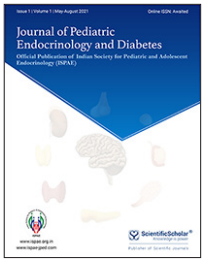
ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://ispae-jped.com/

Journal of Pediatric Endocrinology and Diabetes



Ped Endo Journal Scan

Ped Endo Journal Scan

Kriti Joshi[1]

[1]Department of Endocrinology and Diabetes, Queensland Children's Hospital, South Brisbane, Queensland, Australia.

***Corresponding author:**
Kriti Joshi,
Department of Endocrinology and Diabetes, Queensland Children's Hospital, South Brisbane, Queensland, Australia.

kriti.joshi@health.qld.gov.au

Received: 12 November 2024
Accepted: 12 November 2024
Published: 03 December 2024

DOI
10.25259/JPED_51_2024

Quick Response Code:

Liraglutide for children 6–<12 years of age with obesity – A randomized trial

Fox CK, Barrientos-Pérez M, Bomberg EM, Dcruz J, Gies I, Harder-Lauridsen NM, *et al.* SCALE Kids Trial Group. *N Engl J Med*. 2024 Sep 10. doi: 10.1056/NEJMoa2407379. Epub ahead of print. PMID: 39258838.

Objective: The objective of this study was to evaluate the efficacy and safety of liraglutide, as compared with placebo, as an adjunct treatment to lifestyle interventions for the treatment of obesity in children 6 to younger than 12 years of age.

Study Methodology and Results: This was a phase 3a, multinational, double-blind, randomized, and placebo-controlled trial 6–<12-year-old children with obesity. Participants were randomized in a 2:1 manner to receive once-daily subcutaneous liraglutide at a dose of 3.0 mg or matched placebo, plus dietary interventions for 56 weeks with a 26-week follow-up period. The primary endpoint was the percentage change in body mass index (BMI). The confirmatory secondary endpoints were the percentage change in body weight and a reduction in BMI of at least 5%. The study randomized 82 participants, 56 in the liraglutide and 26 in the placebo group. At week 56, the estimated mean percentage change from baseline in BMI (the primary endpoint) was −5.8% with liraglutide and 1.6% with placebo, representing an estimated difference of −7.4% points (95% confidence interval [CI], −11.6 to −3.2; $P < 0.001$). The estimated mean percentage change in body weight (confirmatory secondary endpoint) was 1.6% with liraglutide and 10.0% with placebo, representing an estimated difference of −8.4% points (95% CI, −13.4 to −3.3; $P = 0.001$). A reduction in BMI of at least 5% occurred in 24 of 52 participants (46%) in the liraglutide group and in 2 of 23 participants (9%) in the placebo group. The odds of a BMI reduction of at least 5% (confirmatory secondary endpoint) were significantly greater with liraglutide than with placebo (adjusted odds ratio, 6.3 [95% CI, 1.4–28.8]; $P = 0.02$). During the follow-up period, BMI and body weight increased in both groups. The incidence of adverse effects was similar in both groups (89%), the most commonly reported one being gastrointestinal disorders, which were reported in 45 of 56 participants (80%) in the liraglutide group and in 14 of 26 participants (54%) in the placebo group; 6 participants (11%) discontinued treatment with liraglutide due to adverse events, including three participants who discontinued due to gastrointestinal disorders.

Critical Review: This trial demonstrated that in children 6–12 years of age with obesity, liraglutide led to a meaningful reduction in BMI as compared to placebo. This study provides much-needed data on interventions for the management of obesity for this cohort of pre-pubertal children. A high percentage of participants had gastrointestinal adverse events. No adverse effects were noted on growth or puberty; however, long-term effects could not be determined with the time duration of this study. Longer-term studies will be needed to assess long-term efficacy and safety; however, the results from this study provide much-needed evidence for the effects of a

glucagon-like peptide-1 (GLP 1) receptor agonist, offering a therapeutic option in prepubertal children with severe obesity as an adjunct to healthy lifestyle interventions.

Analysis of genetic and clinical characteristics of androgen insensitivity syndrome: a cohort study including 12 families

Yuan Z, Fan L, Wang Y, Li L, Ren X, Sui S, *et al*. *Eur J Endocrinol*. 2024 Jul 2;191(1):87-96.

Objective: The objective of this study was to describe the genotype-phenotype relationships and to explore the fertility potential of patients with androgen insensitivity syndrome (AIS).

Study Methodology and Results: This was a cohort study that analyzed the genetic and clinical characteristics of patients with AIS from a single center in China. Patients were evaluated with clinical examination, hormonal assessments, and molecular genetic analysis. AIS was classified as either complete AIS (CAIS) or partial AIS (PAIS) according to the external genitalia phenotype at the first visit. Data from 117 patients were included, 53 with CAIS and 64 with PAIS. The median age of the patients was 1.83 years, with an interquartile range of 0.92–4.17. Sixteen individuals were in mini-puberty, 90 individuals were in prepuberty, and 11 individuals were in puberty. In mini-puberty, patients with CAIS had higher estradiol (E2) compared with those with PAIS ($P = 0.03$). In prepuberty, there were significant differences in hormone levels between the CAIS and PAIS groups, specifically in basal luteinizing hormone ($P = 0.029$) and follicle-stimulating hormone ($P < 0.001$). However, no difference was noted in the testosterone levels. At the last follow-up, 92% (49/53) of patients with CAIS maintained their female gender, and 94% (60/64) of the patients with PAIS were raised as males. Eighty-eight androgen receptor (AR) gene variants were identified, of which 31 were novel. Parental validation was performed in 105 of the cases. Out of these, 87 patients (83%) inherited the variant from their mothers, while 18 patients (17%) had a spontaneous occurrence of the variant. Phenotypic disparities were found even with an identical variant within the same family. External masculinization scores (EMS) for the missense AR variant group were 5.0 (2.0, 6.0), which was significantly higher than that of the null group of 2.0 (1.5, 2.75; $P = 0.001$). Patients with a missense AR variant had a higher EMS, higher testis location score, and penile length-standard deviation score as compared to those with null variants in the AR.

Critical Review: This study presents an analysis of a highly homogeneous Chinese single-center cohort of patients with AR variants. Based on genotype-phenotype correlation, lower EMS and female gender assignment were found to be related to null variants. The presence of maternally transmissible variants suggests that individuals with AIS may have fertility potential. However, this study primarily focused on children making it difficult to draw conclusions about older individuals in particular fertility considerations. It highlights the need for ongoing long-term follow-up studies to elucidate the evolution of the phenotype of this cohort of individuals.

Clinical efficacy of zoledronic acid on fracture reduction in youth with primary and secondary skeletal fragility

Stoffers AJ, Mancilla EE, Levine MA, Mayer M, Monk HM, Rosano J, *et al*. *J Clin Endocrinol Metab*. 2024 Sep 26:dgae661. doi: 10.1210/clinem/dgae661. Epub ahead of print. PMID: 39324646.

Objective: The objective of this study was to investigate the effect of zoledronic acid (ZA) on the fracture rate in a clinical cohort of children and young adults with skeletal fragility and to investigate the impact of other clinical characteristics on ZA efficacy.

Study Methodology and Results: This was a retrospective review of all patients who had received at least one dose of ZA for the treatment of skeletal fragility at the Children's Hospital of Philadelphia. The primary outcome was the change in the annualized overall fracture rate (fractures of all skeletal sites per year) after ZA treatment. Secondary outcomes included long bone fracture (fractures of long bones per year) and long bone plus spine fracture (fractures of long bone plus spine per year) rates. Areal bone mineral density (aBMD) was analyzed in a subset of individuals with dual-energy X-ray absorptiometry scans. A total of 102 individuals met the eligibility criteria. This included 39 subjects (38%) with primary and 63 subjects (62%) with secondary skeletal fragility. Patients with primary skeletal fragility received a greater number of infusions (5 [interquartile range (IQR): 2–8] vs. 3 [IQR: 2–5], $P < 0.001$) and greater cumulative ZA dose (0.18 [IQR: 0.05–0.29] vs. 0.09 [IQR: 0.04–0.14] mg/kg, $P < 0.001$) compared to patients with secondary skeletal fragility. The median fracture rate decreased from 0.6 (0.3–1.1) to 0 (0–0.4) fractures per year in the full cohort of 102 children and young adults treated with ZA, $P < 0.001$. The reductions in fracture rate remained statistically significant when fractures were limited to long bone (0.4 [0–0.7]–0 [0–0.3], $P < 0.001$) or long bone plus spine (0.5 [0.2–0.8]–0 [0–0.3], 2 $P < 0.001$) skeletal sites. Secondary analyses stratified by osteoporosis type confirmed that fracture rate declined following ZA treatment in individuals with both primary and secondary forms of skeletal fragility. The overall fracture rate in the 1st year after starting ZA infusions was significantly lower than the pre-infusion fracture rate, 0.7 ± 0.7 versus 0.3 ± 0.4, $P < 0.001$, and remained lower each year for the 5 years following ZA infusion. The aBMD outcomes in a subset of 41 patients showed that the LS aBMD Z-score increased by a mean of 1.3 ± 1.2 over 2.8 ± 1.4 years from −2.0 ± 1.4 to −0.7 ± 1.7, $P < 0.001$.

Critical Review: This study demonstrated that ZA therapy was effective in reducing fracture rates in this large cohort of pediatric patients with skeletal fragility. This provides crucial real-world data on the efficacy of ZA in this cohort of patients and provides support for the use of this medication in children with skeletal fragility, given the limited therapeutic options available for this age group. However, a prospective larger study would be needed to comprehensively demonstrate efficacy.

Comprehensive study on central precocious puberty: Molecular and clinical analyses in 90 patients

Narusawa H, Ogawa T, Yagasaki H, Nagasaki K, Urakawa T, Saito T, *et al*. *J Clin Endocrinol Metab*. 2024 Sep 26:dgae666. doi: 10.1210/clinem/dgae666. Epub ahead of print. PMID: 39324648.

Objective: The objective of this study was to clarify the contribution of (epi)genetic abnormalities to central precocious puberty (CPP) and clinical and hormonal features in each etiology.

Study Methodology and Results: This was a cross-sectional study that recruited patients with CPP who had no history of central nervous system injuries, no lesions on brain MRI, and no congenital anomalies suggestive of genetic disorders or severe intellectual developmental delay. Clinical and laboratory data was collected from patients. Molecular genetics analysis was conducted for *MKRN3, DLK1, MECP2, KISS1*, and *KISS1R*, and methylation analysis for screening of imprinting disorders such as Temple syndrome (TS14) and Silver–Russell syndrome (SRS) associated with CPP. The study enrolled 90 patients of which 81 had sporadic CPP, and nine patients had familial CPP. Sixty-seven patients were girls (74%), and the remaining were boys (26%). The study detected eight patients with TS14, three female patients with *MKRN3* genetic defects, and no patients with pathogenic variants in *KISS1, KISS1R, DLK1,* and *MECP2* or with SRS. Of the eight patients with TS14, three patients had a prior clinical suspicion of TS14 due to the patient's clinical features; the remaining five patients were not clinically suspected to have TS14. All three patients with MKRN3 genetic defects had a paternal inheritance. Ten patients with CPP were born small for gestational age (SGA), and six of them (60%) had TS14.

Critical Review: This study provides a comprehensive analysis of genetic and epigenetic causes of CPP in a Japanese population and found that 12.2% of their cohort had known etiologies causing CPP. In particular, they found a significant proportion of patients with previously undiagnosed TS14. However, the authors acknowledge that there might have been referral bias leading to the enrichment of the cohort with patients who had an underlying neurodevelopmental diagnosis. In addition, this is data from a very specific ethnic cohort and, therefore, might not be generalizable to other ethnic groups.

Early dysglycemia is detectable using continuous glucose monitoring in very young children at risk of type 1 diabetes.

Haynes A, Tully A, Smith GJ, Penno MA, Craig ME, Wentworth JM, *et al*. Environmental determinants of islet autoimmunity study group. *Diabetes Care*. 2024 Oct 1;47(10):1750-1756.

Objective: The objective of this study was to investigate early dysglycemia using continuous glucose monitoring (CGM) in very young children with and without persistent islet autoimmunity being longitudinally observed in the Australia-wide environmental determinants of islet autoimmunity (ENDIA) study from birth to age 10 years.

Study Methodology and Results: The ENDIA pregnancy-childhood cohort study commenced in 2013 and is observing 1473 children who have a first-degree relative with T1D. It collects health and lifestyle data alongside biological sampling across pregnancy and early life to determine environmental factors that trigger islet autoimmunity in early life. For this stub-study, all ENDIA children with persistent multiple islet autoantibodies (PM Ab^+) were invited to take part. All children had an A1C <5.7%. Participants underwent CGM monitoring by wearing blinded CGM devices every 3–6 months. Children underwent blinded CGM wear for a minimum of 14 consecutive days using the Dexcom G6 CGM device. The primary outcome was the standard deviation of sensor glucose levels (SDSGL), a summary measure of glycemic variability (amplitude, frequency, and duration of fluctuations in glucose measurements). Secondary outcomes included the coefficient of variation (CEV) of sensor glucose levels (CEV = SDSGL/mean) and the percentage of CGM time with sensor glucose levels within specified target ranges. The study enrolled 31 PM Ab^+ children and 24 age- and sex-matched Ab^- children. The mean age at the time of persistent islet autoantibody detection was 2.0 (1.5) years. The median age at first CGM was 4.3 (1.5, 5.9) years, with 15 (48%) of the 31 PM Ab^+ children age ≤3 years and 11 (35%) between 4 and 6 years. PM Ab^+ children had higher median (Q1, Q3) SDSGL (1.1 [0.9, 1.3] vs. 0.9 [0.8, 1.0] mmol/L; $P < 0.001$) and CEV (17.3% [16.0, 20.9] vs. 14.7% [12.9, 16.6]; $P < 0.001$). PM Ab^+ children spent a median (Q1, Q3) 90.7% (83.0, 95.0) of time with sensor glucose values between 3.9 and 7.8 mmol/L (70–140 mg/dL), compared with 95.5% (93.6, 97.1) in the Ab^- group. The median percentage of time spent >7.8 mmol/L (>140 mg/dL) during the first CGM period in PM Ab^+ children was 8.0% (4.4, 13.0) compared with 3.3% (1.4, 5.3) in Ab^- children ($P = 0.005$).

Critical Review: This is an important study adding on to the literature on CGM profiles of young children with presymptomatic T1D. It provides further support for the use of CGM as a noninvasive tool for glycemic monitoring

of at-risk children, particularly those <5 years old who have a higher risk of developing a progressive phenotype of T1D.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

How to cite this article: Joshi K. Ped-endo-journal scan. J Pediatr Endocrinol Diabetes. 2024;4:107-10. doi: 10.25259/JPED_51_2024