UNIT 13 NUTRITIONAL MANAGEMENT OF METABOLIC DISEASES-II: GOUT AND INBORN ERRORS OF METABOLISM

Structure

13.1 INTRODUCTION

Metabolic diseases, as you already know, refer to *those disorders in which the various reactions in the cells are effected (production of energy or utilization of energy) due to abnormal production of one or more hormones, or a deficiency of an enzyme.* Most *metabolic disorders* are genetic, though a few are "acquired" as a result of diet, toxins, infections, etc. Metabolic disorders or inborn errors of metabolism are inherited traits that result in the absence or reduced activity of a specific enzyme or cofactor. In general, these genetic *metabolic disorders* are caused by genetic defects that result in missing or improperly constructed enzymes necessary for some step in the metabolic process of the cell. Phenylketonuria, tyrosinemia, maple syrup urine disease, homocystinuria and galactosemia are some common metabolic diseases caused by genetic defects.

Gout, is yet another metabolic disease caused due to a disturbance of uric acid metabolism occurring chiefly in males, characterized by painful inflammation of the joints, especially of the feet and hands, and arthritic attacks resulting from elevated levels of uric acid in the blood and the deposition of urate crystals around the joints. The condition can become chronic and result in deformity. What is the cause of these metabolic disorders? How to diagnose and prevent them? What is the treatment? These are a few aspects discussed in this unit.

Objectives

After studying this unit, you will be able to:

- enumerate the etiological factors and symptoms of gout and few inborn errors of metabolism,

- describe the metabolic changes in these disease conditions and the complications,
- diagnose the condition(s),
- discuss management of the diseases, and
- provide guidelines for diet counseling, prevention and control.

13.2 GOUT

Gout is a chronic disease due to an inherited abnormality of purine metabolism. What are purines? You may recall studying about purines and their metabolism in Unit 8, sub section 8.3.3, in the Nutritional Biochemistry Course (MFN-002). Purine, is a nitrogenous base found in the nucleotides for the synthesis of DNA and RNA. Let us now understand the role of purines and protein in precipitating the metabolic disorder gout.

13.2.1 Role of Protein and Purines

Cellular materials of plants, grams and legumes and animal glandular organ meats (liver, pancreas brain, kidneys) contain nucleoproteins. The nucleoproteins are digested and converted to purines, which are finally oxidized to uric acid. The steps involved in degradation of purine to uric acid are diagrammatically presented in Figure 13.1. Uric acid, therefore, is a substance that results from the breakdown of purines, which are part of all human tissue and are found in many foods. You may also recall studying that the body can also synthesize proteins from carbon and nitrogen compounds (acetic acid, glycine) from carbohydrates, protein or fat and give rise to uric acid.

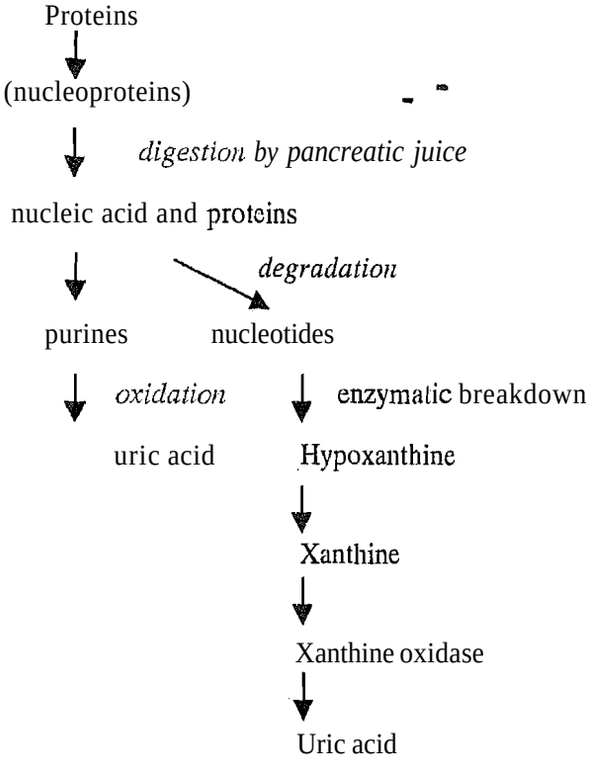

Figure 13.1: Degradation of purine to uric acid

It is important to understand that uric acid is normally excreted in the urine. However, excess of uric acid produced by the body from protein we eat and/or internal cellular or N_2 utilization can increase the uric acid levels of the blood. The range of uric acid is 2-7 mg/100 ml. If the level of uric acid in our body is above 7 mg/100 ml, we have a risk of developing the disorder called gout. In severe gout, the levels of uric acid may go up to 20 mg/100 ml.

Normally, uric acid is dissolved in the blood and passed through the kidneys into the urine, where it is eliminated, If the body increases its production of uric acid or if the

kidneys do not eliminate enough uric acid from the body, levels of it build up in the blood resulting in a condition called hyperuricemia. I-Iyperuricemia also may result when a person eats too many high-purine foods, such as liver, dried beans and peas and gravies. Hyperuricemia is not a disease and by itself is not dangerous. However, if excess uric acid crystals form because of hyperuricemia, gout can develop. The excess crystals build up in the joint spaces, causing inflammation. Deposits of uric acid, can appear as lumps under the skin around the joints and at the rim of the ear. In addition, uric acid crystals can collect in the kidneys and cause kidney stones.

Having understood the role of purines in the development of gout, let us next review its etiopathology.

13.2.2 Etiopathology

Who is likely to develop gout? What are the risk factors? Let us find out.

Gout is caused when there is over production of uric acid in normal purine metabolism in the body. In fact, a number of risk factors are related to the development of hyperuricemia and gout. These factors include:

- Hereditary : Genetics may play-a role in determining a person's risk, since up to 18 percent of people with gout have a family history of the disease.

  Gender and age are related to the risk of developing gout; it is more common in men than in women and more common in adults than in children.

- Being overweight increases the risk of developing hyperuricemia and gout because there is more tissue available for turnover or breakdown, which leads to excess uric acid production.

- Drinking too much alcohol can lead to hyperuricernia because it interferes with the removal of uric acid from the body.

- Eating too many foods rich in purines can cause or aggravate gout in some people.

  An enzyme defect that interferes with the way the body breaks down purines causes gout in a small number of people, many of whom have a family history of gout.

- Exposure to lead in the environment can cause **gout.,**

The disease predominantly affects males after the age of 35 years. Gout starts suddenly with an arthritic pain in the big toe and may continue up to the leg. Small injury or excessive exertion can precipitate the attack. Sometimes exposure to cold, surgery, minor trauma can trigger the attack.

Secondary gout could be due to genetic abnormality of uric acid metabolism.

Let us dwell further on the diagnosis and clinical features/complications of gout.

13.2.3 Clinical Features and Complications

You may be enjoying good health but may suddenly get a severe attack. You wake up in the middle of the night, and your big toe feels as if it is on fire. It is hot, swollen and so tender that even the weight of a blanket on it seems intolerable. These problems could indicate an acute attack of gout characterized by sudden, severe attacks of pain, redness and tenderness in joints.

The big toe gets affected mostly but in chronic conditions, it could be the elbow or the helix (outer fleshy ridge of the ear) can also be the site. The uric acid crystals (called tophi) deposit as urate'in the joint causing swelling and tenderness of the joint with severe pain. Figure **13.2** illustrates the uric acid crystals in the big toe. Presence of uric acid crystals in the joint fluid, therefore, is an important diagnostic test for the

disease. The doctor will take a sample of the joint fluid and look for the presence of uric acid crystals. Gout is also easily identifiable through a physical examinalion The skin is tense, red and shiny and may be associated with fever, anorexia (lack of appetite) and malaise (unwell feeling)

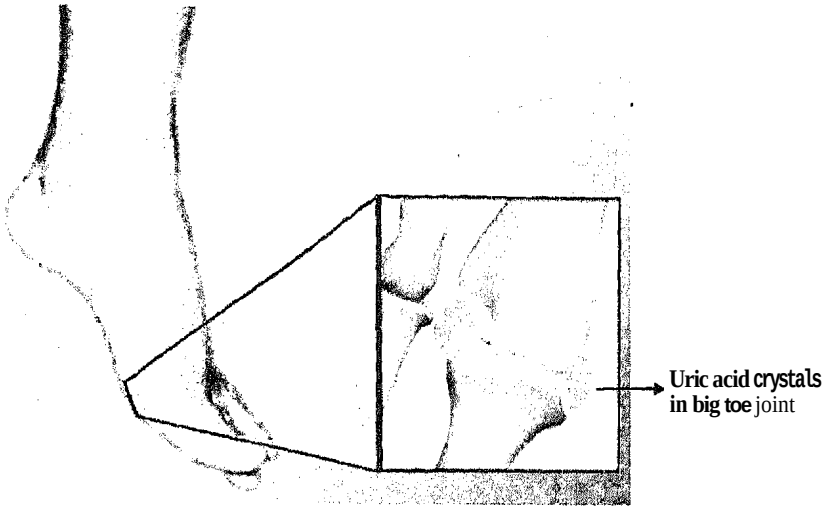

Figure 13.2: Uric acid crystals in the big toe

The main complication of chronic gout is, however, chronic renal failure. That is a big problem! So, what can we do to prevent and treat this metabolic disorder? Let us read the next section and find out.

13.2.4 Management of Gout

The goals of therapy or management of gout is based on the following aspects:

- early resolution of inflammation,
- prevention of recurrent attacks, and
- reversal of complications arising from deposition of urate crystals in joints, kidneys.

To help meet these goals the treatment is based on drug and diet therapy. Let us consider these one by one.

Dietary Management

Treatment for gout often include a diet of lower purine intake. Indeed, about one third of the body's uric acid can be attributed to diet. Changing the diet to foods with lower purines can help relieve the symptoms, as well as, address the actual problem of hyperuricemia (elevated levels of uric acid in the blood).

Since diet is an important factor, exclusion of foods extremely high in purines may be helpful. All meats, fish, poultry contain moderate to high amounts of purine and pulses and lentils need to be avoided. Some vegetables contain low to moderate amounts of purine. Efforts to greatly restrict these foods are generally unnecessary because of their insignificant effect as compared to medications. In fact, drugs are so effective in lowering the serum urate concentration that rigid restriction of dietary purines is rarely necessary. When purine is restricted, as in case of severe gout, it should be restricted to 100-150 mg/day. Some high and low-sources of purines are listed in Table 13.1. This list can serve as a handy guide for the patients in selection of food items. List of foods permitted and to be excluded from the diet of a gout patient are summarized in Table 13.2. The thumb rule for dietary management is to advice the patient to try to cut down or avoid:

- Red meats.
- Organ meats such as brains, kidneys, liver and heart.
- Shellfish such as mussels, oysters, sea eggs etc.
- Peas and beans.
- Alcohol, especially beer and wine.

Table 13.1: Dietary recommendations for gout

Avoid foods highest in purines (150 - 825 mg / 100 gm)	*Limit foods containing moderate amount of purines (50 -150 mg/ 100 gm)*	*Consume foods lowest in purines (0-50 mg / 100 gm)*
Brain Kidney Liver Gravies Herring Sardines Broth Meat Extracts Minced meat Sweet Breads	Whole grain bread or cereals Cauliflower Spinach Fresh saltwater fish Legumes (beans, peas and lentils) Meat soups and broth Mushrooms Asparagus Oatmeal Chicken Spinach Wheat germ and bran	Beverages (coffee, tea and soda) Refined cereals Cheese Eggs Fat Fruits and fruit juices Milk Nuts Sugar syrup Vegetable creamed soups Macaroni/Noodles

Table 13.2: Food items for a patient with gout

Permitted	Excluded
Refined cereals and cereal products-cornflakes, white bread, pasta, flour, arrow-root, sago, tapioca and cakes Milk, milk products and eggs Lettuce, tomatoes and green vegetables Vegetables and cream soups made from vegetables Sugar and sweets, gelatin Butter, polyunsaturated margarine, and fats of any kind Fruit, nuts, peanut butter Beverages – water, fruit juice, cordials,' cabonated drinks, tea, coffee and cocoa	Beans, peas, lentils, spinach, oatmeal, asparagus, cauliflower, mushrooms Fish, seafood Meats, poultry or other flesh; meat extract, gravies, marmite Liver, kidney, Yeast and beer praducts, beer alcohol

Intake of fluids should be encouraged to assist with the excretion of uric acid and to minimize the possibility of renal calculi formation. Fluid intake ≥ = 3 L/day is desirable for all gouty patients, especially for those who chronically pass uric acid or have calcium oxalate renal calculi. Because urate excretion tends to be reduced by fats and enhanced by carbohydrates; the diet should be relatively high in carbohydrates (providing 50% to 55% of calories) and low in fat (30% of calories), modified in cholesterol (≤ 300 mg/day) and protein intake should be moderate.

Further, since being overweight increases the risk of hyperuricemia, patients should be encouraged to lose weight during a quiescent phase of the disease. Finally, avoidance of alcohol should be recommended. The nutritional care summary, and a sample menu for gout patients is presented next.

Nutritional care: *Summary*

Advice the patient to:

- Maintain ideal weight.
- Avoid high purine content foods.
- Take moderate protein, use low fat dairy products, eggs and cheese.
- Take liberal carbohydrates, refined cereals, beverages, fruits and fruit juices, vegetables.
- Take a low fat diet.
- Restrict/eliminate alcohol.
- Take liberal amounts of fluid.

SAMPLE MENU FOR A PATIENT WITH GOUT

Western Diet	Vegetarian Diet
Breakfast	
Breakfast cereal Bread/toast with butter and fat/jam Tea/Coffee	Breakfast cereal Toast/khakhra/Dosa Tea/coffee
Mid-morning	
Tea/coffee Biscuits	Tea/coffee Cream crackers
Lunch	
Shepherd's pie with gravy Parsley potatoes Steamed green beans Bread and butter Pudding	Chapatties/Rice Tomato paneer curry Aloo Methi Butter
Mid-afternoon	
Tea/coffee Biscuits	Tea/coffee Biscuits
Dinner	
Smoked haddock with egg sauce Mashed potatoes Shredded cabbage Tomato and cucumber salad Pudding	Vegetable pulao Kadhi (Spinach pakodi) Salad (cucumber and tomato) Kheer

Diet is an auxiliary measure to medications. Next, let us review the drug management for gout patients.

Drug Management

Drugs are so effective in lowering the serum urate concentration that rigid restriction of dietary purines is rarely necessary. Uricosuric drugs are used to increase uric acid excretion, Allopurinol inhibits the action of enzyme xanthine oxidase, which then produces less uric acid. These drugs must be taken close to the meals as prolonged use could damage the intestinal mucosa resulting in reduced absorption of several

nutrients and large quantities of water. The person will loose weight gradually and must avoid excessive intake of alcohol.

With this, we end our discussion on the management of gout. Let us revise what we have learnt so far by answering the check your progress exercise 1.

Check Your Progress **Exercise 1**

1. Answer the following:

   a) Give the normal blood uric acid levels.

   .....

   b) Mention three characteristic features of gout.

   .....

   c) List three foods highest in purine content (150-825 mg/100 gm)

   .....

   d) List three foods lowest in purine content (0-50 mg/100 gm)

   .....

   e) Define hyperuricemia.

   .....

2. Fill in the blanks:

   a) Gout is a chronic disease due to the abnormality of ....metabolism.

   b) Nucleoproteins are present in .... meats.

   c) Uricosuric drugs increase .....excretion.

   d) Tophi are deposits of .....crystals.

   e) Nucleoproteins are oxidized to.....

3. Give five important aspects of the nutritional care summary.

   .....

   .....

   .....

Next, in this unit we shall learn about the inborn errors of metabolism, which you may recall reading earlier in this unit, are inherited traits that result in the absence or reduced activity of a specific enzyme or a co-factor,

13.3 INBORN ERRORS OF METABOLISM

We are now going to learn about some of the disorders caused by inborn error of metabolism namely phenylketonuria, tyrosinemia, maple syrup urine disease, homocystinuria and galactosemia. You may recall studying about these metabolic disorders earlier in your Nutritional Biochemistry Course (MFN-002) in Unit 12. We hope you remember the information presented there. If not, we suggest yau look up this unit now and read the information given there along with the matter presented here in this section. This will help you consolidate your understanding on this important topic.

An inborn error of metabolism is a genetic error that alters the production of a protein. In many cases, the protein is an enzyme. When the enzyme is absent, the functions that depend on that enzyme can not proceed. Incompletely metabolized products accumulate in the body. This leads to a variety of problems and in many cases it becomes fatal. Further, this imbalance creates problems in other metabolic pathways that adds to existing problem. The goal of therapy is to prevent the accumulation of toxic metabolites and to replace essential nutrients that are deficient as a result of the defective metabolic pathway.

In these metabolic disorders, since there is an inability to metabolize a specific amino acid the basis of dietary management is to restrict the offending amino acid(s) by means of a special low protein diet. In addition, to meet the requirement for growth and development it is essential to supplement the diet with the appropriate amino acid mixture, which does not contain the offending amino acid.

Low-protein food products are recommended to persons with particular types of metabolic disorders such as homocystinuria (HCU), phenylketonuria (PKU), tyrosinemia etc. Each of these disorders requires food products, which are low, in particular type of amino acid i.e. methonine in the case of HCU, phenylalanine in the case of PKU. However, it is not easy to find high protein foods with low content of these amino acids. Hence, the patients are given low-protein foods as you would realize while studying these disorders.

We begin our study of these metabolic disorders with phenylketonuria.

13.3.1 Phenylketonuria

The essential amino acid phenylketonuria is utilized for tissue protein synthesis and hydroxylated to form tyrosine. The hydroxylation reaction requires *phenylalanine* ***hydroxylase.*** Phenylketonuria (PKU) is a group of inherited disorders of phenylalanine metabolism caused by impaired ***phenylulanine hydroxylase*** activity. PKU cannot break down phenylalanine into another amino acid, tyrosine. Phenylalanine then builds up in the bloodstream and causes brain damage.

Phenylketonuria, commonly referred to as PKU, occurs at the age of 3 to 6 months and is characterized by developmental delay, microcephaly (abnormally small head), abnormal electro-encephalogram, eczema, musty odour and hyper activity. If untreated before three weeks of age, the metabolic imbalance produces irreversible mental retardation. The defect in metabolism in classic PKU is associated with less than 2% activity of normal phenylalanine hydroxylase.

Accumulation of phenylalanine and its catabolic products leads to central nervous system damage. The extent of damage caused to the brain depends on the time at which the insult occurs. Deficient myelination and abnormalities in brain proteolipids and proteins occur in late gestation and during first 6 to 9 months of life. In the fully matured brain, the synthesis of neurotransmitters is affected. This might cause nerve degeneration, behavioural difficulties and delayed development.

Aprecise diagnosis is necessary to establish the mode of therapy. Patients with initial blood phenylketonuria level of 121 m mol/l (> 2 mg/dl) should repeat the test. There are several laboratory methods to confirm the disorder. These include ion exchange chromatography for quantification of amino acid concentration, determination of genotype of parents, and assays of bioprotein and dihydropteridine reductase.

Phenylketonuria can now be well controlled by special diet therapy. A low-phenylalanine diet effectively controls the serum phenylalanine levels. This will help to prevent clinical symptoms and promote normal growth and development. Remember that phenylalanine is an essential amino acid and therefore can not be totally avoided. Based on many studies, the following guidelines for dietary management of PKU are being used effectively.

1. Estimate the daily energy, protein and phenylalanine requirements (child's age and weight dependent).
2. Calculate the amount of special formula to be given to provide the recommended allowances.
3. Assess the amounts of other foods to be used.

Lofenalac is a formula which is nutritionally complete except for phenylalanine. This formula is the main diet for the infants suffering from PKU. The diet should be progressed as for a normal infant and child. Utmost care should be taken while introducing new foods to them. Effort should be taken to develop a variety of recipes using foods low in phenylalanine. Phenylalanine is found in milk, cheese, eggs, fish, meat, beans, nuts, and infant formulas (both regular and soy), and to a lesser extent in cereals, vegetables and fruit. People with PKU cannot break down phenylalanine into another amino acid, tyrosine. Phenylalanine then builds up in the bloodstream and causes brain damage as you learnt earlier. To avoid this, a person can eat a healthy diet that includes a low-phenylalanine formula, fruits, vegetables, sugars and other low-protein foods. A list of foods highlighting the phenylalaine, energy and protein content of some common foods is presented in Table 13.3. Figure 13.3, also illustrates the PKU food pyramid, which can be used while counseling patients and their caretakers regarding what to eat and what not to eat.

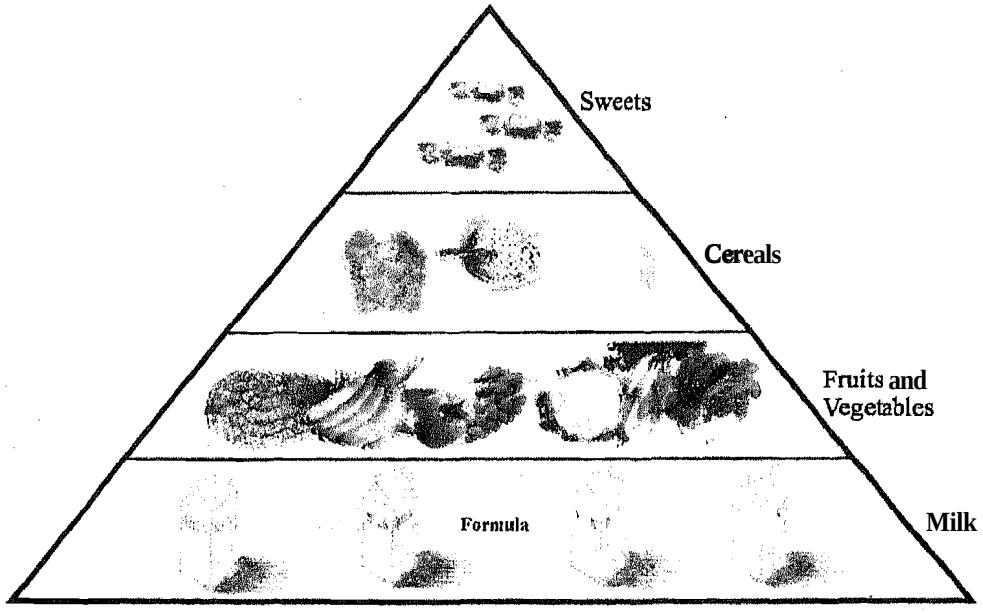

Figure 13.3: PKU food pyramid

The majority of foods for a PKU patient should come from the bottom half of the pyramid. As you may have observed in Figure 13.3, this contains the phenylalanine – free formula. Lofenalac in one such formula. This bottom layer provides the major food needs. The next layer of the PKU food pyramid is built of fruits and vegetables which contain low levels of phenyalanine. Eating a variety of foods (pineapple, banana, grapes, apple, cauliflower, carrots and greens) will help the patient grow strong and healthy. The next layer of the PKU food pyramid is built of low protein foods such as breads, pasta, cereal, and rice. This layer does not contain as much food as the first two layers. Eating low protein foods from this layer will help the patient remain healthy. The top of the pyramid is built of candies and treats, These foods should be eaten just on special days. The foods outside the target as illustrated in Figure 13.4 (in colour red) are not included in the low-phenylalanine meal plan. These are high protein foods, such as milk, dairy products, meat, fish, chicken, eggs, beans, and nuts. These foods cause high blood phenylalanine levels for people with PKU.

Dietary counseling based on the food pyramid concept illustrated in Figure 13.3 and the food to target concept illustrated in Figure 13.4 will be quite useful in the management of the disease.

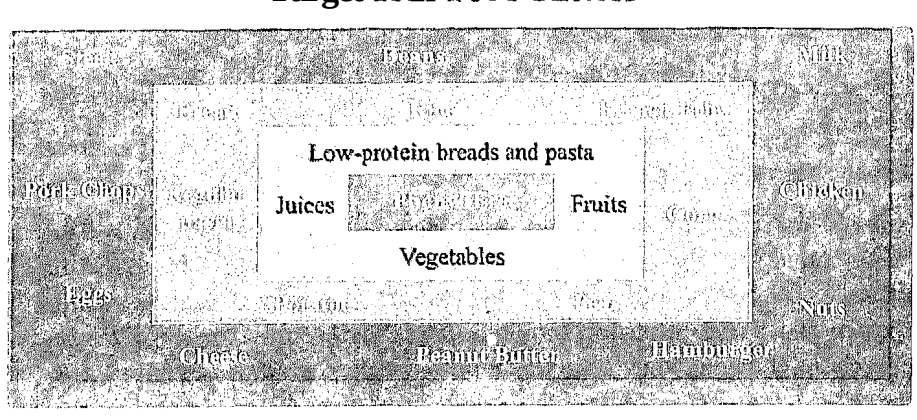

Figure 13.4: Food target

Table 13.3: Food list for PKU patients

Food	Amount	Phenylalanine (milligrams)	Protein (grams)	Energy (calories)
FRUITS AND VEGETABLES				
Fruits				
Apple, fresh, whole, medium	1	9	0.4	106
Cantaloupe, cubes	½cup	21	0.6	22
Grapes, red or green	10	9	0.3	36
Kiwi, fresh medium, peeled	1	6	0.2	12
Orange, fresh, whole medium, peeled	1	38	1.5	70
Strawberries, fresh, whole, medium	5	7	0.5	24
Pears, fresh, whole, medium	1	17	0.7	98
Vegetables				
Broccoli, cooked	½cup	33	1.2	11
Carrot, raw, whole, medium	1	29	0.9	39
Celery, raw, medium stalk	1	10	0.3	7
Corn, cooked or canned	½cup	100	1.8	66
Mushrooms, sliced	½cup	28	0.7	9
Peas, cooked	½cup	144	3.6	60
Potato, all colors, baked or boiled, diced	½cup	72	1.6	66
Tomatoes, raw diced	½cup	18	0.7	17
BEVERAGES				
Apple juice	1 cup	trace	trace	120
Orange juice	1 cup	30	1.4	112
GRAIN PRODUCTS				
Noodels, Macaroni, and Spaghetti				
Macaroni (dry)	1/3 cup	217	2.3	67
Rice and Grains				
While Rice, Long grain (raw)	1/3 cup	234	4.4	224
Bread and Bread Products				
Bread, whole wheat	1 slice	146	3.0	70
VERY HIGH PROTEIN				
Dairy and Eggs				
Egg, whole, medium	1	300	5.6	67
Milk	1 cup	392	8.0	120.
Nuts, Nut Butters, and Sleeds				
Peanut butter, creamy-style	2 Tbsp	488	9.4	190

The optimal age for discontinuing the diet is not known. Phenylalanine restriction is recommended during pregnancy of the phenylketonuric woman. It will be better if these women restrict the diet at the time of conception, in order to prevent the risk of mental retardation, microcephaly and congenital heart disease in infants.

Some important facts related to PKU and its management are highlighted in Box 13.1.

Box 13.1	Important Facts Related to PKU

- The brain of a fetus with classic PKU develops normally in intrauterine stage.
- The critical period of human brain growth and development extends over the first 6 months of neonatal life requiring that dietary therapy to be instituted right after birth.
- Myelination may not be completed until 5 or 6 years of age and hence dietary restriction must be rigidly followed.
- The proportion of dietary phenylalanine that is utilized for protein synthesis varies with age – 50-60% during early growth and only about 10% for normal adult.
- Blood phenylalanine levels must be maintained between 3-15 mg/dl.
- For a phenylalanine- restricted diet 50-80% of the natural protein must be replaced by a protein preparation that contains little or no phenylalanine.
- Most natural proteins contain about 50 mg phenylalanine/g protein.
- The composition of the preparation should meet all nutrient requirements.
- Tyrosine must be supplemented in the diet.
- Usually one-third to one-tenth of normal phenlyalanine content is recommended.
- Infections in the infant should be avoided to prevent tissue catabolism and increased phenylalanine levels in blood.
- Higher dietary phenylalanine intakes may be allowed after 6-10 years of age along with frequent clinical and biochemical supervision.
- Strict dietary restrictions should be adhered to by phenylketonuric women during pregnancy to prevent damage to the foetus.

With these guidelines, we end our study of PKU. Next, we move on to tyrosinemia.

13.3.2 Tyrosinemia

In the Nutritional Biochemistry Course in Unit 12, sub section 12.3.3, you may recall studying about tyrosinemia. There are two forms of hereditary tyrosinemia. They are ***tyrosinemia Type I and tyrosinemia Type II***. Type *I* was thought to be due to a deficiency of ***parahydroxy phenylpyruvic acid oxidase***. But recently secondary impairment in this enzyme has been attributed to a primary defect of ***hepatic fumaryl acetoacetate*** hydrolase. Patients with deficiency show renal tubular impairment, hypophosphatemic rickets, liver failure and hypertension. The plasma concentrations of phenylalanine and tyrosine are elevated.

In tyrosinemia Type II, there is a very elevated concentration of blood and urine tyrosine. Increase in urinary phenolic acids, N-acetyltyrosine and tyramine is seen.

Other symptoms include corneal erosions, hyperkeratosis on the fingers and palms and sole of the feet. Mental retardation may occur.

Dietary modification includes nutritional support that allows normal growth and development. Plasma phenylalanine concentration between the range of 40 and 80 mmol and tyrosine concentration between 50 and 150 μ mol, should be maintained. Phenylalanine - tyrosine restricted diet is advocated. Initially a liydrolysate low in phenylalanine and tyrosine is used with small amounts of milk. If there is an elevation in methionine a syntheticmixture without tyrosine, phenylalanine and methionine should be used.

Individuals with tyrosinemia have food patterns very similar to the one for PKU discussed above. PKU is more common than tyrosinemia. Foods that are high in tyrosine and phenylalanine are high in protein. Thus, children with tyrosinemia should eat foods that are low in protein. Each child can "tolerate" a different amount of tyrosine/phenylalanine, so each child will have a slightly different food pattern. The most important food for a child with tyrosinemia, however, is his/her formula. Formula provides energy (calories), protein, and the vitamins and minerals (including those that are found in high protein foods).

Foods that all children with tyrosinemia should avoid are foods rich in protein i.e. meat, chicken, fish, milk, cheese, beans and legumes, peanut butter, and eggs. These foods are often called "no" foods and are those foods outside the target as illustrated in Figure 13.4 above.

Foods with moderate amounts of protein can be eaten in limited amounts. These foods include grains, bread, pasta, rice, potatoes, corn, and peas. Foods with little or no protein are the mainstay (in addition to formula). These foods include most fruits and vegetables. Low protein products, including bread, pasta, noodles, rice etc. may also be used. Therefore, we may conclude by saying that bread, cereals, fruits and vegetables and fats are allowed. Ahigh carbohydrate feed, providing 65-75% of calories may be recommended.

Next, let us review the management of maple syrup urine disease which is yet another metabolic disorder found in children.

13.3.3 Maple Syrup Urine Disease

Maple Syrup Urine Disease (MSUD) is a group of inherited metabolic disorders of three branched chain amino acids (BCAA) namely *leucine, isoleucine* and *valine*. These three amino acids are normally metabolised to ketoacids and then decarboxylated to simple acids. In MSUD disorder an oxidative decarboxylase in the white blood cells is missing. Since the carboxyl groups can not be removed there is an accumulation of branched chain ketoacids and their amino acid precursors. The branched chain a ketoacids are relatively acute neurotoxins and probably interfere with oxygen consumption and ATP production in the medullary reticular substance of the brain. There is a progressive neurologic dysfunction and production of fragrant urine with the odour of burnt sugar or maple syrup.

Infants with MSUD appear normal at birth. Once they are fed on protein containing feed, they start showing the classic symptoms. Neurologic impairment in the new born is manifested by poor sucking, irregular respiration, and intermittent periods of rigidity and flaccidity.

Clinical manifestations are expressed upon protein loading or with febrile illness. In most severely impaired enzyme deficiency, seizures, apnea (brief pause in breathing) and death may occur. In untreated patients with classic MSUD who survive beyond early infancy, there is retardation of physical and mental development. Early diagnosis and therapy lead to normal growth and development.

Most infants with classic MSUD have greater than 8 mg/dl leucine at 72 hours of age. Diagnosis is confirmed using ion exchange chromatography to quantify plasma isoleucine, leucine, valine and alloisoleucine, and urinary branched chain *a* keto acids.

Special feeds containing energy and proteins without the branched chain amino acids can be given to the infants. In some infants if the orogastric feeding is not acceptable, gastrostomy is initiated for initial care during the neonatal period. Long-term therapy for MSUD is by means of diet. Patients with classic MSUD are unable to terminate diet. Plasma concentration of isoleucine, leucine and valine should be maintained in the range of 40 to 90 m mol; 80 to 200 *m* mol, 200 to 425 m mol, respectively.

Long-term treatment of MSUD involves a carefully controlled diet which strictly limits dietary protein in order to prevent the accumulation of BCAAs in the blood. The major component of the diet is a special formula designed for children with MSUD. These MSUD formulas do not contain any leucine, isoleucine or valine but are otherwise nutritionallycomplete. They contain all the necessary vitamins, minerals, calories and the other amino acids needed for growth. The diet of a MSUD patient (child) should therefore involve:

- Measured quantities of natural protein or leucine from foods.
- A BCAA free protein, vitamin and mineral supplement.
- The natural protein and vitamin/mineral supplement should ideally be evenly distributed through the day to allow maximum utilization of the amino acids for protein anabolism, and for tolerance of the supplement.
- Free foods that are low in BCAA including sugars, fats and oils, as well as, foods specifically produced for a low protein diet (breads, biscuits, pastas elc.) and suppleinents be given.
- Supplements of valine and/or isoleucine are helpful.

The next metabolic disorder under review is homocystinuria.

13.3.4 Homocystinuria

Homocystinuria may result from errors of methionine metabolism. This produces defects in the function of *cystathionine* b ***synthase*** or ***5-mcthyltctrahydrofolate homocysteine methyltransferase.***

The most common form of homocystinuria is caused by a deficiency of the enzyme ***cystathionine*** b ***synthase.*** This enzyme is essential for the conversion of homocysteine to cystathionine. Severely impaired enzyme function produces accumulation of plasma homocysteine and methionine and decreased cysteine in cells. Large amounts of homocystine are excreted in the urine. If this is unattended early'in life, skeletal changes, dislocated lenses, intravascular thrombosis, osteoporosis and mental retardation might occur,

Therapeutic dose of pyridoxine (1g/day) is usually tried in all palients with hypermethioninernia and homocystinemia. For patients who do not respond to pyridoxine, methionine restricted diet supplemented with L-cysteine is used. If plasma folate concentrations are below normal, folate should be given as a supplement. What are the special preparations and foods low in or free of methionine? Table 13.4 lists some common foods and food items rich and low in methionine. This list can be referred to while planning diet plans for patients suffering from homocystinuria. While planning the diet for homocystinuria one must consider energy, protein, methionine, cysteine, folate, vitamins B_6 and B_{12}, and fluid needs.

Table **13.4:** Foods and **food** items containing varying levels of **methionine**

Vegetables that are ***high*** in methionine/ per 100 gm (more than 25 mg-50 mg of methionine/ 100 gm of the product)	Broccoli, Mushroom, Cauliflower, Avocado, Bean sprouts, Potatoes,
Vegetables that are ***high*** in methionine/ per 100 gm (more than 50 mg of methionine/ 100 gm of the product)	Spinach, Green Peas, Corn (boiled),
Vegetables that are *low* in methionine / per 100 gm (less than 25 mg / 100 gm of the product)	Carrot ,Beetroot (boiled), Tomatoes, Green Pepper, Red Pepper, Yellow Pepper, Eggplant, Green Cabbage and Red Cabbage, Kale (boiled), Lettuce, Cucumber, Green Beans (boiled), Red and Brown Onions, Celery, Okra
Fruits that are ***medium high*** in methionine 25-50 mg of methionine/100 gm of the product)	Mandarin Oranges
Fruits that are ***low*** in rmethionine(less than' 25mg of methioninel 100 gm of the product)	Watermelon, Cantaloupe, Honeydew melon, Apples, Pears, Cranberries, Raspberries, Blueberries, Strawberries, Mango, Plums, Dates (dried), Peaches, Nectarines, Banana, Pineapple, Apricots
Snacks that are moderate in methionine (25-50 mg of methionine/ 28 gm of the product)	Potato chips (28 gm), French Fries(10 pieces)
Snacks that are ***high*** in methonine (more than 50 mg of methionine/ 28 gm of the product)	All nuts, like Peanuts, Pistachio and Popcorn
Other foods that arc ***high*** in methionine (more than 100 rng of methionine/ 100 gm of the product)	Tofu, dried beans like Kidney beans, Black beans, Tempeh

The discussion so far focused on the disorders linked to protein metabolism. Disorders of carbohydrate metabolism also exist. One such disorder is galactosemia which is also an inherited disorder characterized by an ability of the body to utilize galactose. Let us get to know more about this disorder.

13.3.5 Galactosemia

Galactosemia is a genetic disorder caused by deficient functioning of any of these three enzymes namely *galactokinase, galactose -1 - phosphate uridyl transferase*, or UDP *galactose - 4- epimerase*. Galactose derived from the hydrolysis of lactose in the intestine is absorbed normally. But in the absence of *gal-1-P-transferase* it leads to the accumulation of galactose, galactose-1-phosphate, and galactitol in the blood and tissues. Accumulation of gal-1-P reduces the intracellular phosphate for high energy phosphate bonds. Thus ATP, GTP and CTP are reduced.

Patients with galactokinase deficiency suffer only from cataract, Galactitol accumulates in the lens of the eye creating an osmotic gradient that allows the glutathione from the lens to efflux. Due to this the concentration of glutathione in the lens is decreased. Glutathione peroxidase and hydrogen peroxidase are inactivated. As a result hydrogen peroxide accumulates in the lens denaturing the proteins of the lens. This leads to the production of lenticular cataracts,

Clinical symptoms of gal-1-P-transferase deficiency is found to appear early in infancy. Some infants are born with cataract, jaundice and cirrhosis. The reason may be due to maternal ingestion of lactose. In untreated patients, development of hepatomegaly is very common. Liver is damaged leading to decreased synthesis of prothrombin and albumin. Glomeruli and tubules of the kidney are affected due to the accumulation of galactose and its metabolites. In addition, active tubular transport is impaired because of deficient ATP. Aminoaciduria occurs. Decreased albumin synthesis, proteinuria, ascites and generalized oedema is seen. Without treatment death usually results. Even if the untreated patients survive, there is retardation of physical and mental growth.

Diagnosis of galactosemia is by measuring the activity of *gal-1-P-transferase* in erythrocytes. Galactose should be restricted if the *gal-1-P-transferase* is elevated above 2 mg/dl.

Objectives of diet therapy in galactosemia are to prevent symptoms and to provide nutrients for normal growth and development. Treatment should begin in the first few days of life itself. The goal of dietary treatment for galactosemia is to minimize galactose intake which in turn minimizes galactose-1-phosphate production. Therefore, dietary treatment of galactosemia is to remove any foods containing galactose from the diet. *Because milk and milk products are the must common food source of galactose, persons with galactosemia should avoid these foods.* The diet allows most protein-containing foods other than milk and milk products. Fruits, vegetables, grains, breads, fats and sugars are acceptable, as long as they do not have ingredients that contain galactose. Some fruits and vegetables do contain small amounts of galactose. However, the form of galactose (bound galactose) found in fruits and vegetables is not usable by the body, and may not contribute to elevated blood gal-1-p. The galactose content of some of the foods is provided as a reference in Table 13.5.

Table 13.5: Galactose content of some common foods

Item	Galactose/100 mg/ml
Cow's milk	227
Human milk	350
Infant formula:	
Soy protein isolate	1.5
Casein hydrolysate	6-7.5
Whole casein	184
Aged cheddar cheese	38-48
Fruits and vegetables	<0.5-35
Legumes, (cooked):	
Garbanzo beans	444
Baby lima	175
Kidney	153
Lentil	116
Soybean	44

All sources of lactose and galactose should be totally removed from the diet. Nutritional requirements for these infants and children are the same as the normal children. Foods that are excluded from the diet therefore, include:

- Milk of any species.
- All products containing milk such as curds, cheese, ice-cream, milk shake, butter, cream, milk sweets.
- Soups containing milk or cream.
- Fruits containing galactose.
- Any processed foods with lactose.
- Salad dressings containing milk.
- Baked products containing milk.

Patient or the family members of the patients must be educated to read food labels while purchasing food. The labels of all processed foods must be read carefully for ingredients it contains. The milk products to be avoided in processed foods are milk, casein, dry milk solids, lactose, curds and whey. The milk proteins casein and caseinate must be limited in the diet. They can provide large amounts of galactose if many foods or large amounts of any food containing casein are eaten. The following products may be used because they do not contain lactose: lactate, lactic acid, lactylates and calcium compounds.

Milk and milk products are the usual dietary source of calcium. Because persons with galactosemia remove milk products from their diet, they need to add calcium back into their diet through supplements. All people with galactosemia should be given a regular daily supplement of calcium. A soy-based formula can be used or tablets can be given. Fermented soy products (fermented soy sauce, miso etc.) are not recommended as galactose can be released in the fermentation process. Non-fermented soy products (tofu, textured vegetable protein, and soybean extract) are acceptable.

We hope having gone through the discussion presented above you would now find yourself better equipped to deal with patients coming to you for dietary management of the metabolic diseases. We suggest you test your understanding on the topic by answering the check your progress exercise *2* given herewith.

Check Your Progress Exercise 2

1. Match the following:

a)	Tyrosinemia	i)	Galactose - 1 - Phosphate uridyl transferase
b)	Homocystinuria	ii)	Oxidative decarboxylase
c)	Galactosemia	iii)	Cystathionine β synthase
d)	Phenylketonuria	iv)	Hepatic fumaryl acetoacetate hydrolase
e)	MSUD	v)	Phenylalanine hydroxylase

2. State whether the following statements are True / False.

i) Uricosuric drugs are used to increase the uric acid excretion.

ii) Lofenalac is a formula which is nutritionally complete except for tryptophan.

iii) Milk of any species should be excluded in galactosemia.

iv) A therapeutic dose of 5 g of pyridoxine per day is recommended to treat homocystinuria.

v) In MSUD, there is a characteristic odour of burnt sugar in the urine,

13.4 LET US SUM UP

In this unit, we studied about the nutritional management of metabolic diseases such as gout and a few inborn errors of metabolism such as phenylketonuria, tyrosinemia, MSUD, homocystinuria and galactosernia.

Gout, we learnt, is a chronic disease due to an inherited abnormality of purine metabolism. Dietary treatment for gout often include a diet of lower purine intake. Drugs are so effective in lowering the serum urate concentration that rigid restriction of dietary purines is rarely necessary.

Finally, in our last section, we dealt with the major diseases of inborn errors of metabolism and their nutritional management. An overview of the disorders of Inborn Errors of Metabolism is given below:

Disorder	Caused due to the Defects in the Function of	Characteristcs	Diet Therapy
Phenylketonuria	Phenylalanine hydroxylase	Developmental delay, microcephaly, nerve degenerations	Low phenylalanine diet, Lofenalac formula
Tyrosinemia	Hepatic fumaryl acetoacetate hydrolase	Corneal erosion, hyperkeratosis on the fingers and palms, sole of the feet, mental retardation may occur	Phenylalanine and tyrosine restricted diet.
MSUD	Oxidative decarboxylase	Accumulation of branched chain amino acids. Production of fragrant urine with the odour of burnt sugar. Retardation of physical and mental development	Special feeds containing energy and protein without branched chain amino acids.
Homocystinuria	Cystathionine β-synthase	Accumulation of homocysteine. Skeletal changes, dislocated lenses, intravascular thrombosis, osteoporosis, mental retardation may occur.	Pyridoxine (1g/day) is usually given methionine restricted diet supplemented with L-Cysteine is given.
Galactosemia	Galactokinase galactose-1-Phosphate-uridyl transferase, UDP galactose-4-epimerase	Lenticular cataract, jaundice, cirrhosis, hepatomegaly etardation of physical and mental growth.	All sources of lactose and galactose should be totally avoided.

13.5 GLOSSARY

Arthritis : inflammation of a joint, usually accompanied by pain, swelling, and structural changes.

Congenital : existing from birth or before

Deamination : removal of amino group (NH_2) from amino acid.

Metatarsal : the five bones of the foot between 'the ankle and the toes.

Microcephaly : pertaining to an abnormally small head.

13.6 ANSWERS TO CHECK YOUR PROGRESS EXERCISES

Check Your Progress Exercise 1

1. **a)** 2-7 mg/100 ml

b) swelling and tenderness of the joints with severe pain, anorexia and malaise.

c) Any three of the following: organ meat such as kidney, liver, red meat, legumes, beans, seafood.

d) Any three of the following: beverages (coffee, tea and soda), refined cereals, cheese, eggs, fat, fruit/fruit juices, milk, nuts, sugar syrup and vegetable and creamed soups.

e) Hyperuricemia refers to elevated levels of uric acid in the blood.

2. a) purine

b) glandular/organs

c) uric acid

d) uric acid

e) uric acid

3. Any five of the following:

- Maintain an ideal weight
- Avoid foods with highest purine content, limit high purine foods.
- Take moderate protein, use low fat dairy products, eggs and cheese.
- Take liberal carbohydrates, refined cereals, beverages, fruits and fruit juices, vegetables.
- Take low fat diet to keep your weight ideal.
- Restrict/eliminate alcohol.
- Take liberal fluid intake.

Check Your Progress Exercise 2

1. **a)** – iv)

b) – iii)

c) – i)

d) – v)

e) – ii)

2. i) True

ii) False

iii) True

iv) False

v) True