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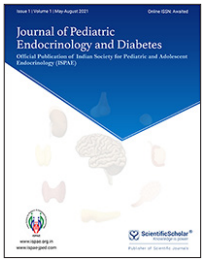

Ped Endo Journal Scan

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Trial of hybrid closed-loop control in young children with type 1 diabetes

Wadwa RP, Reed ZW, Buckingham BA, DeBoer MD, Ekhlaspour L, Forlenza GP, *et al.* PEDAP Trial Study Group. *N Engl J Med.* 2023 Mar 16;388(11):991-1001. doi: 10.1056/NEJMoa2210834.

Objective: The objective of this study was to assess the safety and efficacy of a hybrid closed-loop system in children 2–6 years of age with the use of virtual training and trial visits.

Study Methodology and Results: This was a multicenter, unblinded, parallel-group, randomized, controlled trial that enrolled children between the ages of 2–6 years, with at least a 6 months history of type 1 diabetes and insulin treatment, body weight of at least 9.1 kg, and a minimum insulin dose of 5 units. Patients who were currently using a hybrid closed-loop system were excluded from the study. Families had the option of completing all trial visits virtually or in person. Eligible patients were randomly assigned in a 2:1 ratio to the closed-loop control system or standard care with the use of a continuous glucose monitor (personal pump or multiple daily injections of insulin) for 13 weeks. The primary outcome was the percentage of time spent in the target range of 70–180 mg/dL. Key secondary outcomes were the percentage of time above 250 mg/dL, the mean glucose level, the percentage of time below 70 mg/dL, the percentage of time below 54 mg/dL, and the hemoglobin A1C (HbA1C).

A total of 102 participants underwent randomization of which 101 completed the trial. Training on the hybrid closed-loop system was virtual for 81% of patients. Of these, 91% of visits were virtual in the closed-loop group and 96% in the standard care group. The mean (± standard deviation) % of time that the glucose level was in the target range increased from 56.7 ± 18.0% at baseline to 69.3 ± 11.1% during the 13-week follow-up period in the closed-loop group and from 54.9 ± 14.7% to 55.9 ± 12.6% in the standard care group, with a mean adjusted difference (the value in the closed-loop group minus the value in the standard care group) of 12.4% points (95% confidence interval [CI], 9.5–15.3; $P < 0.001$). Time above 250 mg/dL was found to be higher in the closed-loop group (mean difference between the closed-loop and standard-care group, −5.4%; 95% CI, −7.3–−3.6; $P < 0.001$). The HbA1C levels were also lower in the closed-loop group; however, there was no difference in time spent below 70 mg/dL. The HbA1C target of < 7% was met in 48% of subjects in the closed-loop group and 30% in the standard care group. Adverse events were reported in 60% of the closed-loop participants versus 32% of the standard-care group ($P = 0.001$). Severe hypoglycemia was reported in two cases in the closed-loop group and one in the standard care group. One case of diabetic ketoacidosis related to infusion-set failure occurred in the closed-loop group.

Critical Review: This is a well-done study, with significant implications for achieving glycemic targets in young children and also importantly demonstrates that virtual training in the use of

the closed-loop system is safe and feasible. However, this was a short-term study and it is unknown if these gains would be sustainable in the long term.

Testicular dysfunction in 47,XXY boys: when it all begins. A semi-longitudinal study

Pozza C, Sesti F, Tenuta M, Spaziani M, Tarantino C, Carlomagno F, *et al. J Clin Endocrinol Metab.* 2023 Apr 12:dgad205. doi: 10.1210/clinem/dgad205. Epub ahead of print.

Objective: The objective of this study was to describe the natural history of testicular dysfunction in patients with Klinefelter syndrome (KS) from infancy through adulthood and to explore clinical, endocrine, and testicular ultrasound patterns, which could accurately reflect the progression of testicular degeneration in these patients.

Study Methodology and Results: This was a prospective semi-longitudinal study that included 155 testosterone naïve subjects with a 47,XXY karyotype aged 7 months to 55 years. Subjects were followed until the initiation of testosterone therapy. Participants were evaluated at 6 monthly intervals following pubertal onset and had serial monitoring of clinical and hormonal status along with testicular ultrasound evaluations.

Subjects were predominantly referred following a prenatal diagnosis (67.4%), followed by delayed puberty (22.1%), infertility evaluation (6.6%), and general andrological screening (3.9%). Cryptorchidism was noted in 13.2% of subjects and was bilateral in half. The serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels showed a rising trend from Tanner stage 2 with a pathological increase noted at Tanner stage 5. Inhibin B (INHB) levels and the INHB/FSH ratio demonstrated a sharp decline in stage 4 reflecting Sertoli and germ cell impairment. Testosterone (T) levels showed a progressive increase until Tanner stage 5, plateaued during the transition age group with a significant decline seen in adulthood. The T/LH ratio similarly demonstrated an increase until Tanner stage 3 followed by a decline indicating ongoing worsening of Leydig cell function. Increasing testicular volume was noted until Tanner stage 4 followed by regression. Increasing age was also accompanied by a worsening in testicular echotexture. The presence of both hypoechoic lesions and microlithiasis independently and significantly predicts a lower circulating testosterone level.

Critical Review: This is a useful study that attempts to define the trajectory of testicular dysfunction in young men with KS. The dramatic decline in Sertoli and germ cell function seen in late puberty along with evidence of worsening testicular echotexture seen in adulthood have important implications for fertility preservation and the appropriate age for testosterone initiation in this cohort of individuals.

GH and Childhood-onset Craniopharyngioma: When to Initiate GH Replacement Therapy?

Nguyen Quoc A, Beccaria K, González Briceño L, Pinto G, Samara-Boustani D, Stoupa A, *et al. J Clin Endocrinol Metab.* 2023 Jul 14;108(8):1929-1936. doi: 10.1210/clinem/dgad079.

Objective: The objective of this study was to compare the recurrence or progression of craniopharyngioma (CP) in patients with growth hormone (GH) deficiency treated with GH therapy within or after 12 months following CP primary treatment completion.

Study Methodology and Results: This was a single-center retrospective analysis and included all patients with childhood-onset (<18 years of age at diagnosis) CP treated with recombinant human growth hormone (rhGH). Patients were divided into two groups: Patients treated with rhGH within 12 months after CP treatment completion (<12 months group) and patients treated with rhGH at least 12 months after CP treatment completion (>12 months group). All patients underwent the same imaging surveillance. The primary outcome measure was the development of a new event and was summarized as the progression of residual tumor or tumor recurrence after complete resection. The study included 71 patients of which 27 were in the <12 months group and 44 were in the >12 months group. Of these 23 patients (32%) developed a tumor new event during the follow-up period with a similar event rate in both groups (33% and 32%, $P = 0.99$). In the >12 months group, the 2- and 5-year event-free survivals were 81.5% and 69.4%, respectively, compared with 72.2% and 69.8% in the <12 months group or with 72.4% and 72.4% in the 6–12 months group. There was no significant difference in the event-free survival rate between the two groups ($P = 0.98$) or between the 6 and 12 months group and the >12 months group ($P = 0.91$). The risk of the event was statistically reduced when patients had multiple surgeries (adjusted hazard ratio [HR], 0.44: 95% CI, 0.25–0.768; $P = 0.004$) or had previous radiotherapy (adjusted HR, 0.03; 95% CI, 0.01–0.13; $P < 0.001$).

Critical Review: This is an important study that demonstrates that there is no association between GH replacement therapy time delay after childhood-onset CP treatment and an increased risk of recurrence or tumor progression. It fills a knowledge void in this area and allays the concerns of clinicians regarding rhGH initiation in this cohort. The strengths of this study are the single-center design leading to a homogenous cohort and a long duration of follow-up.

Residual insulin secretion in individuals with type 1 diabetes in Finland: Longitudinal and cross-sectional analyses

Harsunen M, Haukka J, Harjutsalo V, Mars N, Syreeni A, Härkönen T, *et al. Lancet Diabetes*

Endocrinol. 2023 Jul;11(7):465-473. doi: 10.1016/S2213-8587(23)00123-7.

Objective: The aim of this study was to study the residual (≥0.02 nmol/L) C-peptide concentrations during the initial years after the diagnosis of type 1 diabetes and long-term, as well as its determinants and clinical associations with complications.

Study Methodology and Results: This study included longitudinal follow-up data on newly diagnosed individuals with type 1 diabetes who had a measurement of metabolic parameters within 3 months from diagnosis, and at least once later. Cross-sectional long-duration data were collected from two cohorts of people with type 1 diabetes diagnosed below 40 years, the FinnDiane and the DIREVA study. Target genome-wide association studies were also performed to estimate the polygenic risk of type 1 and type 2 diabetes and to study the association of random C-peptide with these risk scores and other clinical features.

The longitudinal analysis included 110 individuals diagnosed at 16 years or older and 847 children. The median random serum C-peptide concentration in this group was significantly dependent on the age at diagnosis with the lowest levels seen in those diagnosed at a young age. Age at diagnosis was also strongly correlated with the decline in C-peptide secretion. The cross-sectional analysis included 3984 individuals from FinnDiane and 645 individuals from the DIREVA study. This analysis too showed a strong correlation between the age at diagnosis and random C-peptide. After a median disease duration of 21.6 years (IQR 12.5–31.2), 776 (19.4%) of 3984 people had a residual C-peptide concentration of 0.02 nmol/L or higher. Participants with C-peptide of 0.2 nmol/L or higher were older at diagnosis than those with a level <0.2 nmol/L (median age 24.3 years [17.9–31.5] vs. 13.3 years [8.6–20.9]; $P < 0.0001$). Interestingly, a higher random serum C-peptide class was associated with a lower type 1 diabetes polygenic risk score ($P < 0.0001$) and those with a serum C-peptide >0.02 nmol/L also had a higher mean type 2 diabetes polygenic risk score than those with levels <0.02 nmol/L ($P = 0.027$). C-peptide levels were inversely associated with HbA1C, insulin dose, hypertension, and cholesterol and were also independently associated with microvascular complications, nephropathy, and ophthalmopathy.

Critical Review: This is a very interesting and topical study that sheds light on the residual beta cell function in individuals with type 1 diabetes and its strong association with age at diagnosis. The study highlights that even low residual C-peptide concentrations were associated with a beneficial complication profile. These results, therefore, make a strong case in point to support interventions to preserve β-cell function even later in the disease process.

Zoledronate increases bone mineral density in non-ambulant children with cerebral palsy: A randomized and controlled trial

Granild-Jensen JB, Møller-Madsen B, Rackauskaite G, Farholt S, Søndergaard C, Sørensen TH, *et al. J Clin Endocrinol Metab.* 2023 May 26:dgad299. doi: 10.1210/clinem/dgad299. Online ahead of print.

Objective: The objective of this study was to evaluate the effect of 2 doses of zoledronate (ZOL) treatment on the lumbar spine (LS) and lateral distal femur (LDF) bone mineral density (BMD) Z-scores in children with cerebral palsy (CP) Gross Motor Function Classification System IV-V.

Study Methodology and Results: This was a multicenter, double-blind, randomized, controlled trial that included children with non-ambulant CP between the ages of 5 and 17 who had an LS or LDF BMD Z-score <−1 standard deviation (SD). Subjects were randomized in a 1:1 manner to receive zoledronate or placebo for two doses, 6 months apart. BMD was assessed at baseline and month 12 using the Hologic DXA machine.

Twenty-four children with CP and a median age of 10.8 years (range, 6.0–17.1) were randomized; all were Caucasian. The BMD Z-score of the LS significantly increased by 0.8 SD (95% CI: 0.4; 1.2) in the ZOL group compared to the change of 0.0 SD (−0.3; 0.3) in the placebo group ($P = 0.01$) at the end of 12 months. The LDF BMD Z-score also showed a significant increase in regions 2 and 3 as compared to the placebo group. No fractures were noted during the study period. Bone turnover markers showed a significant reduction in the ZOL group. Severe acute phase symptoms were seen in 50% of the ZOL group but were reported exclusively after the first dose. No differences were found in growth or quality of life parameters.

Critical Review: This study adds to the limited literature on strategies for improving bone health in children with CP. While the study expectedly showed improvement in BMD with ZOL treatment, it is not apparent yet whether this would translate to a reduction in fracture risk. Longer duration, well-powered studies would be necessary to answer this crucial question.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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

The author(s) confirms 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.

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