

visit. DCE is a quantitative method widely used in health-care to elicit preferences from participants in the absence of revealed preference data. Choice-based conjoint analysis was used to evaluate the relative importance of attributes as choice predictors and determine utilities for each attribute. Of the 47 respondents who participated in this study, 41 were caregivers who responded on behalf of the patients, and the remaining 6 were patients who completed the DCE themselves. All participants were screened by a clinician to ensure they met all eligibility criteria. **Results:** The injection schedule was found to be the most important attribute for both patients and caregivers (Relative importance: 43.6%); a once-weekly injection schedule was preferred over a daily injection schedule. For maintenance of injection devices, patients had a stronger preference for reusable pens which can be used by replacing cartridges, while caregivers preferred disposable pen devices. The storage and preparation attribute was deemed more important to patients than it was to caregivers, with patients preferring storage in room temperature even if it needed an additional mixing (reconstitution) step. Both patients and caregivers showed a clear preference for devices that offered a dose setting memory. **Conclusion:** The results of this study showed that patients prefer a once-weekly injection schedule over a daily injection schedule. A less frequent injection schedule should enhance adherence and compliance to r-hGH treatment over the long term and will also improve QoL in children with GHD. The benefits of a less frequent injection schedule can be further explored using real-world studies.

## Pediatric Endocrinology

### GROWTH AND GROWTH HORMONE

#### *Growth Hormone Stimulation Testing Patterns Contribute to Gender Disparities in Growth Hormone Treatment*

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**Introduction:** Growth hormone (GH) registries demonstrate that males outnumber females 2:1 for all indications combined and 3:1 for the idiopathic short stature indication. The aim of this study was to determine if gender disparities in GH treatment are due to differences in rates of stimulation testing and/or GH prescribing. **Methods:** Retrospective chart review was performed including children aged 2-16 years seen for short stature or poor growth in 2012-2019 at a large tertiary referral center. Children previously diagnosed with GHD were excluded. Continuous variables, reported as medians [IQR], were compared by Wilcoxon rank sum test and categorical variables by Chi-squared test. A two-tailed p-value <0.05 defined statistical significance. **Results:** Of 10,125 children seen for evaluation of short stature or poor growth (35% [3542] females [F], 65% [6583] males [M]), 1,245 underwent GH stimulation

testing (30% [379] F, 70% [866] M). A larger proportion of males than females were tested (M 13.2%, F 10.7%; p <0.001). Amongst the entire study population, females had lower height Z-scores than males (F -1.98 [-2.46, -1.44], M -1.80 [-2.24, -1.31]; p <0.001). This difference persisted in those who proceeded to GH stimulation testing (F -2.52 [-3.00, -2.04], M -2.18 [-2.6, -1.81]; p <0.001) and GH treatment (F -2.62 [-3.11, -2.07], M -2.19 [-2.60, -1.81]; p <0.001). Mean difference between height Z-score and mid-parental height (MPH) Z-score for the entire population did not differ by sex (F -1.52 [-2.17, -0.87], M -1.52 [-2.04, -0.97]; p = 0.76), but the difference was greater in females among those who underwent GH stimulation testing (F -1.95 [-2.57, -1.40], M -1.79 [-2.32, -1.32]; p = 0.009) and started GH treatment (F -1.93 [-2.58, -1.48], M -1.80 [-2.30, -1.32]; p = 0.016). Peak stimulated GH levels were similar for males and females (F 9.6 [6.0, 13.6] ng/mL, M 9.4 [6.1, 13.2] ng/mL, p = 0.62). The proportion of children prescribed GH after stimulation testing did not differ by gender (F 55% [208], M 56% [488]; p = 0.63). This finding did not change upon sub-analysis by peak stimulated GH concentration groups (peak GH concentrations <7 ng/mL, 7-10 ng/mL, and >10 ng/mL). **Conclusion:** The male predominance among children seen for subspecialist evaluation of short stature was compounded by a greater proportion of those males subsequently undergoing GH stimulation testing despite less severe short stature. Although females who underwent GH stimulation testing had greater height deficit from their genetic potential than tested males, peak stimulated GH concentrations and GH prescription rates were similar by sex. Thus, gender disparities in GH treatment occur at the subspecialist referral and stimulation testing, but not GH prescription, steps. Further, GH stimulation test results failed to account for the more severe shortness among tested females, yet another limitation identified with such testing.

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### GROWTH AND GROWTH HORMONE

#### *Growth Outcome and Metabolic Profile of PWS Patients Treated With GH and Differences Between AGA and SGA Group*

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**Objective:** Prader-Willi syndrome (PWS) is a complex genetic disease associated with growth impairment, severe obesity and metabolic dysfunctions. High proportion of PWS patients are born small for gestational age (SGA), which also increase the risk of growth impairment and metabolic dysfunction. The aim of this study was to describe growth outcome and metabolic profiles in GH treated PWS patients. We also investigated the differences in clinical outcomes between AGA and SGA group **Methods:** Data of 55 children and adults with genetically verified PWS aged more than 2 years old (32 male and 23 female, age 2-18.8 years) from single center were studied. Only patients who were treated with GH were included. The clinical characteristics and laboratory findings were reviewed

retrospectively. **Results:** Among 55 subjects, 39 had 15q11-13 deletion and 16 had uniparental disomy (UPD). Twenty (36.3%) were born SGA. All patients received GH treatment, and 11 (20%) discontinued GH treatment. Mean age at GH treatment initiation was 2.5 (range 0.3-12.4) years, and mean duration of treatment was 6.3 (range 1.0-11.3) years. Current height-SDS (-0.36 vs -0.16) and BMI-SDS (1.44 vs 1.33) did not differ between AGA and SGA group. Two patients in SGA group, but none in AGA group had diabetes mellitus. Mean glucose level was also higher in SGA group (100.1 vs 114.4 mg/dL). **Conclusions:** Our report gives an overview of growth profile and metabolic dysfunctions recorded in GH treated PWS patients. Growth profile did not differ between AGA and SGA group. Glucose level was higher in SGA group, so more careful monitoring and prevention for DM will be required in SGA group.

## Pediatric Endocrinology

### GROWTH AND GROWTH HORMONE

#### *Impact of BMI on Growth Hormone Stimulation Tests in Children and Adolescents: A Systematic Review and Meta-Analysis*

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**Background:** Peak stimulated growth hormone (GH) levels are known to decrease with increasing BMI, possibly leading to overdiagnosis of GH deficiency (GHD) in children with overweight and obesity. However, current guidelines do not provide guidance how to interpret peak GH values of these children, nor has this been assessed systematically. The aim of this systematic review and meta-analysis was to study the effect of BMI on stimulated peak GH values in children, and to quantify to which extent peak GH values in children with obesity are decreased. **Methods:** We searched the Medline, Embase, Cochrane, Web of Science, and Google Scholar databases (13 July 2020) for studies reporting impact of BMI on peak GH in children. Where possible, individual participant data was extracted and/or obtained from the authors. Primary outcome was the association between peak GH values and BMI standard deviation score (SDS). Pooled correlation coefficients were calculated under a random effects model, and exploratory moderator analyses and meta-regression were performed. Study heterogeneity was assessed using the  $I^2$  statistic. For studies with available individual participant data, linear mixed-models regression analysis was performed with BMI SDS as predictor and  $\ln(\text{peak GH})$  as outcome, accounting for used GH stimulation agent (fixed effect) and study (random effect). This systematic review was performed in accordance to the PRISMA guidelines. **Results:** In total, 56 studies were included, providing data on  $n=5100$  children (1346 with individual participant data). Across all studies, a pooled  $r$  of -0.37 (95% CI -0.44 to -0.31,  $n=2785$ ) was found. Study heterogeneity was large ( $I^2=58\%$ ). Pubertal status, sex, presence of syndromic obesity, and mean age and BMI SDS of the population did not significantly moderate the pooled  $r$  (all  $p>0.05$ ). Individual participant data analysis

revealed a beta of -0.11 (95% CI -0.08 to -0.15,  $p<0.001$ ), *i.e.*, per 1 point increase in BMI SDS, peak GH decreases by 11% (95% CI 7 to 14%). In the 8 studies performed in children referred for short stature, obesity was present in 27/893 (3.02%) children without GHD and in 36/615 (5.85%) children with GHD ( $p=0.0069$ ). This corresponds to a RR of 1.43 (95% CI 1.14 to 1.78,  $p=0.002$ ) for a diagnosis of GHD in children with short stature with obesity compared to children without obesity. **Discussion:** To our knowledge, this is the first systematic review and meta-analysis to investigate the impact of BMI on peak GH values in children, showing a significant negative correlation and risk of overdiagnosis of GHD in children with obesity. All in all, with ever-rising prevalence of pediatric obesity, our study highlights the urgent need for BMI (SDS)-specific cut-off values for GH stimulation tests in children.

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### GROWTH AND GROWTH HORMONE

#### *Impact of IGF-1 Normative Datasets on Indication and Outcome of Growth Hormone Stimulation Testing*

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In the Netherlands, the diagnosis of growth hormone deficiency in children follows the Dutch national guidelines for Triage and Diagnosis of Growth Disorders in Children. Initial biochemical evaluation includes an IGF-1 measurement as screening parameter for growth hormone deficiency. Based on the clinical probability of growth hormone deficiency and the IGF-1 Z-score, a growth hormone stimulation test is performed if serum IGF-1 Z-score is  $< 0$  SD in case of a high probability and if serum IGF-1 Z-score is  $< -1$  SD in case of low probability. An IGF-1 Z-score  $> 0$  SD virtually excludes a growth hormone deficiency disorder. The interpretation of growth hormone stimulation testing is dependent on both the peak growth hormone concentration, but also on the baseline IGF-1 Z-score, particularly in cases of partial deficiency. Although, nation wide, Dutch laboratories have harmonized their measurement for IGF-1 (as was previously done for growth hormone), a Dutch harmonized normative data set has not been widely adopted. Moreover a clinical evaluation of the implementation of this dataset based on dynamic testing has not been published. To assess the impact of choice of a particular normative dataset on the diagnosis of growth hormone deficiency we recalculated Z-scores of IGF-1 measurements between 2016 and 2019, using our home reference values based on de normative dataset by Elmlinger (E)<sup>1</sup>, and using the normative datasets defined by Bidlingmaier (B)<sup>2</sup> and by the Dutch IGF-1 harmonization program (NL). Based on these three Z-scores, the outcomes of growth hormone stimulation tests performed in this period ( $n=86$ ) were reassessed according to the interpretation described in the Dutch guideline. Using all three normative datasets the same 4 patients were identified as likely to have a growth hormone deficiency, whereas 10(E), 10(B), or 8(NL) patients were identified as possible partial growth hormone deficiency. In 70(E), 66(B) or 72(NL) patients the growth