OCTOBER 2022
Volume 26, Issue 3

CAPE News

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

CONTENTS

Theme: Bone disorders in children

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News

ISPAE

From the Editorial Board

Dr Anju Virmani
Advisor

Dr Hemchand K Prasad
Editor

Dr Ravindra Kumar
Editorial board

Dr Pragya Mangla
Editorial board

Dr Aashima Dabas
Editorial board

Dr Diksha Shirodkar
Editorial board

Dr Nikhil Lohiya
Editorial board

Dear ISPAE members,

It gives our team great pleasure to connect with ISPAE members through this October 2022 issue of CAPE News, themed on Bone Disorders. We have many interesting articles, mini reviews, journal scan, patient corner, biochemistry corner and a case report, pertaining to childhood bone disorders. We also have reports of members' activities, useful information pertaining to pediatric endocrinology, learning pearls from pediatric endocrinology meetings and a Diabetes Educators' corner. Hope you have a good reading experience.

We look forward to contributions and suggestions from all members for the next issue, themed on "Childhood calcium disorders".

Feedback is welcome at: *editor.capenews@gmail.com*

Thank You and Regards,
Team CAPE News 2021-22

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Office Bearers' Message

Dear ISPAE members,

Greetings from Team ISPAE 2021-22!

On behalf of the Executive Council of ISPAE, we wish all the members a very happy and auspicious festive season ahead! We thank God for almost an end to the difficult COVID pandemic for nearly two years and pray for no further COVID waves/pandemics!

We look forward to meeting and seeing you all (physically!) at Chandigarh for the ISPAE-ISPAD Midterm meeting on 19-20 Nov 2022! The conference website (www.ispae2022.com) has all the required registration details, abstract submission, etc. The Scientific Committee has drafted an excellent academic program including all renowned experts from India and abroad (ISPAD). The local organizing team is working hard to make this meeting a grand success.

Dr Shaila Bhattacharyya
President
ISPAE 2021-22

Dr Ganesh Jevalikar
Secretary cum Treasurer
ISPAE 2021-22

Dr Rakesh Kumar
Joint Secretary
ISPAE 2021-22

The tenure for the current Executive Council of ISPAE is completing this December. The elections (e-voting) for the new EC will be held soon. We appeal to all members to update their contact details on the ISPAE website to participate in the elections.

We appeal to all the ISPAE members to contribute manuscripts to the ISPAE's Journal (JPED) and send write-ups for the CAPE News (especially about academic or patient care activities). The members working with allied health care professionals for the care of children with T1D could encourage their staff to enroll in ISPAE's Diabetes Education and Learning (IDEAL) course to create a trained pool of Pediatric Diabetes Educators.

Jai Hind!

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

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Welcome to new ISPAE members

- Dr Deva Priya E, Institute of Child Health and Hospital for Children, Chennai
- Dr Jyotsna Arelli, Niloufer Hospital, Hyderabad
- Dr Trishya Reddy, Manipal Hospital, Bangalore
- Dr Ankita Srivastava, Aster Hospital, Bangalore
- Dr Sumit Arora, Jagdamba Hospital, Jalore, Rajasthan

A warm welcome to the ISPAE family!

Review of Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets

Dr Aashima Dabas, Associate Professor, Department of Pediatrics
Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi.
Prof. Piyush Gupta, Principal, University College of Medical Sciences, Delhi.

Nutritional rickets (NR) remains a common nutritional deficiency disorder in India. Vitamin D deficiency (VDD) is being increasingly recognized and diagnosed in children with non-skeletal complaints or those who are asymptomatic. The strategy for prevention and treatment of nutritional rickets (NR) needed a revisit in light of emerging data from the Comprehensive National Nutrition Survey and evidence for daily doses of vitamin D therapy. In addition, the extra-skeletal benefits of vitamin D therapy required a closer analysis for recommendations. The level of evidence of each recommendation was graded from 1-5 as per the Oxford Centre for Evidence Based Medicine (OCEBM) classification. The following are recommendations by a National Consultative Body of Experts on prevention and treatment of VDD and NR.

Subgroup	Remarks
Definition and Burden of NR	• The measurement of serum 25-hydroxy vitamin D '(25(OH)D)' suffices the need for estimation of vitamin D status and is best done by LC-MS/MS technology. • The Committee concurred with the earlier classification for defining serum 25(OH) D status as deficiency <12 ng/mL, insufficiency: 12-20 ng/mL, and sufficiency >20 ng/mL. • Data on lower serum 25(OH)D levels to be classified as normal, were lacking. • Vitamin D toxicity can be diagnosed in the presence of serum 25(OH)D levels >100 ng/mL with hypercalcemia and/or, hypercalciuria; levels between 50-100 mg/mL to be viewed with caution.

Subgroup	Remarks
Maternal and Childhood Vitamin D Supplementation	• Routine vitamin D supplementation during pregnancy improves maternal and neonatal serum vitamin D levels, but showed unclear benefit on low birth weight and neonatal mortality, and no effect on stillbirths. • Routine maternal calcium supplementation is recommended as it optimizes maternal and neonatal health outcomes, including effect on neonatal skeletal outcomes. • Routine vitamin D supplementation is recommended during infancy to prevent VDD and NR. After infancy, only patients with the conditions listed in Box 1 require vitamin D supplementation. In healthy children, vitamin D requirements are best met through natural sources and diet (mentioned below).
Sunlight exposure	• The efficacy of sunlight exposure alone in prevention of VDD is unreliable in light of several host and environmental factors. However, as per Indian data, daily sunlight exposure of 17-30 min in infants and 30-45 min in older children over 15-40% body surface area is recommended at least five times a week during noontime (11AM-3PM) to prevent VDD. • Other strategies like vitamin D supplementation and food fortification have shown higher efficacy in adult studies, with insufficient evidence in childhood. • Dietary calcium adequacy should be emphasized during childhood and adolescence as per the estimated average requirements (EAR) of 400-500 mg/day during childhood, 650 mg/day for 10-12 yr old and 800-850 mg/day in 13-18 yr old; requirements to be met by both dairy and non-dairy sources of calcium. • The EAR for vitamin D is approximately 400 IU/day in children and 600 IU/day in adolescents (to be obtained from natural sources).
Treatment of VDD and NR	• The treatment of NR is detailed in figure 1 below (reproduced with permission). • Incidentally detected low serum 25(OH)D level <12ng/mL in healthy children or <20 ng/mL in those at high-risk should be treated. • Oral vitamin D3 therapy in doses shown in Table 1 are recommended for treatment. • Intramuscular doses not recommended for routine use, and should be used only when malabsorption is suspected. • An adequate calcium intake of 50-75 mg/kg/day should be continued with vitamin D dosing for optimum skeletal healing.

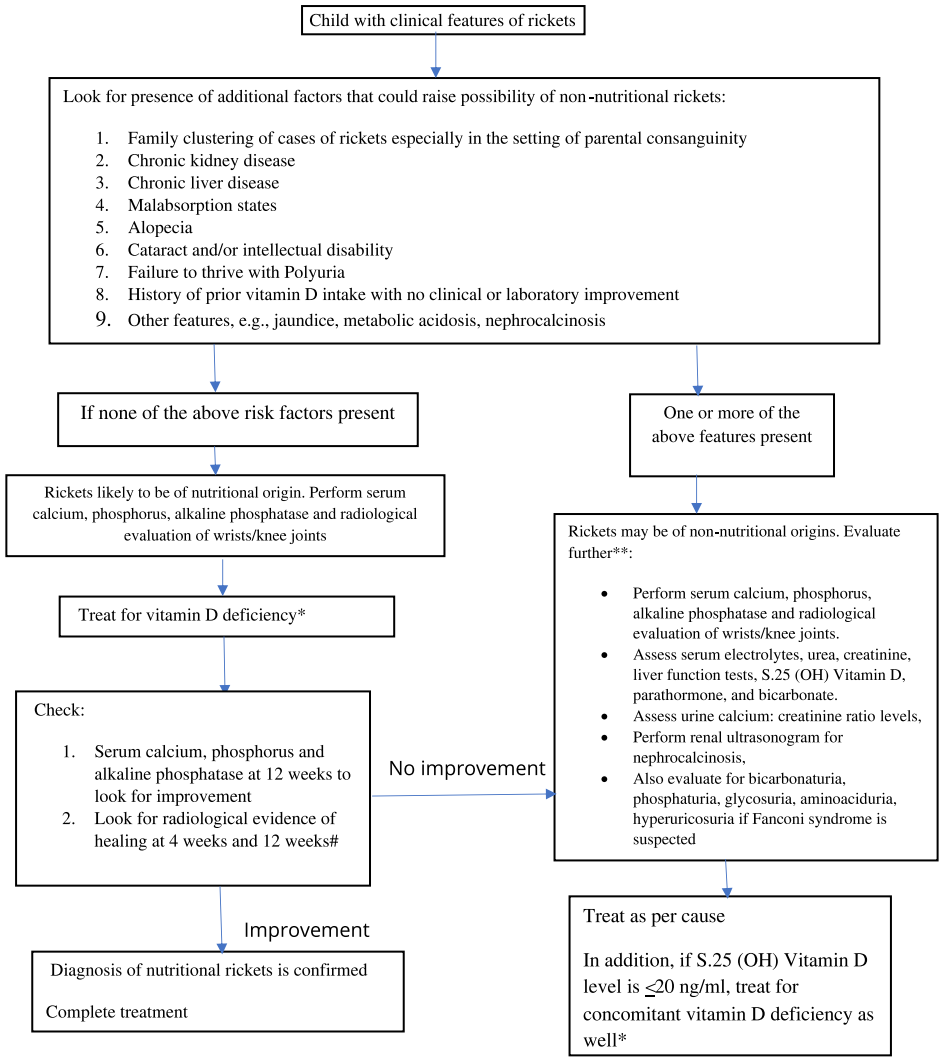
Subgroup	Remarks
	• Monitoring during treatment is recommended with a repeat plain radiograph of wrists at 4 and 12 weeks and biochemical parameters - serum calcium, phosphate, alkaline phosphatase, 25 (OH)D levels at 12 weeks.
Vitamin D and Infective Conditions	• The serum 25(OH)D levels may be lower in patients with pneumonia and tuberculosis: if so, it may be associated with greater disease severity. However, routine supplementation with vitamin D has not been shown to have a beneficial role in treatment of pneumonia or tuberculosis. • Likewise, there exists an association between lower 25(OH)D levels with HIV infection, and with the severity of childhood diarrhea. However, there is no beneficial role of vitamin D supplementation in these two conditions.
Vitamin D and Non-infective Extraskeletal effects	• Serum 25(OH)D levels may be lower in childhood asthma and related to disease severity. Evidence is lacking to recommend routine vitamin D supplementation in asthma. • VDD is associated with obesity and adverse metabolic outcomes, necessitating the need to maintain serum 25(OH) D level of >20 ng/mL. Evidence is insufficient to recommend routine vitamin D supplementation in obesity. • Vitamin D supplementation does not have any additional advantage in atopic dermatitis during childhood. • Serum 25(OH)D levels should be monitored annually in children with nephrotic syndrome and maintained >20 ng/mL with vitamin D and calcium supplementation. • Children with behavioral disorders like autism and attention deficit hyperactivity may have lower serum 25(OH)D levels, but not significant to justify routine vitamin D supplementation.

Box 1: High-Risk Conditions Requiring Routine Vitamin D Supplementation in Children

- Non-ambulatory states like cerebral palsy, neuromuscular disorders
- Chronic kidney disease
- Chronic liver disease
- Malabsorption syndromes
- Long-term use of glucocorticoids, antiepileptic drugs, ketoconazole
- Endocrine disorders like hyperparathyroidism
- Disorders with extensive cutaneous involvement

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE



*Treatment of vitamin D deficiency includes calcium supplements along with vitamin D

Monitoring of therapy is discussed in section 4.4 ** Other investigations as clinically indicated

Figure 1: Approach to management of nutritional rickets [Figure originally published in Indian Pediatrics [1], reproduced here with permission]

Table 1: Treatment of nutritional rickets [IAP 2021 Guidelines]

Age	Daily dose for 12 weeks	Stoss therapy	Maintenance vitamin D dose
< 6 months	2000 IU	Not recommended	400 IU/day
6-12 months	2000 IU	Equivalent of 2000 IU/day may be given on a monthly or weekly basis	400 IU/day
>12 months	3000 IU	60000 IU fortnightly (after every 2 weeks) x 5 doses	600 IU/day

References:

1. Gupta P, Dabas A, Seth A, et al. Indian Academy of Pediatrics Revised (2021) Guidelines on Prevention and Treatment of Vitamin D Deficiency and Rickets. Indian Pediatr. 2022;59(2):142-158.

2. From Indian Academy of Pediatrics 'Guideline for vitamin D and calcium in children' Committee. Khadilkar A, Khadilkar V, Chinnappa J, et al. Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatr. 2017;54:567 73.

3. Ministry of Health and Family Welfare, Government of India. Comprehensive National Nutrition Survey (CNNS) 2016-2018. Accessed March 9, 2020. Available at: https://nhm.gov.in/WriteReadData/l892s/1405796031571201348.pdf

4. WHO antenatal care recommendations for a positive pregnancy experience. Nutritional interventions update: Vitamin D supplements during pregnancy. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.5. Dietary guidelines for Indians - A manual. National Institute of Nutrition. Indian Council of Medical Research. Accessed October 3, 2021. Available at: http://ninindia.org/DietaryGuide linesforNINwebsite.pdf

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Diagnosis of Osteoporosis in Children

Dr. Neha Agarwal, Consultant Pediatric and Adolescent Endocrinologist
Institute of Neurosciences, Kolkata

Background

Osteoporosis is characterized by decreased bone mass and alteration in bone microarchitecture, resulting in increased bone fragility and consequently, an elevated risk of fractures. Although commonly considered a condition of the elderly, it is now increasingly recognized that the risk of osteoporosis has its roots in the childhood. Peak bone mass attained during childhood determines the bone strength and in turn, the risk of fracture during adulthood. Therefore, childhood is a crucial period to build a strong musculoskeletal system for future.

Causes of Osteoporosis in Children

Both genetic and lifestyle associated factors contribute to osteoporosis in children and adolescents. Based upon the underlying etiology, osteoporosis is categorized into primary (due to a genetic cause, such as osteogenesis imperfecta), or secondary osteoporosis (due to an underlying medical illness or medications)[1]. The various causes of osteoporosis in children are listed in ***Table I.***

Primary Osteoporosis	Secondary Osteoporosis	
Osteogenesis Imperfecta	**Chronic Illness**	**Endocrine Disorders**
Ehlers Danlos Syndrome	Malignancy	Turner Syndrome
Marfan Syndrome	Anorexia Nervosa	Growth Hormone Deficiency
Homocystinuria	Rheumatological Disorders	Hyperthyroidism
Cole-Carpenter Syndrome	Renal Disease	Cushing Syndrome
Juvenile Osteoporosis	Cystic Fibrosis	Hyperprolactinemia
Bruck Syndrome	Inflammatory bowel disease	Type 1 Diabetes
	Neuromuscular Disorders	**Medications**
	Cerebral Palsy	Glucocorticoids
	Rett Syndrome	Anti-epileptics
	Duchenne-Muscular Dystrophy	Methotrexate
	Spina Bifida	Proton-pump inhibitors

Diagnosis of Osteoporosis in Children

The diagnosis of osteoporosis in children is essentially based on the presence of fragility fractures. The International Society of Clinical Densitometry (ISCD, 2019) laid down the following criteria for diagnosing osteoporosis in children[2]:

(1) Dual Energy X-ray Absorptiometry (DXA) derived BMD Z score less than -2SD, along with history of fragility fracture (>/= 2 long bone fractures in children below 10y of age, and >/= 3 long bone fractures in children between 10-19y of age),

OR

(2) Vertebral compression fracture, irrespective of BMD Z score.

Secondary osteoporosis is usually suspected in children with an underlying illness, or those who are on bone harming medications for a prolonged period. Less often, it may be the presenting symptom of the underlying condition. A detailed history and thorough clinical examination provide clues to the diagnosis.

Specific investigations can then be done based on the suspected pathology. ***Table II*** enumerates the basic diagnostic tests recommended to be performed in a child with suspected or confirmed secondary osteoporosis[3]. Age-appropriate reference values must be considered while interpreting the reports.

Table II – Basic Diagnostic Investigations

Laboratory Tests	Variables to analyze
Blood Chemistry	Serum calcium, ionized calcium, phosphorus, magnesium, total protein, urea, creatinine, glucose, T4 or freeT4, TSH, PTH, 25-OH Vitamin D
24-hour urine chemistry	Calcium, phosphorus, creatinine, tubular reabsorption of phosphorus,
	sodium
Spot Urine (first sample in the morning)	Calcium/creatinine
Bone turnover marker	Total alkaline phosphatase

Role of Bone Turnover markers (BTMs)

These are certain molecules released into the bloodstream during the process of bone formation and bone resorption. As such, these reflect the metabolic activity at a given point. Although used extensively in adults to monitor osteoporosis treatment, their role in diagnosing and monitoring osteoporosis management in children is still uncertain.

Imaging

Despite certain limitations, dual energy x-ray absorptiometry (DXA) is the modality of choice to ascertain bone health in children. Owing to higher accuracy and ease of reproducibility, lumbar spine and total body less head (TBLH) are the preferred sites for DXA assessment in children[4]. Hip densitometry is not recommended since this site is more affected by mechanical forces. DXA derived bone mineral density (BMD) is adjusted for age, sex and body size, and results are expressed as Z scores. Also, owing to the systematic differences between densitometers made by different manufacturers, direct comparison of the reports obtained from different densitometers should not be done.

The term osteopenia is usually not recommended to be used in children. The proper terminology is "low bone mass for chronological age", which is defined as BMD Z score equal to or less than -2SD adjusted for age, gender and body size[4]. Similarly, the term osteoporosis is used only in context of clinical history of fractures and not merely on the basis of DXA findings. Further, in a child with suspected or confirmed bone fragility, vertebral fracture should always be ruled out by performing a simple lateral x-ray or by DXA vertebral fracture assessment, since they are mostly asymptomatic.

To conclude, diagnosis of osteoporosis in children requires history of fracture and low bone mass.

Learning Points

1. Low bone mass is defined as BMD Z score equal to or less than -2SD (adjusted for age, gender and body size).
2. Management for osteoporosis should not be initiated merely on the basis of densitometry.
3. The lumbar spine (L1-L4) and TBLH are the preferred sites for evaluation, hip BMD is not recommended.

References:

1. Sochett E, Mäkitie O (2005) Osteoporosis in chronically ill children. Ann Med 37: 286-294.

2. Shuhart CR, Yeap SS, Anderson PA, Jankowski LG, Lewiecki EM, Morse LR, et al. Executive Summary of the 2019 ISCD Position Development Conference on Monitoring Treatment, DXA Cross-calibration and Least Significant Change, Spinal Cord Injury, Peri-prosthetic and Orthopedic Bone Health, Transgender Medicine, and Pediatrics. J Clin Densitom. 2019;22:453-471.

3. Galindo-Zavala R, Bou-Torrent R, Magallares-López B, Mir-Perelló C, Palmou-Fontana N, Sevilla-Pérez B, et al. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. Pediatr Rheumatol Online J. 2020;18:20.

4. Baim S, Leonard MB, Bianchi ML, Hans DB, Kalkwarf HJ, Langman CB, et al. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD pediatric position development conference. J Clin Densitom. 2008;11:6–21

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Bone turnover markers in children

Dr Nikhil Lohiya, Consultant Pediatric & Adolescent Endocrinologist
Silver Lining Pediatric Super Speciality Center, Kingsway Hospitals &
Alexis Hosital, Nagpur

Bone is a metabolically active tissue which is constantly in a state of turnover. This process is called remodelling. This process involves resorption of bone by osteoclasts and formation of bone by osteoblasts. It is just like constant servicing of your car, where micro-defects are repaired and bone strength is preserved. In children, longitudinal growth, bone mineralization, growth in bone width and reshaping are all happening simultaneously. This reshaping and bone width increment happen due to muscle action which strengthens the bone. Hence bone and muscle acts as a unit.

Marker	Indicates	Sample	Commercially available
	Bone Formation		
Procollagen type I C- terminal propeptide (PICP)	(PINP) type I collagen synthesis - mainly bone osteoblast – early proliferative phase	Plasma/ Serum	No
Procollagen type I N- terminal propeptide		Plasma/ Serum	Yes
Bone Alkaline phosphatase (Bone ALP)	Osteoblast – maturation phase Matrix vesicles (bone mineralisation)	Plasma/ Serum	Yes
Osteocalcin	Hypertrophic chondrocytes (growth plate)	Plasma/ Serum	Yes
	Bone Resorption		
Hydroxyproline	Collagen turnover (skin & bone)	Urine	No
Pyridinoline (free + peptide- bound) (Pyd)	Breakdown of mature collagen	Urine	No
Deoxypyridinoline (free + peptide- bound) (Dpd)	Breakdown of mature bone collagen	Urine	No
Free deoxypyridinoline (free Dpd)		Urine	No
Tartrate- resistant acid phosphatase, isoenzyme 5b (TRAP5b)	Osteoclast activity	Plasma	No
Receptor activator of nuclear factors kB (RANKL)	Inducer of osteoclastic bone resorption	Plasma	No
Osteoprotegerin (OPG)	Decoy receptor – binds RANKL to prevent RANKL- induced bone resorption	Plasma	No

The bone turnover markers (BTM) listed above are nothing but indicators of bone turnover. They help us in identifying whether the predominant process is resorption or formation. A list of BTMs is as below:

Use of BTMs in Clinical Medicine

Condition	Clinical Application	Comment
Hypophosphatasia	*Low ALP (no need for bone specific ALP)*	Very useful
Osteogenesis Imperfecta	*Low PICP - useful in distinguishing child abuse & OI*	Limited benefit
Juvenile Paget's disease	*Low Osteoprotegerin*	Availability an issue
Rickets	*High ALP (no need for bone specific ALP)*	Very useful
Osteopenia of Prematurity	*High ALP (no need for bone specific ALP)*	Very useful
Idiopathic Juvenile Osteoporosis	*Markers are not so reliable*	Limited benefit
Growth Hormone (GH) Insufficiency	*ALP can be useful predictor of height velocity response to treatment after one year*	Not useful for diagnosis
Impaired Growth in Acute and Chronic Disease	*Low ALP is observed*	Other bone marker measurements not needed

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

BTMs can be studied in research areas of malnutrition, and chronic diseases of childhood like asthma, juvenile idiopathic arthritis, cystic fibrosis, inflammatory bowel disease and acute lymphoblastic leukemia.
Serum markers are preferred over urine markers due to reliability issues. The factors which should be kept in mind before interpreting the results are age, gender, puberty and pathological conditions. Except OPG and RANKL, the relationship of bone metabolites with age and sex generally mirrors the pediatric growth curve. Total ALP is universally available and inexpensive, with results available on the same day. The newer markers complement the bone mineral content and density, and can be useful at times. In research, one should do both formation and resorption markers to have a proper interpretation of both aspects. BTM need more exploration in pediatrics.

References:

1. Ranke MB, Mullis P-E (eds): Diagnostics of Endocrine Function in Children and Adolescents, ed 4. Basel, Karger, 2011, pp 429–447

2. Szulc P. Bone turnover: Biology and assessment tools. Best Pract Res Clin Endocrinol Metab. 2018 Oct;32(5):725-738. doi: 10.1016/j.beem.2018.05.003. Epub 2018 May 26. PMID: 30449551.

3. Chew CK, Clarke BL. Biochemical Testing Relevant to Bone. Endocrinol Metab Clin North Am. 2017 Sep;46(3):649-667. doi: 10.1016/j.ecl.2017.04.003. Epub 2017 Jun 20. PMID: 28760231.

Management of osteogenesis imperfecta

Dr Medha Mittal, Associate Professor, Dept of Pediatrics
Chacha Nehru Bal Chikitsalaya, Delhi
Dr Anil Agarwal, Senior Specialist, Dept of Orthopedics
Chacha Nehru Bal Chikitsalaya, Delhi

Osteogenesis imperfecta (OI, also called brittle bone disease) is the term used to describe a group of inherited disorders characterized by multiple low trauma fractures. The first presentation is often in infancy. There is involvement of the bones, teeth, ligaments, sclerae and skin. The incidence is between 1 in 10,000 to 1 in 20,000.[1]

Sillence suggested the original classification system with four subtypes based on clinical severity, ranging from mild to lethal. Most cases are a result of mutations in the COL1A1 and COL1A2 genes that encode for the alpha chains of type 1 collagen. With discovery of new genes, a new classification system has been suggested, with subtypes, as per the genetic abnormality. These mutations result in defects in synthesis, structure or processing of collagen or its posttranslational modification, or cross-linking or defects in bone mineralization or osteoblast differentiation. These result in increased bone fragility, osteopenia, abnormalities of cortical thickness, trabecular structure and bone matrix. The common clinical features include proneness to fracture and laxity of ligaments. About two-thirds of patients will have blue sclerae and about half will have yellowish or opalescent teeth, prone to breaking (dentinogenesis imperfecta).[2] Other features include flat mid-face, frontal bossing, fragile skin, hearing loss (usually onset in the second to third decade), bone deformity and growth retardation. In a classic case, fractures are discovered during infancy and tend to recur frequently throughout childhood. The resultant callus is abnormally soft, permitting mobility at fracture sites and therefore malunion; further fractures are common. In less severe varieties, the fractures are delayed. They occur 1-2 years after birth, when the child initiates weight bearing. In severe cases, fractures and deformities are common and marked.

The huge advances made in the understanding of the pathophysiology of the condition are, however, unaccompanied by similar advancements in treatment.
The management of OI is best done by a holistic multidisciplinary team of pediatric endocrinologist, orthopedic surgeon, occupational therapist, physiotherapist, counsellor and other subspecialists as needed.

Management includes-

1. Gentle nursing of infants to prevent fractures as far as possible
2. Bisphosphonates therapy given cyclically

3. Prompt splinting when fractures do occur, to prevent deformity
4. Mobilization to prevent further osteoporosis
5. Correction of deformities, if necessary, by multiple osteotomies, bone realignment and intramedullary fixation.

Bisphosphonates are the mainstay of treatment, initiated for those with two or more significant long bone fractures in a year or those with vertebral fractures. Children can be given intravenous pamidronate and zoledronic acid; oral bisphosphonates are not advised. Bisphosphonates exert their action by inhibition of osteoclast activity and inducing osteoclast apoptosis. Pamidronate became widely used in children after the initial observational study by Glorieux et al. [3] There was striking improvement in bone pain, mobility, and bone mineral density; and reduced fracture incidence. There have been several publications since, some with placebo-controlled study design. These generally support the original findings. Bisphosphonates also affect vertebral modelling, preserve vertebral shape, and help in vertebral reshaping after compression fracture. Long bone fractures are reduced, though that could partly be due to reduced risk with skeletal growth in children. They are generally well tolerated, though there may be transient hyperpyrexia or myalgia, especially after the first infusion. Hypocalcemia may occur transiently, is usually asymptomatic, and more common with zoledronate. Bisphosphonates are contraindicated in renal failure.

Pamidronate is administered as an infusion over four hours in the dose of 1 mg/kg/day on 3 consecutive days, repeated every 3 months. For those less than 10 kg, it is infused as 0.5 mg/kg/day on 3 consecutive days, repeated every 2 months. It is diluted in normal saline with a maximum concentration of 360 µg/mL. Zoledronate is infused in the dose of 0.025 mg/kg/day every 3 months for those less than 2 years of age, 0.035 mg/kg/day every 4 months for 2-5 year olds, and 0.05 mg/kg/day every 6 months for those older than 5 years. The annual dose should not exceed 0.1 mg/kg body weight.[4]

Adequate levels of vitamin D and calcium should be maintained to support bone health. New antiresorptive and anabolic agents have been tried in adults but their efficacy and safety in children has not been established. Denosumab is a human monoclonal antibody directed against receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine that mediates osteoclast survival. Thus, the mechanism of action is similar to bisphosphonates in that it inhibits osteoclast activity. It has been used in some pediatric cases who did not respond to bisphosphonates. However, evidence is not yet robust enough to support its general use in children. Bone anabolic agents that are being tried in adults include teriparatide and the sclerostin inhibitor romosozumab.

Functional gains are the main indication for deformity correction; use of intramedullary fixation device is the method of choice. (Image 1) It is much less likely to give rise to a peri-prosthetic fracture, compared to other fixation devices. Telescopic rods such as Frassier Duval and the Sheffield telescopic intramedullary rod system are used to enhance function.[5] Delayed union and non-union may be encountered. Physical therapy and rehabilitation are essential to promote motor development.

References:

1. Marini JC, Forlino A, Bächinger HP, Bishop NJ, Byers PH, Paepe A. Osteogenesis imperfecta. Nat Rev Dis Primers. 2017 Aug 18;3:17052.

2. Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol. 2020 Oct;183(4):R95-R106

3. Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med. (1998) 339:947–52.

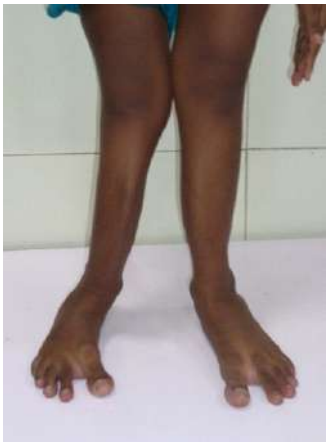
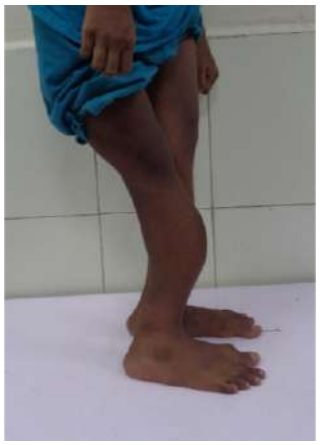
4. Padidela R. Metabolic bone disease in children including rickets. In : Khadilkar V (Ed) IAP Textbook of Pediatric Endocrinology, 1st edition. Jaypee Brothers Medical Publishers ;2019. pp 359-374.

5. Hidalgo Perea S, Green DW. Osteogenesis imperfecta: treatment and surgical management. Curr Opin Pediatr. 2021 Feb 1;33(1):74-78.

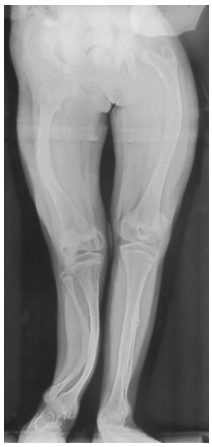
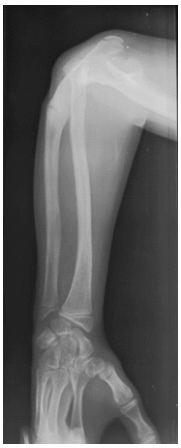
NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

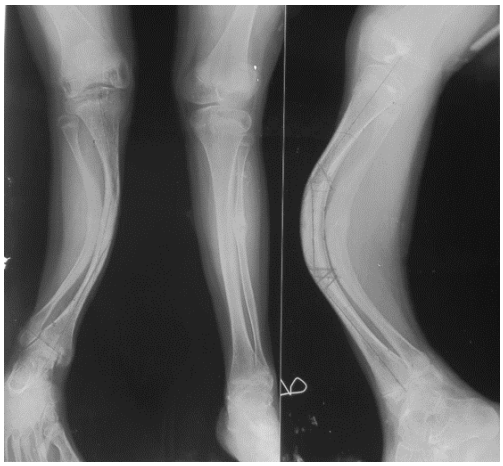
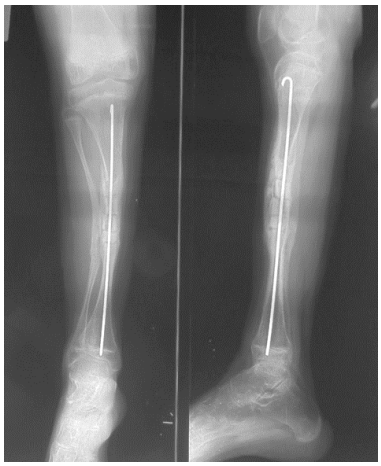
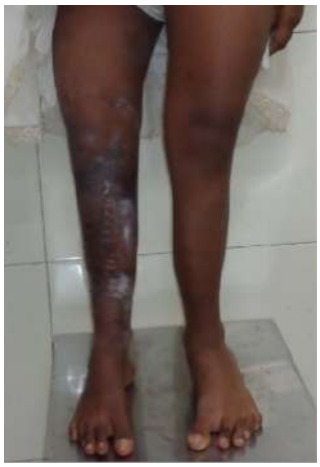
11 year old child with anterior angulation of the right tibia. Deformities are seen in multiple bones

Delayed union is seen post ulnar fracture

The anteromedial tibial bowing was treated with multiple osteotomies and intramedullary rodding. Corrected deformity post operatively.

Metabolic bone disease of prematurity: An overview

Dr Kochurani Abraham

Metabolic Bone Disease (MBD) is a spectrum of clinically different diseases sharing the common finding of an aberrant bone chemical milieu, leading to a defective skeleton.

Incidence of MBD is higher at younger gestational ages and lower birth weights. Nearly 80% of total bone calcium accretion in neonates occurs in the third trimester. Prematurity, coupled with inadequate nutrient intake, and the high rate of skeletal growth occurring after birth, is the leading cause of MBD. The incidence is up to 30% in preterm infants born at less than 28 weeks of gestation. Approximately 10% of preterm infants suffer fractures by a corrected gestational age of 36-40 weeks.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

RISK FACTORS

Antenatal Risk Factors	Postnatal Risk Factors
Placental insufficiency	Prolonged TPN > 4 weeks
Pre-eclampsia	Bronchopulmonary dysplasia
Chorioamnionitis	Necrotising enterocolitis
Neuromuscular disorders, intraventricular hemorrhage, periventricular leukomalacia	Liver disease
Genetic Polymorphism (Vitamin D receptor, estrogen, collagen alpha 1)	Renal disease
Male	Medications - loop diuretics, methylxanthines, glucocorticoids

Laboratory Evaluation for screening of MBD include serum calcium, phosphorus, alkaline phosphatase, 25(OH) Vit D and iPTH, urinary calcium: creatinine ratio, TRP and radiological evaluation. There are no fixed guidelines for evaluation of MBD; more studies on larger groups of patients are needed.
None of the biochemical parameters mentioned can alone be considered a marker of MBD. Serum calcium is no longer considered a reliable screening tool because newborns can maintain normal calcium levels despite bone calcium loss under the effect of PTH, and the levels can also be affected by disorders of phosphate depletion and hypophophatemia.

Hypophosphatemia is the earliest marker of disrupted mineral metabolism, which can be seen as early as 7-14 days after birth. Serum phosphate levels < 3.6 mg/dl (1.16 mmol/L) in exclusively breastfed newborns suggest the depletion of the mineral content and indicate a greater risk for MBD development. Serum phosphate levels <5.6 mg/dl (<1.8 mmol/L) have been strongly associated with the presence of radiologically evident rickets in preterm infants with a mean gestational age of 30.3 weeks (range 24.7–33.0 weeks) and a mean birth weight of 1,490 g (range 735–2,250 g). ALP levels >500 IU/L are suggestive of impaired bone homeostasis and values >700 IU/L are associated with bone demineralization, despite the absence of clinical signs. ALP levels higher than 900 IU/L in preterm infants <33 weeks of gestational age, associated with serum phosphate levels persistently < 5.6 mg/dL (<1.8 mmol/L), have a diagnostic sensitivity and specificity of 70 and 100%, respectively.

Management is not standardised. MBD peaks at 4-8 weeks of age. An early screening of biochemical parameters, timely diagnosis and optimal replacement can improve bone health in the long term. A lookout for antenatal risk factors can also help in early detection of MBD. Targeted mineral supplementation can be initiated in those at risk/ diagnosed MBD with monitoring every 1-2 weeks for potential adjustment in dose. For individuals with significant risk factors for MBD who do not show initial signs of Ca and/or phosphorus deficiency, rescreening every 2-4 weeks can be considered, depending on level of suspicion.
Radiographic evaluation is considered a critical part of screening for MBD but is not widely used, and lacks normative data. DXA has been used in some centres but is not widely available. Tibial quantitative ultrasound shows promise, but remains primarily a research tool.

References:

1.Sperling MA, Pediatric Endocrinology: Disorders of calcium and phosphorus homeostasis in the newborn and infant. 4.USA: Elsevier Saunders;2014.
2.Backström M, Kouri T, Kuusela A-L, Sievänen H, Koivisto A-M, Ikonen R, et al. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta Paediatr. 2000 Jul;89(7):867–73.
3. From Indian Academy of Pediatrics 'Guideline for Vitamin D and Calcium in Children' Committee., Khadilkar A, Khadilkar V, Chinnappa J, Rathi N, Khadgawat R, et al. Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatr. 2017 Jul 15;54(7):567–73.
4. Faienza MF, D'Amato E, Natale MP, Grano M, Chiarito M, Brunetti G, et al. Metabolic Bone Disease of Prematurity: Diagnosis and Management. Front Pediatr. 2019 Apr 12;7:143.
5. Rehman MU, Narchi H. Metabolic bone disease in the preterm infant: Current state and future directions. World J Methodol. 2015 Sep 26;5(3):115–21.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

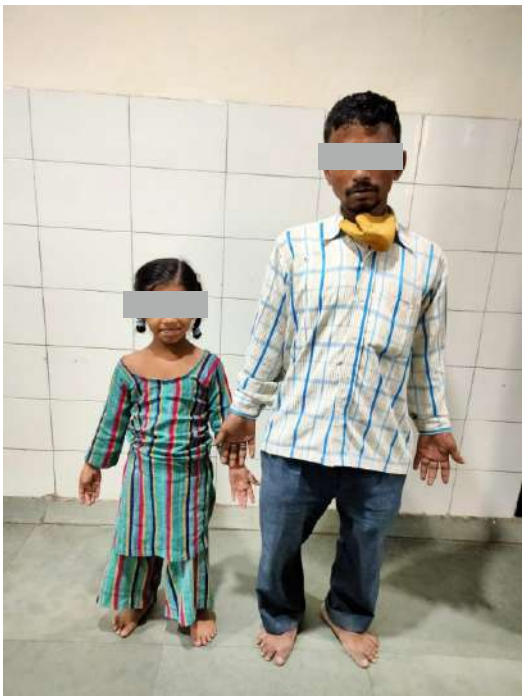
CAPE News | ISPAE

Case Image

Dr Medha Mittal, Associate Professor, Dept of Pediatrics
Chacha Nehru Bal Chikitsalaya, Delhi

Seven year old girl and father with achondroplasia

The 7 year old girl was being worked up for pathological short stature. She had short limbs, lumbar lordosis, limited elbow extension and trident hand, suggesting achondroplasia. The mother who used to accompany her was of average stature. Father came at a later visit and had identical features. The skeletal survey done for both daughter and father was suggestive of achondroplasia, with squared off iliac wings, flat horizontal acetabula, marked narrowing of sacrosciatic notch and narrowing of interpediculate distance of the caudal spine.



Achondroplasia is the most common of the skeletal dysplasias that results in marked short stature. The underlying defect is mutation in fibroblast growth factor receptor type 3 (FGFR3) that is autosomal dominant, freely penetrant and shows only modest variability of expression. An affected individual has 50% risk for each offspring to be similarly affected. While most instances arise from new mutations and 80% of affected children are born to two unaffected, average statured parents, the other 20% may have an affected parent with similar phenotype. The case image above aptly depicts the autosomal dominant inheritance and the importance of observing the siblings and parents which cannot be overemphasized.

DRUG CORNER: Bisphosphonate Therapy in Pediatrics

Dr Nikhil Lohiya, Consultant Pediatric & Adolescent Endocrinologist
Silver Lining Pediatric Super Specialty Center, Kingsway Hospitals & Alexis Hospital, Nagpur

Bisphosphonates (BPNs) are analogs of pyrophosphate in which the oxygen atom is replaced by a carbon atom in the P-O-P skeleton. BPNs are divided into non-nitrogen-containing moiety and nitrogen-containing moiety. They are inhibitors of the enzyme farnesyl pyrophosphate synthase, a key branch point enzyme in the mevalonate pathway. This results in inhibition of osteoclast activity, recruitment and apoptosis, so suppression of bone turnover occurs.

Indications

The major indication to remember is osteoporosis. It is very important to be sure regarding the definition of childhood osteoporosis. ISCD 2013 defines it as 1) the presence of a significant fracture history, indicated by either one or more vertebral compression (crush) fractures, in the absence of local disease or trauma or, two or more long-bone fractures by age 10y or, three or more long-bone fractures at any age up to age 19y; and 2) a low bone mineral content and areal bone mineral density (aBMD) with BMC/BMD Z-score $\leqslant$-2.0 SD. The indications where bisphosphonate therapy has shown positive effects are listed in the table below:

Primary Osteoporosis Osteogenesis imperfecta IJO Osteoporosis pseudoglioma syndrome Neurofibromatosis Gaucher's disease Familial idiopathic hyperphosphatasia	**Secondary Osteoporosis** Glucocorticoid-induced osteoporosis Disuse osteoporosis (neurological diseases with palsy and muscular dystrophies)
Hypercalcemic disorders Vitamin D intoxication Malignancy-induced hypercalcemia Subcutaneous fat necrosis Idiopathic infantile hypercalcemia Neonatal severe primary hyperparathyroidism Immobilization hypercalcemia	**Heterotopic calcification** Fibrodysplasia ossificans progressiva Generalized arterial calcification Juvenile dermatomyositis

Other conditions
Fibrous dysplasia of bone/ McCune-Albright syndrome
Chronic recurrent multifocal osteomyelitis
Osteonecrosis-related chemotherapy

Choice of Bisphosphonate
List of agents which have been studied, with doses, is listed in the table below:

Name	Route & Dose
Pamidronate	Intravenous 0.5–1.5 mg/kg per day for 3 days (200–250 ml ISS 3 h, every 2–6 months)
Alendronate	Oral 1–2 mg/kg per week 5 (<20 kg) to 10 (>20 kg) mg per day 70 mg per week
Zoledronate	Intravenous 0.015–0.05 mg/kg (50 ml ISS 30–45 min, every 3–6 months)
Risedronate	Oral 15 mg per week (<40 kg) 30 mg per week (>40 kg) 2 mg/kg per week

Assessment of Patients on BPN therapy

- Thorough clinical assessment with dental examination, ophthalmological examination and calcium intake history
- Biochemical assessment with CBC, Electrolytes, Alkaline phosphatase, Renal and Liver function, Vitamin D and PTH, Urine routine & urinary calcium: creatinine ratio
- Bone age assessment and Bone mineral studies using densitometric techniques.

Adverse effects

BPNs are generally well tolerated. In most cases, an acute phase reaction is observed, with fever, malaise, abdominal pain, vomiting, muscle pain and bone pain which can last for a few days. Hypocalcemia, hypophosphatemia and hypomagnesemia can rarely cause tetany. Rarely reported in adults are uveitis, thrombocytopenia, oral or esophageal ulcers. Oral agents can cause gastro-esophageal reflux. Osteonecrosis of the jaw is another serious side effect which has been observed.

Pedendoscan- Bone

Dr Pragya Mangla, Pediatric Endocrinologist, Department of Endocrinology
University College of Medical Sciences and GTB hospital, Delhi

1.A Japanese single-center experience of the efficacy and safety of asfotase alfa in pediatric-onset hypophosphatasia.

Sugiyama Y, Watanabe T, Tajika M, Matsuhashi T, Shimura M, Fushimi T, et al. Orphanet J Rare Dis. 2022 Feb 23;17(1):78. doi: 10.1186/s13023-022-02230-y.

Hypophosphatasia (HPP) is a rare inherited metabolic disorder caused by mutations in the ALPL gene, which encodes tissue nonspecific alkaline phosphatase. The age of onset and severity is widely diverse in the six forms (perinatal, benign prenatal, infantile, childhood, adult, and odontohypophosphatasia) of HPP. Enzyme replacement therapy using asfotase alfa (AA) was approved in 2015 in Japan for treating patients with HPP. The authors report the details of AA experience in ten cases of pediatric-onset HPP (one case of perinatal form, two cases of benign prenatal form, and seven cases of mild childhood form of HPP) (median age 11.0 [7.6-12.5] years; 60% male) in nine families from January 2015 to November 2019. The patients with mild childhood form mainly had pain in different joints, poor weight gain, short stature and/or premature loss of deciduous tooth as primary presentation, while the benign prenatal form had unequal length of limbs and bilateral femur deformity. The perinatal form had short limbs. All patients had low baseline serum alkaline phosphatase levels. Eight out of ten patients had compound heterozygosity in genetic analysis. Patients were given AA subcutaneously thrice weekly in a dose of 2 mg/kg or six times a week at a dose of 1 mg/kg, with the maximum volume of a single injection being 1 mL (40 or 100 mg/mL). All HPP patients seem to have responded to the treatment, as evidenced by subjective alleviation of pain and fatigue, no further premature loss of teeth, increased height SD, improvement in respiratory condition and 6-min walk test result, disappearance of kidney calcification, and/or increases in bone mineralization. All patients had injection site reactions and local lipoatrophy. No serious side effects were observed. **Thus, AA seems to be effective in patients with mild to severe pediatric-onset forms of HPP, but long-term studies are required to investigate its efficacy and safety.**

2. Patient-Reported Outcomes from a Randomized, Active-Controlled, Open-Label, Phase 3 Trial of Burosumab versus Conventional Therapy in Children with X-Linked Hypophosphatemia.

Padidela R, Whyte MP, Glorieux FH, Munns CF, Ward LM, Nilsson O, et al. Calcif Tissue Int. 2021 May;108(5):622-633. doi: 10.1007/s00223-020-00797-x.

X-linked hypophosphatemia has conventionally been treated with multiple daily doses of oral phosphate with active vitamin D. Burosumab, a monoclonal antibody targeting fibroblast growth factor 23, has been found to significantly improve phosphorus homeostasis, rickets, lower-extremity deformities, mobility, and growth versus conventional therapy. A randomized, open-label, phase 3 trial was done involving children aged 1-12 years with X-linked hypophosphatemia where patients were randomized (1:1) to subcutaneous burosumab (starting dose 0.8 mg/kg every 2 weeks) or to continue conventional therapy.

Doses were further titrated and individualized according to published recommendations. Children with prior treatment with conventional therapy for ⩾6 consecutive months (children aged <3 years) or ⩾12 consecutive months (children aged ⩾3 years) were taken. Patient-reported outcomes (PROs) were collected and analysed at baseline and weeks 24, 40 and 64. The specific data included the endpoints of Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire, pain interference, physical function mobility, and fatigue, along with overall health-related quality of life (HRQoL) [assessed using the SF-10, which included physical health scores (PHS-10) and psychosocial health score (PSS-10) for children] and pain intensity according to Faces Pain Scale - Revised (FPS-R). PROMIS pain interference, physical function mobility, fatigue scores and PHS-10 improved from baseline with burosumab at weeks 40 and 64 as compared to insignificant change with continued conventional therapy. Pain interference scores differed significantly between groups at week 40 but not at week 64. Between-group differences were not significant at either week for physical function mobility or fatigue. In conclusion, **changing to burosumab versus continuing with conventional therapy improved patient-reported outcome measures, with statistically significant differences in PROMIS pain interference at week 40 (improvement in pain) and better physical health (PHS-10) at weeks 40 and 64 versus baseline.**

3. The efficacy and safety of different doses of calcitriol combined with neutral phosphate in X-linked hypophosphatemia: a prospective study.

Jin C, Zhang C, Ni X, Zhao Z, Xu L, Wu B, et al. Osteoporos Int. 2022 Jun;33(6):1385-1395. doi: 10.1007/s00198-021-06221-w.

A 2-year, randomized, open-label, prospective study recruiting 68 XLH children, aiming to compare the efficacy and safety of calcitriol in doses of 20 ng/kg/d and 40 ng/kg/d, was done in China. For the high dose group, a minimum dose of 0.25 μg/day to a maximum of 1 μg/d; while for the low dose group, a minimum of 0.125 μg/d to a maximum of 0.5 μg/day was used. Efficacy endpoints were the total Thacher ricket severity score (RSS) change from baseline to month 12 and 24, the SAP level, fasting serum phosphate (Pi) level, body height Z-score, and frequency of dental abscess. Safety assessments were done using renal ultrasound for nephrocalcinosis, graded as 0–4, fasting serum and 24 h urine calcium level, and looking for the occurrence of hyperparathyroidism. The calcitriol dose was adjusted to high dose when the serum total ALP (SAP) or PTH level increased over 30%; and decreased to low dose if serum calcium level was over the upper limit, or if hypercalciuria or newly developed or worsened nephrocalcinosis appeared during the follow-up visit. In the high-dose group, the decrease in the total RSS from baseline was more significant at 12 (difference 0.87, p=0.049) and 24 months (difference 1.23, p=0.011). A significant decrease in the SAP levels was observed at 6 months and a significantly lower incidence of secondary hyperparathyroidism was also seen. Pi level, height Z-score change, frequency of dental abscess and ratio of de novo nephrocalcinosis were comparable. **Thus the 40 ng/kg/d calcitriol dose was effective with no increase in adverse events, compared to 20 ng/kg/d in the treatment of X-linked hypophosphatemia.**

4. Vitamin D for Growth and Rickets in Stunted Children: A Randomized Trial.

Crowe FL, Mughal MZ, Maroof Z, Berry J, Kaleem M, Abburu S, et al. Pediatrics. 2021 Jan;147(1):e20200815. doi: 10.1542/peds.2020-0815.

In some districts of Afghanistan, there is a high prevalence of childhood stunting, ranging from 40% to >80%. Vitamin D deficiency and malnutrition are common problems. The objective of this study was to assess the effect of vitamin D supplementation on the linear growth and risk of rickets among Afghan children. In this double-blind, placebo-controlled trial, 3046 children aged 1 to 11 months from lower socioeconomic strata from 5 inner-city districts of Kabul were randomly assigned to receive oral vitamin D3 (1 lac IU) or placebo (total 6 doses) every 3 months for 18 months. Anthropometry was done at baseline and at 18 months. Dietary calcium intake was assessed. The Rickets Severity Score (RSS) was calculated for 631 randomly selected infants at 18 months, with rickets defined as a score of >1.5. The mean serum 25(OH)D level was statistically higher in the vitamin D group after the first 3 doses but the difference was not significant after >4 months of the final (sixth) dose.

The mean RSS does not differ significantly between the two groups. The prevalence of rickets was not statistically different [5.5% (placebo) and 5.3% (vitamin D), P = 0.9]. The mean height-for-age for children with a calcium intake >300 mg/day revealed a slight improvement with vitamin D (mean difference 0.14[95% CI: 0 to 0.29]; P = .05) while for those <300 mg/day, no difference was seen between the groups. Weight-for-age or weight-for-height z scores were comparable. Thus, **authors found no statistically significant reduction in rickets or improved growth with vitamin D supplementation in stunted children though height improved in infants with calcium intake >300mg/day.**

5. Is it important to achieve physical activity recommendations at early stages of life to improve bone health?

Ferrer P, Iglesia I, Muniz-Pardos B, Miguel-Berges ML, Flores-Barrantes P, Gomez-Bruton A, et al. Osteoporos Int. 2022 May;33(5):1017-1026. doi: 10.1007/s00198-021-06256-z.

The World Health Organisation (WHO) has recommended a minimum of 1 h per day of moderate-to-vigorous physical activity (PA) for 5–17 years old children. The authors investigated the association between PA (meeting/not meeting the current WHO recommendations) and bone parameters in 295 Spanish children, taking into account both perinatal and lifestyle behaviour variables. A cohort of children born in Aragon (Spain) in 2009 was followed until the age of 7 years. Of them, in 295 7y old children (154 boys), bone parameters were assessed using dual-energy X-ray absorptiometry (DXA) (whole body scan) and peripheral quantitative computed tomography (pQCT) (tibia scanned at the 8% (distal) and 38% (diaphyseal) of the total tibia length) between 2016 and 2017. PA was assessed using GT3X Actigraph accelerometers. No statistically significant difference was found for perinatal variables. As compared to girls, boys had significantly higher subtotal lean mass, higher MV PA duration, higher body areal bone mineral density (aBMD), significantly higher total bone mineral content (BMC) at 8%, higher trabecular BMC, high volumetric BMD (vBMD), and higher total area at 8%. Similarly they had higher total BMC at 38%, higher cortical BMC and higher cortical thickness at the 38% of the tibial length. Significant differences were found between active boys and inactive boys in aBMD, total spine BMD (0.567 vs 0.544 g/cm^2), and total BMC at 8% site (1.57 vs. 1.45 g/cm) and cortical thickness at 38% site. Similarly, there were significant differences between active girls and inactive girls in total BMC, cortical BMC and cortical thickness and total area at 38% site.While no stratification was done on the basis of sex, significant positive associations were found between MVPA and subtotal BMD (DXA), total BMC at 8% site and at 38% site, cortical BMC at 38% site and cortical thickness. **Thus, meeting WHO PA recommendations has a beneficial effect on bone parameters in childhood, both in boys and girls.**

6. Pediatric Outcomes Data Collection Instrument is a Useful Patient-Reported Outcome Measure for Physical Function in Children with Osteogenesis Imperfecta.

Murali CN, Cuthbertson D, Slater B, Nguyen D, Turner A, Harris G, et al; Members of the BBD Consortium, Nagamani SCS. Genet Med. 2020 Mar;22(3):581-589. doi: 10.1038/s41436-019-0688-6.

Pediatric Outcomes Data Collection Instrument (PODCI) is a PRO measure which consists of scores on seven "core scales," four encompassing physical function and three assessing psychological well-being in children with musculoskeletal disorders. The Brief Assessment of Motor Function (BAMF) is an observer rating of a patient's functional capability, which assesses on Fine Motor, Upper Extremity Gross Motor, and Lower Extremity Gross Motor Scale. The authors have evaluated the validity and reliability of PODCI in children with osteogenesis imperfecta (OI). This multicenter study conducted by the Brittle Bone Disorders Consortium, correlated physical function scores (in PODCI) with a validated BAMF, and with psychological well-being scores (using PODCI) in 459 children with OI types I (203), III (95), IV (119) and others (42). Physical function scores in OI type III were significantly lower than those in OI types I (highest) and IV (between the two). There were no significant differences in psychological well-being.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Thus, PODCI psychological well-being scores do not correlate with known physical function in OI. PODCI physical function scores showed moderate-to strong correlation with BAMF. **In children with OI, PODCI can be used as a reliable measure of physical functioning, and to assess the effect of interventions.**

7. Ectopic Calcification and Hypophosphatemic Rickets: Natural History of ENPP1 and ABCC6 Deficiencies. Ferreira CR, Kintzinger K, Hackbarth ME, Botschen U, Nitschke Y, Mughal MZ, et al. J Bone Miner Res. 2021 Nov;36(11):2193-2202. doi: 10.1002/jbmr.4418.

This retrospective international cross-sectional study included 247 individuals (from birth to 58.3 years of age) with generalized arterial calcification of infancy (GACI) or autosomal recessive hypophosphatemic rickets type 2 (ARHR2), confirmed by imaging, biopsy, biochemical findings, and/or ENPP1 or ABCC6 variants or by parental mutational analysis indicating ENPP1/ABCC6 variants consistent with symptoms of affected individuals. The authors' objective was to characterize survival and natural history of GACI, to elucidate the role of bisphosphonates in survival, and assess clinical differences between ENPP1 and ABCC6 deficiencies. Overall mortality was 54.7% (13.4% in utero or stillborn), with a 50.4% probability of death before the age of 6 months (critical period). Bisphosphonate treatment had no survival benefit. Despite a similar prevalence of GACI phenotypes between ENPP1 and ABCC6 deficiencies, including arterial calcification (77.2% and 89.5%, respectively), organ calcification (65.8% and 84.2%, respectively), and cardiovascular complications (58.4% and 78.9%, respectively), mortality was higher for ENPP1 versus ABCC6 variants (40.5% versus 10.5%, respectively; p = 0.0157). Higher prevalence of rickets was reported (70.8% vs 11.8%; p = 0.0001) in surviving affected individuals with ENPP1, as compared to ABCC6. Eleven patients of ARHR2 presenting with rickets had confirmed ENPP1 variants. Approximately 70% of these patients demonstrated evidence of ectopic calcification or complications similar to those seen with GACI, signifying ARHR2 as a part of the spectrum of ENPP1 deficiency. Thus, **GACI is associated with early mortality, despite attempts to treat with bisphosphonates. The pathology of ENPP1 and ABCC6 variants overlaps. The high prevalence of rickets is almost exclusive to ENPP1 deficiency.**

Patient corner

Dr. Diksha Shirodkar, Clinical Fellow in Pediatric Endocrinology and Diabetes
Bristol Royal Hospital for Children, Bristol, United Kingdom

1. An accomplished actor despite being mocked at as a dwarf

Peter Hayden Dinklage is an American actor who received international recognition for portraying the character of **Tyrion Lannister** in the **Game Of Thrones**. He won many accolades, including the Golden Globe award (2011), Screen Actors Guild award (2020), and the Primetime Emmy for his outstanding performance in a supporting role (4 times).

He was diagnosed to have achondroplasia (current height: 135 cm) soon after birth (no other family member affected), because of which he was ridiculed in school. His desire to act had him enrolling in drama and theatre schools; however, the roles he was asked to play were of an elf or leprechaun, which he did not like to do. After a long struggle, his first breakthrough performance was in **The Station Agent.** Although he acted in some movies before that, **The Station Agent** earned critically acclaimed success, and there was no looking back for Peter from there. Now he has performed in over 50 films and theatrical roles. He appears as a celebrity speaker, and works for the upliftment of the social status of dwarfs. He is an animal lover and supports PETA. He has two unaffected children of his wedlock with a theatrical director. In 2014, Dinklage and 4 other co-stars of **The Game Of Thrones** became some of the highest paid actors on television.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

References:
Reference: Turchiano, Danielle (September 23, 2019). "Emmys: Peter Dinklage Sets Record With Supporting Actor Win for 'Game of Thrones'". Variety. Retrieved September 23, 2019.

Image: https://www.theguardian.com/tv-and-radio/2015/aug/07/peter-dinklage-tyrion-lannister-game-of-thrones-pixels

2. An Indian Prodigy with fragile bones

Sparsh Shah is a young, multitalented 19 year old young man of Indian ethnicity. He is a rapper, singer, songwriter and motivational speaker living in the USA. His fans call him the Brittle-Bone Rapper. Sparsh has Osteogenesis Imperfecta, and had over 35 broken bones at the time of his birth. Till date, he has suffered from over 125 fractures, with countless reparative surgeries.

His Instagram handle for rapping is Purythm - a portmanteaux of pure and rhythm, since he values his traditions from India (hence pure) and he is all about the rhythm. Sparsh wants to keep his rapping all clean and evolving for all ages. He has also been an inspirational speaker, working towards changing many lives through his music and life story. He featured in various programs including *Kaun Banega Crorepati* and also has a documentary released on this life story. He was felicitated with the Global Indian Award in the year 2018. He dreams of performing at a concert with over 1 billion people and also wishes to collaborate with Eminem in the near future.

Image: https://disabilityhorizons.com/2018/10/sparsh-shah-the-15-year-old-rapper-with-brittle-bones/

References:
1. "Meet Sparsh Shah, the kid who rocked Eminem's 'Not Afraid' from his wheelchair". India Today. 12 March 2016. Retrieved 23 July 2020.

2. ^"World's Greatest Motivators Television Series Announces a Special Youth Motivator Edition Featuring Sparsh Shah". www.wboc.com. Retrieved 23 July 2020.

Diabetes Educators' Corner
Common framework to manage Type 1 diabetes in school

Rogini Arun Indrakumar, Certified Diabetes Educator, Chennai

It is necessary to approach the school management to support your child with type 1 diabetes (T1D) in school. Your first step would be creating good communication - give a very simple explanation about T1D. Your words and terms must not create panic or the image of your child's diabetes being a burden at school. Schedule a meeting with the management, with the purpose of ensuring that the school and you, the parents, create a holistic, safe, healthy, and secure atmosphere for the physical and mental health of your child. The basic care points that you give the school will help the staff cater to the child's needs, so he/ she can actively focus throughout the school hours.

Explaining Type 1 Diabetes:

T1D is an autoimmune disease, in which the pancreas stops producing a hormone called insulin which controls the blood glucose (BG). The absence of insulin leads to increased level of sugar in the blood stream.

This can be effectively controlled and managed by injecting insulin. Diabetes is not contagious. It can be controlled well with proper diet, exercise, insulin, and frequent BG monitoring.

There could be chances of diabetic emergencies such as hypoglycemia (low BG) and hyperglycemia (high BG). Hypoglycemia is caused by exercise and excess insulin. Hyperglycemia is caused by excess food with inadequate insulin. So it is very important to balance food, exercise, and insulin.

When can hypoglycemia occur?

A BG level of less than 70mg/dl is hypoglycemia, and less than 54 mg/dl is serious hypoglycemia.

- It can happen when participating in any unplanned intense physical activity without checking BG and having a snack.
- The child can play and exercise, but it may be better to avoid it just before a meal.
- Missing the mid-morning snack or afternoon snack can also lead to hypoglycemia.

Symptoms of Hypoglycemia

Warning symptoms may be

- Sweating
- Shaking
- Headache
- Trembling
- Pallor
- Unable to focus/concentrate in class
- Blurred vision
- Excessive hunger
- Unsteady gait, dizziness,
- Slurred speech
- Irritability, tantrums in toddlers, sudden behavioral change.

How to handle Hypoglycemia:

- If the BG is 70-80 mg/dl, give a snack.
- If the BG is <70mg/dl, give 2 tablespoons of glucose mixed with water or 2 Glucovita tablets or 2 tablespoons of powdered sugar. Do not give chocolate or biscuit, or any food with fat in it, to treat a hypo.
- If the BG is <54 mg/dl ie serious hypoglycemia, give 10-15 gm of glucose, as above, then check the BG after 15 mins. In the meantime, call the parents. If the BG remains low, repeat the 2 tablespoons of glucose again. If the child doesn't respond after the second dose of glucose, call the parents again and take the child to the hospital.
- Don't send the child alone to the school infirmary when he/ she has hypoglycemia. The child may fall or faint on the way. One of the child's friends or the teacher should accompany him/ her.

If the child is unconscious, or having fits/seizures, it is severe hypoglycemia. Turn the child to the left side;do not give the child anything orally. If a glucagon injection has been given to the nurse and stored in the fridge at the school infirmary, it should be given intramuscularly immediately. The entire dose of 1 mg should be given for a child above 10y and 0.5 mg in younger children. Inform the parents and reach out to the doctor on the phone numbers given.

Hyperglycemia:

Hyperglycemia (high BG) is caused by excess food, missed or inadequate insulin, illness, or stress. Symptoms are

- Thirst
- Feeling hot
- Drowsiness, lethargy

- Heavy breathing
- Fruity or wine-like odor while breathing.
- Frequent urination
- Stomach pain
- Vomiting

If the child has any of these symptoms, immediately inform the parents.
Each child is likely to have a particular set of symptoms for both hypo- and hyperglycemia.

How can the school support the child?

- Treat the child normally, like other children in the class. The child has the capability to participate in all school activities, including sports, apart from the times of very high BG or hypoglycemia, when he/ she needs a short time to treat the condition.
- Allow the child to check BG whenever needed, either using a glucometer or using the phone/ reader if it is sensor.
- If BG are below the normal range, the child should be allowed to consume sugar/ glucose and a small snack as above, during classes or exams.
- In case of high BG, the child should be allowed to sip more water or salty liquids and visit the washroom often. He/ she should be allowed to take extra insulin.
- Inform the necessary persons (class teacher, sports teacher, van driver, staff nurse) about the child's condition.

Contact details:

1. Mother's Phone number:
2. Father's phone number:
3. Doctor's phone number:

ISPAE Activities

ISPAE IDEAL PROGRAM - An Update on ISPAE Diabetes Education And Learning (IDEAL) Course

Dr Sirisha Kusuma, Rainbow Children's Hospital, Hyderabad

The IDEAL Core Committee is proud to announce that since the course commencement in October 2021, we successfully trained three batches of students, the last one being of doctors. So far, 46 pediatric diabetes educators have been certified in the first and second batches (Oct-Dec 2021, Feb-Apr 2022). The third batch (June-Aug 2022) was specially tailored for doctors, with a much more detailed curriculum: more on the etiopathogenesis of type 1 diabetes, management of diabetic emergencies, insulin dose adjustments, diabetes care at school, etc.. In this batch, 23 pediatricians and physicians caring for children with diabetes were certified after passing the exit exam.

The three-month course continues to be very rigorous, with pre and post-tests for each teaching session, ample time for discussion during teaching sessions, and practical assignments for the trainees designed to ensure they have understood concepts and are able to deliver the required care. These videos made by the trainees help them practice what they learned in the session by implementing the principles of patient care and counseling in the clinic setting. The success of IDEAL has been made possible by the dedication and commitment of our team of faculty hailing from all over India, volunteering their time, efforts, and expertise. As the veteran faculty continue to lend their support, new members are constantly joining the good cause.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

We invite applications for the next batch of IDEAL for educators, which will be conducted between Nov 2022 and Jan 2023. The last date for application is 30th September 2023. Application procedure and links for registration and entry assessment can be found on the ISPAE website www.ispae.org.in/ideal

Sirisha Kusuma Boddu.
On behalf of the IDEAL Core Committee.

ISPAE BEST PROGRAM

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

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

"The diabetic who knows the most lives the longest,"said Dr. Elliott P. Joslin. He was the first to advocate teaching patients to care for their diabetes, an approach now known as Diabetes Self-Management Education (DSME). DSME is now an integral part of management of children with Type 1 diabetes (T1D). DMSE provides the knowledge and skills necessary to optimize glycemic control, reduce the risk of complications, make informed choices to facilitate self-directed behavior changes, and improve quality of life. Keeping in mind this need, ISPAE has designed a structured diabetes education module called **"Basic Education Series in Type 1 Diabetes" (BEST)** for children with T1D and their caregivers. This course is intended for nursing staff, physician assistants, assistive school personnel, and parents/ caregivers of T1Ds or adult T1Ds, to learn the basics of the ambulatory management of T1D.

Program Implementation
BEST has an eight-member Core Committee and an excellent team of 27 faculty members from across the country, with expertise and rich experience in managing childhood diabetes. The team has developed a series of eight structured online educational modules (power point presentations) to train participants in the basics and essential skills needed to manage T1D. The BEST teaching sessions are conducted over four weeks: one session of 2h duration per week (Tuesday 7-9 PM). A maximum of 30 participants are selected per course to ensure engagement and one-to-one interaction between the faculty and the participants. The first and second batch of BEST participants were successfully trained in April and July 2022, respectively. An e-Certificate of participation was given to all participants at the end. Feedback on the program was taken through an online Google form. It was well received and appreciated by all the participants.

E-learning has added a new dimension as an effective and efficient way of training and education. Team BEST envisages training and empowering children, their caregivers, and assistive health care personnel, mainly from inaccessible and remote areas, with the skills and knowledge needed for ambulatory management of T1D. This will go a long way in improving their quality of life and preventing long-term complications. We plan to train three batches every year, 30 candidates per batch. Applications are invited one month before the start of each batch via an online application form. The enrolment for the next batch will begin in Nov-Dec 2022.

ISPAE 2022 mid-term meeting

The Mid-term meeting of ISPAE, in collaboration with ISPAD, is planned on 19-20 November, 2022 at Chandigarh. A full day program is planned on pediatric and adolescent diabetes; and the next day is dedicated to various pediatric endocrine disorders. The diabetes program will be coordinated with ISPAD, and includes a workshop for trainees and allied healthcare professionals.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Category	Regular (up to October 31)	Late (up to November 19)
Members*	Rs 3000	Rs 8000
Non members	Rs 4000	Rs 10000
Trainees **	Rs 2000	Rs 3000
Accompanying person	Rs 2000	Rs 3000
Senior citizen	Rs 1000	Rs 2000

* ISPAE, ISPAD, Central IAP and IAP Chandigarh.
**Self-certification required. Kindly register online or via email (ispae2022@gmail.com). Payment for registration: debit/credit card, online transfer or by cash to Ms Rupinder Kaur, 3134-B, APC, PGIMER, Sector 12, Chandigarh-160012.
For further details, please visit the website: www.ispae2022.com

Learning pearls from Pediatric Endocrinology meetings ISPAE ACES (Prepared by Editorial board CAPE News 2021-22)

Neonatal DM

(Case presentation by Dr Shankar Dhungel, moderated by Dr V Mohan, and mentored by Dr Medha Mittal; followed by a lecture by Dr Khalid Hussain, UK)

- Wolcott Rallison Syndrome (WRS) is a multisystemic disease with: Neonatal DM, skeletal dysplasia, growth retardation, renal dysfunction, hypothyroidism, intellectual deficit, hepatic dysfunction, exocrine pancreatic dysfunction, neutropenia. It is an autosomal recessively inherited disorder.
- Skeletal survey can be performed even in the 1st year of life to pick up WRS. Long term outcome and prognosis is guarded.
- Neonatal hyperglycemia can be due to hypertonic dehydration, sepsis or neonatal diabetes mellitus (NDM).
- Transient NDM presents early and lacks ketosis/ ketonuria.
- An Indian Monogenic Diabetes Registry showed that of 1562 cases registered, MODY was present in 983 subjects (commonest was HNF1A). NDM was present in 315 subjects (ABCC8 in 37). Syndromic DM was found in 76 subjects (WRS is the commonest).

Obesity in children

(Case presentation by Dr Payal S Kubsad; moderated by Dr Tushar Godbole, and mentored by Dr Raghupathy P and Dr Vani HN; followed by a lecture by Dr Senthil Senniappan, UK)

- Grading of acne is: grade 1: comedones with pustules or papules, but no scarring; grade 2: few papules, comedones and pustules, with mild scarring; grade 3: predominant pustules, nodules, and abscesses with moderate scarring; grade 4: cysts and abscesses, with severe scarring.
- The British charts recommend the diagnosis of overweight, obesity and severe obesity if BMI is above 92nd percentile, 98th percentile and 99.6th percentile, on UK BMI charts, respectively.
- Severe intracranial hypertension is a complication that should be looked for in obese children who have headaches, with a proper fundus examination. Management strategies include lumbar puncture and acetazolamide therapy.
- Clinicians encountering monogenic obesity should look for specific pointers in children with severe early onset obesity: Leptin or leptin receptor mutations (hyperphagia, hypogonadism), POMC deficiency (red hair, adrenal deficiency) and MC4R deficiency (tall stature and hyperinsulinemia).

- ROHHAD syndrome is a clinical diagnosis (rapid onset obesity, hypothalamic dysfunction and autonomic dysfunction), no specific genetic test is available. Recent hypotheses point to a possible autoimmune etiology.
- Poor quality of sleep in obese children often makes it challenging to perform sleep studies to diagnose OSAS. A proper history is pivotal prior to ordering a sleep study.
- Persistent elevation of liver enzymes above 3 times the upper limit warrants inputs from a hepatologist.
- Weight loss plate: fill 1/2 the plate with vegetables/ salad, 1/4 with carbohydrates and 1/4 with protein.
- Restrictive diets like very low calorie diets (800 kcal/day) are not recommended in growing adolescents for weight loss.
- Setmelanotide is a daily subcutaneous injection approved for children of age > 6 years with obesity due to POMC, PCSK1 and LEPR deficiency.
- Emerging forms of therapy in adolescents with obesity include: semaglutide for adolescents with T2DM, and Diazoxide choline for Prader Willi syndrome. Tirzepatide (Combined GIP, GLP-1 receptor agonist) has shown good reduction in BMI in adults with obesity. Bimagrumab (antibody to activin II receptor) is being tried in hypothalamic obesity, and Cagrilinitide (weekly long acting amylin analog) may be available in future.

ISPAE ACES meeting- June 2022: ADOLESCENT ENDOCRINOLOGY

Prof. Margaret Zacharin delivered a talk on adolescent menstrual disorders. A few pearls:

- Menorrhagia is rare in PCO but may occur as the endometrium is abnormal.
- Treatment of menorrhagia is advisable with oral contraceptive pills containing norethistrone acetate.
- Spironolactone is useful in PCO: it requires a higher dose (100 mg OD) for anti-androgenic action.
- Children with developmental delay or disability may benefit with a progestin-containing intrauterine device that can be safely inserted for five years.
- The anovulatory cycles during adolescence can be treated with medroxyprogesterone 10mg/day for 2 weeks in each cycle.

Prof. Paul Hoffmann delivered a talk on delayed puberty in girls. A few salient points:

- The role of GnRH pulse generator is vital in deciding the initiation of puberty. It is composed of neurons that co-express Kisspeptin, Neurokinin B and Dynorphin, whose activity is further influenced by levels of makorin ring finger protein 3 (MKRN3) that inhibits GnRH levels.
- Delayed puberty is defined as the age of puberty 2-2.5 SD more than the age-appropriate normal cut-off.
- Four phenotypes of delayed puberty are known:
  - Constitutional delay in growth and puberty (CDGP): diagnosis of exclusion
  - Functional hypogonadotropic hypogonadism: seen in negative energy balance states like anorexia nervosa, malnutrition
  - Central hypogonadotropic hypogonadism: can be congenital (Kallmann syndrome - normosmic or anosmic) or acquired (intracranial tumors, chemotherapy)
  - Primary hypergonadotropic hypogonadism: girls more frequently affected (like Turner syndrome, primary ovarian insufficiency) than boys (like Klinefelter syndrome).
- CDGP is one of the common causes of delayed puberty (seen more frequently in boys than girls), often with a family history of delayed puberty. It is characterized by delay in growth and pubertal spurt but a growth velocity >25th centile (reassuring), minimal bone age delay of up to 2 years, with an adult height almost matched to the mid-parental height.
- The approach to an adolescent with delayed puberty would constitute:
  - Detailed history (systemic disease, nutrition, psychosocial) and family history of deviant growth pattern
  - Examination for systemic diseases, dysmorphism

- Bone age assessment - GnRH pulse generator would be activated at a bone age of 10 years and more. A serum LH level of > 0.3 IU/mL indicates central onset of puberty
- A GnRH agonist test with a LH value of >10 IU/mL is reassuring for normal puberty.
- The role of genetic testing (whole exome sequencing) in identifying the cause of delayed puberty is emerging, e.g., KAL genes (1-6) in anosmic congenital hypogonadotropic hypogonadism.
- Treatment is with hormone replacement therapy with growth monitoring. The transdermal route of estrogens is preferable to oral estrogens. The initial dose of transdermal beta estradiol patch is 6.25 ug weekly, increased gradually over 6-12 months.

Prof. Olaf Hiort discussed his experience on disorders of sexual differentiation during adolescence. He narrated three different cases reared as girls with a genotype of 46,XY. The following points were highlighted:

- DSD may present with hypo- or hypervirilization during adolescence
- Deviant pubertal patterns should alert towards an underlying disorder
- Primary amenorrhea, clitoromegaly (androgenisation) may be the initial presenting symptoms
- Family history of abnormal puberty, fertility issues should be asked for as clues for androgen insensitivity syndrome
- Workup should include a karyotype, LH, FSH, estradiol, testosterone, inhibin B (sertoli cell marker), and ultrasonography of pelvis (to look for mullerian structures, gonads)
- Genetic testing is advantageous for confirmatory diagnosis
- A multidisciplinary team should be involved in care and to discuss the management options with the family and the affected child
- Gonadectomy is deferred till the adolescent achieves the legal age of consenting (personal practice)
- Psychosocial counselling should be offered to discuss the role of medical management, age-appropriate perspectives of a growing child/ adolescent, and to counsel for puberty, fertility and sex and relationships.

Learning Pearls – IPEDS 2022, MUMBAI

Dr Chirantap Oza, Fellow in Pediatric Endocrinology
Dr Shruti Mondkar, Fellow in Pediatric Endocrinology
Jehangir Hospital, Pune

Growth

- GH has a direct effect on cartilage cells in the growth plate, besides actions in the GH-IGF-1 axis.
- IGF and IGFBP are elevated in ALS deficiency and PAPP-A2 mutations, while the other causes of GH insensitivity are characterized by elevated GH levels, with low IGF-1 levels (< 2.5th percentile).
- Genetic diagnosis is very useful for diagnosis of GHIS but is not essential for rhIGF-1 replacement therapy.
- IGF-1 therapy does not cause local paracrine effects, so linear growth is not as marked as expected.
- rhIGF-1 is the only effective long-term therapy which is well tolerated. Adverse events are most frequent in subjects with severe forms of Laron syndrome.
- Bone maturation is a poor predictor of pubertal timing and height attainment in children with SGA. Yearly bone age assessment is not recommended in pre-pubertal children on GH. Bone age must be evaluated around 8 years of age and regularly from pubertal onset to watch for rapid pubertal progress.
- GH stimulation test is only indicated in those suspected to have GH deficiency (GHD) and not in all SGA-sequelae patients.
- In children with SGA on GH treatment, IGF-1 values are used for assessing safety rather than efficacy.
- Aromatase inhibitors may be considered in growth promotion in boys who have SGA and faltering growth. There is no standard recommendation for its use in girls.
- Sex steroid priming increases the specificity of GH stimulation tests by reducing the percentage of false positives, thus allowing differentiation of GHD from CDGP, and avoiding misdiagnosis of GHD, which increases the burden on the health care system. BSPED 2021 guidelines are available for priming.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

- The compliance to GH Therapy improves by 20% for each reduction in frequency of dosing per day. Thus, long acting growth hormone may be a useful strategy to improve compliance.
- Transition age – the period between late puberty and complete adult maturation i.e. from adult height to peak bone mass. GH is not approved for use during conception and pregnancy.
- Stop GH for 1 month before re-testing. Testing for adult GHD is not required in MPHD ($\geqslant$ 3 hormone deficiencies) with low IGF-1, transcription factor defects (PIT-1, PROP-1, LHX-3/4, HESX-1, PITX-2), GHRH receptor gene defects, GH gene defects, or GHD associated with structural brain defects.

Others

- Syndromes associated with thyroid nodule and risk of malignancy includes MEN2, PTEN, NMTC and FAP.
- The TIRADS radiological scoring system works well for extremely benign and extremely malignant lesions. It does not work well in intermediate lesions with significant crossover.
- Insulin Icodec – Ultra long-acting insulin with once weekly dosing, is undergoing clinical trials. This molecule may be expected for routine use in the days to come.
- Fiasp - higher monomer fraction and permeability across the membrane explains the quick onset and short duration of Fiasp.
- Emerging role for newer therapeutic options in pediatric endocrinology include: Setmelanotide (MC4R agonist), semaglutide, phentermine/ topiramate, bimagrumab and cagrilintide for obesity; long-acting weekly growth hormone – Lonapegsomatropin, Somatrogon, Somapacitan; Burosumab for X-linked hypophosphatemic rickets; Tiptorelin- 6 monthly for precocious puberty; and Chronocort- for CAH >12 years age.

Academic meetings in Pediatric Endocrinology

Neonatal Endocrinology Webinar organized by Dr Kavitha Bhat and Dr Namratha Upadhya, Aster Hospital, Bangalore

The virtual webinar aimed to discuss practical points on approach and management of neonatal hypocalcemia and neonatal hypoglycemia. The target audience was mainly pediatricians, Fellows in neonatology and in endocrinology. Dr Namratha discussed neonatal hypocalcemia, with a few cases. Neonatal hypoglycemia was covered by Dr Kavitha Bhat, and a case discussion by Dr Nikhil, pediatrician. The webinar was attended by about 30 members. It was an interactive session, with questions answered, and some practical considerations in managing these neonates discussed.

Pediatric Endocrinology CME in Chennai, and 4th Dr S Thangavelu oration - Dr Hemchand K Prasad, Chennai

The 7th Annual CME in Pediatric Endocrinology and the 4th Dr Thangavelu S oration were held in Hotel Raintree at Chennai, organised by the Dept of Pediatric Endocrinology of Mehta Hospital and IAP, Chennai City branch on 31.7.2022. The 4th Dr S Thangavelu oration was delivered by Prof Sudha Rao on "Journey of Pediatric Endocrinology in India and its limitations". Practical talks on various endocrine problems were given by Prof Anju Seth, Prof Vandana Jain, Dr Anurag Bajpai and other faculty. The topics covered included: SGA, DKA, bone health, obesity, screening of neonates, hypothyroidism and other common endocrine problems. A case presentation competition was held for post graduates. The program was attended by more than 150 delegates.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Pediatric and Adolescent Endocrinology workshop - Dr Shaila Bhattacharyya, Dr Vani HN, Pediatric Endocrinology Association of Karnataka (PEAK)

As part of the 9th Bangalore Pedicon 2022, PEAK conducted a successful pre-conference workshop on Pediatric Endocrinology for 20 delegates, including pediatricians, Fellows in pediatric endocrinology, DM endocrinology students, dietitians and pediatric nurses. The workshop was inaugurated by PEAK Patron Dr P Raghupathy, IAP-BPS President Dr GV Basavaraja, and Hon. Secretary Dr Priya Shivalli. The workshop started with a Pre-quiz conducted by the President of ISPAE & PEAK, Dr Shaila Bhattacharyya. The delegates were divided into small groups and assigned 5 exciting and interactive stations - Growth monitoring and Puberty assessment, Growth charts with case scenarios, Blood glucose monitoring devices, Insulin delivery devices, and interesting case scenarios, followed by a panel discussion on Diet in Diabetes. The workshop was well-received by the delegates for its highly interactive concept and hands-on experience. In the end, Dr Vani thanked all the delegates for their enthusiastic participation and faculty for their hard work.

Pediatric Endocrinology CME in Nagpur – Dr Nikhil Lohiya

A Pediatric Endocrine CME was organized by IAP at Nagpur on 21st August 2022. The meeting commenced with case presentations by post-graduates. Common endocrine issues were discussed - Dr Hemchand Prasad spoke on SGA, Dr Hari Mangtani on precocious puberty, Dr Shaila Bhattacharya on approach to goiter, Dr Nirali Lohiya on developmental issues in endocrine disorders , and Dr Nikhil Lohiya on newer insulins in Type 1 diabetes. Dr Vaman Khadilkar delivered the keynote lecture on management of growth disorders – an Indian Perspective. The meeting was well appreciated by 80 pediatricians. Pediatric Endocrine Notes for Post-Graduates were also released. The event was sponsored by Novo Nordisk & Pfizer.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Pediatric Endocrinology CME at Aster Health City, Kochi - Dr Parvathy L, Consultant Pediatric Endocrinology, Aster Medcity, Kochi

The 6th Aster Kids Monsoon CME, Pediatric Endocrinology update organised by Aster Child and Adolescent Health, Aster Medcity, Kochi and IAP Kochi, was conducted at IMA House, Kochi on 28th August, 2022. Dr Jeeson C Unni, Lead Consultant, Aster Child Health, delivered the welcome address. Dr PC Alexander Memorial Oration was delivered by Dr PSN Menon on Pediatric Endocrinology - past, present and future. Dr P Raghupathy, from Bengaluru, gave a lecture on skeletal dysplasias in children. Other common newborn and pediatric endocrine disorders were covered in the sessions with case scenario-based discussions. The CME, attended by 90 delegates from across Kerala, was well appreciated. A pre-conference workshop on growth chart plotting on 27th August was attended by almost 45 delegates.

NZ-PEDICON 2022, Dehradun

The North-Zone Pedicon was conducted on 24-25th September 2022 at Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun.

A Pediatric endocrinology pre-conference workshop was organised by Dr IPS Kochar (Workshop Coordinator) and Dr Aashish Sethi (Local Coordinator) on 23 September 2022. Topics included skill stations on growth and diabetes in children. The other faculty were Dr Rakesh Kumar, Dr Smita Ramachandran, and Dr Aashima Dabas. The workshop was attended by 24 delegates.

A panel discussion on Improving Quality of Life in Type 1 Diabetes in Resource Limited Settings was moderated by Dr Aashima Dabas. The panelists were Drs Anju Virmani, Rakesh Kumar, Varuna Vyas and Aashish Sethi. Practical and effective management of T1D was discussed. The details of patient resources available under ISPAE and the IDEAL program were also shared with the delegates.

A postgraduate teaching session on diagnostic approach to a child with DSD was conducted by Dr Ganesh Jevalikar. Dr Richa Arora discussed growth problems in SGA, Dr Jaivinder Yadav talked of interpretation of thyroid function tests, and Dr Kiran Meena spoke on growth and thyroid disorders during adolescence.

International Conference on Children's Bone Health 2022, Dublin

The 10th ICCBH was held on 2-5 July. The conference highlights included pre-meeting workshops on achondroplasia and XLH. The keynote lectures included topics- RANKL and RANK: bone and beyond, CRISPR/CAS9 gene editing and cell therapy in osteogenesis imperfecta, and Meet the Experts sessions for practice based discussions on other bone disorders. The scientific program also covered novel drug targets for bone, genetic and metabolomics of bone signaling and relationship of physical activity and bone.
Dr Sirisha Kusuma had an interesting case presentation 'A toddler with bone pains' at Challenge the Expert, Dr Sapna Nayak presented oral communication on 'Severity of acute phase reaction in children receiving first dose of Zoledronic acid- impact of the underlying condition' Dr Aashima Dabas was presented with the Maria Luisa Bianchi Award, 2022. The Indian representation for posters at ICCBH included Dr Aashima Dabas, Dr Mousin Moustefa, Dr Sapna Nayak, Dr Shivani and Dr Sirisha Kusuma.

Miscellaneous useful information

1. IAP has come up with Standard Treatment Guidelines for management of Hyperthyroidism, prepared by ISPAE members Dr Riaz I, Dr Bhanu K Bhakri and Dr Shalmi Mehta. The link to the guidelines is: https://iapindia.org/pdf/Ch-078-Hyperthyroidism.pdf

2. Dr Mehta Hospital, Chennai, led by Dr Hemchand K Prasad and IAP Chennai city branch has developed a free mobile application called "DIAWALK" to help clinicians manage Type 1 Diabetes in children, based on standard guidelines. The app can be downloaded from Google play store, as well as Apple, using these links:
https://apps.apple.com/in/app/diawalk/id1636091111
https://play.google.com/store/apps/details?id=io.phantom.diawalk
For details please contact: pediatricendocrinology.mehta@gmail.com

3. The Standard Registration rates for the ISPAE-ISPAD 2022 meeting in Chandigarh end on October 31st. All ISPAE members are requested to register and enjoy the academic feast.

4. Dr Leena Priyambada and Ms Sheryl Salis are ISPAE members standing for election for the ISPAD Academic Council. All ISPAE members who are ISPAD members, please don't forget to cast your valuable vote before 12th October.

5. SPEAK - Voice of PEAK (Pediatric Endocrinology Association of Karnataka) is their official newsletter. It aims to highlight the efforts of PEAK members in sensitization of various stake holders including pediatricians regarding Pediatric Endocrine disorders. The Editor is Dr Vijay Sarathi and the Co-editor Dr Diksha Shirodkar. The newsletter carries interesting case reports, drug reviews, critical journal reviews and details of activities by members. Hearty congratulations and best wishes to SPEAK team on the new endeavour!

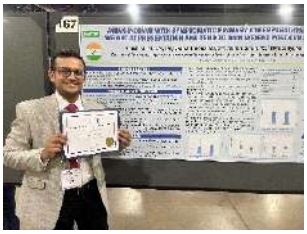
6. XLH INDIA - A request for a patient support group was communicated by Mr Prakalp Sudhakar, Founder of "Patients in India with XLH". The XLH, India support group can be reached out at https://www.xlhindia.org (FB page- XLH India)

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

ACHIEVEMENTS OF ISPAE MEMBERS

Dr Aashima Dabas was presented with the Maria Luisa Bianchi Award, 2022 by Slemenda Award winner, Professor Outi Mäkitie, at the 10th ICCBH meeting, Dublin, 2022. The award acknowledged work of a female researcher in the field of pediatric bone disease in a low-middle income country.



The 2022 annual conference of the Endocrine Society was held at Atlanta, Georgia from June 11-14, 2022. Dr Rimesh Pal, Assistant Professor, Dept of Endocrinology, PGIMER, Chandigarh, attended the event and presented his research. He was awarded the C Wayne Bardin, MD, International Travel Award for the year 2022 (https://www.endocrine.org/awards/c-wayne-bardin-md-international-travel-award). The award was created in honor of Dr Wayne Bardin, who made remarkable research contributions to both reproductive physiology and contraception throughout his long career. The award is given to only one Junior Faculty worldwide. Dr Pal is the only Indian to have received this award.

The Pediatric Endocrinology team of Dr Kavitha Bhat and Dr Namratha Upadhya, Aster Hospitals, had submitted an abstract on PWS - Multidisciplinary clinic in Southern India - Challenges & Outcome of our Maiden Experience. It has been accepted for oral presentation at the Foundation for Prader Willi Research (FPWR) Annual Research Symposium held on 29-30th September 2022 at Chicago, USA.

Dr Meena Chhabra's stellar work in the care of Type 1 Diabetes over the past 3 decades was recognised with the prestigious RSSDI Women Diabetologist Award 2022. She was given the award at the 50th annual meeting of RSSDI at Chennai on 7th October. It carries a cash award, which Dr Chhabra announced she would be giving to charities working with T1D children, including Yog Dhyan Foundation, Delhi.

Publications from ISPAE members

Dr Medha Mittal: Saikia D, Mittal M, Kanakaraju C, Dhingra D, Kumar M. Efficacy and Safety of Low Dose Insulin Infusion against Standard Dose Insulin Infusion in Children with Diabetic Ketoacidosis - An Open Labelled Randomized Controlled Trial. Indian J Endocrinol Metab. 2022 Mar-Apr;26(2):173-179.

Dr Sirisha Kusuma Boddu

- Boddu SK, Lankala R. Are we undertreating calcium deficiency in metabolic bone disease of prematurity? A case report and review. Front. Pediatr. 2022. 10:991488. doi: 10.3389/fped.2022.991488
- Boddu SK, Venkata VKT. Hypophosphatemia and Metabolic Bone Disease Associated With the Use of Elemental Formula: Case Report and Review. Journal of Neonatology. 2022;36(1):58-62. doi:10.1177/09732179211065383

Hearty congratulations to all achievers.

Obituary: Dr Qadeera Rasti Baghban - a crusader for Type 1 DM

Dr Shuchy Chugh and Dr Hemchand

Dr Qadeera, a pediatrician working in Vikram Hospital, Bangalore, will be fondly remembered for her immense contribution to T1DM care in our country. Born on 16th April 1988, she developed T1D in 1996. This did not stop her from being a brilliant student in school, or from entering medicine.

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

She participated in every sport and cultural activity. During her journey with T1DM for 26 years, she was truly a T1DM warrior, an inspiration for so many children and adolescents! She was the director of a charitable trust dealing with educating T1DMs, ran Diabuddies, based in Bangalore, and rendered numerous services for the benefit of children with T1DM. She authored a book "Diabetes Log Book" which is immensely helpful to families with T1DM. She gave motivational talks and wrote numerous articles (including one for CAPE News) on her experiences, including marriage, pregnancy and fighting Covid. She often stressed that the management of T1DM can only be done regular monitoring of blood sugars, carbohydrate counting and regular exercise or workout. She enthusiastically joined the third batch of the ISPAE IDEAL course to improve her skills, and attended sessions even when her son was unwell, passing the exit Exam with flying colors. Even during this course, she inspired her fellow trainees with her grit and determination. She passed away due to a sudden cardiac event on 31 August, leaving an irreplaceable void in the world of T1DM. We in ISPAE, and especially all Idealites, mourn her loss, and pray for the wellbeing of her husband and infant son.

Trainees section : Quiz

Dr Diksha Shirodkar, Clinical Fellow in Pediatric Endocrinology and Diabetes
Bristol Royal Hospital for Children, Bristol, UK

Bone and mineral metabolism- Word Hunt

Search for all the words using the clues given below related to the genetics, syndromic associations and management of the disorders of bone and mineral metabolism. The words could be arranged in a horizontal, diagonal or a vertical fashion. Good luck and Happy Word-Hunting!

E	S	A	N	I	K	E	N	I	T	A	E	R	C	R	A	Y	U	K	G
S	C	I	T	3	E	P	Q	I	B	A	M	U	S	O	N	E	D	Z	C
E	W	X	I	Q	A	W	T	M	T	A	G	s	T	Z	M	F	K	P	N
S	3	A	P	L	I	K	A	H	P	a	E	V	C	K	T	F	3	S	Y
A	A	T	C	U	I	3	R	F	r	K	K	B	V	M	H	A	X	E	S
T	A	A	G	A	O	A	X	C	E	P	T	L	A	f	A	C	J	U	E
A	N	P	J	T	I	o	M	O	A	H	B	U	Z	N	N	Y	w	D	T
H	A	S	N	J	G	F	G	S	S	L	W	E	P	D	a	N	M	O	A
P	T	O	A	I	R	L	D	N	L	E	C	D	Y	F	T	N	S	G	N
S	D	K	N	N	U	E	E	I	H	E	T	I	C	J	O	E	R	L	O
O	R	E	h	O	J	K	M	H	G	N	n	A	D	T	P	K	N	I	H
H	H	Z	M	I	q	A	E	O	O	E	E	P	u	I	H	G	B	O	P
P	A	A	W	Z	H	G	D	I	D	m	O	E	L	V	O	K	O	M	S
D	W	I	L	L	I	A	M	S	B	E	U	R	E	N	R	L	x	A	O
I	R	O	S	I	y	M	L	N	A	E	L	R	G	Z	I	D	3	O	H
C	C	S	G	E	E	R	H	T	E	K	A	I	F	E	C	z	P	B	P
A	V	E	a	Q	Y	R	B	L	I	L	A	T	N	P	E	R	Q	N	S
L	R	I	f	C	A	U	R	T	a	R	I	T	d	G	I	I	U	s	I
C	H	Y	P	O	M	A	G	N	E	S	E	M	I	A	H	T	S	I	B
M	Y	A	c	I	B	A	M	U	H	R	n	D	G	k	Z	Z	L	F	P

Clues:

1. Familial isolated congenital hypoparathyroidism (autosomal recessive, autosomal dominant, or X-linked recessive trait) can be because of gain-of function mutations in ---------- gene
2. Hyperparathyroidism in an infant/neonate due to disturbances in the tryptophan metabolism is called ------- ---------- syndrome.
3. Cardiovascular abnormalities, especially concerning the aorta, facial dysmorphism, behavioral abnormalities and hypercalcemia in a child are seen in --------- syndrome.
4. In SeSAME syndrome, along with hypomagnesemia, what does A stand in the acronym?
5. ----------hypophosphatasia involves premature shedding of teeth with periodontitis.
6. A major cause of humoral hypercalcemia of malignancy.
7. A continuous process in which portions of formed bone are periodically reabsorbed and replaced by new bone.
8. MODY 5 is associated with abnormality of which mineral metabolism?
9. The neurocristopathy caused mostly due to microdeletions of 22q11.2 is --------syndrome.
10. A syndrome with severe growth retardation, dysmorphic features, episodic hypocalcemia, hypoparathyroidism, seizures and medullary stenosis of long bones with thickened cortices.
11. X-linked hypoparathyroidism caused by mutation in ----- gene.
12. The type of Osteogenesis Imperfecta, in which extremities showing flared metaphyses ("popcorn-like calcifications"), bowing and thin cortices, most commonly seen.
13. Mutations in the gene LRP5 (Low density lipoprotein receptor-related protein 5) causing impaired Wnt signalling and osteoblast function causes osteoporosis --------- syndrome.
14. Atypical Femur Fractures are commonly an adverse effect of ----- therapy
15. Mutation in the tubulin co-factor E (TBCE) gene causing primary hypoparathyroidism and craniofacial abnormalities with occasion hyposplenism is ------- syndrome
16. Biomarkers for osteopetrosis are increased serum levels of ------ ------ and the brain isoform of ------ ------.
17. 25-Hydroxycholecalciferol is also called?
18. A lethal form of skeletal dysplasia with micromelia, bowed femurs and varying severity of craniosynostosis.
19. A human monoclonal antibody called as "pseudo-osteoprotegerin"

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

NEWSLETTER
OCTOBER 2022
Volume 26, Issue 3

CAPE News | ISPAE

Trainees' Section
The Adrenal Quiz - June 2022 Answer

Here is yet another exciting quiz on the adrenal gland. Solve this crossword with the help of the clues given below.

Across

2. The new-born adrenal gland weighs _____ to the adult adrenal gland.
4. 80% of patients with triple A syndrome have a mutation in the gene AAAS coding for _____ protein.
7. An effective secretory protein used as a tumor marker helping correlate the malignant potential and size of pheochromocytoma.
8. The 11βOH steroid dehydrogenase 2 is responsible for converting _____to cortisone.
9. The condition with craniosynostosis caused due to P450 oxidoreductase deficiency is called...
11. What is M in IMAGe syndrome?
13. Syndrome with central adrenal insufficiency and common variable immunodeficiency
14. Defects in _____ synthesis or processing leads to red hair, obesity, secondary adrenal insufficiency and pale skin.
16. 17αHydroxylase deficiency presents with_____ puberty
18. The mutation in this gene causes the malignant type of familial paraganglioma syndrome 4.
20. What does N stand in PPNAD?

Down

1. Drug of choice for mineralocorticoid replacement in CAH
3. Intraabdominal paragangliomas, usually secretory in nature arise from the organ of _____
5. Methyl prednisolone is ———— times more potent with respect to the anti-inflammatory action compared to hydrocortisone
6. The most common cause for Cushing's disease is pituitary _____
10. Adrenal insufficiency causes due to mutation in the gene coding sTAR was formerly called _____ CAH
12. In the fetal adrenal gland what does the fetal zone produce?
15. Zellweger spectrum consists of Zellweger syndrome, neonatal adrenoleukodystrophy and infantile _____ syndrome
17. 21 Hydroxylase antibodies are seen in?
19. Type 11βHydroxysteroid dehydrogenase is produced by the _____.