

## Urate (serum, plasma)

### 1 Name and description of analyte

1.1. Name of analyte  
Urate

1.2. Alternative names  
Uric acid. This has four dissociable hydrogen ions: the pKa of the first dissociation is 5.8, so that at physiological pH in the plasma, the majority of uric acid is present as urate ( $1^-$ ) ions.

1.3 NMLC code

1.4 Description of analyte  
Uric acid is a heterocyclic nitrogenous compound (IUPAC 7,9-dihydro-1H-purine-2,6,8-(3H)trione, MW 168 Da). It is the end product of purine breakdown. Urate in the blood is derived from the breakdown of dietary and endogenous purines (e.g. in nucleotides, nucleic acids). It is excreted mainly (two-thirds) by the kidneys and to a lesser extent by the large intestine.

1.5 Function of analyte  
Uric acid is not proven to have any physiological function but does act as an antioxidant; high concentrations have been linked to increased longevity in animals and improved cognitive function in humans.

### 2 Sample requirements and precautions

2.1 Medium in which measured  
Serum or plasma; it may be useful to measure **urinary** urate excretion in the investigation of patients with renal calculi. The identification of urate crystals in synovial fluid using microscopy with polarised light (the crystals characteristically (and uniquely) demonstrate negative birefringence) can confirm a diagnosis of gout (and in particular, distinguish it from septic arthritis).

2.2 Precautions re sampling, handling etc.  
No specific precautions required but see 4.5.

### 3 Summary of clinical uses and limitations of measurements

3.1 Uses

1. The principal use of urate measurements is in the diagnosis and management of gout. Hyperuricaemia is typically, but not always, present in gout. Measurements of urate are essential to the monitoring of urate-lowering treatment.
2. High [urate] can be a feature of pre-eclampsia (though is not one of the diagnostic criteria).
3. High [urate] is a feature of the tumour lysis syndrome and urate should be measured in patients undergoing chemotherapy.

4. Certain drugs (e.g ethambutol, pyrizinamide) can reduce renal urate excretion and cause hyperuricaemia: 50% of patients treated with ethambutol develop hyperuricaemia.

### 3.2 Limitations

Hyperuricaemia predisposes to gout but occasionally gout can present in patients with normal [urate].

## 4 Analytical considerations

### 4.1 Analytical methods

#### 1. Colorimetric

This method is based on the formation of a chromogen (Tungsten blue), measured at 650 – 700 nm, when phosphotungstic acid is reduced by urate in alkaline solution. Its specificity, and thus its use, is limited by interference from a range of substances.

#### 2. Enzymic

These methods use bacterially derived uricase ([urate:oxygen] oxidoreductase, EC 1.7.3.3.) to oxidise urate to allantoin, hydrogen peroxide and carbon dioxide. The reaction can be followed by measuring the decrease in absorbance due to urate at 293 nm; this requires a narrow bandwidth spectrophotometer and is not suitable for automated analysers. Most automated methods use a peroxidase system to link the hydrogen peroxide to an oxygen acceptor (e.g 4-aminophenazone and a substituted phenol) to generate a chromogen. Different chromogens and other components have been used to reduce interference, e.g. by bilirubin, ascorbate and phenolic compounds that accumulate in renal failure. Enzymic methods have been adapted for use in dry chemistry systems.

#### 3. High pressure liquid chromatography (HPLC)

These methods use either ion-exchange or reversed-phase columns, with uv monitoring at 293 nm to detect urate.

### 4.2 Reference and definitive methods

The proposed definitive method is based on isotope dilution-mass spectrometry (ID-MS). Reference methods are based on HPLC.

### 4.3 Reference materials

SRM 909 (National Institute of Standards and Technology, Washington, DC, USA).

### 4.4 Interfering substances

See above; some other purines are substrates for uricase, but are not present in the plasma at sufficient concentrations to cause significant interference.

### 4.5 Sources of error

The major source of error is assay interference (see above). The therapeutic use of uricase to treat hyperuricaemia can cause falsely low [urate] owing to metabolism *in vitro*.

## 5 Reference intervals and variance

- 5.1.1 Reference intervals (adults): 0.21– 0.43 mmol/L (males), 0.16 – 0.36 mmol/L (females); concentrations tend to increase by about 10% between ages 20 and 60, with an additional increase in females during the climacteric to approach values found in men.  
It is arguably more relevant to consider [urate] in relation to the risk of developing gouty arthritis; the annual incidence is 0.1% at concentrations <0.46 mmol/L but 50% at >0.54 mmol/L.
- 5.1.2 Reference intervals (others): <0.3 mmol/L in children <10 years, increasing in males and females at puberty.
- 5.1.3 Extent of variation
- 5.1.3.1 Interindividual CV: 27.1%
- 5.1.3.2 Intraindividual CV: 9.0 %
- 5.1.3.3 Index of individuality: 0.33
- 5.1.3.4 CV of method: 0.7 %
- 5.1.3.5 Critical difference: 25%
- 5.1.4 Sources of variation  
[Urate] rises with increasing age; it tends to be higher in individuals consuming a purine-rich diet (e.g. offal) and is increased acutely (and reversibly) by alcohol intake. It is dependent on renal function, increasing in renal impairment.

## 6 Clinical uses of measurement and interpretation of results

### 6.1 Uses and interpretation

#### 1. Gout

A diagnosis of gout in a patient with an acute inflammatory arthropathy is supported by the finding of a high [urate] although this is not required for the diagnosis and may occasionally be absent. It may be noted that patients with both gouty and septic arthritis may have high white blood cell counts and increased concentrations of inflammatory markers e.g. **C-reactive protein (CRP)**. Patients with hyperuricaemia may develop inflammatory arthritis that is not gout.

The decision to prescribe hypouricaemic drugs (e.g. allopurinol) depends on the number of attacks of gout (almost never one only), the success of any modification of contributory factors (e.g. diet, high alcohol intake), the presence of tophi (an absolute indication) and plasma [urate]. Although there is no agreed value above which hypouricaemic medication is indicated, the risk of acute gout rises considerably at concentrations >0.54 mmol/L. The aim of treatment (which should be life-long) is to maintain plasma [urate] <0.36 mmol/L.

#### 2. Pre-eclampsia

Hyperuricaemia can be an early feature of pre-eclampsia but has poor specificity and sensitivity and is not included in the diagnostic criteria for this condition.

#### 3. Tumour lysis syndrome

Urate should be measured in patients undergoing chemotherapy with regimens known to carry a risk of causing tumour lysis syndrome.

#### 4. Treatment with ethambutol

Urate should be measured in patients being treated with ethambutol.

5. Plasma urate concentrations are low in patients with xanthine oxidase deficiency and urate measurement may be helpful in the investigation of patients with renal calculi if the commoner causes have been eliminated.

## 6.2 Confounding factors

Numerous factors tend to increase [urate] (e.g, a high purine intake, alcohol, obesity, hypertriglyceridaemia, impaired renal function). Modification of these factors can reduce the risk of gout, which is directly related to [urate].

## 7 Causes of abnormal results

### 7.1 High values

#### 7.1.1 Causes

##### 1. Primary

- the majority of patients with primary gout have reduced urate excretion rather than increased production, probably due to increased tubular reabsorption
- there are several rare inherited metabolic diseases in which hyperuricaemia occurs e.g. Lesch-Nyhan syndrome (caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase).

##### 2. Secondary

- acidosis
- alcohol
- drugs
  - increasing tissue turnover e.g. cytotoxics
  - decreasing urate excretion e.g. diuretics, ciclosporin, low dose (<2 g/day) salicylates
- high purine intake
- increased tissue turnover (e.g. tumour lysis syndrome, in which precipitation of urate crystals in the lumen of renal tubules can cause obstructive nephropathy)
- lead poisoning
- obesity
- renal impairment.

#### 7.1.2 Investigation

If a high [urate] is identified in the course of investigating a patient with suspected gouty arthritis or incidentally, measurement of creatinine (and calculation of eGFR) is required to establish any renal contribution; other secondary causes should also be sought. The association of hyperuricaemia with the metabolic syndrome justifies seeking features of this condition if not already diagnosed.

### 7.2 Low values

#### 7.2.1 Causes

Hypouricaemia is uncommon and is usually of no clinical consequence in itself. Causes include proximal renal tubular disorders (e.g. Fanconi syndrome, Wilson disease) and the rare inherited disorder, xanthine oxidase deficiency,

#### 7.2.2 Hypouricaemia does not require investigation as the conditions causing it are usually manifest for other reasons.

### 7.3 Note

Urate measurements are frequently included in 'biochemical profiles' but this is not appropriate: there is no evidence of clinical benefit from using it as a screening test.

## **8 Performance**

- 8.1 Sensitivity, specificity etc. for individual conditions  
No data available.

## **9 Systematic reviews and guidelines**

- 9.1 Systematic reviews  
No systematic reviews identified.
- 9.2 Guidelines  
No guidelines identified.
- 9.3 Recommendations  
No specific recommendations identified but in addition to its measurement in relation to gout and pre-eclampsia, urate should be measured in patients at risk of tumour lysis syndrome, in whom hyperuricaemia may require treatment with uricase, and in patients being treated with ethambutol.

## **10 Links**

- 10.1 Related analytes  
None
- 10.2 Related tests  
The inherited metabolic diseases that can cause hyperuricaemia are diagnosed by measurements of the enzymes concerned.

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Date Completed: 1.2012

Date Revised: