

Uric acid

Biology

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. Both uric acid and ascorbic acid are strong reducing agents (electron donors) and potent antioxidants. 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, resulting in decreased conversion to allantoin, so this breed excretes 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.

Uric acid is more toxic to tissues than either xanthine or hypoxanthine. Uric acid is released in hypoxic conditions.

Medicine

In human blood plasma, the reference range of uric acid is between 3.6 mg/dL ($\sim 214\mu\text{mol/L}$) and 8.3 mg/dL ($\sim 494\mu\text{mol/L}$) (1 mg/dL = $59.48\mu\text{mol/L}$). This range is considered normal by the American Medical Association. Uric acid concentrations in blood

plasma above and below the normal range are known, respectively, as hyperuricemia and hypouricemia.

Similarly, uric acid concentrations in urine above and below normal are known as hyperuricosuria and hypouricosuria. Such abnormal concentrations of uric acid are not medical conditions, but are associated with a variety of medical conditions.

High uric acid

High uric acid values may be caused by:

- Individual differences in the way your body produces or gets rid of uric acid.
- Conditions, such as:
 - Kidney disease or kidney damage.
 - The increased breakdown of body cells that occurs with some types of cancer (including leukemia, lymphoma, and multiple myeloma) or cancer treatments, hemolytic anemia, sickle cell anemia, or heart failure.
 - Other disorders, such as alcohol dependence, pre-eclampsia, liver disease (cirrhosis), obesity, psoriasis, hypothyroidism, and low blood levels of parathyroid hormone.
 - Starvation, malnutrition, or lead poisoning.
 - A rare inherited gene disorder called Lesch-Nyhan syndrome.
- Medicines, such as some diuretics, vitamin C (ascorbic acid), lower doses of aspirin (75 to 100 mg daily), niacin, warfarin (such as Coumadin), cyclosporine, levodopa, tacrolimus, and some medicines used to treat leukemia, lymphoma, or tuberculosis.
- Eating foods that are very high in purines, such as organ meats (liver, brains), red meats (beef, lamb), game meat (deer, elk), some seafood (sardines, herring, scallops), and beer.

Gout

Excess serum accumulation of uric acid can lead to a type of arthritis known as gout.

Elevated serum uric acid (hyperuricemia) can result from high intake of purine-rich foods, high fructose intake (regardless of fructose's low glycemic index (GI) value) and/or impaired excretion by the kidneys.

Saturation levels of uric acid in blood may result in one form of kidney stones when the urate crystallizes in the kidney. These uric acid stones are radiolucent and so do not appear on an abdominal plain x-ray or CT scan. Their presence must be diagnosed by ultrasound for this reason. Very large stones may be detected on x-ray by their displacement of the surrounding kidney tissues. Some patients with gout eventually get uric kidney stones.

Gout can occur where serum uric acid levels are as low as 6 mg/dL ($\sim 357\mu\text{mol/L}$), but an individual can have serum values as high as 9.6 mg/dL ($\sim 565\mu\text{mol/L}$) and not have gout.

Lesch-Nyhan syndrome

Lesch-Nyhan syndrome, an extremely rare inherited disorder, is also associated with very high serum uric acid levels.

Spasticity, involuntary movement and cognitive retardation as well as manifestations of gout are seen in cases of this syndrome.

Cardiovascular disease

Although uric acid can act as an antioxidant, excess serum accumulation is often associated with cardiovascular disease. It is not known whether this is causative (e.g., by acting as a pro-oxidant) or a protective reaction taking advantage of urate's antioxidant properties.

Diabetes

The association of high serum uric acid with insulin resistance has been known since the early part of the 20th century, nevertheless, recognition of high serum uric acid as a risk factor for diabetes has been a matter of debate. In fact, hyperuricemia has always been presumed to be a consequence of insulin resistance rather than its precursor. However, it was shown in a prospective follow-up study that high serum uric acid is associated with higher risk of type II diabetes independent of obesity, dyslipidemia, and hypertension.

Metabolic syndrome

Hyperuricemia is associated with components of metabolic syndrome and it has been debated for a while to be a component of it. It has been shown in a recent study that fructose-induced hyperuricemia may play a pathogenic role in the metabolic syndrome. This agrees with the increased consumption of fructose-base drinks in recent decades and the epidemic of diabetes and obesity.

Uric acid stone formation

Uric acid stones, which form in the absence of secondary causes such as chronic diarrhea, vigorous exercise, dehydration, and animal protein loading, are felt to be secondary to obesity and insulin resistance seen in metabolic syndrome. Increased dietary acid leads to increased endogenous acid production in the liver and muscles which in turn leads to an increased acid load to the kidneys. This load is handled more poorly because of renal fat infiltration and insulin resistance which are felt to impair ammonia excretion (a buffer). The urine is therefore quite acidic and uric acid becomes insoluble, crystallizes and stones form. In addition, naturally present promoter and inhibitor factors may be affected. This explains the high prevalence of uric stones and unusually acidic urine seen in patients with type 2 diabetes. Uric acid crystals can also promote the formation of calcium oxalate stones, acting as 'seed crystals' (heterogeneous nucleation).

Low uric acid

Low uric acid values may be caused by:

- Severe liver disease, Wilson's disease, or some types of cancer.
- The syndrome of inappropriate antidiuretic hormone (SIADH), a condition that causes large amounts of fluid to build up in the body.
- Not eating enough protein.
- Sulfinpyrazone, large amounts of aspirin (1,500 mg or more daily), probenecid (such as Probalan), and allopurinol (such as Aloprim and Zyloprim).

Multiple sclerosis

Lower serum values of uric acid have been associated with Multiple Sclerosis. Multiple sclerosis (MS) patients have been found to have serum levels $\sim 194\mu\text{mol/L}$, with patients in relapse averaging $\sim 160\mu\text{mol/L}$ and patients in remission averaging $\sim 230\mu\text{mol/L}$. Serum uric acid in healthy controls was $\sim 290\mu\text{mol/L}$. Conversion factor: $1\text{ mg/dL}=59.48\mu\text{mol/L}$

A 1998 study completed a statistical analysis of 20 million patient records, comparing serum uric acid values in patients with gout and patients with multiple sclerosis. Almost no overlap between the groups was found.

Uric acid has been successfully used in the treatment and prevention of the animal (murine) model of MS. A 2006 study found that elevation of serum uric acid values in multiple sclerosis patients, by oral supplementation with inosine, resulted in lower relapse rates, and no adverse effects.

Oxidative stress

Uric acid may be 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, uric acid 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.

For example, some researchers propose that 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 urate's antioxidant properties.

Sources of uric acid

- In many instances, people have elevated uric acid levels for hereditary reasons. Diet may also be a factor; eating large amounts of sea salt can cause increased levels of uric acid.
- Purines are found in high amounts in animal internal organ food products, such as liver. A moderate amount of purine is also contained in beef, pork, poultry, fish and seafood, asparagus, cauliflower, spinach, mushrooms, green peas, lentils, dried peas, beans, oatmeal, wheat bran and wheat germ.
- Examples of high purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, meat extracts (e.g., Oxo, Bovril), herring, mackerel, scallops, game meats, and gravy.
- Moderate intake of purine-containing food is not associated with an increased risk of gout. Serum uric acid can be elevated due to high fructose intake, reduced excretion by the kidneys, and or high intake of dietary purine. Added fructose can be found in processed foods and soda beverages as sucrose, or in some countries, as high fructose corn syrup.

Causes of low uric acid

Low uric acid (hypouricemia) can have numerous causes.

Low dietary zinc intakes cause lower uric acid levels. This effect can be even more pronounced in women taking oral contraceptive medication.

Sevelamer, a drug indicated for prevention of hyperphosphataemia in patients with chronic renal failure, can significantly reduce serum uric acid.

Normalizing low uric acid

Correcting low or deficient zinc levels can help elevate serum uric acid

Inosine can be used to elevate uric acid levels.

Other uric acid facts

The high nitrogen content of uric acid makes guano a useful agricultural fertilizer.

The crystalline form of uric acid is used as a reflector in certain species of fireflies.

The uric acid in urine can also dry in a baby's diaper to form a pinkish powder that is harmless.

Urate is being researched for its possible antioxidant properties in treating Parkinson's disease.

Testing for serum Uric acid

The uric acid test is used to learn whether the body might be breaking down cells too quickly or not getting rid of uric acid quickly enough. The test also is used to monitor levels of uric acid when a patient has had chemotherapy or radiation treatments.

The uric acid test is ordered when a doctor suspects high levels of uric acid. Some patients with high levels of uric acid have a disease

called gout, which is an inherited disorder that affects purine breakdown. Patients with gout suffer from joint pain, most often in their toes but in other joints as well.

The test also is ordered as a monitoring test when a patient has undergone chemotherapy or radiation, to learn whether uric acid levels are getting dangerously high. The test may also be ordered if a patient appears to have failing kidneys. Patients who have high uric acid levels are sometimes put on a drug regimen to help lower uric acid levels.

Higher than normal uric acid levels mean that the body is not handling the breakdown of purines well. The doctor will have to learn whether the cause is the over-production of uric acid, or if the body is unable to clear away the uric acid.

Increased concentrations of uric acid can cause crystals to form in the joints, which leads to the joint inflammation and pain characteristic of gout. Uric acid can also form crystals or kidney stones that can damage the kidneys.

Low levels of uric acid in the blood are seen much less commonly than high levels and are seldom considered cause for concern. Although low values can be associated with some kinds of liver or kidney diseases, exposure to toxic compounds, and rarely as the result of an inherited metabolic defect, these conditions are typically identified by other tests and symptoms and not by an isolated low uric acid result.

Many drugs can increase or decrease the level of uric acid. In particular, diuretic drugs like thiazide drugs can cause uric acid levels to go up.

Aspirin (and other salicylates) have varying effects on uric acid. At low aspirin levels (as may occur in persons taking aspirin only occasionally), aspirin can increase blood uric acid. On the other hand,

in high doses (as may be used to treat rheumatoid arthritis), aspirin actually lowers the concentration of uric acid.

For people who have uric acid kidney stones or gout, foods that are high in purine content should be avoided, including organ meats (like liver and kidneys), sardines and anchovies. Alcohol also should be avoided, because it slows down the removal of uric acid from the body. Fasting, a starvation diet, and strenuous exercise all raise uric acid levels.

Although the uric acid test cannot definitively diagnose gout, a test for monosodium urate in synovial fluid (joint fluid) can.

Depending on the condition that causes your high levels of uric acid, you may not need to take drugs. If you have a sudden attack caused by high uric acid, as with an attack of gout, your doctor may treat you with the drug colchicine and a nonsteroidal anti-inflammatory drug, such as aspirin or ibuprofen. This treatment usually is short-term.

However, you may have to stay on a maintenance therapy for a few years, until your uric acid levels come under control. You may be given drugs that help to rid your system of uric acid salts, such as probenecid, or you may be given drugs that interfere with uric acid production, such as allopurinol.

If you have had chemotherapy or radiation, you may have to take uric acid tests more often and possibly treat the condition over time.

The blood uric acid test measures the amount of uric acid in a blood sample. Uric acid is produced from the natural breakdown of your body's cells and from the foods you eat.

Most of the uric acid is filtered out by the kidneys and passes out of the body in urine. A small amount passes out of the body in stool. But if too much uric acid is being produced or if the kidneys are not

able to remove it from the blood normally, the level of uric acid in the blood increases.

High levels of uric acid in the blood can cause solid crystals to form within joints. This causes a painful condition called gout. If gout remains untreated, these uric acid crystals can build up in the joints and nearby tissues, forming hard lumpy deposits called tophi. High levels of uric acid may also cause kidney stones or kidney failure.

A uric acid blood test is done to:

- Help diagnose gout.
- Check to see if kidney stones may be caused by high uric acid levels in the body.
- Check to see if medicine that decreases uric acid levels is working.
- Check uric acid levels in people who are undergoing chemotherapy or radiation therapy. These treatments destroy cancer cells that then may leak uric acid into the blood.

You do not need to do anything before you have this test.

Some medicines can change the results of this test. Be sure to tell your doctor about all the nonprescription and prescription medicines you take.

Results

Normal

Normal values of blood uric acid may vary from lab to lab.

Uric acid in blood		
Men:	3.4–7.0 milligrams per deciliter (mg/dL)	200–420 micromoles per liter (mcmol/L)
Women:	2.4–6.0 mg/dL	140–360 mcmol/L

Children:	2.5–5.5 mg/dL	120–330 mcmmol/L
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Uric acid crystals sometimes form in joints even at levels less than 7 mg/dL, especially in men. This can lead to a gout attack, even though the uric acid levels are within the normal range.

Many conditions can change uric acid levels. Your doctor will talk with you about any abnormal results that may be related to your symptoms and medical history.

What Affects the Test

- Some medicines may increase the level of uric acid in the blood. These include diuretics, theophylline, low-dose aspirin (75 to 100 mg daily), and some medicines used to treat tuberculosis.
- The vitamin niacin, high doses of vitamin C, caffeine, and a substance found in chocolate and tea (theobromine) can cause uric acid levels to be inaccurately high.
- Excessive use of alcohol, starvation, a high-protein diet, or strenuous exercise can raise the level of uric acid in the blood.

What to Think About

- Having a high uric acid level does not mean that you have gout. If your uric acid level is high and you do not have any other symptoms, you will not need to take any medicine to decrease your uric acid level.
- A high level of uric acid in the blood does not always mean that a person with a painful joint has gout. Testing the fluid taken from an affected joint for the presence of uric acid crystals is the only sure method to diagnose gout.
- Uric acid may also be measured in urine. If your blood uric acid level is high, a 24-hour urine collection may help determine

- whether your body is producing too much uric acid or your kidneys are not getting rid of enough of it.
- Uric acid blood levels vary from day to day. The level is usually higher in the morning and lower in the evening.
 - Blood uric acid levels that increase during pregnancy, even if the levels remain within the normal range, may help diagnose pre-eclampsia.

Treatment for low uric acid count

Uric acid is produced by the breakdown of purine bases found in DNA and RNA. Low serum uric acid levels are seen in a number of diseases including Wilson's disease, Fanconi's syndrome, celiac disease, pernicious anemia, Hodgkin's disease, some cancers and as a result of a defect in the tubules of the kidneys.

Many medications can also lower uric acid levels including ACTH, corticosteroids, salicylates, probenecid, allopurinol, coumadins and chlorpromazine. Marijuana use can also lower uric acid levels.

Pregnant women have normally low uric acid levels; *a pregnant woman with a uric acid level in the normal adult range has serious kidney problems.*

Some alternative practitioners have noted an association between low serum uric acid and hypersensitivity problems. This may include increased sensitivities to foods, weather changes, chemicals, pollens, caffeine, light, noise, and hormonal and emotional changes. The low uric acid indicates a general mineral deficiency state. If the BUN (blood urea nitrogen) is also low, then there is also a deficiency of free nitrogen in the body.

Serum uric acid (UA) is reported as an important marker of hypertension, coronary heart disease, and diabetes; diabetic subjects have low UA levels. The relationship between UA and fasting plasma glucose (FPG) and 2-h plasma glucose concentrations in non-diabetic subjects as well as in diabetic subjects in general population is not well known. Serum UA levels tended to increase with increasing FPG levels in non-diabetic individuals, but decrease in diabetic individuals.

Reducing Uric Acid with Low Uric Acid Diet

High uric acid levels in the blood stream can lead to a common form of arthritis called gout. To prevent gout, it is essential to maintain good eating habits and have proper medication. To reduce the uric acid levels in blood, you may need to limit intake of alcohol and reduce purine rich foods. Digestion of purine leads to the formation of uric acid.

If uric acid is not eliminated normally which is seen in gout sufferers, it can build up in the blood stream leading to joint inflammation and pain.

Measures for how to reduce uric acid in diet:

- Tofu which is made from soybean is a good choice than animal foods. Tofu can alter the plasma protein concentration and increase uric acid clearance and excretion.
- Uric acid level in the body can be reduced by cutting down the foods that contain high amount of purines. Foods with high purine content include anchovies, broth, roe, sardines, yeast, sweetbread and mincemeat.
- Avoid these foods totally. Some foods have moderate purine content like fish, lentils, asparagus, mushrooms, spinach and shellfish. One serving of meat, fish or fowl or one serving of vegetable is allowed daily.
- Foods low in purine is fruits, olive, vinegar, cereal and cereal products, and rice. These foods can be consumed daily.
- Have foods that are relatively high in carbohydrates, moderate in protein and low in fat. Complex carbohydrates like whole grain cereals, fruits and vegetables contain fiber that can help in proper digestion of the foods and assimilation of the nutrients. Fiber can avoid excessive build up of the uric acid.
- Reduce the intake of protein rich foods to 15 percent. Prefer soybean that has been defatted, lean meat and sprouts that provide good quality protein but low fat content.

- Fresh fruits like apples, bananas, oranges and lime are beneficial. Cherries are considered to be beneficial in reducing uric acid levels. You can have juice of black cherry which is also called as sour cherry. Cherries contain certain natural chemicals that can lower uric acid levels and reduce inflammation.
- Excess of alcohol can increase the uric acid production. Preferably avoid the consumption of alcohol.
- Drink plenty of water or fluids (3-5 liters/day) like fresh juices or soups that can help in excretion of uric acid.

Certain guidelines that can be helpful in reducing uric acid levels are:

- Maintain an ideal body weight. Gradual weight loss is beneficial rather than drastic loss weight. You can reduce your body weight by dietary modifications and exercise.
- Get the uric acid levels checked regularly.

<i>Food source of uric acid</i>	<i>Uric acid level (mg of uric acid / 100 g food)</i>
Yeast, brewer's	1810
Sheep's spleen	773
Tuna fish	257
Anchovy	239
Mungo bean seed	222
Soybean seed	190
Chicken (breast with skin)	175
Salmon	170
Pork, fillet	150
Ham, cooked	131
Beef	110
Broccoli	81

Tofu	68
Banana	57
Sweet corn	52
Grape	27
Plum	24
Asparagus	23
blueberry	22
White cabbage	22
Strawberry	21
Carrot	17
Apple	14
Cucumber	7.3

When we have a diet that is high in purine-rich foods our uric acid levels can go up, which gives the kidney a harder job to eliminate the excess uric acid in a time. The excess uric acid floats around in our bloodstream until it becomes saturated. At this point uric acid crystals are deposited in the joints.

There are two ways of tackling these high levels of uric acid, either speed up the kidney processes so that uric acid is processed and expelled quickly or reduce the amount of uric acid produced. An effective way to do this is by following a low uric acid diet.

- Getting to grips with a low uric acid diet is not too hard. It boils down to these factors:
Avoid foods high in purine and substitute these with foods with low purine content.
- The basic guideline for this sort of diet is to avoid red meat, processed meat, shellfish and yeast extracts. Instead your diet should consist of gout friendly foods such as, cereals, some green vegetables, fruits and fruit juices, corn and tomatoes.

- By eating foods with low purine content and avoiding those foods high in purine you will start to reduce the amount of uric acid in the body and allow the kidneys to get on top of their processing tasks.
- Stick to the low uric acid diet
- Avoid alcohol.
- Drinking lots of water can offer you the prevention necessary to avoid a further gout attack.

Possible Causes of Low Uric Acid Levels

Uric acid (urate) is an organic compound that is a factor in purine metabolism, which is an important part of RNA and DNA generation. Uric acid is also an important antioxidant and is therefore beneficial to cell regeneration and integrity. The correct levels of uric acid aid the body in fighting oxidative stress, which can cause breakdowns in many systematic functions, leading to stroke, heart disease and cancer.

Mineral Deficiencies

The lack of a sufficient presence of some minerals in the body may contribute to low uric acid levels. Molybdenum deficiency has been linked to low uric acid level as has a deficiency of zinc. Additionally, deficiencies in magnesium, vitamin D and vitamin B-12 have been shown in some studies to contribute to low levels of uric acid. In some cases, low levels of uric acid have been linked to the onset of multiple sclerosis.

Other Causes

Certain dysfunctions in the body may lead to low uric acid levels. Liver disease, some forms of cancer and Wilson's disease (an affliction related to copper that can affect the brain, the kidneys and the liver) may cause a decreased presence of uric acid. A lack of sufficient protein in the diet may also contribute to this condition, as

can hormonal imbalances such as SIADH, a syndrome that causes the buildup of large amounts of fluid in the body.

Significance of Low Uric Acid Levels

The disposal of uric acid is normally handled by the kidneys and the liver. Uric acid is therefore passed out of the body through waste (most often in urine). High levels of uric acid can lead to the collection of urate crystals in the renal organs as well as in the joints of the body, which can result in kidney stones and liver disease such as arthritis and gout. Lower uric acid levels, consequently, can be seen as a positive prognosis relative to the onset of these conditions.

Negative Diagnoses

Diabetes has reportedly been connected with low levels of serum uric acid (uric acid in blood plasma). According to the U.S. National Library of Medicine, there have also been studies that indicate low levels of uric acid may contribute to death in some patients undergoing dialysis treatment. Parkinson's disease has also been linked to low levels of uric acid in a study done by the American Journal of Nephrology that compared patients both with and without this affliction, using factors of body mass, dietary consumption and serum uric acid levels.

Treatment

Gout and arthritis are two of the most common ailments whose treatment focuses on controlling uric acid levels in the body. In general, dietary alterations and exercise are indicated for lowering uric acid levels to prevent the increase of urate crystalline buildup that leads to these joint afflictions. Lowered intake of sugar and salt are recommended, along with incorporating herb seasonings (basil, marjoram, oregano) and increasing the intake of brown rice and whole wheat products.

Low Serum Uric Acid Level Is a Risk Factor for Death in Incident Hemodialysis Patients.

A reverse epidemiology of classic cardiovascular risk factors was observed in hemodialysis patients with a high comorbidity burden. It is hypothesized that uric acid, a novel cardiovascular risk factor, also has an altered association with survival in these patients.