Unit Three

Chemistry of Amino Acids & Proteins

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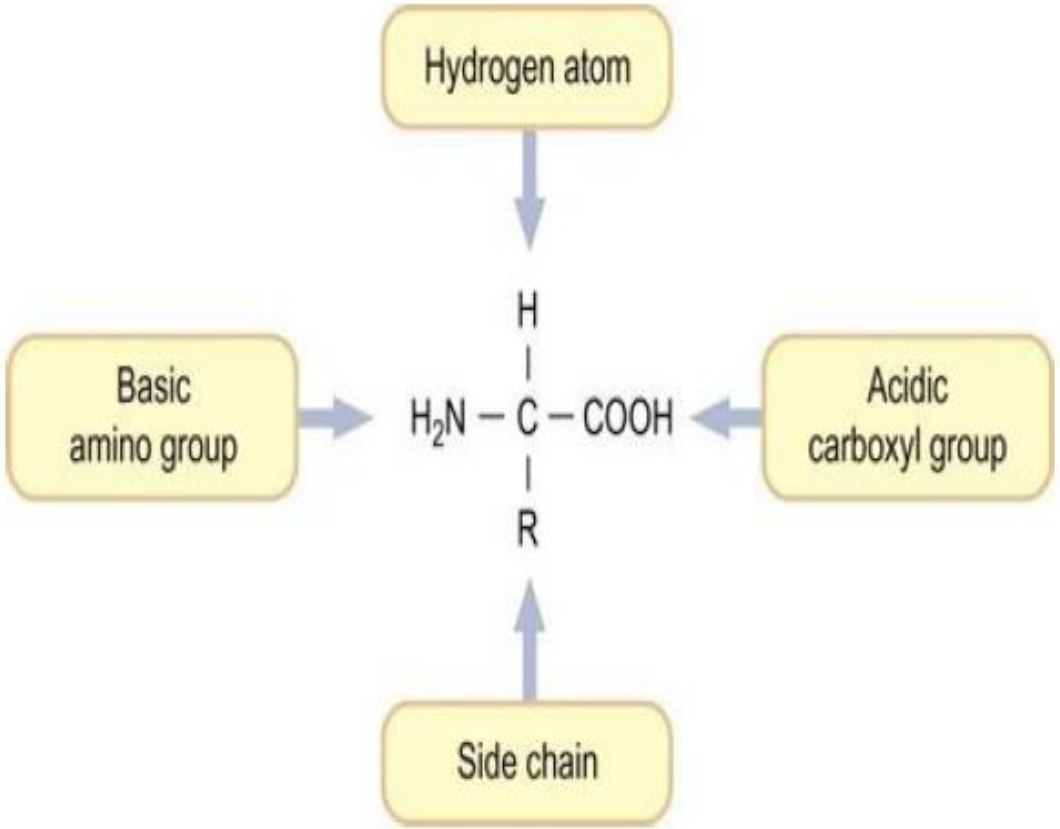
Unit 3. Chemistry of Amino Acids & Proteins

Definition of Amino Acids

Amino acids (AA) are organic compounds that contain amino ($–NH_2$) and carboxyl (–COOH) functional groups, along with a side chain (R group) specific to each amino acid. The key elements of an amino acid are carbon (C), hydrogen (H), oxygen (O), and nitrogen (N), although other elements are found in the side chains of certain amino acids. Although about 300 amino acids occur in nature, only 20 of them are seen in human body.



Unit 3. Chemistry of Amino Acids & Proteins

Classification of Amino Acids

Amino Acids are classified to many types based on many categories:

1- Based on Structure.

2- Based on Side Chain.

3- Based on Metabolism:

A. Purely ketogenic.

B. Ketogenic and glucogenic.

C. Purely glucogenic.

4- Based on Nutritional Requirements:

A. Essential or indispensable: Isoleucine, Leucine, Threonine, Lysine, Methionine, Phenylalanine, Tryptophan, and Valine are essential amino acids. Their carbon skeleton cannot be synthesized by human beings and so preformed amino acids are to be taken in food for normal growth. Normal growth and optimal health will not occur, if one such amino acid is deficient in the diet.

B. Partially essential or Semi-essential: Histidine and Arginine.

C. Non-essential or Dispensable.

D. Conditionally essential amino acids.

Memory aid for essential amino acids:

"**A**ny **H**elp **I**n **L**earning **T**hese **L**ittle **M**olecules **P**roves **T**ruly **V**aluable"

This stands for

Arginine, **H**istidine, **I**soleucine, **L**eucine, **T**hreonine, **L**ysine, **M**ethionine, **P**henylalanine, **T**ryptophan and **V**aline in that order.

Unit 3. Chemistry of Amino Acids & Proteins

Properties of Amino Acids

Some AA are sweet in taste while others are tasteless or bitter. All AA have high melting points (more than 200°C). All amino acids are soluble in water and alcohol (polar solvents); but insoluble in non-polar solvents. The general properties for AA can be described as:

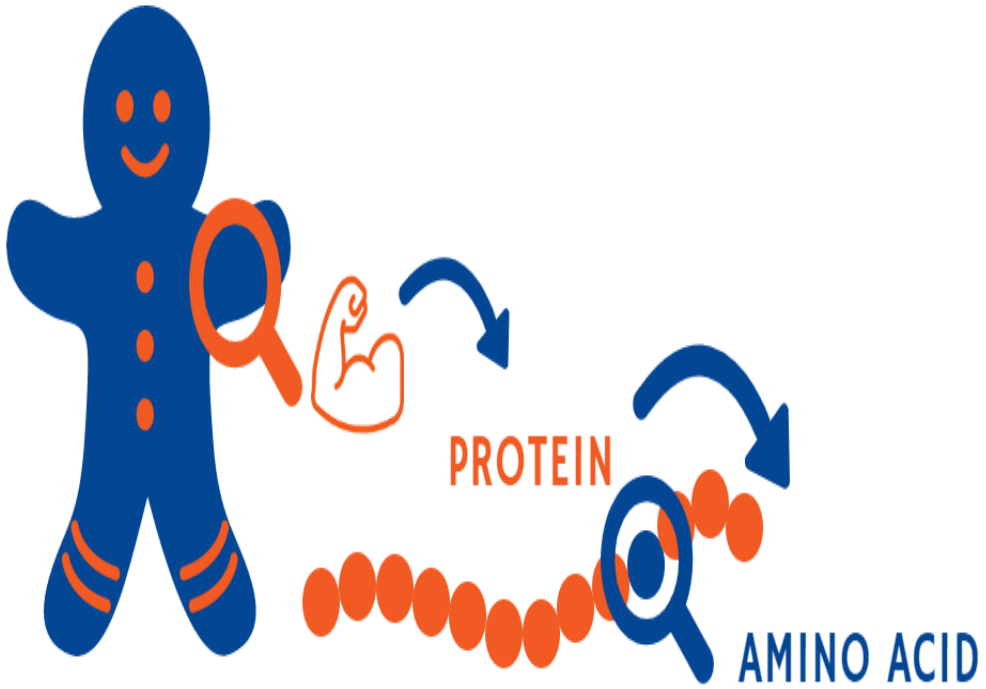
1- Ampholyte and Isoelectric Point: Amino acids can exist as ampholytes or zwitterions (German word "zwitter" = hybrid) in solution, depending on the pH of the medium. The pH at which the molecule carries no net charge is known as isoelectric point or isoelectric pH (pI). At isoelectric point, the amino acid will carry no net charge; all the groups are ionized but the charges will cancel each other. Therefore, at isoelectric point, there is no mobility in an electrical field.

2- Optical Activity: The mirror image forms produced with reference to the alpha carbon atom, are called D and L isomers. The L-amino acids occur in nature and are therefore called natural amino acids. D-amino acids are seen in small amounts in micro-organisms and as constituents of certain antibiotics and bacterial cell wall peptidoglycans. D-amino acids have multiple functions in bacteria, like synthesis of cross-links in cell wall.

Unit 3. Chemistry of Amino Acids & Proteins

Definition of Proteins

Proteins are of paramount importance in biological systems. All the major structural and functional aspects of the body are carried out by protein molecules. All proteins are polymers of amino acids. Proteins are composed of a number of amino acids linked by peptide bonds. Proteins are used for body building; all the major structural and functional aspects of the body are carried out by protein molecules. Abnormality in protein structure will lead to molecular diseases with profound alterations in metabolic functions.



Unit 3. Chemistry of Amino Acids & Proteins

Classification of Proteins

It is almost impossible to correctly classify all proteins. The following classifications are given only to introduce a broader idea. So, proteins are classified to many types based on many categories:

1- Based on Functions:

A. Catalytic proteins, e.g. enzymes

B. Structural proteins, e.g. collagen, elastin.

2- Based on Composition and Solubility:

A. Simple Proteins: they contain only amino acids such as Albumin.

B. Conjugated Proteins: They are combinations of protein with a non-protein part, called prosthetic Group such as Glycoproteins (Blood group antigens), Lipoproteins, Nucleoproteins (DNA), Metalloproteins (Hemoglobin).

C. Derived Proteins.

3- **Based on Shape:** Globular Proteins (albumins) & Fibrous Proteins (Collagen).

4- Based on Nutritional Value:

A. Nutritionally Rich Proteins: They contain all the essential amino acids such as casein of milk.

B. Incomplete Proteins: They lack one essential amino acid. They cannot promote body growth in children; but may be able to sustain the body weight in adults such as proteins of cereals.

C. Poor Proteins: They lack in many essential amino acids and a diet based on these proteins will not even sustain the original body weight such as Zein from corn.

Unit 3. Chemistry of Amino Acids & Proteins

Properties of Proteins

1- Molecular weights of some of the proteins are varying: Insulin (5,700); Hemoglobin (68,000); Albumin (69,000); Immunoglobulins (150,000); Rabbit Papilloma Virus Protein (4,70,00,000).
2- Shape of the proteins also vary: Insulin is globular, Albumin is oval in shape, while Fibrinogen molecule is elongated. Bigger and elongated molecules will increase the viscosity of the solution.
3- Isoelectric pH: Since proteins are made of amino acids, the pI of all the constituent amino acids will influence the pI of the protein.
4- Purification of enzymes and other proteins usually start with precipitating them from solution.
5- Precipitation by Heavy Metal Ions: Salts of Copper, Zinc, Lead, Cadmium and Mercury are toxic, because they tend to precipitate normal proteins of the gastrointestinal wall. Based on this principle, raw egg is sometimes used as an antidote for mercury poisoning.
6- Denaturation of proteins: Mild heating, treating with urea, salicylate, X-ray, ultraviolet rays, high pressure and vigorous shaking produce denaturation. Denatured proteins are sometimes re-natured when the physical agent is removed. For example, Immunoglobulin chains are dissociated when treated with urea. When the urea is removed by dialysis, the subunits are re-associated and biological activity of immunoglobulin is regained. But many proteins undergo irreversible denaturation. For example, albumin cannot be re-natured by removing the physical agent.

Unit 3. Chemistry of Amino Acids & Proteins

Metabolism of Proteins

The main role of amino acids is in the synthesis of structural and functional proteins. Unlike carbohydrates and fats, there is no storage form of proteins in the body. A 70 kg man has an average protein turnover rate of 400 g per day (same amount synthesized and same amount broken down). The non-essential amino acids are either derived from the diet or synthesized in the body. The essential amino acids are obtained from the diet. Even if one is deficient, protein synthesis cannot take place. The body amino acid pool is always in a dynamic steady state. In an adult, the rate of synthesis of proteins balances the rate of degradation, so that nitrogen balance is maintained. The dietary proteins are denatured on cooking and therefore more easily digested. The digestion of protein is effected by enzymes in Stomach, Pancreas and Intestinal cells:

1- Gastric Digestion of Proteins: In the stomach, hydrochloric acid is secreted. It makes the pH optimum for the action of pepsin and also activates pepsin. The acid also denatures the proteins.

2- Pancreatic Digestion of Proteins: The optimum pH for the activity of pancreatic enzymes (pH 8) is provided by the alkaline bile and pancreatic juice. The secretion of pancreatic juice is stimulated by the peptide hormones Cholecystokinin and Pancreozymin. Pancreatic juice contains the important endopeptidases enzymes namely Trypsin, Chymotrypsin, Elastase and Carboxypeptidase.

3- Intestinal Digestion of Proteins: Complete digestion of the small peptides to the level of amino acids is brought about by enzymes present in intestinal juice (succus entericus) like Leucine Aminopeptidase, Proline Amino Peptidase, Dipeptidases and Tripeptidases.

Unit 3. Chemistry of Amino Acids & Proteins

General Metabolism of Amino Acids

1. The anabolic reactions where proteins are synthesized.
2. Synthesis of specialized products such as heme, creatine, purines and pyrimidines.
3. The catabolic reactions where dietary proteins and body proteins are broken down to amino acids.
4. Transamination: Amino group is removed to produce the carbon skeleton (keto acid). The amino group is excreted as urea.
5. The carbon skeleton is used for synthesis of nonessential amino acids.
6. It is also used for gluconeogenesis or for complete oxidation.
7. Other minor metabolic functions like conjugation, methylation, amidation, etc.

Unit 3. Chemistry of Amino Acids & Proteins

Formation of Ammonia & Urea

The first step in the catabolism of amino acids is to remove the amino group as ammonia. This is the major source of ammonia. However, small quantities of ammonia may also be formed from catabolism of purine and pyrimidine bases. Ammonia is highly toxic especially to the nervous system. Detoxification of ammonia is by conversion to urea and excretion through urine. The ammonia from all over the body thus reaches liver. It is then detoxified to urea by liver cells, and then excreted through kidneys.

Urea is the end product of protein metabolism. Since mammals including human beings excrete amino nitrogen mainly as urea, they are referred to as ureotelic. Although, ammonia is toxic and has to be immediately detoxified, in kidney cells, ammonia generated on purpose. This is for buffering the acids, and maintaining acid-base balance. Urea is a small water-soluble molecule with a molecular weight of 60 g/mol which is the end-product of proteins and nitrogen metabolism in humans. It is the compound with the highest level found in the blood of renal failure patients. It is freely filtered by the glomerulus and not secreted by the tubules, but about (40–70%) is passively reabsorbed from the renal tubules. The significant increasing in serum urea could be due to high intake of proteins, increase in serum creatinine level, elevated HbA1c, arterial hypertension, dyslipidemia, obesity, low hepatic function, burns, stress and myocardial infections. Furthermore, hyperglycemia may cause a damage to the kidney or the kidney is not functioning properly by causing irretrievable damage to millions of nephrons - tiny filtering units within each kidney. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis which lead to elevate urea levels in T2DM patients with and without DN.

Unit 3. Chemistry of Amino Acids & Proteins

Disorders of Urea Cycle

1- Hyperammonemia: Deficiency of any of the urea cycle enzymes would result in hyperammonemia. When the block is in one of the earlier steps, the condition is more severe, since ammonia itself accumulates. Deficiencies of later enzymes result in the accumulation of other intermediates, which are less toxic and hence symptoms are less. As a general description, disorders of urea cycle is characterized by hyperammonemia, encephalopathy and respiratory alkalosis. Clinical symptoms include vomiting, irritability, lethargy and severe mental retardation. Infants appear normal at birth, but within days progressive lethargy sets in. Treatment is more or less similar in the different types of disorders. Low protein diet with sufficient arginine and energy by frequent feeding can minimize brain damage since ammonia levels do not increase very high. The accumulation of ammonia in blood (normally less than 50 mg/dL) and body fluids results in toxic symptoms. Nowadays, defects in enzymes of urea cycle are detected in neonatal blood.

Unit 3. Chemistry of Amino Acids & Proteins

2- Hepatic Coma (Acquired Hyperammonemia): In diseases of the liver, hepatic failure can finally lead to hepatic coma and death. Hyperammonemia is the characteristic feature of liver failure. The condition is also known as portal systemic encephalopathy. The signs and symptoms are mainly pertaining to central nervous system (CNS) dysfunction (altered sensorium, convulsions), or manifestations of failure of liver function (ascites, jaundice, hepatomegaly, edema, hemorrhage, spider nevi). The management of the condition is difficult. A low protein diet and bowel disinfection using antibiotics and clearance by lactulose, withholding hepatotoxic drugs and maintenance of electrolyte and acid-base balance are the main lines of management.

Unit 3. Chemistry of Amino Acids & Proteins

Urea Level in Blood

In clinical practice, blood urea level is taken as an indicator of renal function. The normal urea level in plasma is from 20–40 mg/dL. Blood urea level is increased where renal function is inadequate. Urea level in blood may be theoretically increased when protein intake is very high. However, usually this will be only within the upper limit of the normal values. Urinary excretion of urea is 15 to 30 g/day (6–15 grams nitrogen/day). This corresponds to the breakdown of 40 to 80 grams of proteins per day. Urea constitutes 80% of urinary organic solids.

Unit 3. Chemistry of Amino Acids & Proteins

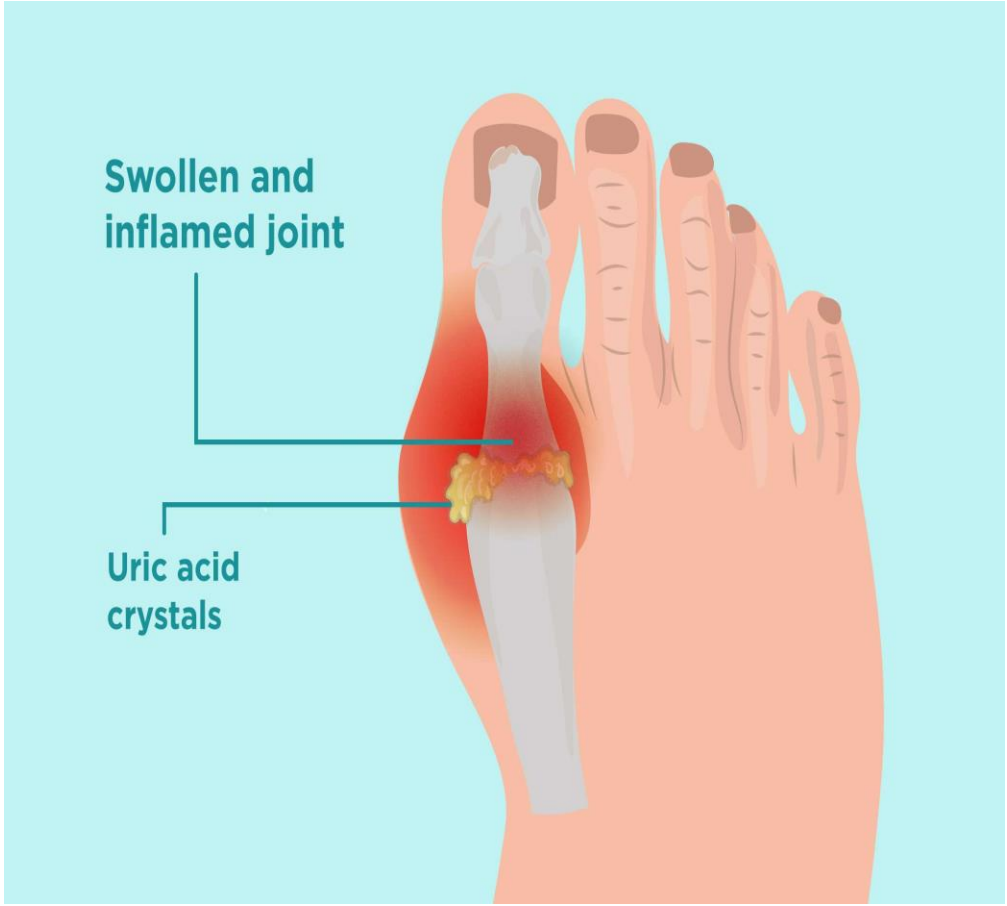
Formation of Creatinine

Creatinine is a waste product produced by muscles from the breakdown of a compound called creatine. The amount of creatine per unit of skeletal muscle mass is consistent and the breakdown rate of creatine is also consistent. Thus, serum creatinine concentration is very stable and a direct reflection of skeletal muscle mass. Creatinine is filtered by the glomerulus, and a small amount is also secreted into the glomerular filtrate by the proximal tubule. The significant increasing in serum creatinine level could be attributed to high muscle mass, high protein meal intake, arterial hypertension, dyslipidemia, obesity and race, prescribed medication, elevated HbA1c, and renal damage. Furthermore, serum creatinine is filtered by the glomerulus; therefore, serum creatinine level is used as an indirect measure of glomerular filtration. So, any decreasing in glomerular filtration rate (GFR) could lead to rise in serum levels of creatinine. From the other hand, serum creatinine is one of the simplest ways to assess the kidney functional because it accumulates in the body in cases of renal dysfunction thus raising their levels in the blood. Moreover, estimation of renal function tests via creatinine is simple, reliable, economic and sensitive that can now be considered as an adjunct in the management and long duration treatment of T2DM disorder. Reference Values of Creatinine are: Adult males= 0.7 – 1.4 mg/dL, Adult females= 0.6 – 1.3 mg/dL and Children= 0.4 – 1.2 mg/dL. The kidney reserve is such that about 50% kidney function must be lost before creatinine level in blood is raised. Serum level usually parallels the severity of the disease. Creatinine level more than 1.5 mg/dL indicates impairment of renal function.

Unit 3. Chemistry of Amino Acids & Proteins

Formation of Uric Acid

Uric acid is the product of catabolism of the purine nucleic acids. Uric acid is relatively insoluble in plasma and, at high concentrations, can be deposited in the joints and tissue, causing painful inflammation.
Purines, such as adenine and guanine from the breakdown of ingested nucleic acids or from tissue destruction, are converted into uric acid, primarily in the liver. Uric acid is transported in the plasma from the liver to the kidney, where it is filtered by the glomerulus. Reabsorption of 98% to 100% of the uric acid from the glomerular filtrate occurs in the proximal tubules. Small amounts of uric acid are secreted by the distal tubules into the urine. Renal excretion accounts for about 70% of uric acid elimination; the remainder passes into the gastrointestinal tract and is degraded by bacterial enzymes. Uric acid is measured to assess inherited disorders of purine metabolism, to confirm diagnosis and renal calculi, to prevent uric acid nephropathy during chemotherapeutic treatment, and to detect kidney dysfunction and monitor treatment of gout.



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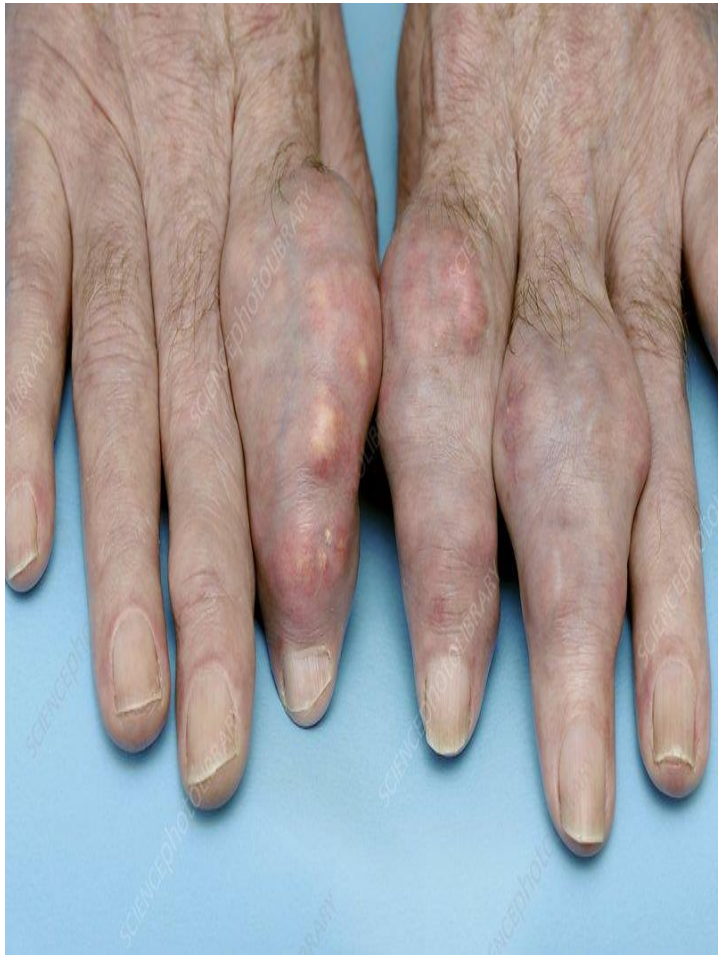
Levels of Uric Acid

mg/dL	µmol/L	mmol/L	Diagnosis
5 or less	300 or less	.30 or less	Safe
5 - 6	300 - 350	.30 - .35	Good
6 - 7	350 - 400	.35 - .40	Warning
Over 7	Over 400	Over .40	Danger

Unit 3. Chemistry of Amino Acids & Proteins

Gout

Gout is a common type of arthritis that causes intense pain, swelling, and stiffness in a joint. It usually affects the joint in the big toe. Gout attacks can come on quickly and keep returning over time, slowly harming tissues in the region of the inflammation, and can be extremely painful. Hypertension, cardiovascular, and obesity are risk factors for gout. It is the most common form of inflammatory arthritis in men, and although it is more likely to affect men, women become more susceptible to it after the menopause. The majority of gout cases are treated with medication. Medication can be used to treat the symptoms of gout attacks, prevent future flares, and reduce the risk of gout complications such as kidney stones and the development of tophi. Commonly used medications include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids. These reduce inflammation and pain in the areas affected by gout and are usually taken orally. Medications can also be used to either reduce the production of uric acid (hyperuricemia) like (allopurinol) or improve the kidney's ability to remove uric acid from the body (probenecid). Without treatment, an acute gout attack will be at its worst between 12 and 24 hours after it began. A person can expect to recover within 1 to 2 weeks without treatment, but there may be significant pain during this period.



Unit 3. Chemistry of Amino Acids & Proteins

There are many lifestyle and dietary guidelines that can be tried to protect against flares or prevent gout from occurring in the first instance: maintain a high fluid intake of around 2 to 4 liters a day, avoid alcohol and maintain a healthy body weight.

Individuals with gout can manage flare-ups by moderating their diet. A balanced diet can help reduce symptoms. Decreasing foods that are high in purines, to ensure that the levels of uric acid in the blood do not get too high, is reasonable to try. Here is a list of some high-purine foods to be wary of: beef kidneys, brains, dried beans and peas, liver, mushrooms, sardines and scallops.

Various epidemiological studies have shown that purine-rich vegetables, whole grains, nuts and legumes, and less sugary fruits, coffee, and vitamin C supplements lower blood uric acid levels, but do not decrease the risk of gout. Red meat, fructose-containing beverages, and alcohol can increase the risk.

Unit 3. Chemistry of Amino Acids & Proteins

Blood Proteins

Blood proteins, also termed plasma proteins, are proteins present in blood plasma. They serve many different functions, including transport of lipids, hormones, vitamins and minerals in activity and functioning of the immune system. Other blood proteins act as enzymes, complement components, protease inhibitors or kinin precursors. Contrary to popular belief, haemoglobin is not a blood protein, as it is carried within red blood cells, rather than in the blood serum. All blood proteins are synthesized in liver except for the globulins. Blood proteins are:

1- Albumin: it accounts for 55% of blood proteins, is a major contributor to maintaining the oncotic pressure of plasma and assists, as a carrier, in the transport of lipids, steroid hormones and drugs. It's normal level is 3.5 - 5 g/dL.

2- Globulin: make up 38% of blood proteins and transport ions, hormones, and lipids assisting in immune function. It's normal level is 2 - 2.5 g/dL.

3- Fibrinogen: comprises 7% of blood proteins; conversion of fibrinogen to insoluble fibrin is essential for blood clotting. It's normal level is 0.2 - 0.45 g/dL.