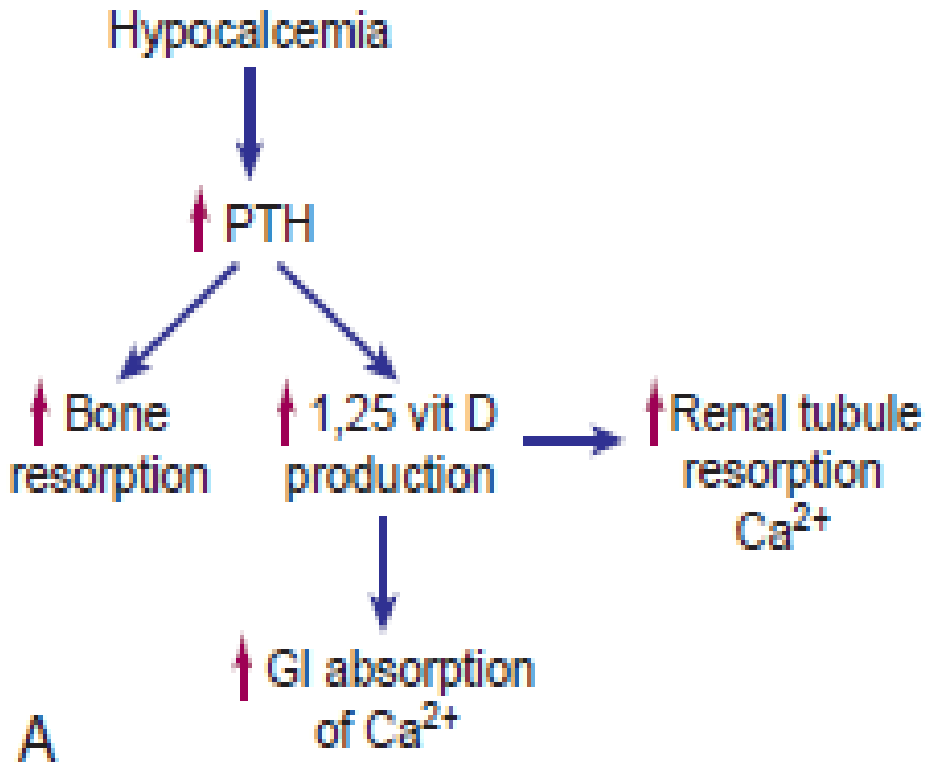
RICKETS

Rickets

- Rickets is a clinical condition associated with bone-deformity due to inadequate mineralization in growing bones .
- First reported in the mid-1600s in Europe
- In Canada prevalence of vitamin D deficiency rickets is 3 per 100,000 children
- In Bangladesh Rickets was first brought to broad attention in 1991
- A public-health problem in Bangladesh during the past two decades, with up to 8% of children clinically affected in some areas , 4% have deformities of the lower limb

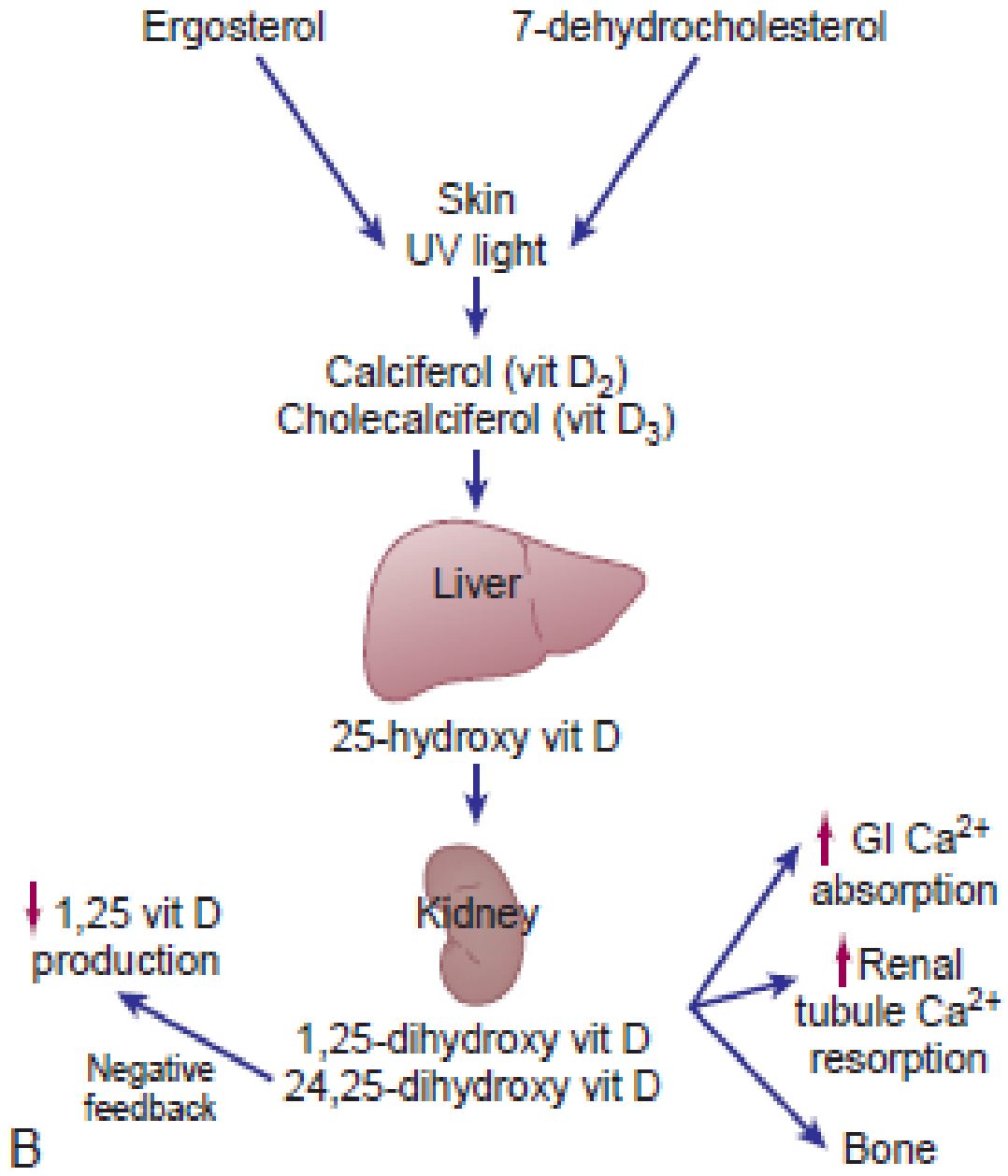
Calcium metabolism



• PTH increase serum calcium levels by increasing osteoclastic bone resorption, renal reabsorption of calcium and stimulating the conversion of inactive 25(OH)D to its active form - 1,25(OH)2D (calcitriol)

•Hypocalcemia itself stimulates the conversion of inactive vitamin D to its active form.

•Active form of vitamin D increases the intestinal absorption of calcium and increases renal reabsorption of phosphate.



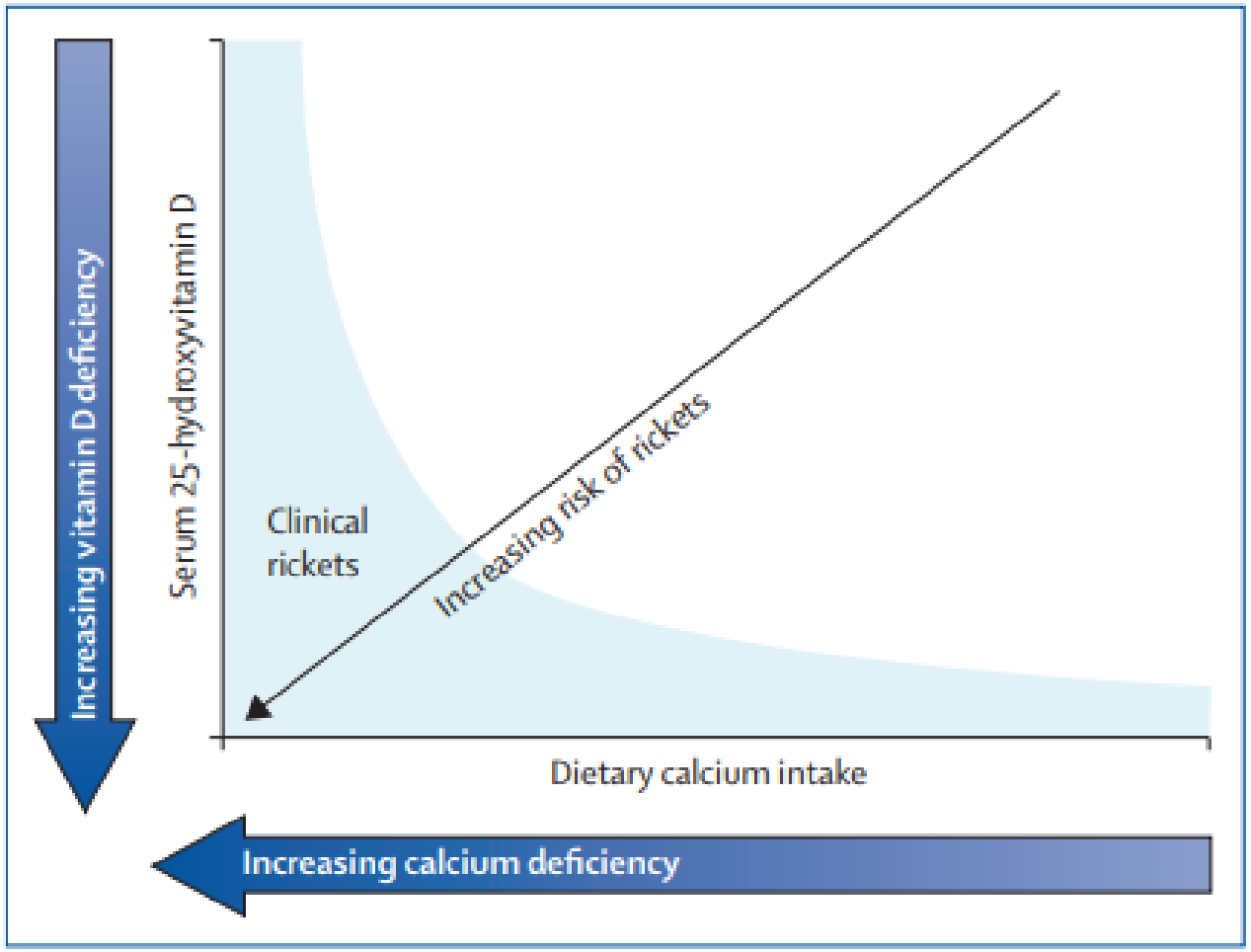
Vitamin D metabolism

•First hydroxylation (liver) to produce 25(OH)D

•Second hydroxylation (kidney) via 1-hydroxylase, which produces the active form, 1,25(OH)2D

• Vitamin D activation is stimulated by hypocalcemia and high levels of PTH and inhibited by FGF23.

•In renal failure, the conversion of inactive to active vitamin D is decreased because of the kidney damage itself as well as an increase in FGF23 production.



- Vitamin D and dietary calcium deficiency- detrimental to bone in combination

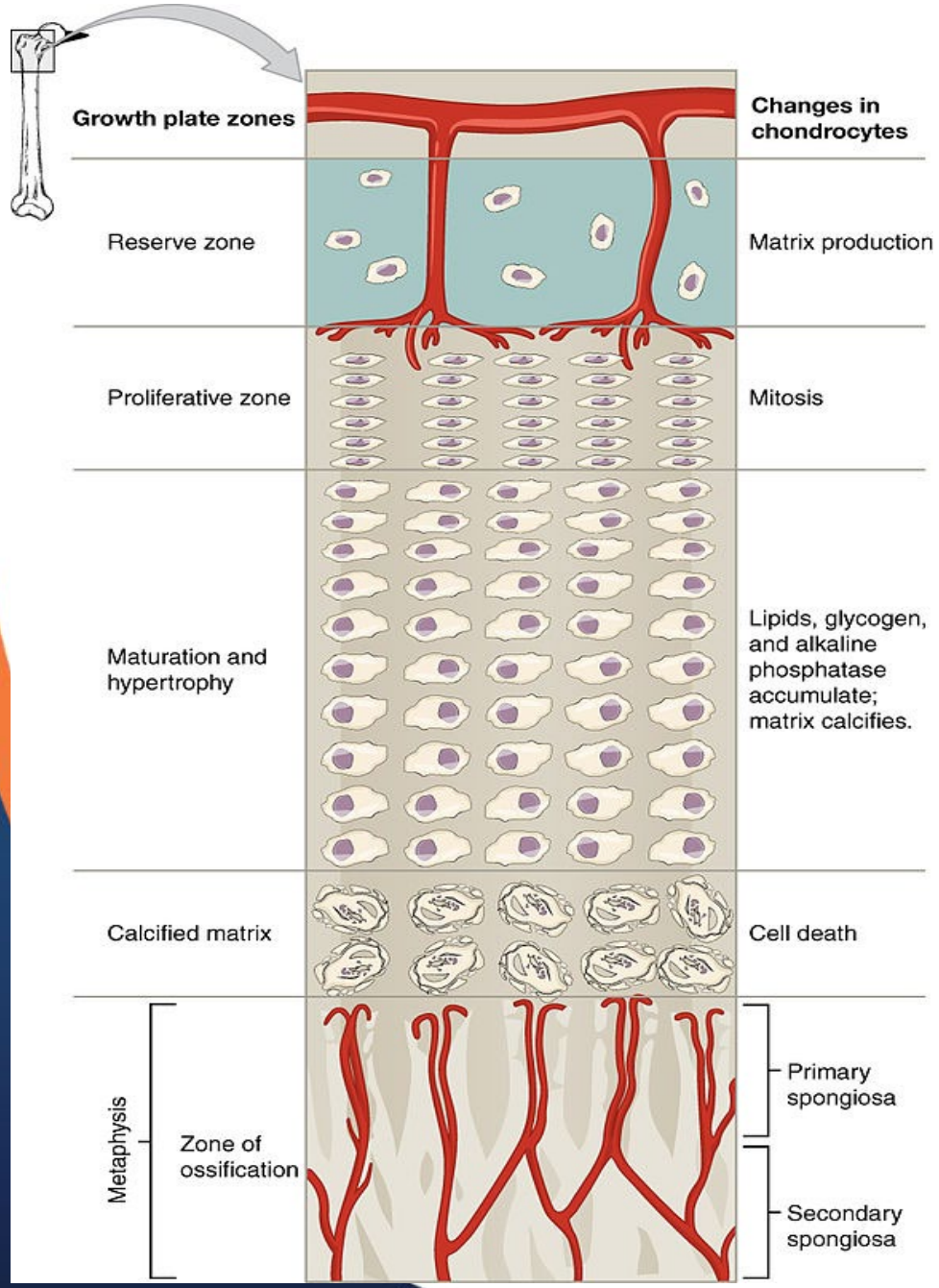
www.thelancet.com/lancetgh Vol 4 April 2016

Classification of Rickets: According to What is Lacking

- **Calcium lacking**
- Nutritional rickets :
  - Vitamin D deficiency (common)
  - Isolated calcium deficiency (rare)
  - Combined calcium deficiency and marginal vitamin D intake(common)
- Gastrointestinal rickets
- Rickets of end-stage renal disease (renal osteodystrophy)
- **Phosphorus lacking**
- X-linked hypophosphatemia (common)
- **Alkaline Phosphatase lacking**
- Hypophosphatasia

Nutritional Rickets

- Vitamin D deficiency in the diet leads to nutritional rickets
- Still a significant clinical problem in developing world
- Certain populations are at risk, including
  - Premature infants
  - Infants with prolonged breast feeding
  - Children on a vegetarian diet
  - Black children
  - Patients with celiac or hepatic disease



Longitudinal bone growth

- Longitudinal growth - result of endochondral ossification
- The key elements of the process :

•Proliferation of chondrocytes in columns

•Cellular maturation to become hypertrophic chondrocytes

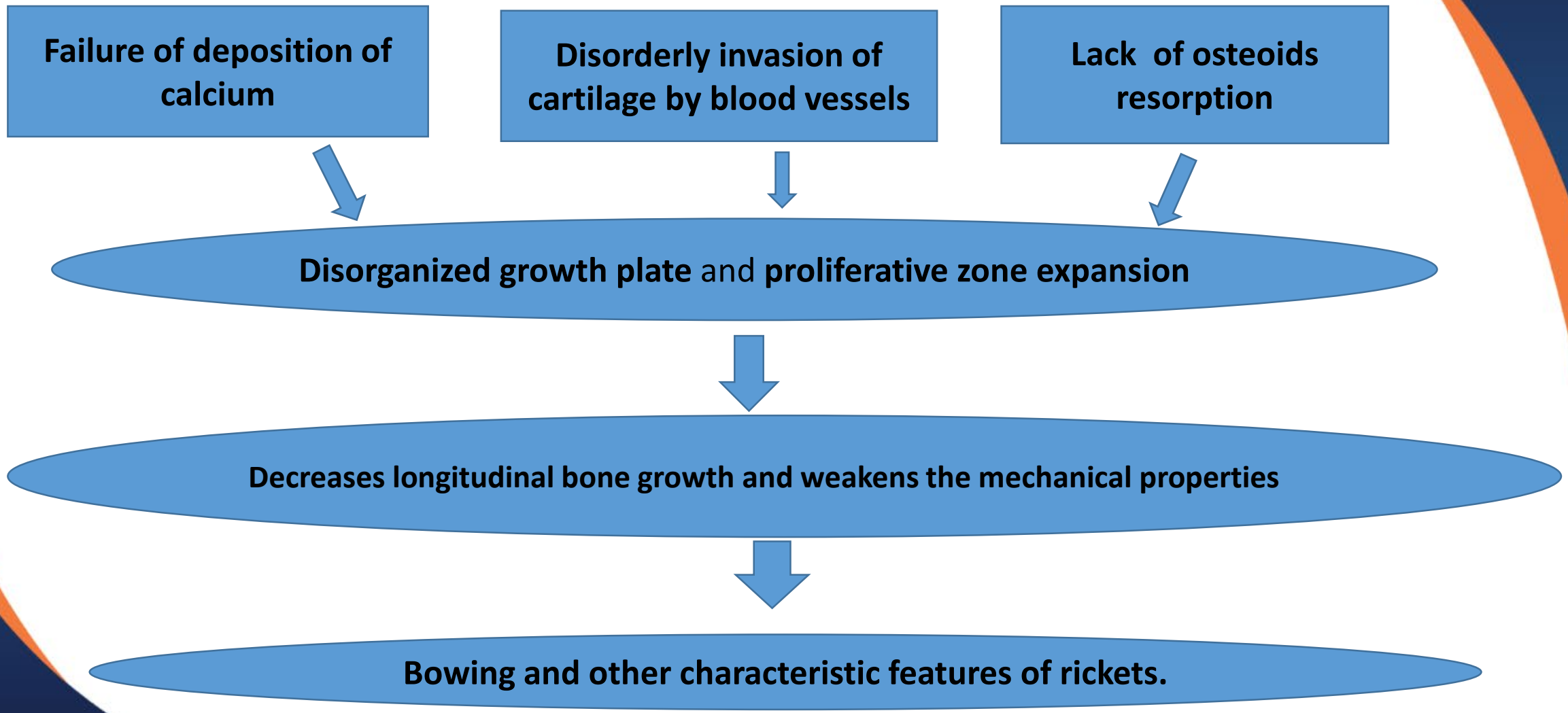
•Death of chondrocytes & **Calcification of the cartilage matrix**

•Vascular invasion of the terminal hypertrophic chondrocytes

• Deposition of new bone.

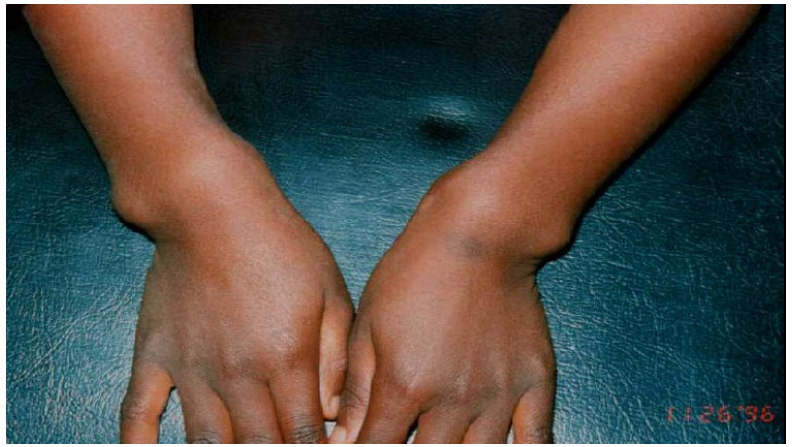
Open Stax College – Anatomy & Physiology, http://cnx.org/content/col11496/1.6/, Jun 19, 2013.

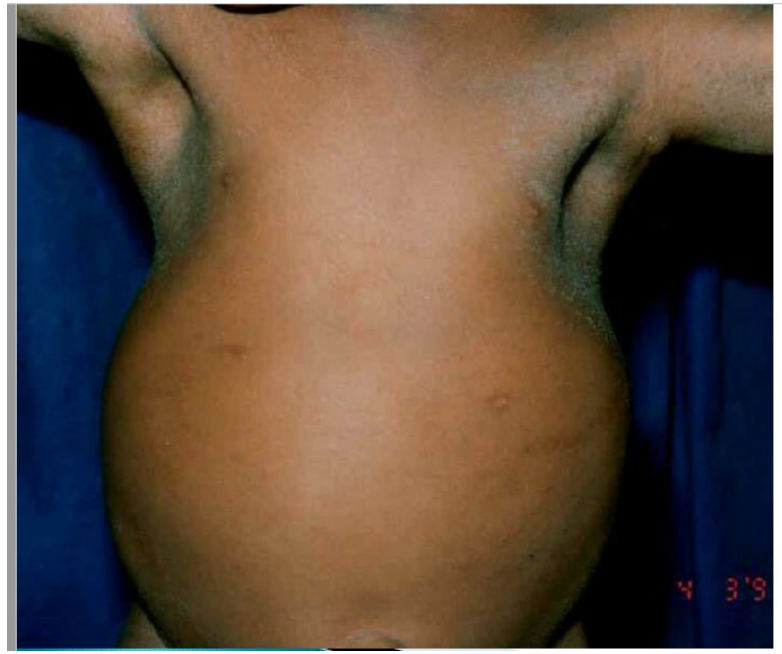
Pathophysiology of Nutritional Rickets



Clinical presentations

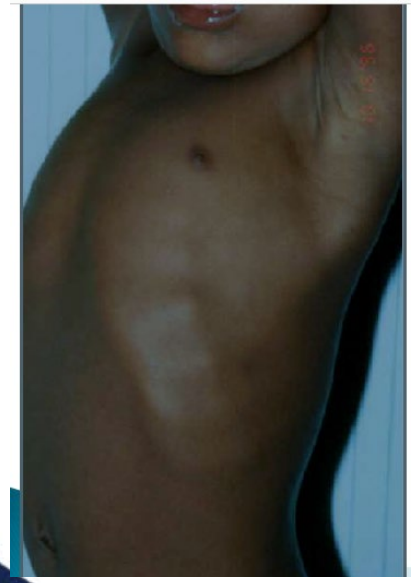
- Initial findings are listlessness, periarticular swelling
- The abdomen may appear protuberant
- Hypocalcemic seizure (common during first 2 years of life)
- Angular deformities

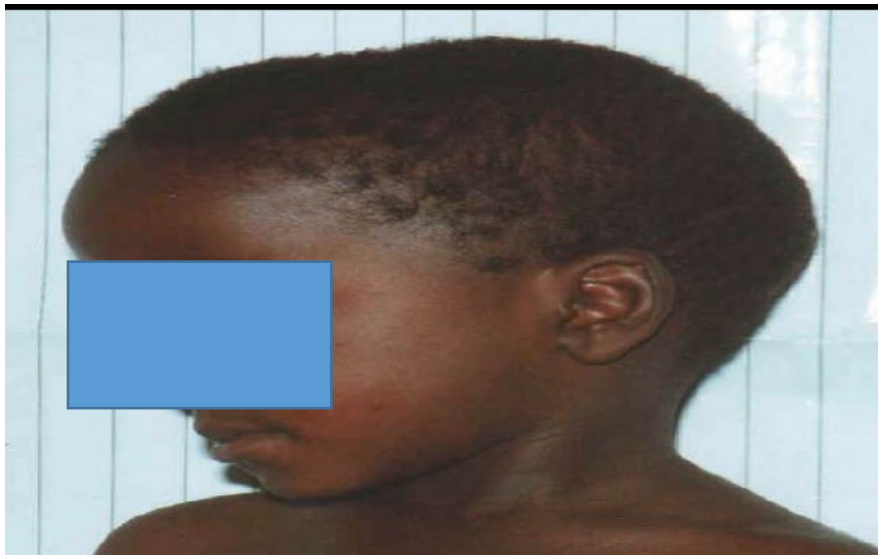


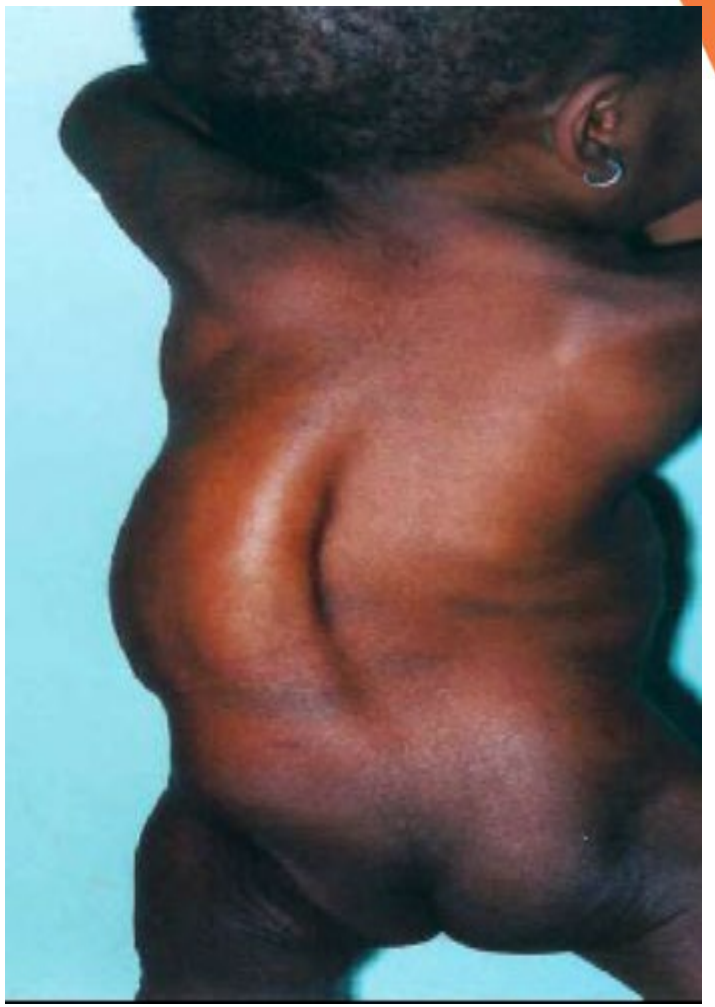


Contd..

- Rachitic rosary (beading of the ribs)
- Harrison’s groove
- Pectus carinatum
- Skull appearance resembling hot cross buns
- Later, kyphoscoliosis may develop

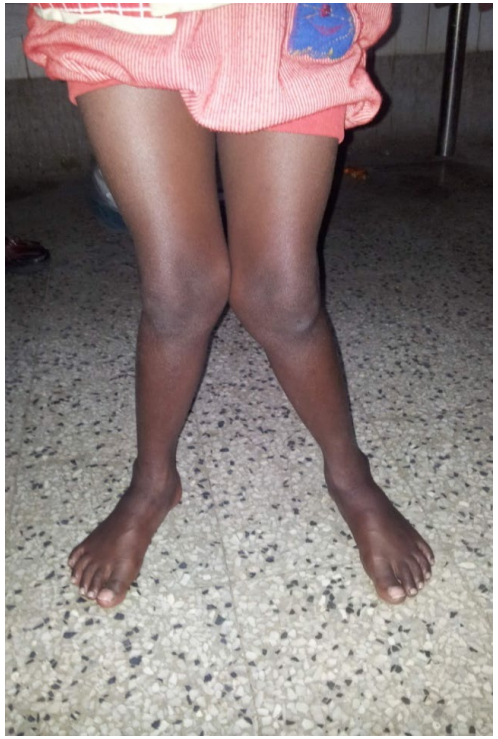




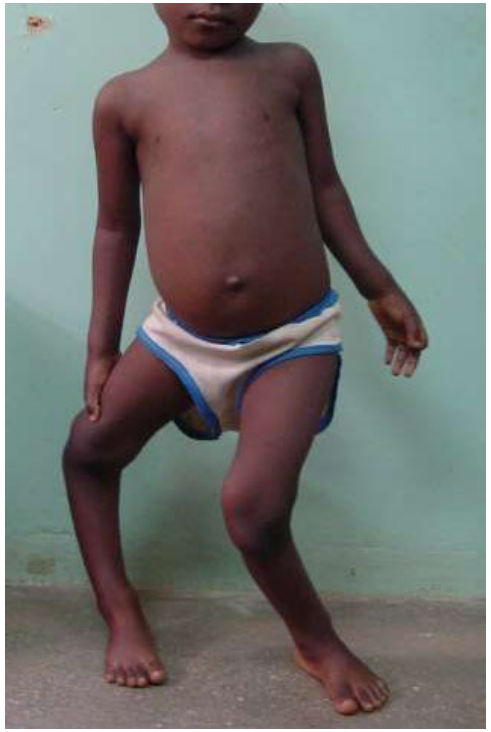


Deformities

Varus deformity



Valgus deformity

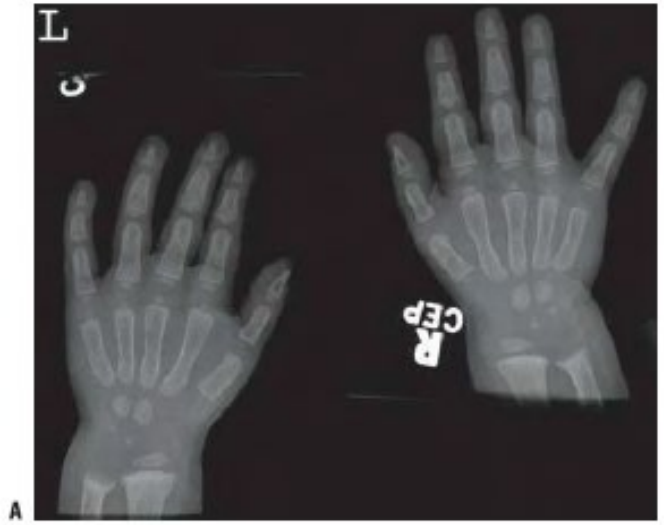


Windswept deformity

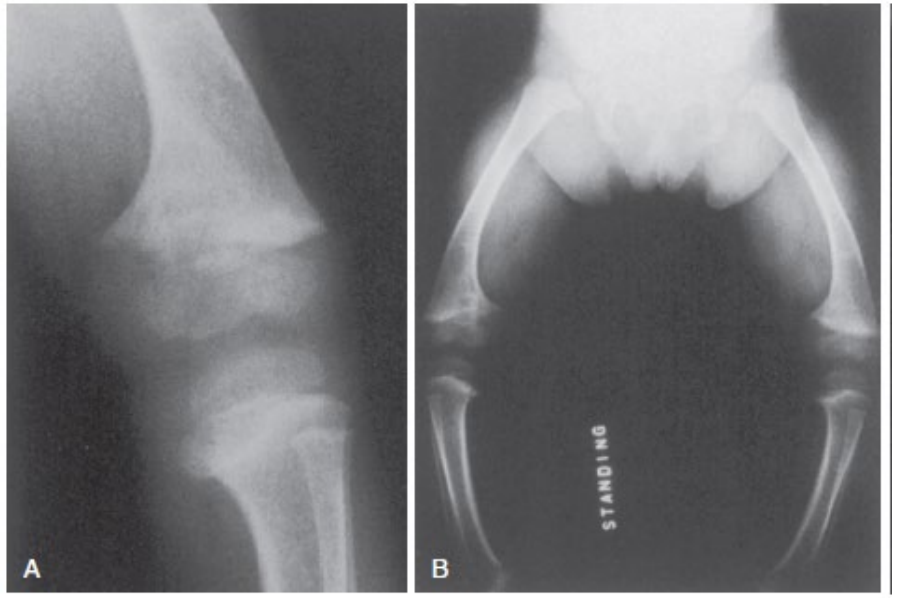
Biochemical abnormalities in Rickets

Type of Rickets	Biochemical Abnormality					
	Calcium	Phosphate	Alkaline Phosphatase	PTH	25-(OH) vitamin D	1,25-$(OH)_2$ vitamin D
Nutritional	Nl	Nl↓	↑	↑	↓↓	↓
Vitamin D–resistant (XLH, RTA, Fanconi, oncogenic)	Nl	↓	↑	Nl	Nl	Nl
Vitamin D–dependent type I (inability to hydroxylate)	↓	↓	↑	↑	↑↑	↓↓
Vitamin D–dependent type II (receptor insensitivity)	↓	↓	↑	↑	Nl↑↑	↑↑↑↑
Renal osteodystrophy	Nl↓	↑	↑	↑↑	Nl	↓↓

Nl, Normal; *PTH*, parathyroid hormone; *RTA*, renal tubular acidosis; *XLH*, X-linked hypophosphatemia.

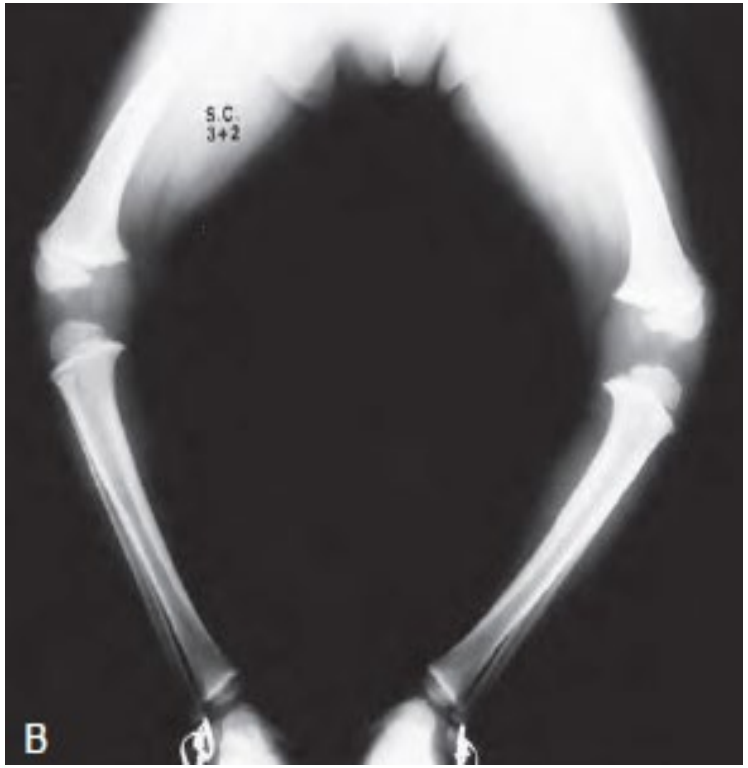


Radiographic Findings

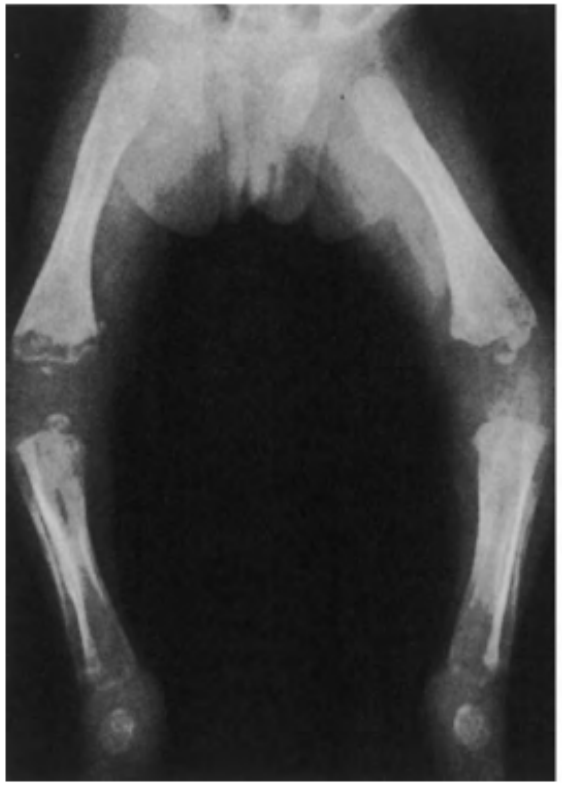


- Widened Physis
- Cupping of metaphysis
- Metaphysis abutting the physis is brush like
- Overall osteopenic appearance of bones with thinning of the cortices.

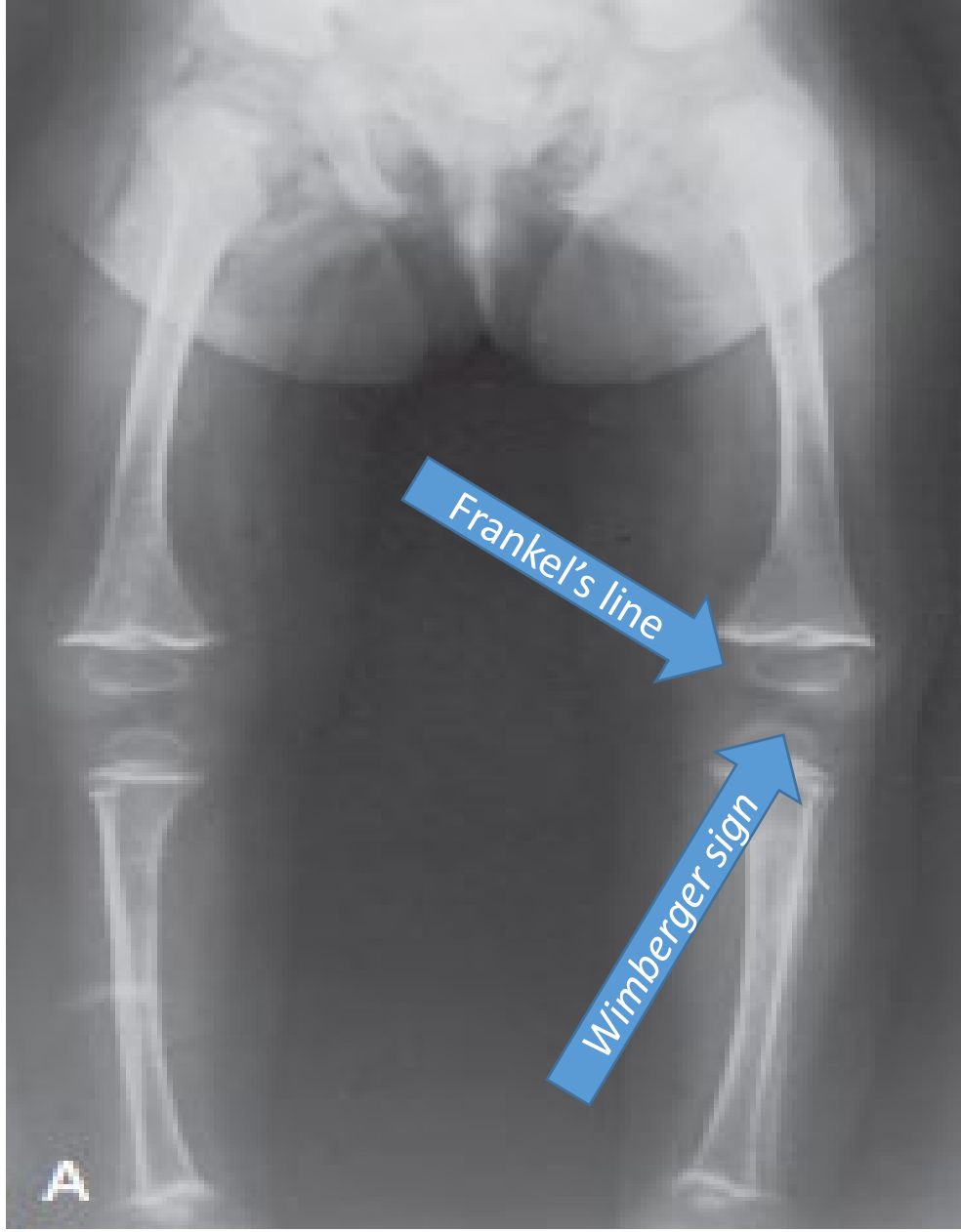
Differential diagnosis



Physiologic Genu Varum



Congenital syphilis



Infantile scurvy

Treatment

- Goals of treatment
  - Relieve symptoms and correct the cause of the condition
- Underlying cause must be treated to prevent recurrence

- Treatment Options :
  - Medical treatment
  - Prevention of deformity
  - Treatment of existing deformity

Medical treatment

- Treatment of nutritional rickets involves adequate provision of vitamin D under the supervision of a pediatric specialist in metabolic bone disease.
- The treatment dose of 5000 to 10,000 international unit per day for 4 to 8 weeks should be provided along with calcium to 500 to 1000 mg per day in the diet
- Where daily dosing and compliance is a problem, much larger doses of vitamin D (200,000 to 600,000 IU orally or intramuscularly) can be given as single dose
- Exposure to moderate amounts of sunlight is encouraged

World Health Organization

Nutritional rickets

A REVIEW OF DISEASE BURDEN, CAUSES, DIAGNOSIS, PREVENTION AND TREATMENT

Supplementation with vitamin D

- The *Global consensus recommendations on prevention and management of nutritional rickets* suggested the following *(4)*:
  - infants younger than 3 months: 2000 IU/day for 12 weeks, with a maintenance dose of 400 IU until the condition is resolved;
  - infants aged 3–12 months: 2000 IU/day for 12 weeks or a single dose of 50 000 IU, with a maintenance dose of 400 IU until the condition is resolved;
  - children aged 1–12 years: 3000–6000 IU/day for 12 weeks or a single dose of 150 000 IU, with a maintenance dose of 600 IU until the condition is resolved;
  - children older than 12 years: 6000 IU/day for 12 weeks or a single dose of 300 000 IU, with a maintenance dose of 600 IU until the condition is resolved;
  - monitoring of nutritional rickets after the onset of treatment.

Nutrition Facts in ONE cup of milk: COW vs. SHEEP vs. GOAT

Winner

	COW	SHEEP	GOAT	Winner
protein	8g	15g	9g	SHEEP
carbs	11g	13g	11g	SHEEP
fat	8g	17g	10g	SHEEP
Vit D	98IU	*ND	30IU	COW
Vit C	0mg	10.3mg	3.2mg	SHEEP
Vit A	249IU	360IU	483IU	GOAT
Vit K	0.5mcg	*ND	0.7mcg	GOAT
Vit E	0.15mg	*ND	0.2mg	GOAT
Vit B6	0.100mcg	0.100mcg	0.112mcg	GOAT
Vit B12	1.10mcg	1.70mcg	0.2mcg	SHEEP
folate	12 mcg	17.2mcg	2.4mcg	SHEEP
calcium	276mg	473mg	327mg	SHEEP
selenium	9mcg	4.2mcg	3.4mcg	COW
magnesium	24mg	44.1mg	34.2mg	SHEEP

*ND - not determined www.weedemandreap.com

Components	Cow (100 mL)	Buffalo (100 mL)	Human (100 mL)
Protein (g)	3.2	6.5	1.1
Fat (g)	4.1	4.3	3.4
Lactose (g)	4.4	5.1	7.4
Calcium (mg)	120	210	28
Energy (kcal)	67	117	65

1 glass=250 ml milk

- Calcium=300 mg
- Vitamin D = 100 IU

Cow's Milk (whole)

Nutritional value per 100 g (3.5 oz)

Energy	252 kJ (60 kcal)
Carbohydrates	5.26 g
Sugars	5.26 g
Lactose	5.26 g
Fat	3.25 g
• saturated	1.865 g
• monounsaturated	0.812 g
• polyunsaturated	0.195 g
Protein	3.22 g
Tryptophan	0.075 g
Threonine	0.143 g
Isoleucine	0.165 g
Leucine	0.265 g
Lysine	0.140 g
Methionine	0.075 g
Cystine	0.017 g
Phenylalanine	0.147 g
Tyrosine	0.152 g
Valine	0.192 g
Arginine	0.075 g
Histidine	0.075 g
Alanine	0.103 g
Aspartic acid	0.237 g
Glutamic acid	0.648 g
Glycine	0.075 g
Proline	0.342 g
Serine	0.107 g
Water	88.32 g
Vitamin A	equiv. 28 µg (3%)
Thiamine (Vit. B1)	0.044 mg (3%)
Riboflavin (Vit. B2)	0.183 mg (12%)
Vitamin B12	0.44 µg (18%)
Vitamin D	40 IU (10%)
Calcium	113 mg (11%)
Magnesium	10 mg (3%)
Potassium	143 mg (3%)

Bracing in Rickets

Rickets: An Overview and Future Directions, with Special Reference to Bangladesh

A Summary of the Rickets Convergence Group Meeting,
Dhaka, 26-27 January 2006

Thierry Craviari[1], John M. Pettifor[2], Tom D. Thacher[3], Craig Meisner[4], Josiane Arnaud[5], Philip R. Fischer[6], and the Rickets Convergence Group

[1]Centre Hospitalier de Gap, Gap, France, [2]University of Witwatersrand, Johannesburg, South Africa, [3]Jos University Teaching Hospital, Jos, Nigeria, [4]Cornell University, Ithaca, New York, USA, [5]Centre Hospitalier Universitaire de Grenoble, Grenoble, France, and [6]Mayo Clinic, Rochester, 200 First Street SW, Minnesota 55905, USA

- Suggest braces to support the limbs and to encourage straighter longitudinal growth associated with medical treatment
- Bracing: If no improvement after 6 months of medical therapy below 7 years of age
- Bracin : Post-surgery

Surgery in rickets

- Surgery will not result in correction of angular deformities in Rickets in absence of correction of the underlying endocrinopathy in the growing child
- Thus, it is important to avoid the temptation for surgical correction of a deformity in a growing child with an endocrine disorder until the endocrinopathy is also treated.
- As residual deformity is rare after medical treatment of nutritional rickets, there is no specific orthopaedic treatment of nutritional rickets.

Prevention of rickets

- 200 IU of vitamin D per day is the recommended dietary amount to prevent rickets
- Increasing amounts are now being recommended for optimization of bone health (Canadian Paediatric Society recommending 800 IU per day and the AAP recommending 400 IU per day)
- Sunlight exposure also prevent rickets
- Children should be weaned to a diet adequate in vitamin D and calcium
- Prevention in preterm infants require fortification of formula /human milk

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

revised 111(4):908
FROM THE AMERICAN ACADEMY OF PEDIATRICS

Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Carol L. Wagner, Frank R. Greer and ; and the Section on Breastfeeding and Committee on Nutrition
Pediatrics November 2008, 122 (5) 1142-1152; DOI: https://doi.org/10.1542/peds.2008-1862

- Full-body exposure during summer months for 10 to 15 minutes with lighter pigmentation and 5 to 10 times more exposure with darker pigmentation will generate sufficient vitamin D_3 to prevent Rickets

- Recommends infants younger than 6 months should be kept out of direct sunlight

European Journal of Clinical Nutrition (2011), 1–7

0954-3007/11
www.nature.com/ejcn

ORIGINAL ARTICLE

A pilot randomized controlled trial of oral calcium and vitamin D supplementation using fortified laddoos in underprivileged Indian toddlers

VH Ekbote[1], AV Khadilkar[1], SA Chiplonkar[1], NM Hanumante[2], VV Khadilkar[1] and MZ Mughal[3]

[1]*Growth and Endocrine Unit, HCJMRI, Jehangir Hospital, Pune, India;* [2]*Department of Pediatrics, Bharati Vidyapeeth University Medical College and Hospital, Pune, India and* [3]*Department of Paediatric Medicine, Royal Manchester Children's Hospital, Manchester, UK*

- It resulted in significantly higher serum concentrations of iCa and a decrease in the serum concentrations of intact parathyroid hormone.
- Demonstrated that one year of calcium supplementation using fortified laddoos as a vehicle and monthly vitamin D supplementation resulted in a significant increase in total body BMC of underprivileged toddlers with g habitually low dietary calcium intake.

World Health Organization

Nutritional rickets

A REVIEW OF DISEASE BURDEN, CAUSES, DIAGNOSIS, PREVENTION AND TREATMENT

Recommendations for calcium intake

- FAO and WHO recommend
  - 300–400 mg/day of calcium for infants
  - 500 mg/day in children aged 1–3 years
  - 600 mg/day in children aged 4–6 years
  - 700 mg/day in children aged 7–9 years
  - 1300 mg/day in children aged 9–18 years

Vitamin D–Resistant Rickets

- Also known as hereditary or familial hypophosphatemic rickets
- A group of disorders in which normal dietary intake of vitamin D is insufficient to achieve normal mineralization of bone because of pathologic renal phosphate wasting.
- Can be X- linked dominant, autosomal dominant, or autosomal recessive form.
- X-linked dominant disease is the most frequent(1 in 20,000) and is considered the prototypic disorder of renal phosphate wasting.
- In 1995, a phosphate-regulating gene with homologies to endopeptidases on the X-chromosome (PHEX) was identified as the cause of X-linked dominant disease.

Clinical Features

- Symptomatic at a slightly **older age** than nutritional rickets
- Initial complaints are delayed walking and angular deformities of the lower extremities
- Unlike nutritional rickets, **systemic manifestations (irritability, apathy)are minimal**.
- Physical findings include skeletal deformities resembling nutritional rickets but becoming **much more severe**
- The deformity most commonly seen is a gradual anterolateral bowing of the femur, combined with tibia vara
- Short stature (Height is usually 2 SDs below the mean for age)

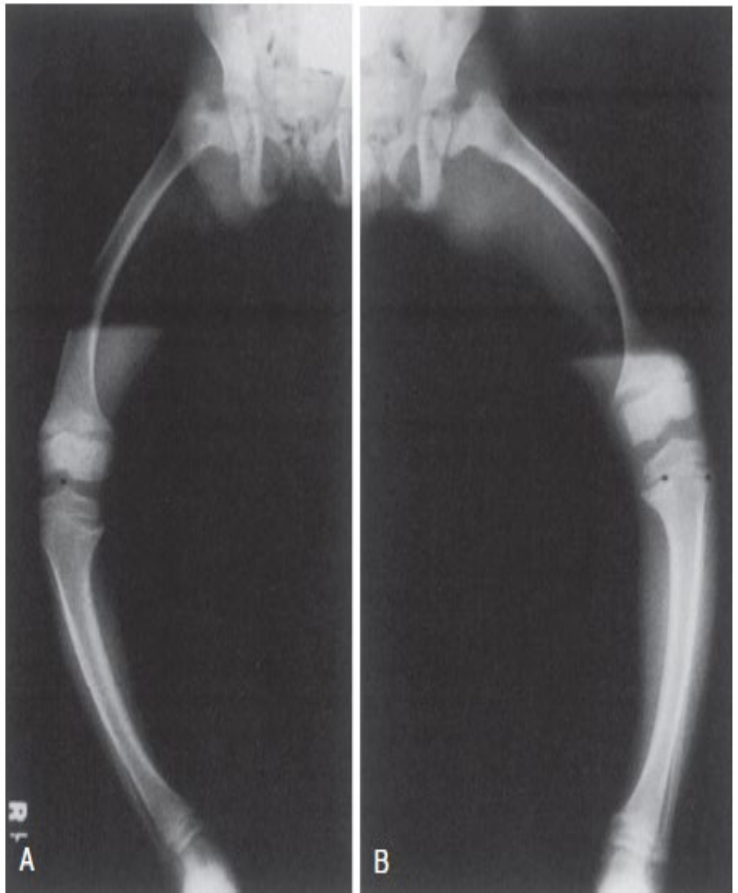
Laboratory Findings

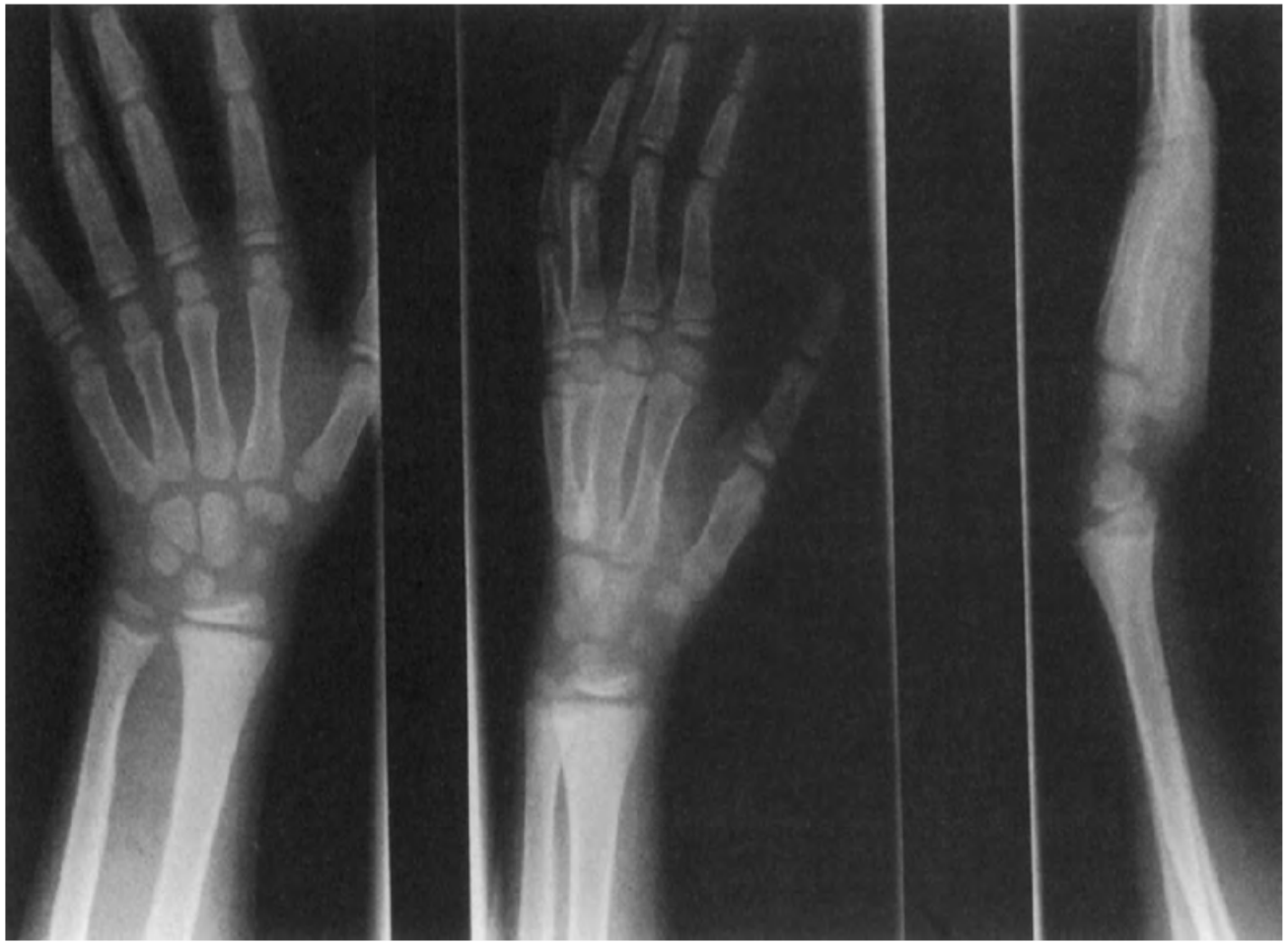
- Normal or almost normal levels of calcium
- Serum phosphate concentration is significantly decreased
- Vitamin D level normal
- PTH level is normal
- Increased concentration of phosphate in the urine
- The serum alkaline phosphatase concentration is elevated but not to the levels seen with nutritional rickets

Radiographic Findings

•Severe genu varum and general anterolateral bowing of the entire femur

• Coxa vara may present





• Same of nutritional rickets (physeal widening , metaphyseal cupping)

Medical Treatment

- Oral replacement of phosphate in large doses and the administration of an active form of vitamin D(calcitriol)
- The therapeutic target of medical therapy should not be to normalize the serum phosphate level because achieving normalization may not be a practical goal and may lead to overmedication and greater side effects.
- Focus should be on improving the skeletal deformity, height, and physeal function. In general, growth and skeletal deformities improve with medical therapy.
- Nephrocalcinosis is a significant complication of medical treatment

Leeds Children's Hospital

The Leeds Teaching Hospitals NHS
NHS Trust

Medicines Management & Pharmacy Services (MMPS)

LTHT Paediatric Administration Guide
Oral Phosphate

Reference range:	Neonate 1.3-2.6mmol/L, Child 4 weeks-1 year 1.3-2.4mmol/L, Child 1 year-16 years 0.9-1.8mmol/L, Adult 0.8-1.5mmol/L
Dose:	**Hypophosphataemia** **Neonate:** 1mmol/kg daily in 1-2 divided doses, dose adjusted as necessary. **Child 1month-4years:** 2-3mmol/kg daily in 2-4 divided doses (maximum initial dose 48mmol per day), dose adjusted as necessary. **Child 5-17 years:** 2-3mmol/kg/daily in 2-4 divided doses (maximum initial dose 96mmol per day), dose adjusted as necessary.
Products available:	Phosphate Sandoz effervescent tablets = 16mmol phosphate per tablet (also contains 20.4mmol sodium and 3.1mmol potassium per tablet). Joulies solution = 1mmol phosphate/mL (also contains 0.76mmol sodium/mL). **For sodium restricted patients - short term use only, only available extemporaneously prepared from pharmacy. Discuss with ward pharmacist:** Potassium acid phosphate oral solution = 1mmol/mL phosphate (also contains 1mmol/mL potassium).
Administration:	**Phosphate Sandoz Effervescent Tablets:** Dissolve one tablet in 16mL of water to give a 1mmol/mL suspension, use the required amount and dispose of any remaining solution.
How to prescribe:	Prescribe on eMeds using the paediatric - oral electrolyte replacement - phosphate protocol. Select the form of phosphate, the dose in mmol, the route and the frequency.
Cautions:	Calcium should not be given at the same time as phosphate. At least two hours should be left between doses of calcium and phosphate.
References:	BNFc online, Evelina London Paediatric Formulary, LTH Tests and tubes guide - Phosphate (ID 159) Published 21/06/2016.

Joulies Solution

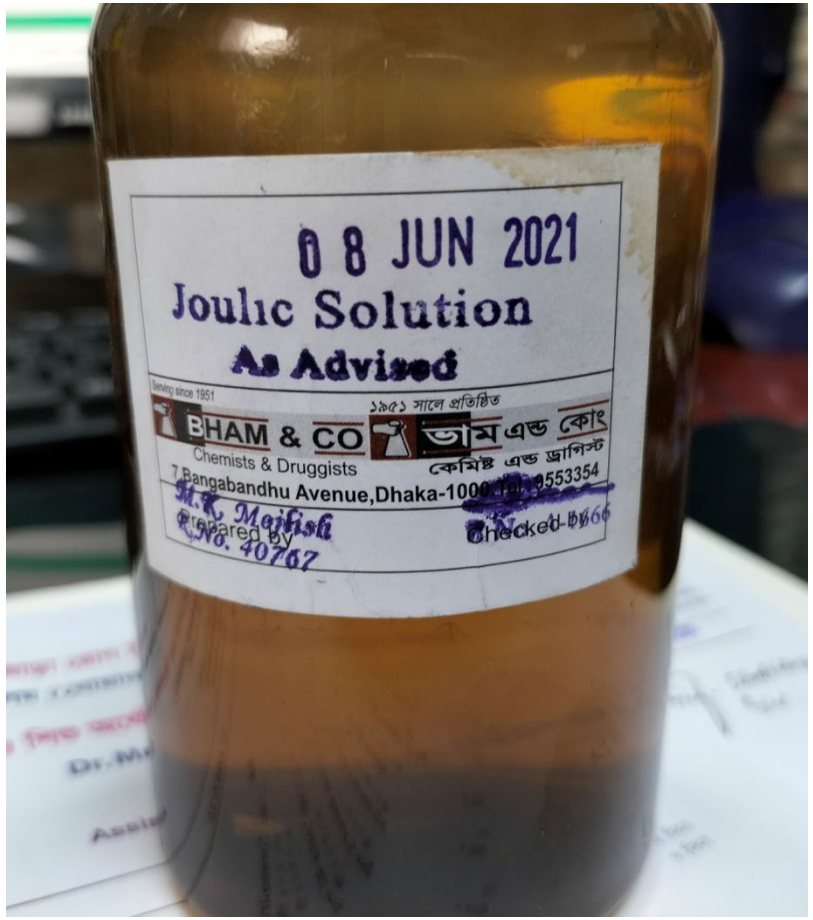
Reference range:

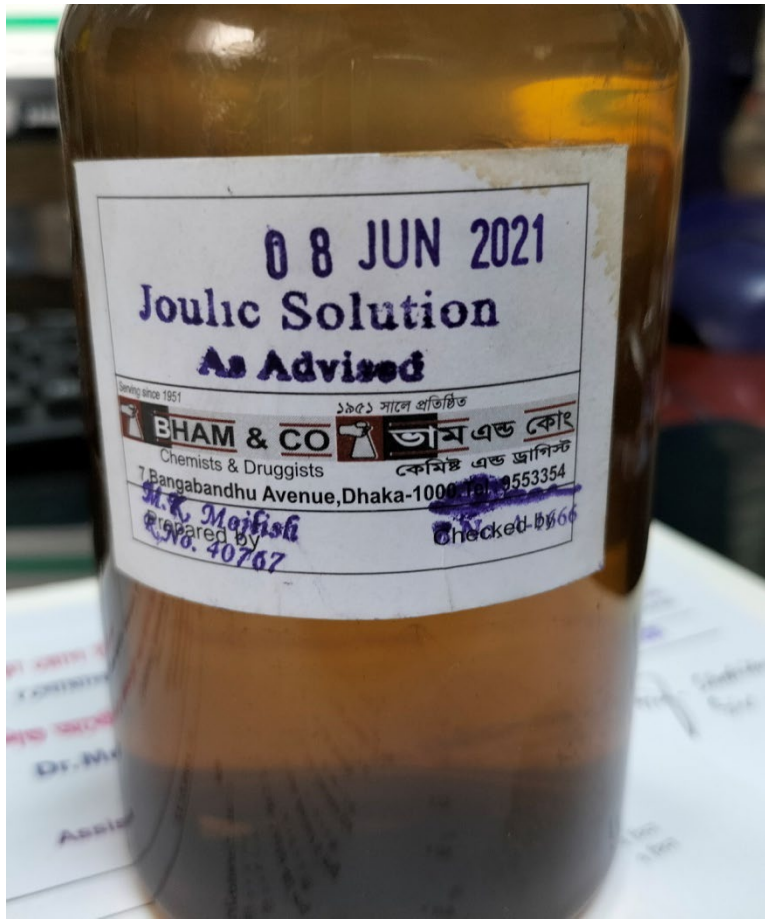
Neonate :1.3-2.6mmol/L,
Child (4 weeks-1 year) :1.3-2.4mmol/L,
Child (1 year-16 years) :0.9-1.8mmol/L,
Adult :0.8-1.5mmol/L

Dose: Hypophosphatemia

- **Neonate:** 1mmol/kg daily in 1-2 divided doses, dose adjusted as necessary.
- **Child (1month-4years):** 2-3mmol/kg daily in 2-4 divided doses(maximum initial dose 48mmol per day),dose adjusted as necessary.
- **Child (5-17 years):** 2-3mmol/kg/daily in 2-4 divided doses(maximum initial dose 96mmol per day),dose adjusted as necessary.

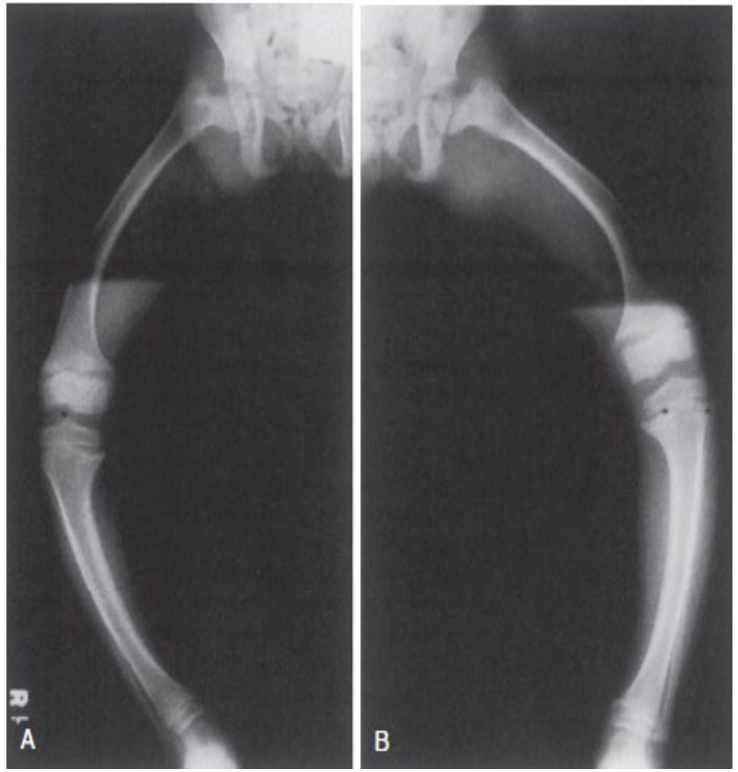
Joulies Solution in Bangladesh



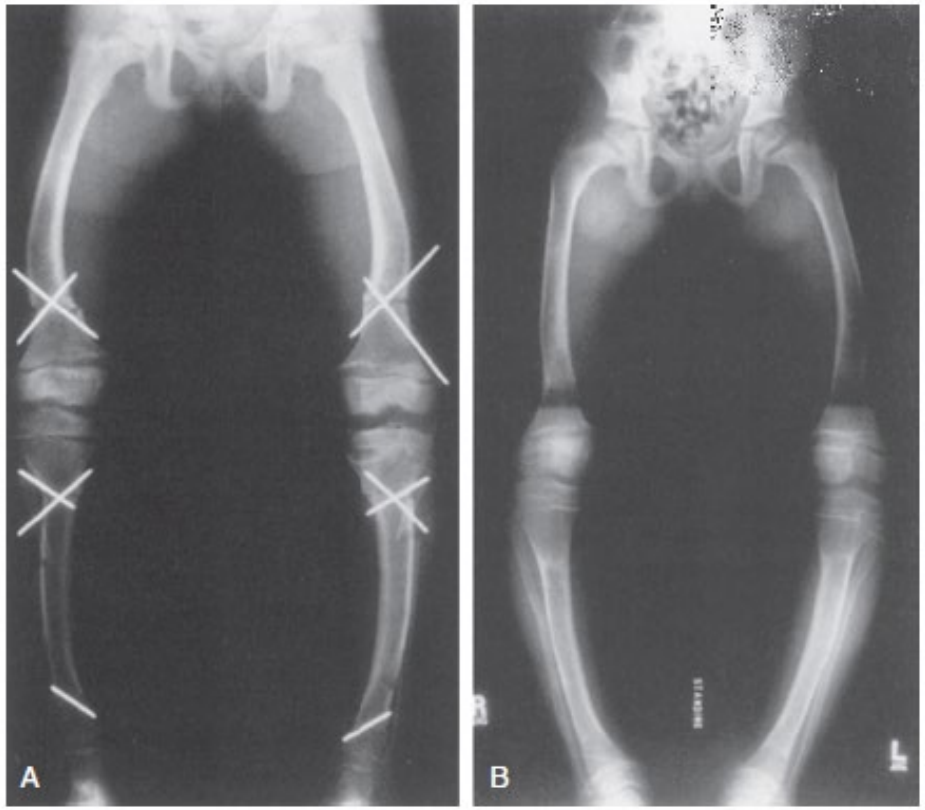


Orthopaedic Treatment

- Orthotic management has not been efficacious
- Surgical correction of angular deformities should be performed in increasing pain or difficulty in walking
- Multilevel osteotomy is generally required to satisfactorily correct the mechanical axis of the limb . The mechanical axis should be mildly overcorrected at surgery.
- Work closely with the nephrologist /endocrinologist managing the medical therapy
- Discontinuation of vitamin D before surgery should be discussed

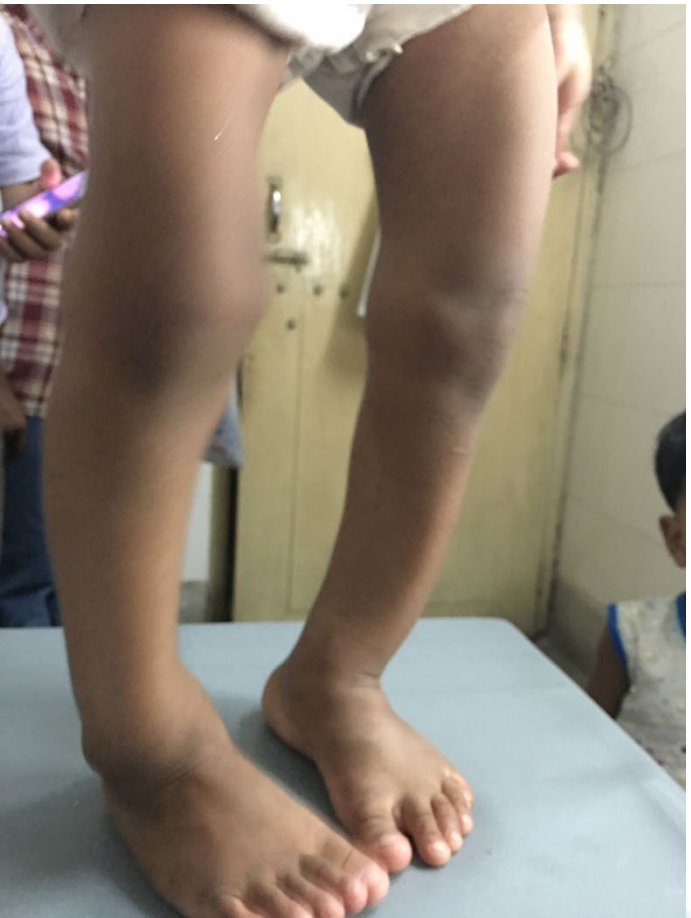


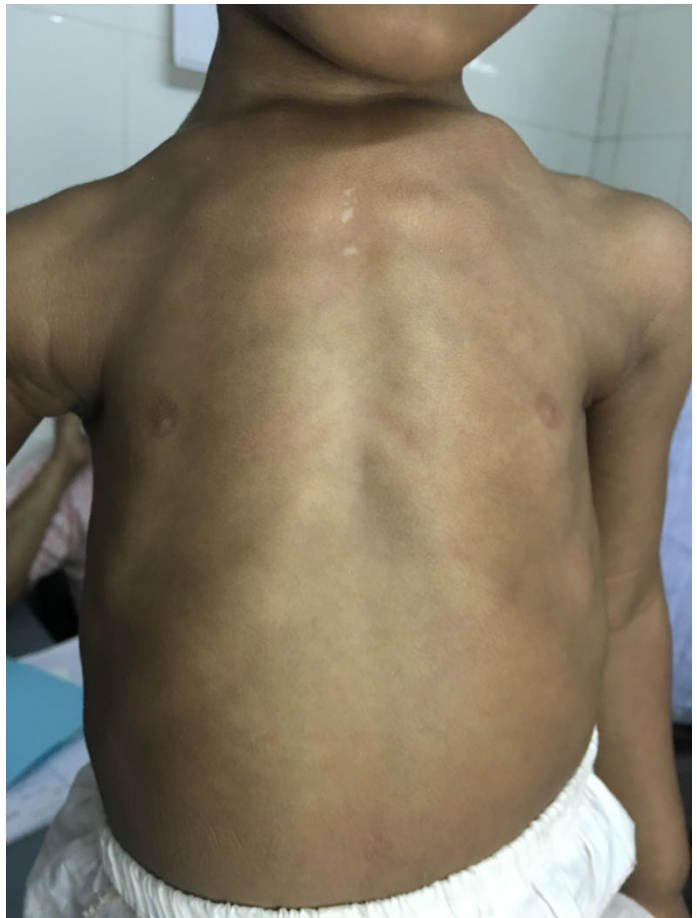
A/P radiographs of both lower limbs of a standing 7-year-old child with familial hypophosphatemic rickets

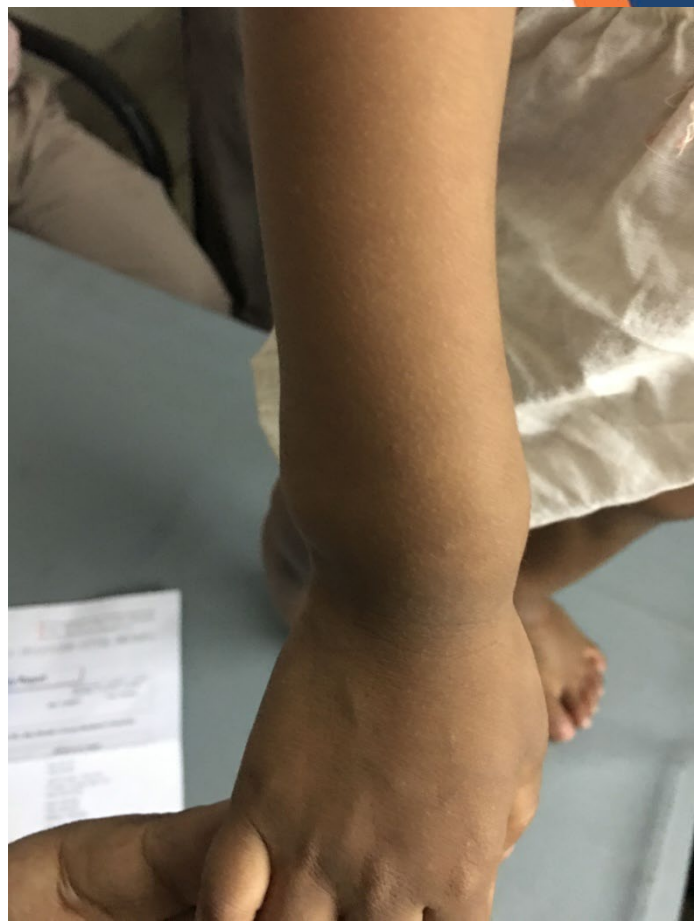


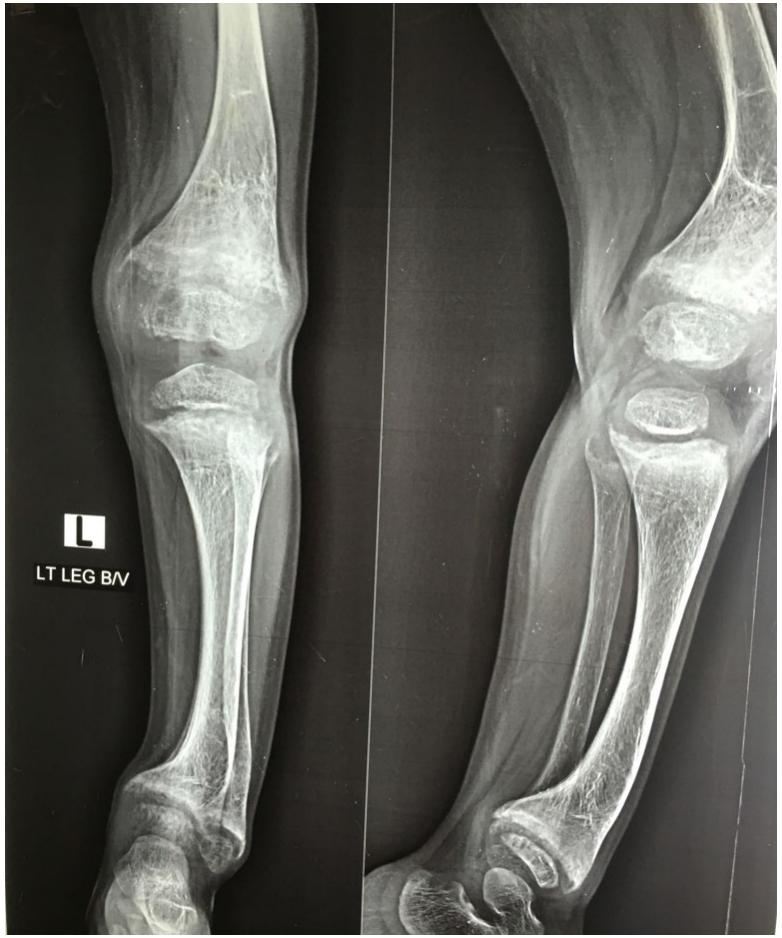
Postoperative radiographs **A, Appearance after** distal femoral, proximal tibial, and distal tibial osteotomies for treatment of genu varum. **B, Varus is recurring 1 year after surgery.**

Case: 1,Fateha ,4 yrs. old girl

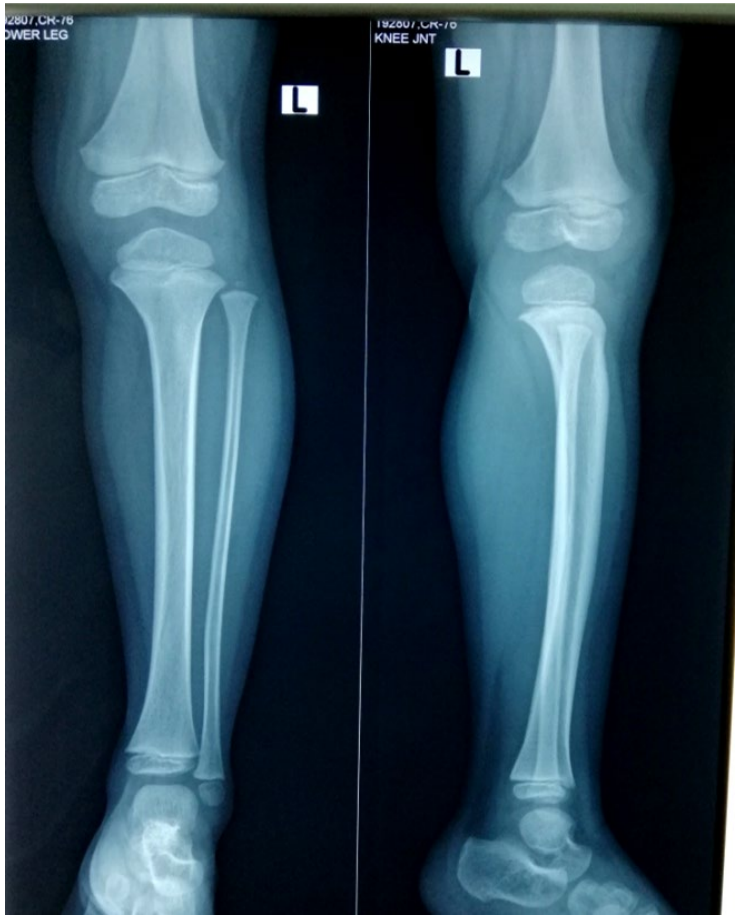




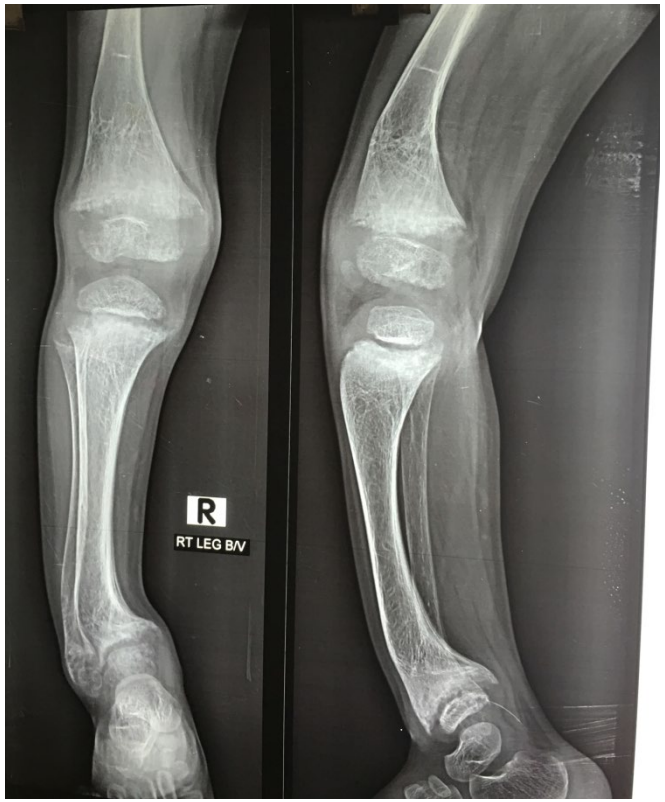




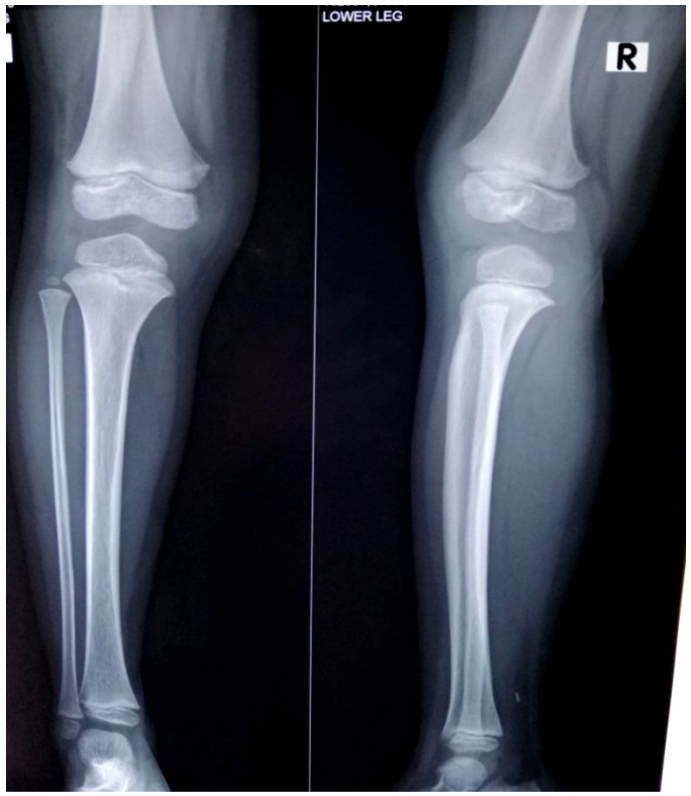
Before treatment



1 year later



Before treatment

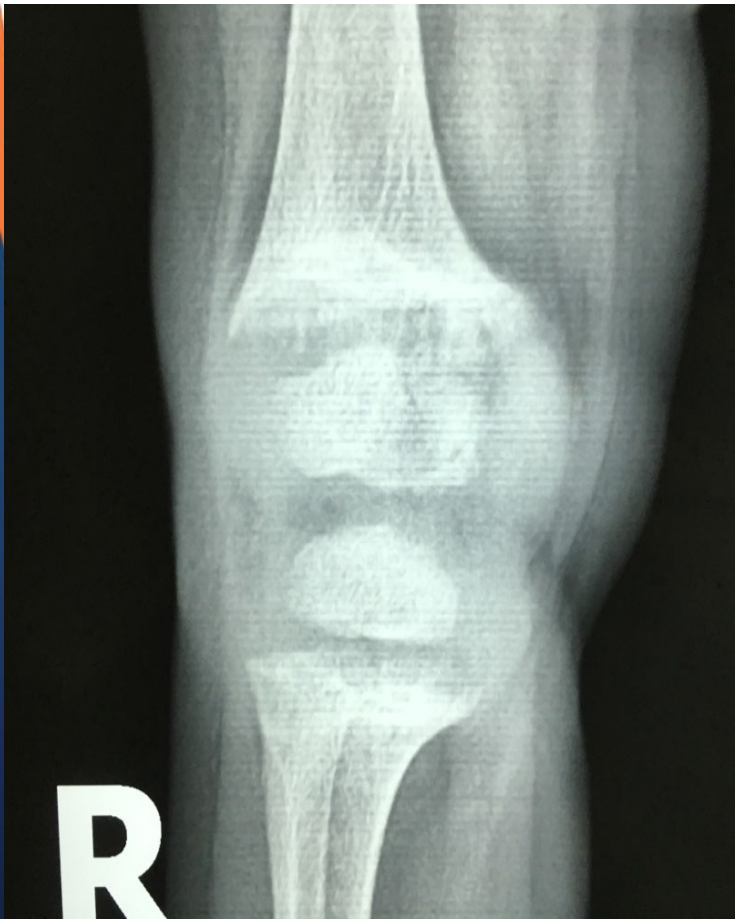


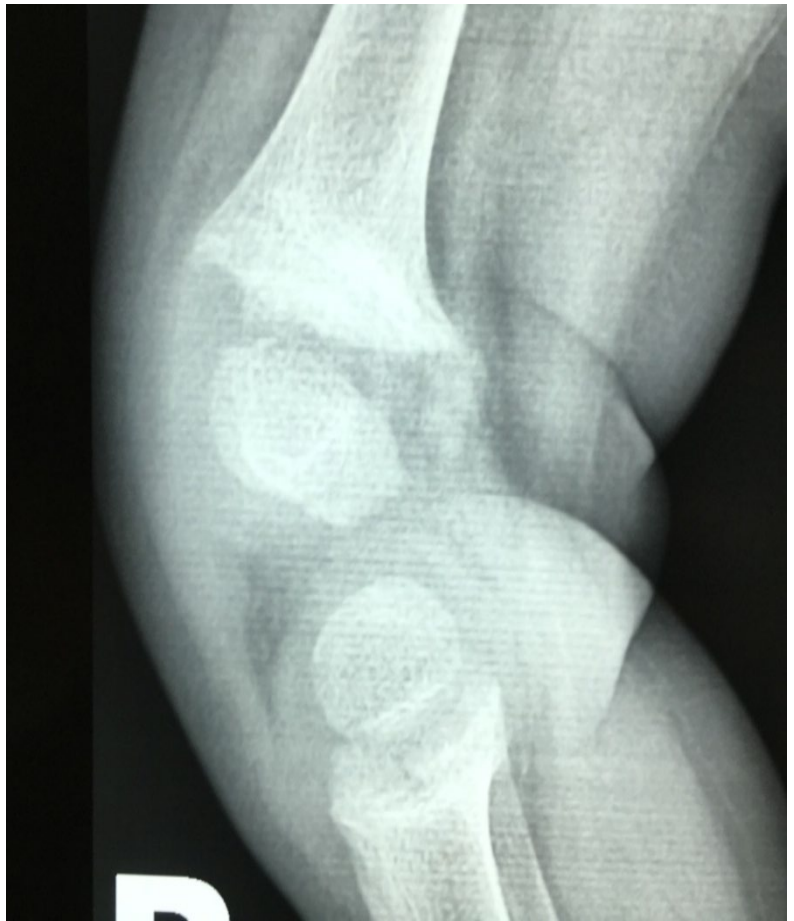
1 year later

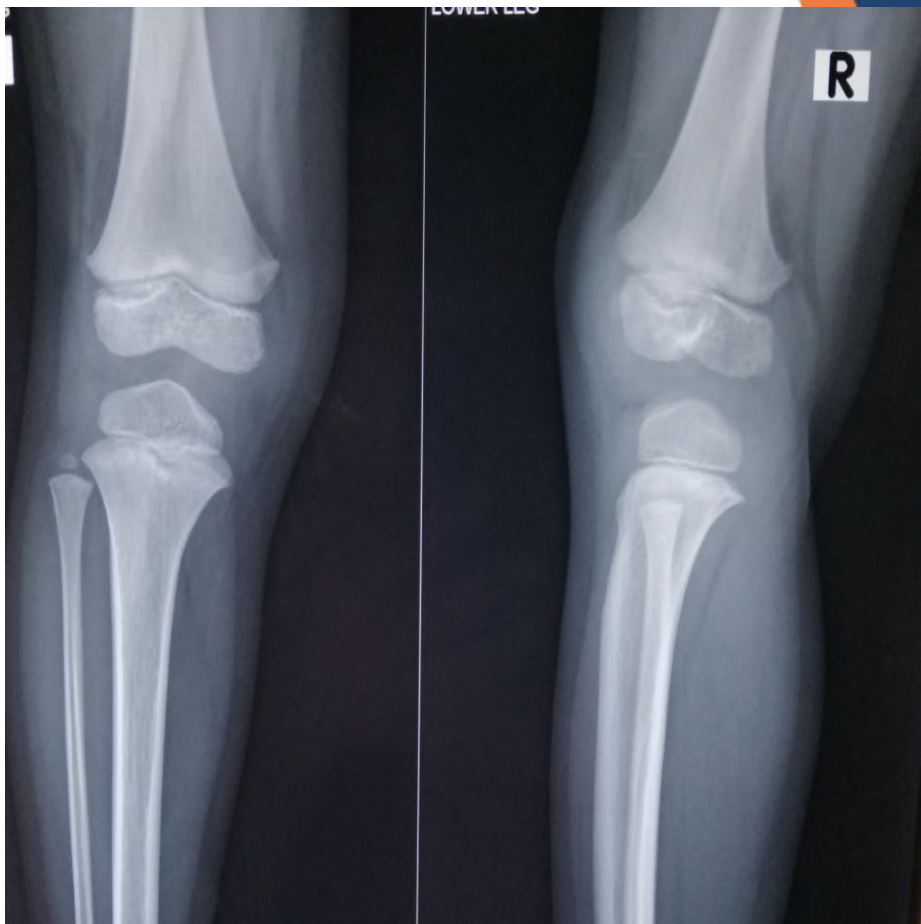
Case 2 : Sawda, 2yrs 8 months old girl

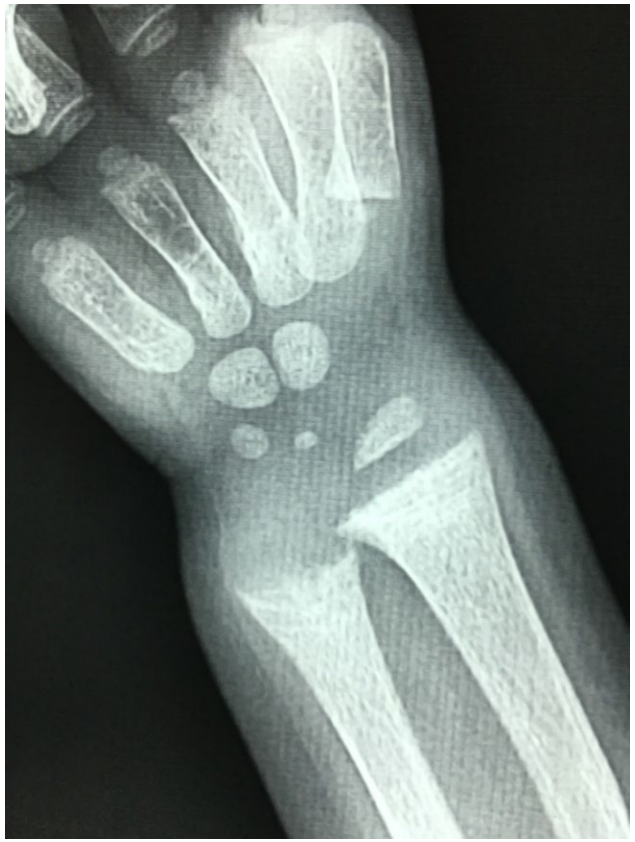
At presentation

10 months after treatment

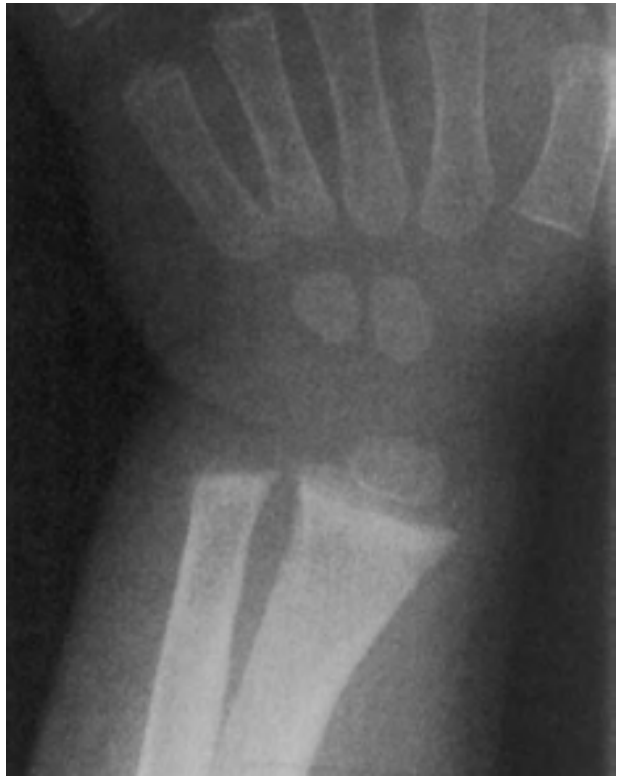






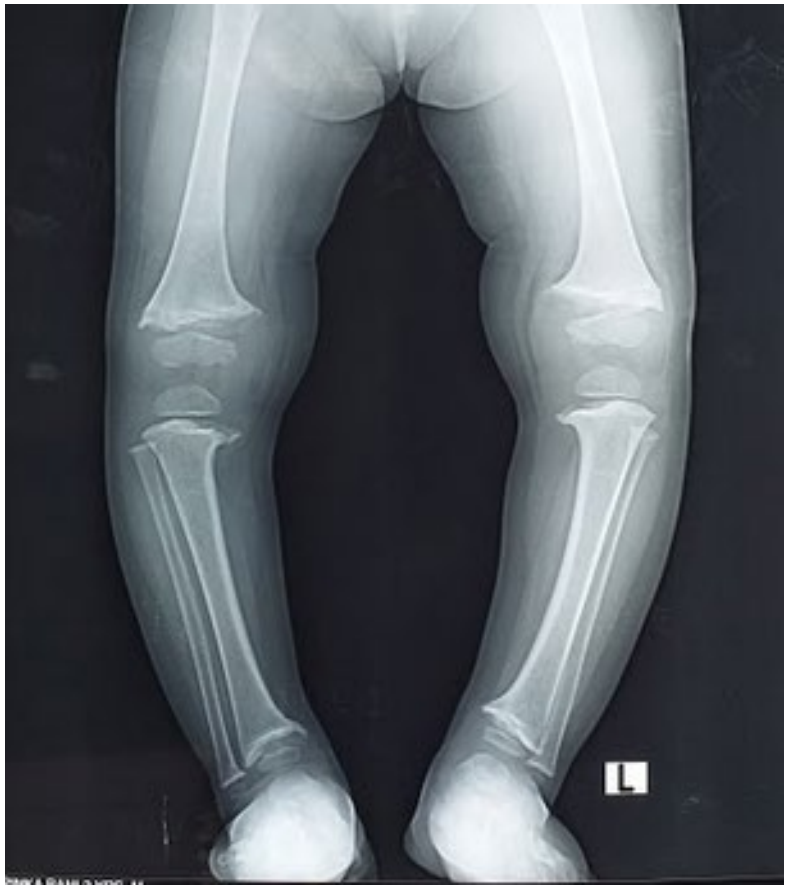


At presentation

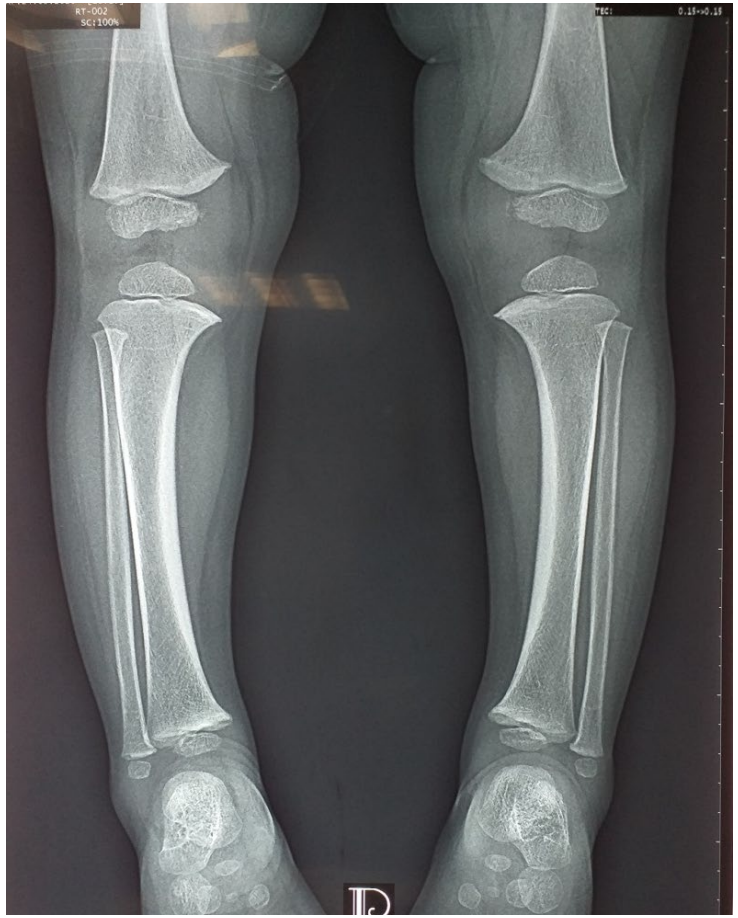


6 months after treatment

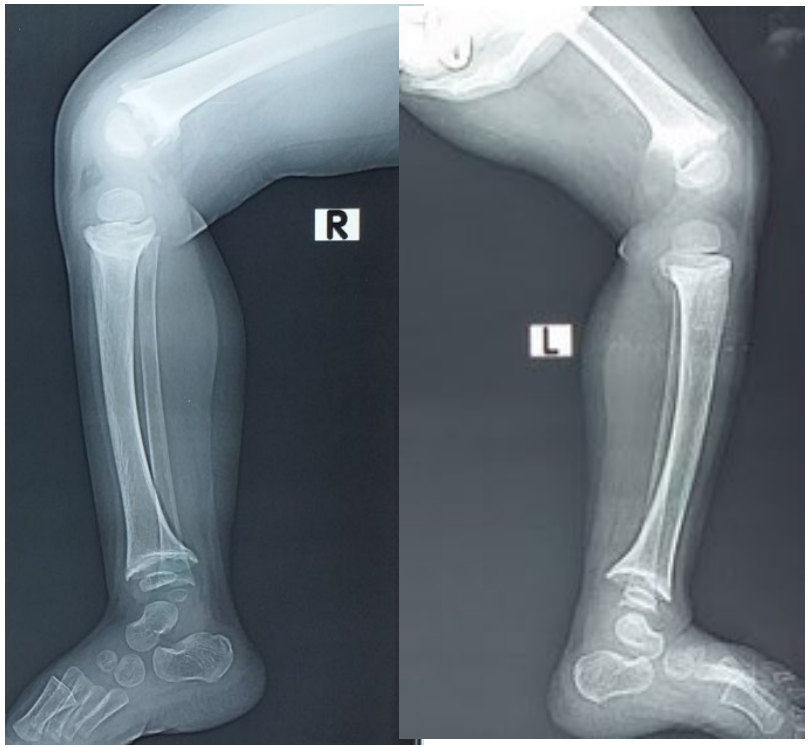
Case 3: Sadman ,1 yrs 9 months, boy



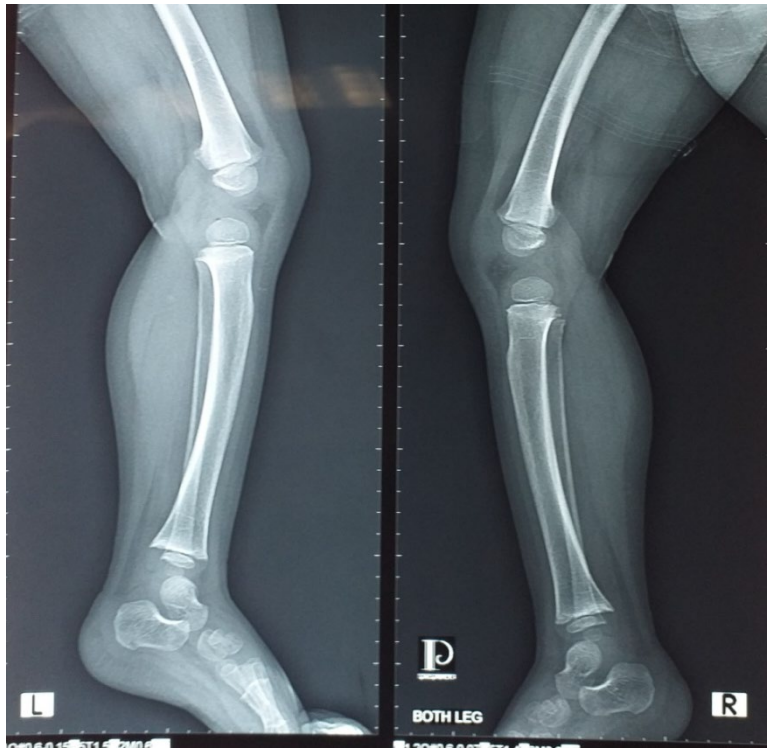
At presentation



6 months after treatment

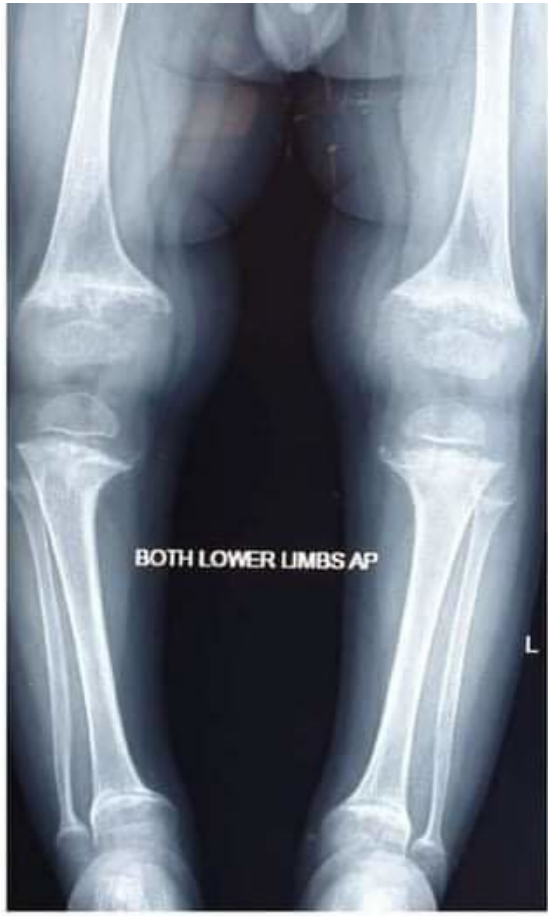


At presentation

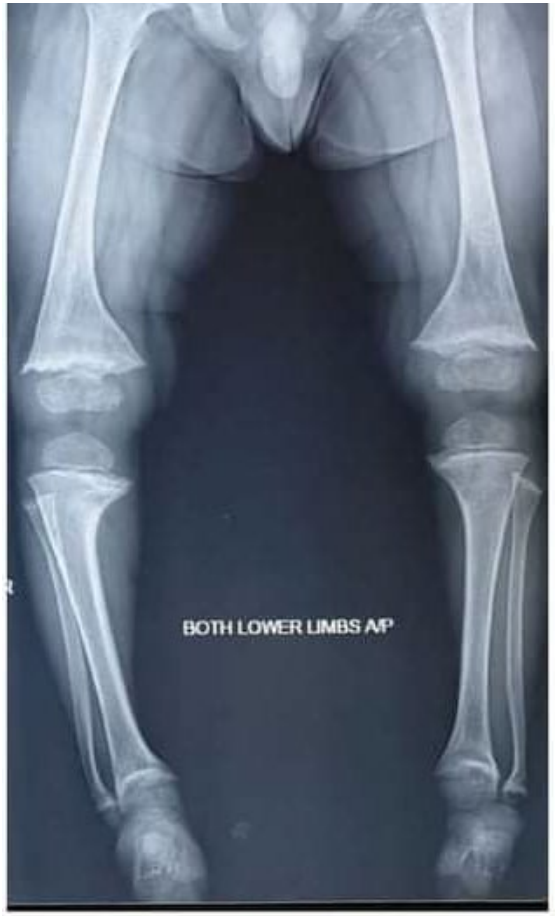


6 months after treatment

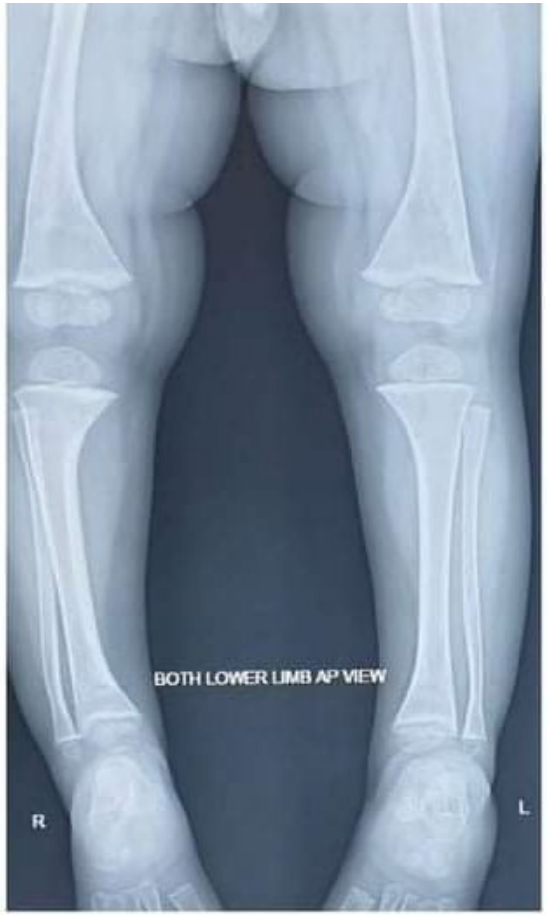
Case 4: Saiful ,2 yrs. 6 months, boy



At presentation

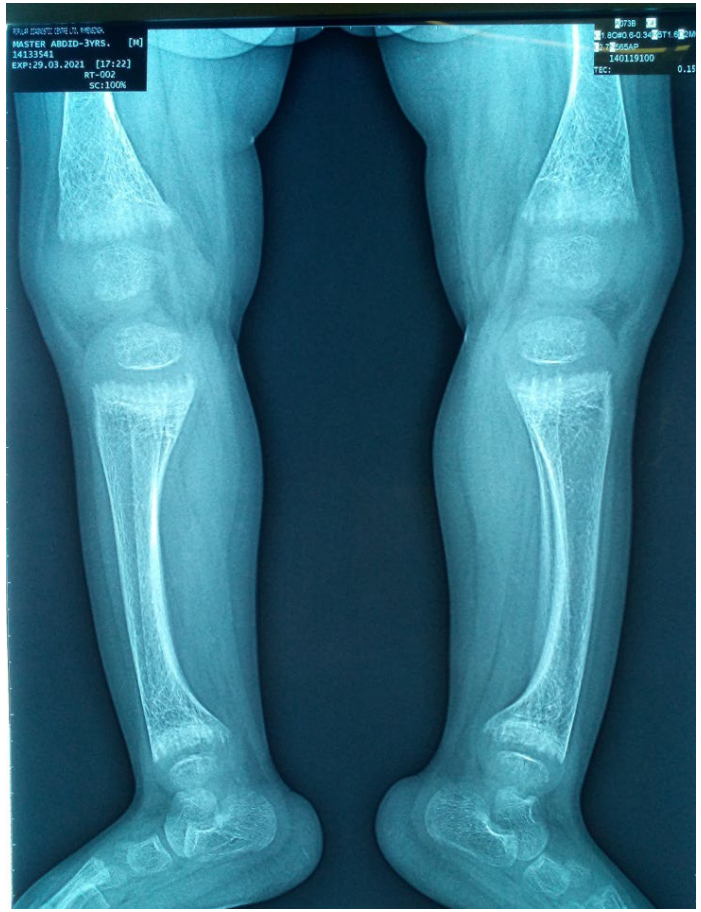


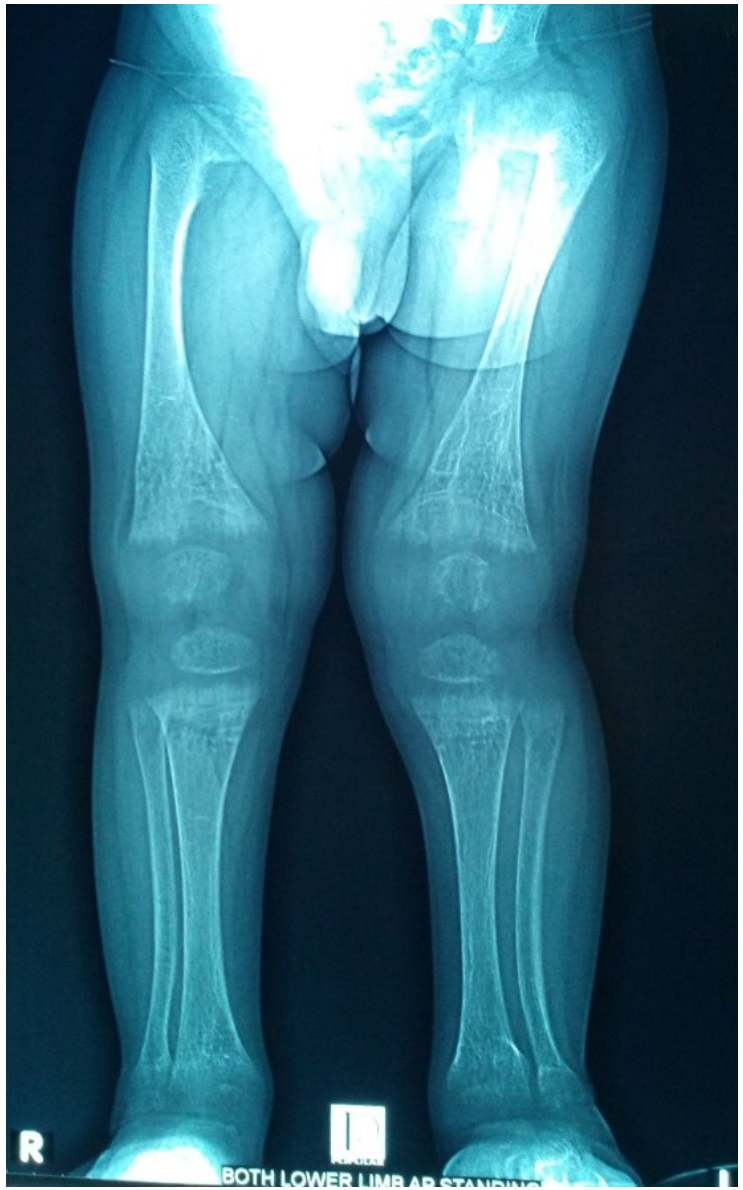
3 months after treatment



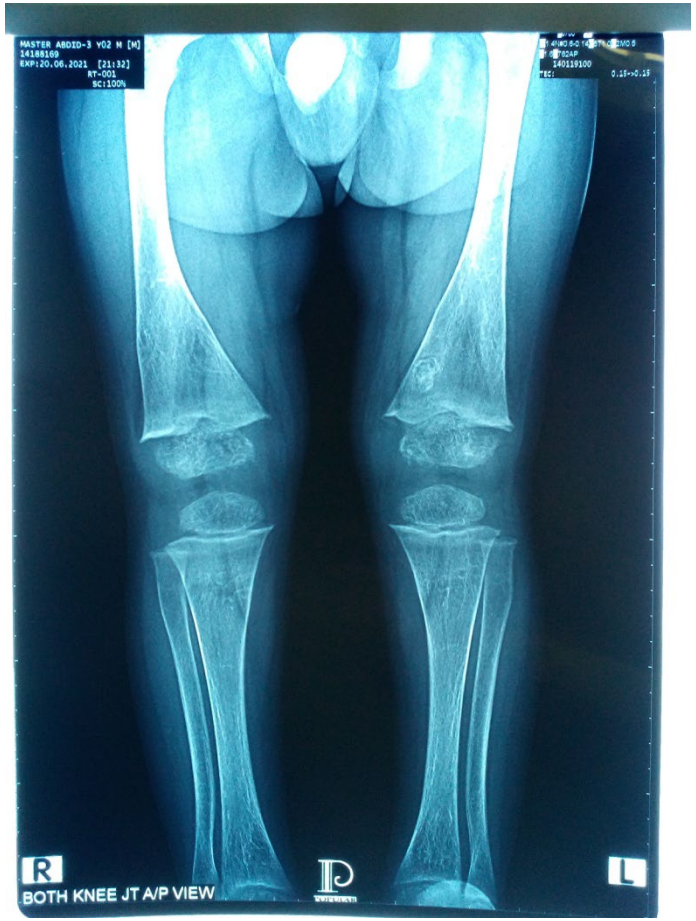
6 months after treatment

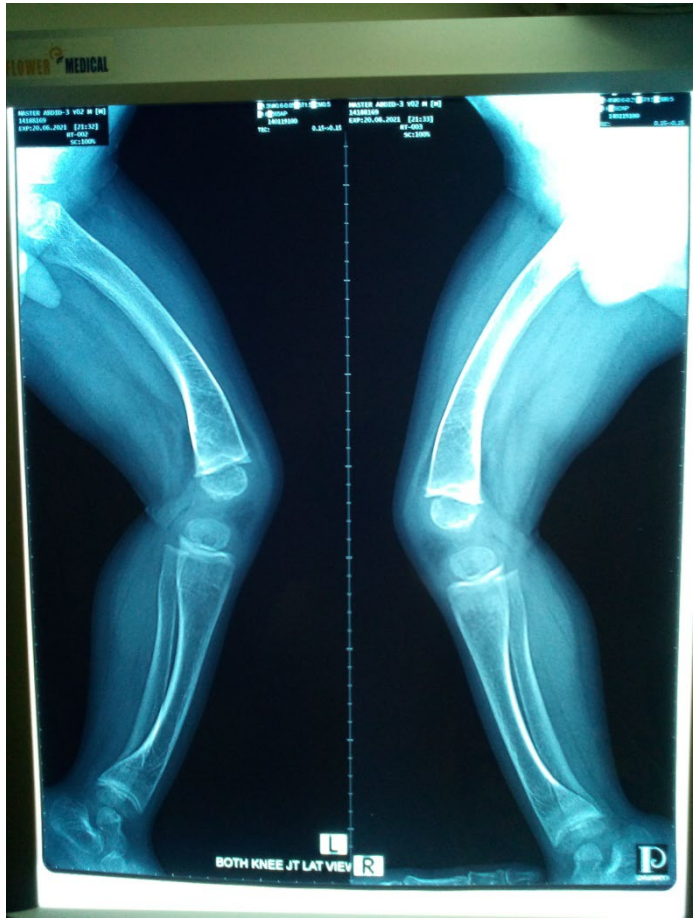
Case 5 : Abid 3yrs 6 months, boy ,Hypophosphatemic

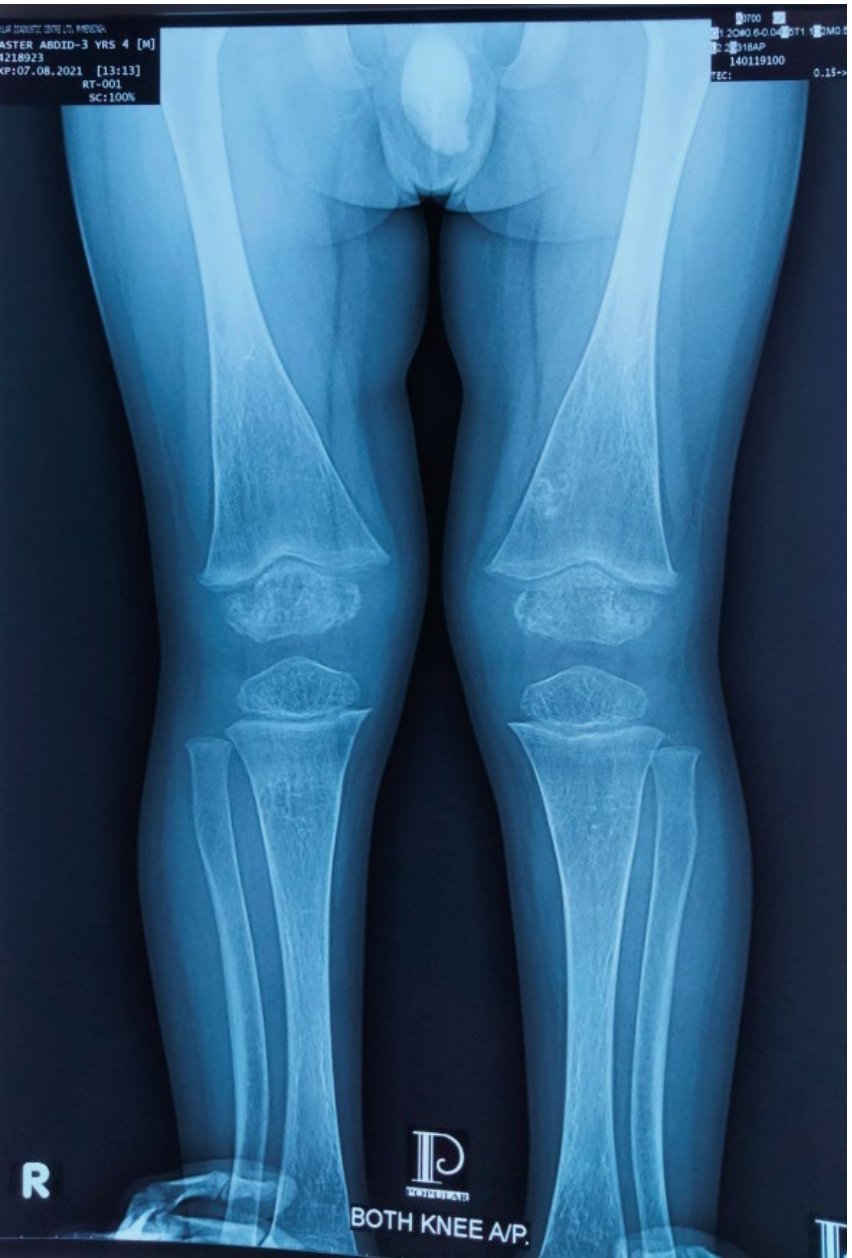




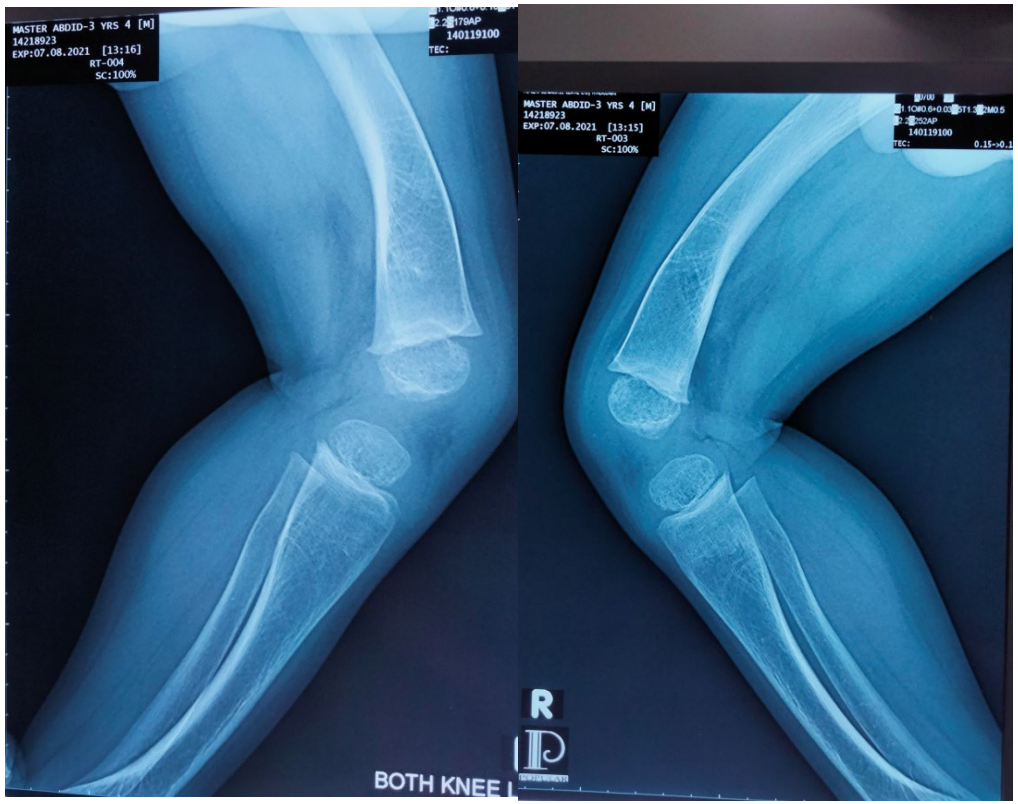
2.5 months after treatment

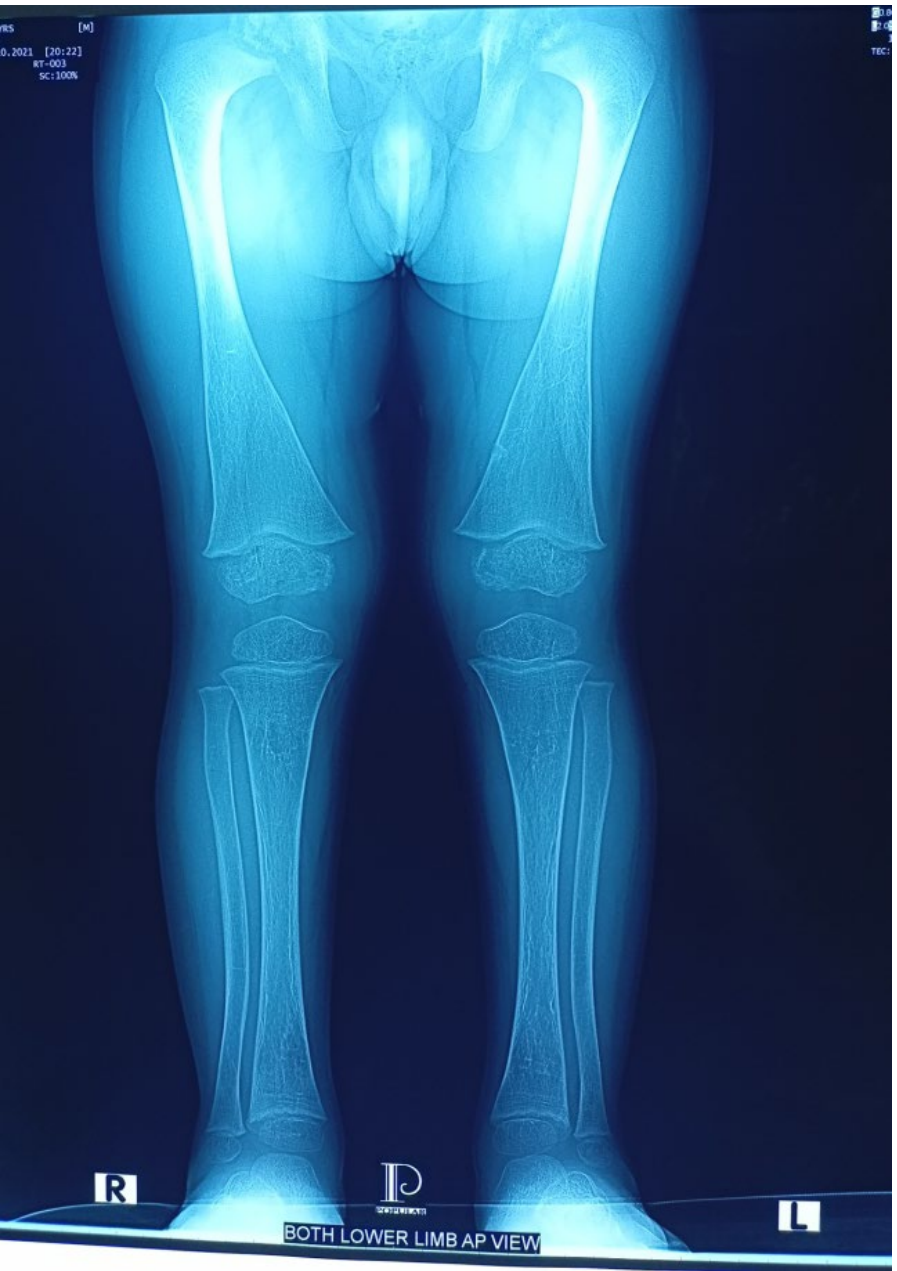




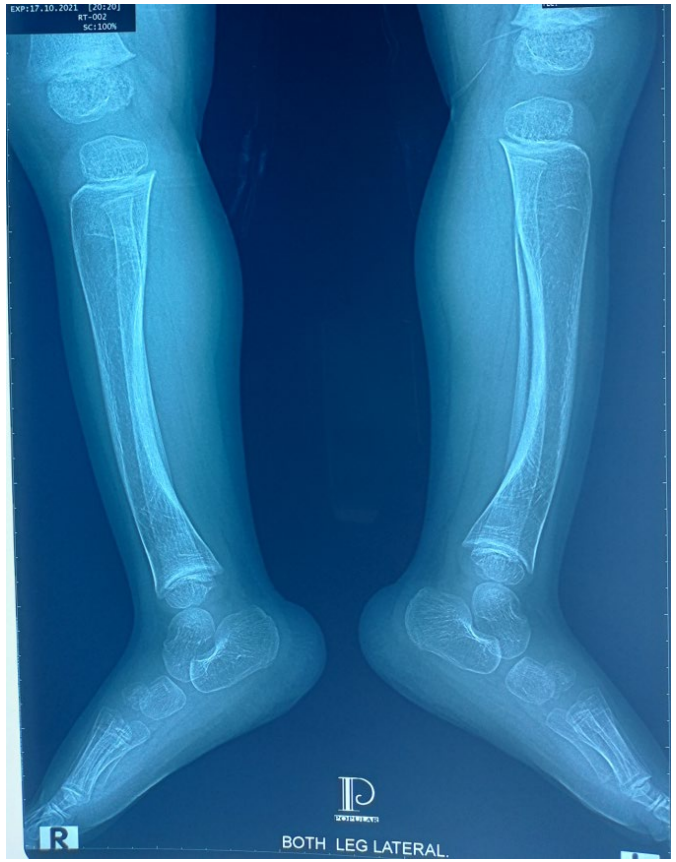


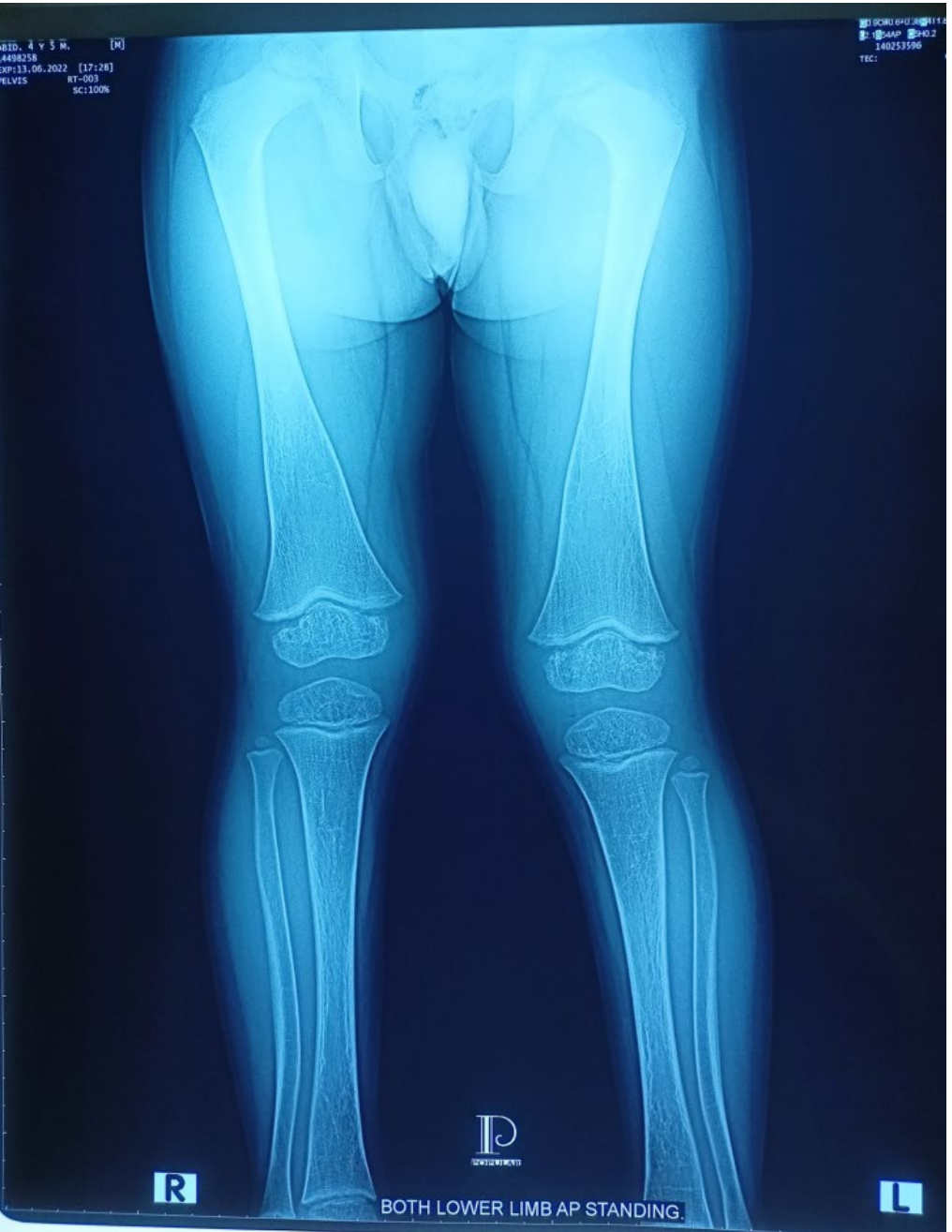
4 months after treatment



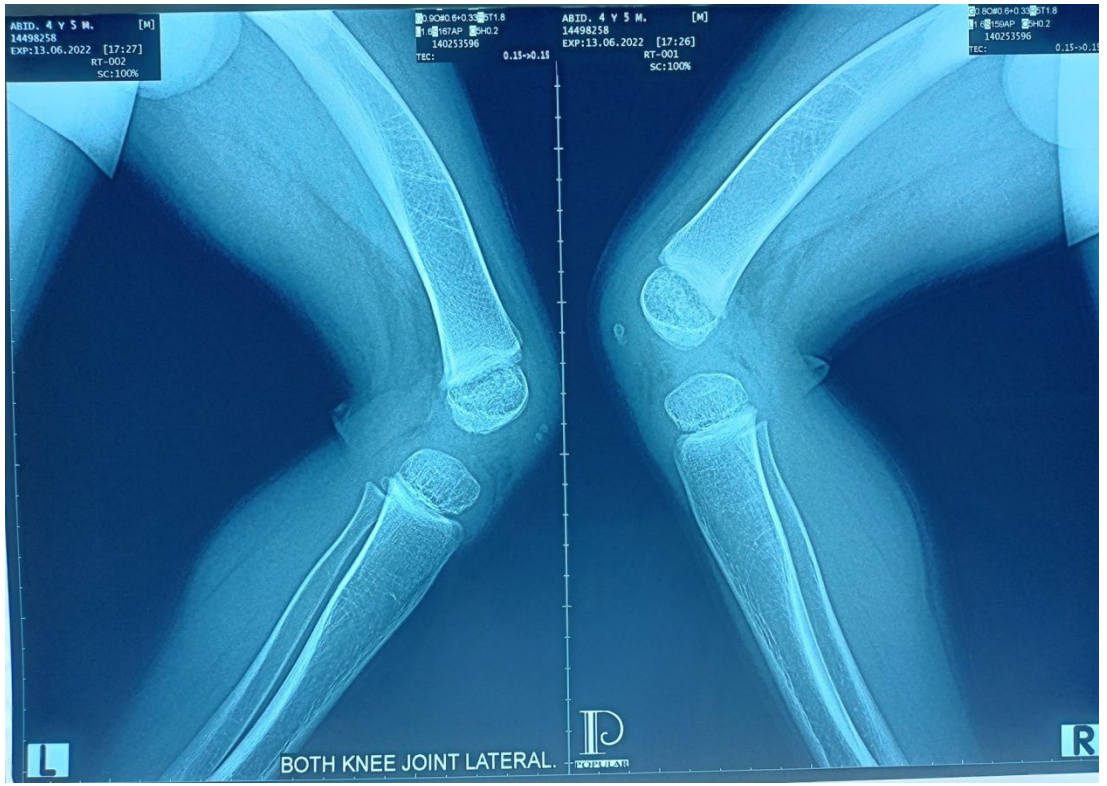


7 months after treatment





10 months after treatment



Take home message

- Rickets is a public-health problem in Bangladesh during the last two decades
- Treatment is effective by providing adequate amounts of the missing nutrient(s)
- Preventive programmes are needed
- Residual deformity is rare after medical treatment of nutritional rickets
- There is no specific orthopaedic treatment of nutritional rickets
- Renal / other causes of Rickets should be treated promptly
- Further studies are needed to determine the details of dosing and duration of calcium & Vitamin D, role of bracing and specific indications for surgical intervention

THANK YOU

Labaid pharma Quality First...