BIOCHEMISTRY- BP203T

UNIT: 4 Nucleic acid metabolism and genetic information transfer

CLASS:4

TOPIC: HYPERURICEMIA AND GOUT

HYPERURICEMIA AND GOUT:

- Uric acid is the end product of purine metabolism in humans.
- The normal concentration of uric acid in the serum of adults is in the range of 3-7 mg/dl. In women, it is slightly lower (by about 1 mg) than in men.
- The daily excretion of uric acid is about 500-700 mg.

Hyperuricemia refers to an elevation in the serum uric acid concentration.

- This is sometimes associated with increased uric acid excretion (uricosuria).

Gout is a metabolic disease associated with overproduction of uric acid.

- At the physiological pH, uric acid is found in a more soluble form as sodium urate.

In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, particularly in the joints.

Such deposits are commonly known as tophi.

This causes inflammation in the joints resulting in a painful gouty arthritis.

Sodium urate and/or uric acid may also precipitate in kidneys and ureters that results in renal damage and stone formation.

Historically, gout was found to be often associated with high living, over-eating and alcohol consumption.

In the previous centuries, alcohol was contaminated with lead during its manufacture and storage.

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Lead poisoning leads to kidney damage and decreased uric acid excretion causing gout.

In general, a diet rich is meat and seafoods is associated with increased risk of gout. The prevalence of gout is about 3 per 1,000 persons, mostly affecting males.

Post-menopausal women, however, are as susceptible as men for this disease.

Gout is of two types—primary and secondary.

1. Primary gout:

It is an inborn error of metabolism due to overproduction of uric acid.

This is mostly related to increased synthesis of purine nucleotides.

● **PRPP synthetase:**

In normal circumstances, PRPP synthetase is under feedback control by purine nucleotides (ADP and GDP). However, variant forms of PRPP synthetase which are not subjected to feedback regulation have been detected. This leads to the increased production of purines.

● **PRPP glutamylamidotransferase:**

The lack of feedback control of this enzyme by purine nucleotides also leads to their elevated synthesis.

● **HGPRT deficiency:** This is an enzyme of purine salvage pathway, and its defect causes Lesch-Nyhan syndrome.

This disorder is associated with increased synthesis of purine nucleotides by a two-fold mechanism.

Firstly, decreased utilization of purines (hypoxanthine and guanine) by salvage pathway, resulting in the accumulation and diversion of PRPP for purine nucleotides.

Secondly, the defect in salvage pathway leads to decreased levels of IMP and GMP causing impairment in the tightly controlled feedback regulation of their production.

● **Glucose 6-phosphatase deficiency:** In type I glycogen storage disease (von Gierke's), glucose 6-phosphate cannot be converted to glucose due to the deficiency of glucose 6-

phosphatase. This leads to the increased utilization of glucose 6-phosphate by hexose monophosphate shunt (HMP shunt), resulting in elevated levels of ribose 5-phosphate and PRPP and, ultimately, purine overproduction. von Gierke's disease is also associated with increased activity of glycolysis. Due to this, lactic acid accumulates in the body which interferes with the uric acid excretion through renal tubules.

● **Elevation of glutathione reductase:** Increased glutathione reductase generates more NADP+ which is utilized by HMP shunt.

This causes increased ribose 5-phosphate and PRPP synthesis. Among the five enzymes described, the first three are directly involved in purine synthesis.

The remaining two indirectly regulate purine production.

This is a good example to show how an abnormality in one metabolic pathway influences the other.

2. Secondary gout:

Secondary hyperuricemia is due to various diseases causing increased synthesis or decreased excretion of uric acid.

Increased degradation of nucleic acids (hence more uric acid formation) is observed in various cancers (leukemias, polycythemia, lymphomas, etc.)

psoriasis and increased tissue breakdown (trauma, starvation etc.).

The disorders associated with impairment in renal function cause accumulation of uric acid which may lead to gout.

Treatment of gout:

- The drug of choice for the treatment of primary gout is allopurinol.
- This is a structural analog of hypoxanthine that competitively inhibits the enzyme xanthine oxidase. Further, allopurinol is oxidized to alloxanthine by xanthine oxidase.
- Alloxanthine, in turn, is a more effective inhibitor of xanthine oxidase.
- This type of inhibition is referred to as suicide inhibition.
- Inhibition of xanthine oxidase by allopurinol leads to the accumulation of hypoxanthine and xanthine.

- These two compounds are more soluble than uric acid, hence easily excreted.
- Besides the drug therapy, restriction in dietary intake of purines and alcohol is advised.
- Consumption of plenty of water will also be useful.
- The anti-inflammatory drug colchicine is used for the treatment of gouty arthritis.
- Other anti-inflammatory drugs such as phenylbutazone, indomethacin, oxyphenbutazone, corticosteroids are also useful.