DECEMBER 2021
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CAPE News

Newsletter of The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE)

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Theme: Childhood Diabetes Mellitus Part - 1

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From the Editorial Board

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Dear Esteemed ISPAE members,

Greetings and wishes for a happy and prosperous New Year 2022! It gives me a lot of pleasure to connect with you over this December issue of CAPE News, themed on Childhood Diabetes Mellitus. The issue has an interesting review of the ADA 2021 guidelines, Mini review of interesting issues pertaining to childhood diabetes, a Pedendoscan of recent publications on diabetes and a History Corner of diabetes, as well as a very interesting compilation of learning pearls from enthusiastic members for the ISPAE 2021 Pune meet, the PET school and ACES meets. There is a compilation of patient and academic activities from our members as well. An interesting pictorial quiz for Trainees is included: we encourage everyone to participate!

The enthusiastic contribution from ISPAE members is very encouraging. Hence, we have decided to include some of the contributions in the next issue: theme - Childhood Diabetes part-2 for March 2022. The subsequent issue for June 2022 will have ADRENAL disorders as its theme.

We hope that you have a good reading experience. Feedback is welcome at editor.capenews@gmail.com

Thank You and Regards,
Dr Hemchand K Prasad
Editor, ISPAE CAPENEWS 2021-22

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Office Bearers' Message

Dr Shaila Bhattacharyya
President
ISPAE 2021-22

Dr Ganesh Jevalikar
Secretary cum Treasurer
ISPAE 2021-22

Dr Rakesh Kumar
Joint Secretary
ISPAE 2021-22

Dear ISPAE members,

Greetings from Team ISPAE 2021-22!

On behalf of the executive council of ISPAE, we wish all the members a merry Christmas and a very happy new year 2022! May the new year bring normalcy back in our lives!

We congratulate Dr Vaman Khadilkar, Dr Anuradha Khadilkar and Dr Supriya Gupte and the organizing team of ISPAE 2021 for a very highly successful ISPAE 2021. The virtual conference was highly successful and a scientific feast. Dr Sarah Mathai and Dr Ahila Ayyavoo conducted the ISPAE PET fellows school in a highly successful and professional manner. This was the first ISPAE event of 2021 being held in person and was greatly enjoyed by the young fellows and all the faculty. We thank our international colleagues for sparing their valuable time and adjusting across various

The first batch of diabetes educators has now completed the ISPAE IDEAL course. The course is highly comprehensive, interactive and is a fruit of passion and hardwork of the entire team. We plan to begin the second batch of this course in the month of February and we will request all the members to nominate their educators for this course so that we are able to cover all the geographical areas of our vast country. We also encourage all these educators to become associate members of ISPAE and contribute to the field of science and education in pediatric diabetes.

The entrance exam for pediatric endocrinology fellowships under ISPAE banner were held in the month of December 2021 and the first batch of the fellows will join in 2022.

We will continue our monthly ACES meeting and urge all the members to encourage budding ped endos to present cases. The PEP meetings will also continue quarterly. We also plan to conduct programs in association with ESPE on a pilot basis for pediatric endocrine fellows.

We request all of you to contribute more ideas, share your initiatives through CAPE News, and contribute scientific articles to our journal, the Journal of Pediatric Endocrinology and Diabetes as well as to CAPE News.

Best Wishes,
Drs Shaila Bhattacharyya, Ganesh Jevalikar, Rakesh Kumar,
Team ISPAE 2021-22

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A very warm welcome to all new members

- Dr Gibi George, Assistant Professor, Department of Pediatrics, Jubilee Mission Medical College and Research Institute, Eastfort, Thrissur, Kerala.
- Dr Dhvani Raithatha, Senior Resident, Jalna Critical Care Hospital, Jalna, Maharashtra.
- Ms Varsha Mane, BAMS, Certified Diabetes Educator, Mane Hospital and Diabetes Care Unit, Takad Gaon Road, Georai, Beed, Maharashtra.
- Dr Sandeep Yadav, New Healthcity Hospital, Panchavati, Wardha Road, Lokmat Square, Near Hitvada Office, Nagpur, Maharashtra 440010.
- Dr Pooja V, Senior Resident, BGS Global Institute of Medical Sciences, Dr Vishnuvardhan Road, Kengeri, Bengaluru, Karnataka 560060.
- Dr Nabanita Kora, Assistant Professor, MVJ Medical College and Research Hospital, Dandyapallya, Hoskote, Bengaluru, Karnataka.
- Dr Anand R, Consultant, Voluntary Health Services, SH 49A, Pallipattu, Tharamani, Chennai 600113, Tamil Nadu.
- Ms Vinti Jain, Diabetes Educator, Jalna, Maharashtra.
- Ms Usha Pinnamaraju, Diabetes Educator, Visakhapatnam, AP.
- Ms Bandhavya N, Diabetes Educator, Mazumdar Shaw medical Center, Narayana Health City, Bengaluru
- Mr Harsh Kohli, Co-founder & President, DIYA (Diabetes India Youth in Action), Delhi
- Dr Utkarsh Bansal, Professor, Hind Institute of Medical Sciences, Safedabad, Barabanki, UP
- Dr Swathi Padmanaban, Fellow in Paediatric Endocrinology, Indira Gandhi institute of child health, Bangalore
- Dr Payal S Kubsad, Fellow in Paediatric Endocrinology, Indira Gandhi institute of child health, Bangalore
- Dr Moumita Saha, Pediatric Endocrine fellow, CMC Vellore
- Ms Shubhra Uppal, Diabetes Educator, Jalandhar, Punjab
- Ms Deepthi S, Diabetes Educator, Bangalore
- Ms Paras Devani, Diabetes Educator, Juvenile Diabetes Foundation, Mumbai Maharashtra Chapter
- Ms Vaishali Vakil, Diabetes Educator, Juvenile Diabetes Foundation, Mumbai Maharashtra Chapter
- Ms Garima Sharma, Dietician, Kalawati Saran Children's Hospital, New Delhi
- Dr Javaid Bhat, Consultant, Endocrinology, Government Super speciality Hospital, Srinagar (J & K)
- Ms Manasa Lakshmi Korada, Diabetes Educator, Vishakhapatnam
- Dr Rekha Bathala, Fellow in Paediatric Endocrinology, Indira Gandhi institute of child health, Bangalore
- Dr Priyanka Gupta, Consultant Paediatrician, Hyderabad

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Review of Recent Guidelines Diabetes in Children and Adolescents: Standards of Medical Care in Diabetes - 2021

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- Individualized medical nutrition therapy (MNT) is recommended for children and adolescents with type 1 diabetes (T1D), along with monitoring of carbohydrate intake, whether by carbohydrate counting or experience-based estimation.
- Exercise is recommended with the goal of 60 min of moderate to vigorous intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week.
- Education about frequent patterns of glycemia during and after exercise, which may include initial transient hyperglycemia followed by hypoglycemia, is essential, ensuring patients have a pre-exercise glucose level of 90–250 mg/dL.
- Frequent blood glucose monitoring (BG) before, during, and after exercise, with or without use of continuous glucose monitoring (CGM), is important to prevent, detect, and treat hypoglycemia and hyperglycemia with exercise.
- Providers should be aware of the differences in accuracy among glucose meters, only US FDA–approved meters with proven accuracy should be used, with unexpired strips.
- Health care providers should be aware of medications and other factors, such as high-dose vitamin C and hypoxemia, that can interfere with glucose meter accuracy.
- Assess youth with diabetes for psychosocial and diabetes related distress, generally starting at 7–8 years of age.
- Starting at puberty, preconception counseling should be incorporated into routine diabetes care for all girls of child-bearing potential.
- All children and adolescents with T1D should self-monitor BG levels multiple times daily (up to 6–10 times/day by glucose meter or CGM), including prior to meals and snacks, at bedtime, and as needed for safety in specific situations such as exercise, driving etc.
- When used properly, real-time CGM in conjunction with insulin therapy, is a useful tool to lower and/or maintain A1C levels and/or reduce hypoglycemia.
- When used properly, intermittently scanned CGM in conjunction with insulin therapy can be useful to replace self-monitoring of blood glucose (BG). Intermittently scanned CGM devices should be scanned frequently, at a minimum once every 8 h.
- CGM metrics derived from CGM use over the most recent 14 days, including time in range, are recommended to be used in conjunction with A1C whenever possible.
- An A1C goal of 7% is appropriate for many children.
- Annual screening for cystic fibrosis–related diabetes (CFRD) with an oral glucose tolerance test should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with CFRD. A1C is not recommended as a screening test for CFRD.
- Patients with CFRD should be treated with insulin to attain individualized glycemic goals.
  All children diagnosed with diabetes in the first 6 months of life should have immediate genetic testing for neonatal diabetes.

- Measure thyroid-stimulating hormone concentrations at diagnosis when clinically stable or soon after glycemic control has been established. If normal, suggest rechecking every 1–2 years, or sooner if the patient develops symptoms or signs suggestive of thyroid dysfunction, thyromegaly, abnormal growth rate, or unexplained glycemic variability.
- Screen children with T1D for celiac disease (CD) by measuring IgA tissue transglutaminase (tTG) antibodies, with one time documentation of normal total serum IgA levels, soon after the diagnosis of diabetes, or IgG to tTG and deamidated gliadin antibodies if IgA deficient.
- Repeat TTG screening within 2 years of diabetes diagnosis and then again after 5 years; consider more frequent screening in children who have symptoms or a first-degree relative with CD.
- Blood pressure (BP) should be measured at each routine visit. If hypertension is confirmed, in addition to lifestyle modification, pharmacologic treatment with ACE inhibitors or angiotensin receptor blockers should be considered, following reproductive counseling for females due to the potential teratogenic effects of both drug classes.
- Initial lipid testing should be performed when initial glycemic control has been achieved and age is $\geqslant$ 2 years. If initial LDL cholesterol is $\leqslant$ 100 mg/dL, subsequent testing should be performed at 9–11 years of age.
- If lipids are abnormal, initial therapy should consist of optimizing glucose control and MNT to limit the amount of calories from fat to 25–30%, saturated fat to <7%, cholesterol <200 mg/day, avoidance of trans fats, and aiming for 10% calories from monounsaturated fats.
- After the age of 10 years, addition of a statin may be considered in patients who, despite MNT and lifestyle changes, continue to have LDL cholesterol > 160mg/ dL or LDL cholesterol > 130mg/dL and one or more cardiovascular disease risk factors, following reproductive counseling for females because of the potential teratogenic effects of statins. The goal of therapy is an LDL cholesterol value < 100 mg/dL.
- Annual screening for albuminuria with a random (morning first sample) spot urine for albumin-to-creatinine ratio (UACR) should be considered at puberty or at age > 10 years, whichever is earlier, once the child has had T1D for 5 years.
- An ACE inhibitor or an angiotensin receptor blocker (ARB), titrated to normalization of albumin excretion, may be considered when elevated UACR (> 30 mg/g) is documented (two of three urine samples obtained over a 6-month period following efforts to improve glycemic control and normalize BP).
- An initial dilated and comprehensive eye examination is recommended once youth have had T1D for 3–5 years, provided they are aged $\geqslant$ 11 years or puberty has started, whichever is earlier.
- After the initial examination, repeat dilated and comprehensive eye examination every 2 years. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of glycemic control with A1C >8%.
- Consider an annual comprehensive foot exam at the start of puberty or at age $\geqslant$ 10 years, whichever is earlier, once the youth has had T1D for 5 years.

Reference:

American Diabetes Association. 13. Children and adolescents: Standards of Medical Care in Diabetes 2021. Diabetes Care 2021;44(Suppl. 1):S180–S199.

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Mini-Reviews Monogenic diabetes - Indian experience

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Type 2 diabetes (T2D) is the most common form of diabetes in adults; almost 90% of people with diabetes in India and worldwide have T2D. The second commonest type, which usually affects children, is type 1 diabetes (T1D), needing lifelong insulin. Many people are unaware that apart from T1D and T2D, there are other forms of diabetes, due to a defect in a single gene, i.e., 'Monogenic diabetes'. Monogenic diabetes usually occurs in children or young adults; these patients are often misdiagnosed as having T1D, and advised lifelong insulin, which may not be necessary.

Type 1 diabetes

T1D, one of the most common endocrine disorders in children, is an autoimmune disease occurring due to interaction of genetic, environmental and immunological factors [1]. Individuals with T1D have higher morbidity and excess premature mortality than their non-diabetic peers; their life expectancy is reduced by an estimated 15 – 20 years [2-4].

Recently we reported the clinical and biochemical profile and diabetes-related complications in a group of long-term survivors with T1D, and compared them with a group of non-survivors with T1D. We also described the causes of death among the non-survivors with T1D. This retrospective study compared 76 individuals with T1D who had survived for at least 40 years ('survivors') with 51 individuals with T1D who had died with shorter duration of diabetes ('non-survivors'), from diabetes clinics in different cities of India. In this first report of long-term survivors with T1D from India, we observed that survivors had better glycemic and blood pressure control, more favorable lipid profiles, and lower prevalence of complications compared to non-survivors. However, there could be other protective factors as well, which merit further studies [5].

Monogenic Diabetes

Maturity Onset Diabetes of the Young (MODY)

This type of diabetes affects children or youth, and family history of diabetes can be traced to three or more generations. There are several subtypes of MODY, many of which can be controlled with oral anti-diabetic drugs (OAD), which may work better than insulin. MODY is commonly caused by variants in the *HNF1A, HNF4A* or *GCK* genes, but up to 14 subtypes of MODY have been described.

Studies on MODY in India

Molecular genetic studies of monogenic diabetes in India have been conducted by us at the Madras Diabetes Research Foundation (MDRF), Chennai, for over 20 years. Our initial genetic studies and screening were performed using the Sanger sequencing method, choosing clinically suspected MODY patients. Among 96 young onset diabetic patients screened for *HNF1A* gene mutation, Radha et al [6] identified nine mutations (9.6%). A novel *HNF1A* gene mutation Arg263His co-segregated with diabetes in a family of 30 individuals; it was not seen in non-diabetic members in the family, thus providing evidence that the mutation was involved in MODY [6].

We also screened 87 patients diagnosed with T2D before 25 years of age and negative for GAD antibodies, for *HNF4A* gene mutation (MODY 1), and identified three mutations in the *HNF4A* gene (3.4%) [7]. We then screened 55 patients for *GCK* gene (MODY 2) mutations and identified two MODY 2 mutations – Met251Thr and Thr206Ala – of which Thr206Ala was novel. The three diabetic members of a family carrying a known Met251Thr mutation were managed without pharmacotherapy; they showed non-progressive mild hyperglycemia over the years [8]. Further, in 50 cases clinically suspected to have MODY 5 based on renal abnormalities such as renal cysts, horse-shoe kidney, etc. on ultrasound, we identified six (12%) different *HNF1B* gene mutations and whole-gene deletion [9]. Very recently, we have used exome and whole genome strategy to analyze 153 clinically confirmed MODY patients from south India [10] and we found MODY 3 *(HNF1A*; 7.2%) to be the most frequent mutation, followed by MODY 12 (*ABCC8*; 3.3%). Our findings showed *HNF1A, HNF4A* and *ABCC8* to be the most frequent MODY subtypes in south India. The majority of these variants were identified in subjects with autosomal dominant family history.

Neonatal Diabetes (NDM)

The second form of monogenic diabetes, which affects children below 6 months of age, is Neonatal Diabetes. At this age, T1D is uncommon. NDM is due to genetic defects in pancreatic insulin secretion, and some cases can be treated by OAD, especially those with mutations in the *KCNJ11* and *ABCC8* genes. Infants with NDM are often wrongly diagnosed to have T1D, and advised insulin unnecessarily. By doing a simple genetic test, if NDM forms which respond to OAD are diagnosed, these children can stop insulin, which is like a miracle for them.

There are very few reports in Indian patients with NDM. Activating or gain of function mutations of KATP channel genes, namely *KCNJ11* and *ABCC8*, are the predominant cause of permanent neonatal diabetes mellitus (PNDM). Our group pioneered studies of the genetics of NDM in India. In our first study, we screened 33 unrelated Indian probands with onset of diabetes below one year of age for the common genes implicated in neonatal diabetes such as *KCNJ11*, *ABCC8* and *INS*; a total of 12 mutations were identified *(ABCC8* mutations in seven, *KCNJ11* mutations in three and INS mutations in two). Our genetic diagnosis enabled successful shifting of some of the children with *KCNJ11* (e.g., Cys42Arg and Arg201Cys) and *ABCC8* (e.g., Val86Ala and Asp212Tyr), mutations from insulin to oral sulphonylurea therapy [11]. This is an important direct translation of genetic analysis from bench to bedside in clinical practice.

We tried to identify the genotype-phenotype correlation of KATP channel gene defects in a large series (n = 181) of Indian PNDM patients. Direct sequencing of all exons of *KCNJ11* and *ABCC8* genes in patients with PNDM was performed, and their clinical and biochemical data collected. We identified the molecular basis of KATP-NDM in 39 of 181 patients (22%). Of them, 20 (51%) had *KCNJ11* mutations and 19 (49%) had *ABCC8* mutations. Three patients with *KCNJ11* mutations had developmental delay with DEND syndrome; while seven of 19 (36.8%) patients with ABCC8 mutations had developmental delay. This is the largest study in NDM patients in India, demonstrating the importance of KATP channel gene mutation screening in PNDM and the efficacy of glibenclamide for Indian patients with KATP-PNDM. The success rate of transfer to OAD is more in patients with *KCNJ11* mutations compared with those with *ABCC8* mutations [12].

In a recent study, we evaluated the *INS* gene mutations in 189 children with PNDM. Two novel mutations (His34Pro, Leu35Met) in a compound heterozygous state and seven known mutations (Gly32Ser, Phe48Cys, Arg89Cys, Cys96Tyr, Ser98Ile, Try108Asp and Cys109Phe) in the *INS* gene were identified in 8 of these patients. Four mutations were involved in defects with disulphide bond formation and hence were in crucial regions of the gene. All the mutations were *de novo* in origin. This is the first comprehensive study from India to investigate the insulin gene mutations in PNDM, and to show that INS gene mutations also contribute to the causation of PNDM [13].

Congenital Hyperinsulinism with Hypoglycemia

This condition is opposite to diabetes. Congenital hyperinsulinism (CHI) is characterized by persistent hypoglycemia due to inappropriate and unregulated secretion of insulin by pancreatic β-cells. CHI typically presents in newborns and infants as severe and persistent hypoglycemia, and is a major cause of hypoglycemia-related brain injury and mental retardation. The molecular basis of CHI involves mutations in *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A* and *UCP2* and hence response to treatment heavily depends on genetics.

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In our center, a molecular abnormality was identified in 45% (10 of 22) children with CHI [14]. This is the first large genetic screening study of CHI in India. Mutations were identified in 88.9% of diazoxide unresponsive cases and in 11.1% of children who were treated with diazoxide. Genetic testing assists in understanding the nature of the molecular abnormality; in most cases, timely prediction of the type of hyperinsulinemia is likely to aid in avoiding hypoglycemia-related brain damage.

Recommended guidelines

The American Diabetes Association (ADA) recommends considering genetic testing for Monogenic Diabetes in the following situations:

- Diabetes diagnosed in the first 6 months of life.
- Diabetes without typical features of type 1 or type 2 diabetes (negative diabetes-associated autoantibodies, non-obese, lacking other features of metabolic syndrome, strong family history of diabetes).
- Stable, mild fasting hyperglycemia (100-150 mg/dl [5.5 – 8.5 mmol/l), stable A1c between 5.6 and 7.6% (35-60 mmol/l), especially if non-obese.

When to suspect monogenic diabetes if initially thought to have type 1 diabetes

- Diabetes diagnosed before 6 months of age.
- Family history of diabetes with at least one parent affected
- Preserved endogenous insulin production outside the honeymoon phase (>3 years), with detectable C-peptide.
- Pancreatic islet autoantibodies (GAD, ICA, Zinc Transporter or IA2) are absent, especially at diagnosis.*
- Clinical features of a specific genetic subtype of monogenic diabetes. (e.g., kidney abnormalities in HNF1B MODY).

* Note that Indians have a much lower rate of antibody positivity than Caucasians, so this factor is less important in the Indian population.

When to suspect monogenic diabetes if initially thought to have type 2 diabetes*

- Young age at onset (<30 years).
- Three generation transmission of diabetes in the family.
- Not markedly obese; or family members with diabetes who are of normal weight.
- No acanthosis nigricans, other evidence of insulin resistance.
- Clinical features of a specific genetic subtype of monogenic diabetes. (e.g., kidney abnormalities in HNF1B MODY)

*Note however that monogenic diabetes may present even without these classical features.

Conclusion

Work done at MDRF over two decades, has tremendously advanced our understanding of polygenic and monogenic forms of diabetes. Progress in the learning process, with new techniques, will continue in the years to come. The genetics of MODY and NDM exemplifies the need to bring the study of genomics of diabetes to the diabetes clinic. The aim of genomic studies in monogenic diabetes is interpretation of sequence variants and their functionality, which will help in tailoring precision drug treatment of diabetes.

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Medical Nutrition Therapy for Type 1 Diabetes

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Type 1 diabetes (T1D) is emerging as a major healthcare challenge, with India having the highest number of children and adolescents with T1D in the world. According to the IDF Atlas, 2021, 10th Edition, India has an estimated 229,442 individuals with T1D in the age group of 0-19 years (1). Diversity in socio-economic backgrounds, lower literacy levels, and inadequate facilities, make timely diagnosis, treatment and management challenging.

Medical Nutrition Therapy (MNT) is one of the cornerstones of diabetes care and education. Dietary recommendations for children with diabetes are based on healthy eating recommendations suitable for all children and adults and therefore, the entire family. The goals of MNT for T1D are:

- Provide sufficient and appropriate energy intake and nutrients for optimal growth, development and good health. Avoid restrictive diets as they may result in poor growth, nutritional deficiencies and increased psychosocial burden.
- Ensure diet diversity and nutrient density by including a wide variety of nutritious foods from all food groups, with appropriate healthy snacks (as necessary), to supply all essential nutrients, maintain a healthy weight and prevent bingeing.
- Achieve a balance between food intake, metabolic requirements, energy expenditure and insulin action profiles to attain optimum glycemic control (maximum Time in Range).
- Encourage appropriate eating behaviors and healthy life long eating habits whilst preserving social, cultural and psychological well-being.
- Achieve and maintain a healthy and appropriate Body Mass Index (BMI), preventing obesity and insulin resistance. This includes a strong recommendation for children, adolescents and young adults to undertake regular physical activity.
- Tailor advice to individual goals, including weight, activity and sports goals.
- Reduce the risk of short-term and long-term complications.
- Develop a supportive relationship to facilitate positive behavior and lifestyle changes.
- Provide a framework for regular monitoring of blood glucose (BG) levels and supervision of insulin doses (as required).
- Encourage use of diabetes technologies such as continuous glucose monitoring (CGM) to aid dietary education and inform prandial insulin adjustments and dietary modifications.

The meal plan may be modified if associated conditions such as celiac disease, hypertension or dyslipidemia are present. (2)
The energy requirement for a child with diabetes is calculated as for any other child of similar age, weight, gender and level of activity. Energy requirements are higher than normal soon after diagnosis, after an episode of diabetic ketoacidosis, and during puberty.
In the first year of diagnosis, there may be a tendency to gain weight as the anabolic action of insulin restores health, and parents are anxious. Hence, it is important to ensure that the calories are adequate but not in excess (3).
Table 1 mentions the age- wise energy requirement of Indian boys and girls.

Table 1: Recommended Daily Energy Intake for Children (NIN-ICMR) (4)

	Age group	Body Weight (Kg)	Energy (Kcal/d)
Infant	0-6mo	5.8	530
	6-12mo	8.5	680
Children	1-3y	12.9	1110
	4-6y	18.3	1360
	7-9y	25.3	1700
Boys	10-12y	34.9	2220
Girls	10-12y	36.4	2060
Boys	13-15y	50.5	2860
Girls	13-15y	49.6	2400
Boys	16-18y	64.4	3320
Girls	16-18y	55.7	2500

The daily meal plan should have three major meals, with two snacks. A bedtime snack may be recommended in case of insulin regimens that have a late-night peak effect.
The recommended macronutrient composition as per ISPAD 2018 guidelines is as in table 2.

Table 2: Recommended Macronutrient Composition of Meals (2)

Macronutrient	Distribution	Recommendations
Carbohydrates	**45 to 50%**	**Focus on high quality carbohydrate sources** Inclusion of fiber rich foods, low GI, low GL No more that 10% of total energy may be sucrose
Fats	**30 to 35%**	**Limit saturated fats (<10%) and trans fats** Focus on including omega 3 fats
Proteins	**15 to 20%**	**50% from good quality protein** Protein intake lowers GI & reduces post-meal BG excursions

Legend: GI: glycemic index; GL: glycemic load; BG: blood glucose.

Indian diets typically contain 65-70% calories from carbohydrates, and only 10-12% calories from protein. Carbohydrates are often from refined sources with high glycemic index (GI) like polished white rice, or refined wheat and its products (5), which must be discouraged, changing to sources with lower GI. Carbohydrate requirements in children and adolescents are individually determined, based on age, gender, activity and previous intake. While planning meals, carbohydrates should be restricted to 45-50% energy intake (40% in overweight adolescents) to achieve optimal postprandial glycemic control (2,3).

As carbohydrates have the greatest short-term effect on BG levels, they should be distributed over the major meals with appropriately matched insulin-to-carbohydrate ratios (ICR), while the snacks should have low or moderate carbohydrate content, depending on the type of insulin (rapid/fast or regular) used. A meal-time routine with limits on snacking can assist in preventing prolonged periods of postprandial hyperglycemia (2,3).

Healthy sources of carbohydrates, such as whole grain cereals, pulses, whole fruits, and vegetables should be encouraged to minimize glycemic excursions and improve dietary quality. Substituting high-GI for low-GI carbohydrates, increasing dietary fiber, increasing resistant starch, and including lente carbohydrates are other useful dietary modifications. Apart from preventing a sharp rise in BG levels, fiber rich foods improve the lipid profile, lower the risk of cardiovascular diseases, improve bowel function and digestive health, while providing much-needed satiety.

Variety can be brought about in the diet with knowledge of carbohydrate exchanges; portions containing 15g carbohydrates can be interchanged, since they are likely to have similar glycemic responses (2,3).

Sucrose must be restricted to less than 10% of total energy. Sweeteners such as stevia, sucrolose and erythritol are considered safe for consumption by children; however, they should be used in moderate amounts as per the Acceptable Daily Intake (ADI) limits (2).

Addition of a moderate amount of protein to a meal containing predominantly carbohydrate assists in reducing postprandial excursions, while providing satiety. Proteins should constitute 20% of the total daily energy intake. The requirements are high (2g/kg/day) in infancy, declining to 1g/kg/day at 10 years and 0.8g/kg/day in adolescence. Protein sources should provide at least 50% of the requirement as good quality protein. Vegetable protein sources are legumes, beans and soy while animal sources are egg, meat and dairy products (2,3).

Fats should constitute 30-35% of total energy intake. The quality of fats consumed is as important as quantity. It is recommended to limit saturated fats to <10% of energy intake, and avoid trans-fats as much as possible. Saturated fats are present in high amount in butter, cheese, whole milk and cream, egg yolks, lard, skin of poultry, red meat and processed meat like sausages, ham and bacon, coconut oil, and palm kernel oils. Trans-fats are present in bakery products, margarine, vanaspati, ready to eat (processed) foods and deep-fried foods. Saturated fats should be replaced by monounsaturated and polyunsaturated fats. Polyunsaturated fats are present in safflower, sunflower and soyabean oil, black gram, kidney beans and flaxseeds. Sources of monounsaturated fats include groundnut oil, rice bran oil, nuts, olives and avocados (6). The family should use the locally available and culturally acceptable cooking oil, preferably two or more different ones (2,3,4)

The Joslin Diabetes Center "Healthy Plate", wherein non-starchy vegetables constitute half of the plate, and a quarter each consists of protein sources and carbohydrate sources, cooked in healthy fats, incorporates all the above principles, provides a good balance of macro- and micronutrients and is a practical way of explaining the meal plan to the family. This should be applied to each meal to make it wholesome, balanced and nutritious (2).

Foods that can be taken in between meal-times (without additional insulin) include buttermilk, small portions or curd or nuts, egg, green vegetables and vegetable soups (6).

The family should be encouraged to incorporate healthy dietary practices for the entire family, have regular meal-times, have meals together, with attention to recommended composition and portions. Physical activity should be encouraged. The dietary intake should be periodically reviewed with a qualified dietitian, along with monitoring of glycemic control, height and weight changes and growth milestones (2,3).

As per ISPAD recommendations, a flexible approach using individualized ICR, which enables the pre-prandial insulin dose to be matched to carbohydrate intake, should be used for children and adolescents on multiple daily insulin (MDI) or insulin pump therapy (CSII). The ICR for each child may vary according to age, pubertal status, duration of diagnosis and activity (2). The accuracy of the ICR can be assessed by testing pre- and 2-3h post-prandial BG. Although this allows increases flexibility of the meal timing and the carbohydrate amount, meal-time routines and dietary quality remain important. For high-fat and high-protein meals, combination/dual wave bolus with sufficient insulin upfront to control the initial postprandial rise, is needed. Pre- and post-prandial BG testing or CGM systems can be useful in guiding insulin adjustments and evaluating the outcomes of changes to the insulin dose or timing (2).

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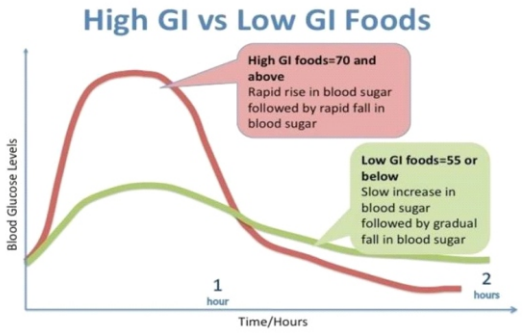
Glycemic Index: The glycemic response of different foods is affected by several factors related to the carbohydrate content and carbohydrate properties, as well as other components in the food like fat and protein, in a particular food. The glycemic response to a certain food is largely dependent on its carbohydrate content, but the pattern of BG rise may differ with different foods even with similar carbohydrate content. This is factored in by assessing the GI of that food. GI is a numerical value assigned to a particular food, based on the speed with which it will raise the BG, compared to the standard of pure glucose which the highest GI of 100. Foods are classified as having a low GI if it is < 55, medium GI if 55-69, and high GI if > 70. The higher the GI of a food, the faster it will rise the BG, i.e., the sharper the BG spike.



This graph explains the difference between high and low GI foods. The high GI food causes a BG spike after 30-45 minutes, followed by a sudden fall; whereas the low GI food gives a nice slow smooth BG rise followed by a gradual fall over 3 hours.
Below are examples of food with low, medium and high GI (8,9)

Low GI (<55)	Medium GI (55-69)	High GI (>70)
All bran	Whole wheat bread Wheat roti	White bread
Long grain basmati rice	Short grain basmati rice	Medium grain white rice (Sona masuri, Surti kolum)
Pearl Barley	Beetroot	Corn and cornflakes
Yam		Mashed potato
Rajma, lentils, Bengal gram, black gram, green gram	Bajra	Baked potato
Soybean	Jowar	Dates
Apple, Pear, Orange	Pineapple, papaya, mango (depends on the ripeness)	Watermelon
Curd (plain)	Quinoa	Glucose
Ice cream (*high in fat)		Ragi (nachni)
Parboiled rice		Short grain white rice (ambemohar)
Steel-cut oats and rolled oats		Quick instant oats/noodles

Factors affecting GI: GI of a particular food depends on an interplay of several factors, including the processes and preparations the food goes through:

- Type of starch: Amylopectin is a branched chain complex which easily breaks down, whereas amylose is a straight chain starch complex which is more resistant to breaking down. The GI is dependent on the ratio of amylose to amylopectin in various foods. Different types of rice have variable GI, depending on this ratio.

- Ripeness: the more the ripe the food, the higher the GI.
- Particle size: the smaller the size of the food particle; the quicker its absorption, i.e., higher the GI. Example: broken wheat (dalia) has lower GI than semolina.
- Heating: leads to breakdown of the outer germ layer of starch, disrupting the granules and exposing amylose and amylopectin for digestion. Moist heat vs. dry heat can change the crystallinity of starch, causing either gelatinization (increased GI) or retrogradation (decreased GI) of starch (10).
- Grinding, milling or rolling: disrupt starch granules, raising the GI (starch becomes easily available for digestion).
- Presence of other macronutrients like fat and protein: leads to delayed gastric emptying and slowed absorption of the carbohydrate, thus slowing postprandial BG rise. Soluble fibers also lead to delayed gastric emptying and thus lesser BG peak.
- Liquid intake: can lead to enhanced gastric emptying, for example: fruit juice (7,8)

Glycemic load is the effect of a carbohydrate on BG rise, taking into account both carbohydrate amount, i.e., the quantity of food eaten, and the quality of food i.e., GI. GL is calculated by multiplying GI with carbohydrate content divided by 100. GL of < 10 is considered low and > 20 is considered high.
A watermelon has a high GI of 72, vs. a banana which has a low GI of 48 ± 3; however, the carbohydrate content in watermelon is low since most of it is water, thus giving it a low GL of 4 vs. banana with a higher carbohydrate content, and thus GL of 11 (8,9).
Glycemic index vs. Glycemic load: GI describes the speed with which a particular food raises the BG, while GL looks at the net effect of a food/ meal on the BG. GI considers the quality of the carbohydrate, whereas GL takes into account the quality and quantity of the carbohydrate.
The key to good control is to match insulin action profile with the post-prandial BG rise. A sharp rise is avoided by including fiber and increasing protein content. Foods with low GI are preferable to those with high GI (2,3,7,8,9), except during exercise or correction of hypoglycemia.
Meal order and sequence:
Carbohydrates have the greatest short-term post-prandial impact on BG levels, by getting converted to glucose within the first two hours of eating. Protein and fat delay gastric emptying, taking up to 3-4 hours to increase BG, and if consumed in small amounts (most home cooked meals), play a minor role in BG control. However, a meal high in fats causes a delayed but prolonged rise in BG. The multiple mechanisms proposed for the decreased immediate postprandial hyperglycemia include: decreased insulin clearance leading to increased availability of insulin, increased GLP -1 hormone effect and insulinotropic action of protein. The timing of protein and fat intake also matters. For example, eating yogurt or an egg before the carbohydrate may help blunt the BG spike (11,12).
Carbohydrate Counting: As per ISPAD guidelines, it is imperative to impart education on carbohydrate counting to caregivers at the time of initial diagnosis itself. While advising a healthy eating pattern, giving overall stable age- and weight-based carbohydrate amounts in a day as per the recommended daily allowance, carbohydrate counting provides additional flexibility. The most widely used methods of carbohydrate counting include counting the exact grams of carbohydrates in a meal, or using a carbohydrate exchange list. Caregivers should be taught about basic macronutrients in each meal, including carbohydrates and low or non-carbohydrate containing foods. Use of food weighing scales or measuring cups and spoons to accurately estimate portion size must be encouraged. A list of carbohydrate containing foods, with serving size and carbohydrate in grams, should be provided. This could be in the form of carbohydrate exchange lists that give a quick visual guide to patients to estimate 15g carbohydrate portions. For those on rapid-acting insulin, low carbohydrate options (<5g/serving) for in-between snacking, like cottage cheese (paneer), egg, salad, fish, chicken, cheese, nuts and seeds in portioned amounts, can be recommended. Care must be taken to ensure they are low in sodium and saturated fat. Patients on short-acting insulin need a moderate carbohydrate snack about 2-2.5 hours after dosing.

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Reading Nutrition labels is an important aspect of carbohydrate counting: the serving size as well as the total carbohydrates in each serving size need to be accounted for, to accurately estimate carbohydrates in the particular food item. Carbohydrate counting should be done when eating out or ordering in, using either online resources or menu cards. For covering the additional carbohydrate, ICR can be used to calculate the prandial insulin dose (2,3).

Several challenges are faced during carbohydrate counting in the Indian scenario:

- Portion sizes need to be quantified. For example, when making rotis, the diameter, thickness and dry flour used to make roti affects the carbohydrate counting. For example: Phulka 15 g flour =10 g carbs, Chapati 30-60 g flour = 21-42 g carbohydrates (6)
  Pulses are usually over-estimated in dietary recalls. In West and South India, dals are usually thin, with 7-10 g carbohydrate per katori. In North India, dal is thicker, with 15-20 g carbohydrates per serving. In some regions like Gujarat, additional carbohydrates need to be considered because sugar/ jaggery is added to food.
- Lack of standardization of carbohydrate content of foods.
- Challenge in counting carbohydrates while eating out/ ordering in.
- Lack of food labels for street foods and commonly consumed snacks.
  Challenge in use of food scales for cooked vegetables that are prepared in combination (e.g., aaloo peas, gobi aaloo, methi aaloo).

Calculating Insulin doses and Insulin Synchronization with meals:

Total Daily Dose (TDD) is the amount of insulin taken in a day = basal + bolus dose. So if bolus doses are 6+5+5 units, and basal dose is 17 units, then TDD = 33 units.

ICR: Amount of carbohydrates (grams) covered by one unit of insulin. The usual formula is 450 (Regular insulin)/ 500 (Rapid acting Analog)* ÷ TDD. For younger children, the 300-350 rule can be used instead of 450-500 to calculate this factor.

Insulin synchronization with food and activity depends on the type of insulin regimen.

Basal + Rapid/ Fast acting insulin analog: For individuals on a combination of long- acting and rapid/fast acting analog insulins, mid-meal and bedtime snacks are not routinely necessary. Any snack eaten between meals should be low in carbohydrate, or covered with rapid acting bolus based on the ICR. Prandial boluses should take into account the pre-meal BG level as well as the composition and size of the meal. If a meal is skipped/ missed, the rapid/fast acting bolus should also be missed; however long-acting insulin should not be skipped. This regimen offers more flexibility.

Basal + Regular Insulin: For individuals on a combination of a long-acting and regular insulin, a small carbohydrate containing snack is usually needed between major meals at the time when insulin action is peaking (depending on BG levels) to prevent hypoglycemia. Carbohydrate should be distributed throughout the day, considering peak periods of insulin action. Consistency in meals, exercise and sleep patterns are necessary in this insulin regimen.

Basal + Regular (BBF, BL) + Rapid/Fast acting insulin analogs (BD): For those on basal insulin once a day, regular insulin before breakfast and lunch, and rapid/fast acting analog before dinner, mid-morning and afternoon carbohydrate snacks may be given, but bedtime is not necessary. Prandial doses of insulin should take into account the pre-meal BG level as well as the composition and size of meals.

NPH + Regular regimen: For those using only conventional insulins - NPH and regular insulin – the regular insulin should be injected 30 min before eating, the dose being based on the pre-meal BG and the composition and size of the meal. NPH may be taken once or twice a day. Carbohydrates should be distributed throughout the day considering peak periods of regular and NPH insulin action. Matching meals to insulin peaks will prevent hypoglycemia. Consistency of meal timings and carbohydrate content, exercise and sleep patterns are necessary in these insulin regimens, giving very little flexibility (2,3,13).

Adjusting Insulin for protein and fat: Clinical guidelines now recommend additional dosing for fat and protein, particularly in meals containing more than 20 gm fat and 25-30 gm protein. Dosing must be individualized as different individuals may have different sensitivity to fat and protein, just as to carbohydrate. Protein and fat blunt the post meal glucose response, causing the BG levels to rise later and stay higher longer.

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Special diets like Low Carbohydrate or Keto Diets: Though low carbohydrate diets and ketogenic diets improve glycemic control, both may be nutritionally inadequate, can result in growth failure, increase the risk of disordered eating behaviors, and if the fat content is too high, unfavorably affect the lipid profile. These diets may be difficult to comply with in the long run as the food choices are limited. Hence, carbohydrates should not be excessively restricted (to below 40%). Most studies are in adults, and found reduced HbA1c (better glycemic control), but with risk of severe hypoglycemia. There is lack of evidence of benefits in children and adolescents.

Key Take Home Messages

- Type 1 Diabetes management calls for a Team Approach including people with diabetes, caregivers, doctor, qualified dietitian, educator and psychologist.
- Meal plans must be personalised at various stages, depending on insulin regimen, routine, activity, social events and growth phase.
- Education on carb counting, stepping up to protein and fat counting with timely follow up sessions have shown improvements in dietary freedom, glycemic control & quality of life if delivered as structured education.

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Back to School Post Covid: some FAQ

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(Talk given to T1D families)

1. Does my child with Type 1 Diabetes (T1D) need COVID vaccination? If yes, which one is preferable?

Yes, when the Government announces COVID vaccination for children, all children with T1D should receive it, exactly the same as children without diabetes. Covaxin (inactivated vaccine) has been announced as approved for use in children 2-17 years old. Other vaccines which have been found safe for children - Pfizer's vaccine (BNT162b2), Moderna vaccine (mRNA-1273) are not available in India at present. In India, ZyCov-D (painless injector used; Cadila Healthcare) has received emergency use authorization (EUA) for 12-17 year olds. The Pfizer and Moderna vaccines have been approved for use in 12-17 years olds, while the Pfizer vaccine was granted EUA by US FDA recently for children aged 5-11 years.

2. Are there any specific side effects after vaccination which a child with T1D should be concerned about?
At present, safety information with Covid vaccines in adults does not show any additional risk of hypoglycemia or hyperglycemia. Extrapolating this could mean that the vaccine is safe for children with diabetes (type 1 and 2) also. However, parents should accompany children and adolescents during vaccination, and should ensure that the meal or insulin have not been missed when they visit the vaccination center. As the vaccines approved for use in children are inactivated (killed) vaccines, there are minimal possible side-effects. However, in children with acute illnesses (like recent episode of DKA, hospitalization), the vaccination may be postponed till clinical recovery.
[Ref: Coronavirus Disease 2019 (COVID-19) Vaccination for Children: Position Statement of Indian Academy of Pediatrics Advisory Committee on Vaccination and Immunization Practices. https://www.indianpediatrics.net/COVID29.03.2020/RECOMM-00381.pdf]

3. What should we do if our friends have not taken the vaccine?
All children are encouraged to follow COVID prevention behavior always. They should encourage their friends to get vaccinated by being role models themselves, since vaccination is safe and necessary.

4. Do I need the vaccine if I/ my family suffered from COVID?
Yes, because natural infection may not offer lifetime protection against COVID, it is advisable to take the vaccine. It can be taken any time after 10-12 weeks of natural infection. As per current data, vaccination offers good immunity after single/ multiple doses, which may possibly decrease with time, underscoring the need for responsible COVID prevention behavior.

5. What precautions should we take before sending our child with T1D to school?
As a parent, it would be useful if you are aware of the school infrastructure at this time, including information about the new class the child will be going to, medical room, playground, toilets, handwash area and canteen. The child should have access to a washing area to wash hands as often as necessary. Children should be encouraged to maintain hand hygiene and practice mask hygiene. A medical room should be available to monitor children for any suspected COVID symptoms and address the needs of the child with diabetes.
If the child has any symptom of COVID, parents should not send the child to school. Likewise, if any family member develops COVID-like symptom, it is advisable to contain the spread of infection at home and send the child to school only if COVID infection has been ruled out.

6. What should we do if our child is stressed or anxious about going to school?
As parents, we have to be aware of valid concerns the child may have. The child may feel worried about joining a new class or school, joining a group of new classmates or meeting a new teacher who may not know about his/ her illness and needs. This may be intensified if the diabetes was diagnosed during the lockdown period. It is advisable that parents meet the school teachers and authorities to make them aware of the child's diabetes and request help for the child's BG monitoring, insulin dose before school snack, and befriending his/ her classmates. The child should feel supported by people around him/ her at school, not stigmatized.

7. What change in meals and exercise pattern should we be prepared for?
Children have been at home with adjustable meal and snacks timings during the lockdown. They will have to adjust to the breaktime/ lunchtime the school offers to adjust their insulin dosing and meal timing. Some students could have moved to senior classes where the schedule and duration of the classes would have changed. The schools may also modify the timetable once they resume physical classes. The school canteens may not serve open food and may instead offer packed foods, in which case parents should plan school meals with greater care. They may need to send two tiffins of low GI foods if required. The insulin dose and frequency will also require adjustment as per the school schedule.

Some schools have increased physical exercise periods; others have decreased or stopped them. Students may now have the added burden of tuitions. Many parents are still reluctant to let their children play outdoors. It is important that parents help their children (including those without diabetes) get the mandatory 60 min of exercise daily. They should adopt a participatory instead of coercive approach to inculcate healthy behaviors in their children.

For details of care of a child with Type 1 Diabetes at school, please refer to material available on the ISPAE website.
https://www.ispae.org.in/category/diabetes/
https://www.ispae.org.in/2021/03/07/before-school-starts/

Pedendoscan- Diabetes

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1. Obesity/insulin resistance

a) Hudnut-Beumler J, Kaar JL, Taylor A, Kelsey MM, Nadeau KJ, Zeitler P, et al. Development of type 2 diabetes in adolescent girls with polycystic ovary syndrome and obesity. Pediatr Diabetes. 2021 Aug;22(5):699-706. doi: 10.1111/pedi.13206.

The goal of this study was to determine the incidence and risk factors for T2D in adolescents with PCOS and obesity. Data of girls aged 11-21 years with confirmed PCOS, diagnosed between July 2013 and Aug 2018, with at least one follow-up visit, and BMI >85%ile, was reviewed, and T2D incidence (defined as HbA1c ⩾ 6.5%) calculated. A nested case-control study with 1:3 matching by race, ethnicity, and BMI was performed to determine predictors of T2D diagnosis. Four hundred ninety-three patients with PCOS (age 15.6 ± 1.9 years, BMI 36.2 ± 6.3 kg/m2) were identified, with follow-up of 1018 person-years. Twenty-three developed T2D (incidence 22.6/1000 person-years) in a median of 1.8 years (2 months - 5.5 years) after PCOS diagnosis. T2D risk was higher in girls with a prediabetes HbA1c (5.7%-6.4%) (HR 14.6 [4.8-44.5]) and among Hispanic girls with an elevated HbA1c and SGPT (HR 19.0 [3.7-97.2]) at the time of PCOS diagnosis. In the 1:3 matched cohort, T2D risk was 18.7 times higher (OR 18.66 [2.27-153.24]) for every 0.1% increase in HbA1c at the time of PCOS diagnoses. **Girls with PCOS and obesity had higher T2D incidence compared to non-PCOS youth. Hispanic girls with elevated HbA1c and SGPT were at particular risk.**

2. Diabetes pathology

a) Goldman S, Pinhas-Hamiel O, Weinberg A, Auerbach A, German A, Haim A, et al. Alarming Increase in Ketoacidosis in Children and Adolescents with Newly Diagnosed Type 1 Diabetes During the First Wave of the COVID-19 Pandemic in Israel. Pediatr Diabetes. 2021 Dec 5. doi: 10.1111/pedi.13296.

This study was planned to evaluate the incidence and severity of DKA at T1D diagnosis during the first wave of the COVID-19 pandemic in Israel. A population-based study where the frequencies of DKA and severe DKA observed during the COVID-19 period from March 15 to June 30, 2020 were compared with the same periods in 2019, 2018, and 2017, using multivariable logistic regression, adjusting for age, sex, and socioeconomic status. In 2020, DKA incidence was 58.2%, significantly higher than in 2019 and 2018 (adjusted OR [aOR] 2.18 and 2.05 respectively, P <0.005 for both); and 2017 (aOR, 1.79, P = 0.022). The incidence of severe DKA was 19.9%, significantly higher than in 2018 and 2017 (aOR, 2.49 and 2.73 respectively, P <0.05 for both). In 2020, admissions and duration of stay in the ICU were higher than in previous years (P = 0.001). During the COVID-19 pandemic, children aged 6-11 years had higher incidences of DKA (61.3% vs 34.0%, 40.6%, and 45.1%, respectively, P = 0.012), and severe DKA (29.3% vs 15.1%, 10.9%, and 5.9%, respectively, P = 0.002). **The dramatic increase in DKA at presentation of childhood-onset T1D during the COVID-19 pandemic mandates targeted measures to raise public and physician awareness.**

b) Taka AM, Härkönen T, Vähäsalo P, Lempainen J, Veijola R, Ilonen J, Knip M; Finnish Pediatric Diabetes Register. Heterogeneity in the presentation of clinical type 1 diabetes defined by the level of risk conferred by HLA class II genotypes. Pediatr Diabetes. 2021 Dec 11. doi: 10.1111/pedi.13300.

This study aimed to examine whether there are differences in the presentation of T1D depending on the HLA genotype. Children belonging to the Finnish Pediatric Diabetes Register, 0 to 14-year-old, diagnosed between January 2003 and December 2019 (N = 5798) were divided into two groups based on the T1D risk conferred by their HLA genotype (high and moderate risk genotypes, Group 1 vs. other genotypes, Group 2). Differences in clinical, metabolic and immunological characteristics were examined. Patients in Group 1 were younger at the time of diagnosis (P < 0.001) and had more frequently family members affected by T1D (P < 0.001). Diabetic ketoacidosis (DKA) was more frequent among participants in Group 2 (P = 0.014) who also had a longer duration of symptoms before diagnosis (P < 0.001) and higher HbA1c (P = 0.001) at diagnosis. The HLA genotype was not directly related to the DKA frequency. The frequency of ICA (P < 0.003), IAA (P < 0.001) and IA-2A (P < 0.001) was higher in Group 1 whereas GADA was more frequent (P < 0.001) in Group 2. Group 1 had more participants with multiple autoantibodies (P = 0.027) whereas antibody negativity was more frequent in Group 2 (P = 0.003). **The findings indicate disease heterogeneity in relation to both clinical disease presentation as well as humoral autoimmunity. This heterogeneity is, at least partly, defined by HLA class II genotypes.**

c) Ray MK, Chen L, White NH, Ni R, Hershey T, Marshall BA. Longitudinal progression of diabetes mellitus in Wolfram syndrome: the Washington University Wolfram Research Clinic experience. Pediatr Diabetes. 2021 Nov 18. doi: 10.1111/pedi.13291.

The objectives of the study were 1) to describe the progression of diabetes mellitus (DM) over time in an observational study of Wolfram syndrome, 2) to determine whether C-peptide could be used as a marker of DM progression in interventional trials for Wolfram syndrome. Forty four (25F/19M) patients with genetically-confirmed Wolfram syndrome attending the Washington University Wolfram Research Clinic annually from 2010-2019 were included. Medical history, physical examinations, blood sampling, and questionnaires were used to collect data about DM and other components of Wolfram syndrome. Beta-cell function was assessed by determination of C-peptide during a mixed meal tolerance test. Random coefficients models evaluated the rate of progression of C-peptide over time, and power analyses were used to estimate the number of subjects needed to detect a change in C-peptide decline during an intervention trial. A total of 93.2% of patients had DM. Mean HbA1c across all study visits was 7.9%. C-peptide significantly decreased with increasing duration of DM (p<0.0001); an optimal break point in C-peptide decline was identified to occur between 0.1 and 2.3 years after DM diagnosis. Twenty patients per group (active vs. control) were estimated to be needed to detect a 60% slowing of C-peptide decline during the first 2.3 years following DM diagnosis. **C-peptide declines over time in Wolfram syndrome and could potentially be used as a marker of diabetes progression in interventional studies for Wolfram syndrome, especially within the first 2 years after diabetes diagnosis.**

d) Nieto J, Castillo B, Astudillo M, Tosur M, Balasubramanyam A, Pietropaolo M, Redondo MJ. Islet autoantibody types mark differential clinical characteristics at diagnosis of pediatric type 1 diabetes. Pediatr Diabetes. 2021 Sep;22(6):882-888. doi: 10.1111/pedi.13238.

Authors aimed to study whether islet autoantibody type marks differential characteristics at the time of T1D diagnosis. Of 711 children with newly diagnosed autoimmune T1D, demographic, clinical (pubertal development, BMI percentile, diabetic ketoacidosis [DKA]) and laboratory (glucose, hemoglobin A1c [HbA1c], C-peptide, tissue transglutaminase antibodies [tTGA], thyroglobulin antibodies, and thyroid peroxidase antibodies [TPOA]) characteristics by presence/absence of autoantibodies (with titres) to insulin (IAA), GAD65 (GADA), or IA-2/ICA512 (IA-2A) were studied with multivariable analysis to adjust for potential confounders. IAA+ was statistically associated with younger age*** and lower HbA1c* while Tanner stage, GADA status and number of positive islet autoantibodies were not significant in the multivariable model. GADA+ was associated with female sex (OR = 4.0, p = 0.002) and negatively with elevated tTGA titers (>50 U/mL) (OR = 0.21, p = 0.026) but not with age, IAA status, IA-2A status, islet autoantibody number, or thyroid autoimmunity. None of the associations with IA-2A positivity was statistically significant in the multivariable analysis. In multivariable models, IAA titer was significantly associated with younger age*, DKA* and higher tTGA levels**; GADA titer with female sex*, racial minority** and TPOA positivity*; and IA-2A titer with older age** and not being African American*. [* p<0.05, **p<0.005, *** p<0.001]
Islet autoantibody type is associated with differential characteristics at diagnosis of pediatric T1D.

e) Al-Kandari H, Al-Abdulrazzaq D, Davidsson L, Nizam R, Jacob S, Melhem M, John SE, Al-Mulla F. Identification of Maturity-Onset-Diabetes of the Young (MODY) mutations in a country where diabetes is endemic. Sci Rep. 2021 Aug 9;11(1):16060.

Genetic variants responsible for MODY in Kuwait were investigated. Pathogenic mutations in GCK, HNF1A, HNF1B, HNF4A, and PDX1 were confirmed in 7 families with novel variants identified in three families in PDX1, HNF1B, and HNF1B. MLPA did not add any value to MODY variant detection rate in sequencing negative cases. **In highly selected familial autoantibody negative diabetes, known MODY genes represent a minority (22.6%) and 77.3% of the familial cases have yet to have a causal variant described.**

f) Chao LC, Vidmar AP, Georgia S. Spike in Diabetic Ketoacidosis Rates in Pediatric Type 2 Diabetes During the COVID-19 Pandemic. Diabetes Care. 2021 Jun;44(6):1451-1453.

A retrospective single center study was done between March and August 2018 to 2020 to evaluate whether the coincidence of DKA noted in adult patients with T2D is an issue for youth during the COVID-19 pandemic. **The proportion of subjects presenting with new-onset T2Ds in DKA dramatically increased in 2020 (9% in 2018, 3% in 2019, and 20% in 2020, P = 0.029).**

3. Clinical care/ technology

a) Varimo T, Pulkkinen MA, Hakonen E, Hero M, Miettinen PJ, Tuomaala AK. First year on commercial hybrid closed-loop (HCL) system - experience of 111 children and adolescents with type 1 diabetes. Pediatr Diabetes. 2021 Sep;22(6):909-915. doi: 10.1111/pedi.13235.

This study investigates the influence of HCL on glycemic control in children and adolescents with T1D in a real-life setting during the first year on HCL. This retrospective study included all the patients (n = 111) aged 3 to 16 years with T1D who initiated the HCL system between 1st December 2018 and 1st December 2019 in the Helsinki University Hospital. Time in range (TIR), HbA1c, mean sensor glucose (SG) value, time below range (TBR), and SG coefficient of variance (CV) were measured at 0, 1, 3, 6, and 12 months. The changes over time were analyzed with a repeated mixed model adjusted with baseline glycemic control. Between 0 and 12 month, TIR increased whereas mean SG values, TBR and SG CV decreased significantly (all $p < 0.001$). The changes occurred regardless of the age of the patient. **Measurements of glycemic control, except HbA1c, improved significantly after the initiation of the HCL system and the favorable effect lasted throughout the follow-up.**

b) Jalaludin MY, Deeb A, Zeitler P, Garcia R, Newfield RS, Samoilova Y, Rosario CA, Shehadeh N, Saha CK, Zhang Y, Zilli M, Scherer LW, Lam RLH, Golm GT, Engel SS, Kaufman KD, Shankar RR. Efficacy and safety of the addition of sitagliptin to treatment of youth with type 2 diabetes and inadequate glycemic control on metformin without or with insulin. Pediatr Diabetes. 2021 Nov 14. doi: 10.1111/pedi.13282.

This study is planned to assess the efficacy and safety of sitagliptin in youth with T2D inadequately controlled with metformin ± insulin. Data from two 54-week, double-blind, randomized, placebo-controlled studies of sitagliptin 100 mg daily or placebo added onto treatment of 10- to 17-year-old youth with T2D and inadequate glycemic control on metformin ± insulin was evaluated. Participants (N = 220 randomized and treated) had HbA1c 6.5% - 10% (7.0% - 10% if on insulin), were overweight/obese at screening or diagnosis and negative for pancreatic autoantibodies. The primary endpoint was change from baseline in HbA1c at week 20.Treatment groups were well balanced at baseline for mean HbA1c, BMI and age.The dose of background metformin was >1500 mg/day for 71.8% of participants; 15.0% of participants were on insulin therapy. At week 20, least squares (LS) mean changes from baseline (95%CI) in HbA1c for sitagliptin/metformin and placebo/metformin were -0.58% (-0.94, -0.22) and -0.09% (-0.43, 0.26), respectively [difference = -0.49% (-0.90, -0.09), p = 0.018] while at Week 54, changes were 0.35% (-0.48, 1.19) and 0.73% (-0.08, 1.54), respectively. **These results do not suggest that addition of sitagliptin to metformin provides durable improvement in glycemic control in youth with T2D, though it was generally well tolerated with a safety profile similar to that reported in adults.**

c) O'Connell SM, O'Toole NMA, Cronin CN, Saat-Murphy C, McElduff P, King BR, Smart CE, Shafat A. Does dietary fat cause a dose dependent glycemic response in youth with type 1 diabetes? Pediatr Diabetes. 2021 Dec;22(8):1108-1114. doi: 10.1111/pedi.13273.

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To determine the glycemic impact of dietary fat alone consumed without prandial insulin in individuals with T1D. Thirty participants with T1D (aged 8-18 years) consumed a test drink with either 20 g glucose or 1, 13, 26, 39, 51 g of fat with negligible carbohydrate/protein on 6 consecutive evenings, in a randomized order without insulin. Continuous glucose monitoring was used to measure glucose levels for 8 h postprandially. Primary outcome was mean glycemic excursion at each 30 min interval for each test condition. Generalized linear mixed models with a random effect for people with diabetes were used to test for an increase in blood glucose excursion with increasing quantity of fat. Glycemic excursions after 20 g glucose were higher than after fat drinks over the first 2 h ($p < 0.05$). Glycemic excursion for the fat drinks demonstrated a dose response, statistically significant from 4 h ($p = 0.026$), such that increasing loads of fat caused a proportionally larger increase in glycemic excursion, remaining statistically significant until 8 h ($p < 0.05$). Overall, for every 10 g fat added to the drink, glucose concentrations rose by a mean of 5 mg/dl from 330 min. **Fat ingested without other macronutrients increases glucose excursions from 4 to 8 h after ingestion, in a dose dependent manner.**

Miscellaneous : Discovery of Pancreatic Diabetes

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Silver Lining Pediatric Super Specialty Center, Kingsway Hospitals & Alexis Hospital, Nagpur

Oskar Minkowski (1858-1931) & Joseph von Mering (1849-1908)

Joseph von Mering and Oskar Minkowski were German physicians whose paths crossed accidentally in a library of Hoppe Seyler's Institute at the University of Strasbourg in the year 1889. Von Mering was working in Hoppe Seyler's Institute and Minkowski was an assistant to Professor Bernard Naunyn (then a leading authority in diabetes). They both had a discussion on Lipanin, an oil containing fatty acids, which von Mering used to treat patients suffering from digestive disturbances. Minkowski was opposed to the idea of using Lipanin. This discussion turned to whether the pancreas had a role in digestion and absorption of fats. The same evening both men decided to perform a pancreatectomy in a dog in Naunyn's laboratory. Minkowski closely observed the dog after pancreatectomy, as von Mering has to go out of town for some personal matter. Soon after the operation, the dog developed polyuria. Minkowski examined the urine and found it to have 12% sugar. Minkowski believed initially that the dog developed diabetes as he was on treatment for a long time under von Mering with phlorizin (a glucoside that could cause transient glucuresis). So he repeated the same experiment in three more dogs and found that all of them developed glycosuria. Minkowski then went a step ahead and implanted a small portion of pancreas subcutaneously in those dogs; he observed that hyperglycemia was prevented until the implant was removed or degenerated.

The Minkowski and von Mering experiment demonstrated that the pancreas was the gland whose secretions were vital for glucose homeostasis. It was this finding that paved the way for Banting and Best to conduct their experiments and discover insulin.

Compendium: Where can a T1D seek help?

Dr Anju Virmani, Senior Consultant Endocrinologist/ Diabetologist
Max, Pentamed & Rainbow Hospitals, Delhi

Presented below are some organizations which help children and adolescents with type 1 diabetes mellitus in India.

- Juvenile Diabetes Foundation, Mumbai: www.jdfmumbai.org: Clinic in Andheri west with full fledged team of doctors, dietician, counsellor, diabetes educator. Subsidized supplies 9free to needy people). Wellness Wednesdays. Contact 022- 26352752, Vaishali Vakil 9223593908, Paras 9867255558
- JDPF Ahmedabad: Savita 7016387740 (Dr Shalmi Mehta)

- Yog Dhyan Foundation (YDF), Delhi: NGO: Dr Anil Vedwal: supplies free/ subsidized diabetes supplies and tests, eye test camps, providing chakkis for T1Ds with celiac disease, twice weekly yoga classes, experienced parents teaching poorly controlled poor families.
- Friends of type 1 diabetes: Dr Ganesh Jevalikar. Telegram app group, educational meetings and sessions.
- Dr Meena Chhabra, Delhi: free insulin and tests, including POC A1c, school awareness programs, sponsoring school fees, helping with funds at time of marriage, working with YDF to provide chakkis and self-employment options.
- Association for Children with Type 1 Diabetes (ACT1D), Chandigarh: www.ACTID.com
- Diabetic Child Society (DCS), Visakhapatnam: free insulin, glucometers, strips, lancets, syringes, doctors' consultations, education, annual retinal examination. A1c once in 3 months. www.diabeticchildsociety.com Ms Usha Raju 9949211022. Dr Mythili 8912531869.
- Kudumbam: Dr Meena Mohan, Coimbatore: type 1 WA group, free insulin, subsidized tests, pumps sponsored.
- Idhayangal Charitable Trust, Coimbatore: snehaswaminathan@gmail.com, 8526421150, 9042858882, 9894948864.
- Tamil Nadu Type 1 foundation: Mr Prashanth, Ms Saranya 9962448099
- Friends Forever, Chennai: Dr Mohan's Hospital: treatment, glucometer, strips, AGP, insulin and tests. Yearly checkup including all complications; insulin pump for few children: direct funds and Hinduja Foundation; WA group, support from Mr Harsh Kohli, Mr Prashanth, Ms Lakshmi.
- Diabuddies of Karnataka: Angad + 91 8960010350
- Sweet 1 India, Bangalore: Dr Shaila Bhattacharya
- KID Benevolent Fund, Bangalore: Karnataka Institute of Endocrinology & Research, Indiranagar, Bangalore: Dr Santhosh Olety: free insulin, syringes, glucometers, strips, subsidized lab tests.
- Sweet Stars, Kerala: parents' group: raise funds and supply necessities free for needy.
- Mittayi Program, Kerala Govt: www.mittayi.org.
- More detailed list at https://www.t1dfindia.org/community
- All India: 16 Govt sponsored health insurance schemes which you should know: https://www.turtlemint.com/government-insurance-schemeses/
- Supplies from Jan Aushadi Kendras much cheaper.

'A Clue within the family'- An interesting case of diabetes in an adolescent

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Introduction

Maturity onset diabetes of the young (MODY) is a clinically heterogeneous group of monogenic disorders characterized by ß-cell dysfunction(1). It is inherited as an autosomal dominant disorder with early onset of hyperglycemia, usually before 25 years of age, with impaired insulin secretion. MODY accounts for 2 - 5% of all diabetes cases; distinguishing it from type 1 and type 2 diabetes is a diagnostic challenge(2).

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There are 14 different forms of MODY known till date, among which MODY 3 (HNF1a mutation) is the most common subtype. MODY 13 (KCNJ11 mutation) accounts for <1%. Here we are discussing a case of MODY 13 who presented with DKA during adolescence, without any history of dysglycemia during infancy; and successfully made the transition to sulphonylureas and achieved euglycemia. Although type 1 diabetes mellitus (DM) is the most common diabetes in this age group, this case, however, emphasizes the importance of considering other causes of diabetes.

Case Report

Master V, a 14.5 year old adolescent, second born to non-consanguineous parents, was born by normal delivery at term with a birth weight of 2.15 kg and had an uneventful perinatal period with no past history of hypoglycemia or hyperglycemia until 14½ years of age. He presented to the emergency department with complaints of polyuria and polydipsia for 3 days and rapid breathing for a day. He had hyperglycemia (RBS – 632 mg%, HbA1c – 13.5%), ketonuria, and severe high anion gap and metabolic acidosis (pH - 6.95 and HCO3 - 5.9 mEq/L). A clinical diagnosis of newly detected diabetes with DKA was made. The patient was started on a basal-bolus regimen with regular and NPH insulin at 0.8 U/kg/day. Over a year, his insulin requirement gradually reduced to 0.4 U/kg/day. Subsequently, he developed episodes of hypoglycemia even while receiving low doses of insulin. His HbA1c was normalized – 5.6%. Appearance of acanthosis nigricans lesions was noted with progressive weight gain – BMI rose to 21.6 kg/m2 (50th to 75th centile) from the earlier 19 kg/m2. Insulin was stopped totally and he was re-evaluated. Oral glucose tolerance test showed insulin resistance with HOMA IR of 7.7 and C-peptide 2.1ng/ml. He was started on metformin at a dose of 500mg and slowly increased to 2g/day over few weeks, as he had features suggestive of metabolic syndrome l – dyslipidemia (serum cholesterol 184.8 mg/dL, triglycerides 226.8 mg/dL, HDL 27.8 mg/dL, LDL 136.2 mg/dL), raised HOMA-IR, overweight and acanthosis nigricans.

A year later, again, he started developing hypoglycemia with metformin at a dose of 2 g/day. A detailed history revealed that both parents and maternal grandmother were diagnosed to have DM after 40 years of age. However, in view of the very low dose insulin requirement and a strong family history, a diagnosis of MODY was suspected. Genetic analysis revealed a heterozygous mutation for the KCNJ11 gene consistent with MODY 13 in both the patient and his father. Hence the patient was started on oral glibenclamide 5 mg/day (0.08 mg/kg/day) with reversal to euglycemia with good glycemic control.

Discussion

The acronym MODY was jointly used by Tattersall and Fajans in 1974, defining it as “fasting hyperglycemia”(3). It is rare in children, and includes several disorders caused by monogenic defects in β-cell function, usually misdiagnosed as type 1 or 2 diabetes(3). The prevalence of MODY in developed countries is 1-2%(3). It has been reported to be highly prevalent in Pima Indians, the Nauru population, and southern India(3). In north Europe, MODY 3 is the most common subtype followed by MODY 2, while in south India, MODY 3 is the most frequent, followed by MODY 12(4). KCNJ11 gene mutation (MODY 13) is a rare entity (prevalence < 1%) identified in 2012(5). KCNJ11 encodes the Kir6.2 subunit of the hetero-octameric KATP channel, which is highly expressed in pancreatic ß-cells. Homozygous or heterozygous mutations in this gene lead to the development of either transient or permanent neonatal diabetes within the first 6 months of life. It usually presents as neonatal diabetes; in some cases, it can present with severe intrauterine growth retardation due to reduced or absent insulin secretion in-utero. However, our patient had normal birth weight with no history suggestive of neonatal diabetes.

There have been many cases reported with KCNJ11 mutations who did not develop neonatal diabetes but developed diabetes later in life, similar to our index case(6). Bonnefond et al. identified a KCNJ11 mutation in several family members who developed diabetes in their adolescence but none had neonatal diabetes(5). The discovery of this genetic mutation and its impact on KATP channels has led to a switch in treatment from insulin to sulphonylureas. The latter acts by binding to SUR1 subunits of KATP channels and closing them via an ATP-independent mechanism. Around 95% of patients who switched to sulphonylureas were able to stop insulin successfully with good glycemic control and reduction in HbA1c(7). Sulphonylurea dose per kg required is much higher than that needed by adults with T2DM. The starting dose is 0.5 mg/kg. The transition from insulin to sulphonylureas is done according to the Hattersley protocol(8).

Differentiating MODY from type 1 and type 2 diabetes mellitus is challenging as there is no single distinguishing laboratory test and the diagnosis cannot be made solely based on family history. Molecular genetic testing is needed for diagnosis: it not only yields diagnosis but also is a guide for the clinical management of the index case and other family members. Single gene testing, such as Sanger sequencing or other methods have been largely replaced by next-generation sequencing which analyses multiple genes simultaneously at a relatively cost-effective price.

Key messages

It is important to consider a diagnosis of MODY when there is an atypical presentation of diabetes. People with KCNJ11 mutations may not present with neonatal diabetes as the age of presentation of diabetes can be highly variable. Most affected individuals can be treated with glibenclamide. All first-degree relatives of the index case should be offered genetic testing including asymptomatic individuals. Offspring of affected individuals should be monitored for neonatal diabetes from birth.

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News useful for ISPAE members

RSSDI Meetings

RSSDI Delhi Chapter has been conducting monthly online meetings, organized by President Dr Meena Chabbra, attended by for type 1 families following up with pediatric endocrinologists in government and private sectors in Delhi-NCR. In October we celebrated Dushera on the 15thwitha session themed on "Back to School- post COVID", moderated by Dr Chabbra. Dr AashimaDabas went into detail about the concerns raised about how to tackle the physical return to school after so many months of being at home and online classes, while maintaining Covid appropriate behavior. Dr Ganesh Jevalikar discussed handling diabetes in school in general, with emphasis on how to maintain glycemic control during school hours.After the detailed talks in simple Hindi, Dr Chhabra and Dr Anju Virmani moderated the open house discussion. The November session fell on WDD, and was a celebratory session with the theme – "I am special – I have T1D", in which more than 25 children, adolescents and young adults with T1D shared their experiences of how T1D made them stronger. It was an inspiring session, full of hope and strength. The December session on 19th with the theme "Volunteering – how it helps the person with T1D" will have Dr Anil Vedwal giving the NGO perspective, and Dr Sumeet Arora the doctor's perspective. Dr Bhanukiran Bhakhri will explain sick day guidelines, in view of winter coughs and colds and the looming fear of Omicron.

Centre for Monogenic Diabetes established at MDRF, Chennai

Dr. V. Mohan, Chairman, Dr. Mohan's Diabetes Specialties Centre & Director, Madras Diabetes Research Foundation, Chennai, India

A 'Centre for Monogenic Diabetes' was recently established at Madras Diabetes Research Foundation (MDRF) and Dr. Mohan's Diabetes Specialties Centre, Chennai. The term "Monogenic Diabetes' refers to a group of relatively rare forms of diabetes caused by a single gene mutation. Included under Monogenic Diabetes are various forms including Maturity Onset Diabetes of the Young (MODY) which itself has several subtypes; Neonatal diabetes, which again has several subtypes and various Genetic syndromes associated with diabetes. Apart from this, Congenital Hyperinsulinemia (CHI) is also a monogenic condition, presenting with persistent hypoglycemia rather than diabetes.

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Inauguration of 'Centre for Monogenic Diabetes'

MDRF has been working for several years on the genomics and clinical characterization of various forms of monogenic diabetes. It is an approved ICMR Center for Advanced Research (CAR) on diabetes. In order to bring about more visibility for Monogenic Diabetes in India, a Centre for Monogenic Diabetes was inaugurated at MDRF, Gopalapuram, Chennai on November 12th, 2021 in connection with World Diabetes Day 2021 by the Hon'ble Health Minister of Tamil Nadu, Sri. Ma.Subrmanian. A national registry for monogenic diabetes has also been established (www.monogenicdiabetes.in). Several members of ISPAE are already sending blood samples to MDRF for genetic screening for MODY, Neonatal Diabetes, CHI and various genetic syndromes. Those of you who are interested to collaborate in studies related to monogenic diabetes may kindly contact us.

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Websites: www.monogenicdiabetes.in; www.mdrf.in; www.drmohans.com

Academic Meetings

GROWTHCON 2021. October 5, 2021, New Delhi (Organized by Dr Ravindra Kumar, Dr Rajesh Khadgawat)

A national conference on growth disorders was organized by IAP North Delhi at New Delhi under the aegis of IAP North Delhi and ISPAE, and sponsored by Novo Nordisk. The conference program covered different aspects of growth monitoring and growth disorders, including algorithm and case-based learning for screening and management of growth disorders, growth hormone deficiency and special cases like small-for-gestational-age. The faculty included senior pediatric endocrinologists from Delhi and NCR region. Ninety delegates from across India attended and responded with positive feedback.

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1st Pediatric Pituitary Conference – 10th October 2021:
organized by Dr V Soundaram, Apollo Hospitals, Chennai

The main objective of the conference was to address practical difficulties in managing rare and complex pediatric pituitary diseases. We had 2 international faculty, 16 national faculty, and 159 participants. It was organized by Apollo Proton Cancer Center, Chennai, with support from ISPAE.

Practical management of diabetes in children – 25th November 2021:
organized by Dr V Soundaram, Apollo hospitals, Chennai

The objective of the event was to reinforce the basics of childhood diabetes, including the spectrum of etiopathogenesis, principles of treatment and monitoring, and medical nutrition therapy, to postgraduates and nurses. Hands-on workshops on continuous glucose monitoring, insulin pens and pumps were included. Faculty included 2 in-house pediatric endocrinologists and 2 registered dietitians; the 75 participants included postgraduates and nurses. It was organized by Apollo Children's hospital with sponsorship from Novo Nordisk.

Virtual CME: "Pediatric Diabetes: Basics and Beyond": for Pediatricians – 11th December 2021: organized by Dr Mounica Reddy, Rainbow Children's Hospitals, Bengaluru

As part of the Pediatric Diabetes Awareness month, recognizing the challenges faced by pediatricians in management of pediatric diabetes, Rainbow Children's Hospitals, Bengaluru organized a virtual CME for pediatricians. The objectives were to increase awareness among them about childhood diabetes, discuss best practices of management, promote early referrals, and participation in shared care. The talks were delivered by eminent national and international faculty members, and attended by about 80 pediatricians.

Dr Preeti Phatale participated as faculty in the Midterm AIAAROCON, organized by the Assam Chapter of AIAARO (All India Association for Advancing Research in Obesity). She discussed 'Evaluation of obesity in childhood and adolescence and its management'.

Patient Meetings by ISPAE Members:

World Diabetes Day Programs
"Access to Diabetes Care": Santhosh Olety Sahyanarayana, Consultant Pediatric and Adolescent Endocrinologist, Karnataka Institute of Endocrinology and Research, Bengaluru

A World Diabetes Day program was organized on 14/11/2021 at the Institute premises, attended by 52 children with T1D and their families, following all possible precautions for Covid 19. The event started with an invocation song by one of the kids, followed by group activities imparting fun and teamwork, a magic show, a mini walkathon, with ceremonial balloon release by the kids as a mark of diabetes awareness, a snack break, talks on health awareness and improving access to diabetes care by a senior diabetologist, podiatrist and retinal specialist, reiterating prevention strategies for diabetes-related long-term complications and importance of quality of life. It ended with a talent show by the kids, a healthy lunch, and vote of thanks to all participants, staff, the Nutrition department, and colleagues for the enormous support in making this a successful event.

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Dr Poorvi Agrawal, Department of Pediatrics, TNMC and BYL Nair Hospital, Mumbai in liaison with "Make a Wish" Organisation, TNMC and BYL Nair Hospital, Mumbai

The Department of Pediatrics, TNMC & BYL Nair hospital, conducted the "World Diabetes Day" celebration program for children with diabetes mellitus on 16.11.2021, liaising with "Pediatric Palliative Care" services at TNMC and "Make A Wish Foundation". It was conducted by faculty from Department of Pediatrics and volunteers from "Make a Wish". The parents were engaged in informative talks about ongoing care of children with diabetes, while addressing their concerns. The caregivers could bond with each other and gain support from each other. The children enjoyed the program by engaging in drawing and painting activities and watching a clown show. Thereafter almost 25 children were gifted with the presents they had wished for, during telephonic interaction. The wishes included gear cycles, toys, and story books.

Dr Zalak Upadhyay (Endocare Clinic for Kids), with support from Juvenile Diabetes Foundation (JDF) Rajkot, and Rotary Club Midtown, Rajkot.

On WDD: 14th November 2021, the celebration for kids with T1D had the theme "Access to Diabetes Care", and motto "Help every child with T1D". Our clinic Endocare for Kids was supported by JDF (running for the last 18 years, doing good charity work for kids with T1D), and Rotary Club Midtown, who provided the venue for the event (Rotary Diabetes Center, Lalitalaya, Rajkot: a dedicated center for treatment of diabetes). Dr Zalak Upadhyay (Pediatric Endocrinologist) gave a talk on control and monitoring in a child with diabetes; Ms Zalak Vaghasia (Dietitian and Clinical Nutritionist) discussed handling diabetes during festivals; and a Yoga expert and Ayurvedic Doctor discussed myths related to diabetes. An enjoyable magic show for kids, was followed by sharing of knowledge and experience by parents whose kids were very well controlled: to motivate all the other kids and parents. Kids were given packs of 100 glucometer strips and 1 box of needles, with the help of JDF; stationary items and snacks. The event was free to attend, publicized in local newspapers the prior day, so that all kids with T1D in Rajkot could take advantage: 42 kids and their families attended.

Dr Zalak Upadhyay delivering her talk

Children enjoying the magic show

WDD celebration and childhood diabetes awareness program "Maadhuryam 2021" - Dr Nithya T, Asst Prof & In-charge, Pediatric Endocrinology clinic, Dept of Pediatrics, Jubilee Mission Medical College, Thrissur, Kerala.

We conducted this program on Zoom platform on 16.11.21 evening, with inauguration by the chief guest, Rev. Fr. Francis Pallikunnath, Director JMMCRI. The guest speaker was Ms. Ambili A, dietitian, Taluk hospital, Kunnamkulam; her talk was followed by an interactive quiz for diabetic children and family members, and online entertainment

programs by the kids. The program was appreciated well by the 70 participants, including children with diabetes and their families, junior residents, interns, nursing staff and students.

Dr Hemchand K Prasad – Webinar for families of children with type 1 Diabetes mellitus. A webinar was held on 26/10/2021 and attended by 40 parents of children with T1D. Dr Aashima Dabas spoke on "Going back to school after COVID"; Dr Thangavelu S spoke on "Covid vaccination for children with T1D".

Dr Hemchand K Prasad, Mehta Hospital, Chennai – Support group for families of children with Prader Willi syndrome (PWS). A support group was formed for 6 families of children with PWS. A multidisciplinary clinic was conducted by Dr Kalpana G (Geneticist), Dr Venkateswaran R (Child psychiatrist), Dr Nithya Franklyn (Sleep specialist) and Dr P Balamourugane (Pediatric surgeon). Families clarified their doubts and were educated on PWS. Prof Timothy Barrett from the United Kingdom provided expert guidance to all families and the treating team.

Dr Pavithra Nagaraj, Narayana Health City, Bangalore – World Diabetes day celebrations.

WDD along with Children's day was celebrated on 14.11.2021. 21 children with newly diagnosed T1DM along with their parents and siblings were the main guests of the program. This year's theme being 'Access to diabetic care', all children with T1DM were brought together where they had a platform to share their thoughts along with an adolescent, who's been diabetic since 9 years, sharing her experience and knowledge about diabetes among the newly diagnosed which motivated the children and their parents. Carbohydrate counting was discussed by nutritionist with a quiz for the kids and the parents on nutrition. The CHIEF GUEST, Miss.Sangeetha Rajeev , an Indian singer and a Pop Icon- best International pop singer award in 2019 at Malaysia(VIMA music award) performed on the stage for the lovely kids with her amazing voice ,her super hit song "Nee Hinga Nodabyada" which not only made the kids but also every person present to move their feet.This was followed by series of performances by children with type 1 DM and concluded with lunch and gifts.

ISPAE MEETING 2021, PUNE - a report

Dr Supriya Gupte
Deenanath Mangeshkar Hospital Pune and DY Patil Medical College, Pune

ISPAE 2021 was conducted in Pune, the Oxford of the East, from 9th -13th November, 2021, the theme being "From Bedside Basics to Molecular Pediatric Endocrinology". The ISPAE PET School was conducted physically, followed by a virtual conference.

The PET school was very successfully conducted at the "Corinthians" resort between 9th -12th November, with Dr. Sarah as Convener and Dr. Ahila as Co-convener; 36 fellows, 9 national and 6 international faculty.

The virtual ISPAE 2021 conference over the next 2 days saw the active participation of 50 national and 12 international faculty; 227 registrations; and submission of 104 abstracts (96 posters and 8 oral presentations) The meeting covered a wide range of topics in pediatric endocrinology. The space required for the arrangements was graciously provided by Jehangir hospital, Pune, free of charge.

The meeting was inaugurated by Sir Cowasji Jehangir, Chairman, Jehangir Hospital, and graced by Dr Shaila Bhattacharyya, President, ISPAE and Dr Ganesh Jevalikar, Secretary cum Treasurer, ISPAE. The E-Posters were well presented by the delegates, and could be accessed on the virtual platform for the following week, thus leading to a remarkable increase in the number of views. All posters had been assessed in a deidentified manner by two judges, and the winners drawn by consensus. Oral papers were judged by senior researchers and clinicians.

Prizes for E-posters ISPAE 2021 Pune were given as below:

Joint 1st Prize

- Relationship of Height Age, Bone Age and Chronological Age in Children (2-17 years) with special reference to Nutrition and Pubertal status. Oza Chirantap, Khadilkar Vaman and Khadilkar Anuradha. (Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India.)
- Clinical characterisation of the largest Indian cohort of X linked Adrenoleukodystrophy: A single centre experience. Arun George, Sophy Korula, Praveen George Paul, Maya Mary Thomas, Sarah Mathai, Anna Simon. (Pediatric Endocrinology and Metabolism division, Christian Medical College Vellore.)

2nd Prize

A single centre experience of pediatric Cushing's disease from Western India. Chethan Y, Kunal Thackar, Rohit B, Saba S Memon, Anurag R Lila, Nalini Shah, Tushar Bandgar. (Dept of Endocrinology, KEM Hospital & Seth GS Medical College, Mumbai.)

Joint 3rd Prize

- Longitudinal growth in children with type 1 diabetes – a study from a tertiary care pediatric unit (Nikhil Lohiya, Chirantap Oza, Vivek Patwardhan and Vaman Khadilkar. (Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India.)
- Gender Specific Pediatric Reference Data for peripheral Quantitative Computed Tomography (pQCT) in Healthy Indian Children and Adolescents aged 5-18 years. Chauthmal Sujata, Kasture Sonal, Bhat Gauri, Khadilkar Anuradha. (Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India.)

A total of 8 papers were presented in the free paper session on the morning on 13th November, 2021. The prizes under the free paper category were as follows:

1st Prize

Prevalence and factors affecting Vitamin D deficiency in Indian children and adolescents: A Multicenter study. Dr. Chirantap Markand Oza. (HCJMRI, Jehangir Hospital, Pune.)

Joint 2nd Prize

1. Endocrine manifestations of paediatric craniopharyngioma – experience from a large cohort at a single centre. Dr. Praveen George Paul. (Christian Medical College, Vellore.)

AND

2. Molecular Genetics and Genotype-Phenotype Correlation in Children and Adolescents with Primary Hyperparathyroidism from A Single Centre in Western India. Dr. Anima Sharma. (Seth G.S. Medical College and K.E.M. Hospital, Mumbai.)

Joint 3rd Prize

1. Effect of BCG vaccination on immune-regulatory markers and glycemic control in children with new onset type 1 diabetes mellitus (T1DM): a randomized double blind placebo-controlled pilot trial. Dr. Alisha Babbar. (Post graduate Institute of Medical Education and Research, Chandigarh.)

AND

2. Dynamic muscle function as assessed by Jumping Mechanography in Indian children and adolescents with Type 1 diabetes mellitus: A case – control study. Ms. Sonal Kasture. (HCJMRI, Jehangir Hospital, Pune.)

The PET School team of Dr Sarah Mathai and Dr Ahila Ayyavoo had put in months of hard work to co-ordinate the sessions and make it an academic feast. The organizing committee, Dr Vaman Khadilkar, Dr Anuradha Khadilkar, and Dr Supriya Gupte worked hard over a short period of 8 months to accomplish a mammoth task, made possible with the constant support of the President Dr Shaila Bhattacharyya, Secretary Dr. Ganesh Jevalikar, and the Executive Committee and Advisors of ISPAE. The program was sponsored graciously by Novo Nordisk, Sun Pharma, Pfizer, Medtronics, Signutra, Cipla, Zuventus, Ferring, British Biologicals and Samarth Pharma. The logistics of the conference was efficiently managed by Marundeshwara Enterprises.

To conclude, it was an academic delight, well attended by delegates and faculty.

Report of ISPAE-PET Fellows' School 2021, Pune

Dr Sarah Mathai
(convener, ISPAE Fellows School 2021, Pune)

Dr Ahila Ayyavoo
(co-convener, ISPAE Fellows School 2021, Pune)

The ISPAE-PET Fellows' school was conducted as a residential program, at "The Corinthians Resort and Club, Undri, Pune", between 9th -12th November 2021, with 36 Fellows from all over India, 9 national faculty and 6 international faculty, including representatives from ESPE, APPES and ISPAD (who participated virtually). The faculty ensured that each session covered from basics to recent advances so as to benefit both the young entrants, as well as those already working in pediatric endocrinology. All the Fellows had the opportunity of presenting individual cases as well as actively participating in the group discussions. Along with academic learning, the Fellows had the opportunity of interacting and networking with their peers and faculty from institutions all over India and abroad.

The local organizing team had chosen a wonderful and serene place, with beautiful ambience conducive for learning and promoting fellowship. We had special sessions for socializing, including ice breaker sessions; even celebrations of a wedding anniversary and a bridegroom-to-be; and on the penultimate day, an evening dedicated for gala dinner and entertainment. The School concluded with a valedictory function with exciting prizes for different categories, including a quiz competition.

The planning and conduct of the Fellows' School were unique this year, in view of the government restrictions due to the Covid pandemic. Although there were many uncertainties, we thank Dr Vaman Khadilkar, Dr Supriya Gupte and the local organizing team for arranging it physically and providing excellent local hospitality. Our appreciation and gratitude to Dr Shaila Bhattacharyya, President ISPAE, Dr Ganesh Jevalikar, Secretary-Treasurer ISPAE, and the entire ISPAE Executive Council for their unwavering support to us at all times. As a team we navigated through the various challenges posed by the pandemic. We had a dedicated Faculty team who spent hours mentoring each Fellow and providing such an academic feast to make this School a grand success. It was very gratifying to have the international faculty on board, contributing immensely with their expertise for several sessions despite differences in time zones. We also thank Marundeswara Enterprises for efficiently managing the travel and logistics. Above all, we thank God Almighty for the divine protection to each of us during our journey and stay at Pune.

Overall, it was a fantastic time of learning and fellowship for fellows and faculty. The physical meeting and opportunity for interaction became particularly meaningful in the context of the prolonged lockdown worldwide. We are sure the Fellows' School 2021 will be etched in our memories for a long time.

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ISPAE PET School 2021 – Fellow's perspective

Dr Sayan Banerjee
Fellow, Regency Centre for Diabetes Endocrinology & Research, Kanpur

It was in July when an email from Dr Rakesh Kumar informed us of a physical PET School which had been finalized. Well, a post-pandemic event with its itinerary boasting of the best international and national faculty did tingle my anxious nerves the day I received the final draft, but when I sit to write the memories today the 'once in a lifetime event' has ended. Events are meant to end but memories remain, and some of them I will be narrating here.

The initial glimpse of our faculty was via emails and WhatsApp. Sarah Ma'am happened to be our first acquaintance. She was always reminding us of what was to be done and lovingly nudging us forward throughout the entire preparatory phase. Preparations being done, we were then all excited to ultimately land in Pune for the PET School. The team of Marundeshwara Enterprises helped us at every step for a smooth check in. Finally, we had reached Corinthians Club Resort, Pune, and it was a spectacle to see. The location was exhilarating to say the least.

The lunch session of Day 1 was the time we would meet the leading pediatric endocrinologists of the country for the first time. Everyone was so welcoming that barriers of fear started to break outright. Here is when I met Dr Sarah Mathai.....her calm smile and caring words still remain inscribed it my mind. The bursting sounds of heartfelt laughter then took me to Dr Ahila Ayyavoo. Then there was someone tasting every meal before it was being served to guests.....any guesses from those who attended the PET School?? Yes, right you are. It was Dr Supriya Gupte.

Oh, in the meantime the first session had already started. I hurried..... to take my seat. Relaxed I was because the session was on the utmost common 'Diabetes' but at the end I realized 'knowing' remains an endless domain. Knowledge is deep and vast as the ocean itself. This statement again proved to be correct in the next session which was on 'Adrenals'. Here I met Dr Nalini Shah and what can I narrate of that? When she spoke, I felt the effortless dance of the ocean itself. She made complex issues of Adrenals so simple that I still feel short of words to describe my state back then. The final session of the day was the 'icebreaker', and gosh, the ice literally broke into pieces. All faculty and fellows suddenly became a single team. The feeling that the PET School had achieved its initial goal of making us a single community was vibrating throughout.

The next two and a half days went through like wildfire. Literally sunrise to sunset passed through in a jiffy. Extensive sessions by Dr Vandana Jain, Dr Preeti Dabadghao, Dr Anna Simon. Dr Ahila Ayavoo, Dr Sarah Mathai, Dr Vaman Khadilkar, Dr Sudha Rao and Dr Rakesh Kumar were indeed a feast for us starting the journey of pediatric endocrinology. Now, even within this jiffy I retain certain memories which I am happy to share. “Please drop a message after you return” was the message from Dr Mathai on the day we had some free time to roam in the evening. This love and care still remain engraved when I sit to write about the PET School. She even took out time to WhatsApp us at 10.33 pm to check whether all of us had safely returned. Thank you, ma'am, for those priceless memories.

Finally, before I end how can I forget Dr Margaret Zacharin? We all saw how even at 3.45 am (local time) she would be up seeing all our presentations. This happened each and every day throughout the events of PET School. We were humbled to have someone like her gracing PET School in its entirety and teaching us so much more by her actions than we could ever learn through words.
Thank you ISPAE and the organizers of the PET school for giving us such a wonderful time. My most important takeaway would be all the wonderful people I came across and got acquainted with throughout those four days. Ending with a wish of meeting everyone very soon again.

The IDEAL program – ISPAE Diabetes Education and Learning

Dr Preeti Singh, Associate Professor
Department of Pediatrics,
Lady Hardinge Medical College, New Delhi

Dr Sirisha Kusuma
Rainbow Children's Hospital,
Hyderabad

Diabetes self-management education (DSME) is the single most important determinant of glycemic control among children and adolescents with diabetes. There is a dearth of well-trained and certified diabetes educators in India, especially for type 1 diabetes in smaller hospitals and cities. Recognizing this need, the ISPAE (2021-2022) Executive launched its flagship program in October 2021, a first of its kind dedicated certified course on diabetes education for childhood diabetes, named **"ISPAE Diabetes Education and Learning Program".**

Objective

The main objective of the IDEAL program is to provide structured diabetes educator training and create a pool of certified diabetes educators with excellent theoretical and practical knowledge in the ambulatory management of pediatric and adolescent diabetes. It envisages enhancing the core skills and competencies of health professionals/ parents working in the field of diabetes education, so that these diabetes educators can disseminate the skill and knowledge gained during this program, to effectively educate and help manage children and adolescents with diabetes, and their parents and family members. This online course is intended for healthcare professionals keen to learn and to provide diabetes education - certified nursing staff, dieticians, assistive school personnel, and a few parents of T1Ds.

Team

IDEAL has a nine-member Core Committee and a team of experienced and learned faculty from all over India with expertise in management of childhood diabetes. After long hours of brainstorming and intensive review sessions, the core committee along with the faculty team has developed a 10 module (17 sessions) comprehensive curriculum that covers both basic and advanced aspect of pediatric diabetes.

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Core Committee:
Dr Shaila Bhattacharyya
Dr Anju Virmani
Dr Aspi Irani
Dr Santhosh Olety
Ms Sheryl Salis
Dr Preeti Singh
Dr Sirisha Kusuma Boddu
ISPAE Office Bearers:
Dr Ganesh Jevalikar
Dr Rakesh Kumar
Our team of 54 faculty members hails from all over India.

Curriculum

IDEAL is a structured online training course consisting of 17 teaching sessions, 6 review sessions, and an exit exam. The two-hour-long sessions are conducted twice a week. Each session has two didactic lectures (30 minutes each) followed by an hour-long interactive and case-based discussion on the module. A pre and post-test is conducted on google forms before and after each session respectively. Practical assignments are given to the participants based on each module, to evaluate their understanding, application of knowledge and communication skills. The participants are expected to complete the entire course module, with >80% attendance, including the pre and post-test, along with the timely submission of practical assignments. The final certificate of successful completion of the course awarded only to those participants who fulfil the above requirements and exhibit reasonable competence as pediatric diabetes educators in the exit examination.

Schedule

The training of our first batch of "Pediatric Diabetes Educators" has been completed in December 2021. The first iteration of the program is very well received. Currently, we plan to take 3 batches every year, 30 candidates per batch.

Application

Applications are invited 1 month before the start of each batch via an online application form that must include a recommendation letter from the pediatrician/ pediatric endocrinologist/ endocrinologist with whom the applicant is working. The call for applicants for February 2022 batch has been announced shortly.
CONTACT Ispae.ideal@gmail.com

Pearls from Pet Fellows School and ISPAE Meeting, Pune

Dr Chirantap Oza,
Clinical and Research fellow
Hirabai Cowasji Jehangir
Medical Research Institute, Pune.

Dr Eshita Bhowmik
PDCC SR,
SGPGIMS, Lucknow

Dr. Madhura Karguppikar,
Clinical and Research Fellow
Pediatric Endocrinology,
HCJMRI, Pune

Dr Meenakshi B R, Fellow
Division of Paediatric & Adolescent Endocrinology,
Indira Gandhi Institute of Child Health

Dr Pinki Vedavanam
Kanchi Kamakoti Childs Trust Hospital
Chennai

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Childhood Diabetes

Pathogenesis:

- In addition to the already known factors implicated in type 1 diabetes (T1D) causation: Heredity (10% new cases in families with known diabetic relative), Autoimmune (ICA and GAD antibodies), Environmental (geographical variation, rising incidence, clustering), Viral etiology (? epidemics of cases, seasonal, rubella), Early introduction of cow's milk, Hygiene hypothesis, there is new hypothesis - Accelerator hypothesis.
- The 'Accelerator Hypothesis' – Type 1 and Type 2 Diabetes Mellitus are two ends of a spectrum distinguished by rate of β cell loss. The three accelerators proposed are: Intrinsic potential for rapid β cell loss, Insulin resistance, and Genetic predisposition to β-cell autoimmunity.
- The HLA locus confers approximately 50% of genetic susceptibility (high-risk DR3/4 versus protective DQA1).
- The Eisenbath model explains the pathogenesis of T1D. It suggests that everyone is born with a susceptibility to T1D.

Glycemic control and complications:

- Each 10% reduction in HbA1c is linked to 50-60% reduction in micro- albuminuria and retinopathy.
- The DCCT and EDIC trials emphasize the importance of 'Metabolic Memory' and the need for early initiation of intensive management.
- Sudden improvement in chronic poor control can lead to rapid deterioration in proliferative retinopathy
- ISPAD recommendation for sugar levels in peri-operative period is 90-180mg/dL and post-operative in ICU setting- 140-180 mg/dL.
- For patients living in remote locations, who cannot visit the healthcare provider often, mobile application for dose reminders, CGMS, bolus calculators, networking with primary healthcare provider should be encouraged.

Insulin treatment:

- Insulin Degludec and faster insulin Aspart (Fiasp) provide full 24 hours of basal bolus coverage and improve time in range (TIR) to 84%. Even after increasing the dose of dinner Fiasp, no increase in frequency of 3am hypoglycemia was noted. Long-acting analogues reduce macrovascular complications by reducing post prandial hyperglycemia.
- Although post-meal dosing cannot be recommended, for patients who may need it, Fiasp may be considered. It is particularly useful for subjects with unpredictable appetite.
- Intensive insulin treatment not only protects against microvascular complications, it gives better long-term protection against all complications due to 'metabolic memory'.
- Comparing rapid-acting analogs with regular insulin, these analogs produce a small but significant reduction in A1c (0.1%). They may also reduce macro-vascular risk by reducing post-prandial hyperglycemia. Long-acting analogs cause less nocturnal hypoglycemia than NPH. Quality of life tends to be better with analogs. However, they cost several times more than conventional insulins.

Neonatal DM (NDM) and non-type 1 DM:

- Neonatal diabetes is a rare disorder. Our understanding has improved regarding pathophysiology and management due to advent of newer genetic diagnostics. Genetic testing is crucial to diagnosis and must be sent even for preterm patients. The range of mutations of NDM vary based on consanguinity. With increasing age of presentation, the likelihood of Permanent NDM and DKA is higher. KCNJ11 mutations are likely to present as DKA.
- Transient NDM: 80% have positive genetic tests. Underlying genetic alterations are paternal uniparental disomy of chromosome 6, paternal duplication of 6q24 or abnormal methylation at 6q24. 50-60% of TNDM relapse.
- TNDM: without differences in phenotype, the mechanism correlates with the inheritance pattern. Disomy – sporadic, Duplication – inherited (children of males are 50% at risk), Methylation may be sporadic or inherited.
  MODY: newer genes are being identified constantly. Mutations can broadly be categorised as the glucokinase group (GCK mutations) and the transcription factor group (HNF-1a, HNF-1b, HNF-4[a]) for prognostication. Broadly, the GCK mutation group has onset at birth, stable hyperglycemia, needs just diet treatment;

complications rare. On the other hand, the transcription factor mutation group has onset in adolescents or young adults, progressive hyperglycemia, and frequent complications; 1/3 need diet control, 1/3 oral drugs, and 1/3 insulin to control hyperglycemia.

- NPH may offer better glycemic control in NDM in comparison to a basal bolus regimen. Normal saline may be used as a diluent for using smaller doses of insulin in infants.
- The IL2RA mutation can present with NDM with immune dysregulation.
- In NDM, HbA1c monitoring is less useful due to presence of high HbF. Fructosamine is the better alternative.

About 50-60% of TNDM patients relapse, at an average age 14y. Treatment for relapsers in a UK study was: 40% diet control and oral drugs, 60% insulin. Successful treatment with OHA raises the question of possible similarity with T2DM and possible role of insulin resistance in pathogenesis.

Newer advances:

- The Medtronic 640G sensor augmented pump (SAP) has a 'Smartguard' function which predicts hypoglycemia 30 min in advance and automatically stops insulin delivery (Predictive Low Glucose Suspend or PLGS), and restarts insulin delivery when glucose levels improve, as well as a 'stop bolus' feature.
- The new MinimedTM 780G has autocorrect every 5 min, with the aim of maintaining TIR >70%. It is safe to use in children aged ⩾7 years. Children less than 15 years achieved the following targets:

  Mean 6.8% GMI- 75% achieve GMI <7%
  Mean 74% TIR- 70% achieve >70% TIR - Time in Range
  Mean 3.2% TBR- 72% achieve <4% TBR - Time below Range

  These achievements were sustained over a 6 months observation period.
- Insulin pump therapy is the most physiological way of insulin replacement. Concerns regarding use of PLGS in India include multiple calibrations, lack of support for education, and high cost. Alarms should be set for when suspensions should occur. If hypoglycemia alert occurs when the patient is awake, carbohydrates may be consumed despite insulin suspension. SAP therapy is superior to MDI + SMBG in reducing HbA1c without increasing risk of hypoglycemia. Low glucose suspends (LGS) reduce severity and duration of hypoglycemia without impacting HbA1c levels.
- The modern approach to medical nutrition therapy includes dosing as per the child's intake at that meal, enabling flexible meal timing and meal composition, rather than compulsive and presumptive eating schedules. It has greater relevance if using CSII. However, the key factors for successful glycemic control using CSII remain carbohydrate counting, consistency (not accuracy), disciplined meal schedules, and awareness of fat and protein composition of common foods.
- Continuous Glucose Monitoring System (CGMS) is particularly required for recurrent DKA, recurrent hypoglycemia, wide fluctuations and variations in SMBG and HbA1c. The CGMS devices available in India are Medtronics and Abbott: LibrePro and and the recently released Libre. CGMS measures glucose concentration in interstitial fluid: lag between blood and interstitial levels must be kept in mind.

Miscellaneous:

- Taxonomic and functional differences exist in gut microbiome of children with T1D. Small chain fatty acids are a must to maintain intestinal barrier and immune homeostasis. Early exposure to probiotics may reduce islet cell autoimmunity, and is a potential low-cost low-risk treatment for children with T1D.

Puberty

Delayed Puberty:

- Family/ twin studies show that 60–80% of timing of onset of puberty is genetically determined.
- Kisspeptin receptors are present in the testis/ ovary and pituitary.
- Difference between constitutional delay of growth and puberty (CDGP) and hypogonadotrophic hypogonadism (HH) can be challenging, though Kisspeptin test can help differentiate the two conditions:

Feature	Self-limited form	Permanent HH
Growth	Retarded	Normal
Bone age	Retarded	Normal
Pubic hair	Absent	Present
Testicular volume	Up to 3ml	<1ml
Post GnRHa FSH	>5IU/L	<1.1IU/L
Post GnRHa LH	>5IU/L	<1IU/L
Inhibin B	>50pg/ml	<50pg/ml
Basal testosterone	>20ng/dl	<20ng/dl
HCG stimulated testosterone	>200ng/dl	<200ng/dl

- Early diagnosis of Turner Syndrome (TS) and starting treatment with GH therapy at age 4-6 years is required for better prognosis. Start low dose E2 at 11-12 years with GH therapy for optimal final height outcomes.
- About 4% girls with TS have spontaneous menses. Inhibin B can help predict entrance into puberty.
- Factors predictive of healthy follicles in TS: Normal FSH, AMH, spontaneous puberty and menarche.
- In anorchia, start HRT at age 12-13 year, either with low dose IM Testosterone (T) enanthate or T gel if available. Later change to IM T 100- 250 mg monthly until epiphyses fuse, and then switch to long-acting T undecanoate 1000 mg/ 3 months.
- Most XXY individuals proceed normally through puberty; first presentation is in late adolescence or adulthood. Testosterone may be required in case of pubertal arrest, increasing gynecomastia or unusual eunuchoid proportions.
- Patients exposed to testicular radiation are unlikely to enter puberty spontaneously. Puberty should be induced at age 13 years, and continued to adulthood.
- Those receiving total body irradiation (TBI) have a 50% chance of entering puberty and/or continuing without pubertal arrest. One can wait a bit longer if bone age allows; if puberty started spontaneously, replacement can start at a higher dose.
- Those treated with high dose alkylating agents may have Leydig cell damage, and usually do not present until adulthood (30 years).
- The cause of HH is a valuable predictor of outcome of gonadotropin replacement in adults. Kallman syndrome and congenital multiple pituitary hormone deficiency (MPHD) have the poorest induction outcomes, compared to acquired HH or pubertal arrest.
- Hormone replacement therapy (HRT) in males: For primary hypogonadism: Testosterone (T) replacement at peer appropriate age. Long-acting T should be avoided until epiphyseal fusion, and should be used for long term management. Watch for rising Hb, T levels in adults. For secondary (central) hypogonadism, pubertal induction with hCG/ FSH and sperm storage at end of puberty are needed. Maintenance is with T, and re-induction done when fertility is desired. Consider rapid induction prior to gonadotoxic treatment e.g., bone marrow transplant.
- HRT in females: TS: Estradiol valerate is the preferred option, starting with a low dose of 0.5mg, gradually increasing to 2 mg/ day over 2.5-3 years, with addition of progestogen at the end of this time. Always use continuous estrogen to prevent bone loss. E2 patch is more physiological and has less adverse effects, if available. After chemotherapy: Start HRT if puberty is delayed or arrested, and for late gonadal failure. The starting dose will depend upon the pubertal status at the time of failure. There is possibility of incomplete failure: raised FSH may allow ovulation at any age, but recovery is unpredictable. Change to long cycles of oral contraceptives in these patients when sexually active. After radiation: HRT should be started when there is evidence of failure of growth spurt, pubertal arrest, or raised FSH/ LH. The starting dose will depend on the stage of arrest. For galactosemia patients, transdermal E2 patch s preferable, as there is lactose in E2 tablets.

- Secondary hypogonadism in females: Chronic disease: E2 fuses epiphyses, so careful assessment and intervention is mandatory to obtain the best possible final height. It is important to choose the window of opportunity when steroid requirements are minimal/ absent and the disease is quiescent. The patient should be taken through puberty completely, then replacement can be stop and it's need reassessed later. In Cerebral palsy (CP) / neuromuscular conditions: many cannot maintain long term hypothalamic-pituitary-gonadal function, so long term replacement is needed for bone health. Transfusion iron overload: Start HRT if growth failure is severe at age 12 years, because sufficient ovarian function exists to fuse epiphyses even without producing feminization or the growth spurt. Do not wait for transfusion effects or correction of anemia to start HRT.
- In a non-verbal child with CP, puberty is the most likely cause for moodiness and distress. Puberty is often very slow, this may need no treatment but it is needed for bone mass accrual and reduction of fracture risk. In case of early puberty, a little height may be lost, but that is not an issue requiring intervention, so GnRH agonists may not be indicated. Progesterone containing IUDs can be used, but only when the uterine cavity is 7+ cm. Most importantly, hysterectomy is never indicated.

Precocious puberty

- Mutation in KISS1, KISS1R and MKRN3 are identified genetic causes of CPP
- MKRN3 is known to affect pubertal timing in patients of PWS, mutation causes withdrawal of hypothalamic inhibition and prompts pulsatile GnRH release
- MKRN3 defects represents the most frequent known genetic cause of Familial CPP
- Progestogen bearing IUD can be inserted under GA only when Uterus reaches adult configuration of 7cm+
- Ovarian cyst/Maccune Albright Syndrome in girls and CAH in boys are the most common cause of GIPP. MAS and testotoxicosis are most challenging GIPP to manage.
- Management of peripheral precocious puberty – Bicalutamide and Anastrozole in MAS boys with Gondotrophin Independent Precocious Puberty, 21OH Deficiency- Glucocorticoid and Mineralocorticoid replacement, Leydig cell adenoma- excision, Adrenal Cortical Cancer- excision + chemotherapy/mitotane, HCG secreting tumor- excision + Radiotherapy/ chemotherapy.
- For hypothalamic hamartoma surgery is indicated ONLY if associated with progressive, severe complex partial epilepsy and surgery usually does NOT alter course of CPP.
- For peripheral precocity in girls, SERM are better treatment modalities than aromatase inhibitor.

More Learning Pearls in CAPE News April 2022 issue !

ACES on PCOS and adolescent menstrual disorders - September 2021

Prof Dr Mahesh Maheshwari, In charge Pediatric Endocrinology, AIIMS Bhopal

Dr. Shantala J from IGICH Bengaluru presented a case of Obesity with polycystic Ovarian Syndrome under the Guidance of Prof. Dr. Preeti Dabadgaho from SGPGI. Another interesting case Puberty Menorrhagia was presented by Dr. Rehana salam from GKNM Coimbatore under the guidance of Dr. Archana D. Arya, SGRH New Delhi. Expert talks were delivered by Dr. Usha Shiram from Chennai on Polycystic Ovarian Syndrome and Dr. Selma Feldman Witchel from Pittsburgh USA on Adolescent Menstrual Disorders respectively.

Polycystic Ovarian Syndrome

- PCOS is a diagnosis of exclusion and present lot of challenges.
- PCOS has strong association with COVID 19.
- Prevalence of PCOS in Indian adolescent ranges from 9.13% - 22.5 %.
- PCOS should be considered in any adolescent girl with hirsutism, treatment resistant Acne, Menstrual irregularities, obesity, Acanthosis Nigricans.

- International consensus diagnostic criteria should be followed.
- Congenital Predisposition and Postnatal provocative hits play the role in etiology.
- Modified F-G and Ludwig score should be used for hirsutism and alopecia.
- Pelvic USG should not be used for diagnosis with a Gynaecological age of less than 8 years.
- Lifestyle modification, Metformin and OCPs play important role in therapy.
- Anti-androgens can be used in resistant/ non responder cases with pinch of side effects.

Adolescent Menstrual Disorders

- Important to understand what is normal or abnormal Menstruation.
- Endocrine, haematological, Thyroid disorders, Medications are important cause.
- Non hormone treatment –NSAIDS, Tanexamic acid
- Progestin only treatment is better in heavy menstrual bleeding.

ACES on Endocrine issues in cancer survivors - October 2021

Dr Parvathy Lalitha
Aster Medcity, Kochi

Dr. Ankitha Srivatsava from Aster Hospital presented a case of MPHD under the Guidance of Prof. Rajesh Khadgawat from AIIMS, New Delhi. Another interesting case Primary ovarian insufficiency was presented by Dr. Manjunath D from KEM Mumbai under the guidance of Dr Pinaki Dutta, PGI. Expert talks were delivered by Dr Laurie E Cohen and Dr Charles Sklar on Growth hormone therapy in Childhood Cancer Survivors (CCS) and Endocrine outcomes in Childhood Cancer Survivors (CCS).

- Growth Hormone Deficiency (GHD) is the most common anterior pituitary hormone deficiency in CCS.
- GHD results from – Hypothalamo-pituitary(HP) tumor, HP axis radiation therapy > 18 Gy, Single Total Body Iradiation dose of 10 Gy/fractionated doses of 12 Gy.
- GHD after cranial RT is dose and time dependent.
- GH neurosecretory dysfunction is seen in lower dose cranial RT due to lower absolute GH peak even if they pass the GH stimulation test.
- IGF-1 is useful as a screening tool,but not to be used solely in diagnosis of GHD in CCS.
- GHST is challenging due to lack of standardisation of diagnostic tests,cut-off values,GH assay variation,obesity etc.
- Formal GHST is not required if there are three other confirmed anterior pituitary hormone deficiencies.
- In several meta-analysis,no tumour recurrence were noted after GH therapy, also there weren't any increase in secondary neoplasms.
- In children & adults treated with GH in craniopharyngioma,there was no increased risk of recurrence in case-control studies.
- In Noonan syndrome with no prior malignancy,there is no increased risk for malignancy with GH treatment.
- A minimum 1 year disease free period following completion of therapy for malignant disease is recommended to initiate GH therapy.
- In children who had spinal radiation, final height may not reach MPH even with GH therapy.
- Five year survival rate of most childhood cancers has gone up from around 65% to over 80% from 1975-2009.
- Burden of chronic health conditions increases as survivors age, based on CCS study,at 30 years from diagnosis around 40% survivors experience at least one chronic health condition.
- As per CCS study, around 44% of survivors developed an endocrine complication at a median age of 26 years from cancer diagnosis.
- Independent risk factors for late effects: Age – Neurocognitive effects were more common in yonger age group; Gender – Females were more affected than males especially in attaining precocious puberty.

- Tumour location-Tumours in hypothalamo-pituitary region had more endocrine effects; Other health conditions; Lifestyle – Physical activity, Smoking.
- Fertility problems more commonly seen with use of high dose alkylating agents like cyclophosphamide and busulfan.
- Radiation induced abnormalities are dose and time-dependent.
- POI was more common when radiation dose was more than 10-15Gy, cyclophosphamide equivalent dose > 8 gm/m2, pelvic radiation with any dose of cyclophosphamide.
- Risk for hypothalamo-pituitary dysfunction was higher when radiation dose is more than 18 Gy for GHD and Precocious puberty,more than 30 Gy for Gonadotropin,TSH and ACTH deficiency,more than 40 Gy for hyperprolactinemia.
- In the Dutch study looking at endocrine effects of surgery,chemoradiation in brain tumours in first 5 years: GHD > Precocious puberty > TSH deficiency > LH/FSH deficiency > ACTH deficiency > ADH deficiency.
- With hypothalamo-pituitary radiation less than 20 Gy there is less chance of GHD, around 50-70% develop GHD within 5 years at radiation dose 30-40 Gy.

Learning pearls from PEP

Dr Amarnath Kulkarni*, *Senior Consultant Paediatric & Adolescent Endocrinologist
DNB Paediatrics Academic Coordinator- Lotus Children's Hospital, Hyderabad

- Most common cause of rickets in childhood is nutritional calcium and Vitamin D deficiency.
- Level 1 investigations for diagnosis includes Calcium, Phosphorus and alkaline phosphatase.
- Calcium and phosphorus may be normal in stage 1 and 2 of rickets, both are reduced only in stage 3 of rickets.
- Hypophosphatemia is the major pathology behind development of rickets.
- Level 2 investigations are RFT, LFT, VBG , 25 hydroxy & 1, 25 dihydroxy Vitamin D, PTH.
- Level 3 investigations include Fractional excretion of phosphorus, bicarbonate, USG KUB and genetic studies.
- Pointers to non nutritional rickets are non-response to standard treatment, polyuria, failure to thrive, family history of rickets, pathological fracture, anemia, hypertension, alopecia, normal vitamin D levels.
- Treatment is always a two pronged attack with Calcium and Vitamin D.
- In nutritional rickets, Phosphorus normalises in a week followed by calcium, the healing line appears in 4-8 weeks.
- Alkaline phosphatase & PTH normalisation takes time, 3-12 months and 3-6 months respectively.
- Measure midparental height in all short children.
- Rule out physiological (familial & constitutional) systemic causes, malnutrition, malabsorption before going for endocrine or syndromic causes of short stature where dysmorphism is not obvious.
- Sex steroid priming should be done in all Puberty age group patients before GH stimulation tests.
- Greulich Pyle atlas should be used bed side for bone age estimation in advanced centres Bone expert computerized application can be used.
- Systemic causes of short stature ruled out when excess weight gain is presenting complaint.
- Longterm ACTH injections given in infantile spasm can lead to short stature.
- Neonatal history of jaundice, hypoglycemic seizures & small Genitalia should be taken for neonatal onset of GH deficiency.
- Assessment of chronological age, weight age, height age and bone age and its arrangement gives valuable clue to the underlying diagnosis.
- The new pediatrician friendly growth chart obviates the need to calculate target height.
- The new BMI look up tool can be used from 8 years.
- Height should be recorded to the nearest 0.1 cm.
- Soto syndrome are caused due to NSD-1 mutation (nuclear receptor SET domain containing protein 1).

- History and clinical examination is very important in guiding the diagnosis.
- Proper growth chart recording in every health care encounter is important and parents can be counseled record and maintain it even at home.
- Systematic approach and planned investigations are important. We should not jump on to some fancy tests. The basic 1st line investigations are the one which will guide us to the proper direction.
- Nutritional counselling is very important part. Malnutrition is an important preventable cause of majority of diseases and health problems
- We should keep our observation and thought process wide so that we will not miss out many causes or comorbidities so we will not miss out any common but important cause..

Pediatric Endocrinology for Postgraduates (PEP) VIRTUAL
Under the auspices of ISPAE
Exclusively for DNB / MD Pediatrics or DCH Postgraduates
(Held once in 3 months)
28th Jan-2022: 5-7pm. Topic: Pediatric Diabetes

Time	Topic	Speaker	Time slot
5.00	Introduction	Prof Shaila Bhattacharyya, President ISPAE	2 min
5.02	PEP	Prof Raghupathy P, Patron, ISPAE	3 min
5.05	Case 1- DKA Lecture 1- Recent Advances in DKA Management	Postgraduate Dr Anurag Bajpai	10 min presentation 10 min DKA case discussion; 20 min lecture
5.45	Lecture 2- Ambulatory Management of T1DM	Dr Ahila Ayyavoo	10 min discussion of case followed by 20 min lecture
6.10	OSCE Pediatric Diabetes & metabolic Syndrome	Dr Riaz I	Interactive session Q in chat box & A: 30 min
6.45	How to answer Theory Questions- CGM, newer Insulins	Dr Amarnath Kulkarni	Outline & division of marks 10 min
6.55	Vote of thanks	Dr Amarnath Kulkarni	5 min

Guide: MD or DNB examiner; Co-guide: Pediatric Endocrinologist (Optional).

Candidates ready to appear for final exam preferred. Certificate from HOD ESSENTIAL.
Instructions for Case presentation: Prepare PPT 10 – 12 slides with clear messages, clinical photos (if any), investigations and short, crisp discussion.
PPT slides for presentation to be sent on or before 15th January 2022 to:
dramarnathkulkarni@gmail.com & drp.raghupathy@gmail.com

PEP ISPAE Virtual 4 (Next Meeting): 8th April 2022: 5-7pm
Topics – 1. Delayed Puberty - Turner Syndrome 2. CAH
Note: Please share this message with all DNB / MD Ped / DCH trainees.

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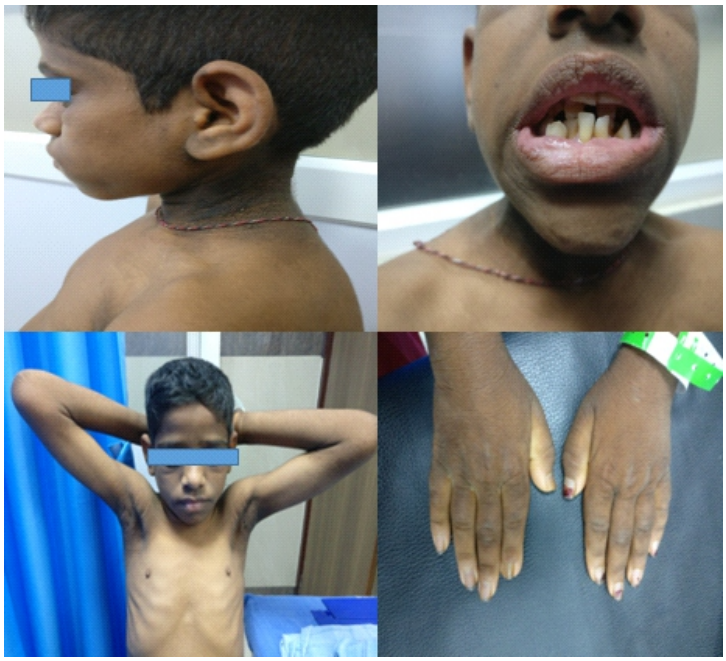
Pictorial case based questions.

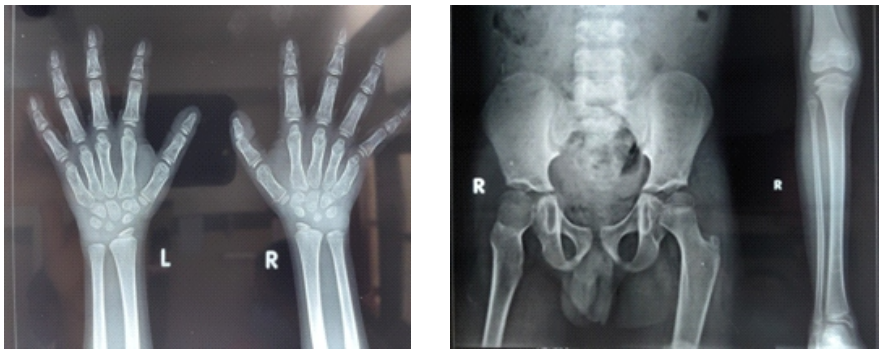
Dr. Diksha Shirodkar, Assistant Professor and Pediatric Endocrinologist
Yenepoya medical college, Yenepoya university

1. A 19 year old adolescent boy presented with short stature (-6SD), hyperglycemia (venous blood glucose 695 mg/dl,HbA1c 18), and extensive hyperpigmentation involving the nape of neck, axilla and groin.



Diagnose the condition and the possible incriminating gene involved.

2. A six year old boy presented with short stature(-3SD), long standing diabetes mellitus (infancy-onset), two episodes of acute liver failure and acute kidney injury requiring hospitalization and attention deficit hyperactivity disorder on Methylphenidate. He also had a femoral fracture at the age of 4 years following a trivial injury. His Roentgenograms are as follows;



Diagnose the condition and the possible incriminating gene involved.

Image courtesy: Dr. Diksha Shirodkar, Department of Pediatric Yenepoya Medical College.
Written informed consent taken from the guardian/patient for the above clinical pictures.

Please send your response to editor.capenews@gmail.com .
Correct entries will be acknowledged in the next issue.

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CAPE News | ISPAE

Double Puzzle – Trainee's Quiz Section

Dr Diksha Shirodkar, Assistant Professor (Pediatrics) and Pediatric Endocrinologist
Yenepoya Medical College and Hospital, Mangalore, Karnataka

Welcome all, to yet another exciting quiz on the thyroid gland. Unjumble the words using the clues given below. Discover the phrase at the end using the numbers.

Clues

1. Pseudohypertrophy of the calf muscles in long standing hypothyroidism.
2. The gene responsible for deiodination using iodotyrosine dehalogenase of DIT and MIT to allow recycling of the iodide.
3. The important micronutrient present in deiodinases.
4. NKX2-1 mutations cause _____ syndrome?
5. This organ has Type 3 iodothyronine monodeiodinase enzymes which degrade T4 to reverse T3 and T3 to 3,3' T2.
6. The most common type of thyroid carcinoma in children.
7. The most important protein useful in outlining the management of differentiated thyroid carcinoma.
8. Hung up reflex is also called as _____ sign.
9. A syndrome of Sensorineural hearing loss and hypothyroidism.
10. An autosomal dominant disorder mostly seen in Hispanic individuals where Free T4 values are normal and total T4 values are high.
11. An X-linked syndrome of severe psychomotor retardation, extrapyramidal signs and seizures combined with mild abnormalities of thyroid function (high T3, low T4, and normal or high TSH).
12. A syndrome of severe long standing hypothyroidism leading to a increased gonadotropin secretion, triggering gonadal activity and hence precocious puberty.
13. The effect wherein excess iodine acutely inhibit organic binding of iodine and thus creates a hypothyroid state.
14. Iodide-induced hyperthyroidism (Low TSH, Low Radioactive iodine uptake).
15. An unusual and old form of exogenous thyrotoxicosis causes by consumption of bovine thyroid in ground beef preparations.
16. What is the sign called when an individual with retrosternal goiter raises his arms leading to facial congestion, respiratory distress and syncope?
17. Classification for cytopathology of thyroid nodule.
18. Large visceral hemangiomas or tumors in infants can cause _____ hypothyroidism.
19. The mutation in this gene causes toxic diffuse thyroid hyperplasia without the pathologic characteristics of autoimmune disease and can have an autosomal dominant inheritance.
20. An X-linked disorder (sometimes associated with colour blindness) resulting in the deficiency of a protein where Free T4 values are normal but Total T4 values are low.

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Winners Of the Obesogenic Hunt: Congratulations!

1. ***Dr Aaradhana, Associate Professor, Dept of Pediatrics***
   UCMS & GTBH, Delhi.

Answers to the double puzzle

Part 1

1. KOCHER DEBRE SEMELAIGNE
2. DEHAL1
3. SELENIUM
4. BRAIN LUNG THYROID
5. PLACENTA
6. PAPILLARY
7. THYROGLOBULIN
8. WOLTMAN
9. PENDRED
10. FAMILIAL DYSALBUMINEMIC HYPERTHYROXINEMIA
11. ALLAN HERNDON DUDLEY
12. VAN WYK GRUMBACH
13. WOLFF CHAIKOFF
14. JOD BASEDOW
15. HAMBURGER HYPERTHYROIDISM
16. PEMBERTON
17. BETHESDA
18. CONSUMPTIVE
19. TSHR
20. THYROXINE BINDING GLOBULIN

Part 2

THE OMNIPOTENT GLAND