MARCH 2022
Volume 26, Issue 1

CAPE News

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

CONTENTS

Theme: Diabetes - Part 2

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

From the Editorial Board

Dr Anju Virmani
Advisor

Dr Hemchand K Prasad
Editor

Dr Ravindra Kumar
Editorial board

Dr Pragya Mangla
Editorial board

Dr Aashima Dabas
Editorial board

Dr Diksha Shirodkar
Editorial board

Dr Nikhil Lohiya
Editorial board

Dear ISPAE members,

It gives our team great pleasure to connect with all of you through this issue of CAPE News: Diabetes II. We have many interesting articles, mini reviews and case reports pertaining to childhood diabetes; as well as reports of members' activities, and useful information pertaining to pediatric endocrinology.

With our IDEAL trainees joining the ISPAE family, we are happy to start a section in CAPE News for our newly minted but experienced diabetic educators. We invite contributions in the area of diabetes education, for this section, in our future issues.

As always, we look forward to contributions and suggestions from all members for future issues.

Thank You and Regards,
Team CAPE News 2021-22

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Office Bearers' Message

Dear ISPAE members,

Greetings from Team ISPAE 2021-22!

As we seem to be finally emerging out of the shadows of the COVID pandemic, we are excited at the prospects of meeting all of you in-person in the year 2022.

The year started with the postponement of PEDICON 2022, the 59th annual meeting of IAP, thanks to the Omicron wave. However, it was finally held in a physical format at Noida, UP, and was highly successful. The team led by Prof Vijayakumar deserves special congratulations for formulating and conducting Endocrinology TOTs at very short notice. A special note to thanks to Dr Remesh Kumar, President IAP, for taking a keen interest in carrying pediatric endocrinology training forward.

Dr Shaila Bhattacharyya
President
ISPAE 2021-22

Dr Ganesh Jevalikar
Secretary cum Treasurer
ISPAE 2021-22

Dr Rakesh Kumar
Joint Secretary
ISPAE 2021-22

While we continue with the ISPAE IDEAL program, we have also started another course "ISPAE BEST" (Basic Education Series in Type 1 Diabetes) meant to train people with type 1 diabetes, their family members, and all the interested health care and allied personnel. The first batch of almost 50 students will start with this course from the month of April 2022.

We would welcome more ideas to make our tenure more engaging and happening. More helping hands to volunteer are always welcome. So, do contribute to the growth of your Society in any form that your busy practice or schedule permits you to.

Please continue reporting all your academic and charitable activities to CAPE News, and contribute articles to CAPE News as well as JPED (Journal of Pediatric Endocrinology and Diabetes).

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

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Welcome to new ISPAE members

- Dr Amit Bang, Consultant Pediatrician, Indore.
- Ms Ayesha Pendhari, Clinical Dietician, Kolar, Karnataka.
- Ms Rachana Dalal, Dietician, Surat, Gujarat.
- Dr Shivangi Sidana, Diabetes Educator & homeopathic physician, Ferozepur, Punjab.
- Dr Jyotsna Padmanabhan, Pediatrician, Manipal Hospital, Bengaluru.
- Ms Syeda Atiba Nousheen, Dietitian and Diabetes Educator, Aster CMI hospital, Tumkur, Karnataka.
- Mr Lakshminarayana Varimadugu, Diabetes Educator, Sweet Souls Foundation, Hyderabad.
- Ms Zankhana Doshi, Diabetes Educator, Fortis Hospital, Mulund, Mumbai.
- Ms Vasavi Pandi, Dietician, Mangalagiri, AP.
- Dr Amit Kumar, Assistant Professor, Indira Gandhi Institute of Medical Sciences, Patna.
- Ms Sukhvir Kaur, Senior Nursing Officer, Kalawati Saran Children's Hospital, New Delhi.
- Ms Idamary Immanuel, Nurse Educator, Christian Medical College, Vellore.
- Ms Khushboo Kumari, Pediatric Dietician, AIIMS, New Delhi.
- Ms Marthal K, Nurse Educator, Christian Medical College, Vellore.
- Ms Karthik Nimmaturi, Diabetes Educator, Hyderabad.
- Ms Beenu Singh, Diabetes Educator, Bengaluru.
- Ms Fareesa Fatima, Registered Dietician, Fernandez Foundation, Hyderabad.
- Ms Kosha Parikh, Diabetes Educator and Dietitian, Bhaktivedanta Hospital, Thane.
- Ms Rogini Arunindrakumar, T1D parent & phonetic teacher, Ambattur, Chennai.
- Ms Sudeepta Rath, Diabetes Educator, Max Healthcare, Saket, New Delhi.
- Dr Poonam Joshi, Principal, College of Nursing, AIIMS, Kalyani, Bengal.
- Ms Chhavi Gupta, Volunteer, Yog Dhyan Foundation, New Delhi.
- Ms Shruthi R, Dietician and Diabetes Educator, Karnataka Institute of Endocrinology and Research, Bengaluru.
- Ms Gunjan Jain, Diabetes Educator, Sanofi, Delhi.
- Dr Rimesh Pal, Assistant Professor, Department of Endocrinology, PGIMER, Chandigarh.
- Dr Saji Kumar, Pediatrician, NIMS, Thiruvananthapuram, Kerala.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Review of Recent Guidelines Diabetes in Children and Adolescents (Part-2): Standards of Medical Care in Diabetes - 2021

Dr. Ravindra Kumar, I/C Pediatric & Adolescent Endocrinology
North DMC Medical College & Hindu Rao Hospital, Delhi

TYPE 2 DM

- Risk-based screening for prediabetes and/or type 2 diabetes (T2D) should be considered in children and adolescents after the onset of puberty or ⩾ 10 years of age, whichever occurs earlier, with overweight or obesity, and one or more additional risk factors for diabetes.
- If tests are normal, repeat testing at a minimum of 3-year intervals, or more frequently if BMI is increasing.
- Children and adolescents with overweight or obesity in whom the diagnosis of T2D is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of auto-immune T1D.
- Home self-monitoring of BG (SMBG) regimens should be individualized and glycemic status should be assessed every 3 months.
- In incidentally diagnosed or metabolically stable patients (A1C <8.5% and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal.
- Youth with symptoms of diabetes and marked hyperglycemia (blood glucose ⩾ 250 mg/dL, A1C ⩾ 8.5%) without acidosis at diagnosis, should be treated initially with basal insulin while metformin is initiated and titrated.
- In patients with ketosis/ ketoacidosis, treat as per DKA protocol. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued.
- In individuals presenting with severe hyperglycemia (blood glucose ⩾ 600 mg/dL), consider assessment for hyperglycemic hyperosmolar nonketotic syndrome.
- If glycemic targets are no longer met with metformin (with or without basal insulin), liraglutide (GLP1 receptor agonist) therapy should be considered in children 10 years of age or older if they have no past medical history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.
- Patients treated with basal insulin who do not meet glycemic targets, should be moved to multiple daily injections with basal and premeal bolus insulins.
- In patients initially treated with insulin and metformin, who are meeting BG targets based on SMBG, insulin can be tapered over 2–6 weeks by decreasing the dose by 10–30% every few days.
- UACR should be obtained at diagnosis and annually thereafter. An elevated UACR (> 30mg/g creatinine) should be confirmed in two of three samples.
- Estimated GFR should be determined at diagnosis and annually thereafter.
- In nonpregnant patients with diabetes and hypertension, either an ACE inhibitor or an ARB is recommended for those with modestly elevated UACR (30–299 mg/g creatinine) and strongly recommended for those with UACR >300mg/g creatinine and/or estimated GFR < 60 mL/min/1.73 m2.
- Screening for neuropathy should be done by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflex tests.
- Screening for retinopathy should be performed by dilated fundoscopy or retinal photography at or soon after diagnosis and annually thereafter.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

- Evaluation for nonalcoholic fatty liver disease (by measuring AST and ALT) should be done at diagnosis and annually thereafter.
- Screening for symptoms of sleep apnea should be done at each visit.
- Evaluate for polycystic ovary syndrome in female adolescents with T2D, including laboratory studies when indicated.
- Evaluation and management of hypertension and dyslipidemia are the same as in T1D.
- Pediatric diabetes care providers should begin to prepare youth for transition to adult health care in early adolescence and, at the latest, at least 1 year before the transition.

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

Update on Management of Diabetic Ketoacidosis, BSPED 2020

Dr Aashima Dabas, Associate Professor, Department of Pediatrics
Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi

Diabetic keto-acidosis (DKA) is a common complication in children with Type 1 Diabetes (T1D). Key critical issues which are endorsed during management of DKA include choice of fluid, rate and volume of fluid administration, and dose of insulin infusion. At present, there is no uniform consensus across different guidelines for these recommendations, though all guidelines concur on the need of an intensive clinical and biochemical monitoring, to prevent cerebral edema and achieve resolution of ketosis and acidosis.

The initial British Society for Paediatric Endocrinology and Diabetes (BSPED) guideline on DKA had proposed liberal fluid volume administration, unlike the ISPAD and NICE guidelines which recommended more conservative fluid administration. However, in light of emerging evidence from clinical trials, notably the Pediatric Emergency Care Applied Research Network (PECARN) DKA Fluid trial, which showed that the sodium content of administered intravenous fluid did not contribute significantly to neurological outcomes in children, the BSPED guidelines were revised. The following table briefly summarizes the Update in BSPED Guidelines 2020.

Focus area	BSPED 2020 Guidelines
Diagnose DKA	Mild (venous pH: 7.2–7.29 or bicarbonate: <15 mmol/L) = 5% dehydration. Moderate (venous pH: 7.1–7.19 or bicarbonate: <10 mmol/L) = 7% dehydration. Severe (venous pH: <7.1 or bicarbonate: <5 mmol/L) = 10% dehydration.
Choice of fluid	Normal saline 0.9% for dehydration correction.
IVF bolus	If child in shock, bolus of 0.9% NaCl at 20 ml/kg over 15 min. Do not subtract fluid volume from total IVF volume. If child is dehydrated but not in shock, bolus of 0.9% NaCl at 10 ml/kg over 60 min
Amount of fluids	Total Fluid = Deficit plus Maintenance Deficit as per dehydration status: 5/7/10% Maintenance for 24h needs to be calculated as per Holiday Segar Formula (maximum weight of the child as 80 kg): · 100 mL/kg/day for first 10 kg · 50 mL/kg for the next 10 kg (11–20 kg body weight). · 20 mL/kg for each subsequent kilogram (>20 kg body weight). · When calculating the total fluid replacement, subtract any initial bolus volumes from the total fluid deficit (unless the patient is in shock).

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Use of potassium	Add 40 mmol/L potassium chloride to all fluids (apart from the initial intravenous bolus). Add only if patient does not have anuria or hyperkalemia. Can start this before the insulin infusion if hypokalemia seen at presentation.
Insulin rate	Start at 0.05 units/kg/hour or 0.1 units/kg/hour, 1–2 hours after intravenous fluids have been commenced. A higher rate of 0.1 U/kg/hour may be used in severe DKA or in an adolescent or in unresolved ketosis. Continuous subcutaneous insulin infusion (CSII i.e. insulin pump) to be disconnected and stopped during intravenous insulin infusion. Basal long-acting subcutaneous insulin may be continued after discussion.
Dextrose in IVF	Dextrose to be added to 0.9% NS when blood glucose below 250 mg/dL (14 mmol/L)

Reference:

- *Rugg-Gunn CEM, Deakin M, Hawcutt DB. Update and harmonisation of guidance for the management of diabetic ketoacidosis in children and young people in the UK. BMJ Paediatrics Open 2021;5:e001079.*
- *Heddy N. Guideline for the management of children and young people under the age of 18 years with diabetic ketoacidosis (British Society for Paediatric Endocrinology and Diabetes). Arch Dis Child Educ Pract Ed. 2021;106(4):220-222.*

MINI REVIEWS

Fibrocalculous pancreatic diabetes

Diksha Shirodkar[1], Gautham Pai[2]

[1]Assistant Professor of Pediatrics and Pediatric Endocrinologist;
[2]Assistant Professor of Pediatrics and Pediatric Gastroenterologist;
Yenepoya Medical College, Mangalore, Karnataka, India.

Introduction

Diabetes due to chronic pancreatitis (non-alcoholic type) in children and adolescents is referred to as type 3c diabetes, as per the classification of the American Diabetes Association. This peculiar form of chronic pancreatitis and the diabetes resulting from it, is called tropical calcific pancreatitis (TCP) and fibrocalculous diabetes (FCPD) respectively. This is an extremely rare cause of diabetes[1] (less than 1% of all cases of diabetes across the world). There are meagre studies describing the incidence of FCPD in children. TCP was first mentioned by Zuidema in 1959 from Indonesia[2], and later seen in tropical Asia, Africa and India (more so in Kerala and Tamil Nadu). Geevarghese et al[3] described the largest group of patients with FCPD from Kerala. FCPD as a proportion of diabetes is declining, likely due to rapid socioeconomic development and improving nutritional status. In a large study of patients with chronic pancreatitis in children from North India[4], about 88% had an unknown etiology, half of them (47%) had chronic calcific pancreatitis, of whom three (6.3%) had diabetes. Whether this calcification and diabetes are related to severity and chronicity of the disease, or whether these patients of idiopathic chronic calcific pancreatitis is a separate entity altogether, is a matter of debate.

Etiology[5,6]

The exact etiology remains unclear. However, the following theories are postulated:

- The Cassava theory: Cassava (tapioca) is a staple which contains lotaustralin and linamarin (cyanogenic compounds) that accumulate in the non-detoxified form in cases of protein malnutrition. This causes cyanide-mediated injury to the exocrine pancreatic tissue. Because non-tropical countries and non-cassava consuming populations also have developed FCPD, this theory isn't definite (extended spectrum of FCPD).
- The Genetic theory: The incriminating gene studied extensively is SPINK (serine protease inhibitor Kazal) type 1. This gene encodes a protein called pancreatic secretory trypsin inhibitor that prevents damage to the pancreas from prematurely activated trypsinogen by cleaving it into inactive metabolites. Defective function or deficiency of this protein lead to recurrent pancreatitis. Other genes implicated include cathepsin B and cationic trypsinogen gene (PRSS1), of which the latter has been notorious in causing hereditary pancreatitis. Overall, the

two-hit hypothesis stands as the explanation by several authors, where the initial brunt maybe due to inappropriate inactivation of trypsinogen (secondary to mutations in PRSS1), along with defects in SPINK1 (and other unidentified genes).

Clinical Picture

It is seen classically as a triad of abdominal pain, steatorrhea and diabetes, each having a heterogenous presentation during different stages of the disease. In the initial stage (usually in the first decade of life), a peculiar abdominal pain (severe, located over the epigastrium with radiation to the back, and often precipitated by fatty foods) exists. Subsequently, features of exocrine pancreatic insufficiency surface, the most prominent symptom being steatorrhea. Finally (which usually develops in early adulthood - but seen in adolescence as well), hyperglycemia crops up, starting with a pre-diabetic stage and landing up with the overt stage. The time span from TCP to overt diabetes is roughly 5 years. FCPD is a brittle form of diabetes (usually ketosis-resistant), with high glycemic variability and unpredictable hypoglycemia.

Reasons for this ketosis-resistant diabetes[7] include

a. Sufficient insulin reserves to prevent lipolysis and subsequent ketone body formation, as the amount of insulin required to prevent lipolysis is much lesser than that needed to maintain euglycemia.

b. Deficiency of the substrate needed for ketone body synthesis, i.e., free fatty acids, due to low levels of subcutaneous fat consequent to long-standing fat malabsorption.

c. Glucagon deficiency which is pivotal in ketogenesis.

d. Deficiency of Carnitine, an important fatty acid transporter that shifts fatty acids into the mitochondria for beta-oxidation.

e. Some authors also believe there is some amount of increased insulin resistance in such individuals.

Diagnosis

Plain X-ray of the abdomen is a simple yet effective modality which will reveal the presence of the pancreatic calculi crossing the midline at the level of the first lumbar vertebra (Fig 1). Ultrasonogram/ Computerized Tomography (CT) scan of the abdomen will show atrophy of the pancreas, associated with pancreatic duct dilatation. These findings are associated with parenchymal calcification and intraductal calculi (Fig 2, a and b). Further imaging like MRCP (magnetic resonance cholangiopancreatography) and ERCP (endoscopic retrograde cholangiopancreatography) may be required for etiological work-up. Laboratory investigations include Blood glucose fasting and 2hr after a glucose load (OGTT), HbA1c, C-peptide (they are low but not absent like in T1D) and a fasting lipid profile. Assessment of exocrine pancreatic function is most easily carried out by measurement of fecal elastase assays. Serum amylase and lipase levels are usually normal unless the patient is seen during an episode of acute (on chronic) pancreatitis.

Diagnostic criteria for FCPD8

1. Patient from a tropical country
2. Presence of diabetes
3. Evidence of chronic pancreatitis: demonstration of pancreatic calculi on abdominal imaging or at least three of the following:
   a. Abnormal pancreatic morphology on ultrasound or CT scan of the abdomen
   b. History of recurrent abdominal pain since childhood
   c. Steatorrhea
   d. Abnormal pancreatic function tests
4. Absence of other causes of chronic pancreatitis (e.g., alcohol abuse).

Complications

1. Patients with FCPD usually have severe, early onset difficult-to-control diabetes with long term micro and macro-vascular complications.

2. Malnutrition due to malabsorption of fat, Vitamin A, D, E and K deficiency, and essential fatty acid deficiency are common.
3. The most dreaded complication is pancreatic adenocarcinoma.

Management[9]

The aim is to alleviate the symptoms and provide the best glycemic control.

1.Glycemic Control

Insulin therapy is the cornerstone of glycemic management of FCPD, especially in adolescents. A multi-dose basal-bolus regimen, using insulin analogs wherever feasible, is the most practical option as it controls the hyperglycemic peaks and prevents hypoglycemia. To pick up such variability in blood glucose it is best recommended to use continuous glucose monitoring system.

2. Nutrition Support - Pancreatic enzyme replacement therapy (PERT) reduces abdominal pain (PERT inhibits endogenous pancreatic secretion, thereby reducing the intraductal pressure and pain), and improves steatorrhea and nutritional status. Supplementation of fat-soluble vitamins and providing a well-balanced diet by judicious calculation of carbohydrates is a must.

3. Endoscopic therapy and/ or surgery - to reduce the intraductal pressure and hence the pain.

4. Management of pain due to chronic pancreatitis.

Conclusion

FCPD is caused by yet unknown environmental influences on a background of genetic susceptibility. Although infrequently seen in recent times, this type of diabetes should be thought of when an adolescent presents with diabetes and history of abdominal pain, growth failure, and steatorrhea. Individuals with new onset diabetes and history of abdominal pain or steatorrhea should be advised formal imaging of the pancreas to rule out FCPD. Management not only includes strict glycemic control, but also very difficult to devise Medical Nutrition Therapy.

References:

1.Hardt PD, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? Diabetes Care. 2008;31(Suppl 2):S165–9.
2. Zuidema PJ. Cirrhosis and disseminated calcification of the pancreas in patients with malnutrition. Trop Geog Med. 1959;11:70–4.
3. Geevarghese PJ. Pancreatic diabetes. Bombay: Popular Prakashan. 1968;110–115.
4. Poddar U, Yachha SK, Borkar V, Srivastava A, Kumar S. A Report of 320 Cases of Childhood Pancreatitis: Increasing Incidence, Etiologic Categorization, Dynamics, Severity Assessment, and Outcome. Pancreas. 2017 Jan;46(1):110-115.
5. McMillan DE, Geevarghese PJ. Dietary cyanide and tropical malnutrition diabetes. Diabetes Care. 1979;2:202–8.
6. Kolly A Shivaprasad C, Pulikkal AA, Atluri S, Sarathi V, Dwarakanath CS. High prevalence of serine protease inhibitor Kazal type 1 gene variations detected by whole gene sequencing in patients with fibrocalculous pancreatic diabetes. Indian J Endocrinol Metab. 2017;21:510–4.
7. Unnikrishnan R, Mohan V. Fibrocalculous pancreatic diabetes (FCPD). Acta Diabetol. 2015;52:1–9.
8. Mohan V, Mohan R, Susheela L, Snehalatha C, Bharani G, Mahajan VK, et al. Tropical pancreatic diabetes in South India: heterogeneity in clinical and biochemical profile. Diabetologia.1985;28:229–32.)
9. Unnikrishnan, R, Mohan, V. Fibrocalculous Pancreatic Diabetes. Curr Diab Rep 20, 19 (2020). https://doi.org/10.1007/s11892-020-01303-1.

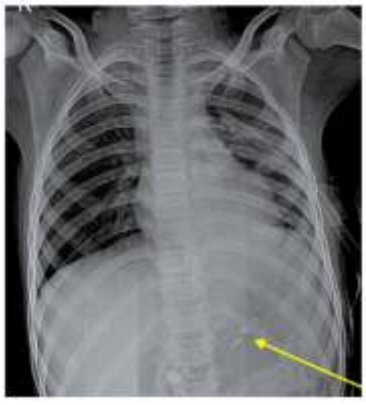


Fig 1: Plain X-ray of the abdomen in a patient with chronic pancreatitis demonstrating pancreatic calculi (yellow arrow)

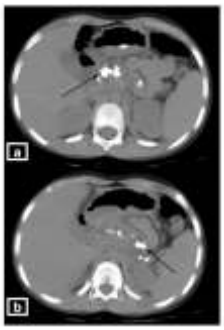


Fig 2 (a) and (b): Axial non-contrast computed tomography sections showing coarse calcific foci in the pancreatic parenchyma and intraductal calculi (black arrows) with atrophy of the pancreatic parenchyma, consistent with a diagnosis of chronic calcific pancreatitis.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

The Not-So-Sweet Sugar!

The following points are summarized by Dr Aashima Dabas, from a talk by Dr Arun Wadhwa at an event organized by the Non-Communicable Diseases Prevention Academy (NCDPA), IAP.

Dr Arun Wadhwa, Pediatrician South Delhi & Visiting Consultant
Rainbow Children's Hospital, New Delhi

Know your sugar!

- Raw sugar is sucrose, which is extracted from sugarcane or sugar beet, but retains some natural nutrients like iron, magnesium, etc. Less processed forms like Khand and Jaggery also contain some iron, calcium and magnesium.
- Refined or white sugar is made by refining raw sugar by removing the molasses.
- Honey has fructose and some glucose. Its glycemic index is lower than that of sugar.

Sugar alcohols or polyols, e.g., sorbitol, xylitol, mannitol, erythritol and lactilol, are carbohydrates with a biochemical structure partially matching the structures of sugar and alcohol, although not containing ethanol. They are less sweet, have half to two-thirds of the calories, and raise blood glucose slowly, as they are converted to glucose slowly.

	High Sugar content	Medium Sugar Content	Low sugar content
Food products (per 100 gm)	>22.5 gm	5-22.5 gm	5 gm or less
Drinks (per 100 mL)	> 11.25 gm	2.5-11.25 gm	2.5 gm or less

Some foods contain sugar, though not in the raw form ("hidden sugar"), e.g., dried fruits, milk, lactose free milks, highly refined carbohydrates such as white rice, white bread, biscuits and pasta, commercial sweetened and low-fat yogurts, packaged soups, fruit juices (including freshly prepared juices), vitamin drinks and sports drinks, canned fruits, ketchups and sauces, and protein bars (sugar content similar to candy bars).

Artificial sweeteners

Artificial sweeteners are zero- or low-calorie sugar substitutes which may be derived from plant extracts or produced by chemical synthesis, used in various foods and drinks (e.g. Diet Coke or Coke Zero).

A. Sugar alcohols - are derived from sugars.
B. Sucralose - a chlorinated sugar about 600 times sweeter than sugar: the most commonly used agent.
C. Aspartame - Unsuitable for use in baking.
D. Acesulfame potassium (Ace-K) is 200 times sweeter than sugar. Like saccharin, it has a slightly bitter after-taste, especially at high concentrations, but is stable on heating.
E. Stevia leaves – Zero-calorie sweetener, widely used in South America for centuries, and in Japan as an extract since 1970; now popular in many countries.
F. Mogrosides (glycoside of cucurbitane derivatives), extracted from monk fruit and commonly called luo han guo, are recognized as safe for human consumption.

Diabetic retinopathy in children

Dr Aaradhana, Associate Professor, Department of Pediatrics
UCMS & GTBH, Delhi

Diabetic retinopathy (DR) is a progressive, potentially sight threatening disease of the retinal neuro-vasculature associated with diabetes. It develops due to chronic hyperglycemia which causes damage to the retinal capillaries, leading to capillary blockage and leakage. Diabetic retinopathy is asymptomatic until advanced stages, and if

undiagnosed and untreated, can progress to severe visual loss. Globally, it is the leading cause of blindness among the working age population (age 16-64 years) and the commonest complication of type 1 diabetes mellitus (T1D). The prevalence of both T1D and type 2 diabetes mellitus (T2D) is increasing, which may lead to increased prevalence of DR. Three strategies to minimize the risk of visual loss due to DR include (1) treatment of the underlying metabolic disorder and its comorbidities effectively; (2) development of optimal treatment modalities for DR; and (3) identifying DR at the latent stage by effective screening programs and identifying risk factors for the development of DR.

Prevalence of DR: Prevalence of DR is variable, as reported in several studies. This variability is due to differences in study populations, such as type of diabetes, age, setting (community or hospital setting), methods of detecting DR (fundus photography, ophthalmoscopy, slit lamp examination) and grading protocols used. In a study by Yau, et al. the global prevalence of DR was 34.6% from a pooled analysis of 22,896 individuals with diabetes [1]. The International Diabetes Federation (IDF) Atlas 9th edition reported any DR to be 27.0%, non-proliferative DR (NPDR) 25.2%, proliferative DR (PDR) 1.4% and diabetic macular edema (DME) 4.6% between 2015 and 2019 [2]. Table 1 summarizes the prevalence of DR in children in various studies globally as well as in India.

Table 1: Studies on diabetic retinopathy in children and adolescents

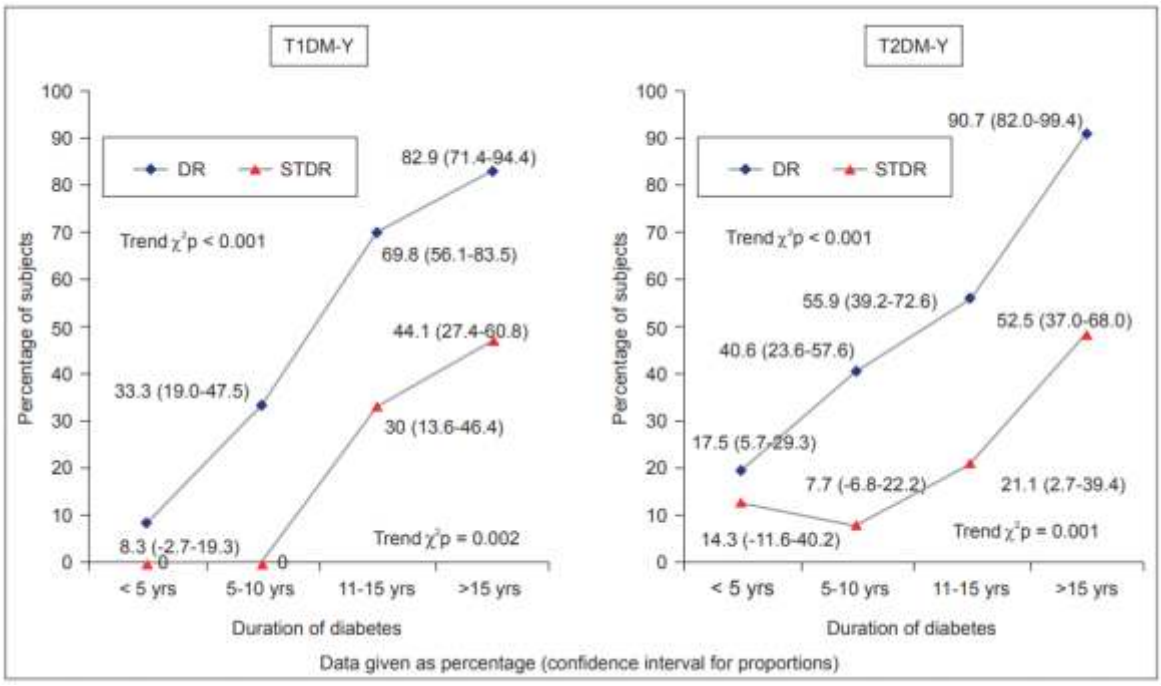
Study	Year & place	Type of DM	No. of patients	Type of study	Method for retinal examination	Prevalence of retinopathy (%)
National Paediatric Diabetes Audit (NPDA) [3]	2018/19 UK	T1DM	28597	Population based	Fundus photography	13.1 (13.4 in England, 7.6 in Wales)
Diabetic retinopathy assessment for type 1 diabetes (DRAFT) study [4]	Chennai, India 2019	T1DM	315	Diabetic Clinic based	Fundus photography	Any DR-37.1 STDR-13.3
Jansson et al. [5]	Norway, 2018	T1DM	237	Population based	Fundus photography	DR 61 PDR 13
Young Diabetes Registry (YDR), Rajalakshmi et al. [6]	Chennai, India 2013	T1DM	150	Diabetic Clinic based	Fundus photography	DR 53.3 PDR 7.3
SEARCH, Pilot Mayer Davis et al. [7]	USA 2012	T1DM	222	Population based	Fundus photography	17
Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [8]	1996 Wisconsin, USA,	T1DM	996	Population based	Fundus photography	10-14 years - 2% 15-19 years- 10%.
Ruhayel SD et al. [9]	Australia 2010	T2DM	33	Clinic based	Fundus photography	25 (any DR)
Type 2 Diabetes in Adolescents and Youth (TODAY) study [10]	US 2013	T2DM	507	Clinic based	Fundus photography	13.7
Eppens et al. [11]	Australia 2006	T1DM T2DM	1433 68	Clinic based	Fundus photography	20 4
SEARCH, Dablea et al. [12]	USA, 2017	T1DM T2DM	1746 1327	Population based	Fundus photography	5.6 9.1
Young diab study [13]	Chennai, India 2017	T1DM T2DM	108 90	Clinic based	Fundus photography	77.4/1000 78.0/1000 person years

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

T1D vs T2D (youth onset -YO-T2D) is associated with higher rates of risk factors and complications than T1D [11-13]. These studies compared participants of comparable age with T1D and YO-T2D. Despite those with T1D having longer duration of diabetes, the YO-T2D group had higher rates of complications. This may be due to late presentation, difficulties in accepting the condition, which leads to poorer control of glycemia, and poor compliance to medication and lifestyle changes in T2D. Figure shows the prevalence DR in T1D and T2D in an Indian Study [13]. This study shows higher prevalence of DR in T2D as compared to T1D even though the duration of diabetes and age at diagnosis were comparable in both study groups.

Figure: Any diabetic retinopathy (DR) and sight threatening diabetic retinopathy (STDR) by duration of disease in people with type 1 diabetes mellitus of young onset (T1DM-Y) type 2 diabetes mellitus of young onset (T2DM-Y)



Pathophysiology of DR- Till recently, DR was considered just a microvascular disease, with the earliest sign being microaneurysms consequent to pericyte loss. However, neurodegenerative changes precede the vascular manifestations of DR. Hyperglycemia causes dysfunction in glial cells, seen as early as retinal inflammatory response in DR. Chronic hyperglycemia in diabetics leads to increased production of superoxide in the mitochondria. This oxidative stress causes upregulation of inflammatory mediators and several growth factors including VEGF causing changes in the retinal capillaries.

Table 2: Risk factors of Diabetic Retinopathy in children and adolescents

Unmodifiable	Modifiable (proven evidence)	Modifiable (variable evidence)
Duration of disease	Hyperglycemia	Dyslipidemia
Type of diabetes	Hypertension	Nephropathy
Pregnancy		Anemia
Puberty (for T1D)		Smoking
		High salt intake
		Glitazone drugs

Duration of diabetes has been shown in many studies to be a risk factor for the development of DR, with the early Wisconsin study showing that 2% of those with a duration of diabetes less than 2 years had DR, increasing to 98% after 15 years [8].
Hyperglycemia has long been associated with an increased risk of developing DR. In the NPDA, young people with T1D and higher HbA1c had an increased risk of abnormal eye screening [3].
Hypertension has also been shown to be a risk factor for DR. In the NPDA, amongst the cohort of young people aged 12 years and above with T1D and an abnormal eye screening result, 61.5% had above average systolic blood pressure, and 93.7% had above average diastolic blood pressure [3]. The audit also showed that high blood pressure (above 98 centile), high cholesterol (above 5mmol/mol), high HbA1c and obesity, were more prevalent in people with abnormal DR screening compared to those without.
Dyslipidemia has less consistent effect on DR. The DCCT study showed that the severity of retinopathy was associated with increasing triglycerides and inversely associated with HDL cholesterol [14]. However, meta-analysis by Yau et al [1] showed that higher cholesterol levels were associated with a higher prevalence of diabetic macular edema but not diabetic retinopathy.
WESDR showed that duration of diabetes after menarche was associated with 30% increased risk of DR compared with duration of diabetes before menarche [8].

Diagnosis of DR -

Clinical examination of the retina is the mainstay in the diagnosis of DR. It includes undilated anterior segment slit lamp examination to examine the iris and angle for rubeosis, and dilated retinal examination using slit lamp bio microscopy, and/or indirect ophthalmoscopy.
Color fundus photography has been established as a standard in screening and as adjunct to clinical examination, to document findings to assess changes at follow-up.
Ultrasound is useful to assess the configuration of the vitreous and retina, particularly if the media are not clear i.e., in the presence of cataract or vitreous hemorrhage.
Optical coherence tomography (OCT) is a non-invasive, quick, cross-sectional imaging tool and has almost replaced fundus fluorescein angiography as the standard of care in DR.
Fundus fluorescein angiography (FFA) provides information on the vascular competency of retinal and choroidal vessels, including at the macula. OCT combined with FFA is called OCT angiography (OCTA). Table 3 shows the International Classification of Diabetic Retinopathy and Diabetic Macular Edema [15].

Table 3: International Classification of Diabetic Retinopathy and Diabetic Macular Edema

Diabetic retinopathy	**Findings by clinical examination (dilated ophthalmoscopy)**
No apparent DR	No abnormalities
Mild non-proliferative DR	Microaneurysms only.
Moderate non-proliferative DR	Microaneurysms with other signs (e.g., dot and blot hemorrhages, hard exudates, cotton wool spots), but less severe than non-proliferative DR.
Severe (high-risk) non-proliferative DR	Moderate non-proliferative DR with any of the following: • intraretinal hemorrhages (20 in each quadrant). • definite venous beading (in 2 quadrants). • intraretinal microvascular abnormalities (IRMA) (in one quadrant). • no signs of proliferative retinopathy.
Proliferative DR	Signs of severe non-proliferative DR, with one or more of the following: • neovascularisation on the optic disc (NVD) and/or elsewhere (NVE). • vitreous/preretinal hemorrhage
Diabetic macular edema (DME)	**Findings by clinical examination**
No DME apparent	No retinal thickening or hard exudates in the macula
Non-central involving DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter
Central involving DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Treatment of DR: Various treatment options for DR include: pan-retinal laser photocoagulation (PRP) commonly known as "laser therapy,", anti- vascular endothelial growth factor (anti-VEGF) and vitrectomy. Which treatment is recommended for an individual patient is influenced by several factors, but principally their ability to comply with the frequent and long-term follow up required for Anti-VEGF agents.

PRP consists of multiple discrete outer retinal burns throughout the mid and far peripheral area but sparing the central macula. However, photocoagulation is not indicated for eyes with mild or moderate non-proliferative retinopathy. Side effects of treatment are decreased night and peripheral vision and subtle changes in color perception. Complications of laser therapy are vitreous and choroidal hemorrhages or visual sequelae of misplaced burns.

Anti-VEGF for PDR, intravitreal injection of anti-VEGF (ranibizumab, aflibercept, bevacizumab) is now increasingly used and shows better results for visual acuity than PRP. This treatment is not destructive but does require repeated visits and injections for efficacy and carries the rare risk of ocular infection. intravitreal steroids are also used at some centers.

Vitrectomy is indicated for persistent vitreous hemorrhage, tractional retinal detachment, or extensive fibrosis.

Screening for DR - Children and adolescents with diabetes are rarely screened for DR. Although STDR is rare in this age group, changes of DR do occur in them. Early recognition may allow modification of some of the risk factors and slow down the progression of DR thus avoiding vision loss at an early age. Direct ophthalmoscopy has low levels of sensitivity and specificity for screening. Retinal digital photography (imaging) using validated imaging systems is recommended for screening as it has high levels of sensitivity and specificity and provides documentary evidence. Several smartphone applications have been developed as effective and accessible techniques for DR detection. An exciting recent development is the potential for automated image analysis/artificial enabled DR screening. Table 4 shows various guidelines for the screening of DR in children.

Table 4: Screening recommendations for diabetic retinopathy in type 1 diabetes by major medical association

Guideline	Age at screening	Frequency	Method
ISPAD 2018 [16]	from the age of 11 with 2-5y diabetes duration	Annual	Fundal photography/ mydriatic ophthalmoscopy
American Academy of Pediatrics [17]	3–5y after diagnosis of diabetes if over age 9y	Annual	Mydriatic ophthalmoscopy
American Academy of Ophthalmology [18]	3-5y after diagnosis	Annual	Mydriatic ophthalmoscopy
American Diabetes Association [19]	3–5y after diagnosis of diabetes and once the child is 10y old	Biennial	Fundus photography
National Institute for Clinical Excellence (NICE) [20]	from 12y onwards	Annual	-
Canadian Diabetes Association	5y after diagnosis in all from the age of 15y	Biennial	-
Retinopathy Working Party	from the onset of puberty	Annual	-

Prevention of DR: Primary and secondary prevention of DR may be done by strict glycemic and blood pressure control. The efficacy of providing intensive treatment of the underlying metabolic disorder was evaluated by the Diabetes Control and Complications Trial (DCCT) in which every 10% decline in HbA1c reduced the risk of DR by 39%. The benefits were maintained 10 years later, with hazard reductions of 53%–56% for progression of DR, and to proliferative DR or worse [19].

Take home messages

- Prevalence of DR in children screened is substantially higher than that previously reported and remains a significant concern in diabetes.
- Diabetic retinopathy is higher in YO-T2D as compared to T1D.
- Increased awareness regarding DR screening among treating physicians is essential to identify DR early on, so

that steps may be taken to slow the progression and/or treat it early.

- Good glycemic and blood pressure control are the cornerstones of prevention of onset as well as progression of DR.

References:

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012 Mar 1;35(3):556-64

2. Thomas RL, Halim S, Gurudas S, Sivaprasad S, Owens DR. IDF Diabetes Atlas: A review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. Diabetes Research and Clinical Practice. 2019 Nov 1;157:107840.

3. Royal College of Paediatrics and Child Health: National Paediatric Diabetes Audit Report 2018/19 https://wwwrcpchacuk/sites/default/files/2020-03/final_npda_core_report_2018-2019pdf 2019.

4. Rajalakshmi R, Shanthirani CS, Anandakumar A, Anjana RM, Murthy GV, Gilbert C, et al. Assessment of diabetic retinopathy in type 1 diabetes in a diabetes care center in South India—Feasibility and awareness improvement study. Indian J Ophthalmol 2020;68:S92-5

5. Jansson RW, Hufthammer KO, Krohn J. Diabetic retinopathy in type 1 diabetes patients in Western Norway. Acta Ophthalmol 2018;96:46574.

6. Rajalakshmi R, Amutha A, Ranjani H, Ali MK, Unnikrishnan R, Anjana RM, et al. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. J Diabetes Complications 2014;28:29197.

7. MayerDavis EJ, Davis C, Saadine J, D'Agostino RB, Jr., Dabelea D, Dolan L, et al. SEARCH for diabetes in youth study group. Diabetic retinopathy in the SEARCH for Diabetes in Youth cohort: A pilot study. Diabetic Med 2012;29:114852

8. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Archives of Ophthalmology.1984 Apr 1;102(4):520-6.Ruhayel SD, James RA, Ehtisham S, Cameron

9. FJ, Werther GA, Sabin MA. An observational study of type 2 diabetes within a large Australian tertiary hospital pediatric diabetes service. Pediatr Diabetes. 2010;11(8): 544-46

10. TODAY Study Group. Retinopathy in youth with type 2 diabetes participating in the TODAY clinical trial. Diabetes Care. 2013;36(6):1772-1774. doi:10.2337/dc12-2387

11. Eppens MC, Craig ME, Cusumano J, Hing S, ChanAK, Howard NJ, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. Diabetes Care 2006;29:13006

12. Dabelea D, Stafford JM, Mayer-Davis EJ, et al; SEARCH for Diabetes in Youth Research Group. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood.JAMA. 2017;317(8):825-835.

13. Amutha A, Anjana RM, Venkatesan U, Ranjani H, Unnikrishnan R, Narayan KMV, et al. Incidence of complications in young-onset diabetes: Comparing type 2 with type 1 (the young diab study). Diabetes Res Clin Pract. 2017;123: 1-8. 18.

14. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–986

15. Wu L, Fernandez-Loaiza P, Sauma J, Hernandez-Bogantes E, Masis M. Classification of diabetic retinopathy and diabetic macular edema. World J Diabetes. 2013;4(6):290-294.

16. Donaghue KC, Marcovecchio ML, Wadwa RP, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes. 2018;19(Suppl. 27): 262–274.

17. American Academy of Pediatrics, Section on Endocrinology and Section on Ophthalmology. Screening for retinopathy in the pediatric patient with type 1 diabetes mellitus. Pediatrics. 1998;101:313-3

18. American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern: Diabetic Retinopathy. San Francisco, CA: American Academy of Ophthalmology: 2003. Available at: www.aao.org/ppp. Accessed March 30, 2005

19. Aiello LP, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL. American diabetes association. Diabetic retinopathy. Diabetes Care. 2002;25(Suppl 1):S90-3. Keel S, Itsiopoulos C, Koklanis K, Vukicevic M, Cameron F, Brazionis L. Prevalence and risk factors for diabetic retinopathy in a hospital-based population of Australian children and adolescents with type 1 diabetes. Journal of Pediatric Endocrinology and Metabolism. 2016 Oct 1;29(10):1135-42.

Comprehensive care for childhood diabetes: The Kerala model

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Introduction: Type 1 diabetes requires (T1D) lifelong treatment with insulin, which not only gives pain to the child, but also results in enormous economic burden to the family, especially if insulin analogs are advised. In the present situation, basal bolus therapy with analogs is the most ideal regimen; some children may require continuous subcutaneous insulin infusion (CSII: insulin pump). Without regular monitoring with glucometer strips at least 4-6 times a day, we cannot assess the glycemic status of the child properly, but this also adds to the pain and cost of treatment. The emotional burden of the disease is tremendous, not only to the child, but also to the entire family. The child has to undergo regular follow up and serial investigations to look for complications. Many of our children cannot afford this comprehensive care, and without any insurance scheme or financial support from the government, optimal management can be impossible.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

The Mittayi Program: This initiative of the Govt. of Kerala, under the Social Security Mission (KSSM), for the comprehensive care of children with T1D, was officially launched in May 2018. Starting with 300 children enrolled in the program, it has 1074 beneficiaries as of now. Under this program, the children are provided insulin (rapid acting bolus and basal analogs), a glucometer and 4 glucostrips per day. Selected children are given continuous glucose monitoring systems (CGMS) and insulin pump. Regular follow up is provided in the clinics.
Nodal Centers and Satellite Centers: Under the program, 2 nodal centers were started initially in the 2 major government hospitals: Govt. Medical Colleges (GMC) in Thiruvananthapuram and Kozhikode. Soon 3 more nodal centers were initiated at GMC at Trissur, Alappuzha, and Kottayam. Subsequently 9 satellite centers were started, one in each district: Kasaragod, Kannur, Kalpetta (Wayanad), Perinthalmanna (Malapuram), Palakkad, Idukki, Pathanamthitta, and Kollam. Each nodal center has either a pediatric endocrinologist or a pediatrician, a nurse educator and a dietician. Regular ongoing training is being given to the pediatrician, nurse and dietician regarding comprehensive management.

Enrollment process: Enrollment is a 3 step process. Children below 18 years of age, with diabetes, can become beneficiaries of this program. They have to get a medical certificate from a pediatric endocrinologist, endocrinologist, pediatrician or physician; an income certificate (annual income under Rs 20,00,00) and the Aadhar card. These documents are to be uploaded on the website www.mittayi.org. The State Technical Committee scrutinizes these documents and decides whether these children should be included in the program. The Committee also allots the nodal center which is closest to their residence.

Care provided: Children who are enrolled in the program have to report to the nodal center with their treatment details. The pediatrician in charge of the center scrutinizes the records, examines the child and plans the treatment. The details are uploaded in the program data, using a software developed for the purpose. The basal bolus regimen with glargine as the basal insulin; and lispro, aspart, or regular insulin as the bolus insulin is being used for all children. In selected children with frequent glycemic variations, a CGMS device is inserted to assess the glycemic status. Children who cannot achieve good control with basal bolus therapy in spite of being well motivated, are provided insulin pump therapy, after scrutiny and approval by the State Technical Committee. Separate criteria have been developed to consider CGM and insulin pump. So far 10 children are on insulin pump therapy. All accessories are being provided free of cost. Once enrolled, the patient must visit the center on regular intervals. The nurse educator is available on all days; she monitors and records the anthropometry, and goes through the log books. The investigations are noted down and if required, the help of pediatrician in charge is sought for dose changes. The pediatrician/ pediatric endocrinologist conducts the clinic once a week. Basic investigations are done in the nodal center itself. The dietician and nurse educator provide awareness classes about diabetes care on a regular basis. A book in Malayalam about comprehensive care of diabetes provided by the Govt., and the clinic phone number is given to all patients so that they can ask the nurse educator about any issues. An ophthalmologist visits the clinic once a month to screen for early detection of retinopathy, in all the major nodal centers. The Technical Committee has decided to appoint a clinical psychologist on a part time basis, to all nodal centers.

Budget allocation: The annual project cost is Rs 380 lakhs. The annual cost of medication and accessories is about Rs 24,000 per child.

Special care: Regular diabetes camps were conducted every year before the COVID 19 pandemic. During the pandemic, insulin pens and strips are being provided to the patients' doorsteps with the help of Kerala police.

Conclusion: A child with diabetes requires lifelong comprehensive care, provided by a team of treating physician, nurse educator, dietician, psychologist, and involving the entire family. The financial burden is enormous, and without external support, proper care is impossible for most families. The Mittayi program initiated by the Govt of Kerala aims to provide comprehensive care under one umbrella, to all our children with this chronic condition, and to mitigate their problems, at least to some extent.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Diabetes in Childhood

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In earlier years, children were more vulnerable to communicable diseases like malaria, pneumonia, diarrhea, and other seasonal infectious diseases. Non-communicable diseases (NCDs) result from the interaction of genetic, physiological, environmental and behavioral factors, and present a significant burden on individuals, communities and economic resources. Indeed, children, adolescents and young adults are increasingly affected by NCDs - a population which remains hidden from global surveillance, targets and priorities. One of the major NCDs that affects children is diabetes.

There are many forms of diabetes in children, which should be differentially diagnosed for the ease of treatment and management. Type 1 diabetes (T1D), type 2 diabetes (T2D), maturity onset diabetes of the young (MODY), neonatal diabetes (NDM) and fibro-calculous pancreatic diabetes (FCPD) are some of the more common forms of diabetes reported in India.

T1D develops due to autoimmune destruction of beta cells so daily insulin shots are needed for survival; it is one of the more prevalent forms of diabetes in children and young adults. T2D is marked by insulin resistance, and there may even be hyperinsulinemia in the initial stages, but beta cell loss develops over time. Previously unheard of in children and teens, T2D is now being diagnosed more often in young people, due to the rising tide of childhood obesity. MODY has several subtypes, but is commonly caused by a variant in the HNF1A, HNF4A or GCK genes. A family history of diabetes traced to three or more generations was considered characteristic, but with rising obesity, this may occur with T2D also. It is useful to diagnose MODY, as some subtypes may be controlled by oral drugs and insulin can be stopped. NDM is caused by genetic defects in pancreatic insulin secretion; some of these patients, especially those with variants in the KCNJ11 and ABCC8 genes, may respond to oral drugs. Therefore, genetic testing is desirable, in case a specific mutation can be identified. FCPD is found in lean young adults belonging to lower socioeconomic strata, presenting with history of recurrent abdominal pain and steatorrhea, and usually severe hyperglycemia. [Unnikrishnan & Mohan;2021]. Figure 1 presents the differential diagnosis of childhood diabetes in India.

The first national-level multicentric clinic-based registry of youth-onset diabetes from India was started in the year 2006 by ICMR: the ICMR Young Diabetes Registry (ICMR YDR). Chennai is one of the major contributors of young diabetes cases to the nationwide data pool. In the Chennai data submitted to the ICMR YDR, we found 1429 children were diagnosed below the age of 15years [Amutha A et al; 2021]. Among them, 88.2% (n=1261) had T1D, 7.6% (n=108) had T2D and 4.2% (n=60) were other diabetes types like FCPD, MODY and other genetic syndromes etc.

The genetic syndromes associated with diabetes include:

- Wolcott–Rallison syndrome (WRS, OMIM 226980) is a rare autosomal recessive (AR) multisystem disorder due to homozygous mutations in EIF2AK3 (PERK), the gene encoding the eukaryotic translation initiation factor-2α kinase 3. WRS is characterized by permanent neonatal diabetes mellitus (PNDM), epiphyseal dysplasia, hepatic, and renal dysfunction [Jahnavi et al 2013].
- Wolfram syndrome, also called DIDMOAD, is a rare AR genetic disorder marked by diabetes insipidus, diabetes mellitus, optic atrophy, and deafness as well as various other possible defects.
- Usher syndrome is a progressive condition characterized by partial or total hearing loss (inner ear abnormalities) and vision loss.

- Ehlers-Danlos syndrome is a group of inherited disorders that affect connective tissues, primarily skin, joints and blood vessel walls.
- Alström syndrome is characterized by a progressive loss of vision and hearing, dilated cardiomyopathy, obesity, T2D, and short stature.
- Down syndrome or trisomy 21, has a higher risk of developing diabetes, along with characteristic physical features and developmental delay.
- Rabson–Mendenhall syndrome is a rare AR disorder characterized by severe insulin resistance.
- Thiamine-responsive megaloblastic anaemia syndrome (TRMA) is an AR disorder due to abnormalities in active thiamine uptake into cells; features include megaloblastic anaemia, mild thrombocytopenia and leukopenia, sensorineural deafness and diabetes.

Figure 2 presents the regional variation in the distribution (%) of diabetes cases in YDR. In the registry, we found a significant variation in the distributions of T1D and T2D from the registered cases from Regional Collaborating Centers (RCCs) like Chennai (42.5 vs. 39.2%) and Dibrugarh (44.5 vs. 43.1%) where equal proportion of T1D and T2D cases were registered with age at diagnosis $\leqslant$25 years. However, this is not the case in other RCCs, where T1D contributed major proportion of their total cases registered [Praveen PA et al; 2021]. Similarly, from Chennai, there were variations in the data collected for e.g., government hospitals mostly had T1D, whereas private hospitals had a large number of T2D and Gestational Diabetes participants [Amutha A et al; 2021]. Even though, the registry data provide us with a wide spectrum of childhood onset diabetes from the geographic based regional centers, the observed intra and inter regional variations in YDR should be interpreted with caution as the distribution of cases might be due to the nature of the reporting centres (e.g., referral centres, speciality clinics, paediatric clinics, etc.) and patient's health care seeking behaviour [Praveen PA et al; 2021].

The bottom line is that, all children with diabetes need not have T1D: in the presence of any atypical clinical features, the aforementioned types of diabetes and syndromes should be thought of, and investigated as necessary.

References:

1. Executive Summary of NCD child. Children and Non-communicable diseases. Global Burden Report 2019.Pg. 3- 7.

2. https://www.hopkinsmedicine.org/health/conditions-and-diseases/diabetes/diabetes-in-children

Unnikrishnan R, Mohan V. Fibrocalculous Pancreatic Diabetes. Curr Diab Rep. 2020 Apr 11;20(6):19. doi: 10.1007/s11892-020-01303-1. PMID: 32277298.

3. Jahnavi S, Poovazhagi V, Kanthimathi S, Gayathri V, Mohan V, Radha V. EIF2AK3 mutations in South Indian children with permanent neonatal diabetes mellitus associated with Wolcott-Rallison syndrome. Pediatr Diabetes. 2014 Jun;15(4):313-8. doi: 10.1111/pedi.12089. Epub 2013 Oct 30. PMID: 24168455.

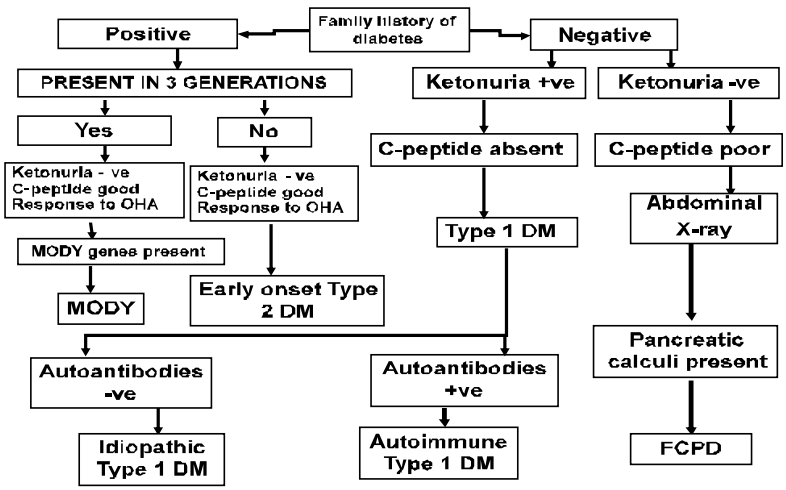
4. Unnikrishnan R, Amutha A, Mohan V. Type 2 diabetes mellitus in childhood and adolescence. In: IAP Speciality Series on Pediatric Endocrinology. (2nd edition). Shah NS, Rao S (eds). IAP National Publicaiton House, Gwalior, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 2013; 147-153.

5. Amutha A, Dhakshayani RV, Dharmarajan P, Suresh E, Periyandavar I, Shanmugam A, et al. Clinical profile and types of youth-onset diabetes in Chennai - the ICMR registry of youth-onset diabetes in India (YDR) – Chennai Centres. J Diabetol 2021;12:492-9.

6. Praveen PA, Madhu SV, Viswanathan M, Das S, Kakati S, Shah N, Chadha M, Bhadada SK, Kaur T, Dhaliwal RS, Das AK, Yajnik CS, Tandon N. Demographic and clinical profile of youth onset diabetes patients in India-Results from the baseline data of a clinic-based registry of people with diabetes in India with young age at onset-[YDR-02]. Pediatr Diabetes. 2021 Feb;22(1):15-21. doi: 10.1111/pedi.12973. Epub 2020 Feb 6. PMID: 31885113.

Figure 1: Differential diagnosis of childhood diabetes in India

Modified from: Unnikrishnan R, Amutha A, Mohan V. Type 2 diabetes mellitus in childhood and adolescence. In: IAP Speciality Series on Pediatric Endocrinology. (2nd edition). Shah NS, Rao S (eds). IAP National Publicaiton House, Gwalior, Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 2013; 147-153.



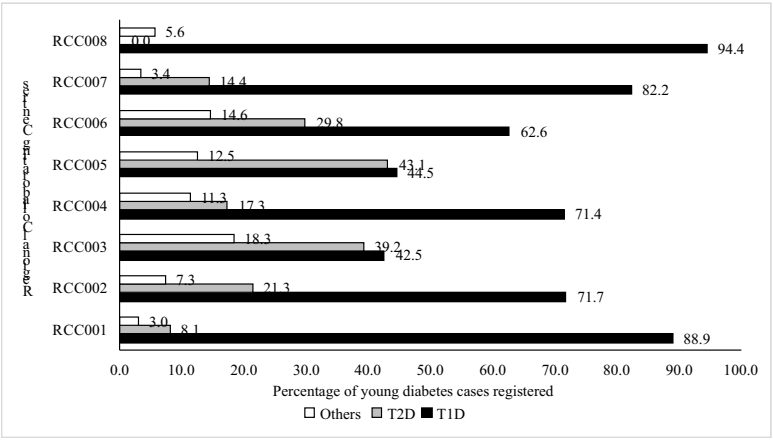
NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Figure 2: Regional variation in the distribution (%) of diabetes cases in YDR registry.

RCC01—All India Institute of Medical Sciences (AIIMS), New Delhi; RCC02—University College of Medical Sciences (UCMS), New Delhi; RCC03— Madras Diabetes Research Foundation (MDRF), Chennai; RCC04—SCB Medical College, Cuttack; RCC05—Assam Medical College (AMC), Dibrugarh; RCC06—KEM hospital, Mumbai; RCC07—P.D Hinduja hospital, Mumbai; RCC08—Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh

Modified from: Praveen PA, Madhu SV, Viswanathan M, Das S, Kakati S, Shah N, Chadha M, Bhadada SK, Kaur T, Dhaliwal RS, Das AK, Yajnik CS, Tandon N. Demographic and clinical profile of youth onset diabetes patients in India-Results from the baseline data of a clinic based registry of people with diabetes in India with young age at onset-[YDR-02]. Pediatr Diabetes. 2021 Feb;22(1):15-21



The not so inert c-peptide (connecting-peptide)

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Insulin synthesized in the beta cell of pancreas, is released into circulation as a molecule composed of two separate polypeptide chains linked by disulfide bridges. The two chains are derived from a larger precursor, proinsulin, in which the NH3 terminus of the A chain is linked to the COOH terminus of the B chain by a connecting peptide, i.e. C-peptide. (1) C-peptide is a polypeptide made of 31 amino acids; its C-terminal pentapeptide interacts with cell membranes to elicit signaling pathways. The mechanism of binding is likely G-protein coupled. It is hypothesized that C-peptide binds to cell membranes coupled to a pertussis toxin sensitive G protein which activates Ca channels, which in turn activate endothelial nitric oxide synthase (eNOS) and Ca calmodulin dependent protein phosphatase 2 B(PP2B), subsequently converting Na-K-ATPase to its dephosphorylated activated form. (2)

C-peptide reflects insulin secretion from the beta cells of the pancreas and helps in assessment of pancreatic beta cell reserve. In view of slower degradation than insulin, negligible first pass metabolism, and stable clearance from peripheral circulation, it is preferred as a marker of beta cell function over insulin assays.

Studies in various experimental and animal models have linked C-peptide to diminished glomerular hyperfiltration and reduced urinary albumin excretion (3); improvement in autonomic symptoms, sensory nerve functions and temperature threshold discrimination (4); improved whole body glucose utilization (5); improved blood flow in muscle (8); and reduced atherosclerosis plaque formation (6).

In healthy individuals: Fasting C-peptide is 0.3-0.6 nmol/L and postprandial C-peptide-1-3 nmol/L. (6) (1 nmol/L= 3 ng/ml). C-peptide can be measured in fasting state or in a random state; testing simultaneous blood glucose is important to interpret it's level. A random sample is convenient to collect but may not be as useful in clinical decision making. For academic purposes, C-peptide is measured after a mixed meal test or glucagon administration. The glucagon stimulation test is most useful clinically, since it is sensitive and specific, needs fewer sampling (0, 2, 4, 6 min) and is shorter in duration, although the majority of patients experience nausea with this test. The sample should be collected in whole blood in EDTA, and is usually stable at room temperature for 24 hours. Fallacies in C-peptide measurement include: Inaccurate result in patients with renal impairment, interference with large anti-insulin antibodies and possible cross reaction with pro-insulin assays.

A fasting C-peptide < 0.2 nmol/L with hyperglycemia strongly suggests type 1 diabetes and < 0.6 nmol/L suggests

likely T1D. However, a child with T2D with marked hyperglycemia may have low C-peptide due to glucotoxicity. A child with T1D may have elevated C-peptide levels during the honeymoon phase. All children with T1D or hypoglycemia need not have C-peptide assessment. The clinical settings where C-peptide assessment is likely to be of utility include:

- In children with a prolonged honeymoon phase and low insulin requirement, where non-T1D etiologies like Monogenic diabetes or T2D are strongly considered. This may help in elucidation of the etiology.
- In children with recurrent hypoglycemia where factitious hypoglycemia is suspected, measurement of C-peptide and insulin levels helps the clinician distinguish between endogenous hyperinsulinism (like insulinoma or persistent hyperinsulinemia: high C-peptide and high insulin levels) versus exogenous insulin administration (low C-peptide and high insulin levels).

C-peptide was previously considered as biologically inert, but it is an active peptide with important physiological effects which are different from insulin. Low C-peptide has been considered as a possible marker for the occurrence of long-term microvascular and macrovascular complications. Modest residual beta cell function (persistent detectable C-peptide) on follow up is associated with reduced hypoglycemia, improved HbA1c and reduced complication rates. It may be useful in the future to select candidates for islet cell transplantation. C-peptide is an exciting area of research to further elucidate its utility in care of children and adolescents with T1D.

References:

1. Sperling MA, Pediatric Endocrinology: Diabetes Mellitus. 5th Edn.USA: Elsevier Saunders;2021.

2. Wahren J, Ekberg K, Johansson J, Henriksson M, Pramanik A, Johansson B-L, et al. Role of C-peptide in human physiology. Am J Physiol-Endocrinol Metab. 2000 May 1;278(5):E759–68.

3. Mogensen CE, Andersen MJF. Increased Kidney Size and Glomerular Filtration Rate in Early Juvenile Diabetes. Diabetes. 1973 Sep 1;22(9):706–12.

4. Johansson BL, Borg K, Fernqvist-Forbes E, Kernell A, Odergren T, Wahren J. Beneficial effects of C-peptide on incipient nephropathy and neuropathy in patients with Type 1 diabetes mellitus. Diabet Med. 2000 Mar;17(3):181-9. doi: 10.1046/j.1464-5491.2000.00274.x. PMID: 10784221.

5. Wu W, Oshida Y, Yang W-P, Ohsawa I, Sato J, Iwao S, Johansson B-L, Wahren J, and Sato Y. Effect of C-peptide administration on whole body glucose utlilization in STZinduced diabetic rats. Acta Physiol Scand 157: 253–258, 1996.

6. Yosten GLC, Maric-Bilkan C, Luppi P, Wahren J. Physiological effects and therapeutic potential of proinsulin C-peptide. Am J Physiol Endocrinol Metab. 2014 Dec 1;307(11):E955-968.

7. Leighton E, Sainsbury CA, Jones GC. A Practical Review of C-Peptide Testing in Diabetes. Diabetes Ther. 2017 Jun;8(3):475–87.

8. Forst T, Kunt T, Pohlmann T, Goitom K, Engelbach M, Beyer J, and Pfutzner A. Biological activity of C-peptide on the skin microcirculation in patients with insulin dependent diabetes mellitus. J Clin Invest 101: 2036–2041, 1998.

Pedendoscan- Diabetes

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a) Battelino T, Tehranchi R, Bailey T, Dovc K, Melgaard A, Yager Stone J, et al. Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: Results of a phase 3, randomized controlled trial. Pediatr Diabetes. 2021 Aug;22(5):734-741. doi: 10.1111/pedi.13220

Glucagon is a well-established first line treatment for severe hypoglycemia in type 1 diabetes (T1D), but is often underutilized because reconstitution of lyophilized glucagon prior to injection poses a significant barrier to timely and accurate administration. Thus, this randomized double-blind trial was planned to evaluate the safety and efficacy of dasiglucagon, a ready-to-use aqueous glucagon analog formulation, in 6-17 year old individuals with T1D, with reference to reconstituted glucagon and placebo. Forty two participants were randomly allocated (2:1:1) to a single subcutaneous (SC) injection of dasiglucagon (0.6 mg), placebo, or reconstituted glucagon (GlucaGen; dosed per label) during insulin-induced hypoglycemia. The primary endpoint was time to plasma glucose (PG) recovery (first PG increase $\geqslant$20 mg/dL after treatment initiation without rescue intravenous glucose). The primary comparison was dasiglucagon vs. placebo; glucagon acted as a reference. The median time (95% CI) to PG recovery following SC injection was 10 min (8-12) for dasiglucagon vs. 30 min (20 to upper limit not estimable) for placebo ($P < .001$); the median time for glucagon was 10 min (8-12), excluding the time taken to reconstitute the lyophilized powder. **PG recovery was achieved in all participants in the dasiglucagon and glucagon groups within 20 min**

of dosing, compared to 2 out of 11 (18%) with placebo. No clinically relevant differences in time to PG recovery were seen woth respect to age group (6–11 years; 12–17 years) or injection site (abdomen; thigh). The most frequent adverse events were nausea and vomiting, as expected with glucagon treatment. The results were consistent with adult phase 3 trials.

b) Graves LE, Pryke AF, Cho YH, Cusumano JM, Craig ME, Liew G, Donaghue KC. Sight-threatening retinopathy in nine adolescents with early onset type 1 diabetes. Pediatr Diabetes. 2021 Dec;22(8):1129-1134. doi: 10.1111/pedi.13265.

The authors report nine cases of sight-threatening proliferative retinopathy and clinically significant macular edema in youth aged 15-17.9 years from 2017 to 2021. The patients were diagnosed with T1D before the age of 10 years and had a history of poor glycemic control (HbA1c 10%-15%). Five adolescents developed retinopathy rapidly within 2.5 years of a previously normal retinal examination on seven-field stereoscopic retinal photography; three required laser photocoagulation therapy. Two adolescents were diagnosed with retinopathy following improvement in diabetes control after being lost to medical follow-up; retinopathy improved with improved glycemic control. **Repeated retinal screening in adolescents with diabetes duration >10 years with suboptimal glycemic control, is required even when initial retinal examination is normal.**

c) Dehn-Hindenberg A, Saßmann H, Berndt V, Biester T, Heidtmann B, Jorch N, et al. Long-term Occupational Consequences for Families of Children With Type 1 Diabetes: The Mothers Take the Burden. Diabetes Care. 2021 Dec;44(12):2656-2663. doi: 10.2337/dc21-0740

This cross-sectional study investigated the occupational and financial consequences for parents following the onset of T1D in their child. A questionnaire assessing these aspects before and in the first year after the onset of diabetes was distributed to all families with a child ⩽14 years of age at diagnosis, with diabetes duration of at least 12 months, in nine German pediatric diabetes centers. Data of 1,144 children (mean age at diagnosis 6.7 [3.6] years; 46.5% female) and their families were obtained. Mothers' occupational status reflected in paid working hours was significantly reduced in the first year after their child's diabetes diagnosis ($P < 0.001$). Overall, 15.1% of mothers stopped working, and 11.5% reduced working hours. Mothers of preschool children were particularly affected. Fathers' working status hardly changed ($P = 0.75$). Changes in career planning were reported by 15.1% of mothers, and 8.7% reported less participation in qualification courses while 50.7% reported no negative impact on their occupational activities. Nearly half of the families (46.4%) reported moderate to severe financial losses. Compared with an earlier similar study in 2003, the situation remained unchanged in 2018. **Mothers of young children with newly diagnosed diabetes are the most affected in their occupational status.**

d) Gibbings NK, Kurdyak PA, Colton PA, Shah BR. Diabetic Ketoacidosis and Mortality in People With Type 1 Diabetes and Eating Disorders. Diabetes Care. 2021 Aug;44(8):1783-1787. doi: 10.2337/dc21-0517.

Eating disorders along with T1D can lead to poorer glycemic control. This population-based cohort study was done to determine the risk of DKA and all-cause mortality among adolescents and young adults with T1D with and without an eating disorder. All people with T1D aged 10-39y in Ontario, Canada, were identified, and those with a history of eating disorders, age- and sex-matched 10:1 with those without eating disorders; they were followed for 6 years for hospitalization/ emergency department visits. The DKA model was adjusted for income, rural residence, and diabetes duration, while the mortality model was adjusted for diabetes duration only. The cohort of 168 persons were mostly females (92.9%). In those with and without eating disorders, the crude incidence of DKA was 112.5 per 1,000 patient-years vs. 30.8 [Adjusted Hazard ratio (AHR) 3.30 (95% CI 2.58–4.23; $P < 0.0001$)]; while all-cause mortality was 16.0 per 1,000 person-years vs. 2.5 [AHR 5.80 (95% CI 3.04–11.08; $P <0.0001$)]. Males with eating disorders had an increased risk for mortality (Hazard ratio 14.17 vs 5.38). **Adolescents and young adults with T1D and eating disorders have more than triple the risk of DKA and nearly sixfold increased risk of death compared with their peers without eating disorders.**

e) Zhang L, Meng Z, Jiang Z, Liu Z, Hou L, Cai G, et al. Indicators of glucose dysregulation and the relationship

with iron overload in Chinese children with beta thalassemia major. Pediatr Diabetes. 2021 Aug 28. doi: 10.1111/pedi.13260.

This study was done to explore the role of HbA1c, fructosamine, and glycated albumin (GA) in evaluating glucose dysregulation and study the potential relationship between iron deposition and disordered glucose metabolism in beta thalassemia major (βTM). A cross-sectional study was performed on 118 children with βTM, aged 6-18y, with normal BMI and no family history of diabetes, who had received at least 20 regular blood transfusions; the control group consisted of 33 healthy children matched for age, sex, and BMI. Fasting plasma glucose (FPG) and insulin (FINS), insulin resistance index (HOMA-IRI), and insulin sensitivity index (HOMA-ISI) were compared. In the patient group, HbA1c, GA, fructosamine, and serum ferritin (SF) were measured; and oral glucose tolerance test (OGTT), as well as heart and liver MRI T2*, were performed. FPG, FINS, HbA1c and HOMA-IRI were significantly higher in the βTM patients, compared to the control group. Seventeen (14.41%) βTM patients were diagnosed to have diabetes, while 48 (40.68%) had both impaired fasting glucose and impaired glucose tolerance. There was a significant decline from the DM-TM group to the IFG/IGT-TM group to the normal OGTT-TM group with respect to HbA1c [8.11±1.15 vs. 6.57±0.71 vs. 6.21±0.61, P=0.001], GA [16.79 ± 4.23 vs. 12.05 ± 1.23 vs. 11.09 ± 1.36, P=0.001] and fructosamine levels [175.54 ± 46.29 vs. 137.85 ± 24.60 vs. 137.05 ± 16.7, P=0.002]. Statistically significant difference was seen in age, SF and cardiac MRI T2* between the abnormal and normal OGTT groups. No significant difference was identified in the mean volume of blood transfused and duration of chelation. **HbA1c may be used as a significant measure, with GA and fructosamine as alternatives, for monitoring worsening glucose metabolism in thalassemic patients with abnormal glucose tolerance. Patients with heart iron deposition or an SF > 4000 µg/L were prone to abnormal glucose metabolism, so chelation therapy should be reinforced.**

f) Unal E, Demiral M, Baysal B, Ağın M, Devecioğlu EG, Demirbilek H, Özbek MN. Frequency of Celiac Disease and Spontaneous Normalization Rate of Celiac Serology in Children and Adolescent Patients with Type 1 Diabetes. J Clin Res Pediatr Endocrinol. 2021 Feb 26;13(1):72-79.

This study aimed to determine the frequency of spontaneous recovery of celiac serology and the frequency of biopsy-proven CD (BPCD) in patients with T1D. Of 779 patients in follow-up for the last 10 years at the Pediatric Endocrinology Clinic of Gazi Yaşargil Training and Research Hospital, University of Health Sciences, Turkey, the data of 668 patients who had available anti-TTG IgA report was retrospectively evaluated. The total serum IgA levels were normal in all. Initially positive anti-TTG IgA antibodies that persistently remained negative (<12 IU/mL) for six months was considered as spontaneous normalization of celiac serology. A pattern of initially positive anti-TTG IgA antibodies, and temporary resolution followed by repeat positivity, was defined as fluctuation of celiac serology. On biopsy, Marsh grade 2 and 3 were taken as BPCD and grade 0 and 1 as potential CD. Positive serology was detected in 103/668 (15.4%) patients. There was spontaneous normalization (in median 9 months) in 24 (23.3%), fluctuation in 11 (10.7%), and permanently positive serology in 68 (66%). Of these 68 with persistent serology, 58 underwent biopsy: 46 were BPCD. Thus, overall frequency of BPCD was 6.9%, of which three fourth were diagnosed at the time of the diagnosis of T1D, and 97.8% within the first five years of T1D. The weight, height and BMI-SDS at diagnosis were lower in patients with BPCD cf. those without CD. **An anti-TTG-IgA level of 11.8 times the ULN was the most sensitive (93%) and specific (90%) cut-off for BPCD (AUC: 0.95; 95% CI: 0.912-1; p<0.001). In view of spontaneous normalization of celiac serology, the authors recommend serological follow up for the initial year or so, instead of immediate duodenal biopsy, especially in asymptomatic patients or those with low TTG levels.**

g) Astudillo M, Tosur M, Castillo B, Rafaey A, Siller AF, Nieto J, et al. Type 2 diabetes in prepubertal children. Pediatr Diabetes. 2021 Nov;22(7):946-950. doi: 10.1111/pedi.13254.

This study was done to describe the clinical characteristics of children with T2D diagnosed before the onset of puberty. Electronic medical records of all children with autoantibody-negative T2D and documented tanner staging, between July 2016 and July 2019, were studied retrospectively (n = 376, mean age 13.6y, females 66%) and data was compared between those at Tanner stage I (prepubertal) (n = 35) with those at Tanner II-V (pubertal)

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

(n = 341). At T2D diagnosis, prepubertal children were younger (mean age 10.6y), had higher BMI z-score (p = 0.003), higher C-peptide (p = 0.003), more dyslipidemia (100% vs 89.7%; p = 0.036) with higher LDL and non-HDL- c. Of 24 (6.4%) children diagnosed with T2D under age 10y, 13 were prepubertal: 69.2% were female, all were obese, 15.4% had hypertension, 30.8% had NAFLD; none had diabetic ketoacidosis. Only 2% of the pubertal children and 5.7% of the prepubertal children had a genetic syndrome associated with obesity and/or T2D. **Thus, T2D in prepubertal children is associated with obesity, insulin resistance, and a more adverse cardiometabolic risk profile.**

h) Snell-Bergeon JK, Waugh K, Dong F, Steck AK, Norris JM, Rewers M. Physical Activity and Progression to Type 1 Diabetes in Children and Youth with Islet Autoimmunity: The Diabetes Autoimmunity Study in the Young (DAISY). Pediatr Diabetes. 2022 Feb 9. doi: 10.1111/pedi.13323.

This study was planned to study the effect of physical activity, assessed by accelerometer, as an independent risk factor for progression to clinical diabetes of genetically at risk (for T1D) children and youth with islet autoimmunity. Accelerometer data along with log of sleep and physical activity were obtained, with prospective follow up every 6 months for up to 7y. Physical activity (PA) was classified according to counts per minute and evaluated for planned as well as overall PA with parameters like metabolic equivalent tasks, steps per minute, percent of time spent sedentary, percent of time spent in moderate or vigorous PA (MVPA), and number and minutes spent in bouts of MVPA lasting 10 minutes or more (Freedson bouts). Of 262 antibody positive participants from the DAISY cohort (n = 2547), 56 already developed T1D, 14 were lost to follow up; 103 wore an accelerometer, of whom only 95 had sufficient data for analysis. During prospective follow-up, 13 of the 95 participants progressed to clinical diabetes. There were no significant associations between body mass index, fasting or random glucose, or PA parameters, and risk of developing T1D. In multivariable survival analysis, none of the PA parameters examined predicted a higher risk of developing diabetes. In survival analysis with time-varying PA parameters, none of the PA parameters over time were associated with the risk of developing T1D. On food frequency questionnaire, there were no differences in total caloric intake, carbohydrate or fat intake as a percentage of daily calories, or intake of either sucrose or all sugars. There was a small but statistically significant difference in protein intake, with higher intake of protein as a percentage of total calories reported in the group that went on to develop T1D. There were no correlations between carbohydrate and protein intake and any of the PA parameters. There were no significant differences in height, weight or BMI between progressors to T1D and non-progressors. **The authors did not find adiposity, less physical activity or inactivity as risk factors for progression from islet autoantibodies to diabetes in children and youth at high genetic risk for T1D.**

Case report: Type 1 Diabetes mellitus and Precocious puberty – an uncommon association

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Precocious puberty is generally defined as the appearance of secondary sex characteristics before age 8 years in girls and 9 years in boys [1]. The overall incidence of sexual precocity is estimated to be 1:5,000 to 1:10,000 children, with a female-to-male ratio of approximately 10:1. It is classified as isosexual or heterosexual; etiology may be central (GnRH dependent) or peripheral (GnRH dependent) [1]. Childhood Type 1 Diabetes Mellitus (T1DM) is due to pancreatic beta cell autoimmunity which, over a period of few months to years results in beta cell destruction, gradually diminishing insulin production and eventual hyperglycemia. The incidence peaks in two age groups: between age 4-7y, and then 10-14y. The physiological increased insulin resistance of puberty may contribute to the timing of the latter peak.

Poorly controlled T1DM may be associated with delayed puberty, while the onset of puberty has been associated with worsening of glycemic status due to increased insulin resistance [2]. So, there is a complex relation between these two entities, where puberty can worsen diabetes and diabetes can delay pubertal onset. On the other hand, childhood obesity, insulin resistance and type 2 DM have been associated with precocious puberty. However, precocious puberty is uncommon in the background of T1DM [3].

We report a case of an 8y10m old girl who presented with osmotic symptoms for 3 months, associated with a history of weight loss despite increased appetite; but no history suggestive of diabetic ketoacidosis. She had been noticed to have breast development since the age of 6y, with menarche at age 8y4mo, and 4 cycles of menstrual bleeding in the following 6 months. She had no history of associated autoimmune disorders, malabsorption, diarrhea, ocular, ear or skeletal abnormalities. She was the only child born of a non-consanguineous marriage. There was no family history of diabetes mellitus or early puberty.

Clinical assessment revealed a height of 142.7cm (+1.93 SDS), cf. mid-parental height of 147.8 cm and target height SDS of -2.1 SDS. She weighed 33 kgs (+1.09 SDS); with BMI 16.6 kg/m2, which was at the median for her age and sex (0 SDS). Sexual maturity rating was B4 P2 A0. She had grade I goiter. There was no dehydration or acidotic breathing; and no acanthosis nigricans.

Investigations confirmed diabetes mellitus with FBG 368 mg/dl, PPBG 677 mg/dl, and HbA1c 15.6 g%. Antibody testing (GAD 65) was negative. The bone age was advanced, at 13 years. Ultrasound of the abdomen did not reveal any pancreatic anomaly. The uterine and ovarian dimensions were consistent with pubertal onset. The uterus measured 5.5 * 2.3 * 4 cm and the ovaries had a volume of 4.4 cc (R) and 2 cc (L). Basal LH values was 0.1 mIU/ml and post triptorelin stimulation it rose to 30.8 mIU/ml at 40 minutes and 24.5 mIU/ml at 4 hours i.e., in the pubertal range. MRI of the hypothalamic-pituitary region showed no abnormality There were no stigmata of skin or bone changes.

The child was diagnosed to have T1DM (idiopathic), with idiopathic central isosexual precocious puberty. She was initiated on a basal-bolus regimen. Serum C-peptide levels were tested after achieving adequate glycemic control, and were 0.395 ng/ml and 0.891 ng/ml for the fasting and post mixed meal values respectively suggestive of a suboptimal response.

This case highlights an unusual occurrence of T1DM with precocious puberty. Our patient clearly developed precocious puberty. The thelarche occurring at 6y of age, and menarche starting approximately two years later, suggested that, though precocious, she had followed the usual tempo of pubertal progression. If she coincidentally was developing beta cell autoimmunity, the insulin resistance of puberty may have precipitated the development of the T1DM.

References:

1. Partsch, C-J. "Pathogenesis and Epidemiology of Precocious Puberty. Effects of Exogenous Oestrogens." Human Reproduction Update, vol. 7, no. 3, 1 May 2001, pp. 292–302, 10.1093/humupd/7.3.292.

2. Chowdhury, Subhankar. "Puberty and Type 1 Diabetes." Indian Journal of Endocrinology and Metabolism, vol. 19, no. 7, 2015, p. 51, 10.4103/2230-8210.155402.

3. Hur, Jin Ho, et al. "Insulin Resistance and Bone Age Advancement in Girls with Central Precocious Puberty." Annals of Pediatric Endocrinology & Metabolism, vol. 22, no. 3, 1 Sept. 2017, pp. 176–182, www.ncbi.nlm.nih.gov/pmc/articles/PMC5642083/, 10.6065/apem.2017.22.3.176.

Drug Corner- Intranasal Glucagon

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Deeb et al conducted a multicenter, open-label study to evaluate real-world effectiveness and ease of use of nasal glucagon (NG) in treating moderate or severe hypoglycemic events in children and adolescents with type 1 diabetes (T1D) (1). The authors used a dose of 3 mg during symptomatic moderate-to-severe hypoglycemia, and assessed the treatment response by measuring the blood glucose every 15 min after administration. Adverse events and ease of use was also assessed. Data on 14 patients who suffered 33 moderate-to-severe hypoglycemic episodes were analyzed. Patients returned to normal status within 30 minutes of nasal glucagon administration in all 33

events. There was a rise in mean blood glucose from 55.5 mg/dL to 113.7 mg/dL within 15 minutes of administration. In the majority of hypoglycemic events (93.9%), the caregivers reported that nasal glucagon administration was easy or very easy and that they were able to administer it within 30 seconds in 60.6% of events. There were no serious adverse events. This study reinforced the data from Seaquist et al, in adults, showing the effectiveness and ease of using nasal glucagon for moderate-to-severe hypoglycemia in T1D (2). It is no surprise that in July 2019, the FDA approved the use of nasal glucagon for management of moderate and severe hypoglycemic in patients older than 4y of age (3). The currently available brand, BAQSIMI (by Eli Lilly), comes as an intranasal device containing one 3mg dose of glucagon as a white powder for one actuation in one nostril. Each Baqsimi device contains one dose of glucagon and cannot be reused. It can be procured in India by ordering online.

Contraindications: Pheochromocytoma, insulinoma, known hypersensitivity to glucagon.

Drug interactions: patients on β-blockers can have transient tachycardia and elevation in blood pressure. Indomethacin may impair the ability to increase blood glucose. Glucagon may increase the anti-coagulant effect of warfarin.

Common adverse reactions: Nausea, headache, vomiting, URTI, watery eyes, nasal congestion, nasal itching, runny nose and itchy eyes.

References:

1. Deeb LC, Dulude H, Guzman CB, et al. A phase 3 multicenter, open-label, prospective study designed to evaluate the effectiveness and ease of use of nasal glucagon in the treatment of moderate and severe hypoglycemia in children and adolescents with type 1 diabetes in the home or school setting. Pediatr Diabetes. 2018;19:1007-1013. doi:10.1111/pedi.12668

2. Seaquist ER, Dulude H, Zhang XM, et al. Prospective study evaluating the use of nasal glucagon for the treatment of moderate to severe hypoglycaemia in adults with type 1 diabetes in a real-world setting. Diabetes Obes Metab. 2018;20:1316-1320. doi:10.1111/dom.13278

3. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-severe-hypoglycemia-can-be-administered-without-injection

Diabetes Educators' Corner
Safe Fasting practices with Type 1 Diabetes Mellitus

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With Lent going on and Ramzan fasting approaching, pre-teens, adolescents and young adults with T1D might want to fast, especially to be on par with their peers, and sometimes because fasting together as a family is what they may have practiced before T1D diagnosis. Lent fasting requires eating one meal a day. Ramzan fasting involves managing without food and water from dawn to dusk. Hindu and Jain fasts may allow having only fruits and milk during the day, or eating only one meal. Whatever the type of fasting, I personally believe nothing should stop T1D individuals from living a normal life. So, they can fast, but only if they follow certain prerequisites and safe practices, are aware and conscious of hypos, and are willing to test frequently.

Who can fast?

Adolescents and young adults who have had good glycemic control before the fasting period and preferably who have fasted before, may plan to do so. It is important that they have hypoglycemia awareness, and are very clear that they would be willing to break the fast in case hypoglycemia occurs, and treat the hypoglycemia. The goal is to frequently test blood glucose and adjust insulin doses accordingly, so that fasting is done safely, with no hypoglycemia or DKA. Use of a Continuous Glucose Monitoring System (CGMS) is helpful, but the user and family should be familiar with the device and how to interpret readings. Even if the person with diabetes cannot afford CGMS on a regular basis, it's use may be planned during the fasting period. Fasting should not be undertaken if glycemic control is poor, or if there are any symptoms of any infection or other intercurrent illness like fever, cough, cold, stomach pain, diarrhea, vomiting, etc.

The Need to Fast

Ramzan fasting is considered obligatory for all healthy adolescents and adults. Individuals may choose to fast to

avoid social stigma and boost their self-esteem, but those with poor glycemic control or with chronic complications are exempted from fasting as it adversely affects their health. They should be discouraged from doing so till they can achieve good glycemic control.

Why Frequent Monitoring and Dose Adjustment?

In people with T1D, the glucagon response to hypoglycemia is blunted. Changes in sleep pattern, timings of meals, quality and quantity of food intake, and resultant changes in cortisol response will cause fluctuating BG values. This can lead to hypoglycemia, with or without starvation ketosis (because fat is used as the main fuel source, leading to production of ketone bodies) in people with diabetes.

What and when to eat, how much to eat?

Before the fasting begins, eat as late as possible, e.g. for Ramzan, just before dawn. Ensure the meal is rich in protein and contains low glycemic index (GI) carbohydrates which will give satiety by delaying digestion and absorption, e.g., cheese, milk, yoghurt, nuts, eggs, fruit, and vegetables. Typically, the fast is broken with high GI, high carbohydrate foods such as dates or fresh fruits or sherbet, but the high fat content of the post-fasting meal reduces the GI. It is ideal to avoid large portions of high GI food. Pulses and other legumes are great sources of complex carbohydrates that can be filling and nutritionally dense. Meals can include whole grains, fruits, vegetables, yogurt, meat. Carb counting to match insulin is useful.

How to adjust insulin during fasting?

Just as T1D management is tailored for individual requirements, so is the insulin regimen during the fasting period. Usually, the basal dose is somewhat reduced, and a bolus dose given before each meal, based on the carbohydrate content of the meal. A weekly review with the medical care team (educator/ doctor) is necessary, but sometimes, even a daily contact may be desirable, to avoid acute complications like hypoglycemia or DKA.

Exercise and Physical Activity

Generally, when not fasting, additional carbohydrates are recommended for unplanned /spontaneous activities, to avoid hypoglycemia. During most Hindu and Jain festivals, reasonable levels of activity can be managed during fasting hours, with fruit and milk intake, ensuring adequate hydration and calories. This is not possible during Ramzan, so it is best to avoid strenuous activities, especially in the last few hours before the fasting period ends, when hypoglycemia is most likely to happen. Frequent monitoring through the day is important to detect hypoglycemia early, in case it happens.

When should the fast be broken?

It is important to make sure that the fast should be broken regardless of the time of the day if -

1. Any symptoms /signs of hypoglycemia occur
2. Any BG is < 70mg/dl even without symptoms
3. Any symptoms of an intercurrent illness mentioned above develop, e.g. fever, etc.
4. There is any weakness or general deterioration in health.

How to manage hypoglycemia?

If hypoglycemia occurs, it should be treated as per standard guidelines.
Give carbohydrate snack if BG trending sharply downwards or close to 70 mg/dl.
If BG < 70 mg/dl give 15 gm simple sugar followed by carbohydrate snack.
If BG < 54 mg/dl give 2 doses of 15 gm simple sugar 15 minutes apart followed by carbohydrate snack.
Carefully monitor BG: every 15 minutes till the BG improves to > 70 mg/dl.

How to manage hyperglycemia?

When BG is > 250mg/dl, blood ketone (by finger prick), or urine ketones (where blood ketone testing not available)

have to be checked.

- If ketones are positive (blood >0.6mmol, or urine 2+), the fast has to be broken, and the doctor contacted.
- If ketones are negative, a correction dose of insulin has to be given, and hydration maintained. This means the fast has to be broken. BG should be checked every hour.

In conclusion

With appropriate diabetes education, frequent BG monitoring, checking ketones as needed, correct carb counting, reduced basal dose, and correctly determined boluses doses based on insulin sensitivity factor (ISF), adolescents can stay on top of BG values and safely practice religious fasting.

Life long journey with Type 1 Diabetes mellitus

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Living with a chronic illness like type 1 diabetes (T1D) for 25 years has made me grow stronger day by day. I belong to a lower middle class family, and was diagnosed at the age of 8yrs on my birthday in the year 1996, in an era when T1D was the rarest illness, with the basic categories of insulins, and no awareness of the illness.

Childhood with T1D during the 90's era was an absolute challenge: it was scary as a child to repeatedly visit hospital emergency with DKA. Getting hypos during school hours, taking insulin shots in the class among my schoolmates, answering them for every insulin shot, was a mental trauma until I started visiting different endocrinologists and studying more about T1D. It was the time when I decided never to give upon my illness as "type 1 diabetes is not a death sentence". I participated in every sport and cultural activity, proved to be a brilliant student in high school, and entered medicine. Another challenge began when doing under-graduation, as studying medicine itself is stressful and requires a lot of stamina and patience throughout. But again, I started understanding diabetes in a better way and began my journey of advocacy.

Life of a girl with T1D is no less than a war when it comes to entering the phase of womanhood that is marriage. I would definitely call it no less than a miracle to make my life partner understand about the condition we have to share throughout life. I got married but before that I took every possible care to make my life partner understand about diabetes.

Life doesn't end at marriage, it's the dream of every girl to experience motherhood and I did too. People have a misconception or myth that those with T1D can never bear a child. I am currently in a beautiful phase of motherhood with a healthy baby. I feel all you need is a positive attitude and good control of sugar, and life is all yours.

Living with this chronic condition, and having faced many major hurdles with the help of diabetes advocacy throughout my childhood, I have always been motivated to help others by educating them about the importance of Diabetes Education and its awareness.

"DIABETES IS NOT A DEATH SENTENCE."

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

PEARLS FROM PET FELLOWS SCHOOL AND ISPAE MEETING, PUNE

Compilation from Fellows and attendees:

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Kanchi Kamakoti Childs Trust Hospital, Chennai





Thyroid

- Clinical diagnosis of congenital hypothyroidism in the newborn period is almost impossible.
- Accurate, timely diagnosis is needed. Treatment may be lifelong, timing of the diagnosis is crucial, and parental counseling plays a major role in outcome.
- In hyperthyroidism, the indications for second line therapy are: no response to medical management or major side effects. Radioiodine ablation is appropriate for post-pubertal subjects while surgery is suggested for prepubertal patients.
- Thyroid hormone resistance, although uncommon, is easily misdiagnosed and mistreated. Always repeat and confirm confusing thyroid function tests. Early genetic diagnosis avoids drastic mistreatment.
- Causes of high TSH: Obesity, drugs (e.g., sodium valproate, phenytoin), monoallelic mutations inactivating TSH receptors, maturational defects of the HPT axis.
- Long term risks of thyroxine overtreatment are hyperactive behavior, learning difficulties, bone age advancement, cranial synostosis.
- Measurement of TSH alone is misleading in: Central hypothyroidism, non-thyroidal illness, recent treatment of hypothyroidism or thyrotoxicosis, resistance to thyroid hormones, and TSH-secreting pituitary adenoma.
- Screening for interference in thyroid hormone (T4 and T3) and/or TSH laboratory assays should be considered in any patient with apparently anomalous or discordant TFTs.
- Confounding factors that might influence thyroid status (intercurrent non-thyroidal illness or medications) should be excluded before embarking on further biochemical, radiological, or genetic testing.
- TIRADS score (based on USG findings) can be used for cancer risk stratification.

Obesity

- Insulin clamp study is the gold standard for diagnosis of insulin resistance in children.
- Higher visceral fat is associated with worse outcomes of insulin resistance.
- Apart from weight loss, micronutrient status is important for regulation of insulin action.
- Goals of treatment of metabolic syndrome: body mass index (BMI) <85th centile for age and gender; blood pressure (BP) <90th centile for age and gender; low density lipoprotein (LDL) <100 mg/dl; fasting blood sugar <100 mg/dl; HbA1c <7%.
- Atorvastatin and pravastatin are approved for use in children over 8 years of age. Evolocumab is a monoclonal antibody against PCSK-9, approved for use in children over 10 years in hypercholesterolemia.
- Newer drugs under evaluation for use in dyslipidemia in children are mipomersin, lopitamide and inclisiran.
- Fructose consumption contributes to hyperinsulinemia in adolescents with obesity.
- The beneficial effect of resistance exercise on insulin sensitivity (IS) remains uncertain, though it could be

considered as an alternative, and probably is the more attractive type of exercise for obese adolescents. There is inadequate evidence about the optimal form, intensity, duration of exercise to improve IS.

- The US FDA has approved metformin for the treatment of T2DM in children age 10y and older.
- Primary intervention is life style modification: only if non-responsive, should pharmacotherapy be advised. (American Heart Association, Circulation 2019).
- Screen yearly for lipid disorders with non-fasting non-HDL, followed by fasting lipid profile if initial TC > 200, HDL < 45mg/dl and non-HDL > 145 mg/dL.
- Statin therapy is indicated for patients above 8-10 years of age. The choice of the type and dose of the statin should be based on the level of LDL and the presence of additional CV risk factors. It is suggested to use a high potency, maximally effective, and well-tolerated dose.
- Ezetimibe represents a second-line pharmacological option in children with the most severe lipid abnormalities (e.g., HoFH) in order to achieve the LDL therapeutic target. It inhibits the intestinal cholesterol absorption (blocking the Niemann-367 Pick C1 Like Intracellular Cholesterol Transporter 1). It is currently approved for children with FH from 10 years of age. The licensed formulation is 10 mg. It may be used as monotherapy or combined with statins. Ezetimibe in children is generally effective and safe @ 10 mg/day.
- Approved medications for obesity include Orlistat (> 12 years), Liraglutide (> 12 years) and Setmelanotide (> 6 years). For T2D, Metformin, Liraglutide and Exenatide are approved. Potential new therapies include Dizoxide Choline (PWS), Topiramate, Tirzepatide, Bimagrumab and AM833. Leptin deficiency can be treated with Metreleptin (Recombinant methionyl human leptin). Setmelanotide is a MC4 (Melanocortin) receptor agonist used in treatment of obesity resulting from Leptin Receptor deficiency, POMC deficiency, or PCSK1 deficiency. Novel lipid lowering drugs which have shown promising outcomes are Evolocumab, Alirocumab, Inclisiran, Evinacumab, Mipomersen, and Lomitapide.
- It is recommended to use ethnic population-specific criteria for diagnosis of dyslipidemia. Indian cut-offs for various parameters of lipid profile including triglycerides for Indian children are available. (Marwaha RK, Khadgawat R, Tandon N, Kanwar R, Narang A, Sastry A, Bhadra K. Reference intervals of serum lipid profile in healthy Indian school children and adolescents. Clin Biochem. 2011 Jul;44(10-11):760-6.)
- Surgical treatment for intervention in hypothalamic obesity includes truncal vagotomy and implantation of deep brain stimulating electrodes to bilaterally stimulate the nucleus accumbens.

Menstrual Disorders

- Oligoamenorrhea is defined as below:

Post menarche (y)	Cycle duration	No of periods per year
1	> 90 days	< 4 periods
2	> 60 days	< 6 periods
3-5	> 45 days	< 8 periods
>5	> 35 days	< 9 periods

- PCOS is diagnosed on the basis of: Menstrual Irregularity AND Hyperandrogenism (clinical or biochemical) with other causes excluded. Clinical hyperandrogenism is suggested by severe acne and hirsutism; biochemical hyperandrogenism is measured by calculated free testosterone, free androgen index or bioavailable testosterone.
- Functional hypothalamic amenorrhea: Improve BMI >19 kg/m2. Cognitive behavioral therapy may be needed. Evidence does not support use of OCP, as it does not revert the neuroendocrine changes, rather it masks hypothalamic-pituitary deficits. The only indication for OCPs is longstanding amenorrhea. Other experimental modalities are Kisspeptin infusion and recombinant leptin SC injections.

Disorders of sexual development (DSD)

- Sertoli cells produce high amounts of AMH from early fetal life, until onset of puberty, while granulosa cells of the small antral ovarian follicles produce small amounts of AMH from late fetal life until menopause. In patients

with DSD, AMH estimations can be useful to:
- Detect existence of testicular tissue and determine function of Sertoli cells,
- Direct the diagnosis of PMDS to study of the AMH gene,
- Distinguish congenital disorders affecting testicular differentiation, and
- Detect existence of ovarian follicles, when planning to preserve fertility in Turner Syndrome.

- Sex is the biological description, while gender is the personal attribute of an individual: the two terminologies cannot be used interchangeably.
- For genetic diagnosis, Sanger sequencing has a yield of 10%; micro-array based comparative genomic hybridisation has a yield of 15-20%; and next generation sequencing has a yield of 30-40%.
- Multiplex-ligation dependent probe amplification (MLPA) is useful for diagnosis of microdeletions (example: microdeletions in Congenital Adrenal Hyperplasia).
- Androstenedione is a better predictor of control than testosterone estimation during therapy for CAH.
- Normal measurements: SPL: Full term - 3.5 (± 0.7) cm, preterm: 2.27 + (0.16 × weeks of gestation) cm. Micropenis: < -2.5 SD (< 2.0 cm). Penile diameter 1.1 ± 0.2 cm. Clitoral assessment - measure the length/ width: calculate the clitoral index (length x width). Normal clitoral length - 2.0-8.5 mm (mean 4.0 mm), clitoral width is 2.0-6.0 mm (mean 3.32 mm), clitoral index is 13.3. At birth: Ano-scrotal distance (boys) - 21±3.0 mm; Ano-fourchettal distance (girls)- 11± 2 mm.
- Limitation of External Masculanization Score: Cannot be applied in assigned females because of the gender specific design and vocabulary (e.g., micropenis yes/no, scrotal fusion yes/no). Does not capture the full phenotypic spectrum of genital variation that characterizes DSD conditions due to its dichotomous nature.
- Screening for 17 OHP: False positives can be seen in prematurity, cross-reacting steroids, sampling before 48-72 hours of age, heterozygosity for 21-hydroxylase deficiency, stressed infant.
- Genetic testing in DSD: Y chromosome detection can be to be done with karyotype or Quantitative Fluorescent PCR (turn-around time 1-2 days). In western countries, karyotype testing has been replaced by aCGH (array comparative genomic hybridization) or SNP array due to faster turn-around time, but these cannot detect structural chromosomal rearrangements, and are less effective in determining sex chromosome mosaicism.

Adrenal gland

- CRF antagonists

CRF1 receptor antagonist	Advantages
Crinecerfont Neurocrine Biosciences, Inc, USA	Effectively reduced ACTH and adrenal androgen levels I n phase 2 trial; reduced Glucocorticoid requirements; favorable safety profile.
Tildacerfont Spruce Biosciences, USA	Effectively reduce ACTH and androgen levels; reduced GC requirements; favorable safety profile; associated with testicular adrenal rest reduction.

- Modified release and dual release HC (Chronocort, Plenadren) have shown promising results in overcoming the shortcomings of standard therapy. Infacort granules can be safely, easily and effectively used in children with Adrenal Insufficiency and are approved for use in Europe.
- Carbamazepine affects cortisol metabolism - urinary free cortisol may not be elevated in a child with Cushing's syndrome on carbamazepine.
- A single center study has shown calcium channel blockers provide better and more even control of hypertension in children with pheochromocytoma than alpha blockers or beta blockers.
- 80% pediatric cases of pheochromocytoma are genetic. Siblings of patients with genetically proven pheochromocytoma require monitoring for pheochromocytoma.
- Primary Adrenal Insufficiency (PAI) can be present at different ages and can be due to:
  1) Adrenal dysgenesis/ Hypoplasia- SF1, DAX-1 mutation
  2) Impaired steroidogenesis- ACTH resistance, cholesterol metabolism, Side Chain Cleavage, Steroid Acute regulatory protein mutation, CAH
  3) Adrenal destruction- Autoimmune, Adrenoleukodystrophy, Infection, Hemorrhage

- The biochemical test with the highest sensitivity and specificity for diagnosis of pheochromocytoma and paraganglioma is plasma free normetanephrine by enzyme immunoassay.
- The Endocrine Society recommends CT scanning as the first choice for imaging in pheochromocytoma and PGL. Multiphase CECT is specific in radiographical differentiation of pheochromocytoma from other malignant adrenal masses, showing significantly greater arterial enhancement in PCC/ PGL.
- Volume interpolated 3D Spoiled Gradient Echo Sequence is better for MRI detection of corticotrophin secreting pituitary microadenoma.
- The treatment of choice of Cushing's Disease (CD) is trans-sphenoidal surgery. On follow up, the basal cortisol should be done on day 5 to decide the need for steroid replacement. This should be repeated at 3 months. Hypocortisolemia indicates delayed cure.

Bone and calcium disorders:

- Hypocalcemia cut-offs:

Birth weight (gm)	Total calcium (mg/dl)	Ionized calcium (mg/dl)
>1500	8	4.4
<1500	7	4

- Familial hypocalcemia with hypercalciuria: hypocalcemia associated with a normal PTH. It occurs due to heterozygous gain of function mutations in the CaSR. The set point for PTH secretion is lowered and the renal calcium excretion increased. If the person is asymptomatic, no treatment is needed.
- Familial hypocalciuric hypercalcemia (FHH): is due to a heterozygous inactivating CaSR mutation (autosomal dominant). The PTH is normal or slightly elevated. The diagnosis of FHH is important as avoids over-investigation and unnecessary parathyroidectomy.
- International Society of Clinical Densitometry Position Statement 2019 - Childhood osteoporosis: ⩾1 vertebral compression (crush) fractures, in the absence of local disease or high-energy trauma, is indicative of osteoporosis. In the absence of vertebral compression fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score ⩽ -2.0 SD. A clinically significant fracture history is one or more of the following: two or more long bone fractures by age 10y, three or more long bone fractures at any age up to age 19y. A BMC/ BMD Z-score > -2.0 SD does not preclude the possibility of skeletal fragility and increased fracture risk.
- Spine Bone Mineral Apparent Density & TBLH-BMC are the best predictors of childhood fracture. Spine BMD should be adjusted for height. TBLH-BMC predicts long bone fracture only.
- Approach to disorders of parathyroid hormone:
  Serum PO4 is low in hypocalcemia associated with high PTH in a Ca deficiency state
  Serum PO4 is high in hypocalcemia associated with high PTH in PTH resistance
  Serum PO4 is high in hypocalcemia associated with hypoparathyroidism
- In hypophosphatemic rickets, alkaline phosphatase may never normalize, despite adequate treatment.
- Estrogen causes narrowing of the medullary cavity while testosterone causes increase in bone girth.
- The fracture incidence in fibrous dysplasia peaks at age 6-10 years.
- During parathyroidectomy, 4 intraoperative PTH samples (pre-skin-incision, pre-gland excision, 5 minutes post-gland-excision, 10 minutes post-gland excision) are recommended to construct a curve for PTH values. Decrease in PTH value of > 50% from the higher level of either the pre-skin-incision level or pre-gland-excision level is taken as the criterion to conclude surgery.

Growth and its disorders

- New growth promoting therapy targets the growth plate. Vosoritide, Infigratinib (tyrosine kinase inhibitor), Recifercept (soluble FGFR3), Vofotomab (monoclonal antibody), Meclizine (anti-histaminic), Statins, PTH and PTHrP, Aptamer, and FGFR inhibitor are various agents under clinical trial.
- Growth Hormone (GH) treatment in short Small for Gestational Age (SGA) – Heterozygous mutation in ACAN

and NPR2 are present in short child with SGA. In case of high serum IGF-1 levels, think about IGF-1R mutations and other syndromes like Bloom syndrome and Fanconi syndrome, where GH therapy is not advocated.

- Suboptimal response to recombinant GH therapy is defined as ΔGV <3cm/year, or Δ Height SDS <0.3, or an increase in GV SDS <+1 SDS compared to healthy children.
- Macimorelin as a peptidomimetic GH secretagogue: maximal GH levels are observed 30-90 minutes after oral administration. The dose is 0.5mg/kg with t1/2 of 4.1 hours.
- Vosorotide in the dose of 15mcg/kg/day as once daily SC injection is approved in Europe for achondroplasia, but is still awaiting FDA approval. It is not available in India yet.
- Intra-tumoral chemotherapy with interferon alpha can delay disease progression and offer a protracted time to definitive surgery or radiotherapy in pediatric cystic craniopharyngioma.
- Post operative follow up of Somatropinomas: IGF-1 level and random GH should be tested at 12 weeks.
  GH < 0.14 g/L suggests "surgical remission"
  GH < 1 g/L indicates "control" and normalization of the mortality risk.
- Typical skeletal findings
  - NPR2 – short metacarpals,
  - SHOX – short 4th and 5th metacarpals,
  - GNAS – shortening of middle phalanges and distal phalanx thumb/ subcutaneous ossifications,
  - IHH – shortening of middle phalanx of 2nd and 5th fingers with cone shaped epiphysis.
- In any mass or Langerhans cell histiocytosis compressing the pituitary stalk, all anterior pituitary hormones decrease, except prolactin, which increases.
- Concept of "growth without GH": during the post-operative course of craniopharyngioma, hypothalamic obesity also makes the child gain height even with very low GH and IGF-1. This is not desirable as it has a deleterious effect on the metabolic profile.
- Thyroxine and GH are interdependent. Thyroxine increases the secretion and effect of GH and regulates the effect of IGF-1. GH regulates thyroxine secretion and causes deiodination of T4 to T3.
- A difference of > 2 SD between the upper segment and lower segment is significant. Any difference below that is taken as milder disproportion.
- Conditioned mid-parental height (MPH) is obtained by adjusting the MPH for secular trend, the formula for which is 0.72 * MPH z score.

Water and electrolytes:

- Effective osmolality or tonicity reflects osmotic activity and determines the force drawing water across fluid compartments, excluding solutes such as urea that freely diffuse across cell membranes and have little or no effect on water shifts.
- Vaptans are AVP receptor antagonists: they have been FDA-approved for patients with euvolemic and hypervolemic hyponatremia. These are aquaretic agents, which enhance electrolyte free-water clearance. Conivaptan is V1A/V2 AVP receptor antagonist. Given as an initial IV bolus followed by a continuous infusion, it increases serum Na up to 6 mEq/L compared with placebo. Tolvaptan is an oral V2-receptor antagonist, used in the dose of 0.1-0.8 mg/kg.
- Serum Copeptin levels: are a more stable surrogate and equimolar marker of AVP secretion. If serum copeptin increases after water deprivation or administration of hypertonic saline, this excludes central DI. The copeptin level is useful to distinguish between primary polydipsia (>/=4.9 pmol/L) and partial DI (< 4.9 pmol/l). In hyponatremic states, the copeptin level is > 8.4 pmol/L in hypovolemic hyponatremia as well as SIADH.
- Management of DI: For central DI: DDAVP (synthetic analogue, about 3000-fold lower pressor effects) is used most commonly. Intranasal dose: 5 to 20 mcg daily. Rhinitis/ sinusitis affect absorption by the intranasal route, making dose titration difficult. The oral dose is 20-fold greater (100- 400 mcg/day as 1-2 doses).
- As the urine osmolality is fixed at about 1000 mOsm/Kg on chronic DDAVP therapy, there is risk of developing hyponatremia if fluid intake is excessive.
- Adipsic DI: There is destruction of the osmoreceptors that relay osmolar information to the magnocellular

neurons and the thirst center. So the thirst mechanism which protects against severe hypernatremia is lost. Delay in diagnosis leads to a chronic hyperosmolar state. Patients present with severe dehydration, hypernatremia and complications (seizures, thromboembolic events).

- Hyponatremia should be corrected more slowly in chronic than in acute onset hyponatremia. Correction should not exceed 0.5mEq/l/hour or 6mEq/l/day.
- Refrain from using oral desmopressin in the first phase of polyuria after CNS surgery (transient DI). This phase should be managed with replacement of fluids and intravenous infusion of vasopressin, if required.
- Osmolarity is the amount of solute per liter; osmolality is the amount of solute per kilogram.
- Urea does not contribute to osmolality.

ISPAE ACES series - January 2022- Thyroid disorders in children- Learning Pearls

Dr Deepa Anirudhan, Associate Professor of Pediatrics and Pediatric Endocrinologist
Govt Medical College, Thrissur

The first case was a baby with neonatal hyperthyroidism, presented by Dr Sudhir Ranjan Senapati, MKCG Medical College & Hospital, Berhampur, and moderated by Dr Anil Bhansali, PGI, Chandigarh. The second case was a severely stunted child, presented by Dr Rekha Bathala, Fellow, Pediatric Endocrinology, IGICH, Bengaluru, and moderated by Dr Vijayakumar M. The Expert Talks were on Treatment and prognosis of Grave's Disease in children by Dr Andrew J Bauer, Children's Hospital of Philadelphia, and an Update on Congenital Hypothyroidism by Dr Susan Rose, University of Cincinnati College of Medicine.

Learning pearls:

- Neonatal hyperthyroidism occurs in approximately 2% of infants born to mothers with history of Grave's disease.
- The clinical features include low birth weight (LBW), fixed stare, periorbital edema, retraction of eyelids, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, organomegaly, cholestasis, jaundice, thrombocytopenia and hyperviscosity.
- Tests show supressed TSH, elevated fT3, fT4, T3, T4, and markedly elevated TRSAbs at birth, which usually resolve by age 3 months.
- Treatment consists of antithyroid drugs, propranolol, Lugol's iodine and steroids; it is monitored by clinical examination and measurement of TSH and fT4 every 10-14 days and TRAb every 3-4weeks. Treatment can be stopped when TRAb have become undetectable.
- If the mother is on the antithyroid drug carbimazole, breast feeding can be safely continued as long as her dose is 15 mg/day or lower.
- Central hypothyroidism can occur sometimes after resolution of neonatal thyrotoxicosis, especially in untreated mothers with Grave's disease.
- Grave's disease can present as late onset Attention deficit hyperactive disorder (ADHD).
- There is no correlation between levels of T3, T4 and the severity of symptoms.
- In case of pregnancy with Grave's disease, maternal auto-antibodies (TSI and TRAb) should be checked between 20-24 weeks of gestation. If these are elevated, the cord blood levels should be checked.
- Propylthiouracil is no longer used in the pediatric age group.
- Methimazole can be started at a dose 1mg/year of age, e.g. 10mg for a 10 year old. Its tissue T1/2 is 20 hours, so it can be advised once daily.
- Papillary thyroid cancers can occur in Grave's disease. So, an ultrasound (US) of the thyroid gland should be done for all patients to look for nodules. The US can help differentiate Grave's (diffuse enlargement) and Hashimoto's thyroiditis (cobblestone appearance) in the thyrotoxic phase.
- Exchange transfusion in severe neonatal hyperthyroidism can be very effective in reducing maternal TSH R antibodies.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

- Scintigraphy is not required for diagnosis of Grave's disease.
- Whenever there is clinical suspicion of hypothyroidism, TFT should be repeated even if newborn screening (NBS) was normal.
- A second screen of TFT at age 2-4 weeks is required in acute illnesses, monozygotic twins/ multiple births, Trisomy 21, blood transfusion prior to obtaining NBS, and in babies born by IVF.
- Repeat TFT screening should be done at 36 weeks corrected gestational age, if baby was preterm (<32 weeks) or LBW (< 1500g).
- Start thyroxine at 10-15 mcg/kg/day (i.e. term baby 50 mcg/day), when indicated.
- Repeat fT4, TSH after 2 weeks and 4 weeks of starting treatment. If any change in dose is needed, repeat TFTs is needed 4 weeks later. T4 or fT4, whichever is tested, should be maintained in the upper half of the normal range, and TSH between 0.5-2 mIU/L.
- Congenital Hypothyroidism is permanent if the initial nuclear scan shows absent/ ectopic gland or the TSH rises >10 mIU/L during therapy due to undertreatment.
- Prematurity can impair T4 T3 conversion. Transient hypothyroxinemia in premature babies can lead to loss of 7-8 IQ points as thyroxine is needed for myelination and neuronal migration. The risk of cerebral palsy also rises.
- **Thyroid follow-up is needed in VLBW infants after hospital discharge.** As high as 18% can have high TSH on follow-up.
- **Lowering NBS cut-off for abnormal TSH does not detect most infants who later have elevated TSH on retesting.**

ISPAE ACES Meet - February 2022 - Disorders of Water balance

Dr Hari Mangtani, Consultant Pediatric Endocrinologist
Pearl Endocrine Clinic, Nagpur

Dr Payal Kubsad, Fellow, Department of Pediatric & Adolescent Endocrinology, Indira Gandhi Institute of Child Health, Bengaluru, presented a case of Diabetes Insipidus (DI), moderated by Dr Rakesh Kumar, PGI Chandigarh. Another interesting case of Distal Renal Tubular Acidosis was presented by Dr Anshika Singh, Clinical Fellow, Pediatric & Adolescent Endocrinology, Manipal Hospital, Bengaluru, moderated by Dr Rahul Jahagirdar, Bharti Vidyapeeth, Pune. The first Expert Talk was by Professor Daniel G. Bichet, University of Montreal, Quebec, Canada on diabetes insipidus; the other was by Dr Uma Ali, Professor, Pediatrics & Pediatric Nephrology, Lilavati Hospital, Mumbai, on renal function tests in disorders of salt and water balance.

Learning pearls:

- DI (abnormally large volumes of hypo-osmotic urine [<250 mmol/kg]) should be differentiated from osmotic diuresis caused by glucose, mannitol, urea, glycerol, contrast media and loop diuretics.
- Idiopathic central diabetes insipidus (CDI) and brain tumors are responsible for the majority of cases.
- The posterior pituitary "bright spot" reflects AVP/copeptin reserve and could be decreased in both central and nephrogenic DI.
- For emergency treatment of hypernatremic dehydration in a patient with nephrogenic diabetes insipidus (NDI), consider using hypotonic fluid or DW5, rather than 0.9% saline, as this may worsen the hypernatremia, and can cause osmotic demylination.
- MAGE-D2 (melanoma-associated antigen D2), encoded by MAGED2, stimulates the membrane expression of NKCC2 (Na-K-Cl cotransporter) and NCC (thiazide-sensitive sodium chloride cotransporter), mutations in which could be the cause of severe polyhydramnios and transient NDI, which reverses spontaneously.
  AVP is responsible for AVP synthesis and mutations in AVP is responsible for autosomal dominant CDI.
- Adipsic hypernatremia without a hypothalamic lesion can be due to auto-antibodies towards and subsequent destruction of the subfornical organ (SFO), causing defective vasopressin regulation, thirst and salt appetite sensation.

- Salt restriction, hydrochlorothiazide, amiloride, acetazolamide may prove useful in cases of NDI.
- Maintenance of the cell volume is the fundamental property of all living organisms. The endocrine system and the renal function orchestrated by the brain helps in maintaining the salt and water homeostasis and thus the volume and tonicity of the cell environment.
- Plasma osmolality is maintained at around 280mOsm. A rise in serum osmolality triggers ADH release, which concentrates the urine. The maximal urinary osmolality of 1200mOsm/L is reached with an ADH of 5pg/mL at serum osmolality of 290mOsm/L, beyond which the thirst corrects the serum osmolality.
- The proximal tubule is responsible for reabsorption of majority of filtered salt and water. Any proximal tubular dysfunction will have polyuria, metabolic acidosis, hypokalemia, hypophosphatemia, aminoaciduria and glycosuria, as seen in Fanconi syndrome.
- The loop of Henle is involved in active reabsorption of sodium, chloride and potassium; its defective function presents with hypokalemia, hyponatremia, hypochloremia and metabolic alkalosis, as seen in Barter syndrome.
- Urinary osmolality and solute parameters can sometimes be more useful than blood parameters in reaching a definitive diagnosis that may include fractional excretion of Na or Urea, or urinary potassium, glucose, amino acids or phosphate.
- Urinary osmolality of >300mOsm/L suggest solute diuresis, while an osmolality of <150mOsm/L points towards water diuresis.

NEWS: Activities of ISPAE members

Academic Activities

Dr Sumana Kundagrami, Kolkata: Bengal Pediatric Endocrinology group (supported by West Bengal Academy of Pediatrics) 27th February, Sunday. This was the first CME by this newly formed group of Pediatric Endocrinologists and pediatricians with interest in Pediatric Endocrinology in Bengal. The objective was to create awareness about this subspeciality amongst general pediatricians and postgraduate trainees. It was well attended, and there was enthusiastic interaction with the 3 eminent speakers and faculty from West Bengal and Bangladesh.

Patient Related Activities

The Presidential Action Plan - "Universal screening of congenital hypothyroidism" - Prof M Vijaykumar and Dr Deepa Anirudhan.

The Presidential action plan of Dr Vijayakumar, Kerala State IAP President 2022, was inaugurated on 17th Feb 2022 on Online zoom platform by Dr PSN Menon. Dr Shaila Bhattacharya, President, ISPAE, gave the keynote address. Dr Vijayakumar explained the need for universal screening of newborns in both the public and private sectors and mandatory follow-up of affected children. The module on "Screening for congenital hypothyroidism" was presented by Dr Deepa Anirudhan, Chairperson for the Action Plan, 2022. The meeting was attended by 70 pediatricians from across the state, with good interaction. It was planned to present the module in all IAP branches in the state, to sensitize pediatricians. Plans are also being made to spread this message to the general public through Asha workers, mass media etc. to achieve this goal. The meeting was hosted by IAP Thrissur.

Public awareness program on World Obesity Day - Dr Bhanu Kiran Bhakhri

Dr Bhanu Bhakhri, Pediatric Endocrinologist, PGICH Noida, UP, conducted a public awareness program on World Obesity Day. The organisers urged everyone to break the habit of frequent consumption of unhealthy food items, which had occurred during the Covid period. It was emphasized that children with rapid weight gain should be screened for hormonal derangements presenting as obesity, as well as for the timely screening of metabolic derangements secondary to obesity. The Director of the Institute, Prof Ajai Singh addressed the gathering and emphasized the need of obesity prevention for healthy and active childhood. He emphasized the need for consumption of fiber rich food items like fresh vegetables, fruits and whole grain cereals regularly in the diet. The Dean, CMS, MS, faculty members and resident doctors from other departments were involved in the discussion. The program was well attended by institute employees, family members of the patients visiting the Institute and other general visitors.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Laron syndrome support group formation - Dr Hemchand K Prasad, Chennai
A support group of 4 families of children with Laron syndrome was formed at Mehta Hospital, Chennai. The families were assessed and a virtual discussion conducted with experts in the field. Dr Rajni Sharma, Pediatric Endocrinologist, AIIMS, Delhi and Dr Kalpana Gowrishankar, Geneticist, provided expert advice in Insulin-like-growth-factor (IGF) therapy. The families highlighted the practical difficulties in procuring recombinant IGF.

Obesity awareness program - Dr Priti Phatale & Dr Hemant Phatale, Samrat Endocrine Institute of Obesity Diabetes & Thyroid, Aurangabad
Drs Hemant and Priti Phatale created awareness among various stake holders in childhood obesity. Dr Priti spoke about obesity, its future consequences and the way to tackle it in time, to 942 girls of Sharada Mandir Girl's School; followed by 375 students of Dr Desarda Public School. Essay writing, Poster making, and Healthy Recipes offline/ online competitions were held in different schools for 5th to 9th standard. A public awareness program was conducted at IMA Hall, Aurangabad, followed by felicitation of winners of Essay & Poster competitions. On 6th March morning a cycle rally organized by Samrat Endocrine Institute in affiliation with various associations, flagged off by the Additional Collector, Aurangabad district, Dr Anant Gavhane. More than 100 cyclists participated in the rally, with effective catchy slogans on obesity being displayed on each bicycle.

Miscellaneous Useful information for ISPAE members

Revised 2022 guidelines on Vitamin D:
The Indian academy of Pediatrics (IAP) has published revised 2022 guidelines on Vitamin D for practitioners.
The link is: https://www.indianpediatrics.net/mar2022/235.pdf

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Standard Treatment guidelines:
The IAP has prepared Standard Treatment Guidelines for Practitioners on various endocrine disorders. The link are as follows:

https://iapindia.org/pdf/Ch-026-Childhood-Obesity.pdf
https://iapindia.org/pdf/Ch-022-STG-Diabetes-Mellitus.pdf
https://iapindia.org/pdf/Ch-012-Hypothyroidism.pdf
https://iapindia.org/pdf/Ch-009-Menstrual-Irregularities.pdf
https://iapindia.org/pdf/X9ceMoHV2pAF6UR_STG-NEONATAL-HYPOGLYCEMIA.pdf

Completion of ISPAE observership program - Dr Nithya T, Assistant Professor, Jubilee Mission Medical College, Thrissur
Dr Nithya completed the ISPAE observership program under the mentorship of Dr Parvathy L, Consultant Pediatric Endocrinologist, Aster Medcity Kochi, Kerala during July-August 2021. During this period, she was involved in the management of pediatric endocrine conditions like congenital hypothyroidism, juvenile hypothyroidism, goiter, thyroid malignancy, growth hormone deficiency, SGA, precocious puberty, delayed puberty, type 1 diabetes mellitus, rickets, obesity, metabolic syndrome, osteogenesis imperfecta, CAH and autoimmune polyglandular syndrome. Dr Nithya participated in interdepartmental and postgraduate case discussions, and visited the nuclear medicine department. She has joined back her parent unit and established a pediatric endocrinology clinic.

ISPAE Activities
ISPAE ACES QUIZ 2021 – Report

Dr Deepa Anirudhan, Associate Professor of Pediatrics and Pediatric Endocrinologist
Govt Medical College, Thrissur

The ISPAE ACES preliminary round was conducted on 18th December 2021 on Zoom, chaired by Dr Shaila Bhattacharya, President, ISPAE. Fourteen teams participated from all over India: Fellows from BJ Wadia, Mumbai (Dr Divya Pujari and Dr Rachna Keshwani), HCJMRI, Pune (Dr Madhura Karguppikar and Dr Chirantap Oza), CDER Kanpur (2 teams: Dr Navin Narayanan and Dr Sayan Banerjee; Dr Manoj Kumar Agrawal and Dr Vibha Yadav), IGICH, Bangalore (Dr Meenakshi and Dr Tejaswi), AIIMS Jodhpur (Dr Abhishek Kothari and Dr Vivek Parihar), and DM Trainees from AIIMS, New Delhi (Dr Kiran Kumar Golla and Dr Uthara Elsa Mathew), PGI, Chandigarh (Dr Arti Yadav and Dr Pamali Nanda), IPGMER, Kolkata (Dr Debaditya Das and Dr Subhashis Neogi), Narayana Medical College (NMC), Nellore (Dr Afsar Fathima and Dr Vishal Lahoti), SVIMS, Tirupati (Dr Shruthi B and Dr Likhitha), AIIMS, Jodhpur (Dr Parul Gupta and Dr Vanishri Ganakumar), Govt Medical College (GMC), Thiruvananthapuram (Dr Soumya S and Dr Karthik), and Madurai Medical College (Dr Rameez Raja and Dr Priyanka R). The Quiz Master was Dr Ahila Ayyavoo, Pediatric Endocrinologist, GKNM Hospital, Coimbatore. There were 20 multiple choice questions for the preliminary round. The 4 teams qualifying for the finals were GMC, Thiruvananthapuram; IPGMER, Kolkata; NMC, Nellore, and BJ Wadia, Mumbai.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

The finals, conducted on Zoom on 19th December, were attended by about 70 people. Quiz Master Dr Ahila Ayyavoo was helped by Drs Dhivyalakshmi, Deepa Anirudhan and Nithya T as scorers. There were 5 rounds of questions, with one Audience Round. The team from GMC, Thiruvananthapuram, won first place and a cash award of Rs 10,000/-; NMC, Nellore came second with an award of Rs 6000/-; and IPGMER, Kolkata came third. We congratulate all the winning teams!

Hearty congratulations to the winners of the ISPAE ACES quiz

First Place
Government Medical College, Thiruvananthapuram
Dr Soumya S and Dr Karthik


Second place
Narayana Medical College, Nellore
Dr Afsar Fathima and Dr Vishal Lahoti


Third place
IPGMER, Kolkotta
Dr Subhashis Neogi and Dr Debaditya Das


Inaugural and Installation Ceremony of Pediatric Endocrinology Association of Karnataka (PEAK)

The Pediatric Endocrinology Association of Karnataka (PEAK), the very first State Branch of ISPAE, was officially launched on March 6th, 2022 with grandeur at the Taj, MG Road, Bangalore. This was aptly preceded with an academic activity, viz., a Clinical Workshop, organized by Medtronics on the use of Insulin pumps in children, attended by fellows in Pediatric Endocrinology, practicing Pediatric Endocrinologists, senior Pediatricians and postgraduate students in Pediatrics from across the state.

The Inaugural function began with an invocation song seeking the blessings of Lord Ganesha. Dr Vani welcomed the gathering. Dr Shaila Bhattacharyya spoke about the vision and mission of PEAK to encourage and promote teaching, training and research in the field of Pediatric and Adolescent Endocrinology, by conducting CMEs and conferences across the state amongst the Pediatricians, Physicians, General practitioners, Postgraduates and Parents. She also requested everyone to join hands in the care of the children with diabetes not only in their growth, immunization but also financially to provide easy access to insulin, regular check-ups and psychosocial counselling.

The Chief Guest of the function, Dr. Ramesh S. Kaulgud, Joint Director, National Vector Borne Disease Control Program, Directorate of Health and Family Welfare Services, Government of Karnataka, delivered the Inaugural Address and assured complete support from his team in all the projects by PEAK.

Our guest of honor, the pioneer in the field of Pediatric Endocrinology in India, Dr. Raghupathy Palany, spoke about the beginnings of the specialty in India, the difficulties and challenges faced, contrasting with the welcome changes now; how the current generation of young Pediatric Endocrinologists evolved, and the active interest evinced by these Pediatricians to specialize and devote themselves to serve children in need of specialist care and attention in this important field. Our Chief Guest and Guest of Honor, were felicitated by office bearers, executive committee members of PEAK and Senior Pediatricians. This was followed by the Installation ceremony. Installation of office bearers was done by Dr Kaulgud, and of executive committee by Dr Raghupathy, Advisor of PEAK. The office bearers of PEAK are Chairperson: Dr Shaila Bhattacharya; Vice Chairperson: Dr Vijaya Sarathi; Secretary: Dr Vani HN; Joint Secretary & Treasurer: Dr Pavitra Nagaraj. The Executive Committee members are: Drs Santhosh Olety, Anjana

Hulse, Poornima RN, Suman Rath, Shaila Pachapure, Diksha Shirodkar and Mounica Reddy. The e-newsletter which will be the voice of PEAK - hence named SPEAK - was launched by Dr Vijaya Sarathi and Dr Diksha Shirodkar. They enumerated the details regarding their plans for the newsletter to be published in future. The day concluded with a vote of thanks by the Joint Secretary and Treasurer, Dr Pavithra Nagaraj. All the participants of the workshop were gifted a plant, signifying the concept of a new life filled with dreams and desires for growth.

IDEAL– ISPAE Diabetes Education And Learning – program: A report

Dr Preeti Singh, Associate Professor, Department of Pediatrics
Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi

The first batch (Oct-Dec 2021) of the IDEAL program successfully completed 3 months of structured intensive online training in December 2021. An online Exit exam was conducted on 21st & 22nd December as part of summative assessment. Of the 25 participants enrolled, 20 successfully cleared the assessment process, with 6 securing Distinctions for their outstanding performance. An online certification ceremony was organized Zoom on Republic Day 26th January, 7-8 pm to felicitate the successful participants. It was attended by the IDEAL Core Committee members and Faculty. It was indeed a moment of pride for each one of us. The participants shared their experience of the IDEAL journey and gave valuable feedback for future courses, as their e-certificates were individually displayed, to be later mailed to them. The IDEAL program has been highly appreciated by participants and the dedicated Faculty alike. The ceremony ended with the vote of thanks to the Core Committee team, esteemed Faculty, support staff, and participants.

The ceremony was followed by a separate online feedback session for the IDEAL faculty, wherein they shared their suggestions to improve future courses. The Faculty has spent a lot of time and effort in developing the teaching modules, conducting each session, assessing the participants' assignments and discussing those assignments in the feedback sessions. The Core Committee thanked the Faculty and expressed gratitude towards them for sparing their valuable time and expertise. Most of the Faculty generously agreed to continue to guide and teach subsequent IDEAL batches. The critical and constructive feedback given by them and the participants to improve and facilitate learning, are being incorporated for the second batch.

During the Covid pandemic, E-learning has added a new horizon as an effective and efficient way of training and education. Using this model, the IDEAL team envisages creating a cadre of pediatric diabetes educators all over India, especially for the underprivileged and remote areas of the country. These IDEAL pediatric diabetes educators are expected to disseminate the skill and knowledge gained during the program, for optimizing the management of children and adolescents with diabetes.

After the grand success of the first batch; the training of the second batch started off with the blessings of "Maa Sarasvati" on 5th February 2022. The IDEAL team intends to conduct 3 batches every year, with 30 participants in each batch.

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Upcoming meetings in Pediatric Endocrinology please block your dates

ISPAD 2022 – 48th Annual meeting of ISPAD: Abu Dhabi (UAE) – 13-16 October, 2022. https://2022.ispad.org/
ISPAE 2022 - Chandigarh, 19-20 November, 2022
ISPAE 2023 Bengaluru, November 2023 (dates to be finalized)

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

ISPAE - BEST (Basic Education Series in Type 1 Diabetes)

COURSE OBJECTIVE:
To provide basic education on the ambulatory management of children and adolescents with type 1 diabetes

COURSE MODALITIES:
Structured online training course consisting of 8 teaching sessions (each session one hour, two sessions/day)

COURSE DURATION:
4 weeks, (Tuesday 7-9 PM), two-hour duration

LANGUAGE OF COMMUNICATION:
English. Essential to have a laptop/ Desktop/ Tablet/ Smartphone; Chrome and Firefox (latest versions); IOS 9 and above (all iPad & Android devices), with good connectivity.

ELIGIBILITY CRITERIA:
This course is intended for trained nursing staff, physician assistant, assistive school personnel, parents/caregivers of children with T1D, or adults with T1D, to learn basics of type 1 diabetes and its ambulatory management

COURSE FEE:
1000 INR/person (to be paid before the start of the course: **non-refundable**)

COURSE COMMENCEMENT DATE:
5th April 2022

CANDIDATE SELECTION:
A maximum of 30 participants will be selected per course.

APPLICATION:
To apply, fill in the online registration form.
https://docs.google.com/forms/d/1Te_Pq4SHhEqgFkAc6WFMbCTu0SsxsY2meHP_kX719XQ/edit

LAST DATE FOR SUBMISSION OF APPLICATION:
24th March 2022

BEST-CORE COMMITTEE

Program Directors:

Dr. Shaila Bhattacharyya

Dr. Aspi Irani

Dr. Santhosh Olety

Ms. Sheryl Salis

Dr. Preeti Singh

Dr. Sirisha Kusuma B

ISPAE OFFICE BEARERS:

Dr. Ganesh Jevalikar

Dr. Rakesh Kumar

NEWSLETTER
MARCH 2022
Volume 26, Issue 1

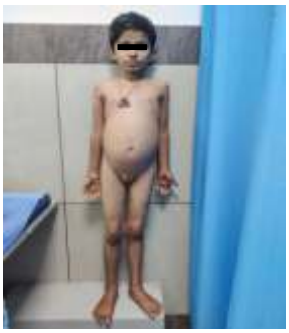
CAPE News | ISPAE

Pictorial case based questions-Part 2

Dr Diksha Shirodkar, Assistant Professor (Pediatrics), & Pediatric Endocrinologist
Yenepoya Medical College, Yenepoya University

A 10 year old girl presented with hyperglycemia of 7y duration, HbA1c 16.9 %, short stature, mild diabetic ketoacidosis, multiple areas of lumpy-bumpy deposits over the arms, abdominal distension and hepatomegaly. The clinical pictures are below.

a. Diagnose the condition
b. If at all for academic purposes, a liver biopsy was performed, what histopathology picture would you expect to see?



Written informed consent taken from the guardian/ patient for the above clinical pictures

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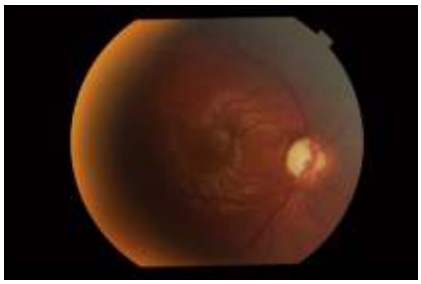
A 15 year old boy presented with long standing polyuria, polyphagia and visual difficulty. His fundus image was as follows

a. What is the condition and gene involved?
b. Any other evolving impairment you would expect over time?



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

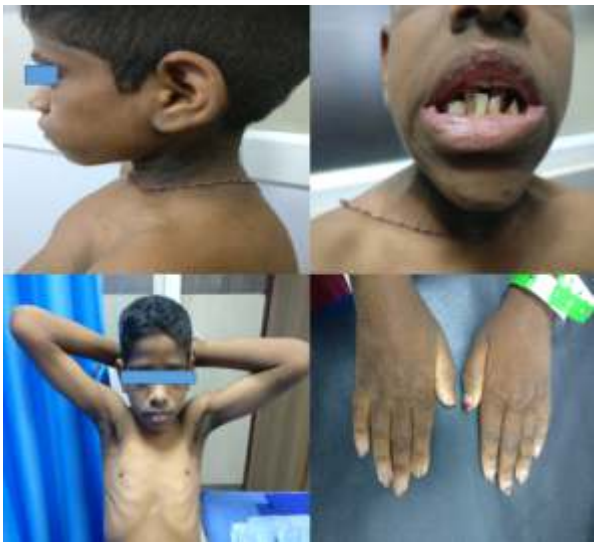
NEWSLETTER
MARCH 2022
Volume 26, Issue 1

CAPE News | ISPAE

Pictorial case based questions-Part 1 (Answers)

Congratulations to Dr Aaradhana for the correct answer!

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.

RABSON MENDELHALL SYNDROME, INSR

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;

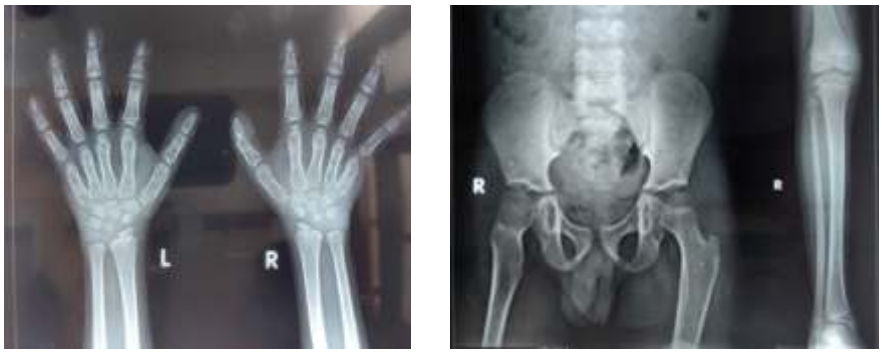


Image courtesy: Dr. Diksha Shirodkar, Department of Pediatric Yenepoya Medical College.
Written informed consent taken from the guardian/patient for the above clinical pictures.

Diagnose the condition and the possible incriminating gene involved.

WOLCOTT RALLISON SYNDROME EIF2AK3