Growth Hormone Therapy in the Pediatric Population is Associated with Increased Risk of Upper and Lower Extremity Physeal Fractures: A PearlDiver Dataset National Analysis

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INTRODUCTION:

Growth hormone (GH) therapy is increasingly used in children, treating numerous pathologies including GH deficiency, idiopathic short stature (ISS), Turner syndrome, small for gestational age, and Prader-Willi syndrome. While the clinical benefits may include increased height, growth velocity, bone mineral density, and improved body composition and metabolic parameters, GH has been associated with orthopaedic complications, such as progression of scoliosis and increased risk of slipped capital femoral epiphysis (SCFE). A recent retrospective study identified a 15x increased odds of GH exposure among children and adolescents with proximal tibial physeal avulsion fractures compared to matched midshaft tibial fracture controls. Although this prior study was not designed to identify causation, the authors postulated that GH may cause physeal weakening, leading to fracture. Another retrospective study focusing on upper extremity tension injuries found no increased odds of physeal fracture compared to non-physeal fractures, leading the authors to postulate that GH may not confer an increased risk of upper extremity physeal fractures. With prior studies potentially being underpowered, we wished to address the potential association between GH and physeal fractures on a national basis. The aim of this study was to identify national incidences and hazard ratios of physeal fractures in the upper and lower extremities within the pediatric population with and without GH exposure using a nationwide administrative claims database.

METHODS:

The Mariner170 dataset, which is housed within the HIPAA-compliant PearlDiver national insurance claims platform (PearlDiver Technologies; Fort Wayne, Indiana, USA), was queried from 2010 to April 2022 for patients aged 4 to 18 years old with a minimum follow-up of 2 years. Patients were included if they had a minimum one-month duration of GH therapy, identified using National Drug Codes. The primary outcome of interest was the incidence of upper and lower extremity physeal fractures following exposure to GH therapy. Physeal fractures, identified using ICD-9 and ICD-10 codes, included fractures at the proximal humerus, proximal radius, distal radius, distal ulna, distal femur, proximal tibia, and distal tibia. Distal humerus and proximal femoral physeal fractures were excluded due to potential misclassification/miscoding as supracondylar humerus fractures and SCFE, respectively. The patients in the GH therapy cohort were propensity-score-matched with control patients who did not have GH exposure at a 1:1 ratio using a nearest-neighbor matching algorithm at a caliper of 0.1, controlling for age, sex, obesity, and Charlson Comorbidity Index (CCI). Standard descriptive statistics summarized patient demographics, and duration of GH therapy. Univariate analysis of physeal fracture incidence was performed via Chi-Squared or Fisher's exact test, as appropriate. Multivariable cox regression analysis, controlling for baseline variables, was utilized to determine the hazard ratio (HR) and 95% Confidence Intervals (95% CI) of physeal fractures associated with GH therapy. A p-value less than or equal to 0.05 was set as statistical significance. Statistical analysis was performed using R (Foundation for Computational Statistics; Vienna, Austria) integrated within the PearlDiver interface.

RESULTS:

A cohort of 34,196 patients receiving GH therapy was successfully matched to a control cohort of 34,196 patients who did not receive GH therapy. The cohorts were a mean age of 11 ± 3.7 years old, 65% male, 33% obese, and had a mean CCI of 0.2 ± 0.6. The GH cohort had significantly higher proportions of GH deficiency (46.6 versus 0.2%, $p < 0.001$) and ISS (37.8 versus 0.5%, $p < 0.001$). The GH cohort received GH therapy for a mean of 2.8 ± 2.4 years. The incidence of physeal fractures and univariate and multivariable cox regression results are reported (Table 1). In multivariable cox regression analysis, GH therapy was associated with an increased HR of physeal fracture at the distal femur (HR: 5.5, 95% CI: 1.6 - 19.3, $p = 0.008$), proximal tibia (HR: 2.5, 95% CI: 1.1 - 5.4, $p = 0.022$), distal tibia (HR: 2.9, 95% CI: 1.9 - 4.4, $p < 0.001$), proximal radius (HR: 6.7, 95% CI: 1.5 - 30.7, $p = 0.014$), distal radius (HR: 2.2, 95% CI: 1.7 - 3.0, $p < 0.001$), and proximal humerus (HR: 3.2, 95% CI: 1.0 - 10.0, $p = 0.050$) (Table 1).

DISCUSSION AND CONCLUSION:

There is a strong association between GH therapy and an increased risk of upper and lower extremity physeal fractures. When counselling patients regarding risks and benefits of GH therapy, clinicians should bear in mind that it is not possible to determine causation with the current study design, and the incidence of physeal fractures associated with GH therapy is low. Further prospective research is required to confirm the findings of this retrospective database query.

Table 1. Univariable and Multivariable Cox Regression Analyses of Physeal Fracture Rates between Control and Growth Hormone Therapy Cohorts

Rates of Physeal Fractures between Control and GH Therapy Groups			Univariate Chi-square vs Fisher's exact test		Multivariable cox regression analysis controlling for patient baseline variables
Physeal Fractures, n (%)	GH therapy (n=34,196)	Control (n=34,196)	P-value	HR [95% CI]	P-value
Distal Femur	14 (0.04%)	4 (0.01%)	**0.034**	5.5 [1.6, 19.3]	**0.008**
Proximal Tibia	18 (0.05%)	10 (0.03%)	0.186	2.5 [1.1-5.4]	**0.022**
Distal Tibia	76 (0.2%)	34 (0.1%)	**<0.001**	2.9 (1.9-4.4]	**<0.001**
Distal Ulna	19 (0.06%)	13 (0.04%)	0.377	2.1 [0.99-4.3]	0.051
Proximal Radius	8 (0.02%)	2 (0.01%)	**0.043**	6.7 (1.5, 30.7]	**0.014**
Distal Radius	133 (0.4%)	80 (0.2%)	**<0.001**	2.2 [1.7-3.0]	**<0.001**
Proximal Humerus	11 (0.03%)	5 (0.02%)	0.211	3.2 [1.0-10.0]	**0.050**

GH = Growth hormone. HR = Hazard Ratio. **Bolded** indicates statistical significance.