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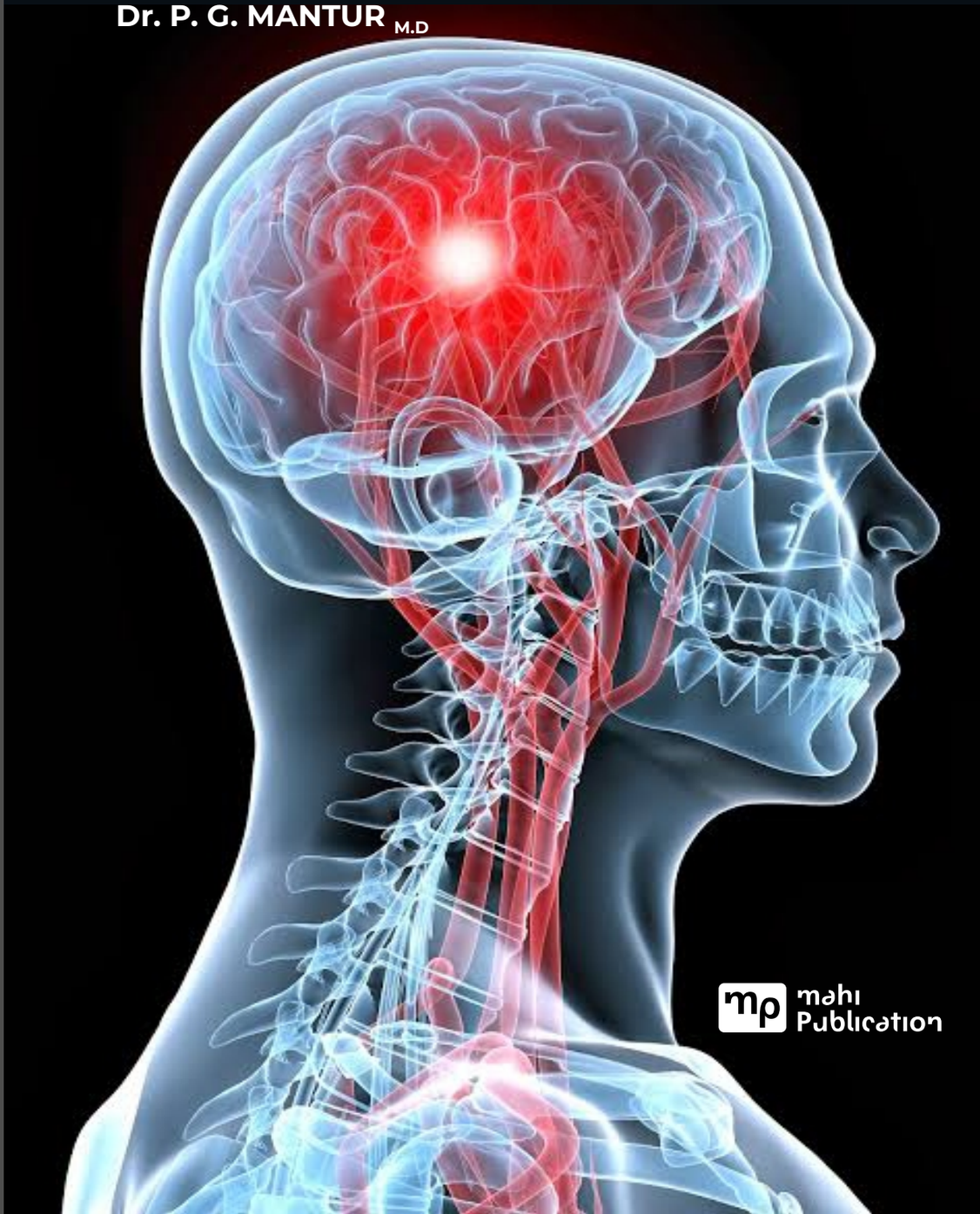
"SERUM URIC ACID, AND SERUM LIPID LEVELS IN ISCHAEMIC CEREBROVASCULAR ACCIDENT"

Dr. P. G. MANTUR M.D



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"SERUM URIC ACID, AND SERUM LIPID LEVELS IN ISCHAEMIC CEREBROVASCULAR ACCIDENT"

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LIST OF ABBREVIATIONS

TC	-	Total cholesterol
VLDL	-	Very low density lipoprotein
LDL	-	Low density lipoprotein
TG	-	Triglycerides
HDL	-	High density lipoprotein
CAD	-	Coronary artery disease
SUA	-	Serum uric acid
CBC	-	Complete blood count
CT	-	Computerised tomography
MRI	-	Magnetic resonance imaging
RBS	-	Random blood sugar
ECG	-	Electrocardiogram

TABLE OF CONTENTS

1 INTRODUCTION

A stroke or cerebrovascular accident is defined as an abrupt onset of a neurological deficit that is attributable to a focal vascular cause. A definition of stroke is clinical and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature. Cerebral ischemia is caused by reduction in blood flow that last longer than several seconds.[1]

Stroke is the second leading cause of death worldwide and it is also one of the leading causes of adult disability.[2] Numerous risk factors are involved in the development of stroke such as hypertension, smoking, dyslipidemia and diabetes mellitus. Hyperuricemia has been reported to be an independent predictor of stroke.[3]

There is a pressing need to identify these treatable risk factors that can be easily measured and are highly prevalent, in order to identify patients at high risk for stroke.

Hyperuricemia have also been suggested as one of the factors in the pathogenesis of an atheroma. Significant association was found between serum uric acid and serum triglycerides. This implicates that a rise in serum uric acid and serum triglyceride may play some part in the etiology of ischemic cerebrovascular disease.[4]

But contrary to this, other studies have also advocated uric acid to be neuroprotective due to its anti-oxidation action. Considering these conflicting data, we undertook this study to evaluate serum uric acid and serum lipid levels in patients with ischaemic cerebrovascular stroke.

2 REVIEW OF LITERATURE

Uric acid is the ultimate catabolite of purine metabolism in human and higher primates. It exists in the extracellular compartment as sodium urate, and it is cleared from the plasma through the kidney. It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome.[5-9]

Uric acid is the breakdown product of purines. In this process hypoxanthine is converted by the enzyme xanthine oxidase to xanthine and further to uric acid. Both steps induce the release of free radicals. Increased uric acid levels promote oxygenation of low-density lipoprotein cholesterol and facilitate lipid peroxidation. Uric acid may stimulate vascular smooth cell proliferation, and reduce vascular nitric oxide production. Moreover, higher uric acid levels may be associated with increased platelet adhesiveness predisposing to thrombus formation. SUA has also been found to stimulate the synthesis of pro-inflammatory factors like monocyte chemoattractant protein-1, interleukin-lβ, interleukin-6, and tumor necrosis factor-α. Experimental findings indicate that uric acid might have a role in the development of hypertension through stimulation of the renin-angiotensin system and induction of sodium sensitivity.

In rats, uric acid has been shown to mediate renal disease development by causing glomerular hypertension and hence renal hypertrophy, glomerulosclerosis, and interstitial fibrosis. Uric acid also induces renal arteriolar thickening independently of its effect on blood pressure. Each of these factors can play a pivotal role in the progression of atherosclerosis. As compared to control coronery artery walls, urate crystals are more abundant in diseased atherosclerotic plaques. It has been suggested that serum uric acid may cause endothelial dysfunction. Even a mild elevation of serum uric acid was associated with cerebral ischemia in adults. It was suggested that impaired vascular tone and endothelial dysfunction could contribute

because they permit cerebrospinal fluid to cross the blood-brain barrier and cause areas of edema.[10-21]

LIPIDS AND ATHEROSCLEROSIS

Several evidences have contributed to our current understanding of the relationship between increase in plasma cholesterol and development of CAD. Premature atherosclerosis results from high cholesterol levels, even in the absence of other cardiovascular risk factors.

The onset of atherosclerosis occurs early in life with diffuse regular thickening of the arterial intima in childhood. The smooth appearance of the arterial tree is usually lost during the teenage years with formation of nodular aggregates or cushions of fibro-elastic tissue, termed fatty streaks.[22]

Fatty streaks are collections of lipid, mainly cholesterol esters in macrophages and smooth muscle cells deposited in the intima of the artery. These fatty streaks are the precursors of the hallmark of atherosclerosis, the fibrous atheromatous plaque. The fibrous plaques are white lesions that usually protrude into the vessel lumen and consists of a core of cholesterol, cholesterol ester, phospholipid and necrotic cells covered by a fibrous cap of elastin and collagen. There is also proliferation of the smooth muscle cells into the media. Another important component is the foam cells, which contain a large quantity of lipid.[23]

Hypertriglyceridemia also maybe a marker of an individual with a genetic defect of lipoprotein metabolism, such as accumulation of VLDL remnants which are associated with premature atherosclerosis.An important factor for the development of atheromatous plaques is oxidized LDL, which causes increased chemotaxis of monocytes, and increased uptake of oxidized LDL by macrophages.[24]

URIC ACID

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen and hydrogen with the formula C5H4N4O3. It is the final breakdown product of purine metabolism in humans.

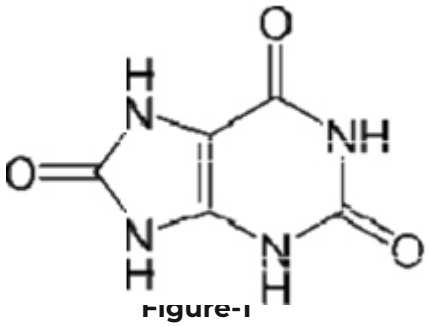


Figure-1

HISTORY

In 1776, the Swedish chemist Scheele isolated uric acid from a calculus of urinary tract and in 1797, the British chemist Wollaston isolated the substance from a tophus which he removed from his own ear. 50 years later, these observations led the British Physician, Alred Barry Garrod to show by chemical isolation, the presence of higher concentrations of uric acid in the blood of gouty patients. Garrod s subsequent studies formulated, for the first time, a rational relationship between hyperuricemia and the clinical symptomatology of gouty arthritis. Later, in 1913, Folin F. Denin developed a more reliable method of chemical determination of uric acid which led to rejection of Garrod s concept.[25-29]

STRUCTURE AND CHEMISTRY

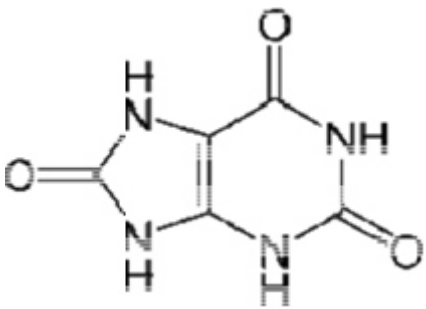


Figure - 2

The chemical nature of uric acid was shown by Fisher to be 2,6,8

trihydroxypurine. Uric acid is a diprotic acid with pka1=5.4 and pka2=10.3. Thus in strong alkali at high pH or in the presence of carbonic acid or carbonate ions, it forms the singly charged hydrogen or acid uric acid ion as its pKa2 is greater than the pKa1 of carbonic acid. As its second ionization is so weak, the full uric acid salts tend to hydrolyze back to hydrogen uric acid salts and free base at pH values around neutral. It is aromatic because of the purine functional group.[30]

SOLUBILITY

Generally, the water solubility of uric acid and its alkali metal and alkaline earth salts is rather low. All these salts exhibit greater solubility in hot water than cold, allowing for easy recrystallization. This low solubility is significant for the etiology of gout. The solubility of the acid and its salts in ethanol is very low or negligible. In ethanol water mixtures, the solubilities are somewhere between the end values for pure ethanol and pure water.

BIOLOGY

The enzyme xanthine oxidase makes uric acid from xanthine and hypoxanthine, which in turn are produced from purines. Uric acid is released in hypoxic conditions.[31]

In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine metabolism and is excreted in urine. In most other mammals, the enzyme uricase further oxidizes uric acid to allantoin. The loss of uricase in higher primates parallels the similar loss of the ability to synthesize ascorbic acid, leading to the suggestion that uric acid may partially substitute for ascorbate in such species. Both uric acid and ascorbic acid are strong reducing agents (electron donors) and potent antioxidants.[32]

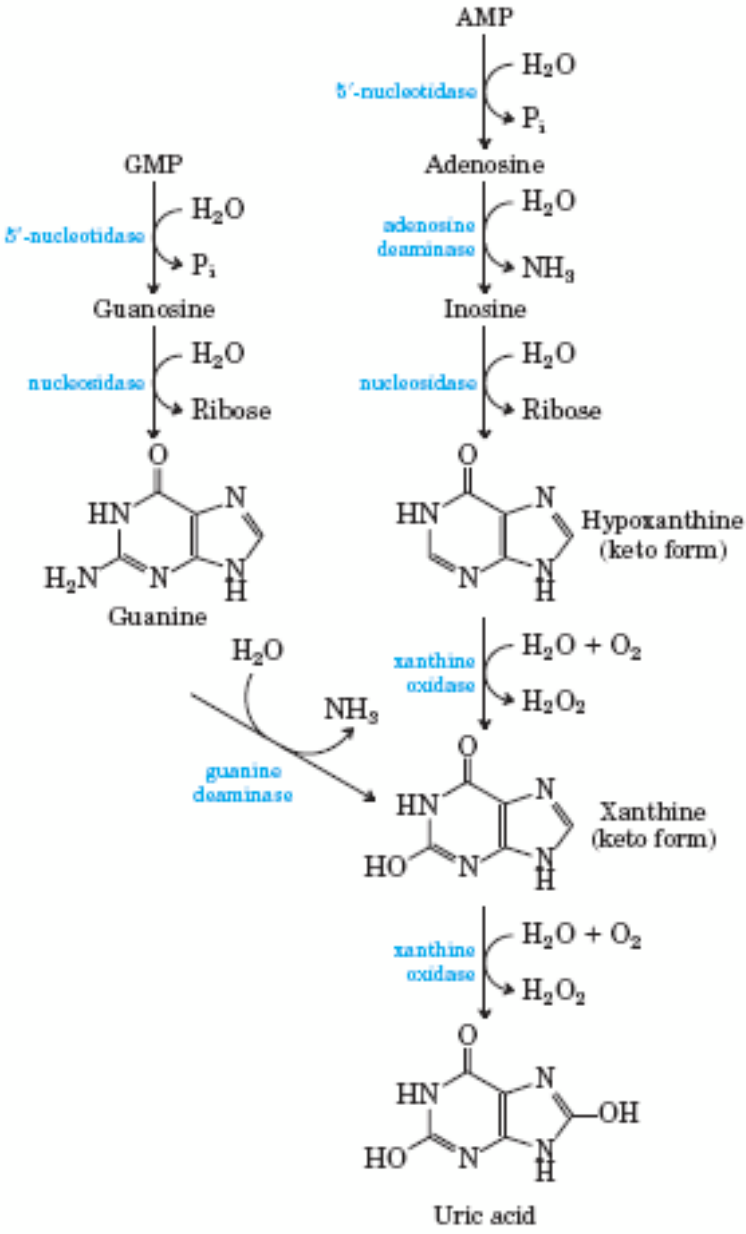
In humans, over half the antioxidant capacity of blood plasma comes from uric acid. The Dalmatian dog has a genetic defect in uric acid uptake by the liver and kidneys, resulting in decreased conversion to allantoin, so this breed excrete uric acid, and not allantoin, in the urine. In birds and reptiles, and in some desert dwelling mammals (e.g., the kangaroo rat), uric acid also is the end product of purine metabolism, but it is excreted in feces as a dry mass.

This involves a complex metabolic pathway that is energetically costly in comparison to processing of other nitrogenous wastes such as urea (from urea cycle) or ammonia, but has the advantage of reducing water loss.

In humans, about 70% of daily uric acid disposal occurs via the kidneys, and in 5-25% of humans, impaired renal (kidney) excretion leads to Hyperuricemia.

GENETICS

A proportion of people have mutations in the proteins responsible for the excretion of uric acid by the kidneys. Nine genes have so far been identified: SLC2A9; ABCG2; SLC17A1; SLC22A11; SLC22A12; SLC16A9; GCKR; LRRC16A; and PDZK1.SLC2A9 is known to transport both uric acid and fructose.[33]



Synthesis of Uric Acid Figure

Degradation of Purines and Pyrimidines Produces Uric Acid and Urea, Respectively.Purine nucleotides are degraded by a pathway in which they lose their phosphate through the action of 5"nucleotidase. Adenylate yields adenosine, which is deaminated to inosine by adenosine deaminase, and inosine is hydrolyzed to hypoxanthine (its purine base) and D-ribose. Hypoxanthine is oxidized successively toxanthine and the nuric acid by xanthine oxidase,a flavoenzyme with an atom of molybdenum and four iron-sulfur centers in its prosthetic group.

Molecular oxygen is the electron acceptor in this complex reaction. GMP catabolism also yields uric acid as end product. GMP is first hydrolyzed to guanosine, which is then cleaved to free guanine. Guanine undergoes hydrolytic removal of its amino group to yield xanthine, which is converted to uric acid by xanthine oxidase.

DIETARY INTAKE

Diet provides an important exogenous source of purines. Dietary intake of purines, nucleic acids contribute to the serum uric acid level and the daily excretion of uric acid, this contribution being proportional to the intake. However, the magnitude of this component of daily uric acid production is usually relatively small, since serum uric acid levels decrease by only 1 mg/dl or less when an individual changes from a normal to purine free diet.

On the other hand, diets unusually high in purines (such as liver, meat sweet breads, kidney and anchovy) have the potential to raise the plasma uric acid concentration significantly. Because about 50% of the ingested RNA purine and 25% of the ingested DNA purine appear in urine as uric acid, foods high in nucleic acid content have a significant effect on the serum uric acid level.

NORMAL VALUES

Usually, the uric acid pool size of an adult male, is about, 1200mg, and 700mg uric acid is produced daily. The production is balanced by the excretion of 500mg of uric acid into the urine and 200mg into the small intestine, Any imbalance in the two, results in hyperuricemia or hypouricemia.

The normal serum values vary with age and sex. Most children have serum uric acid concentrations of 3 to 4 mg/dl. Levels start rising during puberty in males, but remain low in females till menopause. The gender variation could probably be due to higher excretion in females. Normal values in females are 2.5-5.6 mg/dl and males is 3.1-7mg/dl.

After menopause, values for women increase to approximate those at men. Among adults, concentrations vary with height, body weight, blood pressure and renal function as well as alcohol intake.

URIC ACID EXCRETION

In a normal person on a normal diet about 700-1000 mg of uric acid is produced daily. If a person takes a diet rich in nucleoproteins (meat, particularly glandular meat, meat extracts, legumes) he/she will excrete little excess of uric acid.

On a purine free diet some uric acid is constantly excreted in urine amounting to about 200-500 mg/day. This fraction is referred to as endogenous uric acid. If it is determined for a given individual, the excess above this figure which he/she excretes on a purine containing diet is termed exogenous.

About 70% of uric acid is excreted by the kidneys. The remainder is excreted via the gastro intestinal tract, where it is degraded by uricolytic bacteria to carbon dioxide and ammonia. In patients with renal insufficiency, this extra renal elimination of uric acid may be a major route of disposal.

The mechanisms controlling intestinal elimination of uric acid are not well understood. The amount secreted into the lumen is probably related to the plasma concentration, so that a higher fraction of daily uric acid production may be excreted via gastro intestinal tract in hyperuricemic individuals than in normal. It is not thought that intestinal elimination of uric acid represents an important regulator of the plasma uric acid concentration.[34]

On the other hand, renal excretion is the major regulator of plasma uric acid, decreases or increases in renal clearance are readily

reflected by inverse changes in plasma uric acid concentration.

Steele and Rieselbach proposed the four component model of renal handling of uric acid mechanism. It includes-

1. Glomerular filtration
2. Presecretory tubular reabsorption.
3. Tubular secretion
4. Postsecretory reabsorption

Normally, uric acid is totally filtered in the renal glomeruli and then the filtered load is completely reabsorbed in the proximal tubules. 5-10% is later secreted into the distal tubules and excreted in the urine. The filtered uric acid undergoes extensive absorption with atleast 98% of the filtered load reabsorbed. Recent evidences suggest that much of the secreted uric acid undergoes extensive reabsorption.

All four components are influenced by other factors. Since uric acid binding by plasma protein is thought not to be important, the rate of uric acid filtration should vary directly with changes in glomerular filtration rate. Tubular reabsorption is an active process closely related to sodium reabsorption. Expansion of extracellular fluid volume increases the uric acid clearance by inhibiting its tubular reabsorption. Conversely, contraction of extracellular fluid volume, decreases the uric acid clearance, enhancing its tubular reabsorption, thereby leading to hyperuricemia.

The tubular secretory component is directly proportional to plasma uric acid concentration. Secretion may be decreased, if the transport pathway is competitively inhibited by other organic acids. In summary, normally kidneys excrete an amount equivalent to 5-10% of the filtered load of uric acid.

Altered renal excretion of uric acid exhibiting hyperuricemia could be due to -

1. Reduced filtration of uric acid
2. Enhanced reabsorption.

3. Decreased secretion.

No unequivocal data establish any one of these mechanisms as the basic defect, and it is likely that all three are operative within the hyperuricemic population.

Patients with renal disease usually have a reduction in glomerular filtration rate leading to decreased filtered load of uric acid and thus hyperuricemia.

Tubular reabsorption of uric acid is an active process that is closely related to sodium reabsorption. Therefore states of volume contraction (with enhanced sodium reabsorption) are accompanied by increased uric acid reabsorption and decreased uric acid clearance. Diuretic induced volume depletion leads to enhanced tubular reabsorption of uric acid as well as decreased uric acid filtration.

In some situations hyperuricemia has been attributed to competitive inhibition of uric acid secretion by excess organic acids thought to be secreted by the same renal tubular mechanism responsible for uric acid secretion. Examples include starvation (ketosis and free fatty acids), alcoholic ketosis, diabetic ketoacidosis, maple syrup urine disease and lactic acidosis of any cause.

HYPERURICEMIA

This may either be due to increased production or decreased excretion of uric acid or from a combination of the 2 processes. It is defined as a serum concentration more than 420 µmol/L is 7mg/dl as based on physicochemical, epidemiologic and disease-related criteria, in epidemiologic studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population. When measured, in unselected individuals, 95% have serum uric acid concentration <420µmol/L (7mg/dl). In relation to the risk of the disease, uric acid levels 420µmol/L is associated with the risk of gouty arthritis and escalates in proportion to the degree of elevation. Hyperuricemia is reported in 2-13.2% of ambulatory adults.

CAUSES:[35-38]

1) Uric acid overproduction

- Primary idiopathic
- HGPRT deficiency
- PRPP synthetase overactivity
- Hemolytic processes
- Lymphoproliferative diseases
- Myeloproliferative diseases
- Polycythemia vera
- Psoriasis
- Paget s disease
- Rhabdomyolysis
- Exercise
- Alcohol
- Obesity
- Purine-rich diet
- Glycogen storage diseases (types V, VII)

2) URIC ACID UNDER EXCRETION

- Primary idiopathic
- Renal insufficiency
- Polycystic kidney disease
- Diabetes insipidus
- Hypertension
- Acidosis-lactic acidosis, ketoacidosis
- Berylliosis
- Hypothyroidism
- Hyperparathyroidism
- Toxemia of pregnancy
- Lead intoxication
- Bartter"s syndrome
- Down"s syndrome
- Drugs
- Salicylates (>2 g/d)
- Diuretics

- Alcohol
- L- dopa
- Ethambutol
- Pyrazinamide
- Nicotinamide
- Cyclosporine

3) COMBINED MECHANISM

- Glucose-6-phosphate Dehydrogenase deficiency
- Alcohol
- Shock
- Fructose-1-phosphate aldolase deficiency.
- Physical exercise
- Status epilepticus
- Myocardial infarction
- Acute respiratory failure

HYPOURICEMIA:

It is defined as a serum uric acid concentration less than 180 µmol/L; i.e. 3mg/dl. It may occur as a consequence of decreased formation of uric acid or increased renal clearance of uric acid. It can also result when the activity of xanthine oxide is reduced, either because of deficiency of the enzyme, as in xanthinuria, or when there is pharmacologic inhibition of xantine oxidase by allopurinol.

Renal causes of hypouricemia range from isolated defects of uric acid reabsorption to more complex abnormalities of renal tubular function. The amount of uric acid finally excreted in urine appears to depend on the balance between tubular secretion of uric acid and the so-called post- secretory reabsorption of secreted uric acid. In contrast to hyperuricemia, which has been studied extensively, only recent observations have suggested that hypouricemia may prove an important clue for the existence of underlying disease processes.

30 years ago, Ramsdell and Kelley in a short communication, looked at the clinical significance of hypouricemia in a hospital population, but some of their plasma uric acid determinations were

performed using the colorimetric phosphotungstate method which is not as specific for uric acid as the uricase method which is now preferred.[39],[40]

In a study done in UK, the prevalence of hypouricemia in hospital population was studied. Prevalence was reported to be 6.5% among the males and 4.8% among the females. The large group displaying hypouricemia, was intensive care patients, possibly due to a combination of alteration in the renal handling of uric acid and reduced dietary intake of protein. The author reports that in the study, a large group of patients (14%) who manifested hypouricemia, were those with diabetes mellitus, 10% of whom were on insulin and 4% on sulphonylureas.[41]

CAUSES OF HYPOURICEMIA:[42]

- Total parenteral nutrition
- Cirrhosis
- Neoplasms
- Diabetes mellitus
- Syndrome of inappropriate secretion of ADH
- Fanconi syndrome
- Xanthine oxidase deficiency
- Drugs
  - Ascorbic acid
  - Dicoumarol
  - Diflunisal
  - Sulfinpyrazone
  - NSAIDs
  - Probenecid
  - Estrogen

OXIDATIVE STRESS[43]

UA is a marker of oxidative stress, and may have a potential therapeutic role as an antioxidant .On the other hand, like other strong reducing substances such as ascorbate, UA can also act as a pro oxidant, particularly at elevated levels. Thus, it is unclear whether elevated levels of uric acid in diseases associated with oxidative stress such as stroke and atherosclerosis are a protective response or a primary

cause. Some researchers propose Hyperuricemia-induced oxidative stress is a cause of metabolic syndrome. On the other hand, plasma uric acid levels correlate with longevity. In primates and other mammals. This is presumably a function of uric acid's antioxidant properties.

INDICATIONS FOR URIC ACID LOWERING THERAPY:

- Initiation of chemotherapy or radiation therapy.
- History of kidney stones.
- History of gouty attacks (>2 per year), tophi.
- Moderate Renal function impairment (creatinine clearance <42 mL/min) Renal dysfunction.
- Markedly elevated uric acid levels (12 mg/dL in men or women).

Hyperuricemia is a biochemical abnormality, Not a disease. Indications for lowering uric acid is clear. Drug therapy to lower UA (ULT) for CVD prevention is not advised as per current evidence.

URIC ACID ESTIMATION [44].

The method used for analysis is enzymatic method (Uricase method) by using auto analyzers. In our laboratory, values taken as normal range is as follows :

Males 3.1 – 7.0 mg/dl
Females 2.5 – 5.6 mg/dl

Methods using Uricase, the enzyme that catalyses the oxidation of uric acid to allointoin are most specific. The simplest of these methods measures the differential absorption of uric acid and allointoin at 293nm.The differential absorption before and after incubation with Uricase is proportional to uric acid concentration.

This method has been proposed as candidate reference method, and is the most specific method.

BRIEF ACCOUNT OF THE LIPID CHEMISTRY

The lipids are a heterogenous group of compounds including fats, oils, steroids, waxes and related compounds that are related more by

their physical than chemical properties.

The lipids have following functions.

1. They are important dietary constituents not only because of their high energy value, but also because of the fat soluble vitamins and essential fatty acids contained in the fat of natural foods.
2. Fat is stored in adipose tissue, where it also serves as a thermal insulator in the subcutaneous tissues and around certain organs.
3. Non polar lipids act as electrical insulators, allowing rapid propagation of depolarization waves along myelinated nerves.
4. Combination of lipid and protein (lipoproteins) serve as the means of transporting lipids in the blood.

The lipids are classified as given below.[45]
A) Simple lipids :(esters of fatty acid with various alcohols)

- Fats: esters of fatty acids with glycerol. Oils are fats in liquid state
- Waxes: esters of fatty acids with higher molecular weight monohydric alcohols.

B) Complex lipids: These are esters of fatty acids containing groups in addition to an alcohol and a fatty acid groups)

- Phospholipids: lipids containing in addition to fatty acids and an alcohol, a phosphoric acid residue.
- Glycolipids: lipids containing a fatty acid, sphingosine and carbhohydrate.
- Other complex lipids: lipids such as sulfolipids and aminolipids. Lipoproteins may also be placed in this category.

C) Derieved lipids: These include fatty acids, glycerol, steroids, other alcohols, fatty aldehydes, hydrocarbons, lipid soluble vitamins and hormones.

FATTY ACIDS
They are present as such in minute concentrations in plasma cells. Fatty acids occur mainly as esters in natural fats and oils but do occur in the unesterified form as free fatty acids, a transport form found in the

plasma. Fatty acids that occur in natural fats are usually straight chain derivatives containing an even number of carbon atoms.

Lipid Chemistry

Fatty acids are of two types

a. Saturated fatty acids - Those which contain no double bonds.
b. Unsaturated fatty acids- Those which contain one or more double bonds.

Saturated fatty acids having 10 or less carbon atoms are called "Lower fatty acids" e.g. - Acetic acid, butyric acid

Saturated fatty acids having more than 10 carbon atoms are Called "higher fatty acids". e.g. - Palmitic acid, stearic acid. Unsaturated fatty acids are classified according to degree of saturation.

1. **Mono unsaturated fatty acids -** These are those fatty acids which contain one double bond. E.g. Oleic acid.
2. **Polyunsaturated fatty acids -** These are fatty acids which contain more than one double bond.
   eg. Linoleic acid
   series Linolenic acid
   series Arachidonic
   acid series

Essential fatty acids are those which cannot be synthesized in body and must be provided in the diet. Lack of these essential fatty acids in diet can produce growth retardation and other deficiency syndromes. Free fatty acids are immediately available energy source and provide much of the energy requirements of body. Normal value ranges from 250 - 400 mg / dl.

CHOLESTEROL

Cholesterol is widely distributed in all cells of the body. It is the best known steroid because of its association with atherosclerosis and heart disease.

It occurs as a white or faintly yellow, almost odorless, pearly leaflets

or granules. It is insoluble in water. Sparingly soluble in alcohol and soluble in ether, chloroform, hot alcohol, ethyl acetate alcohol and vegetable "oil.

Cholesterol is found in largest amounts in normal human adult brain and nervous tissue of about 20%, in liver - 0.3%, skin - 0.3%, intestinal mucosa 0.2% and certain endocrine glands namely adrenal cortex contain about 10%.

The normal level of serum total cholesterol in adults varies from 150-**250 mg/dl**

TRIGLYCERIDES (NEUTRAL FATS)
These molecules are used to provide energy. In the body, stored fat in adipose tissue is the storage form of energy.

Important sites of adipose tissue are subcutaneous tissue around some internal organs and omentum. Fat under the skin prevent heat loss in winter and the intestinal organs get support from fat around them. The triglycerides constitute the body's main caloric reserve. Normal value ranges from 40-150 mg %.

PHOSPHOLIPIDS
Phospholipids are compound lipids. They contain in addition to fatty acids and glycerol one more alcohol or phosphatidic acid, residue nitrogen containing base and other substituents.

Phosphatidic acid is important as an intermediate in the synthesis of triacylglycerols as well as phosphoglycerols but is not found in any great quantity in tissues.

They are classified into 3 groups.
1. Glycerophopsholipid - Here glycerol is the alcohol group.
eg - Lecithin, Cephalin

2. Phospho inositides - Here inositol is the alcohol group.
eg - phosphatidylinositol

3. Sphingophospholipids - Here sphingol is the alcohol group.

sialic acid. Neuraminic acid is the principal sialic acid found in human tissues. Gangliosides are present in nervous systems in high concentration.

LIPO PROTEINS OF PLASMA

In plasma, cholesterol and triglycerides form integral component of macromolecule complex called lipoprotein which are conjugated proteins. Lipid part is the prosthetic group and lipid free protein are designated as apolipoproteins or apo proteins. Protein separation including electrophoresis and ultracentrifugation shows progress in lipoprotein chemistry.

Teselius et al in 1941 reported existence of two lipoprotein classes separated by moving boundary electrophoresis.

In 1954 Gofmen et al separated lipoproteins by ultra centrifugation into five major density classes.

Lipoproteins have been classified on the basis of their densities during ultracentrifugation into46:

OVERVIEW OF LIPOPROTEINS AND LIPOPROTEIN METABOLISM

Lipoproteins are microemulsions composed of lipids (cholesterol, cholesteryl ester, triglyceride and phospholipid) and proteins (apoproteins). Their function is to transport non water soluble cholesterol and triglycerides in plasma. Lipoproteins are spherical particles containing a central core of non-polar lipids (primarily triglycerides and cholesteryl ester) and a surface monolayer of phospholipids and apoproteins

1) Chylomicrons
2) Very low density lipoprotein (VLDL)
3) Low density Lipoprotein (LDL)
4) High density lipoprotein
5) Lipoprotein a

eg - Sphingomyelin

The lecithins are the most abundant phospholipids at the cell membrane and represent a large portion of body's store of choline.

Dipalmitoyl lecithin is a very effective surface active agent and a major constituent of the surfactant preventing adherence, due to surface tension of the inner surface of lungs.

Phosphatidylethanolamine (cephalin) and phosphatidyl serine differ from phosphatidylcholine ony in that ethanolamine or serine, respectively replaces choline.Sphingomyelins are found in large quantities in brain and nerve tissue.

On hydrolysis, the sphingomyelins yield a fatty acid, phosphoric acid, choline and a complex amino alcohol, sphingosine. No glycerol is present. The combination of sphingosine plus fatty acid is known as ceramide, a structure also found in the glycophospholipids.
glycophospholipids.

GLYCOLIPIDS

Glycolipids are widely distributed in every tissue of the body, particularly in nervous tissue such as brain. They occur particularly in the outer leaflet of the plasma membrane, where they contribute to cell surface carbhohydrates.

The major glycolipids found in animal tissues are glycosphingolipids. They contain ceramide and one or more sugars. Galactosylceramide is a major glycosphinglipid of brain and other nervous tissue, found in relatively low amounts elsewhere. It contains a number of characteristic C24 fatty acids, eg, cerebronic acid.

Galactosylceramide can be converted to sulfogalactosylceramide (sulfatide), present in high amounts in myelin. Glucosylceramide is the predominant simple glycosphingolipid of extraneural tissues, also occurring in the brain in small amounts.

Gangliosides are complex glycosphingolipids derived from glucosylceramide that contain in addition tone or more molecules of

CLASSIFICATION OF LIPOPROTEINS

Lipoproteins	Source	Diameter(nm)	Density(g/ml)	Composition		Mainlipid components
				Protein(%)	Lipid(%)	
Chylomicrons	Intestine	90-1000	<0.95	1-2	98-99	Triacylglycerol
VLDL	Liver	30-90	0.95-1.006	6-8	92-94	Triacylglycerol
LDL	VLDL	20-25	1.019-1.063	21	79	Cholesterol
Lp(a)		25-35	1.040-1.063	36	55	Cholesterol
HDL	Liver,intestine,VLDLchylomicrons					PhospholipidsCholesterol
HDL1		20-25	1.019-	32	68	
HDL2		10-20	1.063-1.125	33	67	
HDL3		5-10	1.125-1.210	57	43	

CHYLOMICRONS

Chylomicrons are the largest of lipoproteins. They measure about 90-1000nm in diameter and they have the least density as compared to other classes of lipoproteins.

These are particles that are primarily triglyceride bearing and are produced by the intestine after exogenous fat undergoes digestion. These are responsible for the transport of dietary triglycerides and cholesterol. Dietary triglycerides are hydrolyzed in the gut, releasing monoglycerides and fatty acids that are then reesterified to form triglycerides in the intestinal mucosal cell.

These triglycerides are assembled with newly absorbed cholesterol, apoprotein B48 and the A apoproteins. Upon secretion from the enterocyte, these assembled particles enter the lymphatic circulation and then the bloodstream, where they acquire C apoproteins and apo E by transfer from HDL.

As chylomicrons enter the plasma, the triglycerides are rapidly hydrolyzed by the enzyme lipoprotein lipase (LPL), which resides on the surface of capillary endothelial cells. LPL is synthesized primarily in adipose tissue and striated muscle. It is secreted and transported to the endothelial surface, where it acts on triglyceride rich particles. Its action requires the presence of apo CII on the surface of the lipoprotein, whereas apo CIII inhibits LPL.

As triglyceride is depleted from the chylomicrons, phospholipids and A and C apoproteins are transferred to HDL. The residual chylomicron particle, which has lost 80 to 90 % of its triglyceride and is now relatively cholesterol enriched is called chylomicron remnant.

VERY LOWDENSITY LIPOPROTEINS

VLDLS are synthesized in the endoplasmic reticulum of hepatocytes and are composed of endogenous triglyceride derived from plasma free fatty acids, chylomicron remnants and from de novo lipogenesis.

Nascent VLDLs are secreted into the circulation; contain apoB100 and small amounts of apo C and apo E. After VLDLs enter the circulation, they are metabolized in the same manner as chylomicrons by the

particle stays in circulation for longer periods of time, and becomes more vulnerable to undesired modifications (e.g. oxidation). As high levels of oxidized LDL are commonly found in atherosclerotic plaques, they are thought to be the major inducer of atherosclerotic lesions. Hence, LDL became known as bad cholesterol

HIGH DENSITY LIPOPROTEINS

HDLs also are represented by a spectrum of particles of various sizes and densities. HDLs are 18-25nm in diameter.

HDL is synthesized in the liver and intestine as a nascent, discoid-shaped particle that contains predominantly apoA-I, and some phospholipids.46 Upon maturation, HDL assumes a spherical shape, and the composition of its core lipids becomes very similar to that of LDL. However, the relative higher protein content in HDL renders the particle denser and more resistant to undesired modifications.

Unlike LDL, HDL is not recognized by LDL-R, and cannot deliver cholesterol to tissue cells. Instead, it has the ability to remove excess peripheral cholesterol and return it to the liver for recycling and excretion. This process, called reverse cholesterol transport, is thought to protect against atherosclerosis. Observational studies over the last 2 decades have consistently shown strong correlation between elevated HDL levels and low incidents of coronary artery disease (CAD). Hence HDL has been dubbed "good" cholesterol.

LIPOPROTEIN (a)

Lipoprotein (a) or Lp (a) has been established as an independent CAD risk factor. The structure is similar to that of an LDL molecule linked by a disulphide bridge to apoprotein A.

Lp (a) levels range from 1-100mg /dl with the largest number of values below 20 mg/dl.

Although Lp (a) is structurally similar to LDL, the former appears to be regulated independently and carries an independent relation to overall coronary risk. If serum levels of both LDL and Lp (a) are elevated the risk of CAD is markedly increased.

enzyme LPL, with the fatty acids that are liberated following the same fate as those liberated from chylomicrons. After secretion, VLDLs acquire more C and E apoproteins by transfer from HDL. In addition, free cholesterol is progressively exchanged to HDL, where it is esterified and the cholesteryl ester is returned to VLDL.

As VLDLs become progressively depleted of triglyceride, a portion of the surface, including cholesterol, apolipoproteins C and E and phospholipids is removed and contributes to nascent HDL particles.

LOW DENSITY LIPOPROTEINS

LDLs are products of the metabolism of VLDL. They have got a diameter of 18-25nm. The only apoprotein in LDL is apo B and only one molecule of apo B is present per particle of LDL. Clearance of LDL is mediated by a specific receptor present on the surface of both liver and peripheral cells. Once it is bound to the receptor, the lipoprotein is internalized by an endocytic process. The vesicle then fuses with a lysosome, where enzymes degrade the apoB and hydrolyze the cholesteryl ester to free cholesterol.

The smaller remnants of VLDL are triglyceride depleted, cholesterol rich particles, some of which are isolated in the IDL compartment, although some remain in the VLDL compartment.

VLDL particles are believed to be secreted in a spectrum of sizes with various degrees of triglyceride enrichment. The larger VLDL particles appear to be more rapidly cleared and less likely to be converted to LDL. On the other hand, smaller VLDL particles that are richer in cholesterol may be preferentially converted to LDL.

All peripheral cells express the LDL-receptor (LDL-R), and recycle it to the cell surface upon need for cholesterol. Cholesterol is delivered to these cells through binding of LDL to LDL-R, which triggers endocytosis (internalization) of both species. When the need for cholesterol is satisfied, the recycling of LDL-R is discontinued. Normally, an LDL particle stays in circulation for no more than a few days before being consumed by a cholesterol needing cell.

However, under conditions of sustained cholesterol excess, the

The mechanism by which high levels of Lp (a) are related to coronary atherosclerosis is unclear. It has been suggested that because of the structural similarities of Lp (a) to plasminogen, high levels of Lp (a) may inhibit the thrombolytic activity of naturally occurring tissue plasminogen activity.

An alternative explanation for the association between elevated Lp (a) levels and atherosclerosis in that Lp (a) may somehow alter the LDL mediated delivery of cholesterol to the atherosclerotic plaque.

APO PROTEINS

Apo proteins are key lipoprotein components that serve both as enzymatic cofactors and as recognition elements that bind to specific receptors on peripheral tissues, including the vascular endothelial cells.

It is the Apo E component of the chylomicron remnant that is recognized by receptors on the hepatocyte. This apoproteins are distinguished alphabetically and numerically as Apo A I through Apo E.

A great deal of research has been conducted in the use of apoproteins as CAD markers. Some investigations have found that the concentration of Apo AI and Apo B 100 are better predictors of CAD then are measurements of total plasma lipids or lipoprotein.

Apoprotein – A

Apo AI, the prototype of Apo A, is a major protein in HDL and also is seen in chylomicrons.

Apo AII is a minor constituent of HDL and does not appeal to be present in all species. Human Apo AII is of hepatic origin. Apo AII maybe an activator of hepatic triglyceride lipase which hydrolyses triglyceride and phospholipid while utilizing HDL2 as its preferred substrate. Apo A IV is synthesized in the gut and is present in HDL, chylomicrons and as a free protein. It may also be an activator of LCAT.

The genetic codes for Apos AI, A IV and CIII are close together on the long arm of chromosome II. Combined AI CIII deficiency is associated with severe premature atherosclerosis.

Apoprotein - B

Apo B occurs in two forms namely Apo B 100 and B28. Apo B 100 is found in VLDL, IDL, and LDL. Apo B 100 is the primary apoprotein of LDL and accounts for 25% of its weight. It is also the recognition site for the LDL, or Apo B/E receptor on cell surfaces. The gene for Apo B 100 has been localized to chromosome 2.

The structure in the amino acid sequence of human Apo B 100 and the corresponding CDNA messenger CID has recently been determined. A unique editing mechanism introduces a stop codon into the mRNA for Apo B by means of single base change. This allows the biosynthesis of two proteins from a single gene and mRNA with either Apo B -100 or Apo B 48 being synthesized. Apo B 48 is synthesized by small intestine and Apo B 100 is secreted by the liver.

Apoprotein - E

Apo E accounts for about 15 percent of the protein content of VLDL, 7 percent of chylomicron remnants and 2 percent of protein content of HDL.

It can be recognized by the LDL or Apo B/E receptor and by specific Apo E receptors in the liver whose function appears to be the removal of chylomicron remnants Apo E is polymorphic and contains three major alleles, Apo E2, E3 and E4. The various combinations results in homozygote are Apo E2/2 EG/4. Also Apos E2/3, E2/4 and E3/4 exist in the heterozygous state. The polymorphism of Apo E has been determined on a molecular basis and results from the substitution of an amino acid at residues 112 and 158 in the protein. Apo E isoform may account for as much as 15 percent of variability of cholesterol and LDL levels in the population.

Recent Finnish studies suggest that Apo E4 may be associated with increased cholesterol absorption in the GI tract.

ATP 3 guidelines of Dyslipidemia:

- Total Cholesterol >200 mg/dl
- Triglycerides >200 mg/dl
- HDL <40 mg/dl
- LDL >190 mg/dl

3 CONCLUSION

Developing countries like India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India. Stroke is becoming an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors like hyperuricemia and dyslipidemia. Both of these factors are involved in atherosclerosis and endothelial dysfunction which leads to narrowing of vessels and leads to ischaemia.

In conclusion hyperuricemia and dyslipidemia can be taken as risk factors for ischaemic cerebrovascular accidents.

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