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Ped Endo Journal Scan

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Once-weekly semaglutide in adolescents with obesity

Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, *et al.* for the STEP TEENS Investigators. *N Engl J Med*. 2022 Dec 15;387(24):2245-2257.

Objective: The objective of this study was to study the efficacy and safety of once-weekly subcutaneous semaglutide, a glucagon-like peptide-1 (GLP-1) analog, in addition to lifestyle modification in obese adolescents.

Study Methodology and Results: This was a double-blind, placebo-controlled, multinational, randomized phase 3a trial that enrolled adolescents between the ages of 10–18 years with obesity (body-mass index [BMI] ≥95th percentile) or those overweight (BMI ≥85th percentile) with one or more comorbidity. Participants were randomized in a 2:1 manner to receive 2.4 mg semaglutide subcutaneously once a week or placebo for 68 weeks in addition to behavioral lifestyle therapy. The primary endpoint was a change in BMI (%) at week 68 and the secondary endpoint was a 5% decrease in body weight. The study randomized 201 youth with 180 completing the trial. At baseline, 4% of the participants had type 2 diabetes and 13% had hypertension. All except one were obese. At week 68, the treatment group demonstrated a BMI reduction of 16.1% with a 0.6% increase in the placebo group (estimated difference, −16.7%; 95% confidence interval [CI], −20.3–−13.2; $P < 0.001$). About 73% of the participants receiving semaglutide had at least a 5% weight loss versus 18% in the placebo group (estimated odds ratio, 14.0; 95% CI, 6.3–31.0; $P < 0.001$). Absolute weight reduction and change in waist circumference was higher in the semaglutide group. Other cardiometabolic risk factors such as glycated hemoglobin, lipid parameters, and alanine aminotransferase levels were lower in the semaglutide group. A higher rate of gastrointestinal side effects was reported in the semaglutide group (62% vs. 42% in placebo) and was overall the most common adverse effect. Pancreatitis was not reported in the semaglutide arm. Cholelithiasis was noted in 4% in the semaglutide and none in the placebo group. Serious adverse events were reported in 11% of the participants in the semaglutide group and 9% in the placebo group.

Critical Review: This study provides important data on therapeutic options in pediatric obesity. It demonstrates that semaglutide plus lifestyle intervention is effective in producing clinically relevant decreases in BMI and body weight and also leads to improvement in cardiometabolic risk factors with an acceptable safety profile. The reported reduction in BMI is much higher than that reported with the use of other GLP-1 agonists in pediatric obesity. The availability of a weekly medication is a welcome addition to the pharmacopeia.

Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes

Bionic Pancreas Research Group; Russell SJ, Beck RW, Damiano ER, El-Khatib FH, Ruedy KJ, Balliro CA, *et al. N Engl J Med*. 2022 Sep 29;387(13):1161-1172.

Objective: The objective of this study was to study the efficacy and safety of the insulin-only configuration of the bionic pancreas in adults and children with type 1 diabetes.

Study Methodology and Results: This was a multicentric parallel group unblinded trial which enrolled adults and children ≥6 years with type 1 diabetes who had been on insulin for at least a year. Participants were randomly assigned in a 2:1 ratio to the bionic pancreas with insulin Aspart or insulin Lispro (bionic-pancreas group), or standard-care insulin delivery plus use of the unblinded Dexcom G6 continuous glucose monitor (standard-care group) for 13 weeks. The primary outcome was the glycated hemoglobin (HbA1C) level at 13 weeks. Key secondary outcome was the percentage of time spent below 54 mg/dL with a non-inferiority margin of 1%. An intention-to-treat analysis was performed. The study enrolled 219 participants in the bionic pancreas arm and 107 in the standard-care group (of which 30% were on a hybrid closed-loop system). Three hundred twenty-three participants completed the trial. The bionic pancreas system administered insulin autonomously for 96% of the time. The mean HbA1C reduced from 7.9% to 7.3% in the bionic-pancreas group at week 13 with no change in the standard-care group (7.7% at baseline and week 13) (mean adjusted difference at 13 weeks, −0.5% points; 95% CI, −0.6–−0.3; $P < 0.001$) and this was similar in the adult and pediatric cohort. The percentage of time spent below 54 mg/dL was non-inferior in the bionic-pancreas versus the standard-care group and the 13-week adjusted between-group difference was 0.0% points (95% CI, −0.1–0.0; $P < 0.001$ for non-inferiority). There was an increase of 2.6 h/day spent within the target range (70–180 mg/dL) in the bionic-pancreas group.

Two hundred and fourteen episodes of hyperglycemia with or without ketosis due to infusion-set failure were reported in the bionic-pancreas group and two episodes in the standard-care group. No diabetic ketoacidosis episodes were reported. Ten episodes of severe hypoglycemia in ten participants were reported in the bionic pancreas and three episodes in two participants in the standard-care group (incidence rate, 17.7 events, and 10.8 events/100 participant-years, respectively; $P = 0.39$).

Critical Review: This trial presents very important data that suggest that the use of a nearly fully automated system such as the bionic pancreas led to a significant reduction in the HbA1C level with an increase in the time spent in the target glucose range. This has important implications as it means that simplified, automated insulin delivery can be safely offered to most individuals irrespective of health literacy status and access to specialist endocrine care.

Prevalence and characteristics of gonadoblastoma in a retrospective multi-center study with follow-up investigations of 70 patients with Turner syndrome and a 45,X/46,XY karyotype

Karila D, Donadille B, Léger J, Bouvattier C, Bachelot A, Kerlan V, *et al*. *Eur J Endocrinol*. 2022 Nov 24;187(6):873-881.

Objective: The objective of this study was to evaluate the prevalence of gonadoblastoma (GB), its characteristics, and its risk factors, according to the type of Y chromosomal material in the karyotype.

Study Methodology and Results: This was a retrospective multicenter study from 10 French centers and included participants with Turner syndrome and a mosaic 45,X/46,XY karyotype with a normal female phenotype. The investigators collected demographic, clinical, and laboratory data including histological data of the gonads. Karyotype and FISH analysis for each patient included the determination of the regions of the Y chromosome present, the degree of 46,XY mosaicism, and the presence of the TSPY- and SRY-containing regions.

The study included 70 patients with a median age of 29.5 years (21.0–36.0) at the end of the follow-up. No patients showed evidence of hyperandrogenism. Fifty-eight patients underwent gonadectomy at a mean age of 15.1 ± 8.5 years. The mean delay between the diagnosis of TS and the gonadectomy was 5.2 ± 5.8 years. Ultrasound results were available in 40 patients before gonadectomy and showed atrophic gonads in most cases ($n = 35$) with one tumor detected. 16/58 patients had gonadectomy before 12 years of age, 21.4% of those operated after 12 years had spontaneous puberty, with 2 having spontaneous menarche and with spontaneous pregnancies in one subject. GB was detected in nine patients (12.8%) at a mean age of 13.4 years, of these two were malignant and identified at 14, and 32 years of age; however, neither was metastatic. No clinical differences were identified between those with or without a GB. The entire Y chromosome was detected in 6/9 with GB. The percentage of XY cells within the 45,X/46,XY mosaicism was not statistically different in the patients with or without GB ($P = 0.37$). The TSPY-containing chromosomal region was present in a single copy in eight of nine patients with GB and two copies in one of nine.

Critical Review: This study provides important data on GB risk and its correlation with cytogenetic characteristics. The authors suggest that the prognosis of patients with GB is good, and therefore, early gonadectomy may not be necessary particularly as many patients with *in situ* gonads had evidence of spontaneous puberty. However, no clinical or radiological features were predictive of GB development; therefore, close follow-up is necessary particularly in those with an entire Y chromosome. The study was also limited by the fact that all patients did not undergo a gonadectomy thereby perhaps underestimating GB risk.

Hyperinsulinemic hypoglycemia diagnosed in childhood can be monogenic

Hopkins JJ, Childs AJ, Houghton JA, Hewat TI, Atapattu N, Johnson MB, *et al*. *J Clin Endocrinol Metab*. 2023 Feb 15;108(3):680-687.

Objective: The objective of this study was to investigate the prevalence of monogenic hyperinsulinism in patients with onset of disease after 12 months of age and to explore potential factors leading to later age at presentation of the disease.

Study Methodology and Results: This study included data from 1848 individuals with hyperinsulinemia (HI) diagnosed before 16 years of age. The cohort was divided into those with infancy-onset HI (<12 months) and those with onset in childhood (1–16 year of age). The genetic testing protocol included initial Sanger sequencing for those with clinical features highly suggestive of a particular mutation (such as hyperammonemia for GLUD1), followed by targeted next-generation sequencing for 11 HI-causing genes. The authors then compared clinical features and genotype differences between those with an earlier versus a later onset of HI.

A total of 1675 (90.6%) of the individuals had infancy-onset HI with 73 (9.4%) diagnosed in childhood with a median age at diagnosis of 1.75 years (IQR, 1.17–4 years). Monogenic HI was diagnosed in 24.3% (n = 42/173) of the childhood cohort versus 74.5% (n = 1248/1675), of the infancy cohort, $P < 0.00001$). The median age at diagnosis of childhood-onset monogenic HI was 1.71 years (IQR, 1.02–2.73 years). GLUD1-HI was most common in those diagnosed in childhood (n = 16/42, 38%), with ABCC8-HI most common in the infancy-onset group (n = 907/1248, 73%). Variants in six genes (*KCNJ11, HNF4A, KDM6A, HNF1A, INSR,* and *CACNA1D*) were identified only in individuals diagnosed in infancy, while *TRMT10A* gene mutation was identified exclusively in the childhood-onset cohort. Mosaic variants were detected more often in the childhood versus the infancy-onset HI group (10% vs. 0.9% (n = 4/42 vs. 11/1248), $P < 0.00001$. About 81% (n = 34/42) of variants in the childhood-onset group were detected in individuals diagnosed with HI in infancy.

Critical Review: This interesting study shows that monogenic causes can be detected in a significant proportion of childhood onset HI particularly in those presenting before the age of 2.7 years, suggesting, that genetic testing should be pursued in this cohort. The higher detection of mosaic variants in the childhood HI group suggests that pancreatic tissue might consist of a mixed population of cells which could potentially affect disease severity and age at presentation.

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Conflicts of interest

There are no conflicts of interest.

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