CAPE NEWS

Newsletter of the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) *www.ispae.org.in*

July, 2020
Volume 24, Issue 2

Contents

From the Editor's Desk

Dear Friends,
Greetings from CAPE NEWS TEAM!
I hope you are all keeping safe while working as front-line warriors.

We are happy to present another interesting issue of CAPE NEWS. This issue has many interesting and new items including a *Special Article* on Synthetic Growth Charts and a *Mini-Review* on Potential therapies for T1DM (apart from Insulins).

We have also included a supplement with Abstracts of papers presented at ISPAE 2019 held at Kolkata. The Abstracts are arranged, as per poster numbers assigned during the conference, in three sections (in different colours) of Oral Papers, E-posters, and Posters.

Rakesh Kumar and team CAPE NEWS

Message from the ISPAE Office Bearers

Dear Friends,

Greetings! We hope all of you are safe and healthy.

It has been a hard year for all of us and our patients, with the threat of COVID19. This has turned the world upside down in terms of worries about delivery of care and medications to vulnerable populations, which include children with type 1 diabetes. An enormous change has been brought in the delivery of care including the introduction of telemedicine.

Scientific meetings have seen a sea of change from physical meetings to virtual ones. This may alter the method of conducting future meetings. It has affected the plans for the mid-term meeting of 2020 in Chandigarh, which may be getting postponed to 2022. Meanwhile, a huge number of web-based meetings have been happening around the country and the world.

Dr Sanjay Bhadada of Chandigarh and Dr Hemchand Prasad of Chennai are the recipients of the ISPAE Charity Awards for the year 2020. The time frame to complete ISPAE Observership of 2020 has been extended to March 2022 due to prevailing circumstances. The GPED activity of producing videos to raise awareness on newborn screening for hypothyroidism is facing some hurdles which will be sorted out soon.

We wish you the best of health.

Warm regards,

Preeti Dabadghao, Ahila Ayyavoo, Leena Priyambada & Executive Committee.

Special Article

Synthetic Growth Charts – the way forward?

Madhura Karguppikar [1], Vaman Khadilkar[2]

[1]Fellow Pediatric Endocrinology, Jehangir Hospital, Pune
[2]Consultant Pediatric Endocrinologist, Jehangir Hospital, Pune

India is in a phase of economic development and changing nutrition trends. This has brought about westernisation of food habits, resulting in rapid increases in overweight, and changes in growth patterns. The World Health Organisation (WHO) recommends updating growth charts once a decade in rapidly changing societies.[1] Therefore, it is necessary to update growth charts in India, decade after decade. The under-five growth standards developed by the WHO in 2006 are based on the assumption that "given optimal environmental conditions, all children around the world grow in a similar pattern, and hence a single standard can be used to assess children everywhere, regardless of ethnicity, socio-economic status and type of feeding". There is a large body of data from Asian countries suggesting that these charts may not be appropriate for all populations across the world.[2]

While the Indian government continues to collect data on lower and lower middle socio-economic classes through national family health surveys, data pertaining to middle and upper socio-economic classes is difficult to collect on a national scale. A study planned to collect such data requires huge funding, manpower and planning. Besides this, by the time it is collected, it may already be outdated. To overcome this, newer methods of constructing anthropometry based on limited data, have evolved in the recent times - many countries are adopting such growth charts.[3]

Growth prediction models date back to 1976 (triple logistic model of Bock and Thissen).[4] This was followed by models by Preece and Bains (1978) [5], Karlberg's ICP model [6] and JPPS seven parameter model (1988) [7], among others. In 1999, Hermanussen et al developed a method for generating distance standards of height without the need for extensive *de novo* measurements.[8] This method was further refined in 2012. Other methods used to synthesize anthropometry include quantile regression, principle component analysis, and regression equations, to name a few. These methods are used to generate the missing medians from birth to 18 years for height, weight, and BMI from available data at key ages. These generated means are further fitted using well established models of human growth, such as Preece Bains and JPPS models. [5,7] Once smoothed, the median curves thus produced are used to generate percentiles. Percentiles can be generated using global LMS values derived from a massive database from growth studies (more than 24000000 readings!) conducted on children over the last 50 years.

Thus, local growth parameters from any population growing in optimal environment and health, may be loaded to this global model for synthesising anthropometry. The recent publication in the Indian Journal of Endocrinology of Metabolism (IJEM) shows how this method can successfully produce growth charts for Indian children, which are similar to

growth charts produced using the standard LMS method (e.g. IAP 2015 charts). It also demonstrates that the spread of BMI and weight percentiles are narrower, thus preventing 'normalising obesity'. We request the reader to refer to the paper published in IJEM for a detailed understanding of this method. [9] The figure shows comparison of boys' height and weight synthetic charts and IAP 2015 charts to highlight the differences.

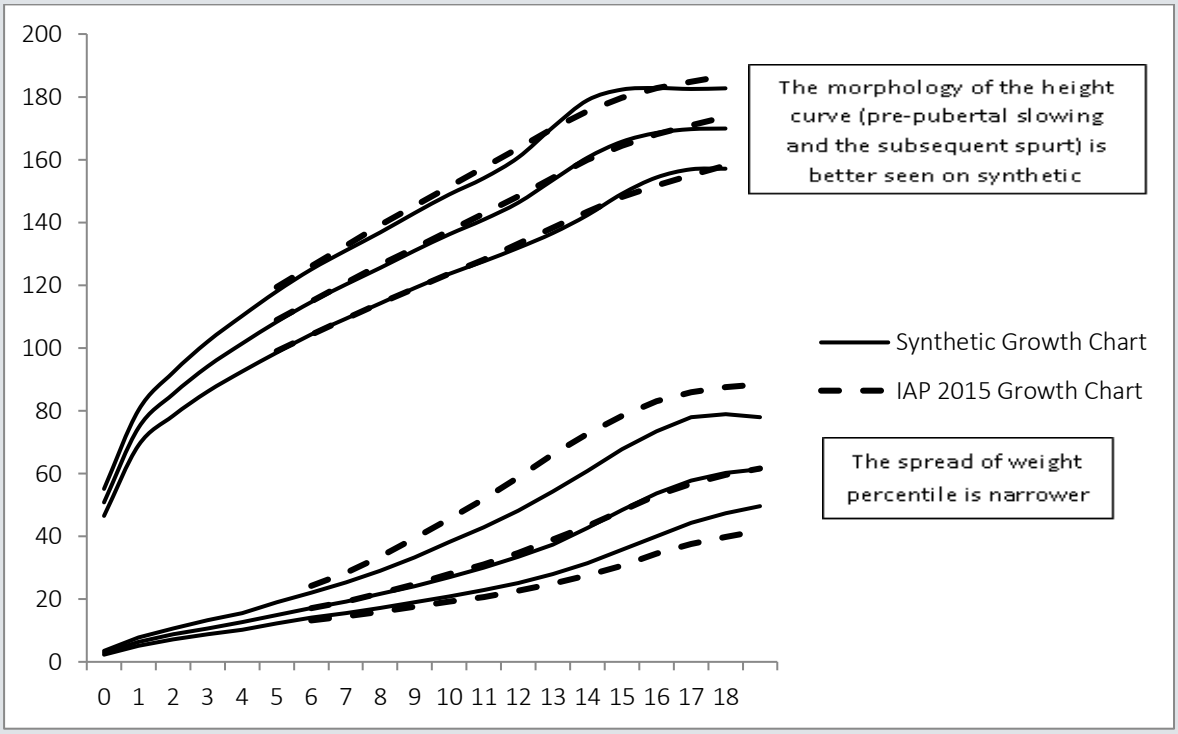

Figure 1: Comparison of IAP 2015 growth chart for boys with synthetic growth chart

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Excerpts from Recent Guidelines

SCREENING, ASSESSMENT AND MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS: AUSTRALASIAN PAEDIATRIC ENDOCRINE GROUP GUIDELINES

Compiled by Dr Nikhil Lohiya, Consultant Pediatric Endocrinologist, Jupiter Hospital and DY Patil Medical Hospital & Research Center, Pune

Citation: Peña AS, Curran JA, Fuery M, George C, Jefferies CA, Lobley K, Ludwig K, Maguire AM, Papadimos E, Peters A, Sellars F. Screening, assessment and management of type 2 diabetes mellitus in children and adolescents: Australasian Paediatric Endocrine Group guidelines. Medical Journal of Australia. 2020 Jul 6

https://onlinelibrary.wiley.com/doi/epdf/10.5694/mja2.50666 (Free download)

Screening & Diagnosis

Targeted screening for non-Indigenous populations should occur in children and adolescents (age > 10 years or at onset of puberty, whichever occurs earlier) who are overweight (BMI ≥ 85th percentile) or obese (BMI ≥ 95th percentile) and have one or more additional risk factors:

• maternal history of diabetes, including gestational diabetes during the child's gestation.
• first degree relative with type 2 diabetes.
• race or ethnicity (South Asian, South East Asian, Middle Eastern, North African and Latino) — for Indigenous populations: Aboriginal, Torres Strait Islander, Māori and Pacific Islander (see section below on considerations for children and adolescents of Indigenous backgrounds in Australasia).
• signs of insulin resistance (acanthosis nigricans).
• other conditions associated with obesity and metabolic syndrome (i.e., hypertension, dyslipidaemia, fatty liver disease, polycystic ovary syndrome, small for gestational age); and
• use of psychotropic medications.

Diagnosis of type 2 diabetes (T2DM) can be made using fasting glucose, 2-hour glucose level from oral glucose tolerance or HbA1c tests.

- Diabetes autoantibodies testing (glutamic acid decarboxylase and islet tyrosine phosphatase 2) should be considered in all children and adolescents with clinical phenotype of T2DM due to higher prevalence of type 1 diabetes mellitus in this age group.
- Genetic testing for monogenic diabetes should be considered if diabetes is present in two or more consecutive generations and diabetes autoantibodies are negative.

Diabetes education

- All children and adolescents with T2DM need comprehensive and specific diabetes self-management education that is family-centred, individualised, and developmentally and culturally appropriate.
- Education should be delivered by a specialised multidisciplinary team with expertise in managing pediatric T2DM.

Monitoring glycaemia

- Self-monitoring of blood glucose needs to be individualised according to treatment type and need to improve glycemia.
- Aim for blood glucose levels 4–6 mmol/L (fasting) and 4–8 mmol/L (2 hours postprandial).
- Target HbA1c levels should be ≤ 48 mmol/mol (≤ 6.5%) given the significant morbidity and mortality, but without causing hypoglycemia and/or undue treatment burden.
- HbA1c should be assessed every 3 months.

Healthy lifestyle

- Weight management and multicomponent approach to lifestyle modification is required at diagnosis and ongoing.
- Diet - Aim for healthy eating: eliminate sugar-sweetened beverages, reduce calorie-dense and nutrient-poor foods, provide education regarding carbohydrates (role, sources, portion control and, if appropriate, counting of carbohydrates) and ensure adequate intake of nutrient-dense and low glycemic index foods.
- Reduce total energy intake to achieve ≥ 7% decrease in excess weight.
- Physical activity - Aim for at least 60 min/day of moderate to vigorous physical activity to improve body composition, glucose management and insulin sensitivity.
- Exercise programs should include resistance activities to increase muscle mass, contributing to improved blood glucose management.
- Sedentary behavior - Recreational screen time should be limited to ≤ 2 hours a day.
- Sleep - Encourage quality sleep of 8–11 hours duration according to age, with consistent bed and wake-up times and reduction of electronic media use in the evening.

Pharmacotherapy

- Metformin up to 2 g per day should be used as the first line medication in patients presenting with mild symptoms or in those who are diagnosed after screening.
- Insulin should be the first line treatment for patients who present with diabetes ketoacidosis, hyperglycemic hyperosmolar state or ketosis, and should be added to metformin where glycemic targets have not been achieved or maintained with metformin monotherapy.
- If glycemic targets are not achieved with metformin (with or without insulin), other glucose-lowering medications approved for adults should be considered. Such medications should only be prescribed under the guidance of a paediatric endocrinologist, given limited evidence for safety and efficacy in children and adolescents.

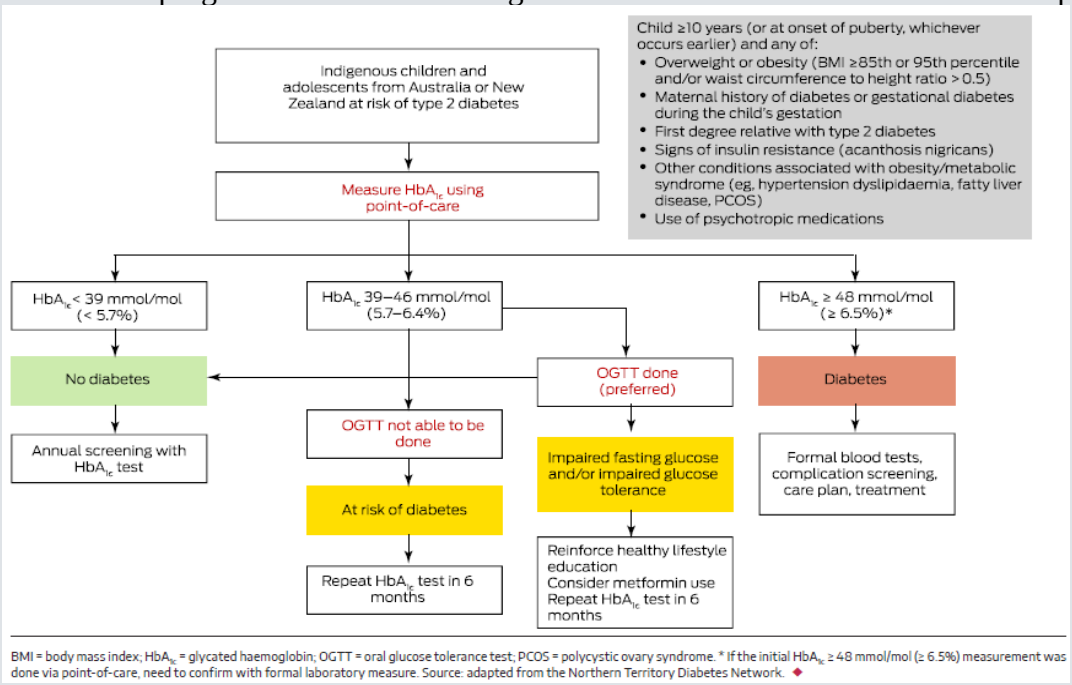
Complications and comorbidities

- Screen for all complications and comorbidities soon after diagnosis of T2DM to establish prompt management and ongoing assessment and management.
- Retinopathy - Assess retina using dilated pupil exam or retinal photography by an optometrist or ophthalmologist at diagnosis and yearly unless abnormal.
- Nephropathy - Assess early morning urine albumin to creatinine ratio at diagnosis and yearly unless abnormal.
- Neuropathy - Foot examination at diagnosis and yearly unless abnormal.
- Overweight/obesity - Optimise weight management as well as glycemia to reduce risk of comorbidities and complications.

- Consider bariatric surgery for selected post-pubertal adolescents with T2DM with severe obesity, taking into account special considerations in relation to consent, procedure, family support and availability of adequate services.
- Psychosocial - Quick screening tools for psychosocial comorbidities and diabetes distress should be used regularly after diagnosis.
- Consider screening for disordered eating behaviour
- Reproductive health for adolescent girls, a review of menstrual cycle regularity, symptoms and signs of hyperandrogenism, and need of contraception should be done at every visit, especially if the HbA1c level is above target or the patient is using teratogenic medications.
- Liver disease - Assess liver function test (aspartate aminotransferase and alanine aminotransferase) at diagnosis and yearly unless abnormal.
- Obstructive sleep apnea - Evaluate symptoms of obstructive sleep apnoea in children and adolescents with obesity.
- Hypertension - Assess blood pressure using appropriate cuff at every visit.
- Lipids - Assess lipid profile when glycemic targets have been achieved after diagnosis and yearly unless abnormal.

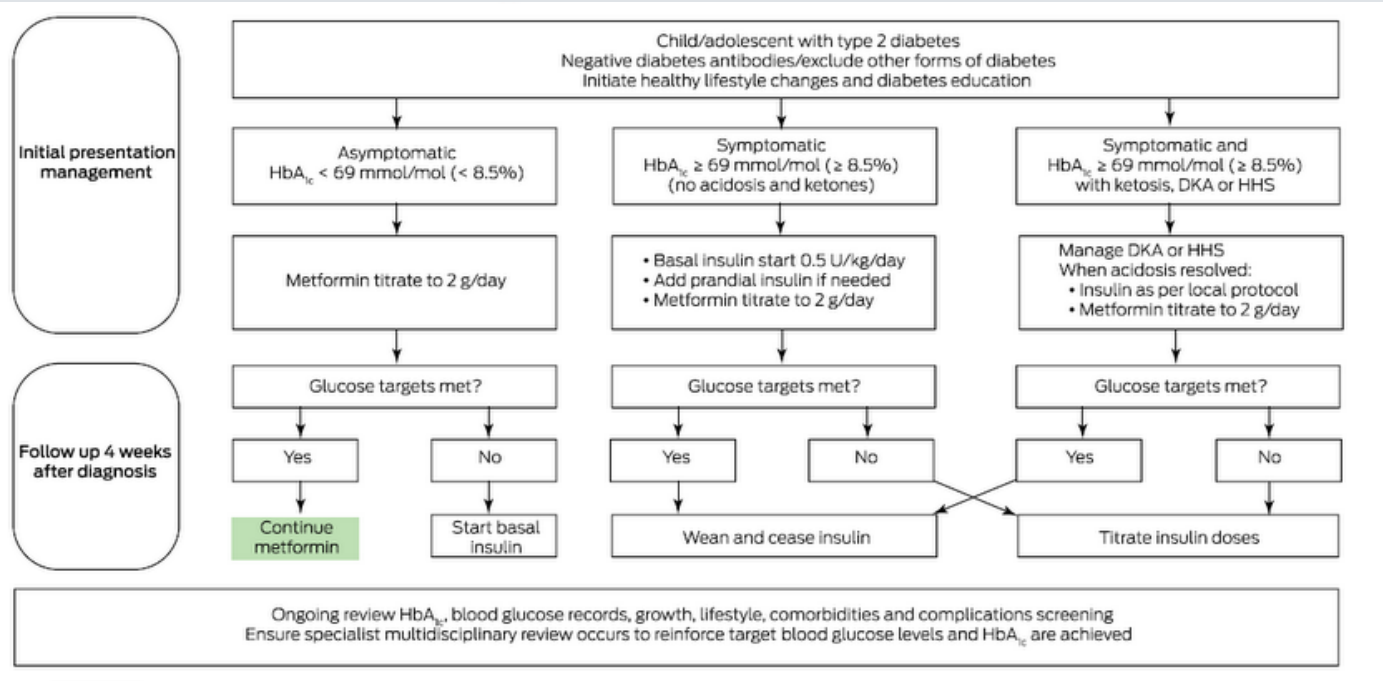
Transition

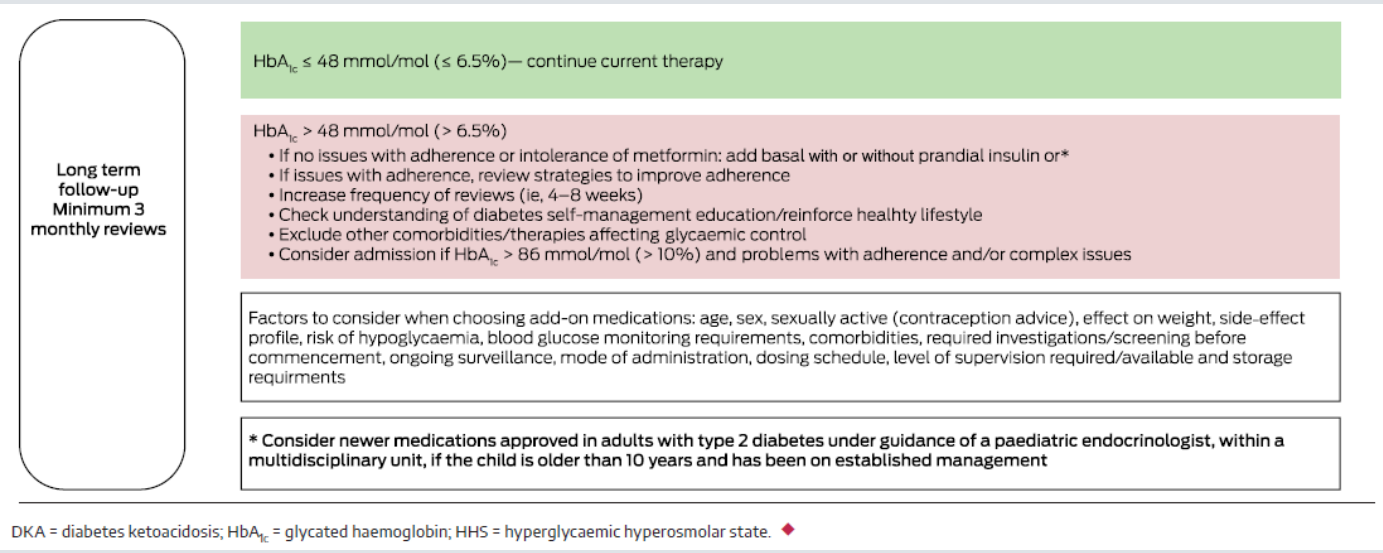
Transition to adult endocrinologist within a multidisciplinary team due to the severity of disease progression and higher risk of diabetes complications.



BMI = body mass index; HbA_{1c} = glycated haemoglobin; OGTT = oral glucose tolerance test; PCOS = polycystic ovary syndrome. * If the initial HbA_{1c} ≥ 48 mmol/mol (≥ 6.5%) measurement was done via point-of-care, need to confirm with formal laboratory measure. Source: adapted from the Northern Territory Diabetes Network.

Recommendations for type 2 diabetes screening in Indigenous children and adolescents from Australia or New Zealand





DKA = diabetes ketoacidosis; HbA1c = glycated haemoglobin; HHS = hyperglycaemic hyperosmolar state.

Treatment in children and adolescents with type 2 diabetes

MINI REVIEW

TYPE 1 DIABETES UPDATE- *beyond injectable Insulin*

Dr Sirisha Kusuma B, Consultant - Pediatric Endocrinologist, Rainbow Children's Hospital, Madhapur & Hydernagar, Hyderabad. E mail: sirisuma@gmail.com

Although necessary, insulin alone is not enough in achieving glycemic control in type 1 diabetes (T1D). It can only work in conjunction with diet and exercise. However, even with state-of-the-art diabetes care facilities, glycemic control is currently sub-optimal worldwide.

HOW ARE WE FARING WITH THE AVAILABLE THERAPIES AND TECHNOLOGIES?

In a 2010-2013 multi-center study conducted in 19 countries across 4 continents, involving 324,501 subjects with T1D, on an average, a mere 30% of patients across all age groups could achieve a glycemic target of less than 7.5%. This number is even less (20-24%) in young adults (15-24 years). Glycemic control varied significantly between countries and regions, probably reflecting differences in care, like diabetes education, frequency of contact between patient and diabetes team, access to specialist care, and differences in government or private insurance coverage of health care costs (1).

Data from T1D Exchange Study network in USA (2016-2018) has shown similarly poor glycemic control, with only 17% achieving the HbA1C goal of <7.5%, despite increases in insulin pump usage from 57% to 63% and CGM usage from 7% to 30%. In addition, 40% children with T1D above 13 years and > 65% adults above > 26 years are overweight or obese. Severe hypoglycemia (SH) and diabetic ketoacidosis (DKA) remain all too common complications of treatment, especially in older (SH) and younger patients (DKA) (2). So, the search for newer therapies that could improve glycemic control without additional side effects continues.

C-PEPTIDE AND TYPE 1 DIABETES

T1D results from immune mediated destruction of pancreatic beta cells. The American Diabetes Association (ADA) 2014 Standards of Care describes T1D as *"beta-cell destruction, usually leading to absolute insulin deficiency"*. This statement leads many clinicians to believe that residual insulin is not expected in these patients.

However, persistence of β-cell function many years after the diagnosis of T1D is being increasingly observed. The Joslin Medalist study (2010) found detectable insulin secretion in approximately two-thirds of those who had lived with T1D for at least 50 years (3). The SEARCH study (2012) involving only children and using fasting C-peptide values, reported similar findings (4).

More robust data comes from T1D Exchange Network (2014) with 919 patients in a wide age range of 3-81 years, demonstrating that 1 out of 3 patients have residual insulin secretion, as evidenced by C- peptide levels of > 0.05 ng/ml, 3 or more years from the onset of T1D. The overall frequency of detectable non-fasting C-peptide (>0.05ng/ml) was 29%, and the frequency of significant non-fasting C-peptide (>0.6ng/ml) was 10%. This frequency was consistently higher when diabetes onset was at age >18 years compared with onset at age <18 years (78% vs. 46%). Although C-peptide

positivity decreases with diabetes duration, 16% of adult-onset and 6% of childhood-onset patients continue to have residual C-peptide even 40 years from diagnosis (5).

The ever-elusive glycemic targets even with the best available insulins and technologies, increasing overweight and obesity especially with intensive insulin therapy, and the evidence for continued production of C-peptide in T1D make a strong case for exploring non-insulin therapeutic options. Four important factors need to be taken into account while considering emerging therapeutic options to optimize glycemia (6).

A) Presence or absence of anti-pancreatic islet cell autoimmunity
B) Persistence of residual pancreatic insulin production (C-Peptide > 0.05 ng/ml)
C) Presence of overweight or obesity
D) Special circumstances like renal insufficiency or cardiac vascular (CV) adverse events.

WHAT ARE THE EMERGEING NEW THERAPIES?

1. Technosphere Insulin (Afrezza)
2. Amylin analog (Pramlintide)
3. Metformin
4. GLP1-Receptor Analogs (Exenatide, Liraglutide)
5. SGLT 1 & 2 Inhibitors (Dapagliflozin, Empagliflozin, Sotagliflozin)

TECHNOSPHERE INSULIN (TI): (Afrezza, Mankind Corp)

TI is a major find in the search for an ideal rapid acting insulin that has evaded us for decades. Even the fastest acting Insulin Fiasp neither has fast enough onset of action to effectively control postprandial glycemic excursion (PPGE), nor has short enough duration of action to prevent postprandial hypoglycemia. PPGE is the difference between pre-meal blood glucose and highest post-meal (1-4 hour) blood glucose level.

TI is a dry-powder formulation of recombinant human insulin adsorbed onto inert technosphere micro particles for oral inhalation. It has a faster onset of action (12 min) with a peak effect of 35–45 min due to its rapid absorption from the lung and shorter duration of action (less than 2h) compared with the currently available rapid acting Insulin analogs. With a time to peak almost similar to endogenous insulin, it can be taken at the beginning of the meal or 10-15 minutes after starting the meal. Due to its short duration of action, many need a follow-on dose 1-2 hours after the meal to correct high blood glucose values (7).

Afrezza provides flexibility with mealtime dosing, decreases injection burden, and is helpful in those with frequent hypoglycemia after meals. The inhaler comes with 4 Unit incremental dosing. TI starting doses are usually 1.5 times the subcutaneous doses and need to be titrated based on PPG. It is initially started as an add-on Insulin to an existing regimen, later being used as an exclusive prandial insulin. TI can be used in combination with pre-meal subcutaneous insulin in 50/50 dosing split for high protein and high fat meals, like dual wave bolus with pump. Using TI demands more frequent blood glucose monitoring, ideally CGM.

A small study with 26 subjects over 28 days has shown significant improvement in postprandial glycemic excursions when compared with Aspart, with decreased time spent in hypoglycemia (8). It is not recommended in patients with asthma/ COPD/ smokers.

Afrezza was approved by the U.S. Food and Drug Administration (FDA) in 2014 as a bolus insulin therapy to improve glycemic control in adults (>18 years) with type 1 and type 2 diabetes (T2D).

PRAMLINTIDE:

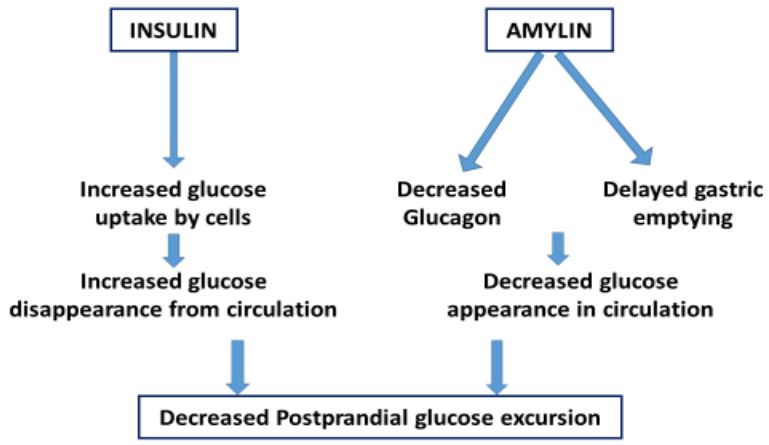
In healthy individuals, meal ingestion leads to the rapid release of two glucoregulatory hormones, insulin and amylin. Acting in concert, insulin and amylin decrease PPGE (Figure 1). In people with T1D, postprandial insulin and amylin responses are absent, leading to excessive PPGE.

Pramlintide is an amylin analog, approved by the US FDA in April 2005 for bolus pre-meal administration adjunct to insulin therapy in adults (>18 years) with T1D and T2D. It is the only anti-diabetes therapy other than insulin which is approved for use in patients with T1D. Results from a 2017 systematic review and meta-analysis by YC Qiao et al, showed that pramlintide treated patients had significantly reduced HbA1c, postprandial glucose concentrations, mealtime insulin dose and body weight, sustained over a period of 29 weeks. However good-quality, long-term data is lacking. Common adverse effects are nausea, vomiting, anorexia at the initiation of therapy, that get better with continuation. The risk of severe hypoglycemia is slightly increased. Both efficacy and adverse effects are dose dependent.

It is administered subcutaneously, 0 - 15 min before meal ingestion, in addition to pre-meal insulin. A reduction of the pre-prandial insulin dose (up to 30–50%) is advised when initiating pramlintide treatment unless subjects persistently have pre-prandial blood glucose concentrations of 250 mg/dl (9, 10).

A novel dual-hormone artificial pancreas that delivers pramlintide in addition to insulin, in a glucose responsive, basal-bolus manner, and with a fixed ratio relative to insulin is being studied. Efforts to develop co-formulations of insulin and pramlintide that would eliminate the need for a second injection are underway (11).

Figure 1. The interplay between insulin and amylin in controlling postprandial blood glucose



Metformin:

Metformin is one of the most widely used antidiabetic drugs for improving cardiovascular prognosis in patients with T2D. Intensive insulin therapy results in substantial weight gain, which adversely effects CV disease risks. A 2018 meta analysis by Meng et al looked at 13 RCTs (6 in adolescent age group) with data from 1183 participants with T1D. Compared with placebo, metformin added to insulin therapy did not result in improvements in HbA1c. However, it exhibited other benefits, such as lower BMI and reduced insulin requirements, total cholesterol and low-density lipoprotein (LDL) cholesterol. However, most of the studies included have small sample sizes and with short duration of follow up (12). Metformin might be a promising adjunct to insulin in patients with T1D with good

renal function, in controlling body weight and lipid profiles. The frequent gastrointestinal adverse effects and slight increase in risk of severe hypoglycemia need to be considered. It is not FDA approved for use in T1D.

GLP1-R analogs:

Glucagon like peptide-1 (GLP1), released by L cells in the gut, delays gastric emptying, decreases appetite at the brain level, promotes glucose dependent/ potentiated insulin release, and might indirectly suppress glucagon release by increasing local insulin concentration. GLP1 analogs have shown major and consistent improvement in major adverse cardiovascular events (MACE) end points, for T2D. Exenetide and Liraglutide are stable GLP1 analogs.

Two recent studies looked at the safety and efficacy profile of liraglutide in patients with T1D. ADJUNCT 1 was a 52-week, double-blind RCT to investigate the safety and efficacy of adding liraglutide to a continuously adjusted treat-to-target insulin dose in people with T1D with inadequate glycemic control at baseline. 1,398 adults with T1D were randomized 3:1 to receive once-daily subcutaneous injections of liraglutide (1.8, 1.2, or 0.6 mg) or placebo added to insulin. A modest reduction in HbA1c (0.2%) was seen with the highest dose of liraglutide (1.8 mg). Subgroup analysis has shown a greater reduction in HbA1c level in C-peptide–positive subjects compared with C-peptide–negative subjects. A reduction in body weight of up to 4.9 kg was achieved. These beneficial findings come at the expense of a higher rate of symptomatic hypoglycemia and more episodes of hyperglycemia with ketosis. Gastrointestinal adverse effects led to premature discontinuation of treatment in up to 14.7% subjects within the first 8-12 weeks of the trial (13).

The ADJUNCT 2 study was a 26-week RCT with capped insulin dosing – the results are largely in agreement with those from ADJUNCT 1.

The higher number of events of hypoglycemia and of hyperglycemia with ketosis may ultimately limit the clinical utility of GLP-1R analogs in a less well-supervised population with T1D (14).

SGLT 1 & 2 inhibitors:

SGLT 1 causes glucose absorption in the gut, SGLT 2 in the renal proximal tubule. By causing glycosuria, osmotic diuresis, decreased blood pressure and weight, SGLT-2 inhibitors are known to improve cardiovascular end points and renal function in T2D. Many recent trials explored the utility of SGLT 1 & 2 inhibitors in T1D.

DEPICT-1, a phase 3, multicentre RCT assessing the efficacy and safety of dapagliflozin as an add-on to adjustable insulin among eligible 18–75 year olds with inadequately controlled T1D, has shown significantly reduced HbA1c (0.42%) compared with placebo (15).

The EASE trial evaluated the efficacy and safety of empagliflozin as an adjunct to intensified insulin in patients with T1D. Improvement in glycemic control (HbA1C, time in range, total daily insulin dose) and weight loss was noted without increasing hypoglycemia. However, the DKA rate increased significantly with 10 mg and 25 mg doses (16).

The TANDEM trials have shown that sotagliflizin, a dual SLGT 1 and SGLT 2 inhibitor, resulted in significant HbA1c reductions (0.36% and 0.41% with sotagliflozin 200 and 400 mg doses respectively) when compared with placebo, with fewer episodes of SH. There was a 3-4-fold increase in risk of DKA. Genital mycotic infections and diarrhea occurred more frequently with sotagliflozin. Though not approved by FDA, it is in use in the European Union.

SGLT 2 inhibitors might have a role in carefully selected and highly compliant T1Ds (17, 18, and 19). While on SGLT inhibitors, a daily ketone check is mandatory, preferably blood ketones. It is important to note that these patients can have DKA with blood glucose values <150 mg/dL (so-called "euglycemic DKA"). Moreover, measurements of ketonuria and bicarbonate may not accurately reflect patients' metabolic state due to the renal action of SGLT inhibitors. Direct measurement of β-hydroxybutyrate and pH is recommended to confirm DKA diagnosis in patients taking SGLT inhibitors. Patients should be advised to carry a wallet card with information about how their DKA presentation may differ from standard DKA. SGLT inhibitor therapy should be temporarily discontinued 24 h in advance of any planned activity that might precipitate DKA — mainly situations that result in decreased insulin doses such as surgery, fasting, reduced carbohydrate intake, ketodiet or prolonged activity, and also for illness and dehydration. SK Garg et al, proposed the STICH (ST - Stop SGLT-2 Inhibitors, I - take extra Insulin, C - take extra Carbohydrates, H – Hydrate) protocol for treatment of SGLT inhibitor associated DKA (20).

To summarize, the struggle to achieve glycemic control with available management options, the increasing incidence of intensive insulin treatment-related overweight and obesity with consequent increased renal and CV risk, and the evidence for continued production of C-peptide even years later in T1D have resulted in a striving for options other than injectable insulin. The currently available choices look promising in adults (>18 years) with T1D, though not without the increased risks of SH and DKA.

Based on currently available evidence, in adults (>18 years) with T1D, metformin might be considered in those who are overweight with good renal function for helping with weight and lipid profile, GLP-1 analogs in those who have residual pancreatic insulin production for better glycemia and weight loss, and SGLT inhibitors in those who are highly motivated and highly compliant, for improvement in glycemia, blood pressure and weight loss, with appropriate training for mitigation of DKA.

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Pedendoscan

Dr Nikhil Lohiya, Consultant Pediatric Endocrinologist, Dr DY Patil Medical College, Hospital & Research Center, & Jupiter Hospital, Pune

1. **Near-Adult Height After Growth Hormone Treatment in Children Born Prematurely—Data From KIGS. Boguszewski, Margaret CS, et al. J Clin Endocrinology & Metabolism 105.7 (2020): dgaa203.**

About the study- The authors evaluated the influence of prematurity on near-adult height (NAH) after GH treatment from the KIGS Database. A total of 586 short children, born preterm, with varying GH status, with information available on gestational age (GA), birth weight, and NAH, treated with GH, and outcome measured being NAH, were analysed. The values were expressed as median. Of the 586 children, 482 were born appropriate for GA (AGA; median age 8.26 years) and 104 small for gestational age (SGA) (median age 8.54 years). Peak GH < 7 μg/L during a provocation test was seen in 66.6% of preterm AGA but only 8.6% of preterm SGA. Change in height standard deviation scores (SDS) from GH start to NAH after 8.04 years of GH treatment was 1.82 in preterm AGA. Respective values were 7.08 years and 1.08 SDS for preterm SGA ($P < 0.001$); 57% of the variability of the growth response to NAH could be explained, with the distance to parental height being the strongest predictor. No significant changes in height SDS were observed from puberty start to NAH. No correlation was found with GA. GH treatment was well tolerated. From the results they concluded that GH treatment resulted in significant improvement in height in children born preterm, particularly during prepubertal years and for those with GH deficiency. The degree of prematurity did not influence the growth response.

Critical Appraisal- KIGS is a well appreciated and reputed database. The analysis has shown a good improvement in height SD in the prepubertal period. However, once puberty kicks in, GH therapy does not help in height gain. These findings are irrespective of their status as SGA or AGA. This stresses the importance of early GH therapy. The relatively better height gain in AGA children is due to the fact that many more of them had GHD than the SGA children. Whether combining a GnRH analog with GH will help in these preterm children still needs to be explored.

Application in Our Clinical Practice - Preterm children commonly presents with growth failure. They need to be monitored carefully as catch-up growth can be seen by 4 years in preterm SGA children. The take home for clinical practice is early intervention, have knowledge of what to expect from GH therapy in children who are born preterm, and carefully consider whether treatment during puberty is worthwhile.

2. **Messina V, Hirvikoski T, Karlsson L, Vissani S, Wallensteen L, Ortolano R, Balsamo A, Nordenström A, Lajic S. Good overall behavioural adjustment in children and adolescents with classic congenital adrenal hyperplasia. Endocrine. 2020 Mar 9:1-1.**

About the study- Patients with classic congenital adrenal hyperplasia (CAH) are treated postnatally with life-long glucocorticoid (GC) replacement therapy. Although prolonged exposure to GCs may have a negative impact on behavior, few studies have looked at this issue. In this observational study, the authors compared Swedish and Italian children and adolescents with CAH identified through neonatal screening for CAH (n = 57, age range 7–17 years) with healthy population controls matched for age and sex (n = 72, age range 7–17 years). Thirteen (eight females) of the 57 patients had been treated prenatally with dexamethasone (DEX). Standardised questionnaires for parents and self-report scales for children/ adolescents were used to assess behavioral and emotional problems, social anxiety, temperament, and scholastic competence. The results showed that there were no statistically significant differences between CAH patients who were not prenatally treated with DEX, and controls, on most of the scales measuring adaptive functioning or behavioral problems.

However, children with CAH were rated by their parents to have more social problems than controls (Child Behaviour Checklist, CBCL social problems, p =0.032). In the small sub-group of 13 prenatally DEX-treated cases, the parents rated their children/ adolescents to have more mood problems than non-DEX-treated cases (CBCL - withdrawn/ depressed, p = 0.019). The authors concluded that children/ adolescents with CAH showed good overall adjustment, though the clinical significance of the parentally perceived increase in social problems in them requires further investigation. The findings underline the importance of psychological support for children/ adolescents with a chronic condition.

Critical Appraisal - This is one of the few studies assessing behavioral issues performed in a systematic way in children with CAH. The tools used by the authors are very appropriate, and the generally positive conclusion gives us hope. They have attributed the positive adjustment to close monitoring and access to continuity of care and psychological support. However, they have not mentioned anything about social factors. The sample size was modest and included a small sub-group on which no formal conclusion can be drawn.

Application in Our Clinical Practice- The study from European countries, with greater social homogeneity as well as continuity of care and psychological support, may not be applicable to the Indian setting. We need to keep in mind, to an even greater extent, the importance of behavioral aspects and providing psychological support where possible, in chronic illnesses, especially DSD like CAH.

3. **Zung A, Radi A, Almashanu S. The natural history of congenital hypothyroidism with delayed TSH elevation in neonatal intensive care newborns. Clinical Endocrinology. 2020 May;92(5):443-9.**

About the study- The objectives of this observational study were to assess the clinical and neurological outcomes in a cohort of 113 newborns with primary congenital hypothyroidism (CH) presenting with delayed TSH elevation (dTSH), and to define parameters that may predict the evolution of transient vs. permanent hypothyroidism in these newborns. The parameters measured were birth parameters, thyroid screening results, thyroid gland imaging, levothyroxine dose and neurological outcome compared between newborns with spontaneous recovery and children with a final diagnosis of either transient or permanent hypothyroidism. Of the 113 children with dTSH, 93% demonstrated recovery, either spontaneously or following levothyroxine treatment (transient hypothyroidism). Newborns with spontaneous recovery demonstrated milder thyroid dysfunction at the newborn screening compared to those who needed levothyroxine treatment. Levothyroxine dose was lower in children with transient vs. permanent hypothyroidism only during the first 6 months of life; otherwise, these groups were similar in birth parameters, thyroid screening results and gland images. Seventeen of 61 children (28%) who underwent neurological assessment demonstrated developmental delay. Duration of treatment was highly variable in children with transient hypothyroidism. The study concluded that thyroid dysfunction is transient in most cases of dTSH. No reliable parameters can predict a priori transient vs. permanent hypothyroidism.

Critical Appraisal- This is probably the largest follow-up study published till date. About half of the dTSH children recovered spontaneously. The authors stress the importance of higher developmental issues in children with transient TSH elevation. However, the cut-off of 7.5 IU/L to define permanent hypothyroidism despite having normal T4 needs to be taken with a pinch of salt. Other lacunae include lack of NICU stay data including prematurity and concomitant issues, lack of precise diagnosis of developmental delay, and lack of developmental assessment in over half the children. Moreover, developmental issues are known to be common in NICU graduates and elevated TSH might not be the reason for them.

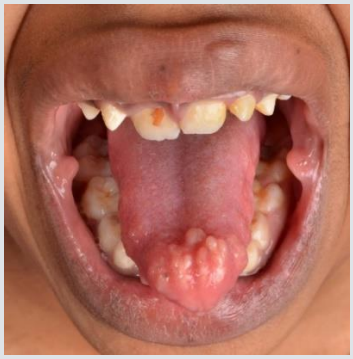
Application in Our Clinical Practice- The issue of transient elevation of TSH is more important in our setting especially after ISPAE released Guidelines for CH, more so with the continuous improvement in new-born care in several centres in our country. Pediatric endocrinologists would do

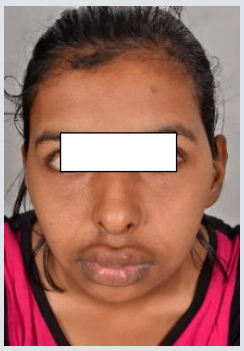
well to highlight the need of a second screening in NICU graduates, so that a preventable cause of developmental delay can be picked and treated.

PHOTO QUIZ

Saniya Gupta, DM (Pediatric Endocrinology) Fellow, Endocrinology and Diabetes Unit, Advanced Pediatrics Centre, PGIMER, Chandigarh

A 15 yo girl, second born to a non-consanguineous couple, presented with complaints of multiple nodular swellings over the tip of the tongue, lips and angle of mouth noticed since the age of 9y. The swellings were non-progressive, with no associated pain or discharge. There was no significant family history. Clinical examination revealed long narrow face, high arched palate, bilateral ectropion (upper eyelids) and pes cavus. There were small nodular swellings in both upper eyelids. She had joint hyperlaxity and a marfanoid habitus. Ophthalmological examination revealed bilateral ectropion. Her clinical pictures are shown below.





Events/Activities organised by ISPAE members

ACTIVITY 1: Webinar: 14 April, 2020: **Practical points for insulin injections in Paediatric diabetes**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: The educational program was sponsored by Alembic.

ACTIVITY 2: Webinar: 18 April 2020: Pediatric Endocrinology – Today & Tomorrow
Moderator: Dr Ahila Ayyavoo
Faculty & Topics:

1. Dr P Raghupathy, Bangalore – Difficulty in interpretation on Newborn Thyroid Screening Results
2. Dr Vaman Khadilkar, Pune – Biosimilar Growth Hormone vs Innovator Growth Hormone
3. Dr Ahila Ayyavoo, Coimbatore – Developmental outcomes of children with congenital hypothyroidism diagnosed at various ages
4. Dr Anurag Bajpai, Kanpur – Advances in the management of low bone mass in children.

Report: This educational activity was conducted under the aegis of ISPAE & GHRS, supported by an educational grant from Cipla. It was well attended and highly interactive with 560 participants logging in.

ACTIVITY 3: Webinar: 8 May 2020: **Hormonal perturbations**
Faculty & Topics:

1. Dr Anna Simon, Vellore: Understanding congenital hypothyroidism
2. Dr Shaila Bhattacharyya, Bangalore: Type 1 diabetes mellitus - What a Paediatrician should know
3. Dr Preeti Dabadghao, Lucknow: Practical approach to oligomenorrhoea and hyperandrogenism
4. Dr Ahila Ayyavoo, Coimbatore: Interesting case scenarios

Report: This educational activity was conducted under the aegis of the digital initiative of the Indian Academy of Pediatrics – dIAP to promote e-learning during the COVID lockdown.

ACTIVITY 4: Webinar: 9 May 2020: **KIDS: Growth and Gut Health**
Moderators: Dr Vaman Khadilkar, Pediatric Endocrinologist, Pune & Dr Rajendra Setty, Pediatric Gastroenterologist, Panchkula
Faculty & Topics:

1. Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore: Healthy Growth and Weight Management in Growing Kids
2. Dr Lait Verma, Pediatric Gastroenterologist, Mumbai: Gut, Health & Microbiome – Are they united?

Report: This international webinar was sponsored by Signutra and had 2200 logins from Asia & Africa.

ACTIVITY 5: Webinar: 19 May 2020: **Short Stature in Children**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: This webinar was sponsored by Pfizer.

ACTIVITY 6: Webinar: 4 June 2020**: Remote Diabetes Management in the times of Social Distancing**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: This educational program was sponsored by Medtronic, organized to remotely educate families managing children with type 1 diabetes.

ACTIVITY 7: Webinar: 12 June 2020: **Turner Syndrome**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore

Report: This webinar was sponsored by Cipla.

ACTIVITY 8: Webinar: 16 June, 2020: **Management of DKA in resource poor settings**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: The educational program was sponsored by Alembic.

ACTIVITY 9: Webinar: 22 June, 2020: **Clinical clues to diagnosis in Paediatric Endocrinology**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: The educational program was sponsored by Cipla.

ACTIVITY 10: Webinar: 30 June, 2020: **Helping hands**
Faculty: Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore
Report: No sponsors

ACTIVITY 11: Webinar: 7 July, 2020: **Sub-cutaneous insulin in the management of diabetic ketoacidosis**
Faculty & Topics:

1. Dr Chizo Agwu, **Consultant Paediatrician in Diabetes and Endocrinology, University of Birmingham:** Subcutaneous Insulin in DKA management: Review of scientific evidence
2. Dr Ahila Ayyavoo, Pediatric Endocrinologist, Coimbatore: Real Life experience of Using Subcutaneous insulin in DKA management

Report: This educational activity was conducted under the aegis of the Pediatric Endocrinology Training Center for West Africa (PETCWA), Nigeria, to share experience with Paediatric Endocrinologists in PETCWA to improve outcomes in children with type 1 diabetes mellitus in resource poor settings.

ACTIVITY 12: Webinar: 16 July, 2020: **Short Stature**
Moderator: Dr Ahila Ayyavoo, Coimbatore
Faculty:

1. Dr Ankita Maheswari, Indore
2. Dr Aashima Dabas, New Delhi
3. Dr Akansha Parikh, Mumbai
4. Dr Zalak Shah Upadyay, Rajkot

Report: This educational activity is conducted under the aegis of the digital initiative of the Indian Academy of Pediatrics – dIAP and as a part of the educational activity to promote e-learning.

ACTIVITIES BY DR MEENA MOHAN, PSG Super Speciality Hospital, Coimbatore

IN PERSON DIABETES SUPPORT GROUP MEETING
On 26th Jan 2020, 40 T1D families met at the Seminar Hall, PSG Super Speciality Hospitals, Coimbatore. Group sessions were held by diabetes educators on hypoglycemia management, reasons for post prandial hyperglycemia, the need to give rapid insulin 15-20 minutes before food except to toddlers, etc.
Take home message: In smaller groups, discussing topics like hypoglycemia, hyperglycemia, insulin delivery site, sick day management, etc. was useful as parents opened up more easily. These were people who would otherwise be resistant to expressing their views and clarifying their doubts in larger groups.

ONLINE MEETINGS

I. 30.4.2020: **Remote diabetes management:** A live session was held to improve the quality of care for children and adolescents with T1D on insulin pumps. 20 families and diabetes educators participated in this online session and found it very useful.

II. 3.5.2020 & 10.5.2020: **Yoga for children:** A live demo was given online to 20 T1D children and families by a qualified yoga instructor Dr Anil Dev over 2 weekends. All the children and parents participated live during both sessions and found the program very useful.

III. 18.06.2020: **Carb counting session** was held online by Ms Sheryl Salis, renowned dietician from Mumbai for 23 families and diabetes educators. The families had a similar session in the past with Ms Salis, when they were all given measurement cups - some of them have been using them regularly. The importance of carb counting for all children with T1D, whether on MDIs or pumps, was reinforced.

IV. Online group sessions: over five sessions between 24 June and 3 July: were held for T1D children and families. 3-4 children were chosen for every session. Their day to day activities, eating patterns, types of exercises, their effect on blood glucose levels, insulin delivery, type of food, type of bolus, whether before or after food, etc. were discussed. The massive changes due to COVID in the children's behavior, waking times and eating patterns, and how to eat healthy were also discussed. Inputs were sought from the other attending parents too, and a healthy information exchange was encouraged. In this way focus was provided to individual children and their families to go into detail, with other parents also contributed to dealing with daily issues. These sessions were very much welcomed by most parents.

V. Special session: Dealing with Adolescents: 8 July 20: 50 adolescents and parents participated in the session, which had 3 special guests: 1. Dr Poongodi Bala, Child Psychiatrist, Chennai, 2. Dr Lakshmi, Consultant Pediatrician with special interest in Adolescent Care, Coimbatore, and 3. Dr Vanithamani, Director, Faculty of Management Studies, Karpagam College of Engineering, Coimbatore, and T1D parent. The adolescents and their parents were very thankful for the session and agreed that they would modify themselves subtly to accommodate the situation and reduce arguments within the family.

Take home message: The main complaint of the adolescents was that they were constantly nagged by their parents, and never appreciated for whatever tasks they accomplished. They

wanted their parents to be accommodative and appreciative. **Dr Bala** talked about the **CALM** model, **C**ommunicate, **A**uthoritative Parenting, **L**isten and Role **M**odel for the parents; and the **WOW** approach for the adolescents – You are **W**orthy, You are **O**riginal, You are **W**orthy. **Dr Lakshmi** touched upon the different stages of brain maturation at different points in time, impulsive behaviour and exploring adventures in adolescence, different parenting styles and how to move around between different styles according to the situation. **Dr Vanithamani** touched upon the role of peer pressure in causing major conflicts with parents and different ways to develop the art of acceptance for both parents and adolescents.

Publications by ISPAE members

Ruchi Parikh: Daphne Yau, Kevin Colclough, Anuja Natarajan, **Ruchi Parikh**, Natalie Canham, Mohammed Didi, Senthil Senniappan, Indraneel Banerjee. Congenital hyperinsulinism due to mutations in HNF1A. European Journal of Medical Genetics 63 (2020) 103928. https://doi.org/10.1016/j.ejmg.2020.103928

ANSWER TO PHOTOQUIZ

MEN2B (Multiple endocrine neoplasia Type 2B)

In view of the multiple nodular mucosal swellings, long narrow facies, high arched palate, pes cavus, bilateral ectropion and Marfanoid habitus, a clinical possibility of MEN2B was kept.

MEN2B or Multiple endocrine neoplasia type 2B is caused by activating germline mutations in the RET proto-oncogene located on chromosomal location 10q11.2. More than 90% are sporadic; the rest have an autosomal dominant inheritance. MEN2B is characterized by the development of Medullary Carcinoma Thyroid (MTC) in 100% of cases, Pheochromocytoma in up to 50% cases, and a highly penetrant and characteristic clinical phenotype. The clinical features include presence of ganglioneuromas on the lips, tongue, or conjunctiva ("mucosal neuromas"), occasionally also in the urinary system and gastrointestinal tract, leading to constipation and feeding problems in infancy and the development of megacolon. Other features include pubertal delay, Marfanoid body habitus, narrow long facies, pes cavus, pectus excavatum, high-arched palate, scoliosis, slipped capital femoral epiphysis, joint laxity, hypotonia or proximal muscle weakness, and thickened lips. Ophthalmologic findings like inability to make tears in infancy; thickened and everted eyelids; mild ptosis and prominent corneal nerves are also found. Primary hyperparathyroidism is not a feature of MEN2B.

Oral findings are highly penetrant and often leads to the clinical diagnosis. MTC is extremely aggressive and usually develops by second decade of life. Ultrasound (USG) thyroid and serum calcitonin aid in the diagnosis. Pheos usually develops by the 3-4th decades of life, are frequently benign, and bilateral in more than 50% cases.

Besides the characteristic clinical phenotype which led to the clinical suspicion of diagnosis in the index case, she was found to have elevated serum calcitonin and bilateral calcifications in the thyroid gland on USG. Fine needle aspiration cytology of the thyroid gland revealed MTC. Biopsy of mucosal lesions confirmed mucosal neuromas. There was no pheochromocytoma or hyperparathyroidism.

Surgery, comprising total thyroidectomy with dissection of cervical lymph node compartments, is the recommended treatment for hereditary MTC, as it offers the best chance of achieving cure. Prophylactic thyroidectomy is recommended in individuals identified at risk of developing hereditary MTC through germline RET mutation. The age of prophylactic surgery is determined by the American Thyroid Association mutation risk stratification. Surgical removal is the treatment of choice for pheochromocytoma as well.

Information on Upcoming important Conferences

1. 59th ESPE Meeting, at Liverpool, UK, will now be held from 7-9 May 2021.
2. **46th ISPAD Annual Conference will be "virtual": Thu-Sat October 15-17, 2020. It will be in a different format to the previously planned meetings. Visit 2020.ispad.org to remain informed. Registrations are open.**
3. 54th Annual JSPE Meeting postponed (new date to be announced).
4. ISPAE-ISPAD Midterm Meeting 2020, Chandigarh likely post-poned to 2022.
5. 11th Biennial Scientific Meeting of APPES and Fellows' School: postponed to November 2021.