared to the experimental group (mean 59.5, SD 6.8 points and mean 61.33, SD 6.5 points according to the children’s responses and their parents’ responses, respectively). The differences between the groups were statistically significant ($P<.05$ for children's responses and $P<.01$ for parents’ responses). Importantly, 6 months after surgery, these quality-of-life indicators, as reported by children in the experimental group, averaged 70.25 (SS 4.8) points. Similarly, their parents reported a mean of 70.54 (SD 4.2) points. In the control group, the corresponding values were 69.64 (SD 5.6) and 69.35 (SD 6.2), respectively. There was no statistically significant difference between the groups.

Conclusions: The external fixator with modified distraction control developed by the authors provides a higher standard of living compared with the circular multiaxial system during the latency phase.

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Introduction

Achondroplasia is a hereditary disease characterized by a deceleration in bone and cartilage growth. The term “achondroplasia” was first used in 1878 by Jules Parrott, and in 1900, the neurologist Pierre Marie first described the main features of the disease in children and adults. According to the International Classification of Diseases (ICD-10), this pathology is classified in chapter XVII “Congenital malformations, deformations, and chromosomal abnormalities” (Q00-Q99), specifically in the section “Congenital malformations and deformations of the musculoskeletal system.” More specifically, it falls under code Q77, which encompasses osteochondrodysplasia with defects of growth of tubular bones and spine. Within this category, Q77.4 is specifically designated for achondroplasia. This congenital skeletal disorder in children belongs to the group of systemic dysplasias [1] and is associated with a defect in the zone of cartilage proliferation [2].

At birth, children in this nosological group display a proximal shortening of the upper and lower extremities, a relatively short and narrow trunk, trident-shaped hands, and macrocephaly with hypoplasia of the middle third of the face and a protruding forehead. Growth parameters at birth are usually slightly less than normal, but with age, there is a progressive lag from the normal values (total shortening of the limbs is especially pronounced in the upper arms and thighs). Infants with achondroplasia are most characterized by decreased muscle tone, causing them to learn movement and walking skills later in life. Intellect and cognitive abilities are not affected by this malformation [3,4]. A review of the specialized literature showed that the incidence of achondroplasia varies widely from 1:15,000 to 1:30,000 newborns, regardless of gender or race [5]. The main cause of achondroplasia is a de novo mutation in fibroblast growth factor receptor-3 (FGFR3), which leads to a disruption of the endochondral ossification mechanism [6].

Despite a wide array of pathological symptoms, disproportional dwarfism remains central in defining the stereotypes and lifestyle of patients living with this condition. It is characterized by significant limb shortening and deformity. The combination of external and radiological manifestations in the musculoskeletal system, which are exacerbated in the process of growth, strongly influences the way these patients perceive themselves and lead their lives. This issue is particularly marked in childhood, where more attention is paid to a person’s appearance [7,8].

Currently, transosseous distraction osteosynthesis is prioritized in orthopedic care [9,10]. This method is based on the general biological property of tissues to respond by regeneration to dosed stretching [11]. The conventional approach for uniform tubular bone lengthening typically involves 1 mm per day in 0.25 mm fractions across 4 sessions [12]. However, the period of osteosynthesis in this mode varies from 4 to 18 months, which correlates with the planned magnitude of lengthening [13,14]. Challenges encountered during treatment and rehabilitation significantly impact patients’ quality of life [15]. Traditionally, the Ilizarov circular system has been utilized for limb lengthening in patients in this nosological group [9]. The features of this equipment, as well as the fundamental studies on reparative tissue regeneration processes and the proposed surgical intervention options, remain highly relevant to this day. [16]. However, the complexity of the design, its excessively bulky nature, and its many parts can lead to long assembly times and require an increased time under anesthesia. In turn, these factors contribute to challenges during rehabilitation, limiting the use of this type of external fixator in pediatric practice [17]. Nevertheless, external fixators are the most common in the treatment of patients with achondroplasia in many countries [18-20]. According to the available literature, osteosynthesis with rod external fixators based on a semicircular frame is less traumatic compared to spoke circular devices. Moreover, rod fixators lead to less disruption of venous and lymphatic outflow in the postoperative period [20]. Rod fixators are more compact in appearance and provide sufficient rigidity to aid in bone fragment stabilization. Their straightforward assembly and mounting on the limb segment can help significantly reduce surgery duration, which is important in paired limb lengthening [21]. The authors developed a bar external fixation device with a distraction control system that showed better results than the circular multiaxial system regarding fixation time, regenerative length, deformation angles, pain intensity indexes, and complication rates [11]. This study aims to compare the quality of life (focusing on postoperative pain syndrome, physical activity, and emotional state) of children with achondroplasia undergoing paired limb lengthening using 2 different methods: an external fixator with modified distraction control and a circular multiaxial system developed by the authors.

Methods

Study Design

This was an observational, prospective, nonrandomized, and longitudinal study with a historical control. The experimental group included 14 patients, including 8 (57%) males and 6 (43%) females, aged between 5 and 15 (mean 7.6, SD 2.3) years. All patients had a genetically confirmed diagnosis of achondroplasia and received treatment at the state municipal enterprise “Multiprofile City Children’s Hospital No 2” in Astana, Kazakhstan, spanning from August 2018 to January 2020. All patients underwent paired limb lengthening using a rod external fixator with modified distraction control developed by the authors. A total of 28 limb segments, including 4 (14%) humeri, 8 (29%) femurs, and 16 (57%) tibias, were lengthened in 1 round. All operations were performed by the same team of surgeons. The patients were dynamically followed up for 18 months.
Unpublished data from the previous study were used as the control group, which comprised 9 patients, including 3 (33%) males and 6 (67%) females, matching the same age group (mean age during surgery 8.6, SD 2.3 years). Patients in the control group also had a genetically confirmed diagnosis of achondroplasia and underwent limb lengthening surgery using a circular multiaxial system between January 2012 and July 2018. A total of 18 segments of tubular bone were lengthened in the control group—comprising 2 (11%) humeri, 6 (33%) femurs, and 10 (56%) tibias. All operations were performed by the same team of surgeons as in the experimental group. This study did not involve a clinical trial.

**Clinical Examination**

Patients underwent preliminary clinical and radiological assessments. The clinical evaluation included orthopedic and neurological status: assessment of ligamentous elasticity and mobility of the knee joint, presence of torsional deformities of the lower extremities, child growth, and proportionality of the skeletal structure. The radial diagnostic protocol included radiographs of both lower extremities in straight projection over the entire length in a bipedal standing position with the correct orientation of the patellas (facing forward). Angular changes in the extremities were analyzed based on the radiographs obtained. The patients were examined by various specialists, including a pediatrician, endocrinologist, neurologist, cardiologist, and otolaryngologist, during the preoperative phase to identify any concomitant pathologies and mitigate intra- and postoperative complications.

**Operative Technique**

Surgical treatment was performed under general endotracheal anesthesia. During the surgical procedure, a semicircular external rod fixator design with a distraction mechanism of the authors’ modification was used (Figure 1). The operations were performed simultaneously on 2 identical segments, according to the tibia-tibia and femur-femur schema. To minimize the traumatic nature of the surgical intervention, a closed corticotomy of the middle third of the diaphysis was performed.

![Figure 1](https://rehab.jmir.org/2024/1/e49261/fig1.png)

*Figure 1. A semicircular external rod fixator design with the authors’ modified distraction mechanism. (1) Mechanism of the fixator in the form of a 2-section sliding structure. External rod section with internal thread and 2 rods with an external millimeter thread. (2) Supporting bases on which the distraction system is fixed when installing an external fixation device on a limb segment. The 1-mm distraction step is performed by axial rotation according to the marks. (3) Nut stabilizing internally threaded rods on the proximal threaded rod.*
Postoperative Rehabilitation

Postoperative rehabilitation for patients with achondroplasia comprised 3 stages: a latency phase, a period of distraction and consolidation, and a period of functional adaptation of patients after device removal. The latency phase lasted 7 to 10 days, depending on the duration of postoperative edema recession and pain intensity. Lengthening was initiated at the end of the latent phase on the 7th to 10th day after surgery, with an average daily distraction rate of 0.75 mm. Restorative treatment was initiated on the second day after surgical intervention with constant parental involvement.

The amount of exercise depended on pain levels, distal limb swelling, and the patient’s psychological state. To prevent contractures of adjacent joints, the focus was on passive-active exercises ranging from 5 to 10 minutes, up to 3 times a day. Under medical supervision, patients were gradually mobilized to stand upright using walkers for up to 5 minutes and were taught to walk within the room. During distraction, the time of passive and active joint development sessions increased to 40 minutes, occurring 5 to 6 times a day, while the walking duration extended to 15 minutes.

The hospital stay for patients typically ranged from 10 to 14 days, adhering to the Republic of Kazakhstan’s Standard of Medical Care in Hospital Conditions. The hospital stay was determined based on the duration of the latency phase (period of postoperative edema recession and reduction of pain intensity). Subsequently, patients were discharged to outpatient treatment. Distraction and consolidation timing were assessed using radiographs. Control examinations with radiographs were performed every 10 days. During the examination, external fixator stability, joint function, and the presence of neurological and vascular disorders were evaluated. Based on the radiological appearance of the regenerate and assessment of joint mobility, the distraction rate was corrected (either decreased to 0.75 mm/day or increased to 2 mm/day). During the stabilization period, when performing joint development, an emphasis was placed on increasing muscle strength. Moreover, physical therapy classes remained intense, and the patients were taught to walk without additional support.

After reaching the possible segment length, the distraction process for the regenerate was halted, and the patients were examined monthly during the consolidation phase. After removing the fixators, a period of functional adaptation began that lasted up to 18 months after surgery. A key principle during this stage involved a gradual and appropriate increase in load. The treatment approach involved massaging the muscles of the thigh, lower leg, and humerus, coupled with physical therapy and thermal procedures. Furthermore, passive mobilization of all ranges of motion in the hip and knee joints was undertaken, with an emphasis on enhancing knee joint flexion. Patients were recommended to swim and exercise using simulators. Additionally, sanatorium-resort treatment was geared toward recovering all body systems following inpatient surgical treatment. Patients and parents were trained in the proper care of the medical device and rods and were instructed to adhere to the prescribed limb lengthening (distraction) schedule.

Quality of Life Assessment

Postoperative pain is a complex response to tissue trauma during surgery. A pronounced postoperative pain syndrome increases the likelihood of postoperative complications, prolongs the patient’s recovery period and subsequent rehabilitation, reduces physical activity, and worsens the patient’s psychoemotional state. Postoperative pain intensity is determined not only by the extent of damage but also by psychological factors (accompanying emotional state and anxiety). In this regard, postoperative pain syndrome, physical activity, and patients’ emotional states were considered when assessing quality of life.

The Wong-Baker Faces Rating Scale was used to assess the pain syndrome [22]. When working with this rating scale, a child had to choose 1 of the 6 faces drawn that corresponded to how they felt. The first face represented 0 points and indicated “no pain,” while the sixth face represented 5 points and indicated “severe pain.” Pain was assessed in the latency and distraction phases.

To assess the quality of life, a questionnaire was administered using the Russified Pediatric Quality of Life (PedsQL) v4.0 questionnaire [23]. This questionnaire has 23 five-point scales reflecting the patients’ current state: level of physical activity, emotional state, satisfaction with social role (satisfaction with communication with peers), and engagement in kindergarten/school. During this study, it was not feasible to correctly assess outcomes related to social role satisfaction and kindergarten/school attendance using the scales while the patients were still in the hospital. Therefore, quality of life was assessed only on the scales of level of physical activity and emotional state. The questionnaire consists of 2 parts: an assessment of a child's quality of life (from age 5 years) and an assessment of a child's quality of life by their legal representative. The children and their parents were instructed to select a number that reflected the frequency of difficult situations over a certain period, where 0 was never, 1 was almost never, 2 was sometimes, 3 was often, and 4 was almost always. The number of points was calculated by the questionnaire key. First, the results were reversed and converted to a linear 100-point scale, where 0 was 100, 1 was 75, 2 was 50, 3 was 25, and 4 was 0. Next, the survey results were tallied. The results of each item in the block were added up, and the resulting sum was divided by the number of items in the block. A score higher than 75 was considered optimal. In the third stage, the authors calculated the total score for each item and divided the result by the number of items. The questionnaire was administered in the preoperative, latency, distraction, and consolidation phase, as well as during dynamic follow-up (6, 12, and 18 months after surgery). The questionnaires were processed blindly.

Statistical Analysis

The t test for the independent samples was used to assess the reliability of the differences between the experimental and control groups. The Student t test for dependent samples was also used to assess the reliability of differences within the groups at different stages of the study [24]. At P<.05, the null hypothesis of no relation between the parameters was rejected. Statistical calculations were performed using the SPSS software (IBM Corp.).
Ethical Considerations
The research was conducted in accordance with the Standard of Good Clinical Practices (GCP) to the Order of the Minister of Health and Social Protection of Kazakhstan (May 27, 2015; no 392) and the ethical standards of the Declaration of Helsinki, amended in 2013. Parents were informed in advance about the purpose of the planned surgery. Parents or legal guardians signed informed consent for the surgical intervention, rehabilitation treatment, and publication of the findings without identifying themselves. The study was reviewed and approved by the Human Research Ethical Committee of Astana Medical University (reference number 333).

Results
In 9 (64%) patients in the experimental group, the lengthening results were evaluated as "excellent." This means that the planned elongation value had been reached, the deformation of the bone regenerate did not exceed 2 degrees, joint function was excellent (absence of contractures), and consolidation was successful based on radiographs. In 4 (29%) of patients, the lengthening results were evaluated as "good," indicating the planned elongation value had been attained, with slight deformation of the bone regenerate (not exceeding 4 degrees), the presence of easily treatable contractures, and successful consolidation confirmed by radiographs. In 1 (7%) case, the results were classified as "satisfactory." In these cases, the planned elongation was not fully achieved, there was some deformation of the bone regenerate (not exceeding 8 degrees), and there was a presence of contractures, but consolidation was successful according to radiographs.

Most patients achieved a lengthening value close to the planned value and correction of deformity, with minimal deviation that was not statistically significant. The average lengthening values were 8.5 (SD 0.6) cm, with the humerus length increasing by an average of 53% (SD 5%), the tibia by 52% (SD 8.2%), and the femur by 30% (SD 6%). The fixation period, including the distraction phase, averaged 83.8 (SD 3.7) days, with a specific average duration of 76 (SD 1) days for the humerus, 83.9 (SD 3.2) days for the tibia, and 87.5 (SD 2.5) days for the femur.

No contractures were observed during the latency phase or after the end of the distraction phase. However, during the distraction stage, 1 (7%) patient experienced knee joint contractures during hip lengthening, and 2 (14%) patients had ankle joint contractures due to heel tendon shortening, which resulted from failure to follow the treatment regime and joint development recommendations. The most common complaint reported by patients and their parents was minor inflammation of the soft tissues around the rods, which was resolved with conservative treatment. No cases necessitating rod removal or a second operation were noted. In the control group, the fixation time in the device averaged 101.4 (SD 5.4) days and the length of the regenerate averaged 6.6 (SD 0.8) cm. In 4 (29%) cases, knee joint contracture persisted, and 1 (7%) case of needle fracture was recorded.

Regarding pain, on the second day after the operation, the pain index in 13 (93%) patients in the experimental group was rated at 3 points on the Wong-Baker scale and at 4 points for 1 (7%) patient. However, by the end of the latency phase, the pain index in all patients was 0. In the control group, the Wong-Baker pain score was 4.1 (SD 1.02) on the second day and decreased to 1.7 (SD 0.8) at the end of the latency phase.

Before the surgery, quality of life scores on the PedsQL v4.0 questionnaire (measuring physical activity and emotional state) in the experimental group averaged 78.67 (SD 5) in the children's responses and 78.25 (SD 5.1) in their parents' responses. In the control group, these scores were 78.8 (SD 4.4) for the children and 78.0 (SD 5.4) for their parents. Thus, there were no differences in quality-of-life scores between the 2 groups before surgery.

As expected, during the latency phase following surgery, there was a significant decrease in physical activity and emotional state scores on the PedsQL v4.0 questionnaire in both groups when compared to the preoperative period. However, this decrease was more pronounced in the control group, with scores averaging 52.4 (SD 4.8) points by the children and 52.8 (SD 5.5) points by their parents. In contrast, in the experimental group, these quality-of-life scores decreased to 59.5 (SD 6.8) points according to the children's responses and 61.33 (SD 6.5) points according to their parents. These differences between the groups were statistically significant (P < .05 for the children's answers and P < .01 for their parents). At the same time, the experimental group showed a statistically more pronounced decline in the quality of life when the humerus was lengthened compared to the tibia and femur (P < .01). However, in the control group, such differences in quality-of-life changes between the lengthened segments were not observed.

By 6 months after surgery, there were improvements in physical activity and emotional state scores in both groups. These quality-of-life indicators on the PedsQL v4.0 questionnaire in the experimental group averaged 70.25 (SD 4.8) points according to the children's responses and 70.54 (SD 4.2) points according to their parents. In the control group, the corresponding scores were 69.64 (SD 5.6) points and 69.35 (SD 6.2) points, respectively. There was no statistically significant difference between the groups. There was also no difference between the lengthening segments in either group.

At 18 months after surgery, quality-of-life indicators (physical activity and emotional state scores) in both groups exceeded preoperative scores. In the experimental group, the average score was 84.3 (SD 2.5) group for the children and 85 (SD 2.5) points for their parents. These increases were statistically significant (P < .01). In the control group, the average score was 81.33 (SD 3.5) points for the children and 82.0 (SD 3.6) points for their parents, but the differences from preoperative scores were statistically unreliable. Furthermore, differences in quality-of-life scores between the experimental and control groups 18 months after surgery were statistically unreliable. The results of the PedsQL v4.0 quality of life questionnaire, completed by the patients and their parents in both groups, are shown in Tables 1 and 2.

https://rehab.jmir.org/2024/1/e49261

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(page number not for citation purposes)
Table 1. Results of transosseous osteosynthesis using the advanced rod monolateral external fixator and PedsQL<sup>a</sup> v4.0 questionnaire scores completed by patients and their parents in the experimental group (N=14).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Segment</th>
<th>Consolidation period (days)</th>
<th>Planned lengthening (cm)</th>
<th>Lengthening results (cm)</th>
<th>PedSQL&lt;sup&gt;a&lt;/sup&gt; v4.0 questionnaire scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preoperatively</td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>Tibia</td>
<td>82</td>
<td>10</td>
<td>Right: 8.3</td>
<td>Child: 72</td>
</tr>
<tr>
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<td>7</td>
<td>Tibia</td>
<td>85</td>
<td>10</td>
<td>Right: 8.9</td>
<td>Child: 78.3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Left: 8.2</td>
<td>Parent: 80</td>
</tr>
<tr>
<td>Female</td>
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<td>Tibia</td>
<td>79</td>
<td>10</td>
<td>Right: 8.3</td>
<td>Child: 78</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Left: 8.3</td>
<td>Parent: 77</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>Tibia</td>
<td>80</td>
<td>10</td>
<td>Right: 10</td>
<td>Child: 87</td>
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<td>Left: 8.9</td>
<td>Parent: 75</td>
</tr>
<tr>
<td>Female</td>
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<td>Tibia</td>
<td>85</td>
<td>10</td>
<td>Right: 8.2</td>
<td>Child: 80</td>
</tr>
<tr>
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<td></td>
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<td>Left: 8.5</td>
<td>Parent: 80</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>Femur</td>
<td>85</td>
<td>8.5</td>
<td>Right: 8.3</td>
<td>Child: 83</td>
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<tr>
<td></td>
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<td>Left: 8.3</td>
<td>Parent: 84</td>
</tr>
<tr>
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<td>12</td>
<td>Femur</td>
<td>90</td>
<td>8.5</td>
<td>Right: 7.2</td>
<td>Child: 82</td>
</tr>
<tr>
<td>Male</td>
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<td>Femur</td>
<td>90</td>
<td>8.5</td>
<td>Right: 9</td>
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<tr>
<td>Male</td>
<td>6</td>
<td>Femur</td>
<td>85</td>
<td>8</td>
<td>Right: 8</td>
<td>Child: 80</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>Humerus</td>
<td>75</td>
<td>9</td>
<td>Right: 7.5</td>
<td>Child: 85.3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Left: 7.8</td>
<td>Parent: 86</td>
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<tr>
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<td>Humerus</td>
<td>77</td>
<td>8</td>
<td>Right: 8.1</td>
<td>Child: 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left: 8.2</td>
<td>Parent: 78.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>PedSQL: Pediatric Quality of Life.
Table 2. Results of transosseous osteosynthesis using the circular multiaxis system and PedsQLα v4.0 questionnaire scores completed by patients and their parents in the control group (N=9).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (years)</th>
<th>Segment</th>
<th>Consolidation period (days)</th>
<th>Lengthening results (cm)</th>
<th>PedsQLα v4.0 questionnaire scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preoperatively</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Latency phase (7-10 days after surgery)</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>Humerus</td>
<td>90</td>
<td>Right: 7</td>
<td>Child: 75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left: 8</td>
<td>Parent: 75</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>Femur</td>
<td>105</td>
<td>Right: 8</td>
<td>Child: 80</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>Femur</td>
<td>105</td>
<td>Right: 7</td>
<td>Child: 76</td>
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<tr>
<td>Female</td>
<td>14</td>
<td>Tibia</td>
<td>103</td>
<td>Right: 7</td>
<td>Child: 78.3</td>
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<tr>
<td>Female</td>
<td>14</td>
<td>Tibia</td>
<td>110</td>
<td>Right: 5</td>
<td>Child: 76</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Left: 6</td>
<td>Parent: 72</td>
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<tr>
<td>Male</td>
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<td>Femur</td>
<td>107</td>
<td>Right: 5</td>
<td>Child: 76</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left: 5</td>
<td>Parent: 73</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>Tibia</td>
<td>97</td>
<td>Right: 6</td>
<td>Child: 86</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>Femur</td>
<td>105</td>
<td>Right: 6.5</td>
<td>Child: 80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left: 6.5</td>
<td>Parent: 82</td>
</tr>
</tbody>
</table>

*PedsQL: Pediatric Quality of Life.*

**Figure 2a-c** also shows the postoperative progression of a 10-year-old patient diagnosed with achondroplasia who underwent paired limb lengthening with a rod external fixator equipped with the authors’ modified distraction control. The patient and her parents reported a significant improvement in her quality of life after the surgical intervention and rehabilitation.
**Discussion**

**Principal Findings**

This study compared quality-of-life indicators (measured by postoperative pain syndrome, physical activity, and emotional state) in children with a genetically confirmed diagnosis of achondroplasia undergoing transosseous distraction osteosynthesis using 2 different external fixators systems: a rod system with the authors’ modified distraction control and a circular multiaxial system (Ilizarov system).

As expected, the results confirmed a decline in the quality of life for patients in both groups during the latency phase. However, patients in the control group (using the circular multiaxial system) experienced a more significant decrease in quality-of-life satisfaction, as reported by both the children and their parents/caregivers, compared to the experimental group using the rod fixator with the authors’ modified distraction control. Moreover, the control group reported more intense pain syndrome compared to the patients using the authors’ modified semicircular distraction system. During the later postoperative period under a dynamic observation, these differences decreased, and the level of satisfaction with the quality of life was statistically significantly higher in the main group 18 months after surgery than in the preoperative period.

Although orthopedic surgery for the treatment of achondroplasia has made significant advancements and continues to evolve, most practitioners have yet to agree on a surgical approach to the treatment of children and adolescents with this condition. Furthermore, the optimal fixator compositions for different age groups of patients are not specified [9]. A high rate of complications persists, which may be due to noncompliance with age-specific aspects of surgical treatment [17]. Several postoperative management issues remain unresolved [16].

In a recent study utilizing the PedsQL 4.0 questionnaire to assess the quality of life in children with achondroplasia (reported by the children and their parents/caregivers), it was observed that parents perceived their child’s quality to be lower in all domains compared to people of average height. This is due to physical limitations, barriers, and various challenges reported by children and adolescents to their parents. Notably, the children themselves also rated their quality of life significantly lower than the healthy control group, except in the emotional domain, where their scores were similar to the healthy group. It is important to understand that the diagnosis of achondroplasia and its consequences impact not only a child but also the entire family, as family members must adapt to the unique needs of the child [7].

Surveys conducted among patients with achondroplasia and their family members, both before and after treatment, consistently answer in favor of the need for limb augmentation [8,17]. Currently, the primary method for addressing growth deficit in patients with achondroplasia involves surgical distraction osteosynthesis [9,10]. The possibility of drug-assisted limb lengthening, particularly with the drug Vosoritide, is being studied. While the results are encouraging, at present, this trend cannot serve as an alternative to surgical treatment [4].

During surgical treatment, transosseous osteosynthesis is the most commonly used method, involving the use of external bone-anchored supports placed above the skin’s surface. However, patients are required to wear these systems throughout the distraction and consolidation period of the regenerate, which can last up to 18 months, depending on the planned degree of limb lengthening. This inevitably impacts a patient’s quality of life. In response to this concern, internal fixation systems have
been developed, such as the Precice system with magnetic control over distraction speed [25,26], and combined systems like LON (Lengthening Over Nail) and LATN (Lengthening and Then Nailing), which halve the time of fixator use [27-29]. However, these systems cannot always serve as an alternative to fixators because they use expensive titanium rods. The Precice system has limitations in bone diameter, cannot be used for humerus lengthening, and the procedure itself must be well planned since no postoperative changes (other than distraction rate) can be made [27]. The LON and LATN systems require additional surgical intervention. Consequently, the development of lighter and more comfortable fixators remains urgent.

Traditionally, limb lengthening for patients in this nosological group has been performed using a multiaxial system, known as the Ilizarov system. While this system shows good results in reparative tissue regeneration processes, its complex design and cumbersomeness can impact patients’ quality of life, which is especially significant in pediatric practice [9,16,17]. To address this, rod fixators built on a semicircular frame with a simpler and lighter design are gaining popularity [20,21]. The authors have introduced a rod fixator with modified distraction control. A previous article demonstrated the advantage of this system over the circular multiaxial system, highlighting improvements in fixation time, achieved regenerative length, correction of deformities, pain intensity, and complication rates [11].

This study establishes that the authors’ rod fixation with modified distraction control facilitates an improved standard of living compared to a circular multiaxial system in the latent phase. Consequently, this advancement not only allows patients with achondroplasia to move freely from the first days after surgery but also to gradually develop strength in the lengthened limb.

Conclusions
The rod fixator with modified distraction control developed by the authors significantly enhances the quality of life compared to the circular multiaxial system in the latency phase. Employing this fixator technique for paired surgical lengthening in children with achondroplasia ensures stability throughout the distraction process, provides a strong and uniform regenerate, contributes to a significant reduction in complications, and allows patients to regain full physical activities in a shorter time. With its high stability, the device creates favorable conditions for psychological and physical adaptation during treatment and demonstrates a significant advantage over the circular multiaxial system. Considering the cost-effectiveness of this developed fixation system, it can contribute to delivering quality orthopedic care for patients with achondroplasia.

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Declaration of Patient Consent
The patient’s parent has given informed consent for the patient’s images and other clinical information to be published in a medical journal. The patient’s parent understands that the patient’s name and initials will not be published and due efforts will be made to conceal their identity, but complete anonymity cannot be guaranteed.

Data Availability
The data sets generated and/or analyzed during this study are available from the corresponding authors upon reasonable request.

Authors’ Contributions
All authors contributed to the study’s conception and design. VT, BD, VL, SK, AD, AA, AP, and OZ performed the material preparation, data collection, and analysis. VT wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest
None declared.

References


Abbreviations

ICD: International Classification of Diseases
FGFR3: fibroblast growth factor receptor-3
GCP: Good Clinical Practice
LON: Lengthening Over Nail
LATN: Lengthening and Then Nailing
PedsQL: Pediatric Quality of Life