CAPE NEWS

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

ISPAE ELECTIONS: 2017-2018

The following candidates are hereby declared elected:
President: Dr Anju Seth
Honorary Secretary-Treasurer: Dr Anurag Bajpai
Joint Secretary: Dr Rajni Sharma
Executive Members: Dr Abhishek Kulkarni, Dr Anjana Hulse, Dr Hemchand Prasad, Dr Preeti Singh, Dr Rakesh Kumar, Dr Saurabh Uppal, Dr Vijaya Sarathi

Signed: Dr Leena Piyambada (Returning Officer)

From the Editor's Desk

Dear members,

The breaking news in this new issue of CAPENEWS, of course, is the announcement of the ISPAE Elections for the term 2017-2018! We are all grateful to Dr Leena Priyambada for conducting the elections meticulously as Returning Officer. She announced:
The opening of ballot papers and counting of votes for ISPAE elections for executive committee members was done at the Office of Department of Paediatrics, Unit -1, Christian Medical College, Vellore by myself, other ISPAE members; Prof Anna Simon, Prof Sarah Mathai, Asso Prof Dr Sophy Korula, and independent observers Dr Urmi Ghosh and Mrs Victoria Jared.
The results you would already have read on page 1. We congratulate all the members of the new team! They would definitely take ISPAE to new heights, so we can provide better care to our children!
This new issue of CAPENEWS, brings you three interesting mini-reviews on various aspects of diabetes in children. The first one by Dr Sirisha Kusuma B discusses the role of artificial pancreas in children with type 1 diabetes mellitus (T1D) with special emphasis on the Indian set-up. The second one by Dr Ganesh Jevalikar focusses on management of glucocorticoid induced diabetes, which is increasing in prevalence in recent days. The third mini-review reviews available literature on the efficacy and safety of metformin in adolescents with T1D.
We have interesting case reports: of a child with recurrent hypoglycemia for 4 years before a diagnosis of fructose 1,6-biphosphatase deficiency was finally made; challenges in making the diagnosis of pseudohypoaldosteronism in a neonate presenting with electrolyte abnormalities; and a child with osteopetrorickets.
I am sure all those interested in pediatric endocrinology will find this issue useful. I thank all my team members, Dr Rajni Sharma, Dr Sachin Mittal, Dr Ravindra Kumar, Dr Reetha Gopinath and Dr Anju Virmani, for their active participation in designing this issue and for their valuable contributions.

Dr Vijaya Sarathi
Editor, CAPENEWS

ISPAE Biennial Meeting 2017: Coimbatore, Tamil Nadu, Nov- Dec 2017

Organizing Chairperson: Dr P Raghupathy, drp.raghupathy@gmail.com
Organizing Secretary: Dr Ahila Ayyavoo, ahila.ayyavoo@gmail.com

We are proud to announce the 44th annual ISPAD meeting, ISPAD 2018,

to be held in Hyderabad, India 11-14 Oct 2018, in association with ISPAE.
This is the time to become an **ISPAD member** - the discounted 3y membership for us in India (LMIC) is just $ 80/ year. Membership allows discounted rates for attending the **43rd Annual ISPAD Conference, ISPAD 2017** in Innsbruck, Austria (18-21 October 2017), and of course **ISPAD 2018.** Click ispad.org and become part of this vibrant community.

Message from the Secretary

Congratulations to "Team CAPE NEWS" for yet another marvellous effort, coming out with a newsletter with lot of useful articles, in a reader-friendly manner, on time!

We had ISPAE 2016, our Mid-term Meet "Sugars and Beyond", at Nashik in October. Dr Tushar Godbole and his team conducted in a fantastic way a multi-tiered meeting which will be remembered for years to come: a session for children with diabetes and their families, a workshop primarily aimed at educators and dietitians, and the main meeting, during which we had both our annual GBM and the Special GBM needed to ratify previous minutes and decisions. Quite a number of young and talented members were enrolled in our society: they actively participated in the scientific program as well as the GBM.

We are heading towards 2017. The time has come for handing over the baton. The current team of ISPAE office-bearers, elected for 2 years, is completing their term and now the new team will take over. On behalf of the entire team, I express our sincere thanks and gratitude to all ISPAE members: you had given us enough strength and courage to move the chariot forward in a smooth, cool and quiet manner. Best wishes for the new office-bearers who, I am sure, will take ISPAE to new heights. All our best wishes also to the organizing team of ISPAE-2017, Coimbatore!

Let the coming year be full activities, both academic and patient-friendly, so that we can fill our brains with new knowledge, and our little children's hearts with joy and happiness!

Wish you all a happy new year 2017!

Dr M Vijayakumar

Secretary, ISPAE

Hearty Welcome to New ISPAE Members	
Rabi Biswas, Ped, Dhaka	Shaila Sankeshwar, Ped, Gadag
Ashok Kumar, Ped, Kolkata	Anushree Mehta, MBBS, Mumbai
Sharmila Nayak, ped, Bangalore	Smita Ramachandran, Ped, Delhi
Suchit Gupta, Ped, Lucknow	Suhitha Chittamuru, Ped, AP
Ankita Maheshwari, Ped, Pune	Poornima R Naidu, Ped, Bangalore
Anuja Pethe, Ped, Mumbai	Prachi Bansal, Ped, Mumbai
Sandhya Kondpalle, Ped, Aurangabad	Shreya Sharma, Ped, Mumbai

Artificial Pancreas - Where do we stand?

Dr Sirisha Kusuma B, Pediatric Endocrinologist, Rainbow Children's Hospital, Hyderabad

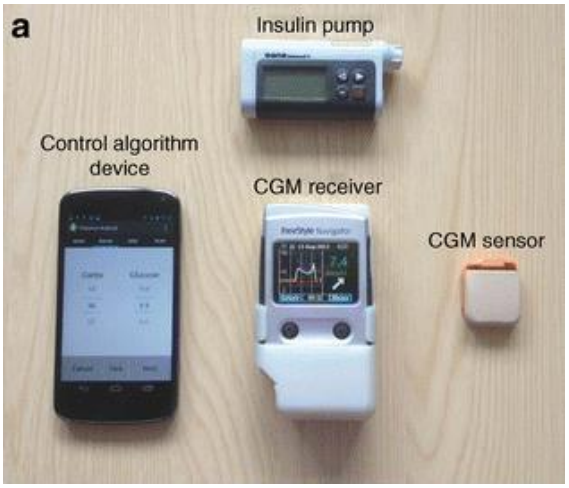
Background

"We have come a long way, but we have a long way to go."

What is Artificial Pancreas?

From times when getting diagnosed with diabetes mellitus was considered as a death sentence, the treatment of diabetes has come a long way. The combined efforts of Frederick Banting, Charles Best and James Collip led to the breakthrough discovery and first clinical use of insulin in 1921 and 1922. It was another 20 years before the technique of crystallization was used to develop extended action insulins: Protamine Zinc Insulin and NPH. We changed to human insulins by the 1980s, and analog insulins by 1996. Since the advent of blood glucose (BG) monitors with reagent strips in late 1960s, and the introduction of Insulin pumps in 1970s, technology has progressed tremendously. Now, insulin pumps are increasingly being utilized by the pediatric diabetic population, many a times as a first-line treatment modality. Meanwhile, minimally invasive continuous glucose monitoring (CGM) became available in 2000s, and was very soon upgraded to systems which are real time, factory calibrated (e.g. the Freestyle Libre), and insulin-dosing approved (which means one can use CGM values to decide pre-meal insulin dosing without a confirmatory finger prick glucose, e.g. the Dexcom G5).

A technology that combines these two modalities, establishing a closed loop to mimic the glucose-responsive function of β cells: a hybrid closed-loop 670G insulin pump by Medtronic (also known as Artificial Pancreas), has very recently been approved by the United States Food and Drug Administration.



What is Closed Loop?

A Closed Loop system consists of a combination of continuous BG monitoring, insulin pump, and control algorithms. The patient has to wear an insulin infusion cannula, and a glucose sensor, separately. The currently approved system is called hybrid closed-loop, which relies on manual administration of pre- meal boluses. Research has been going on to develop fully automated closed-loop systems without prandial bolus. Developing a single port device is also being worked upon.

Challenges to glycemic control and how closed loop helps

The revolutionary DCCT (Diabetes Care and Complications Trial) study demonstrated that tight BG control reduces risk of diabetes related micro and macro-vascular complications in

the long term, although at the cost of increased risk of hypoglycemia. While the use of analog insulins and insulin pumps lowered hypoglycemia risk, the key challenge to perfecting glycemic control remains the inherent unpredictability of BG levels and intra-individual variability in insulin requirements. Due to innate fluctuations in insulin sensitivity over the day, variable meal composition and activity levels, insulin requirements can vary between one third to three times the actual planned insulin delivery.

The main advantage of the closed-loop system is that it modulates insulin delivery in a glucose responsive fashion, and minimises the day-to-day and within-day hypo or hyper-glycemic excursions. The closed loop system also has potential to alleviate the psychological burden of T1D, by giving the patient some "time off" from the demands of therapy, and assuage the fear of hypoglycemia. Moreover, the fact that the use of biological alternatives like islet cell and pancreas transplantation is very limited and, despite significant improvements in such technology, cannot meet the needs of the general diabetic population, makes the closed loop system more relevant to the present day.

The efficacy of the closed loop system is diminished by the 5-15 min lag time between glucose values in the interstitial fluid and the blood, and the relatively slower onset of action of the currently available "rapid acting" insulins. Studies are underway to develop faster acting Aspart, and alternative delivery routes to prandial insulin, with a faster onset of action. Studies are in progress looking at a bi-hormonal / dual-hormone closed loop system, which delivers glucagon in addition to modulating Insulin delivery, further minimizing the risk of hypoglycemia. The subgroups of patients who benefit from closed loop systems still need to be identified, to maximize cost-effectiveness. Long term studies are underway to evaluate its performance, not just in terms of optimizing HbA1c, but also in improving the quality of life.

The Indian scene: This is really exciting!!

Well...Not exactly!

The Problem

According to the International Diabetes Federation 2015 report, there are 542,000 existing children with T1D, and an expected 86,000 new cases each year, of which nearly 20% are in India alone. That is a staggering 70,200 children under 15 years. Over the years, different prevalence studies in India have shown numbers anywhere between 3.7-10.5 per 100,000, and the incidence is increasing by 3-5% annually. These are numbers not counting those who succumb to diabetic ketoacidosis before even getting diagnosed. Epidemiological studies have shown that, in developing countries, the majority of T1D cases are from underprivileged sections of society. In India, less than 20% of the population has any kind of health insurance, and 70% lives in rural areas with poor medical facilities and no access to physicians or educators trained in diabetes management.

The Cost

The cost of T1D care in limited resource settings is over *INR 2000 per month* (NPH + Regular insulin = Rs 320, 2-3 BG strips per day = Rs 1500, 15 Syringes /month with re-using = Rs 150), not counting doctor visits and lab tests e.g. HbA1c. For those on multiple daily BG tests and analog insulins, the cost inclusive of doctor visits and blood tests can be well over INR *6000-10000 rupees per month* which can be a burden even for middle to upper-middle class

families. With the Indian government health care spending being a dismally low 1.4% of the GDP, against a global average of 5.9%, and in the absence of affordable and all-inclusive health insurance systems, most health care expenses are paid out of pocket by patients and their families. In the absence of time-based physician/educator reimbursement facilities, establishing dedicated diabetic teams with well-trained dietician, nurse educator, psychologist in addition to physician, is not a viable option. Often the burden falls upon the physician to fulfil all these roles, without any financial reimbursement for the additional time spent doing so. As a result, patients are often left with inadequate education and motivation to adhere to appropriate treatment plans, dietary and exercise recommendations. The strong social stigma associated with the word "diabetes", the need to take daily injections, the lack of safe spaces at schools or work places to take injections, add to the problem. It is common for parents to turn to alternative medicine systems, to the detriment of their own child. Many physicians treating children with T1D are not trained enough themselves, and end up treating T1D in the same way as type 2 diabetes, resulting in significantly suboptimal glycemic control.

Absence of government support leaves the burden on independent trusts, and programs like CDiC (Changing Diabetes in Children) and Life for a Child (LFaC). However, even at a stretch, these programs can only help so many. The CDiC program is currently helping almost 2000 children in India, i.e. 2% of all cases. The lack of access to the bare minimum needs of the child with T1D, i.e. insulin and glucostrips, leaves us wondering if we are really ready for the technological advancements happening in the developed world.

Finally...

At an individual level, as pediatric endocrinologists, it is our responsibility to get familiar and keep up-to-date with the new innovations in technology that improve glycemic control, so that we will be prepared to offer them to families who can afford them. At the same time, until some sort of health-care reforms are instituted by the Government to make at least basic care accessible to these children, as a community of pediatric endocrinologists, we should be focussing strongly on advocacy for T1D. We should be looking at ways and means to provide more inclusive and comprehensive diabetes care to the maximum number of children who need it, resigning ourselves to the fact that technologies like closed loop systems are only for the privileged few.

Further Reading:

1. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ArtificialPancreas/default.htm
2. Thabit, H. & Hovorka, R. Coming of age: the artificial pancreas for type 1 diabetes Diabetologia (2016) 59: 1795.
3. Prasanna Kumar KM. Incidence trends for childhood type 1 diabetes in India. Indian J Endocr Metab 2015;19, Suppl S1:34-5.
4. Pacaud D, Lemay J-F, Richmond E, Besançon S, Hasnani D, Jali SM, Mazza C, the Sweet Study Group. Contribution of SWEET to improve paediatric diabetes care in developing countries 2016. 17 (Suppl. 23), 46–52.

Management of steroid induced hyperglycemia in children

Ganesh Jevalikar, Senior Pediatric Endocrinologist, Medanta Medicity Hospital, Gurgaon

Introduction

Glucocorticoid therapy is the most common cause of drug induced hyperglycemia and diabetes in children. This is mostly associated with the supraphysiologic doses of systemic steroids typically used during cancer chemotherapy or organ transplantation, pulse steroid therapy used in immunosuppression, and high dose dexamethasone in neurosurgical patients. There is limited literature on prevalence, risk factors and management of steroid induced diabetes. In a retrospective Canadian study of children < 18 years of age, those with medication-induced diabetes were less likely to be obese, have a positive family history of type 2 diabetes (T2D), and have obesity-related co-morbidities, compared to children with T2D. Therefore, evaluating for the typical T2D risk factors may not be sufficient for identifying children at-risk of developing steroid-induced hyperglycemia or diabetes.

This article outlines the practical management of steroid induced hyperglycemia in children not previously known to have diabetes.

Mechanisms of hyperglycemia in steroid therapy

Glucocorticoids induce hyperglycemia by several mechanisms. Impaired insulin dependent uptake of glucose (mediated by GLUT4) and post receptor insulin signalling in peripheral tissues mainly leads to postprandial hyperglycemia. In addition, glucocorticoids stimulate breakdown of proteins and fats, stimulate hepatic gluconeogenesis, and potentiate the effects of counter-regulatory hormones. High dose steroids may also lead to β cell dysfunction. Chronic therapy is postulated to increase β cell apoptosis and lipotoxicity-associated impaired insulin secretion.

The pattern of hyperglycemia is different, depending on the steroid used. Typically, peak glucose levels following administration of intermediate acting steroids like prednisolone or methylprednisolone are seen in 4-8 hours and the effects lasts for about 12- 16 hours. Long acting steroids like dexamethasone cause sustained hyperglycemia lasting for nearly 24 hours after administration. Sustained hyperglycemia is also seen when intermediate acting steroids are given in two or three doses in a day.

Diagnosis

Diagnostic cut-offs are similar to the American Diabetes Association criteria for diagnosis of diabetes. For screening children on single daily dose prednisolone therapy, it is recommended to check post prandial (mainly post lunch) levels, as fasting glucose or oral glucose tolerance testing (OGTT) may miss several cases. For diagnosis, high capillary BG values can be confirmed by testing venous samples. Both fasting and post meal readings should be checked in patients on multiple doses of intermediate acting steroids or long acting steroids like dexamethasone or betamethasone. Glycosylated Hb (A1C) can be helpful to distinguish pre-existing diabetes, but only in recent onset hyperglycemia on steroids. Rarely, documentation of diabetes autoantibodies may be useful if the differential diagnosis of T1D is being considered.

Table1: Factors determining treatment in steroid induced hyperglycemia

Factor	Remarks
● Type of steroid	● Morning once-daily prednisolone causes hyperglycemia mainly post-lunch and pre-dinner, whereas dexamethasone causes sustained hyperglycemia
● Dose per day	● Higher dose is associated with higher chance of hyperglycemia
● Frequency	● Prednisolone in 2-3 doses/day causes sustained hyperglycemia
● Tapering schedule	● Change in steroid doses should be associated with anticipatory reduction of insulin doses
● Concurrent medications	● Concurrent administration of medications like calcineurin inhibitors (CNI), L-asparaginase, is associated with higher risk of hyperglycemia
● Underlying clinical condition	● Stressful illnesses like organ transplantation add to hyperglycemia
● Clinical presentation	● Decompensated patients need IV fluids and insulin presentation, whereas asymptomatic mild hyperglycemia can be managed with diet modification ± SC insulin

Management

BG testing is of paramount importance in managing steroid induced diabetes, because the changing clinical condition and the tapering of steroid doses are associated with fluctuating insulin requirements. Factors important in deciding the plan of care are listed in Table 1.

In pediatric patients, insulin is the mainstay of treatment, but recently metformin has also been found to be safe and effective in children with leukemia and therapy-induced hyperglycemia. Management is based on BG levels, and presence/ absence of ketosis. Those with mild hyperglycemia (i.e. < 180-200 mg/dL) can be managed with lifestyle changes (dietary modification and increased physical activity) and careful BG monitoring. On the other hand, those with ketoacidosis should be managed with a DKA protocol similar to T1D. Stable patients with persistent post-meal BG values ≥180-200 mg/dL should be advised subcutaneous insulin along with lifestyle changes. Patients with isolated post-lunch rise can be managed with a single dose of prandial insulin given before lunch. It can be started at a dose of 0.1-0.2 unit/kg, and adjusted based on results of post meal capillary BG. Patients with high fasting as well as post-meal BG are best managed with basal bolus insulin therapy.

The total daily insulin dose depends on the severity of hyperglycemia and the dose of steroid being given, and needs to be individualized. Typically, the dose requirement is high (even up to 2- 2.5 unit/kg body weight/day) when the patient is on large doses of steroid.

Of the total dose, 20-30% is given as basal insulin. Some centres prefer NPH as the basal insulin in view of its action profile being similar to that of prednisolone, but there are no randomized pediatric studies proving the superiority of a particular approach. A recent study in adults has documented the beneficial effect of adding NPH to basal bolus insulin in terms of significantly lower values of mean BG on day 3 of treatment, without an increase in total daily dose.

The remaining 70-80% daily dose is divided into 3 or 4 prandial doses. In case of single dose of prednisolone, the lunch and evening snack doses are usually relatively higher than the breakfast and dinner doses. Insulin pump therapy offers advantages with respect to multiple boluses, including correction for high BG, without multiple pricks to the child, and can be considered in cases where control is difficult using basal bolus therapy.

Identification of the appropriate caregivers and adequate diabetes care education of the family is essential, similar to T1D. The discharge advice should include guidelines for dose adjustments as per the steroid dose, and prevention and management of hypoglycemia.

Further course

Frequent and careful BG monitoring and communication with caregivers are the cornerstones of management in these patients. The insulin requirement tends to be transient (ranging from few days to months), for a variable period of time, depending on the steroid regimen and clinical condition, with resolution of hyperglycemia after tapering or stopping of steroids. However recurrence of diabetes with repeat course of steroids and sometimes permanent diabetes can also be seen.

Suggested readings

1. Amed S, Dean H, Sellers EA et al. Risk factors for medication-induced diabetes and type 2 diabetes. J Pediatr 2011, 159:291–296.
2. Ho J, Pacaud D: Secondary diabetes in children. Can J Diab 2004,28:400–405.
3. Roberson JR, Raju S, Shelso J et al. Diabetic ketoacidosis during therapy for pediatric acute lymphoblastic leukemia. J Cardiovasc Pharmacol Ther. 2008;13:298-300
4. Perlman K, Ehrlich RM.Steroid diabetes in childhood. Am J Dis Child. 1982;136:64-8.
5. Umpierrez GE, Hellman R, Korytkowski MT et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:16-38.
6. Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R et al. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. World J Diabetes. 2015;6:1073-81.
7. Bostrom B, Uppal P, Chu J, Messinger Y, Gandred L, McEnvoy R. Safety and efficacy of metformin for therapy induced hyperglycemia in children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013; 35(7): 504-8.

Role of metformin in type 1 diabetes mellitus

Dr Vijaya Sarathi, Associate Professor, Department of Endocrinology, Vydehi Institute of Medical Sciences and Research Center, Bangalore

Achieving euglycemia is challenging in patients with type 1 diabetes (T1D). It is mainly due to the increasing incidence of hypoglycemia as patients approach euglycemia. Since even mild hypoglycemia is associated with reductions in quality of life, this becomes a key factor preventing further improvement in glycemia. Hence, there is a constant search for adjuvant agents which can overcome this barrier and help achieve euglycemia without concomitant increase in hypoglycemia.

Insulin is the only drug approved for management of children and adolescents with T1D. Pramlintide (Amylin analogue) has also been approved for management of T1D in adults, but its glycemic efficacy is limited. Hence, there has been a lot of interest in the role of other adjuvant drugs like metformin, glucagon like peptide 1 analogues (GLP-1a), dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium glucose transporter 2 (SGLT2) inhibitors. This article discusses the role of metformin in the management of T1D with special focus on pediatric T1D.

Insulin resistance is closely associated with overweight and obesity. Approximately 40% of T1D adolescents in the USA are overweight (24%) or obese (15%). In addition, a significant proportion of them are not meeting the blood pressure (22%), low-density lipoprotein-cholesterol (LDL-c) (38%) and triglyceride (10%) targets recommended by the ADA. Prevalence of obesity in Indian children and adolescents in general is rapidly increasing, and a similar trend is being observed in those with T1D.

In a recent meta-analysis including eight randomised controlled trials in T1D patients, although metformin did not improve glycemic parameters (HbA1c or fasting plasma glucose), it was associated with a reduction in daily insulin dosage, body weight, total cholesterol and LDL-c levels. Metformin did not alter the risk of severe hypoglycemia or diabetic ketoacidosis, but was associated with an increase in risk of gastrointestinal adverse events (GIAEs).

The largest RCT evaluating the use of metformin in overweight and obese T1D adolescents did not demonstrate glycemic benefit, though it did show significant decrease in body weight and BMI, and reduction in total daily dose of insulin irrespective of BMI. However, a recent meta-analysis limiting the analysis to studies including T1D youth, concluded that administering adjunctive metformin therapy in addition to insulin was associated with improved HbA1c levels. Severe hypoglycemia (5.2% vs 0.7%), GIAEs (43.8% vs 27%) and diabetic ketoacidosis (3.3% vs 1.4%) were numerically more common with use of metformin, but the difference was not statistically significant. The higher incidence of GIAEs and severe hypoglycaemia with the use of metformin was biased due to use of a higher dose of metformin (2000 mg/day in 10-16 years old T1D) in the large RCT which did not

demonstrate significant glycemic benefit. A smaller daily dose, such as 500mg twice daily, would probably lessen GIAEs and severe hypoglycemia.

Use of metformin for a duration of 9 months in T1D adolescents with hyperandrogenemia did not significantly improve glycemia or BMI. Nevertheless, it was associated with significant reduction in serum estradiol, serum total testosterone and free androgen index levels. The reduction in hyperandrogenemia was associated with reduction in the frequency of moderate to severe acne, but did not affect hirsutism or the ovulation rate.

In adults with type 2 diabetes (T2D), metformin provides cardiovascular (CV) benefit in addition to glycemic control. Adolescents with T1D are also considered to be at increased risk for CV events, and most Guidelines recommend aggressive management of CV risk factors in them. However, the limited data on the effect of metformin on CV risk factors in youth with T1D does not demonstrate significant CV benefit. Hopefully, the ongoing trials REMOVAL (Reducing with metformin vascular adverse lesions in type 1 diabetes) and EMERALD (Effect of metformin on cardiovascular function in adolescents with type 1 diabetes) may provide a clearer idea of the CV benefit of metformin in patients with T1D.

To summarise, available data are not sufficient to suggest routine use of metformin in youth with T1D. There is a great need for larger studies.

Recurrent hypoglycemia in a young girl: tracking a missed diagnosis!

Somashekara H Ramakrishna[1], Siddram J Patil[2], Anil Kumar Sapare[3], Hiremath Sagar[3], Anusha AJ[4], Subramanian Kannan[5]

1 Consultant Paediatric Gastroenterology, 2 Consultant Department of Genetics, 3 Consultant Department of Paediatric Pulmonology and Intensivist, 4 Resident, Department of Paediatrics, 5 Consultant and HOD, Department of Endocrinology, Narayana Health City, Bangalore, Karnataka

Introduction:

Fructose 1, 6-bisphosphatase (FBPase) deficiency is a rare inborn error of metabolism. FBPase is a key enzyme in the gluconeogenetic pathway, whose deficiency results in severe hypoglycemia, ketonuria and metabolic acidosis [1]. Initial symptoms tend to appear in early postnatal life, but the disease is often not diagnosed at this age [2]. Attacks are precipitated by prolonged fasting, infections or ingestion of fructose containing formulas. The following is a case report of an 8yo girl who presented to us with a history of recurrent episodes of hypoglycemia since age 4y: the diagnosis of FBPase was finally made after 4 years of multiple hospitalizations and evaluation.

Case presentation:

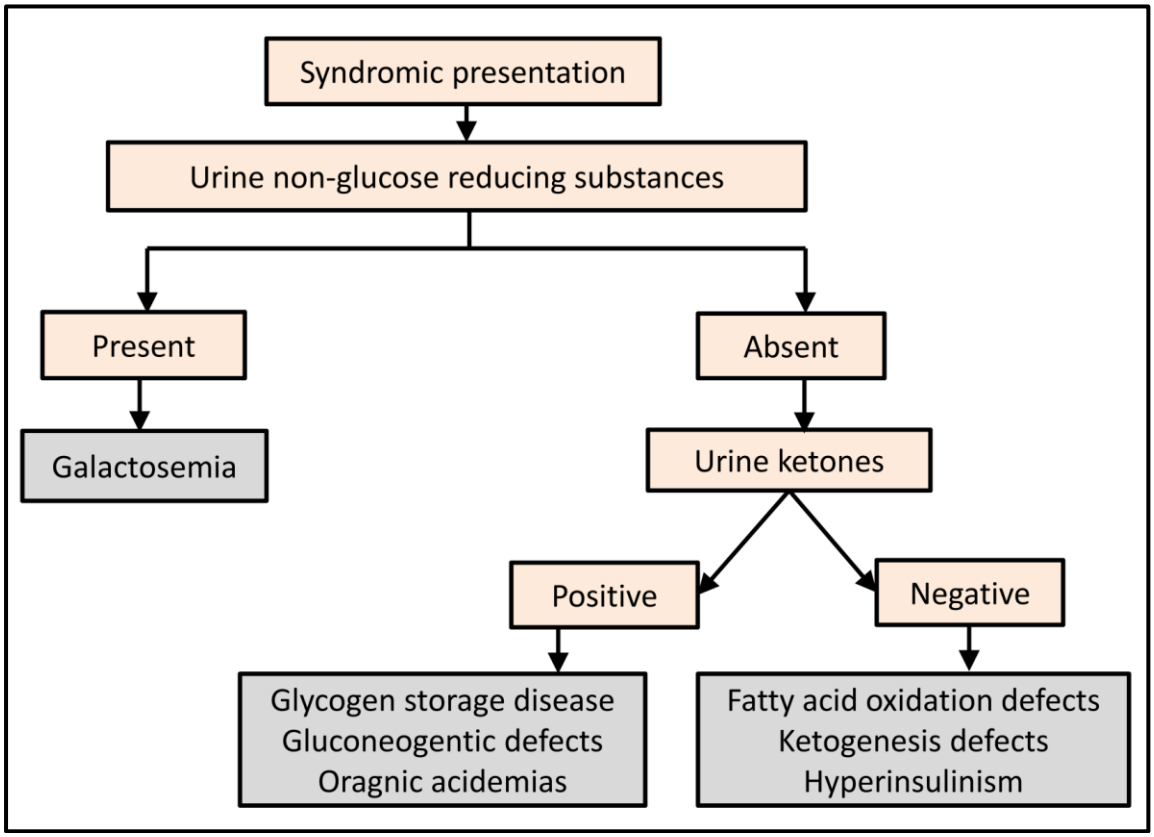
An 8yo girl born to third-degree consanguineous parents had been symptomatic since age 4y with recurrent episodes of hypoglycemia and seizures. She was admitted with history of abdominal pain, vomiting and lethargy for the past two days, and drowsiness for the past one day.

She had at least 4-5 similar episodes in the past, with extensive work up for hypoglycemia and seizures. Every episode was precipitated by poor appetite, fever, and either an upper respiratory or gastrointestinal infection, with hypoglycemic seizures typically occurring after 8-16 hours of prolonged fasting. Past work up confirmed hypoglycemia, and revealed lactic acidosis, ketonuria and suppressed insulin levels. Her thyroid, adrenal functions were normal. Work up for in-born errors of metabolism panel was done twice and was reportedly negative. Clonidine stimulation test was positive for growth hormone (GH) deficiency (2h post-clonidine GH level of 6 ng/ml). She was treated with GH injections for 1 year: this was stopped as her hypoglycemia and seizures persisted despite GH.
During the current admission, she was noted to be drowsy, with altered sensorium (GCS-12/15), but hemodynamically stable. Systemic examination was unremarkable apart from hepatomegaly 4cm below the right costal margin. On presentation at the local hospital, her capillary blood sugar was 26 mg/dL, and after multiple dextrose injections, rose to 96 mg/dL on 12.5% dextrose infusion. Urine ketone bodies were 1+ and arterial blood gas showed severe anion gap metabolic acidosis (pH: 6.88, bicarbonate: 3, lactate: 7, BE: -12, anion gap: 32). Uric acid level was high: 17 mg/dL, as was the triglyceride level: 509 mg/dL though the total cholesterol was normal. Urine for reducing substances was negative. She was treated with intravenous infusion of glucose, bicarbonate and antibiotics. There was a dramatic clinical improvement in 48 hours and she was shifted to the ward. Keeping in mind a differential diagnosis of mitochondrial defect versus gluconeogenic versus glycogen storage disorders, liver and muscle biopsies were done. Histopathology revealed mild to moderate macrovesicular steatosis in the liver, and steatosis in the muscle, with no evidence of glycogen. Tandem mass spectrometry (TMS) showed elevated blood C4OH carnitine, suggestive of severe ketosis. Urine organic acid profile revealed elevated ketones, and lactic acid metabolites, including glycerol. Based on this clinical profile, FPBase deficiency was strongly suspected. Molecular analysis of blood fructose-1, 6-bisphosphatase (FBP1) gene showed a homozygous 'pathogenic' variant, with a 331bp ALU sequence element insertion detected in exon 2 of the FBP1 gene, confirming diagnosis of FBPase deficiency.
She was discharged with advice of frequent feeding, use of uncooked corn-starch, and avoidance of sweets. There had been no hypoglycemic episode till 6 months of follow up.

Discussion:
FPBase deficiency is a very rare autosomal recessive disorder caused by a mutation of the FPB gene (*FBP1*). During periods of trivial illness, individuals with FBP deficiency may develop ketotic hypoglycemia, metabolic acidosis, lactic acidemia, and an increased anion gap (3). Hypoglycemia and lactic acidosis are characteristic of an enzymatic block in the last steps of the gluconeogenesis. Our patient had multiple episodes of hypoglycemia precipitated by short periods of fasting, for which she was extensively investigated without a proper diagnosis, and managed with anticonvulsants with a misdiagnosis of seizure disorder, and GH with a misdiagnosis of GHD. At presentation, she had the classical features of FBPase deficiency described in literature (3).

We followed the following simple approach for the diagnosis (4). The possibility of glycogen storage disorders was ruled out by absence of glycogen in the liver histology. Urine organic acids did not suggest organic academia. Based on this algorithm, a diagnosis of probable FBPase deficiency (gluconeogenetic defect) was made, which was confirmed by genetic analysis. The diagnosis of FBPase deficiency should be made by molecular analysis on DNA

from peripheral leukocytes. Our patient was found to have a homozygous pathogenic variant that resulted in a 331bp ALU sequence element insertion in exon 2 of the *FBP1* gene. If no mutation is found despite highly suggestive clinical and laboratory findings, the determination of enzymatic activity in a liver biopsy is recommended.



Conclusion:

Clinicians must consider the diagnosis of FBPase deficiency when a patient presents with episodes of severe hypoglycemia and lactic acidosis, especially accompanied by metabolic acidosis and ketonemia, typically triggered by infection and fasting. Early diagnosis, urgent treatment of hypoglycemia, and appropriate diet control can prevent death, improve growth and quality of life of these children. Our report also confirms that this very rare disease can be misdiagnosed, as other carbohydrate metabolic defects are usually suspected initially.

References:

1. Lubna Jafri, Osman Farooq. Fructose 1,6-bisphosphatase Deficiency Causing Cerebral Hypoxic Ischemic Injury in a Pediatric Patient. Journal of Neurology and Neurosurgery. Vol 2. Issue 1.1000007.
2. Kamate M, et al. BMJ Case Rep 2014. Sep 22. doi:10.1136/bcr-2013-201553.
3. Santer et al. A summary of molecular genetic findings in fructose-1,6-bisphosphatase deficiency with a focus on a common long-range deletion and the role of MLPA analysis. Orphanet Journal of Rare Diseases (2016) 11:44.
4. Jalan AB. Inborn errors of metabolism in critically ill Newborns. First edition. New Delhi. Nobel Vision. 2012(4). Basic investigations in a critically ill baby with suspected IEM. 22-31.

Pseudohypoaldosteronism type 1: a challenging diagnosis

Dr Shaila Bhattacharya, Consultant Pediatric Endocrinologist; Dr Kirti Prabhu, Fellow, Pediatric Endocrinology, Manipal Hospitals, Bangalore

Case Report:

A 5 day old female baby, first by birth order, born of 2nd degree consanguineous marriage was brought with complaints of not feeding well and lethargy since 1 day. She was born at term by normal delivery, with a birth weight of 2.5 kg (5th percentile) and normal APGAR scores. There were no perinatal problems, and the family history was unremarkable. The baby was on exclusive breast feeding, and had a weight loss of 17% from birth weight. Her pulse rate was 89/min, respiratory rate was 68/min, mean arterial blood pressure (BP) of 52 mm Hg. She was hypothermic with cold peripheries, prolonged capillary refill time, acidotic breathing and respiratory distress. She had poor tone, anterior fontanelle was sunken and skin turgor decreased. She had normal external female genitalia, no hyperpigmentation, no signs of virilisation, and other physical examination findings were unremarkable. Laboratory examination demonstrated hyponatremia (serum sodium 118 mEq/L), hyperkalemia (potassium 8 mEq/L), and metabolic acidosis (pH 7.22, serum bicarbonate 7 mmol/L). Her sepsis work up was normal with sterile blood culture and normal C- reactive protein. The BUN (49.50 mg/dl) and creatinine (0.7 mg/dl) were elevated. Serum glucose, calcium, magnesium were within normal limits. The ammonia (173 µg/dl) and lactate (20 mg/dl) were mildly elevated but the TMS/GCMS was normal. A provisional diagnosis of adrenal insufficiency was considered and relevant hormonal assays were sent. Neonatal screening tests, however, revealed a normal 17-hydroxyprogestenone (1.67ng/ml), thyroid stimulating hormone (7.20 µIU/ml) and cortisol (1721 nmol/L) level. Renal ultrasonography showed no abnormal findings.

In the NICU, the baby was treated with calcium gluconate, soda bicarbonate, glucose-insulin infusion, potassium binding resins and 3% saline. The serum electrolytes levels and renal function returned to normal with initial parenteral hydration and sodium supplementation but the baby continued to have recurrent persistent hyperkalemia and hyponatremia. She also required ventilatory support on and off and continued having intermittent seizures. In view of persistent, severe hyperkalemia, hyponatremia and metabolic acidosis, she was suspected to have adrenal insufficiency, but the normal 17-OHP and cortisol levels suggested the diagnosis of pseudohypoaldosteronism (PHA). This was confirmed by increased serum aldosterone level of 1544 pg/ml (normal 20-1110) and increased plasma renin activity (PRA). The treatment was continued with high oral sodium supplements, K+ binding resins, and later oral fludrocortisone was added. After a prolonged NICU stay, she was discharged on oral sodamint tablets, 3% sodium chloride solution, and fludrocortisone.

The baby was lost to follow up after that, but after 4 months was brought to emergency with complaints of vomiting, decreased activity and poor feeding for 2 days. There was history of missing medications. She had ventricular tachycardia with heart rate of 196/min, respiratory rate of 64/min, and BP of 84/52 mmHg, hyperkalemia (potassium 9.8 mmol/L), hyponatremia (sodium 125 mmol/L), and metabolic acidosis (pH 7.25, bicarbonate 13

mmol/L). The treatment was started for correction of hyperkalemia and hyponatremia: the ventricular tachycardia reverted on correction of hyperkalemia. Treatment with calcium gluconate, soda bicarbonate, glucose-insulin infusion, potassium binding resins, 3% saline was continued, and genetic testing was sent for PHA. Genetic testing revealed a homozygous insertion of 2 nucleotides at 744 and 745 positions (c.744_745insTG;p. Arg249*) in the Exon 3 of the *SCNN1A* gene.

Discussion

Pseudohypoaldosteronism type 1 (PHA1) is a rare disease of mineralocorticoid resistance, characterized by renal salt wasting, dehydration and failure to thrive in the neonatal period[1, 2]. The cardinal laboratory abnormalities of PHA1 are hyponatremia, hyperkalemia, and metabolic acidosis, despite elevated PRA and aldosterone levels. There is an apparent unresponsiveness of the renal tubules to the action of aldosterone. PHA1 occurs in two forms – renal and generalized[3]. The two forms are genetically different and vary considerably in clinical severity and phenotypic expression. The renal form, AD-PHA1, is autosomal dominantly inherited, and is due to a heterozygous mutation of the mineralo-corticoid receptor gene NR3C2. Since ENaC is expressed not only in the distal nephron, but also in the colon, sweat glands, salivary glands and lung epithelial cells, AR-PHA1, which is caused by mutations in one of the three subunits (alpha , beta or gamma) SCNN1A, SCNN1B, SCNNIG of the ENaC2[4], presents with salt wasting from these various organs as well as from the kidneys[5]. Also, the salt loss in AR-PHA1 is severe and does not improve with age; therefore, patients require massive sodium supplementation throughout life. Infants who present with electrolyte imbalance like hyperkalemia and/or hyponatremia, and weight loss, should be evaluated for adrenocortical function. While evaluating any infant with suspected CAH, one should consider PHA as one of the differential diagnoses. It is important to differentiate PHA1 from CAH since the former does not respond to corticosteroid therapy.

References:

1. Sartorato P, Khaldi Y, Lapeyraque AL, Armanini D, Kuhnle U, Salomon R, et al. Inactivating mutations of the mineralocorticoid receptor in Type I pseudohypoaldosteronism. Mol Cell Endocrinol. 2004;217: 119–125.
2. Geller DS. Mineralocorticoid resistance. Clin Endocrinol (Oxf) 2005;62:513–520.
3. Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res. 2009;72:1–9.
4. Chang SS, Grunder S, Hanukoglu A, Rosler A, Mathew PM, Hanukoglu I, et al. Mutations in subunits of the epithelial sodium channel cause salt wasting with hyperkalaemic acidosis, pseudohypoaldosteronism type 1. Nat Genet. 1996;12:248–253.
5. Kuhnle U. Pseudohypoaldosteronism: mutation found, problem solved? Mol Cell Endocrinol.1997;133:77–80.

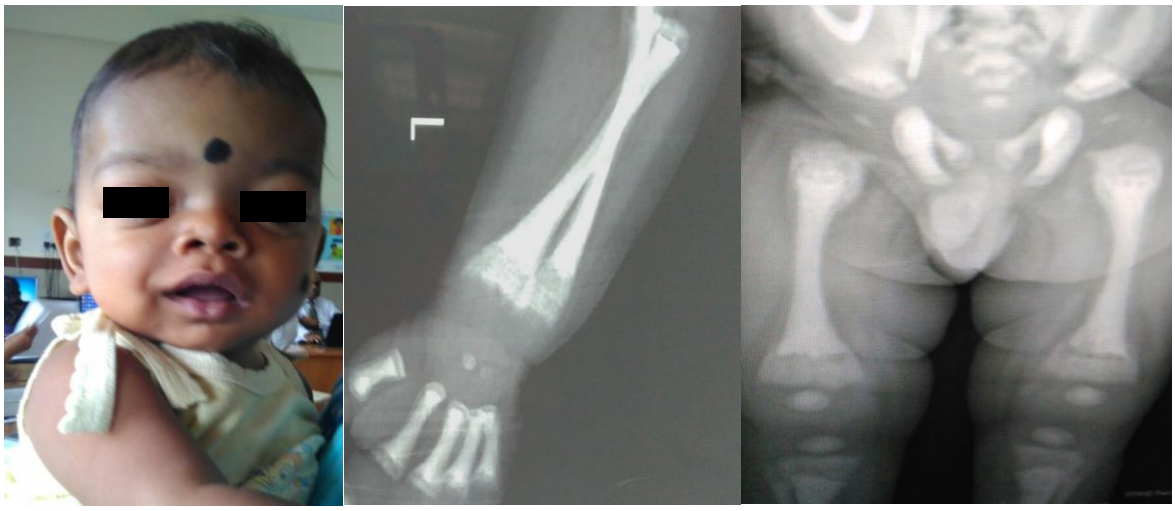
Osteopetrorickets: a rare skeletal association

Dr Deepa Anirudhan & Dr P Raghupathy, Indira Gandhi Institute of Child Health, Bangalore

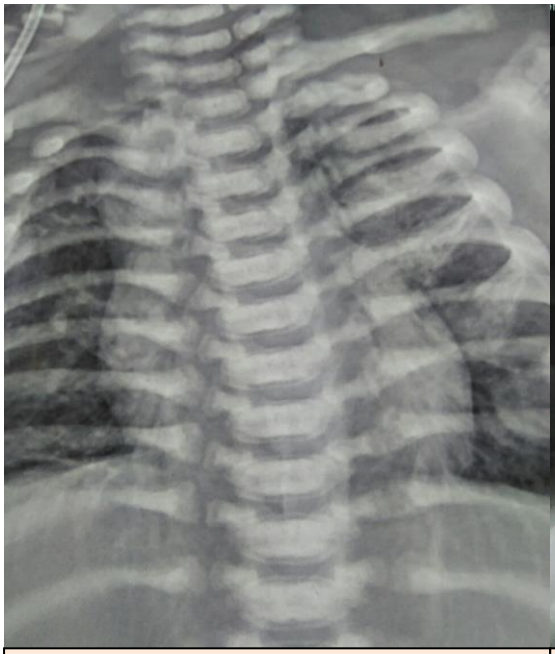
A 9 month old infant was brought with the complaints of developmental delay, and increasing abdominal distension for the past 4 months. He is the only child of a non-consanguineous marriage, born by normal delivery with a birth weight of 3.2 kg. At the age of 6 months, he was diagnosed to have hydrocephalus and underwent a VP shunt surgery. The parents noted progressive abdominal distension around the same time. No history of recurrent respiratory infections or blood transfusions in the past was reported.

On examination, the infant's weight was 6.5 kg, length was 61 cm and head circumference was 42 cm. He had mild pallor, coarse facies, prominent orbital margins ("Mephistophelian appearance"), depressed nasal bridge, frontal bossing, bilateral proptosis, nystagmus, and widening of both wrists. His anterior fontanelle was small (1 X 1 cm), and posterior fontanelle was closed. There was gross hepatosplenomegaly: liver measuring 6 cm below right costal margin in the midclavicular line with a span of 9 cm, and spleen enlarged 7 cm below left costal margin, firm in consistency. There was no cranial nerve palsy or hypotonia. There were no other systemic abnormalities.

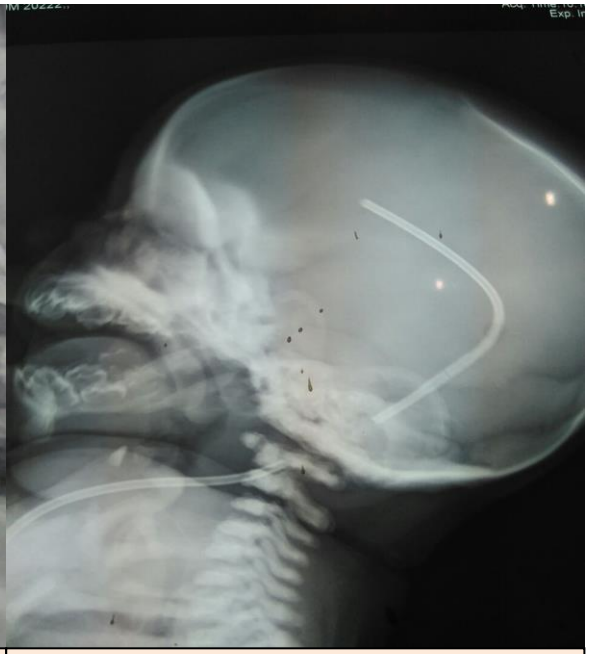
Investigations revealed a serum calcium of 9.7 mg/dL, phosphorus of 2 mg/dL and alkaline phosphatase of 1388 U/L, consistent with rickets. His hemoglobin was 11.5 g/dl, total leucocyte count 36,770/mm^3 (N25, L69, M6) and platelet count 105,000/mm^3. Renal and liver function tests were normal. Bone marrow aspirate was reactive with no blasts.



Radiographic findings were consistent with osteopetrosis, which included diffusely increased density of the entire skeleton, typical "bone in bone appearance" in the diaphyses of the long bones, "Sandwich vertebrae", with areas of translucency encircling the vertebral bodies, increased thickening of skull vault and sclerosis over the skull base. In addition, changes suggestive of rickets viz., cupping, fraying of metaphyseal ends of long bones and widening of the growth plates were also seen.



Sandwich vertebrae: translucency surrounding the vertebral bodies



Increased density around the orbits

Discussion: Rickets is a well-known complication and a paradoxical feature of infantile malignant osteopetrosis, the latter resulting from the defect in osteoclastogenesis, or a lack of functional osteoclasts. Impaired bone resorption and continuing new bone formation (manifesting as bone density on x-ray) cause abnormal bone marrow cavity formation, leading to the chain events of pancytopenia, extramedullary haematopoiesis and hepatosplenomegaly. In the absence of bone resorption, >99% of the calcium gets sequestrated in the bone, and with a low serum calcium, the Ca X P product falls to <30, which is insufficient for mineralisation. In osteopetrorickets, osteopenia is not seen on x-rays because of bone sclerosis. Appropriate treatment leads to improvement of rickets, besides ensuring improved general wellbeing of the patient, and protects against respiratory tract infections. The mainstay of treatment is 1,25 dihydroxy Vitamin D3 (calcitriol) and high dose calcium supplementation. Calcitriol promotes absorption of calcium and phosphorus from the gastrointestinal tract and renal reabsorption of calcium. It also enhances the effect of parathormone on bone resorption. Bone mineral density measurements show clear improvement with the treatment of rickets. The progress in rickets can be monitored biochemically and radiologically. However the treatment of osteopetrorickets is complex. Bone marrow transplantation (BMT) helps in providing hematopoietic stem cells from which normal osteoclasts differentiate. In rickets, normal osteoclasts cannot resorb the unmineralized osteoid. In other words, BMT alone cannot cure rickets. Hence, for BMT to be successful, rickets should be treated first.

References

1. Kaur, S., Kulkarni, K. (2010) Osteopetrorickets: a twin paradox. *BMJ Case Reports*
2. Kaplan FS, August CS, Fallon MD, et al. (1993) Osteopetrorickets: the paradox of plenty. Pathophysiology and treatment. *Clin Orthop* **294**: 64–78.
3. Gonen KA, Yazici Z, Gokalp G, Ucar, AK. (2013) Infantile Osteopetrosis with superimposed rickets. *Pediatr Radiol* **43**: 189-195.

Finding ways to tackle unmet needs of children with chronic endocrine problems

Santhosh Olety, Pediatric and Adolescent Endocrinologist, Karnataka Institute of Endocrinology and Research, Bangalore

Working in the West, where health care costs are covered by the State, I hardly thought about cost implications for patients. Here in India, it becomes an art to customise and individualise management based on what the family can afford. I would like to share examples of two chronic conditions, namely diabetes and growth hormone deficiency (GHD), where I have learnt ways of managing poor patients, by helping them to overcome financial difficulties.

Childhood diabetes is a global problem, with enormous psychological impact on the entire family. The International Society for Pediatric and Adolescent Diabetes (ISPAD) developed guidelines in 2000, updated regularly since, to assist health professionals in the management of young people with diabetes. These guidelines are based on the St. Vincent Declaration, the Declaration of Kos, and the Declaration of the Americas, which define the rights of all people with diabetes and focus on significant areas of responsibility for those involved in the care of diabetic children and adolescents to promote optimal health, social welfare, and quality of life for *all* children and adolescents with diabetes around the world.

There are multiple challenges for both the professionals and the families looking after diabetes, such as acceptance of diagnosis, compliance, poor understanding, psychological impact, financial issues etc. In our country where most patients come from low socioeconomic strata and where health care expenses for chronic disorders are borne by families themselves, financial difficulties become a big challenge for ensuring optimal diabetes care. I had a small peek of how the medical community has been supporting these families to cope with this. I understand many centres throughout India are registered with and getting international support such from Life For a Child (LFC), Changing Diabetes in Children (CDiC) etc. Many other centres get local philanthropic support to provide holistic support including free or subsidized insulin, glucometers, glucose strips, counselling and lab investigations. An example is our Autonomous Government Institute (Karnataka Institute of Diabetology), where we started a Children Benevolent Fund to be used exclusively for overall welfare of childhood diabetes. We receive contributions from philanthropists, medical societies, our well-to-do patients, pharma companies, and a few corporate establishments, as a part of corporate social responsibilities. This helps us meet the needs of our 330 patients with diabetes. There are also many patients who have no access to such benefits since they live far from such centres. So, we as care providers need to look for ways which has are sustainable in a long run to provide support to such patients, with the help of local government agencies. This can be driven through societies such as ISPAE.

I am very sure most of us are working hard to arrange similar types of support mechanisms, and I have started believing there are always some ways of getting help to poor families.

Pedendoscan

Dr Sachin Mittal, Consultant Endocrinologist, Fortis Hospital, Chandigarh

Diabetes Mellitus

Efficacy and implementation of an Internet psychoeducational program for teens with type 1 diabetes. Whittemore R et al. Pediatr Diabetes. 2016 Dec;17(8):567-575.

Teens with type 1 diabetes (n = 124, 11-14 yr) were randomly prescribed either an Internet psychoeducational program (Teens.Connect) shown to be efficacious under controlled conditions or an open-access diabetes website for youth (Planet D.) Participation in the Teens.Connect lessons was low, with only 69% of teens completing any lesson. After 6 months there were no significant differences in A1C, QoL or secondary outcomes between groups. Teens in the Teens.Connect group reported lower perceived stress over time ($p < 0.01$). The authors concluded that teens do not actively participate in an Internet psychoeducational program when they do not have frequent reminders, which may have contributed to a lack of treatment effect.

Incidence and predictors of early adulthood pre-diabetes/type 2 diabetes, among Iranian adolescents: the Tehran Lipid and Glucose Study. Mirbolouk M et al. Pediatr Diabetes. 2016 Dec; 17(8):608-616.

To evaluate the incidence and predictors of early adulthood pre-diabetes/type 2 diabetes (T2D) among Iranian adolescents, 2563 subjects aged 10-19 yr, without pre-diabetes/T2D were enrolled and followed up for 9.2 yr. Pre-diabetes was defined as fasting plasma glucose (FPG) 5.6 to <7 mmol/L. T2D was defined as anti-T2D drug consumption or FPG ≥7 mmol/L. During follow-up, 208 cases of pre-diabetes/T2D occurred, resulting in an incidence rate of 9.61 per 1000 person-years. Among the non-modifiable risk factors, paternal history of T2D, and among modifiable risk factors, the presence of general adiposity as well as the higher level of FPG, should be considered among adolescents for development of pre-diabetes/T2D later in the young adulthood.

Evaluation of a novel continuous glucose monitoring guided system for adjustment of insulin dosing - PumpTune: a randomized controlled trial. Anderson D et al. Pediatr Diabetes. 2016 Nov;17(7):478-482

The glycaemic profiles of children using CSII, CGM after their diabetologist or a novel algorithm (PumpTune) adjusted their insulin pump settings, were compared in a randomized cross-over trial of 22 patients aged 6-14 yr with type 1 diabetes with mean Hba1c 7.4% (57 mmol/mol), over two periods each of 6.5 d. A total of 63.4% of the sensor glucose levels were within target range with PumpTune settings and 57.4% were within range with the clinician settings ($p = 0.016$). The mean number of times when a sensor glucose level <2.75 mmol/L was recorded with PumpTune settings was 2.9, compared with 3.7 with clinician settings ($p = 0.39$). There were no serious adverse outcomes and no difference in parent-assessed satisfaction, leading authors to conclude that the automated insulin pump adjustment with PumpTune is feasible.

Disorders of Sexual Development

The Long-Term Outcome of Boys with Partial Androgen Insensitivity Syndrome (PAIS) and a Mutation in the Androgen Receptor Gene. Lucas-Herald A. J Clin Endocrinol Metab. 2016 Nov; 101 (11):3959-3967

To assess the clinical characteristics and long-term outcomes in 52 young men with suspected PAIS who presented before the age of 16 years and had genetic analysis of the AR gene. The median ages at presentation and at the time of the study were 1 month (range, 1 day to 16 years) and 22 years (range, 16 to 52 years), respectively. Of the cohort, 29 men (56%) had 20 different AR mutations reported. Thirty-five men (67%) required at least one surgical procedure, and those with a mutation were more likely to require multiple surgeries for hypospadias (P = .004). All cases with an AR mutation had gynecomastia, compared to 9% of those without an AR mutation. The authors concluded that boys with genetically confirmed PAIS are likely to have a poorer clinical outcome than those with XY DSD, with normal T synthesis, and without an identifiable AR mutation. Routine genetic analysis of AR to confirm PAIS informs long-term prognosis and management.

Growth and Development

The Influence of Growth Hormone Treatment on Glucose Homeostasis in Growth Hormone-Deficient Children: A Six-Year Follow-Up Study. Baronio F et al. Horm Res Paediatr. 2016;86 (3):196-200.

99 GHD (62 male, 37 female; age 8.9 ± 3.5 years) children under GH treatment were studied for a median period of 6 years (range 1.5-16.2). Every year, patients underwent an oral glucose tolerance test to longitudinally study the insulin sensitivity (HOMA-S), insulin secretion [insulinogenic index (IGI)] and capacity of β-cells to adapt to changes in insulin sensitivity [oral disposition index (ODI)]. Although HOMA-S remained unchanged, an increase in IGI and ODI was observed, becoming significant after 6 years of treatment (1.25 ± 1.28 vs. 2.35 ± 2.38, $p < 0.05$ and 0.57 ± 0.68 vs. 1.50 ± 1.92, $p < 0.01$, respectively).The results suggest a positive influence of GH treatment on the β-cell secretory capacity in children with GH deficiency.

Puberty

Changes in Body Mass Index in Girls with Idiopathic Central Precocious Puberty under Gonadotropin-Releasing Hormone Analogue Therapy: The Spanish Registry. Corripio R. Horm Res Paediatr. 2016;86(3):154-160.

To evaluate the effect of GnRHa treatment on BMI-standard deviation score (SDS) from diagnosis of idiopathic CPP until adult height, an observational study of 333 girls (22.2% adopted) girls diagnosed with CPP in 55 departments of pediatric endocrinology throughout Spain was carried out. During treatment, there was an increase in BMI-SDS of 0.43 ± 1.17 (95% CI: 0.20-0.64). At adult height (n = 49), BMI-SDS was 1.51 ± 1.38, which was 0.60 ± 1.09 higher than at diagnosis (95% CI: 0.43-0.75). Thus the authors concluded that during treatment with GnRHa, girls experience a significant increase in BMI-SDS that persists after therapy is stopped and adult height has been reached.

Bone and Mineral Metabolism

Vitamin D status in youth with type 1 and type 2 diabetes enrolled in the Pediatric Diabetes Consortium (PDC) is not worse than in youth without diabetes. Wood JR et al. Pediatr Diabetes. 2016 Dec; 17 (8):584-591.

25-hydroxy vitamin D (25OHD) levels in 215 youth with T1D and 326 youth with T2D enrolled in the Pediatric Diabetes Consortium (PDC) were compared with those of youth of the same age without diabetes from the 2005-2006 NHANES Survey. Vitamin D deficiency (<21 ng/mL) was present in 36% of PDC participants, and insufficiency (21-29 ng/mL) was present in an additional 34%. Youth with T2D had significantly lower 25OHD levels than youth with T1D ($p < 0.001$), but this difference was largely eliminated after adjusting for race/ethnicity and socio-economic status. The authors concluded that Vitamin D deficiency/insufficiency is present in a substantial proportion of youth with diabetes but the prevalence appears similar to that in youth without Diabetes.

Adrenal

Assessment of early atherosclerosis and left ventricular dysfunction in children with 21-hydroxylase deficiency. Özdemir R et al. Clin Endocrinol (Oxf). 2016 Nov 7.

25 children with 21-hydroxylase deficiency who received glucocorticoid and/or mineralocorticoid treatment for at least 12 months were analysed to determine the effects of the disease and its treatment on vascular structures and ventricular function. Tissue Doppler imaging measurements revealed left ventricular diastolic impairment in the patient group compared to the controls. Carotid intima-media thickness, stiffness index, elastic modulus of the aorta and carotid artery were significantly higher; meanwhile, aortic distensibility and carotid distensibility were lower in the patient group, all of which indicates the presence of subclinical atherosclerosis. Cardiovascular function and the elastic properties of major arteries are disturbed in children and adolescents with 21-hydroxylase-deficient CAH.

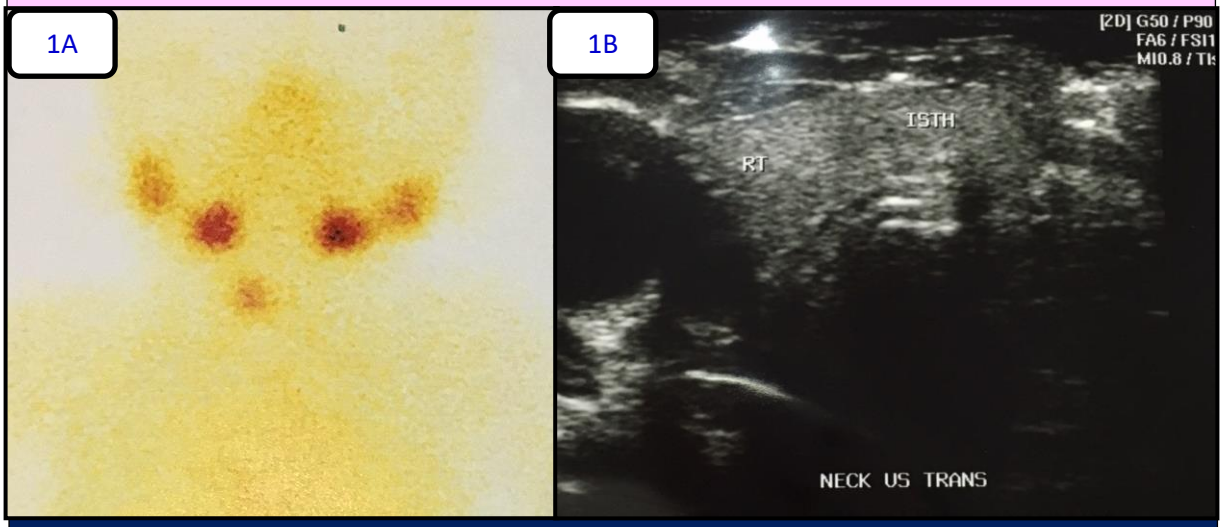
Establishing Normal Ranges of Basal and ACTH-Stimulated Serum Free Cortisol in Children. Eyal O et al. Horm Res Paediatr. 2016;86(2):94-99.

To establish the normative data in children for serum free cortisol, 85 subjects (28 male; 57 female) with a median age of 8.5 years who were referred for ACTH testing to rule out adrenal insufficiency were enrolled. Only children with normal response and normal androgen levels were included. Total cortisol was determined by a chemiluminescence method, and free cortisol was measured by the same method following equilibrium dialysis. The mean basal and peak total cortisol levels were 11.5 ± 5.7 and 32.9 ± 6.2 µg/dl, respectively. The mean basal and peak free cortisol levels were 0.4 ± 0.3 and 1.8 ± 0.6 µg/dl, respectively. The 3rd and 97th percentile values for peak free cortisol were 0.94 µg/dl (26 nmol/l) and 2.97 µg/dl (82 nmol/l), respectively. This study provides reference ranges for stimulated free cortisol in children, with a cutoff value of 0.9 µg/dl (25nmol/l) as a normal response to a standard ACTH test.

Photo Quiz 1

Subramanian Kannan[1], Siddram J Patil[2]
1 Consultant and HOD, Department of Endocrinology, 2 Consultant, Department of Genetics, Narayana Health City, Bangalore, Karnataka

A-6-years old boy awaiting device closure for patent ductus arteriosus referred to the endocrine department for an elevated TSH of 10 µIU/ml. The child had history of seizures during infancy, poor feeding and global developmental delay. On examination the child had dysmorphic features including microcephaly, flat nasal bridge and low set ears. There was hypotonia of all limbs. Technetium thyroid scan (1A) and Ultrasound of thyroid (1B) are shown in the figure below.



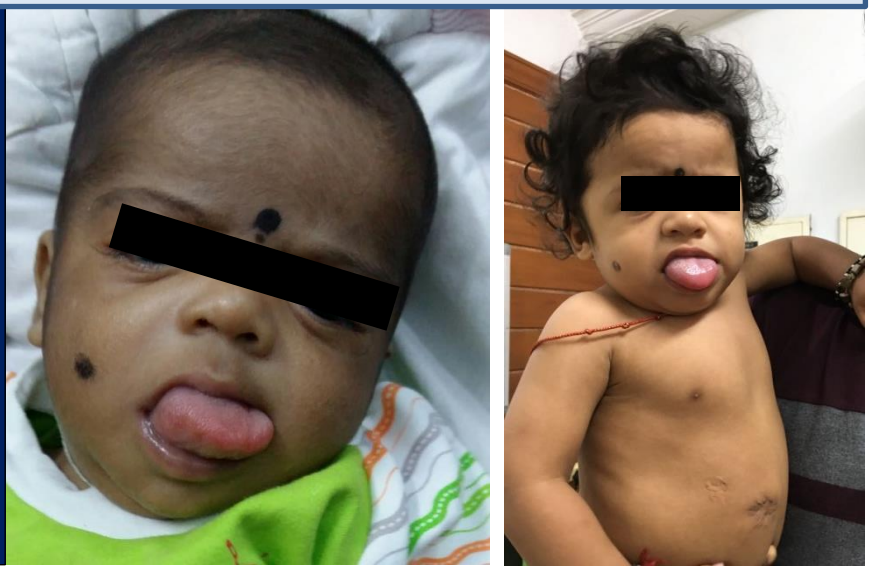
Identify the abnormality on Technetium thyroid scan (1A) and Ultrasound of thyroid (1B)
What is the most likely genetic defect associated with this child?

Photo Quiz 2

Dr Shaila Bhattacharya, Consultant Paediatric Endocrinologist; Dr Shobhi AV, Fellow, Pediatric Endocrinology, Manipal Hospitals, Bangalore

Identify the abnormalities in this child.

What is the most likely diagnosis of this child?



Conference Report: "ISPAE 2016- Sugars & Beyond"

Dr Tushar Godbole, Organizing Secretary, ISPAE Mid-term Meet 2016

ISPAE conducted its midterm meeting at Nashik, Maharashtra on 15th and 16th of October 2016, with special focus on pediatric diabetes. It was organized in association with the International Society for Pediatric and Adolescent Diabetes [ISPAD], our team comprising of Dr Sudha Rao [Organizing Chair], Dr Preeti Dabadghao [Scientific Chair] and Dr Tushar Godbole [Organizing Secretary].

The preconference workshop "Nuts and Bolts of Pediatric Diabetes" was conducted on 15th morning, where hands-on training on various practical topics in managing of pediatric diabetes was imparted. Sixty five participants: a mixed bag of mainly nutritionists and diabetes nurse educators, with some pediatricians, diabetologists, physicians, and fellows, were chosen from applicants across the country. Each participant presented a brief clinical scenario and how to handle it. The conveners, Drs Anju Virmani and Vijayalakshmi Bhatia, designed the workshop module. The faculty were Dr Carine de Beaufort (Luxemburg: Secretary General, ISPAD), Dr Asma Deeb (Abu Dhabi: Secretary General, Arab Society for Pediatric Endocrinology & Diabetes), Dr Aspi Irani and Dr Sheryl Salis (Mumbai), Dr Leena Priyambada (Vellore), and Dr Meena Mohan (Coimbatore).

This was followed by the main meeting, attended by 152 national delegates and 16 faculty members. On the first day, Dr Irani summarized the latest DKA management protocols and Dr Ganesh Jevalikar dealt with management of hyperglycemia in the ICU setting. Dr Vandana Jain gave practical tips in managing infections and immunizations in children with diabetes. Dr Yashpal Gogate discussed screening for complications; Dr Vijayasarathi the role of oral medicines in pediatric diabetes; and Dr Nihal Thomas the current scenario of research in monogenic diabetes in India and abroad. In the meet-the-expert sessions, Dr de Beaufort elaborated on the key aspects in managing infants and toddlers; while Dr Deeb touched upon diagnostic and management challenges, including managing adolescents.

The brief inaugural function touched all hearts: children with endocrine problems from an orphanage did the lamp-lighting ceremony. Dr Vijayakumar M presented the ISPAE annual report. Dr Virmani gave a brief report on the workshop. Dr de Beaufort appealed to all to become members of ISPAD, and extended an invitation to the 44th Annual Meeting of ISPAD in Hyderabad (first ISPAD meeting in India!) in October 2018, supported by ISPAE. Dr Godbole expressed the vote of thanks. The evening ended with a song recital by children with diabetes, followed by an entertainment program and dinner.

On the second day, Dr Dabadghao discussed PCOD and the metabolic syndrome in Indian adolescent girls, while Dr Deepak Dalal and Dr Archana Sarda emphasized social aspects of diabetes care in children. Dr Salis discussed various dietary options and counting beyond carbohydrates. In the plenary session, Dr de Beaufort threw light on recent advances in insulin pump therapy and newer devices; while Dr Deeb gave an overview on managing pediatric T2D. Dr Sudha Rao and Dr Vaman Khadilkar presented the two ends of the glucose homeostasis, hyperglycemia and hypoglycemia in neonates. Dr Abhishek Kulkarni

discussed the recent advances in management of CAH. Dr Vijayalakshmi Bhatia emphasized the need for newborn screening for congenital hypothyroidism and its methods.

26 abstracts were presented as posters from various institutions. This conference was paperless, with all the proceedings being given on a pen-drive to the delegates, and conducted very successfully despite many last-minute adversities. I thank Dr Yashpal, Dr Ganesh, and Dr Ruchi Parikh for their painstaking efforts, Dr Dabadghao for the wonderfully designed scientific program, Dr Sudha Rao for her constant support and feedback; and Dr Bhatia and Dr Virmani for their ideas and encouragement.

PEARLS FROM ISPAE 2016

Dr Ruchi Parikh, Pediatric Endocrinologist, Bai Jerbai Wadia Hospital for Children, Mumbai

- Diagnosis of Diabetic Ketoacidosis (DKA) can be confirmed at the bedside with the help of P.O.C meter (measuring blood glucose and if possible, β-hydroxybutyrate) and urine ketone strips; treatment must be started immediately without waiting for laboratory reports.
- During the management of DKA, maintain BG between 150-200 mg/dL till insulin infusion is being continued.
- In toddlers with T1D, the insulin pump is the best option for management. Optimal metabolic control can be achieved in toddlers by targeting low HbA1c with no increased risk of severe hypoglycemia.
- Hyperglycemia in a sick child increases the risk of mortality, morbidity and sepsis, therefore, accepting hyperglycemia as an adaptive response to critical illness and treating it only when it crosses the renal threshold is not justified.
- Maintain target BG between 110-180 mg/dL in sick children with stress hyperglycemia.
- MODY accounts for up to 2% of patients with diabetes in India.
- Though MODY has been perceived to be present before the age of 25 years, diagnosis can be delayed beyond 35 years.
- Next generation sequencing is the modality of choice for assessing the genetic profile of young onset diabetes, MODY, syndromic disorders and neonatal diabetes.
- Insulin resistance and resulting hyperinsulinemia is seen in three fourths of patients with polycystic ovary syndrome (PCOS) irrespective of BMI, but it is not essential for diagnosis, hence, there is no role of measuring insulin.
- Life style measures are an important aspect of management of adolescents with PCOS, while insulin sensitizers have a role in limited situations.
- Currently available data does not support the routine use of metformin or glucagon like peptide 1 analogues (GLP1a) in youth with T1D.
- The Artificial Pancreas could be available in the near future to optimize metabolic control in children with T1D.
- The aim of NBS-CH is not to miss severe permanent congenital hypothyroidism and at the same time have a minimum recall rate and minimum false positives.
- It is useful to have a confirmatory test once a screening test is positive.
- A recent report from India showed that on re-evaluation of children with CH at age 3y, thyroid hormone supplementation could be discontinued in 50% of them.

Activities by ISPAE Members

Dr Shaila Bhattacharyya, Shivajoyti Clinic, Bengaluru

On the occasion of World Diabetes Day and Children's Day, "Walkathon 2016" was organized by Shivajoyti Clinic at Cubbon Park, Bangalore, to create awareness about the disease. The theme for the event was "Wake up and walk for children with Diabetes". Children as well as adults participated enthusiastically: even a 2y old kid walked happily while her parents watched, stunned. This was followed by a drawing competition for the children, to bring out their artistic abilities. They were encouraged to paint on dried leaves. Following this was a quiz competition consisting of topics related to day-to-day management of diabetes. Winners of the drawing and quiz competitions were rewarded. This was followed by a yoga demonstration, various games and dance performances by the kids, which were thoroughly enjoyed by the audience.

It was nothing but sheer coincidence that "Makkala Habba" or "Children's Festival" was being held at Cubbon Park as a part of Children's Day celebrations. The Habba was one place where chaos, excitement, energy, ideas and imagination were running high, against a background of rich greenery, colourful flowers, chirping birds and a pleasant climate. It was an opportunity for children to truly appreciate nature's beauty at its fullest. They witnessed the age old culture and traditions of Karnataka like bullock cart rides, delicacies like ragi dosa and spiced buttermilk, sports such as Mallakhamba and Kusti, games like Lagori, Pagade and Kunte-Bille or Hopscotch, and tried their hands on pottery.

The event also turned out to be an opportunity for parents and children to interact: they actively discussed amongst themselves about diet, insulin schedules and physical activities. The adolescents with diabetes were seen encouraging the younger ones to follow regular diet and exercise for optimal control of diabetes. Dieticians clarified diet plans and answered various queries posed to them by parents and children.

On the whole, it was a fun filled day at Cubbon Park.

Dr Shalmi Mehta and Dr Ruchi Shah at Endokids Clinic, Ahmedabad, Gujrat

World Diabetes Day, celebrated on 20th November, 2016, was well attended by more than 200 people (including children with T1D and their parents). It started with a warm up session of yoga, followed by sports events where different competitions were organised for all age groups. 13 children participated in the talent evening after the sports events, and showcased their talents in dance, music and gymnastics. The fun filled event concluded with cutting a less-sugar cake, prize distribution ceremony and dinner.

Professor P Raghupathy, Department of Pediatric Endocrinology, Indira Gandhi Institute of Child Health, Bangalore, 12th November 2016

A comprehensive educational program was arranged for observance of World Diabetes Day, at the Indira Gandhi Institute of Child Health, Bangalore, as an annual event. There was enthusiastic participation from the children and their parents - this year 158 children with diabetes attended the function. Professor P Raghupathy, with the team of doctors (Drs HN Vani, Parvathy Lalitha, L Sireesh, Deepa Anirudhan, Shaila Sankeshwar), nurse (Ms Anitha), dietitian (Ms Rachitha) and volunteers (Ms Jamuna, Ms Pushpalatha, Dr Akanshka and others) from the Institute conducted the program, which was well received by the children and their parents.

Parents and children were provided educational sessions (low or high BG values, sick day management, insulin action and adjustment of daily dose, self home BG monitoring, etc.) in the daily management of childhood diabetes, and their questions and problems were addressed in detail. Nutritious, healthy, well-balanced meal planning was demonstrated by Ms Rachitha, with clear explanations of all aspects of nutrition that the children need to follow. Older patients shared their experience with diabetes and provided useful suggestions. The children and their parents actively took part in quiz competitions testing their knowledge in diabetes, bagging prizes. It was heartening to note that even young children had clear ideas and knowledge regarding their diabetes.

The occasion was made more memorable and lively by a drawing/ painting competition for the children, for which prizes were given. They were also encouraged to take part in singing and dancing. A child film actor, Miss Unnathi, also participated in the program and entertained the audience. All those who attended the function enjoyed the learning experiences, while also relishing the opportunity to participate in singing, dancing, poem recital, demonstration of yoga and other exercises, etc.

Such annual events have helped the children to develop self-confidence in managing their diabetes independently, complemented with help and support from their parents and

family members. The function was held under the auspices of ISPAE, and supported by the Changing Diabetes in Children (CDiC) Program of Novo Nordisk Education Fund.

The free monthly supplies of insulin, syringes, glucostrips, lancets etc. were distributed as usual to all the children who attended. A cool pouch to carry insulin during travel, was also given to all children.

Meena Mohan, Pediatric Endocrinologist, Kurinji Hospital, Coimbatore

During this year, three diabetes support group activities were conducted on 14.02.2016, 07.08.2016 and 13.11.16. Each support group activity was attended by about 30 families. Another activity was also held on Insulin Pump Day (09.10.16) which was attended by 15 families. The first two support group activities were conducted in the auditorium in Kurinji Hosptal whereas the last one conducted for World Diabetes Day was at Kovai Kondattam, a water theme park in Coimbatore. Competitions were held for drawing, musical chairs, and races for boys, girls, dads and the para-medical group. The families and children thoroughly enjoyed the day and everyone had fun. With increasing number of support group activities, the families have started to network, communicate and play an active role in inviting and organising for the activity days.

Dr Anjana Hulse, Pediatric Endocrinologist, Apollo Hospital, Bangalore

On the occasion of World Diabetes Day, a half-day workshop for children with T1D and their parents was organised at Apollo Hospital, Bangalore on 13th November 2016. In addition to talks on dietary management, injection techniques etc., parents were updated about newer advances (insulin pumps, AGP, iPort advance etc.). A 'Master Chef Competition' on healthy packed lunch was held for parents. Over 25 children and their parents attended

Hemchand K Prasad, Pediatric Endocrinologist, Mehta Children's Hospital, Chennai

IAP CCB and Mehta Children's Hospital jointly conducted a CME on "World Thyroid Day", the theme being congenital hypothyroidism (CH). The speakers were Prof Anna Simon from CMC Vellore, Dr Hemchand KP (Pediatric Endocrinologist) and Dr Trimurthi (Nuclear Physician) from MMM Hospital. It was attended by 80 practicing pediatricians in Chennai. Topics discussed were the role of cord TSH screening, approach to a positive screen, and role of thyroid scintigraphy in CH, followed by a discussion on interesting cases of CH.

Tushar Godbole, Nashik

Patient education program: Dialogue with International Faculty

On the eve of 14th October, Dr Tushar Godbole and Dr Yashpal Gogate organized a small question answer session for children with diabetes and their parents at Nashik. Dr Carine de Beaufort [Luxemburg] and Dr Asma Deeb [Abu Dhabi] kindly agreed to address the queries of parents of children with diabetes. 45 children and their parents attended the program, which was very interactive. Children cleared their doubts regarding need for multiple pricks, stem cell therapy, insulin pumps, self-care and other social issues with the international duo.

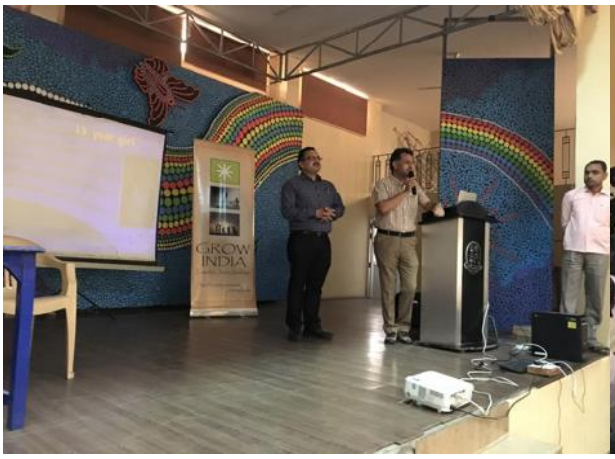
Dr Anurag Bajpai, Pediatric Endocrinologist, Kanpur

VIII GROW India Type 1 DM empowerment program

The program was attended by over 100 children with diabetes and their families, 150 school children from 20 schools across the region, eminent educationalists, social groups, and leading physicians working for children with diabetes. The highlights of the program included stellar performance by school teams in a Design workshop to solve complex health problems, release of T1D educational video, Launch of Type 1 Together We Win program with schools, Search for Diabetes to identify children with diabetes at an early stage, and cultural programs by children with diabetes.

GROW India Student sensitisation Program Nov 11 2016

The program provided education to over 500 school children about endocrine disorders.



III GROW India Day May 1 2016.

The program showcased work done by GROW India towards improving lives of children with growth disorders. The program was attended by over 500 children, parents, educationalists, doctors and social activists. The Theme for the program was "Childhood Obesity- From Fat to Fit". Key initiatives in the program included release of "Obesity - From Fat to Fit" and Obesity documentary. The program witnessed the launch of Road to Growth, From Fat to Fit and Together We Win projects with schools to increase awareness about growth, obesity and childhood diabetes. The Chief Guest Mr Kaushal Raj Sharma,

DM Kanpur highlighted the need for intervention towards improving lives of children with growth disorders. The program also included poster competition for students and exhibition on growth disorders.

Second Grow India IIT Kanpur Design Workshop October 1 2016

The workshop provided exposure for young students to the latest concepts of designing. 120 children from 20 schools across the region were mentored by 20 design students from IIT Kanpur under the stewardship of Prof Satyaki Roy, Design Department, IIT Kanpur. The teams underwent validated design exercises. As part of the workshop the teams designed solutions for health problems ranging from growth, type 1 DM, celiac disease and malnutrition.

Sixth Annual Grow INDIA Celiac Support Group Meeting October 18 2016

GROW India Workshops

1. Calcium disorders. IAP Allahabad. June 2016
2. Thyroid disorders. IAP Agra. July 2016
3. Growth disorders. IAP Jhansi. October 2016
4. Thyroid disorders. IAP Lucknow. October 2016
5. Glucose disorders. IAP Kanpur, October 2016
6. Puberty disorders. IAP West Delhi, November 2016

Ganesh Jevalikar, Senior Pediatric Endocrinologist, Medanta Medicity, Gurgaon

The "Mission Halt Diabetes" initiative by Division of Endocrinology and Diabetes, Medanta Medicity Hospital, Gurgaon was launched on 24th Nov 2016 with over 50 schoolchildren participating in myriad competitions at the hospital. These included workshops on diabetes, Nukkad Natak, slogan writing, and logo designing. The Mission includes continuous engagement with schools, envisaged around making schoolchildren the most vociferous ambassadors of leading good lifestyles. Diabetes Educators and Endocrinologists from Medanta have partnered with prominent Gurugram schools to educate and raise awareness about diabetes.

Awards and Fellowships

Dr KVS Harikumar, Senior Adviser, Command Hospital, Haryana, received fellowship by the Indian Society of Hypertension on 07.10.2016

Answers to Photo Quiz:

Photo quiz 1: Hemi-agenesis of left lobe of thyroid, 1p3 monosomy

Photo quiz 2: Beckwith-Wiedemann Syndrome; macrosomia, macroglossia, prominent ear crease, scar of surgery for umbilical hernia

Publications

Devi Dayal, Pediatric Endocrinology & Diabetes Unit, Advanced Pediatric Center, PGIMER, Chandigarh

1. Menon P, Dayal D, Rao SG, Bhattacharya A, Narasimha Rao KL. Childhood parathyroid adenoma: a rare but important cause of nephrolithiasis. *J Pediatr Endocrinol Metab*. 2016;29:853-56.
2. Dayal D. Comment on: "Therapies to Preserve β-Cell Function in Type 1 Diabetes". *Drugs.* 2016;76:625-6.
3. Ponnarmeni S, Angurana SK, Singhi S, Bansal A, Dayal D, Kaur R, Patial A, Savita Attri SV. Vitamin D deficiency in critically ill children with sepsis. *Paediatr Int Child Health.* 2016;36:15-21.
4. Dayal D. Non-invasive blood glucose monitoring is an elusive goose. *Int J Diabetes Dev Ctries.* 2016 April 16. DOI:10.1007/s13410-016-0493-6.
5. Dayal D, Soni V, Jayaraman D, Sindhuja L, Sachdeva N. Cultural gynecomastia in the 21st century India: “Witch's milk” revisited. *Pediatr Pol*. 2016;91:472-75.
6. Dayal D, Jayaraman D, Sankhyan N, Singhi P. Acute Painful Neuropathy in a Girl with Type 1 Diabetes: Long Term Follow-Up. *J Clin Diagn Res.* 2016;10: SD01-SD02.
7. Dayal D, Hansdak N, Vir D, Gupta A, Bakshi J. Hearing impairment in children with permanent congenital hypothyroidism: data from Northwest India. *Thyroid Res Pract.* 2016;13:67-70.
8. Dayal D. Thyroid ectopia is distinctly uncommon in Indian children with permanent congenital hypothyroidism due to dysgenetic glands. *Thyroid Res Pract.* 2016;13:94-95.
9. Agrawal J, Kumar R, Malhi P, Dayal D. Prevalence of psychosocial morbidity in children with type 1 diabetes mellitus: a survey from Northern India. *J Pediatr Endocrinol Metab.* 2016;29:893-9.
10. Dayal D. A Multimodal Approach is Necessary to Manage Mucormycosis in Patients with Diabetes. *J Clin Diagn Res.* 2016;10:SL01.

Anjana Hulse, Pediatric Endocrinologist, Apollo Hospital, Bangalore

1. Hulse A, Rai S, Prasanna Kumar KM. Evaluation of accuracy of ambulatory glucose profile in an outpatient setting in children with type 1 diabetes. *Indian Journal of Endocrinology and Metabolism*. 2016;20(5):643-647.
2. Rai S, Hulse A, Prasanna Kumar KM. Feasibility and acceptability of ambulatory glucose profile in children with Type 1 diabetes mellitus: A pilot study. *Indian Journal of Endocrinology and Metabolism*. 2016;20(6):790-794.

Meena Mohan, Pediatric Endocrinologist, Kurinji Hospital, Coimbatore, Tamilnadu

Verloo H, Meenakumari M, Abraham EJ, Malarvizhi G. A qualitative study of perceptions of determinants of disease burden among young patients with type 1 diabetes and their parents in South India. Diabetes Metab Syndr Obes. 2016 May 19;9:169-76.