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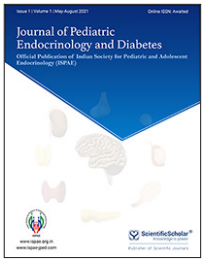

Ped-Endo-Journal Scan

Ped Endo Journal Scan

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Effect of verapamil on pancreatic beta cell function in newly diagnosed pediatric type 1 diabetes: A randomized clinical trial

Forlenza GP, McVean J, Beck RW, Bauza C, Bailey R, Buckingham B; CLVer Study Group. *JAMA*. 2023;329(12):990–999. doi:10.1001/jama.2023.2064

Objective: The objective of this study was to assess the safety and efficacy of verapamil in preserving beta cell function in children and adolescents with newly diagnosed type 1 diabetes.

Study Methodology and Results: This was a multicenter, double-blind, randomized, controlled trial that enrolled children and adolescents aged 7–17 years within 31 days of diagnosis of type 1 diabetes mellitus (T1D), and a body weight of at least 30 kg. Eligible patients were randomly assigned in a 1:1:1:1 ratio to the verapamil group or the placebo group and also to receive either intensive diabetes management with an automated insulin delivery system (from either Tandem Diabetes Care or Medtronic) or standard care diabetes management.

The primary outcome was area under the curve (AUC) values for mixed-meal tolerance test stimulated C-peptide level at 52 weeks from diagnosis of T1D. Key secondary outcomes were (1) peak C-peptide level and the proportion with a peak C-peptide level of 0.2 pmol/mL or greater; (2) hemoglobin A1c (HbA1c) levels; and (3) various glucose metrics measured with continuous glucose monitoring (CGM) during the 28 days before each visit.

A total of 88 participants underwent randomization, of which 83 completed the trial, in the verapamil group, 44 of the 47 participants (94%) and 39 of the 41 participants (95%) in the placebo group. In addition to the five participants who dropped out of the trial, the study drug was discontinued due to presumed adverse drug events by three participants in the verapamil group and one in the placebo group, and for other reasons by two participants in the verapamil group.

In the verapamil group, the mean C-peptide AUC was 0.66 pmol/mL at baseline and 0.65 pmol/mL at 52 weeks from diagnosis compared with 0.60 pmol/mL at baseline and 0.44 pmol/mL at 52 weeks in the placebo group. The adjusted between-group treatment difference at 52 weeks was 0.14 pmol/mL (95% confidence interval [CI], 0.01–0.27 pmol/mL; $P = 0.04$). The 52-week peak C-peptide level was ≥0.2 pmol/mL in 41 of 43 participants (95%) in the verapamil group compared with 27 of 38 participants (71%) in the placebo group.

Assignment to intensive diabetes management versus standard diabetes management did not influence the primary outcome results.

HbA1c decreased in the verapamil group from 10.3% at baseline to 6.6% at 52 weeks and in the placebo group from 10.2% at baseline to 6.9% at 52 weeks (mean between-group difference, −0.3% [95% CI, −1.0–0.4%].

There was no significant difference in the various CGM metrics between the verapamil and placebo groups. In the verapamil group, the total insulin dose was 0.74 units/kg/d at baseline and 0.65 units/kg/d at 52 weeks compared with 0.64 units/kg/d and 0.74 units/kg/d, respectively, in the placebo group (mean between-group difference at 52 weeks, −0.12 units/kg/d [95% CI −0.30–0.05 units/kg/d]). Eight participants (17%) in the verapamil group and eight participants (20%) in the placebo group experienced a non-serious adverse event considered to be related to treatment.

In the verapamil group, three participants experienced electrocardiogram abnormalities (prolonged PR interval in one participant, second-degree heart block and prolonged PR interval in one participant, and first-degree heart block in one participant), and one participant experienced hypotension.

Critical Review: This study demonstrates marginal preservation of beta cell function with the use of verapamil in children and adolescents with newly diagnosed T1D. This study does have some important strengths, such as the use of a medication that is distinct from immunotherapeutic agents and has a demonstrable safety profile in this age group. However, this was a short-term study, and it is unknown if these gains would be sustainable in the long term. Furthermore, whether the partial preservation in C-peptide translates to obvious clinically meaningful benefits is unknown.

Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: A population-based study

Karges B, Tittel SR, Bey A, Freiberg C, Klinkert C, Kordonouri O, *et al. Lancet Diabetes Endocrinol*. 2023 May;11(5):314-323. doi: 10.1016/S2213-8587(23)00061-X. Epub 2023 Mar 30.

Objective: The aim of this study was to determine whether the rates of severe hypoglycemia and diabetic ketoacidosis (DKA) are lower with continuous glucose monitoring (CGM), compared with blood glucose (BG) monitoring, in people younger than 25 years with type 1 diabetes (T1D), and to investigate which CGM metrics are informative for these uncommon but clinically relevant acute diabetes complications.

Study Methodology and Results: This population-based cohort study included patients identified from the diabetes prospective follow-up (DPV) database, covering an estimated proportion of more than 90% of all pediatric patients with diabetes in Austria, Germany, and Luxembourg. Inclusion criteria were age between 18 months and 25 years, diabetes duration of >1 year, treatment between January 1, 2014, and June 30, 2021, and observation time of 120 days or less in the most recent treatment year.

The primary outcome was the difference in event rates of severe hypoglycemia and DKA between patients using CGM and patients using BG monitoring during the most recent year of treatment.

Of the 32,117 eligible individuals with T1D, 10,883 patients used CGM for a mean of 289 days (95% confidence interval [CI] 284–294) per year. 21,234 individuals used BG monitoring, with a median frequency of four (interquartile range 3–6) measurements per day. Severe hypoglycemia rates were significantly lower in individuals using CGM than in those using BG monitoring (6.74 [95% CI 5.90–7.69]/100 patient-years vs. 8.84 [8.09–9.66]/100 patient-years; difference/100 patient-years of −2.10 [95% CI −3·42−−0·79]; incidence rate ratio 0.76 [95% CI 0.64–0.91], P = 0·0017). Rates of DKA were also significantly lower in individuals using CGM (3.72 [95% CI 3.32–4.18]/100 patient-years vs. 7·29 [6.83–7.78]/100 patient-years in those using BG monitoring; difference/100 patient-years of −3.57 [95% CI −4.26−−2.88]; incidence rate ratio 0.51 [95% CI 0.44–0.59], P < 0·0001). In patients with CGM, event rates for severe hypoglycemia did not differ by hemoglobin A1c (HbA1c) level (ptrend = 0.15, all $P \geq 0.31$ between categories). In patients with BG monitoring, severe hypoglycemia rates were lower with HbA1c level of ≥90% than with <70% (P = 0.0071; ptrend = 0.0011). Event rates for DKA rose with increasing HbA1c levels in patients with CGM and in patients with BG monitoring (both ptrend < 0.0001).

A higher rate of severe hypoglycemia and hypoglycemic coma was noted with an increased percentage of time below the target glucose range (both ptrend < 0.0001). In addition, higher event rates for severe hypoglycemia were observed with higher glycemic variability comparing patients with a coefficient of variation ≥36% versus <36% (incidence rate ratio 1·52 [95% CI 1.06–2.17]; P = 0.022). Rates for DKA increased with higher mean sensor glucose (ptrend < 0.0001). Event rates for DKA increased with a lower percentage of time in the target glucose range (ptrend < 0.0001) and also in those with a higher percentage of time above the target glucose range (ptrend < 0.0001).

Critical Review: This is a useful study demonstrating the effectiveness of CGM use in preventing acute complications in a real-world cohort of individuals with T1D. The study also identified CGM metrics that can be useful in predicting the risk of DKA and severe hypoglycemia. However, this was not a randomized controlled trial; hence, important differences between the groups in terms of education, socioeconomic disparity, health literacy, etc., were not accounted for.

Genotype-specific cortisol reserve in a cohort of subjects with non-classic congenital adrenal hyperplasia

Koren I, Weintrob N, Kebesch R, Majdoub H, Stein N, Naor S, *et al. J Clin Endocrinol Metab*. 2023 Sep 16:dgad546.

doi: 10.1210/clinem/dgad546. Epub ahead of print. PMID: 37715965.

Objective: This study aimed to compare ACTH-stimulated cortisol and 17-hydroxyprogesterone (17OHP) levels and the rate of partial cortisol insufficiency in non-classic congenital adrenal hyperplasia (NCCAH) subjects carrying one mild and one severe (mild/severe) mutation versus subjects with biallelic mild (mild/mild) mutations.

Study Methodology and Results: This study was a retrospective analysis of 122 patients with NCCAH. Subjects presented with postnatal virilization, and the diagnosis of 6 NCCAH was made by the standard ACTH stimulation test with a peak 17OHP level ≥40 nmol/L was considered diagnostic of NCCAH. A stimulated cortisol level below 500 nmol/L was defined as a partial cortisol 14 deficiency. All patients had genetic analysis for disease-causing *CYP21A2* gene mutations and were divided according to genotype into three groups: Patients with biallelic mild mutations (mild/mild); patients exhibiting a compound heterozygosity for one mild and one severe mutation (mild/severe), and patient 11 with only one mutation.

The study included data from 122 subjects of which 77 had the mild/mild genotype, 29 had the mild/severe genotype, and 16 patients were heterozygous (these were removed from the final analysis). The mean basal and stimulated 17OHP levels were significantly higher in the mild/severe than in the mild/mild group 6 (44.8 ± 45.0 vs. 28.2 ± 25.0, 198.6 ± 85.4 vs. 118 ± 49.8, P = 0.007 and <0.001, respectively). The mean basal and stimulated cortisol levels were significantly lower in the mild/severe group than in the mild/mild group (267 ± 102 17 vs. 346 ± 152 nmol/L [P = 0.024], 480 ± 90 vs. 569 ± 125, [P < 0.001], respectively). Overall, 50% (49/99) of the study cohort failed the ACTH test; namely, 75% 20 (21/28) in the mild/severe group compared to 39% (28/71) in the mild/mild group 21 (P = 0.004).

Critical Review: This study demonstrates that genotype determines the biochemical severity of patients presenting with features of NCCAH and that individuals with a compound heterozygous genotype who carry a mild/severe may have an intermediate severity between classic and NCCAH. Therefore, these subjects may need ongoing steroid coverage even in adult life.

Rare variants in the *MECP2* gene in girls with central precocious puberty: A translational cohort study

Canton AP, Tinano FR, Guasti L, Montenegro LR, Ryan F, Shears D, *et al. Lancet Diabetes Endocrinol.* 2023 Aug;11(8):545-554. doi: 10.1016/S2213-8587(23)00131-6.

Objective: This study aimed to explore whether *MECP2* variants were associated with an idiopathic central precocious puberty (CPP) phenotype.

Study Methodology and Results: This was a translational cohort study that enrolled patients with idiopathic CPP from five countries. Children with a known cause of CPP, such as central nervous system lesions or known monogenic or syndromic causes, were excluded from the study. Whole-exome sequencing was done in 62 patients who presented with CPP and familial form or association with congenital malformations or neurodevelopmental abnormalities, and targeted gene sequencing was mainly done in patients who presented with CPP in association with other clinical features, such as reproductive, metabolic, or growth phenotype. The *MECP2* gene was screened by Sanger sequencing (candidate gene approach) in a larger cohort of patients with isolated CPP. *MECP2* expression analysis was also assessed in hypothalamic tissues of pubertal mice to study its regulation in relation to pubertal timing.

The study included 404 patients with precocious puberty. 133 (33%) patients were enrolled for a multigene sequencing approach: 62 patients had whole-exome sequencing, and 71 patients had targeted gene sequencing. 271 (67%) patients with isolated CPP were screened for *MECP2* by Sanger sequencing. The study identified four rare heterozygous MECP2 variants in seven girls with CPP. *MECP2* variants were classified as likely pathogenic in three (43%) of the seven girls and as a variant of uncertain significance (VUS) in four (57%) girls by ACMG criteria. Three of the four *MECP2* variants were identified in five girls and were predicted to be pathogenic. In addition, a *MECP2* insertion located at the 3' untranslated region was identified in two unrelated girls by Sanger sequencing analysis. Three of the patients had additional neurobehavioral phenotypes; however, none of the patients manifested features of Rett syndrome. *MECP2* showed abundant staining in hypothalamic nuclei with colocalization of *MECP2* and GnRH in more than 70% of GnRH neuronal cells visualized.

Critical Review: This is an interesting study that expands the genetic spectrum of CPP. However, while this data is novel, it has some limitations as it lacks functional studies, and the mechanisms by which *MECP2* might influence hypothalamic GnRH secretion are not yet known.

Risk factors associated with incident vertebral fractures in steroid-treated males with duchenne muscular dystrophy

Phung K, McAdam L, Ma J, McMillan HJ, Jackowski S, Scharke M, *et al. J Clin Endocrinol Metab*. 2023 Aug 23:dgad435. doi: 10.1210/clinem/dgad435. Epub ahead of print.

Objective: This study aimed to describe the incidence and characteristics of vertebral fractures (VFs) in a cohort of glucocorticoid (GC)-treated, bisphosphonate-naive males with Duchenne muscular dystrophy (DMD) and to identify clinical predictors of incident VFs.

Study Methodology and Results: This longitudinal prospective cohort study enrolled subjects aged 4–25 years

with genetically confirmed DMD (with or without muscle biopsy) who were initiating or receiving daily GC treatment for DMD. Assessment for VFs was performed by lateral thoracolumbar spine radiographs at baseline and 12 months and was scored as per the Genant classification followed by calculation of the spinal deformity index (SDI; the sum of the Genant grades from T4 to L4). Clinical and radiological data, including bone mineral density (BMD), were assessed at baseline and 12 months.

A total of 60 patients were enrolled and completed the baseline visit. Twelve patients (20%) had prevalent VFs at the baseline visit, necessitating osteoporosis therapy, and were subsequently withdrawn from the study. An additional 10 children were withdrawn from the study for incomplete data at the 12-month follow-up, and thus, 38 children completed the study and were included in the analysis. There were no incident non-VFs observed during the 12-month study period. Nine of 38 participants (24%) sustained 17 incident VFs, an incidence rate of 44.7/100 person-years. Fourteen of 17 (82%) incident VFs occurred in previously normal vertebral bodies, and 3/17 (18%) were worsening pre-existing VFs. Fifty-six percent of patients (5/9) with incident VFs at 12 months had a history of any fracture (VFs and/or non-VFs) at baseline, compared with 21% of patients (6/29) without incident VFs. The mean baseline lumbar spine and total body less head areal BMD Z-scores. Z-scores were significantly lower in patients with incident VFs, with 1.0 ($P = 0.049$) and 1.5 ($P = 0.036$) Z-score differences between the two groups, respectively. Multiple linear regression analyses identified fracture status at baseline (presence of any fracture and number of prevalent VFs and non-VFs) and delayed bone age as significantly associated with an increase in the SDI at 12 months.

Critical Review: This is an important study that demonstrates the high prevalence of baseline and incident VFs in children with DMD treated with GCs. The study also highlights that an initial fracture is linked to an increased risk of new VFs at a subsequent time in DMD and, therefore, suggests the need for efforts to address the prevention of first-ever fractures in this context.

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: This study aimed to study the residual (≥0.02 nmol/L) C-peptide concentrations during the initial years after the diagnosis of type 1 diabetes mellitus (T1D) 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 T1D 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 T1D diagnosed below 40 years, the FinnDiane and the DIREVA study. Target genome-wide association studies were also performed to estimate the polygenic risk of T1D and type 2 diabetes (T2D) 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 is also strongly correlated with the decline in C-peptide secretion. The cross-sectional analysis included 3,984 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 (interquartile range 12.5–31.2), 776 (19.4%) of 3,984 people had a residual C-peptide concentration of 0·02 nmol/L or higher. Participants with C-peptide of 0·2 mmol/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 T1D polygenic risk score ($P < 0.0001$), and those with a serum C-peptide >0.2 nmol/L also had a higher mean T2D 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 T1D 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, 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. Online ahead of print. PMID: 37235798

Objective: The objective of this study was to evaluate the effect of two doses of zoledronate (ZOL) treatment on 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 5–17 years who had an LS or LDF BMD Z-score <−1 standard deviation. Subjects were randomized in a 1:1 manner to receive ZOL 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 standard deviations (SD) (95% confidence interval: 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 consent was not required as the patient's identity was not disclosed or compromised.

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 author 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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