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Research Article

Real-World Efficacy of Weekly Somatrogon on Growth and Bone Health in Pediatric Growth Hormone Deficiency: A 12-Month Retrospective Cohort Study

Awad MH et al. Real-World Somatrogon Efficacy in Pediatric GHD

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What is already known on this topic?
• Daily GH therapy is effective but often limited by poor adherence.
• Weekly Somatrogon offers a convenient alternative, with early data showing comparable growth outcomes.
• Effects on bone health (BHI, bone age) remain underreported.

What this study adds?
• Weekly Somatrogon improved height and IGF-1 SDS over 12 months in prepubertal GHD.
• It increased BHI without advancing bone age or MCI.
• Supports Somatrogon as a safe, effective once-weekly GH option.

Abstract
Background: Growth hormone deficiency (GHD) in children results in short stature and impaired bone health. While daily growth hormone (GH) injections are effective, they are associated with adherence challenges. Somatrogon, a long-acting recombinant human GH, allows weekly administration, potentially improving treatment compliance.
Methods: This retrospective cohort study included 39 prepubertal children with GHD treated with weekly Somatrogon at Al Jalila Children's Hospital, Dubai. Diagnosis was based on clinical, biochemical, and radiological criteria, including height standard deviation score (SDS) < –2.0, subnormal growth velocity, and subnormal peak GH in one stimulation test (<10 ng/mL) supported by low IGF-1 and/or abnormal MRI. Growth outcomes and bone health indices were assessed over 12 months using auxology, IGF-1 levels, and BoneXpert-derived Bone Health Index (BHI) SDS and Metacarpal Index (MCI) SDS.
Results: After 12 months of therapy, mean height SDS improved significantly from –2.16 ± 0.80 to –1.65 ± 0.71 ($p < 0.001$). IGF-1 SDS rose from –1.38 ± 1.02 to 0.88 ± 1.57 ($p < 0.001$). Adult predicted height and BHI SDS also improved significantly ($p = 0.005$ and $p < 0.001$, respectively). No significant changes were observed in bone age SDS or MCI SDS.
Conclusions: Weekly Somatrogon significantly improved linear growth, IGF-1 levels, and cortical bone health without advancing bone age in children with GHD. These findings support the efficacy of long-acting GH therapy and its potential to optimize growth and skeletal outcomes in clinical practice.
Keywords: Growth Hormone Deficiency; Somatrogon; bone health; IGF-1; Children.

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Introduction:
Growth hormone deficiency (GHD) in children is characterized by short stature, reduced growth velocity, and failure to achieve normal adult height, negatively impacting quality of life and future outcomes (1,2).
Growth hormone replacement has enabled children with GHD to achieve height within the normal accepted adult range (1). However, conventional daily growth hormone therapy has a short half-life. (3) , and requires frequent injections (4), which contribute to caregiver burden (5) and poor adherence (6) . This leads to frequent missed doses (7) and eventually a poor clinical outcome (8).
Efforts have focused on developing long-acting GH formulations to improve convenience, reduce injection burden, and enhance clinical outcomes (9,10). Somatrogon (Ngenla®) is a long-acting recombinant human GH with three C-terminal peptide extensions, designed to extend half-life and enable weekly dosing. Clinical trials have demonstrated that Somatrogon achieves growth outcomes comparable to daily GH therapy (11–13).
GHD also impairs bone health, leading to reduced bone mineral density (BMD), as shown by dual-energy X-ray absorptiometry (DXA) (14) and computed tomography studies (15). GH replacement promotes osteoblast activity, new bone formation, and improved BMD (16,17).
The Bone Health Index (BHI), derived from hand radiographs using the automated BoneXpert® software, serves as a robust indicator of cortical bone strength in children (18) . Prior studies have demonstrated that daily growth hormone (GH) treatment is associated with significant improvements in BHI (19).
The Metacarpal Index (MCI), another parameter generated through radiogrammetry, estimates cortical thickness and has been validated as a predictor of fracture risk (20,21). Both BHI and MCI are calculated from metacarpal dimensions: BHI is defined as the cortical area divided by width^1.33 multiplied by length^0.33, while MCI is calculated as cortical area divided by width². These indices correlate strongly with DXA findings and provide a reliable, non-invasive means of assessing skeletal integrity in growing children (22,23).
This study aims to evaluate the real-world effects of weekly Somatrogon therapy on growth outcomes—height velocity, adult predicted height (APH), and IGF-1 stability—as well as bone health indices (BHI and MCI) in children with GHD.

Patients and Methods

This retrospective cohort study assessed pre- and post-treatment outcomes over 12 months in children diagnosed with GHD who received Somatrogon therapy at Al Jalila Children's Hospital in Dubai, UAE. The Institutional Review Boards of Al Jalila Children's Hospital and Mohammed Bin Rashid University approved the study. Participants were consecutively recruited from January 2023 to June 2024.
The study population included children who received Somatrogon therapy at a dose of 0.66 mg/kg/week (11), all patients remained on the same dose throughout the 12 months of the study. Their age was between 3.0 and 10.0 years for girls and 3.0 and 11.0 years for boys. All were prepubertal, defined as Tanner stage 1 on physical examination (24,25). All patients remained prepubertal (Tanner stage 1) throughout the entire 12-month study period.
The diagnosis of GHD was established through an integrated approach combining clinical, radiological, and biochemical evidence. An auxological assessment was performed, with growth failure defined as a height standard deviation score (SDS) below –2.0 for age and sex or a growth velocity 1 SD below the mean for chronological age over the 12 months prior to treatment (26,27).
Participants were included if they exhibited a peak GH <10 ng/mL in one stimulation test, supported by either: (1) height SDS <–2.0 + growth velocity <–1 SDS, or (2) low IGF-1/IGFBP-3 (insulin-like growth factor binding protein-3), or (3) abnormal MRI. This approach aligns with guidelines for severe phenotypes (28,29).
Exclusion criteria included previous exposure to growth-promoting agents, abnormal thyroid function, or significant medical conditions. Data was collected anonymously using medical record numbers to ensure confidentiality.

Auxologic measurements

Height was measured using a wall-mounted stadiometer (Seca216®). Height SDS was calculated using CDC 2000 references (30) .

Laboratory investigations

GH stimulation tests were performed using the Siemens Immulite® assay (sensitivity: 0.01 ng/mL). Serum IGF-1 was measured at baseline and 96 hours after the most recent Somatrogon dose to reflect weekly pharmacokinetics (31). using the Roche Elecsys® ECLIA (range: 0.25–1600 ng/mL; CV <5%) (32). IGF-1 values were expressed as SDS based on age- and sex-specific norms; eligible patients had baseline IGF-1 at least 1 SD below the mean (11,32).

Radiographic assessments

An automated radiographic analysis of the left hand and wrist radiographs was performed using BoneXpert® software before the initiation of Somatrogon therapy and after 12 months of treatment. This automated analysis determined bone age, bone health index, and metacarpal index.
Bone age assessment using the BoneXpert® method is based on the Greulich-Pyle bone age standard, and it analyses the image completely automatically using artificial intelligence (AI). It can provide accurate data on a patient's bone age, in addition to analysis of bone health index and metacarpal index (33).
BoneXpert® offers an automated assessment of bone age and cortical bone geometry using radiographic measurements. Specifically, it evaluates the width (W), cortical thickness (T), and length (L) of the second, third, and fourth metacarpal bones. From these parameters, it calculates key indices:
Cortical Area (A): Computed using the formula $A = \pi \times W \times T \times (1 - T/W)$, representing the area of the cortical bone cross-section.
Metacarpal Index (MCI): Defined as $MCI = A / W^2$, this index expresses cortical bone thickness relative to the overall bone width.
Bone Health Index (BHI): Calculated as $BHI = A / (W^{1.33} \times L^{0.33})$, this index integrates bone dimensions to reflect cortical bone robustness.
These indices provide a detailed profile of cortical bone structure and are interpreted against standardized reference values for bone age. Although BoneXpert's normative dataset is based on Caucasian populations (34), it remains the most widely validated tool for pediatric skeletal assessment. To mitigate ethnic bias, we report results as standard deviation scores (SDS) relative to each patient's bone age rather than relying on raw values.
APH was calculated using BoneXpert® software, which applies the Bayley-Pinneau method to deliver accurate and standardized predictions of final adult height, minimizing variability associated with manual calculations (35).

Sample size:

The sample size was calculated based on Horikawa et al study (2022) (11), in which Somatrogon increased height SDS in children with GHD by 0.94 after 12 months of treatment. Accordingly, at significance level of 0.05 and power of 80%, a total of 30 subjects were required to clarify our hypothesis.

Ethical Approval:

This study was approved by the Dubai Scientific Research Ethics Committee (DSREC), Dubai Health Authority, and the Institutional Review Board of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU IRB-2024-562; Ref: DSREC-SR-11/2024_04). Given the retrospective design, the requirement for informed consent was waived.

Statistical analysis:

Statistical analysis was done using SPSS version 29 (IBM, Armonk NY). Continuous variables were assessed for normality using Shapiro-Wilk tests. Paired t-tests compared pre/post outcomes for parametric data. Continuous variables were summarized as means with standard deviations and/or medians with minimum and maximum values, as appropriate. Categorical data were presented as frequencies and percentages within the study cohort. To assess the primary endpoint, annual height velocity, comparisons between baseline and the end of therapy were conducted using a t-test, with statistical significance set at a p-value of less than 0.05.

Results

The study included 39 patients with a mean age of 9.63 years, of whom 64% were male (Table 1). Height SDS improved significantly from a mean of –2.16 ± 0.80 at baseline to –1.65 ± 0.71 after 12 months of treatment ($p < 0.001$) (Figure 1). When analysed separately by sex, both boys and girls demonstrated a similar and statistically significant increase in absolute height over 12 months. In boys (n = 27), mean height increased from 123.73 ± 8.74 cm to 132.06 ± 8.55 cm (mean change +8.33 cm, $p < 0.001$). In girls (n = 12), mean height increased from 122.23 ± 14.88 cm to 130.97 ± 13.82 cm (mean change +8.73 cm, $p < 0.001$).
Adult predicted height improved from 161.86 ± 7.2 cm to 164.88 ± 6.4 cm ($p < 0.001$) (Figure 2). Bone age SDS showed no improvement ($p = 0.269$) (Table 2).
The IGF-1 SDS improved significantly from a mean of -1.38 (SD 1.02) at baseline to 0.88 (SD 1.57) after treatment, with a p-value of < 0.001 (Figure 3). BHI SDS improved from –1.29 ± 1.50 to –0.83 ± 1.41 ($\Delta = +0.46$; $p < 0.001$). MCI SDS showed no significant change (–1.33 ± 1.18 to –1.16 ± 1.07; $\Delta = +0.17$; $p = 0.106$) (Table 2).

Discussion

In our real-world setting, treatment with Somatrogon significantly increased height APH, and IGF-1 SDS levels after one year of treatment. In addition, Somatrogon treatment for one year was associated with improved BHI without significant change in bone age or MCI.
The significant height SDS gain observed aligns with findings from Deal et al. (2022), where Somatrogon demonstrated non-inferiority to daily somatropin in terms of height velocity and height SDS with the least squares mean (LS mean) treatment difference: 0.06 (95% CI, −0.01, 0.13) (13) . Horikawa et al. (2021) similarly reported robust growth outcomes with Somatrogon in naïve prepubertal children where the LS mean change in height SDS from baseline to 12 months was greater in the Somatrogon group (0.94) compared to the daily GH group (0.52) (11). Our height SDS improvement (Δ0.51) closely mirrors daily GH outcomes in Deal et al. (Δ0.52)(13).

Our study's observed increase in IGF-1 SDS is consistent with previous findings. Deal et al. (2022) reported similar findings, noting that IGF-1 profiles with Somatrogon were higher compared to daily GH regimens, where the mean IGF-1 SDS was −1.95 at baseline and increased to 0.65 at 12 months post-baseline (13). Similarly, Horikawa et al (2022) reported significant increase in IGF-1 SDS in Japanese children with GHD after treatment with Somatrogon (11) .

Improvements in Bone Health Index (BHI) observed in our study with Somatrogon treatment are consistent with findings from Wydra et al. (2023), which emphasized the anabolic effects of GH on bone mineralization (36) . Another study showed that in short-statured children, daily GH treatment significantly improved BHI, where BHI SDS increased from −0.97 to −0.17 after 1 year of GH ($p<0.001$). The BHI increased initially with GH treatment and plateaued over time, suggesting sustained improvement in bone health (19)

The absence of significant bone age (BA) advancement in our study differs from results commonly observed with previous studies, where Deal et al. (2022) in a phase 3 study comparing Somatrogon to daily rhGH found significant BA progression after one year of treatment, which was comparable to BA progression rates seen on daily rhGH (13). Similarly, Horikawa et al. (2022) reported significant BA advancement on Somatrogon treatment (11). This discrepancy may be explained by the different methods used to assess bone age. In our study, BA was determined using an automated AI-based analysis, whereas the previous studies relied on manual evaluation.

However, the lack of significant improvement in the Metacarpal Index (MCI) is notable. This aligns with findings from Bettendorf et al. (1998) (37) and Radetti et al. (2000) (38), which reported no substantial alteration in metacarpal proportions during GH therapy. However, the findings diverge from Martin et al. (2019), who also used BoneXpert and observed significant improvement in MCI within the first year of daily GH therapy (23). The discrepancy with Martin et al.'s results could stem from differences in GH regimens. Daily GH therapy may exert a more consistent anabolic effect on bone geometry compared to the intermittent stimulation provided by weekly Somatrogon.

While BoneXpert software represents a validated and widely-used automated tool for bone health assessment in pediatric populations, it is important to acknowledge that its reference standards are derived from a Dutch Caucasian population (34). To address this potential limitation in our ethnically diverse cohort, we employed standard deviation scores (SDS) relative to bone age rather than absolute values, a recommended approach that helps normalize for population differences (39). Although ethnic variations in bone mineral density and skeletal architecture have been documented in pediatric populations, BoneXpert has demonstrated acceptable performance and has undergone validation across diverse populations (40). The Bone Health Index provided by BoneXpert has been shown to reflect cortical bone mineral density effectively in pediatric and adolescent patients (41), and the use of SDS values in our analysis provides a standardized approach that accounts for individual variation, allowing for meaningful clinical interpretation of bone health parameters (42). While population-specific reference data would be ideal for Middle Eastern children, BoneXpert remains the most extensively validated automated tool available for pediatric bone health assessment, and our findings using SDS-based analysis provide valuable real-world evidence of skeletal outcomes following Somatrogon therapy(43). In addition, the paired design of our analysis, where each participant served as their own control, further mitigates the influence of any systematic bias in the reference data.

The observed improvement in the Bone Health Index (BHI), despite the absence of significant changes in the Metacarpal Index (MCI) or bone age, suggests a nuanced shift in cortical bone geometry. Given that MCI is calculated as the ratio of cortical area (A) to the square of bone width (W^2), its stability implies that any increase in cortical area occurred proportionally to changes in bone width. In contrast, BHI incorporates both width and bone length in the denominator with lower exponents ($W^{1.33}$ and $L^{0.33}$), making it more sensitive to subtle increases in cortical area. The improvement in BHI, therefore, likely reflects a disproportionate increase in cortical thickness relative to width, resulting in a net gain in cortical area that was not substantial enough to affect MCI. Moreover, the lack of advancement in bone age suggests that these structural changes occurred independently of accelerated skeletal maturation.

Limitations

This study has several limitations. Its retrospective cross-sectional design, absence of a daily GH control group, and relatively small sample size may restrict the generalizability of the results. DXA-the gold standard for assessing bone mineral density, was not employed (44). Bone age assessments were conducted using BoneXpert, which, while the most practical and validated tool available in the absence of local reference data, may be less accurate in a cohort with diverse ethnic backgrounds (34). Additionally, systematic safety data were not collected due to the retrospective nature of the study.

Conclusion

In a real-world setting, our study adds to the growing body of evidence supporting Somatrogon as an effective option for GHD treatment. Weekly Somatrogon therapy led to significant improvements in growth parameters and IGF-1 levels, as well as enhancements in the bone health index. However, the nuanced effects on cortical bone geometry underscore the need for further research. Future studies should include the assessment of bone health using dual-energy X-ray absorptiometry (DXA) to provide a more comprehensive evaluation of skeletal outcomes.

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Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest: No potential conflict of interest relevant to this article was reported.

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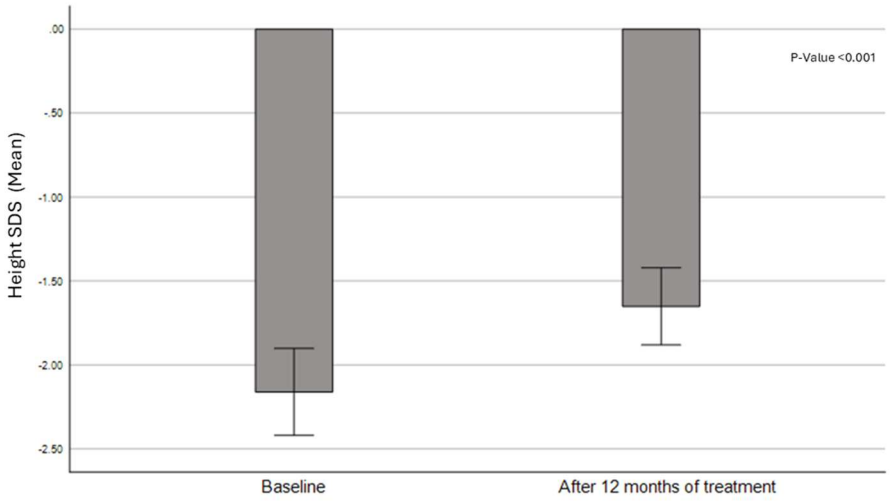

Figure 1. Change in height SDS before and after 12 months of weekly Somatrogon therapy in children with growth hormone deficiency
SDS, standard deviation score. P < 0.001

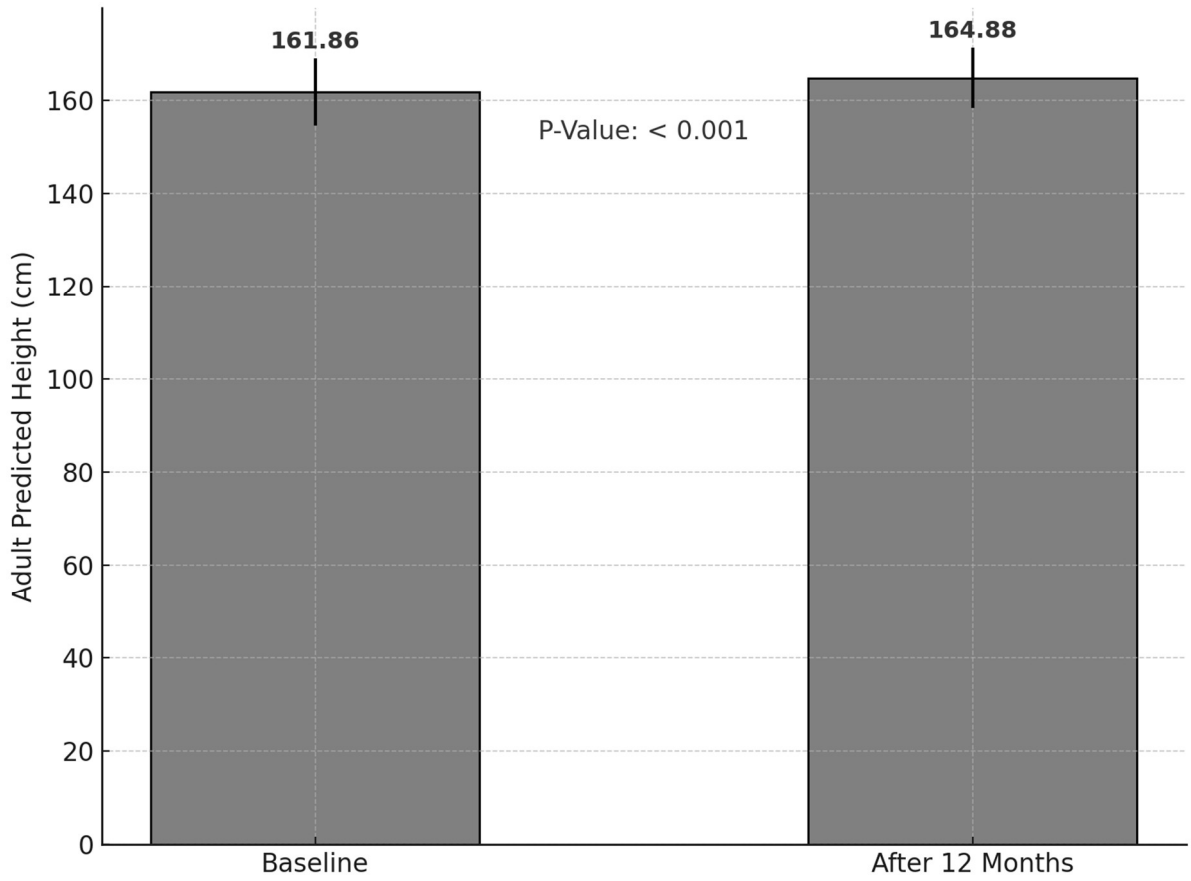

Figure 2. Change in predicted adult height (APH) before and after 12 months of weekly Somatrogon therapy in children with growth hormone deficiency. P < 0.001

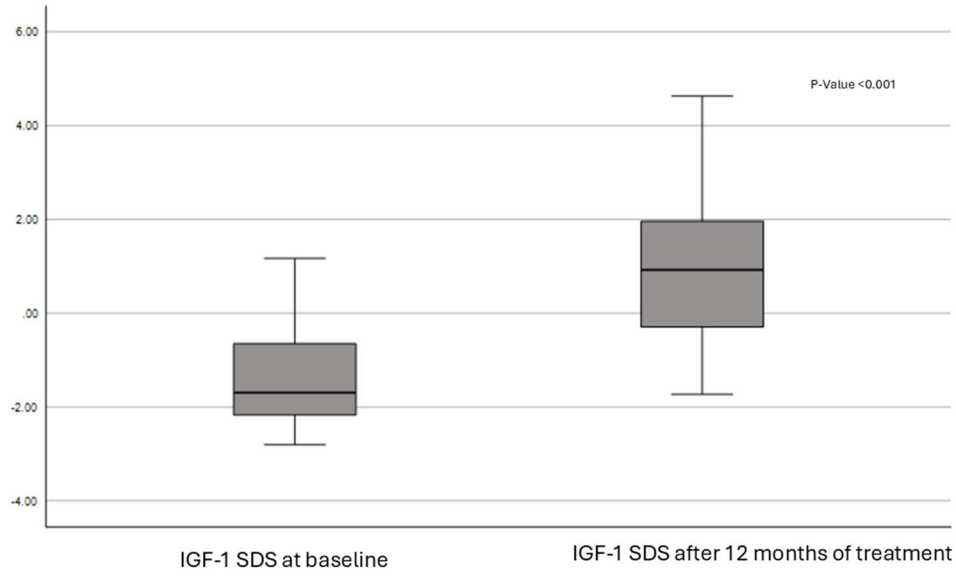

Figure 3. Change in IGF-1 SDS before and after Somatrogon treatment. IGF-1, insulin-like growth factor 1; SDS, standard deviation score. P < 0.001

Table 1: Characteristics of patients of the study at baseline	
Number	39
Age, years Mean (SD)	9.63 (2.19)
Males N(%)	27 (64%)
Bone age, years Mean (SD)	7.5 (2.37)
Bone age SDS Mean (SD)	-1.53 (1.30)
Mean height SDS Mean (SD)	–2.16 ± 0.80)
Mean APH, cm Mean (SD)	161.73 (7.60)
APH: adult predicted height, N: number, SDS: standard deviation score.	

Table 2: Effect of Somatrogon on bone geometry after 12 months of treatment			
Variable	**Baseline (Mean ± SD)**	**After 12 Months of Somatrogon Treatment (Mean ± SD)**	**P-Value**
Bone age SDS	-1.53 (1.30)	-1.44 (1.28)	0.269
BHI SDS	-1.29 (1.50)	-0.83 (1.41)	<0.001
MCI SDS	-1.33 (1.18)	-1.16 (1.07)	0.106
BHI: bone health index, MCI: metacarpal index, SDS: standard deviation score. P-values calculated using paired t-tests comparing baseline and 12-month post-treatment values			