2007 and 2018, the prevalence of diabetes among Korean adolescents increased. Further studies are required to determine the causes of these increases.

Pediatric Endocrinology

DIABETES, INSULIN, AND LIPIDS IN PEDIATRIC ENDOCRINOLOGY

Youth With Type 1 Diabetes Experienced a Higher Level of Anxiety During the COVID-19 Pandemic Compared to Healthy Control; A Cross-Sectional Study

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Background and Aims: Diabetes is highly associated with depression and anxiety. With the coronavirus disease 2019 (COVID-19) pandemic, the prevalence of mental health issues in the general population appears to be increasing rapidly (1). Thus, we evaluated psychological heath in pediatric type 1 diabetes (T1D) patients and caregivers during the lockdown phase of the COVID-19 pandemic. Our objective was to compare the levels of depression and anxiety in youth with T1D and their caregivers to those of healthy controls. We hypothesized that youth with T1D would experience higher levels of depression and anxiety than healthy controls during the COVID-19 pandemic (Aim 1). We also explored potential causes of increased depression/anxiety in T1D (Aim 2). We aimed to further understand psychosocial well-being in T1D during the COVID-19 pandemic and identify mechanisms to support this population in global crises. **Methods:** A week after the start of Tennessee's shelter-in-place order, we performed 15-minute phone surveys to screen for anxiety and depression in families with children with T1D (n=100, mean age of children=13.8 years, mean HbA1c=8.95%, Race=Caucasian (55%)/African American (43%)) and healthy children (mean age of children=5.7 years, Race=Caucasian (24%)/African American (69%)). Depression and anxiety were assessed by a standard assessment tool, the Patient Health Questionnaire (PHQ-4), a 4-item inventory rated on a 4-point Likert scale that briefly assesses depression and anxiety. Anxiety/depression-related variables were compared based on T1D status using the Chi-square test or t-test, as appropriate. The association between T1D and risk of anxiety and depression was examined using logistic regression adjusted for potential confounders. For families with T1D, additional questions were administered to identify specific concerns associated with T1D care. **Results:** Compared to controls, T1D was associated with a five times higher risk of anxiety in multivariable adjusted models, OR=5.02 (95% confidence interval: 1.83, 14.84), P=0.002. Additionally, 26/52 T1D families (50%) had significant concern for being at a higher risk for severe COVID-19 infection due to T1D and 14/52 T1D families (27%) were worried about obtaining insulin and diabetes supplies. **Conclusions:** Pediatric T1D is associated with an increased risk of anxiety but not depression in the acute phase of the COVID-19 pandemic. Elevated anxiety in T1D during the COVID-19 pandemic appears to be, at least in part, due to fear of higher risk of severe COVID-19 infection and uncertainty regarding access to insulin and diabetes supplies. Further studies to address mental health in T1D during global emergencies and advocacy to develop systems to ensure access to medical resources for pediatric T1D are warranted.

1. Stein MB. EDITORIAL: COVID-19 and Anxiety and Depression in 2020. Depress Anxiety. 2020;37(4):302.

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DISORDERS OF PUBERTY

6-Month Subcutaneous Leuprolide Acetate Effectively Suppresses Clinical Signs of Puberty in Children With Central Precocious Puberty

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Objective: Gonadotropin-releasing hormone (GnRH) agonists, such as intramuscular leuprolide acetate, triptorelin and the subcutaneous histrelin implant, are standard treatment for central precocious puberty (CPP). Implants require surgery and sometimes anesthesia, while frequent intramuscular injections can be painful. A shift to longer acting-formulations and subcutaneous injections has been proposed for the treatment of CPP. Therapies with convenient administration, prolonged duration of action and favorable safety profile may be beneficial, improving patient adherence. 87% of subjects achieved stimulated LH suppression to <4 IU/L by Week (W) 24 in a Phase III trial evaluating the efficacy and safety of the first6-month subcutaneous injectable in situ gel leuprolide acetate for CPP. We present secondary analyses of bone age (BA) advancement, weight, BMI, and pubertal maturation from this trial.
Methods: 62 children (60 girls, 2 boys) with CPP (naïve to treatment) received 2 doses of 45 mg subcutaneous leuprolide acetate at 24-week intervals, constituting the intent-to-treat population. Radiographs of the left hand and wrist were used to determine BA using the Greulich and Pyle method. BA was assessed by a blinded central reader. Rate of BA advancement was determined by the ratio of BA to chronological age (CA, BA/CA). Pubertal maturation was categorized with the Tanner staging system using breast development, external genitalia, and pubic hair. Safety outcomes were measured.
Results: Mean age at onset of treatment was 7.5 ± 0.9 (SD) (range 4-9) years. BA/CA consistently declined throughout treatment, from 1.4 ± 0.2 at baseline, to 1.3 ± 0.1 at W24 and 1.3 ± 0.1 at W48. Although mean weight increased 8.7% from screening to W24 (34.8 kg vs 37.7 kg) and 16.9% from screening to W48 (40.4 kg), mean BMI remained stable throughout the study. The proportion of girls with early breast Tanner stage development (stage 1 and 2) increased from 9% at baseline to 37% at W48. The proportion of girls with late breast Tanner stage development (stage 4 and 5) decreased from 18% at baseline to 5% at W48. Both boys regressed from Tanner stage 3 to stage 2 for external

genitalia development by W48. Tanner staging for pubic hair development remained stable for approximately 80% and decreased for 7% of children by W48. 52/53 treatment emergent adverse events were mild or moderate.
Conclusions: 6-month 45 mg subcutaneous leuprolide acetate is a promising treatment for CPP. It effectively suppressed LH, suppressed clinical signs of pubertal maturation and demonstrated a good safety profile. It also has the beneficial features of subcutaneous administration, small injection volumeand twice a year dosing. This may be a welcome addition to the armamentarium given the proposed shift in CPP therapies towards longer-acting formulations and subcutaneous injections.

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A Clinical Experience of Pubertal Induction in Female Patients With Congenital Hypogonadotropic Hypogonadism (CHH) From an Endo-ERN Referral Center

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Female congenital hypogonadotropic hypogonadism (CHH) is a rare condition, with a strong genetic background, characterized by absent or incomplete pubertal development, for which inductive treatment with sex-hormone is required. Although the available data, mostly coming from studies in patients with Turner syndrome, indicate transdermal estradiol (TDE) as the first-choice formulation, no internationally validated therapeutic schemes are currently available. Furthermore, data on CHH patients are certainly lacking and there is no standard of care for pubertal induction in this specific population. The aim of our work was the retrospective analysis of the data from a collection of case reports of pubertal induction in CHH patients referred to our Center. Six patients underwent induction with transdermal estradiol (TDE) at the starting dose of 0.1μg/kg/day (night-time for the first 4-6 months), increased every 4-6 months up to the adult dose, for a mean period of 2.86 ± 0.45 ys. Micronized progesterone (200 mcg) was introduced at reaching of 50μg dose or if breakthrough bleeding occurred. Treatment was monitored through clinical and anthropometric evaluations at each dose modification. The average age of induction was 17.25 ± 1.41 ys, with each bone age> 13 ys. Three out of six patients already had a Tanner B2 stage at diagnosis. The mean times of pubertal advancement were respectively 1.3 ± 0.46 ys for the achievement of B3, 2.13 ± 0.29 ys for the B4 and 2.35 ± 0.77 ys for menarche; all the patients reached an adult breast conformation (B5) in 2.81 ± 0.28 ys. These data are consistent with physiological pubertal progress. All of them achieved adequate uterine development (medium longitudinal diameter 72.2 ± 3.37mm), except one patient with suboptimal development (54mm). The final height (FH) was adequate in all patients, with SDS FH +1.6 (-0.43 - +3.38), in spite of an average growth of 4.11 cm (2.5-6) during the induction period and a growth rate > 2cm/year only in 50% of patients. No side effects were reported, and individual compliance and satisfaction were quite high. This clinical experience suggests that the adopted regimen, consistent with current literature, guarantees excellent efficacy and safety. However, further studies are needed to identify the optimal treatment in adolescents with CHH, taking into account their higher age at the start of induction, the modest impact on growth and final stature, to focus on the specific clinical objectives in these patients

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Defects in the GnRH Neuronal Migration factor, CCDC141, Lead to Self-Limited Delayed Puberty

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GnRH neuronal biology has been identified as a critical element in the pathogenesis of self-limited DP, previously implicated exclusively in the pathophysiology of idiopathic hypogonadotropic hypogonadism (IHH). We hypothesise that this condition may be inherited via genetic variants discoverable through whole-exome sequencing (WES), by focusing on genes involved in GnRH neuron development and function, and genes reported in IHH. We analysed WES data from large Finnish cohort with familial self-limited DP, focusing on genes recently reported in IHH. WES data of 100 DP families have been analysed with a total of 193 individuals: 100 probands, 158 affected and 35 unaffected family members. Potentially pathogenic rare variants segregating within cohort families were identified using a virtual panel of recently reported IHH genes (n=13). This analysis identified 6 rare potentially pathogenic variants in *CCDC141* in 25 individuals of 8 families which account for almost 10% of self-limited DP cases in this cohort, without variants identified in cohort control cases. Previous studies reported that homozygous or compound heterozygous mutations of *CCDC141* cause Kallmann syndrome and IHH, due to impaired GnRH neuronal migration. In this study, all 6 *CCDC141* variants were heterozygous missense variants predicted to be deleterious by *in silico* prediction tools. Most probands were male (n=7) with typical features of self-limited DP, with absence of secondary sexual characteristics, delayed bone age, and low gonadotropins and sex steroids at first presentation and spontaneous entry into puberty later than age of 14 years without treatment. The majority of pedigrees displayed good segregation of variants with the DP trait, following an autosomal dominant inheritance pattern. However, in two families, there was a complex inheritance pattern with compound heterozygosity (p.Ser55Cys and p.Asp767Asn) and possible incomplete penetrance. *In vitro*