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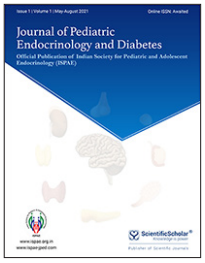

Ped Endo Journal Scan

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Randomized trial of closed-loop control in very young children with type 1 diabetes

Ware J, Allen JM, Boughton CK, Wilinska ME, Hartnell S, Thankamony A, *et al.* for KidsAP Consortium

N Engl J Med. 2022 Jan 20;386(3):209-219.

Objective: The objective of the study was to study the safety and efficacy of a closed loop system versus standard sensor-augmented pump therapy in improving glycemic control for 16 weeks in children with type 1 diabetes (T1D) aged 1–7 years.

Study Methodology and Results: This was an open-label, multicenter, randomized, and crossover design RCT which enrolled T1D children with a prior minimum 3 months experience on an insulin pump and an HbA1c <11%. The closed loop system utilized the Cambridge proprietary model predictive control algorithm used with the Dana Diabecare RS insulin pump (Sooil) and the Dexcom G6 transmitter (Dexcom). The primary end point was the between-treatment differences in the percentage of time that sensor glucose was in the target range (70–180 mg/dL) during each 16-week period. Key secondary end points included percentage of time spent in hyperglycemic state (glucose >180 mg/dL), the HbA1c, the mean glucose level as per device sensor, and percentage of time spent in a hypoglycemic state (glucose <70 mg/dL). Additional secondary end points included the coefficient of variation and SD of glucose level; the percentages of time spent with glucose levels <54 mg/dL (3.0 mmol/L), <63 mg/dL (3.5 mmol/L), and >300 mg/dL (16.7 mmol/L); and insulin metrics. An intention to treat analysis was performed. Seventy-four children with a mean age of 5.6 ± 1.6 years and mean HbA1c of 7.3 ± 0.7% were randomized.

The percentage of time spent in the target glucose range was 8.7% higher (95% CI, 7.4–9.9) during the 16-week closed-loop period than the sensor-augmented pump period ($P < 0.001$). The percentage of time spent in a hyperglycemic state was 8.5% (95% CI, −9.9–−7.1) ($P < 0.001$) lower in the closed-loop period (equating to an extra 125 min per day in range). The glycated hemoglobin level was 0.4% lower (−95% CI, −0.5–−0.3%) ($P < 0.001$), at the end of the closed-loop period. The mean sensor glucose was also significantly lower during the closed-loop period (mean adjusted difference, −12.3 mg/dL; 95% CI, −14.8–−9.8 mg/dL $P < 0.001$). However, the period of time spent in hypoglycemic range was not significantly different between the groups. The basal insulin delivery was higher and bolus amounts lower in the closed loop period, although the total daily dose did not vary between the groups. The closed loop period demonstrated tighter glucose control during night-time than during daytime. Sensor use was similarly high in both the periods and during the closed loop period the system remained in closed loop mode 95% of the time. One severe hypoglycemic event was reported in the closed loop period.

Critical Review: This is a well-done study, which has important implications for achieving glycemic targets in this vulnerable age group and also addressing parental fears of hypoglycemia. However, it should be noted that this group included children who were already on a pump with excellent control at baseline, and thus was most likely to be a highly motivated and educated cohort. Thus, the results here may not be generalizable. In addition, there was limited representation of ethnic minorities. Moreover, finally, the trial utilized the Cambridge proprietary algorithm, which is not commercially available in most countries around the world and hence the results would need to be replicated with other closed loop systems in different ethnic groups.

Zoledronic acid versus placebo in pediatric glucocorticoid-induced osteoporosis: A randomized, double-blind, and phase 3 trial

Ward LM, Choudhury A, Alos N, Cabral DA, Rodd C, Sbrocchi AM, *et al*.

J Clin Endocrinol Metab. 2021 Nov 19;106(12):e5222-e5235.

Objective: The objective of the study was to establish the efficacy and safety of zoledronic acid (ZA) versus placebo in treating pediatric glucocorticoid (GC)-induced osteoporosis (GIO).

Study Methodology and Results: This multicentric double-blind RCT enrolled 6–17-year-old children treated with systemic GC who developed low trauma fractures. Patients were randomized to intravenous (IV) ZA 0.05 mg/kg, or IV placebo at baseline and 6 months and followed up for 1 year. The primary end point was the change in lumbar spine (LS) bone mineral density (BMD) z-score from baseline to 12 months.

The study enrolled 34 children, 18 in the ZA group and 16 in placebo, all with vertebral fractures (VF). The ZA treated group was found to have higher increase in LS BMD z-score (−2.13 ± 0.79 at baseline to −1.48 ± 1.08 at 12 months), versus placebo (−2.38 ± 0.90−−2.33 ± 1.03); least squares mean difference (0.43; 95% CI, 0.03–0.83; $P = 0.04$). No children in the ZA arm developed new low-trauma VFs, compared with two children on placebo. Adverse events were found to be higher in the ZA treated group, however, did not lead to treatment discontinuation. Hypocalcemia was seen in 11% patients in the ZA arm.

Critical Review: This is the first placebo controlled RCT of ZA use in pediatric GIO and shows the efficacy of ZA in a group of children with heterogeneous disorders treated with GCs. Children with VFs due to GC use may have severe disabling pain and loss of ambulation, and this trial provides useful insight into ZA use in this group. Importantly, there was a trend of reduction of fractures in the ZA (study under-powered to report this) and major side effects such as symptomatic hypocalcemia were not reported.

Additional insulin is required in both the early and late postprandial periods for meals high in protein and fat: A randomized trial

Keating B, Smart CEM, Harray AJ, Paramalingam N, Smith G, Jones TW, *et al*.

J Clin Endocrinol Metab. 2021 Aug 18;106(9):e3611-e3618.

Objective: The objective of the study was to assess the amount and pattern of insulin needed to ensure euglycemia up to 5 h following consumption of a high-protein high-fat (HPHF) meal as compared to a low-protein low-fat (LPLF) meal.

Study Methodology and Results: This randomized crossover clinical trial enrolled 10 youth (12–21 years) with T1D >1 year and HbA1C <8% into a HPHF meal arm (60 g protein and 40 g fat) or LPLF meal arm (5 g protein and 5 g fat) with identical carbohydrate content (30 g). A modified insulin clamp was used to calculate insulin requirements in postprandial period. The primary objective was the amount of insulin required to maintain a blood glucose level of 5.0 mmol/L in the 5 h following each test meal.

Significantly higher insulin delivery was needed to maintain euglycemia following HPHF meal than for a LPLF meal (11.0 [CI 9.2, 12.8] units vs. 5.7 [CI 3.8, 7.5] units; $P = 0.001$). The pattern of insulin delivery varied in the postprandial period, an extra 1.2 (CI 0.6, 1.8) U/h for the first 120 min, as compared to 1.1 (CI 0.6, 1.6) U/h in the second 120 min and 0.6 (CI 0.1, 1.1) U/h during the final 60 min. Significant inter-individual differences were seen in insulin requirements and delivery pattern.

Critical Review: This is an interesting study which attempts to analyze the insulin requirements following a high protein high fat meal and suggests that such a meal may require doubling of insulin doses. It also indicates that a dual pattern of insulin delivery may be needed for this macronutrient combination. However, the significant interindividual variability may limit the applicability of these results. In addition, this is a small study with a limited time period of glycemic analysis, therefore, is not powered to defect differences in insulin requirement based on age or sex.

Low adrenomedullary function predicts acute illness in infants with classical congenital adrenal hyperplasia

Weber J, Tanawattanacharoen VK, Seagroves A, Liang MC, Koppin CM, Ross HM, *et al*.

J Clin Endocrinol Metab. 2022 Jan 1;107(1):e264-e271.

Objective: The objective of the study was to assess plasma epinephrine levels in infants with classical congenital hyperplasia (CAH) and to study its clinical correlates.

Study Methodology and Results: This study recruited 36 neonates with biochemically and/or genotypically confirmed 21-hydroxylase deficiency (28 salt-wasting [SW] and eight

simple-virilizing [SV]) and a control group of 27 newborns with congenital primary hypothyroidism. The main objectives of the study were to assess plasma epinephrine levels, the CYP21A2 genotype, and incidence of acute illnesses during the first year of life.

The epinephrine levels in newborns had a negative correlation with the 17-hydroxyprogesterone (17OHP) levels at diagnosis (n = 27, R = –0.51, P = 0.007) and were a significant predictor of acute illnesses in the first year of life (β = –0.018, P = 0.02). The number of illnesses had a significant negative correlation with the newborn epinephrine levels (n = 28, R = –0.45, P = 0.02); however, these were not correlated with the 17OHP levels (R = 0.33 and P = 0.1). Infants with a null genotype had lower epinephrine levels and more illnesses as compared to those with other mutation types. In a similar trend, those with SW-CAH also had lower levels of epinephrine (51.0 pg/mL range, 39.7–84.8 pg/mL]) compared to newborns with SV-CAH (87.0 pg/mL [range, 83.5–137.0 pg/mL]; P = 0.02). When compared with the control group, newborns with CAH had significantly lower levels of plasma epinephrine at birth {(80.0 pg/mL [range, 40.0–93.5 pg/mL]) vs. (101.0 pg/mL [range, 89.0–152.0 pg/mL]; P = 0.007)}. A longitudinal paired analysis also demonstrated that plasma epinephrine levels declined significantly from birth to age one {(84.0 pg/mL [range, 60.0–155.0 pg/mL]) vs. (40.0 pg/mL [range, 40.0–70.0 pg/mL]; P = 0.04)}.

Critical Review: This is an interesting study that highlights epinephrine deficiency in newborns with CAH. Epinephrine deficiency is associated with increased illnesses and hypoglycemia in infants with CAH and therefore could be used for risk prediction in this group. The study, however, assessed only a small group of children and there were significant technical issues in epinephrine measurements in many cases, which might have led to a bias in analysis. Therefore, even though this is a novel finding, the results are preliminary to be applied to clinical practice and need to be confirmed by more studies in larger cohorts.

Blakemore-Durmaz-Vasileiou syndrome: An emerging syndrome with profound obesity and neurodevelopmental delay resembling Prader–Willi syndrome

Bosch E, Hebebrand M, Popp B, Penger T, Behring B, Cox H, *et al*.

J Clin Endocrinol Metab. 2021 Nov 19;106(12):3413-3427.

Objective: The objective of the study was to report four individuals from three unrelated consanguineous families, who presented with severe obesity and neurodevelopmental delay and were found to have homozygous loss of function variants of the carboxypeptidase E (CPE) gene.

Study Methodology and Results: After the exclusion of Prader-Willi Syndrome (PWS), a whole exome sequencing of these individuals was performed. *In silico* analysis of detected variants was done to study their effect on protein function.

The study included two siblings of Syrian origin, and one each of Egyptian and Pakistani origin. They were all found to have morbid obesity with hyperphagia. The affected individuals had profound neurodevelopmental delay, along with other endocrine disorders such as hypogonadotropic hypogonadism, hypocortisolism, and hypothyroidism. Genetic analysis revealed a CPE homozygous truncating variant c.361C > T, p.(Arg121*) in three individuals while the fourth was found to have the c.994del, p.(Ser333Alafs*22) variant. *In silico* modeling indicated that the CPE protein was highly conserved and intolerant to loss of function and also to missense variants. The authors of this paper also collated and summarized data from similar patients reported in two previous reports which suggested a clinically recognizable phenotype which has been designated as Blakemore-Durmaz-Vasileiou syndrome.

Critical Review: This study adds to the genetic list of causes of severe childhood obesity and provides a differential diagnosis for individuals presenting with features similar to PWS. Additional clinical descriptions, molecular and *in vitro* studies will be needed to define the clinical and pathological features in further detail.

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.

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