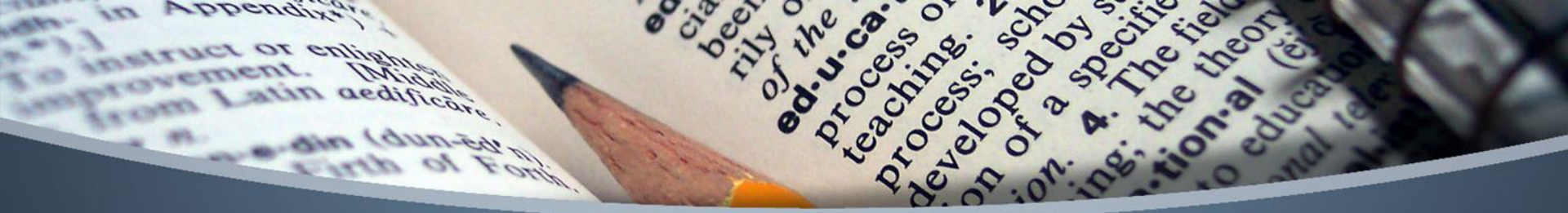
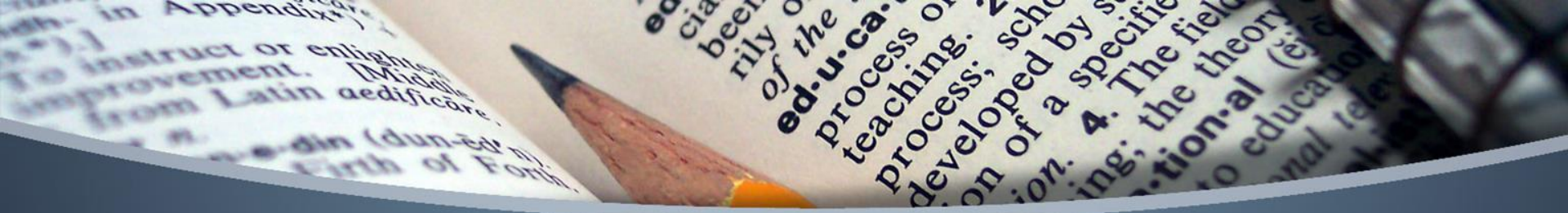


In The Name of GOD

Renal Envolvement in Galactosemia



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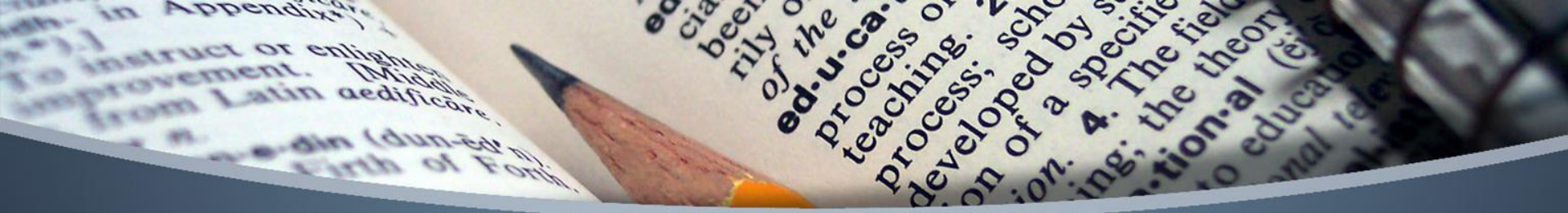
- Galactosemia denotes the elevated level of galactose in the blood and is found in 3 distinct inborn errors of galactose metabolism in 1 of the following enzymes:
- galactose-1-phosphate uridyl transferase (GALT).
- galactokinase (GALK).
- and uridine diphosphate galactose- 4-epimerase (GALE).
- The term galactosemia, although adequate for the deficiencies in any of these disorders, generally designates the transferase deficiency.



GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY GALACTOSEMIA (GALT)

- Transferase deficiency is an autosomal recessive disorder.
- Prenatal diagnosis can be performed by direct enzyme analysis of amniocytes or chorionic villi.
- Two forms of the deficiency exist: infants with complete or nearcomplete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency.
- Classic galactosemia is a serious disease with onset of symptoms typically by the 2nd half of the 1st wk of life.

- Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to **kidney, liver, ovary, eye and brain**.
- The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features within a few days or weeks after birth: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birthweight, and aminoaciduria.

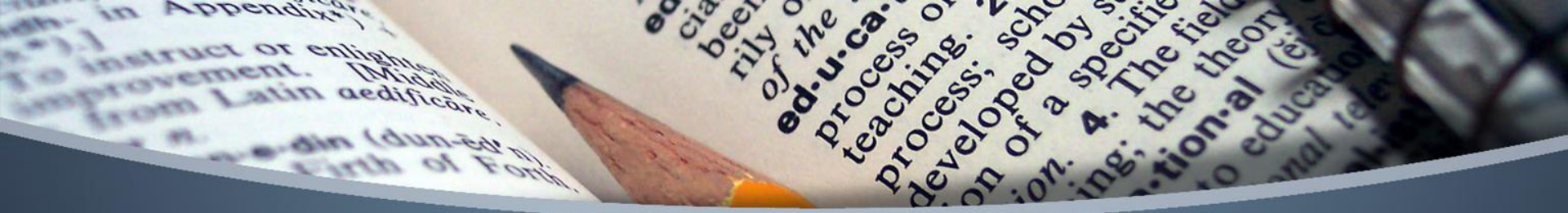
- Patients with galactosemia are at increased risk for Escherichia coli neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia.
- Pseudotumor cerebri can occur and cause a bulging fontanel.
- If untreated, death from liver and kidney failure and sepsis may follow within days.
- Complete withdrawal of lactose from the diet results in improvement of the acute symptoms.

- When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.
- Partial transferase deficiency is generally asymptomatic.
- It is more common than classic galactosemia and is diagnosed in newborn screening because of moderately elevated blood galactose and/or low transferase activity.

- The initial diagnosis of galactosemia is done by demonstration of a reducing substance in several urine specimens collected while the patient is on a diet containing human milk, cow's milk, or any other formula containing lactose.
- Galactose can be detected in urine, provided the milk feeding was within the last few hours and the child is not vomiting excessively.
- Direct enzyme assay using erythrocytes establishes the diagnosis.

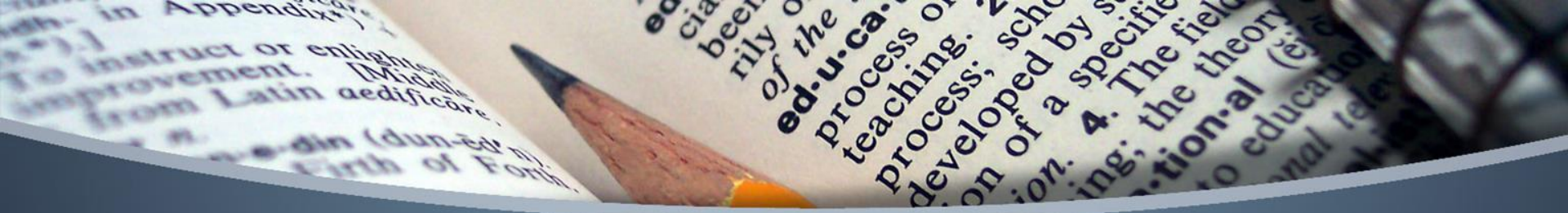
- All galactose containing foods should be removed from the diet on initial suspicion of galactosemia.
- Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula).
- **Elimination of galactose** from the diet along with **adequate calcium** supplementation **reverses** growth failure and renal and hepatic dysfunction.
- Cataracts regress, and most patients have no impairment of vision

- On longterm follow-up, however, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age.
- Hypergonadotropic hypogonadism is reported in 80% to >90% of female patients with classic galactosemia.
- Although most women with classic galactosemia are infertile when they reach childbearing age, a small number have given birth.



GALACTOKINASE DEFICIENCY (GALK)

- The deficient enzyme is galactokinase, which normally catalyzes the phosphorylation of galactose.
- Cataracts are usually the sole manifestation of galactokinase deficiency; pseudotumor cerebri is a rare complication.
- The affected infant is otherwise asymptomatic.
- Heterozygous carriers may be at risk for presenile cataracts.
- The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts.
- Transferase activity is normal.
- Treatment is dietary restriction of galactose.

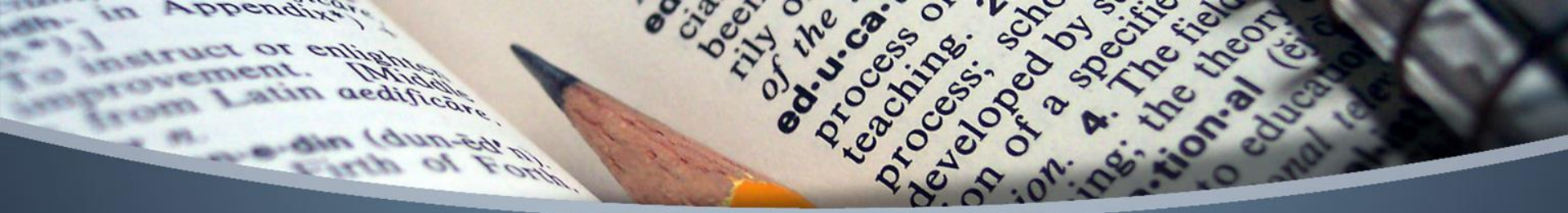


URIDINE DIPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY (GALE)

- There are 2 distinct forms of epimerase deficiency.
- The first is a benign form that is **diagnosed incidentally** through newborn screening programs.
- Affected individuals are **asymptomatic** because the enzyme deficiency is limited to leukocytes and erythrocytes.
- **This form does not require treatment.**
- The second variety is **severe** because the epimerase deficiency is more **generalized**.
- Clinical manifestations resemble transferase deficiency, with the additional symptoms of hypotonia and nerve deafness.

- Clinical symptoms improve with **restriction** of galactose in diet.
- Although the severe form of galactosemia is rare, it must be considered in a symptomatic patient with measurable galactose- 1-phosphate who has normal transferase activity.
- The abnormally accumulated metabolites are similar to those in transferase deficiency; however, there is also an increase in cellular uridine diphosphate (UDP) galactose.
- Diagnosis is confirmed by the **assay of epimerase** in erythrocytes.

- Patients are placed on a galactose-restricted diet rather than a galactose-free diet.
- Infants with the mild form of epimerase deficiency have not required treatment.
- Prenatal diagnosis for the severe form of epimerase deficiency can be done using an enzyme assay of cultured amniotic fluid cells.



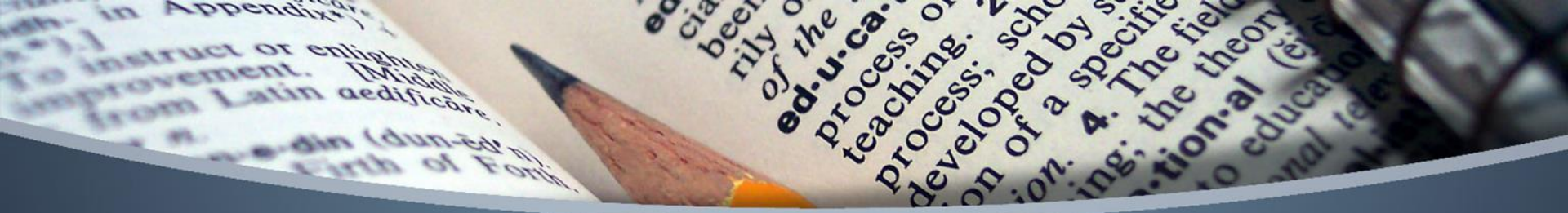
Fanconi syndrome

- The predominant sign of kidney damage in Galactosemia is Fanconi syndrom.
- Fanconi syndrom is due to distrbance in reabosorbtive function of proximal tubules.
- The renal proximal tubules reabsorb the majority of almost all of physiologically filtered load of proteins including of albumin, LMW proteins, amino acids, glucose, bicarbonate, sodium, choloride, phosphate and uric acid.
- FS includes hyperaminoaciduria, LMW proteinuria, hyperphosphaturia and bicarbonaturia.

- Causes of FS can be divided into three main categories namely hereditary, acquired and toxic subestances (Exogenous compounds).
- Most hereditary FS occures in context of cogenital inborn errors of the metabolism or more rarely as sporadic or familial disorders.
- Acquired forms are mostly secondry to immunoogical disorders, nephrotic syndrome, or accumulation of abnormal proteins in renal tubules.
- Exogenous substances include drugs, chemical compounds, and heavy metals.

Table 1 Causes of Fanconi syndrome

Hereditary
Dent disease
Lowe syndrome
Mitochondriopathies
Cystinosis
Galactosemia
Hereditary fructose intolerance
Glycogen storage disease type I (von Gierke disease)
Fanconi–Bickel syndrome
Tyrosinemia
Wilson disease
Lysinuric protein intolerance
Microvillous inclusion disease
Autosomal dominant Fanconi syndrome with macrosomia and young onset diabetes mellitus
Autosomal recessive Fanconi syndrome due to NaPi-IIa gene mutation
Fanconi syndrome secondary to EHHADH mutations
Idiopathic Fanconi syndrome
Acquired
Nephrotic syndrome
Myeloma
Sjögren syndrome
Renal transplantation
Acute tubulointerstitial nephritis with uveitis (TINU) syndrome
Autoimmune interstitial nephritis and membranous nephropathy
Anorexia nervosa
Untreated condition of distal renal tubular acidosis
Toxic
Drugs
Chemical compounds
Heavy metals



Sign and symptoms

- **Growth Retardation**
- FTT is a common feature of FS in children.
- The physiopathology of growth failure in FS is complex:
- Malnutrition
- Hypokalemia
- Hypophosphatemia
- and Metabolic acidosis
- Can all contribure to growth retardation in these patients.

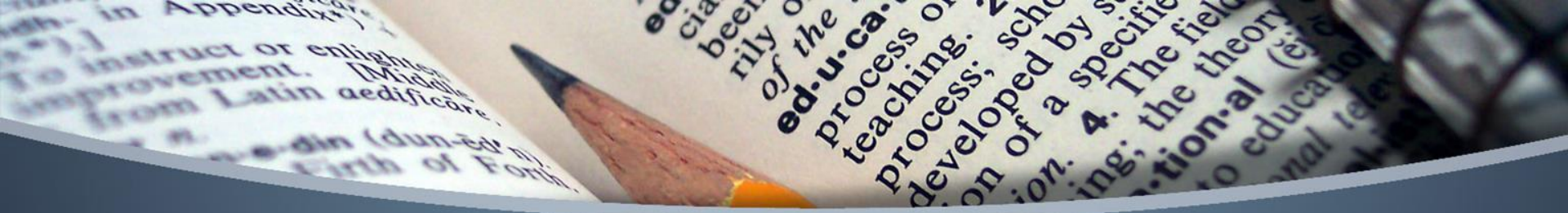
- **Polyuria , polydipsia, and dehydration** are frequenly observed.
- polyuria is secondry to the:
- osmotic diuresis
- and Urinary consentration defect
- That urinary concenteration defect is due to choronic hypokalemia and interestitial calcium deposits.
- Recurent acute episodes of fever due to dehydration are frequent manifestation of FS in infants.

- **Generalized Aminoaciduria**
- **Glucosuria** is a common manifestation in FS.
- patients can lose 0.5-20 g/day of glucose in their urines.
- **Hypophosphatemia**
- **Metabolic Acidosis**

- **Sodium losses:**
- 60-80% of filtered load of Na+ is reabsorbed in the proximal tubules in the normal condition.
- Renal Na+ reabsorbtion in the proximal tubules is decreased in patients with FS, this may cause hypotension and dehydration. some patients develop hyponatremia.

- **Potassium losses**:
- Hypokalemia is secondry to
- increase delivery of Na+ to the distal segments
- and activation of the RAAS by hypovolemia.
- Potassium wasting may cause life–threatening sever hypokalemia.

- **Hypercalciuria** is commonly observed in FS.
- **Hyperuricosuria** is often present in FS leading to secondry hypouricemia.
- **LMW proteinuria** in FS is caused by impaired reabsorbtion.



Theratment

- **Identification of the underlying cause for FS** is a first step in establishing a specific therapy in patients with FS.
- Avoidance of offending nutrients in galactosemia, Hereditary Froctose Intolerance, and tyrosinemia .
- Avoidance of Cu-rich foods in Wilson Disease are therapeutically critical.
- Specific treatments with Cu-chelating agents including :

D-penicillamine, trientine, and ammonium tetrathiomolybdate, and zinc are effective for WD.

- Immunosuppressive drugs are used for immunologically induced disorders including Sjögren syndrome, TINU syndrome, and autoimmune interstitial nephritis and membranous nephropathy.
- If exogenous substances are suspected as the cause of FS, they should be stopped or reduced in dose.
- When specific therapy does not exist, therapy is directed at the biochemical abnormalities secondary to renal solute and fluid losses and the metabolic bone diseases.

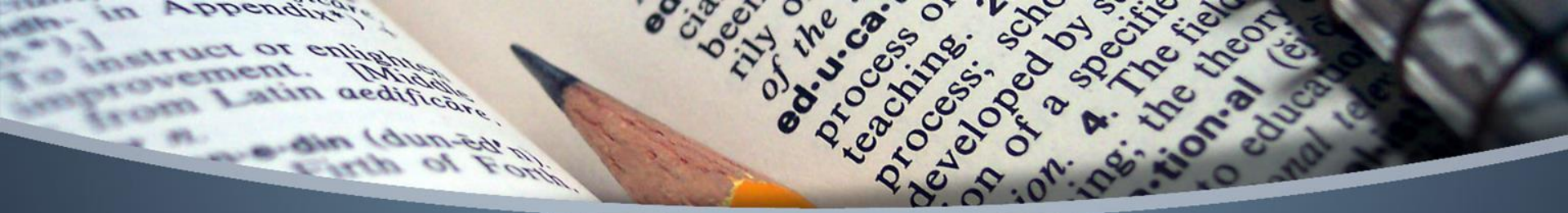
- Proximal renal tubular acidosis usually requires large amount of alkali (2–15 mEq/Kg / day) divided into four to six daily doses.
- High dose of alkali can produce volume expansion, further bicarbonate wasting, and potassium loss in the patients with FS.
- In very selected cases, 1–3 mg/Kg/day of hydrochlorothiazide can reduce the dose of alkali by preventing the volume expansion.

- Administration of potassium salt of citrate, bicarbonate, or acetate fulfills the dual purpose of treating acidosis and preventing hypokalemia.
- Sodium wasting and dehydration are treated with combination of sodium bicarbonate, citrate, and chloride, depending on the degree of acidosis.
- Ensuring adequate fluid and electrolyte intake is essential, especially in the case of infants or gastrointestinal diseases.
- Early intervention with intravenous replacement therapy is required for the patients with FS who manifest vomiting and diarrhea.

- Hypophosphatemia and impaired renal vitamin D3 metabolism in patients with FS lead to rickets and other metabolic bone diseases.
- Phosphate supplementation is necessary .
- Supplementation of 1,25- dihydroxyvitamin D3 is effective to treat or prevent rickets and osteomalacia.
- Vitamin D3 therapy improves the hypophosphatemia and lessens the risk of hyperparathyroidism.
- Hypercalcemia and hypercalciuria are toxic side effects of vitamin D3 therapy.
- An adequate amount of **physical activity, as well as appropriate diet** with **calcium, phosphate, and vitamin D3**, is necessary to prevent bone deformations .

- Growth failure is a major complication in FS.
- Despite correction of electrolyte abnormalities, some patients manifest severe growth retardation, especially those with cystinosis and FBS.
- Supplemental growth hormone has been used successfully in a few patients with FS .

- Aminoaciduria,
- glucosuria,
- LMW proteinuria,
- and uricosuria
- usually do not induce clinical symptoms and do not require specific treatments.



Thanks for your Attention