Etiology of Hyperuricemia

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ABSTRACT

The purpose of this review is to provide a survey of the mechanisms by which hyperuricemia may occur and to acquaint the reader with the specific and numerous etiologies of hyperuricemia.

Introduction

The automated biochemical analysis of patients undergoing routine and diagnostic evaluations has made the serum uric acid (SUA) determination much more generally available. As a result, there is an increasing number of cases of hyperuricemia. The incidence of hyperuricemia in apparently healthy subjects has been estimated to be between 4.5 percent and 12 percent; in the overall population (including patients), the incidence has become as high as 15.5 percent.\(^1\) The discovery in such an instance of hyperuricemia has implications beyond merely the confirmation of the presence of gout. The significance of the discovered hyperuricemia lies in the detection of an impending hyperuricemic nephropathy, the uncovering of diverse and interesting enzyme disorders, the elucidation of associated biochemical mechanisms of disease and, more importantly, the potential seriousness of the underlying etiology (for example, leukemia). The literature has been reviewed to indicate that there are many different factors influencing the level of SUA. The commonest of the numerous etiologies of hyperuricemia appear to be renal failure, ketoacidosis or lactate excess and the use of diuretics.

Homeostatic Mechanisms

The level of SUA is determined by such factors (figure 1) as inflow of uric acid precursors from dietary intake as well as endogenous purine sources, the integrity of the outflow systems of urinary and fecal excretion, the volume of the extracellular compartment and probably the state of urate binding plasma proteins. Much of the daily production of uric acid is eliminated in gastrointestinal outflow (9 to 45 percent) but there is little or no primary influence of this fecal excretion in the pathogenesis of hyperuricemia.\(^1\) Despite the absence of uricase in humans, uricolyis does occur in the intestinal tract by bacterial degradation.

Almost always hyperuricemia means an increase in total body uric acid and the SUA is usually proportional to the size of the uric acid pool. As shall be seen, the usual causes of hyperuricemia are overproduction or underexcretion of uric acid or a combination of both.

Cellular endogenous sources of uric acid include de novo synthesis, alternate mechanisms of formation of purine nucleotides, cell destruction, the various enzyme disorders as well as the disorders inducing an overproduction of such uric acid precursors as adenosine monophosphate (AMP), gua-
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**METABOLIC PATHS**

- De Novo Synthesis (enzyme disorders)
  - Glutamine and Phosphoribosylpyrophosphate
- Preformed nucleotides
  - Salvage pathway (necrosis, myeloproliferative disease, enzyme disorders)
- Purine Nucleotides
  - AMP
  - GMP
  - XANTHINE
- Adenine
- Hypoxanthine
- Guanine

**GASTROINTESTINAL + RENAL PATHS**

- Diet
- Uric Acid
- Renal disease Drugs, Lactate, Enzyme disorders
- Liver

Figure 1. Uric acid inflow to and outflow from the serum.

Uric acid is regulated in the kidney by bi-directional transport. About 98 percent of the uric acid filtered is reabsorbed in the proximal tubule; tubular secretion is believed to be the major route of excreted urate. The normal renal response to an increased uric acid load is by augmented tubular secretion, thus tending to prevent hyperuricemia.

Variables which normally influence the SUA level include:

**Sex.** Males have approximately 1 mg per 100 ml higher values than females and an endocrine basis for this is quite likely rather than differences in body mass.

**Age.** There is a particularly sharp rise at puberty and in the female an 0.8 mg per 100 ml increase at middle age; otherwise there is no direct relationship between age and SUA.

**Body Weight.** The SUA is approximately 4 mg per 100 ml at 100 pounds and 6 mg per 100 ml at 180 pounds. The Tecumseh Health Study demonstrated a direct relationship computed by regression equations.

**Exercise.** The SUA may rise as a result of the influence of exercise on lactate suppression of urate clearance, on diminishing glomerular filtration and on increasing tubular reabsorption.

**Diet.** Purines are derived from such sources as nucleoproteins, chromosomes, ribonucleic acids and adenosine triphosphate. Thus, guanine, hypoxanthine and xanthine coming from such sources are degraded to uric acid by guanase and xanthine oxidase in the intestinal epithelium. The SUA in any one individual may vary as much as 1 mg per 100 ml depending on the load of preformed purines ingested.
Method of Laboratory Determination.
The difference between one method and another may be as much as 1 mg per 100 ml. A wide variety of phosphotungstic acid, enzymatic, colorimetric and spectrophotometric procedures have been available for the determination of SUA. Because of numerous technical variables and inherent errors, the proper interpretation of the results requires comparing an individual value with the range of normal levels of SUA for that particular laboratory method used.

Definition
As frequently used, the term hyperuricemia refers to those values of SUA extending beyond two standard deviations from the mean of a total population sampled. Using the enzymatic ultraviolet spectrophotometric method, the normal adult male SUA is 5.5 with a range of 3.1 to 7.9 mg per 100 ml. That of females is 1 mg per 100 ml lower until after the menopause. Some authorities define hyperuricemia as levels greater than 7.0 for men and 6.0 mg per 100 ml for women.

Factitious Hyperuricemia
Drugs may produce an artifact when chromogens interfere with the colorimetric technique. The automatic clinical Analyzeraca (Dupont copper chelate method) exhibits falsely high levels particularly with L-dopa, ascorbic acid, glutathione and resorcinol. The Technicon SMA 12-60 is influenced by L-dopa, ascorbic acid, isoniazid, alpha-methyladopa and, to a slight extent, phenacetin. Alpha-methyladopa and L-dopa interfere with the phosphotungstic acid cyanide colorimetric technique. The phosphotungstate method of Folin and Dennis and its many variations are the most commonly used methods for SUA determination; these can be either manual or autoanalyzer (both colorimetric). The enzymatic ultraviolet spectrophotometric method of Liddle et al utilizing uricase is specific for urate and is not affected by reducing agents or chromogens.

Alcaptonuria can cause spuriously elevated SUA from homogentistic acid. Ingestion of caffeine and theophylline may reduce phosphotungstic acid and may falsely elevate the SUA level. Eliminating caffeine-containing beverages is not therapeutically appropriate.

Decreased Outflow
The commonest cause of all hyperuricemia is renal (table 1), particularly when one considers the increasing number of survivors of chronic renal disease with azotemia. The use of diuretics and the influence of fasting and drinking alcohol on urate retention also contribute to the prevalence of the decreased outflow mechanisms of hyperuricemia.

RENAL FAILURE
In renal failure, the SUA does not usually rise above 10 mg per 100 ml, even in severe uremia apparently because of active gastrointestinal uricolysis. The hyperuricemia has been attributed to reduced glomerular filtration rate with a reduction in the filtered urate load. This hyperuricemia of renal insufficiency (chronic nephritis, pyelonephritis, etc.) only rarely results in classic gout (gout occurring in one percent of uremics). Occasionally, hyperuricemia precedes the elevation in plasma urea nitrogen in chronic renal disease, but in many patients the uric acid levels are not elevated to the same degree as the urea nitrogen. In fact, markedly enhanced renal urate excretion may be another inhibiting factor in the prevention of extreme hyperuricemia in chronic renal failure; reabsorption of filtered urate also diminishes under these circumstances. Although the hyperuricemia of chronic renal failure is generally attributed to diminished glomerular filtration, glycine uptake studies indicate that excessive purine synthesis contributes to the high SUA.
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TABLE I

Etiology of Hyperuricemia

I. Decreased Outflow
1. Renal failure
2. Organic acids (lactate and ketoacids): alcohol, starvation, diabetic acidosis, catecholamines, smoke inhalation, fructose ingestion or infusion, glycogen storage disease type I, branched-chain ketonuria, ethylene glycol poisoning
3. Drugs: diuretics, pyrazinamide, ethambutol, angiotensin, methoxyfluorane anesthesia and low dose probenecid, salicylate and sulfinpyrazone
4. Primary gout (some of the cases)
5. Hypertension
6. Toxemia of pregnancy
7. Down's syndrome
8. Polycystic kidneys (in absence of azotemia)
9. Beryllium poisoning
10. Lead poisoning

II. Increased Inflow
1. Myeloproliferative diseases: leukemia, lymphoblastoma, polycythemia, multiple myeloma, myelofibrosis, megalakocyte myelosis, non-myeloproliferative malignant neoplasms
2. Tissue catabolism, necrosis or excessive release of nucleotides: hemolytic anemia, sickle cell anemia, immunosuppressive agents, alkylating drugs, x-ray therapy, cerebral and myocardial infarction, fructose, psoriasis, heat stress
3. Increased de novo synthesis of purines: HGPRT deficiency, increased PRPP synthetase activity, APRT deficiency, glycogen storage disease type I, glutamic acid dehydrogenase, benign symmetric lipomatosis, branched-chain ketoaciduria, primary gout (some cases), autism, absence of tears and dental dysplasia
4. Diet

III. Miscellaneous Etiologies
1. Endocrine: hypothyroidism, acromegaly, hypoparathyroidism, hyperparathyroidism, nephrogenic diabetes insipidus, hyperglycemia, epinephrine-injections
2. Intoxications: barbiturates, methyl alcohol, chloroform, carbon monoxide, ammonia
3. Contracted extracellular volume: dehydration, salt restriction, diuretics
4. Associations with unclear mechanisms: psychosocial factors, vitamin B12 treatment in B12 deficiency states, during labour and immediately after delivery, obesity, idiopathic hypercalciuria, Gilles de la Torette syndrome, sarcoidosis, liver disease

ORGANIC ACIDS

Most cases of hyperuricemia of renal origin appear to be caused by diminished tubular secretion of urate rather than reduction in glomerular filtration rate. The formation of organic acids appears to be a factor common to such hyperuricemia etiologies as ingestion of alcohol, starvation, diabetes, following exercise, administered loads of acetooacetate, fructose and beta-hydroxybutyric acid, catecholamines, high fat diet as well as smoke inhalation. The mechanism appears to be diminished tubular secretion when lactate, branched chain ketoacids, beta-hydroxybutyrate and acetocacetate are increased.

When alcohol is metabolized in the liver, it is converted to acetaldehyde with the aid of alcohol dehydrogenase. The parallel reduction of nicotinamide adenine dinucleotide couples the reduction of pyruvate to lactate. The resultant excess lactate competes with urate at the tubular secretory site. The SUA has been known to increase from a baseline of 4 to a level of 11 mg per 100 ml with acute alcoholic intoxication, but the trend is a twofold rise in blood lactate and a 50 percent increase in SUA.

Although starvation may lead to hyperuricemia and even precipitate gout, the process of slowly losing weight by diminishing caloric intake (in contrast to complete fasting) is effective in alleviating the hyperuricemia of obesity. The plasma acetone of obese subjects in non-diabetic fasting states may increase to marked levels and the SUA to more than 150 percent of the control level; the SUA in a total fast may reach 15 mg per 100 ml.

Hyperlactic acidemia may be the important factor in the hyperuricemia of pregnancy particularly with toxemia. In addition to this inhibition of tubular urate secretion, the hyperuricemia of pre-eclampsia may also be attributable to postural alterations, the associated changes in renal solute disposition in pregnancy or an enhanced activity of the renin-angiotensin system.

An increased concentration of acetooacetate and beta-hydroxybutyrate is probably responsible for the hyperuricemia of diabetic ketoacidosis during which the SUA may reach 17.6 mg per 100 ml.
ditions may lead to lactate-induced hyperuricemia but the long term influence of exercise in athletes induces a decreased SUA. 4

Glycogen storage disease type I is due to glucose-6-phosphatase deficiency, and the high incidence of hyperuricemia and gout in this enzyme disorder is caused by lactic acidemia and/or excessive purine biosynthesis. The range of SUA levels in some series is 11 to 16 mg per 100 ml.

Another example of an enzyme disorder resulting in organic acid as a mechanism in inducing hyperuricemia is branched chain ketonuria; classic maple syrup disease is a disorder of diminished ketoacid decarboxylase activity manifesting retardation of mental and motor development, convulsions, coma and short survival. Intermittent and mild forms of this disease occur.

Smoke inhalation (other than cigarette smoking) can elevate the SUA to 9 to 14 mg per 100 ml, presumably by the hypoxic stimulus to lactic acidemia. 2

Ethylene glycol poisoning may increase SUA to 15.6 mg per 100 ml in association with elevated lactic acid levels.

Forty percent of patients with beryllium poisoning develop hyperuricemia. 13 This chemical intoxication occurs with long term exposure to beryllium in such industries as ceramics, foundry work and fluorescent bulb manufacture. The SUA is as high as 12 mg per 100 ml. Although the exact cause for the diminished urate excretion is unknown, hyperlacticacidemia again may be a contributing factor.

DRUG-INDUCED HYPERURICEMIA

Drugs which inhibit uric acid excretion include chlorthiazide, hydrochlorothiazide, furosemide, acetazolamide, ethacrynic acid, clopamide, quinethazone, triamterene and bendroflumethiazide and clonidine (catapres). Low doses of uricosuric drugs such as probenemid, sulfipyrazone and salicylate, may cause urate retention. 35 Other drugs such as angiotensin, catecholamines and the anti-tuberculous agents pyrazinamide and ethambutol increase SUA by renal mechanisms. The diuretics have variable mechanisms including volume depletion (diminished extracellular compartment), stimulation of uric acid synthesis (acetazolamide), inhibition of tubular secretion and enhanced reabsorption. 30 In those patients exhibiting a diuretic-induced hyperuricemia, the increase above the pretreatment level has ranged from a 1 to 4 mg increment. For example, patients with hypertension may have a pre-treatment SUA of 10 and then 14 mg per 100 ml after 6 days of a customary dose of a diuretic (e.g. 500 mg chlorthiazide or 50 mg hydrochlorothiazide). With discontinuation of the diuretic, the SUA can be expected to drop to 10 mg per 100 ml within a few days.

Methoxyfluorane anesthesia is occasionally associated with hyperuricemia, probably caused by fluoride-induced dysfunction of distal tubular secretion; in fact, the SUA is used as the most sensitive test for uncovering methoxyfluorane nephrotoxicity.

HYPERTENSION

Hypertensive patients exhibit a high incidence of hyperuricemia (separate from the influence of thiazide drugs and the possibility of hyperuricemic nephropathy). Although the specific renal mechanism has not been elucidated, reduced urate excretion may be secondary to intrarenal circulatory changes. A fairly direct relationship exists with the diastolic level in some patients. 7

PRIMARY GOUT

Primary gout (those idiopathic cases not considered secondary to such etiologies as myeloproliferative diseases or diuretics) has been conceived of as deriving from an intrinsic impairment of renal urate excretion at least in some cases, estimated as 30 to 40 percent of idiopathic gout cases. In these patients, an insufficient tubular secretory mechanism appears to be the fault while
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purine synthesis is normal. Thus, in patients with primary gout and their non-gouty relatives with hyperuricemia, impaired outflow alone can elevate the SUA. However, only a small number of gouty patients are known to have a specific renal lesion or known enzyme disorder. This complex subject has been adequately reviewed by others.30 Primary gout associated with increased inflow of uric acid into the serum or intracellular compartment is discussed in another section.

OTHER RENAL ETIOLOGIES

The hyperuricemia of Down's syndrome may be primarily caused by diminished renal clearance of uric acid,12 but overproduction of uric acid has been evident in some cases. Most of the hyperuricemic cases have only slightly higher SUA than normal, but some of the levels are in the 9 to 11 mg per 100 ml range.

Patients with polycystic kidney have as high as a 59 percent incidence of hyperuricemia as well as predisposition to gouty arthritis despite the absence of azotemia.22 The hyperuricemia of polycystic kidney disease is not related to the conventional form of renal failure in the late stage of this condition. A genetic coexistence of polycystic malformation and an unrelated hyperuricemia is therefore suspected.

Studies from different countries indicate that about half of the patients with chronic lead nephropathy have gout compared to an incidence of gout of approximately 5 percent with renal insufficiency unassociated with lead intoxication. Saturnine gout therefore appears to be a distinct entity, among the features of which is the high SUA (up to 10 mg per 100 ml) with normal BUN and creatinine.6 The hyperuricemia has been attributed to defective renal excretion of urate.

Increased Inflow

The inflow channel for uric acid, as it pertains to increasing the uric acid pool or the SUA, includes sources arising from dietary means, neoplastic overproduction, cell destruction characteristic of neoplasms, the excessive release of purine nucleotides as a result of disease processes and the increased synthesis of the immediate and remote precursors of uric acid. A 24-hour urinary uric acid determination is helpful in distinguishing between increased production from decreased renal clearance; patients with increased inflow into the serum will have a high urinary excretion, greater than 600 mg per 24 hours in association with normal or high urate clearance. Those with diminished urate renal outflow will have normal to low urine urate levels despite the high SUA.

MYELOPROLIFERATIVE OVERPRODUCTION

Among patients with gouty arthritis, as many as 10 percent have myeloproliferative disorders. These examples of secondary gout have higher levels of SUA than those with primary gout. Most of the hyperuricemia in leukemia, lymphoblastoma, macroglobulinemia of Waldenström, polycythemia, multiple myeloma, myelofibrosis and megalakaryocytic myelosis appears to derive from the breakdown of the increased mass of nucleoprotein inherent in these hematologic disorders. Other mechanisms include increased de novo synthesis of the immediate purine precursors of uric acid, the response to chemotherapy and radiation therapy in terms of cell lysis and further acceleration of nucleic acid turnover rates, and the infiltration of the kidney itself with leukemic or lymphomatous cells. Uric acid excretion is highest in acute lymphoblastic leukemia. The SUA in this form of leukemia has been reported to be 44 mg per 100 ml in one patient. However, the highest known SUA was reported recently, 92 mg per 100 ml, in a patient with lymphosarcoma being treated with prednisone, thioguanine and cytarabine.15 The incidence of gout in polycythemia vera is about 10 percent. Even the polycythemia of high altitude causes
hyperuricemia and the level of SUA correlates well with the patient’s hematocrit. Curiously, Hodgkin’s disease can sometimes lower the SUA by an as yet unidentified product of tumor metabolism that enhances renal tubular secretion of uric acid.

Hyperuricemia is seen in other malignant neoplasms such as neuroblastoma, Wilm’s tumor, rhabdomyosarcoma and may occur in any patient with disseminated neoplasm, particularly in the more anaplastic or rapidly growing tumors. There appears to be a direct relationship between the incidence of hyperuricemia and the mass of tumor cells, the rapidity of proliferation of neoplastic cells and the turnover of nucleic acid. However, patients with metastatic, non-myeloproliferative neoplasms do not show the high levels of SUA and the uric acid nephropathy as is seen in leukemia and lymphoma.

That the mechanism of hyperuricemia in neoplasms (table II) may not always be the release of purines from the nucleoprotein of destroyed cells is suggested by at least one tumor, a hepatoma, which exhibited the property of phosphoribosylpyrophosphate (PRPP) synthetase prompting the overproduction of purines.

OTHER DISEASES WITH EXCESS RELEASE OF NUCLEOTIDES

Hemolytic anemias and sickle cell anemia even in the absence of hemolysis have been associated with hyperuricemia and hyperuricosuria. Sickle cell anemia has a 40 percent incidence of hyperuricemia. Immuno-suppressive drugs, alkylating agents and x-ray therapy accelerate the process of released purines when administered to patients with malignancy. In some series of cerebral infarction cases, 30 percent have hyperuricemia. Similarly, a high incidence of hyperuricemia is seen after myocardial infarction. There is a controversy as to whether or not the necrosis is the cause of the hyperuricemia or if the two conditions are merely co-existing genetic traits. It is beyond the scope of this review to discuss the issue of validity regarding hyperuricemia as a so-called risk factor in coronary arteriosclerosis. Although more than 75 percent of gout patients have hypertriglyceridemia, the pathogenesis of hyperuricemia in these cases is obscure. In fact, in an attempt to correlate the serum uric acid with severity of coronary lesions and angiography, it has been concluded that there may not be a relationship between SUA concentrations and coronary heart disease.

Fructose ingestion in patients with congenital fructose intolerance as well as in normals can elevate the SUA by mechanisms other than the influence of the increased lactate on urate clearance. Fructose loading causes a rapid degradation of preformed purine nucleotides with the resultant production of inosine, hypoxanthine, xanthine and uric acid. In normals the SUA may increase by 1 mg, in gout patients by 2 mg and in relatives of gouty patients by 2 mg per 100 ml. In the process of increased uric acid production, there is some inhibition of de novo uric acid synthesis. While intravenous fructose and rapid ingestion of fructose cause hyperuricemia, the ingestion of even large loads of fructose more gradually over 24 hours in normals does not induce hyperuricemia.

Psoriasis, a condition of accelerated epidermopoiesis, is associated with an increased turnover of nucleoprotein and, hence, hyperuricemia.

Short term exercise has been known to elevate the SUA by virtue of the lactate interference with tubular secretion of urates.
However, heat stress as it occurs during intense physical training in hot climates causes uric acid overproduction and a high uric acid excretion. Probably during the course of skeletal muscle injury, heat stress causes a peak hyperuricemia by the 11th day reaching levels in some cases of 12 mg per 100 ml.16 Although acute renal failure does not occur, there is some nephropathy.

INCREASED DE NOVO SYNTHESIS OF PURINES

In a large percentage of gout patients, hyperuricemia is caused by increased rates of purine biosynthesis.34 The individual underlying enzyme disorders in some cases of primary gout are being discovered and suggest a heterogenous group of hyperuricemic metabolic errors (table III). Purine overproduction appears to be possible from the effects of a surplus of PRPP which by mass action promotes the amidotransferase sequence of biosynthesis thus:

PRPP and glutamine → PRPP amidotransferase → phosphoribosylamine

This is the first step programmed for purine synthesis. The phosphoribosylamine is then converted by a series of enzymatic reactions to the parent ribonucleotide inosinemonophosphate (IMP), and IMP is subsequently converted to AMP and GMP.

Underutilization of PRPP results in increased concentrations of PRPP, and this can be a driving force in purine biosynthesis. Thus, to some extent, purine synthesis de novo is controlled by the intracellular concentration of PRPP. Furthermore, when subjected to purine overproduction, a decrease in purine synthesis will occur owing to feedback inhibition of amidotransferase. Allopurinol effectively lowers the SUA probably by depleting PRPP.

DEFICIENCY OF HYPOXANTHINE GUANINE PHOSPHORIBOSYL TRANSFERASE (HGPRT)

This sex-linked enzyme disorder causing hyperuricemia accelerates the rate of purine synthesis de novo by increasing the concentration of PRPP. HGPRT catalyzes the transfer of the phosphoribosyl moiety of PRPP to form nucleotides (inosinic acid and guanylic acid)23 potentially depriving the amidotransferase reaction of a purine substance, PRPP (underutilization). The deficiency of HGPRT permits a load of PRPP to promote the rate-limiting amidotransferase reaction to accelerate. The specific mechanism may be that these nucleotides cause the small active form of the

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<td>Metabolic Lesions Causing Hyperuricemia</td>
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<td>By Means of a Surplus of Phosphoribosylpyrophosphate Promoting the Initial Step (Phosphoribosylamine Synthesis) in Purine Formation</td>
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1. Diminished activity of hypoxanthine guanine phosphoribosyl transferase (HGPRT) results in underutilization of phosphoribosylpyrophosphate (PRPP):

   Hypoxanthine + PRPP → inosinemonophosphate (IMP) + inorganic pyrophosphate
   Guanine + PRPP → guanosine monophosphate (GMP) + inorganic pyrophosphate

2. Greater than normal activity of PRPP synthetase results in excess PRPP:

   Ribose-5-phosphate + adenosine triphosphate (ATP) → PRPP + adenosine monophosphate (AMP)

3. Diminished activity of adenine phosphoribosyltransferase (APRT) results in underutilization of PRPP:

   Adenine + PRPP → AMP + inorganic pyrophosphate
amidotransferase enzyme to revert to a large catalytically inactive form of amidotransferase. The complete absence of HGPRT activity is seen in the Lesch-Nyhan syndrome.

The clinical features are mental retardation, choreoathetosis, compulsive self-mutilation and aggressiveness. This may be the first instance in which a stereotyped behavior pattern in humans has been associated with a distinct enzyme abnormality. Allegedly, every patient has bitten his lip destructively (unless dental extractions have been carried out). This disease represents the one cause of hyperuricemia with the highest rate of purine overproduction (eight times more urinary uric acid than normal). Urate nephropathy is probably the commonest cause of early death. The SUA in the children is usually 10 mg per 100 ml. Partial deficiency states (mutants of HGPRT) of this enzyme also cause hyperuricemia, sex-linked (male) inheritance, a high incidence of renal calculi and gout.

EXCESS PHOSPHORIBOSYLHYDROXYPHOSPHATE SYNTHETASE

Increased activity of the PRPP synthetase enzyme is associated with the production of a surplus PRPP which plays the key role in the formation of the purine precursors of uric acid. These patients have gout with SUA levels around 10 mg per 100 ml. This is the first demonstration in man of excess activity of a regulatory enzyme causing an overproduction disease as a direct result of mutation.

DEFICIENCY OF ADENINE PHOSPHORIBOSYLTRANSFERASE (APRT)

APRT catalyzes the transfer of the ribosyl-phosphate moiety of PRPP to adenine to form AMP. Patients with a deficiency of APRT have hyperuricemia and occasional gout; the SUA may reach 13.4 mg per 100 ml.

OTHER ENZYME DISORDERS

Glycogen storage disease type I is associated with enhanced de novo synthesis possibly owing to the inability to form free glucose, shunting sugar phosphates to ribosephosphate and then to increased PRPP (prompted through increased hepatic hexose monophosphate shunt?). SUA levels average 13 mg per 100 ml.

There is a possibility that reduced activity of glutamic acid dehydrogenase results in high intracellular glutamate thus preparing for augmented de novo purine synthesis. These patients have high plasma glutamate and high SUA levels.

Benign symmetrical lipomatosis (Launois-Bensaude disease) is a familial condition manifesting an excessive rate of incorporation of glycine into uric acid resulting in SUA levels of 8 to 12 mg per 100 ml.

Maple syrup disease (mutants of branched chain ketoaciduria) also exhibit this excessive rate of de novo synthesis with analogous results.

The fact that there are several inherited enzyme defects supports the contention that a wide variety of primary genetic abnormalities are responsible for hyperuricemia and gout. The vast majority of the specific metabolic anomalies remain to be uncovered.

A case has been described with mental retardation, fluorescent staining of dysplastic teeth and failure to cry with tears in a three year old mute, autistic boy. His SUA ranged from 8.5 to 23.5 mg per 100 ml. His accelerated synthesis of purines de novo was revealed by a rate of conversion of glycine to uric acid seven times that of normal. There was no defective activity of the HGPRT enzyme, but there was abnormal adeninephosphoribosyl transferase activity. The specific metabolic defect remains poorly understood.

Some gout patients are over-excretors of uric acid and have increased xanthine oxidase activity four-fold greater than control
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However, it is not known whether their hyperuricemia is the result of or the cause of the xanthine oxidase disorder or a coincidence.

DIET

The ingestion of a diet rich in purines will increase SUA. Non-gouty patients given 4 grams of ribonucleic acid per day exhibited an increase in SUA from 4.6 to 8 and even 9.2 mg per 100 ml. When gouty patients are studied, a group having an average of 9.5 mg per 100 ml before any dietary change will manifest a drop to 8.4 mg per 100 ml after one week of a purine-free diet.31

Miscellaneous Etiologies

ENDOCRINE

In hypothyroidism, repeated observations reveal that there is a higher incidence of hyperuricemia than expected; the mechanism is probably renal. The SUA averages about 7 but reaches 9 mg per 100 ml.

In acromegaly, the hyperuricemia has not been specifically correlated with growth hormone activity. Both hypoparathyroidism and hyperparathyroidism have associations with hyperuricemia, the mechanism of which is poorly understood.

Paradoxically, some patients with nephrogenic diabetes insipidus exhibit diminished urate clearance despite the massive polyuria they have since infancy.9 These cases of congenital, vasopressin-resistant diabetes insipidus are prone to developing gouty arthritis. Since chlorothiazide drugs appear to be the only effective antidiuretic therapy initially for these nephrogenic cases, it is important to realize the additional therapeutic need for allopurinol.

Despite the structural resemblance of uric acid to the experimental diabetogen, alloxan, there is no convincing evidence of a higher incidence of overt diabetes mellitus among gouty patients. However, hyperuricemia is associated with diminished carbohydrate intolerance. Further confusion arises from the concept of uric acid, hyperlipemia and hyperglycemia as “potential risk factors” in myocardial infarction. When one considers the numerous and heterogeneous etiologies behind hyperuricemia and the speculated analogous state of multiple etiologies in diabetes mellitus, it is not surprising that the lingering dilemma (the questioned coexistence of hyperuricemia and hyperglycemia) remains unresolved.

Injections of epinephrine can cause a rise in the SUA with an associated increase in renal urate excretion (urate overproduction?). However, to some extent a contrary mechanism may involve that of catecholamine-induced hyperlacticacidemia.

INTOXICATIONS

The hyperuricemia in severe barbiturate poisoning may be related to hypoxia and tissue destruction. Methyl alcohol is metabolized to formic acid which may cause hyperuricemia through its effect on the kidney, but the more likely mechanism is through the lactic acidosis seen in methyl alcohol poisoning. The hyperuricemia of chloroform poisoning may have either catecholamine or direct renal mechanism. Carbon monoxide poisoning causes severe central nervous system and myocardial injury. The reason for hyperuricemia in ammonia intoxication is unclear.

CONTRACTED EXTRACELLULAR VOLUME

This is at least the partial explanation for the occurrence of hyperuricemia in dehydration, salt restriction and the use of diuretics. The depletion of volume would then be a pre-renal cause for hyperuricemia.

UNCLEAR ASSOCIATIONS

Numerous investigations have indicated a probable relationship between levels of SUA
and achievement, fear, arduous physical tasks and challenging psychological techniques. Not only is the cause of elevated SUA in these psychosocial situations poorly understood but apparently conflicting results (showing a fall in SUA) may occur. Explanations involving altered plasma volume and release of catecholamines have been invoked. Following the use of vitamin B₁₂ injections for vitamin B₁₂ deficiency states, the SUA is known to increase to 9 and 10 mg per 100 ml. Likewise, during labor and immediately after delivery of the baby, hyperuricemia is a characteristic development.

Obese people have a tendency toward hyperuricemia which is intensified by starvation with the risks of acute gout but which is improved on a program of gradual weight reduction. Although there are data suggesting racial predominance in hyperuricemia, for example Micronesians with SUA levels reaching 8.5 mg per 100 ml, it is probably more correct to attribute the hyperuricemia to obesity. The Chamorro population of Micronesia has a 44 percent incidence of hyperuricemia among their males, and there is a general association of the SUA level with total daily caloric intake.

Idiopathic hypercalciuria has been reported to be associated with hyperuricemia. Patients with the Gilles de la Tourette syndrome (compulsive swearing) have SUA levels in the 6 to 9 mg per 100 ml range. In about 9 percent of sarcoidosis, mild hyperuricemia is said to occur, but the significance has been questioned.

LIVER DISEASE

A relation between the liver and gout has been discussed for many years. Conflicting results have been observed in evaluating liver function tests in drinking and non-drinking gouty patients. In fact, hypouricemia has been observed in severe alcoholism and liver disease. It is speculated that in these conditions, liver dysfunction may alter xanthine oxidase activity or conjugated bilirubin may influence tubular reabsorption of urate. Acute fatty liver of pregnancy (acute obstetric yellow atrophy) is a rare and usually fatal condition characterized by occurring in the first or second trimester, with massive hepatic necrosis, coma, hyperbilirubinemia and often hypoglycemia. The pathogenesis is unknown. Although an SUA of 20.6 mg per 100 ml has been reported in the absence of azotemia, usually the hyperuricemia is mild.

It has been estimated that the average biliary excretion of uric acid in normals is 50 mg per day compared to approximately 200 mg per day of uric acid excreted in the gastrointestinal tract. However, it may be speculated that the mechanism of the possible hepatic influence on uric acid would more reasonably be determined by disturbed enzyme activity than by biliary excretory means.

Summary

Hyperuricemia is a common laboratory finding with significant clinical implications. It is easily detected, but its mechanisms may not be clearly elucidated. A scheme of pathogenesis has been outlined and diagrammed but much is conjectural; therefore, the classification is merely tentative. About 45 diseases or categories of conditions, 20 drugs, and nine states of intoxication have been surveyed.

Hyperuricemia can be a multifactorial genetic disorder or a discrete response to a specific stimulus. It may be governed by a complex interplay of biochemical disorders for a lifetime duration, or it may be determined by environmental forces for a very transient course. Some conditions have both increased production of uric acid as well as decreased renal outflow. For many patients, the underlying mechanisms have not yet been elucidated.
References


