

Dear Dr. ....

Thank you for your enquiry regarding the test for Trimethylamine which we perform routinely here at Sheffield Children's Hospital.

To test for Trimethylaminuria (TMAU) we require a 20cc urine sample and a doctor's referral letter or request form.

For intermittent odours, which may be associated with ingestion of certain foods (or in women may occur in the pre-menstrual period), it is important to collect this sample at the time of the odour (this may necessitate 'loading' with the foods known to produce the odour eg beans, eggs, liver).

The type of urine sample we would require is known as a 24 hour urine collection - during this period urine is collected into a 2.5 litre container with approximately 10cc of '5M' Hydrochloric acid to acidify the sample and stabilise the trimethylamine. (This is the same sample collection as for a urine Calcium test).

The doctor's surgery should then send us a 20cc portion of this sample for us to measure:

- 1 Trimethylamine
- 2 Trimethylamine-oxide.

The sample must be sent by express courier to arrive within 2 days or as soon as possible.

The current price for this test is £134 + tax or approximately 160 Euros\* (this includes additional testing for dimethylglycine if the TMA test result is normal).

We should be able to return the results with interpretation to your doctor within 3 weeks of receipt of the sample.

If you wish to phone me to discuss this test or sample please don't hesitate.\*\* I've attached some more information about TMAU which I hope you may find useful.

Yours sincerely

Nigel Manning  
Principal Clinical Scientist  
Dept. Clinical Chemistry  
Sheffield Children's Hospital  
Sheffield S10 2TH  
UK  
Phone: 0114 271 7307  
Fax: 0114 270 6121

\*subject to £/Euro or £/other applicable currency exchange rate

\*\*Office personnel usually only speak English

## **INTRODUCTION TO TRIMETHYLAMINURIA [TMAU]**

Disorder nomenclature / synonyms:

- Trimethylaminuria (TMAU)
- Primary TMAU (TMAU1) (Inherited FMO3 deficiency)
- Secondary TMAU (TMAU2)
- Fish Odour Syndrome (FOS) (Fish Malodour Syndrome)
- Primary FOS / Secondary FOS
- Flavin-containing mono-oxygenase type 3 (FMO3) deficiency.

Trimethylaminuria (TMAU) is a disorder defined by the excessive urinary excretion of the volatile tertiary amine trimethylamine (TMA). This reflects an increase in body fluids which results in TMAU patients exuding the odour of rotten fish (similar to ammonia), as the excess TMA is excreted in sweat. Body odour of rotten fish is not unsurprisingly accompanied by the same odour on the breath of TMAU sufferers.

TMAU is therefore a potentially distressing condition of social exclusion resulting in depression and other psychological problems. Patients may start to show signs of the condition at various ages from infancy to adulthood depending mainly on whether the disorder is inherited or acquired.

### TMAU1

The inherited form of TMAU is known as Primary TMAU or TMAU1. The result of a faulty recessive gene, TMAU1 patients have impaired activity of a liver enzyme known as FMO3 (flavin-containing mono-oxygenase type 3). FMO3 oxidises chemical compounds and has a wide range of substrates including many drugs. TMA is oxidised to the non-odorous TMA-oxide (TMO) by FMO3 which can then be excreted. TMA itself is generated in the large intestine by bacteria which break down compounds such as choline (in meat, liver, eggs and beans/peas), carnitine (meat) and TMO from seafood (hence TMA from rotting fish).

TMAU1 therefore results from FMO3 deficiency with an increase in the ratio of TMA to TMO in urine which can be used for diagnosis.

Due to the low specificity of FMO3 and the large number of drugs detoxified, TMAU1 patients may suffer from adverse drug reactions (eg with codeine; tamoxifen; ketoconazole; nicotine; cimetidine; ranitidine; phenothiazine). Hypertension may result from ingestion of red wine and cheese (and chocolate), which produce the neurotransmitter tyramine, another FMO3 dependent compound. Many people suffer from migraines associated with tyramine containing foods and perhaps FMO3 deficiency may explain some of these cases, but overall this demonstrates the adverse medical consequences as well as the odour related psychosocial aspects.

### TMAU2

The acquired form of TMAU is covered by the term Secondary TMAU or TMAU2 where TMA excretion is high even though FMO3 activity is normal.

Most TMAU2 patients produce too much TMA from intestinal bacteria due to excessive bacterial growth of TMA-generating species. The TMA burden is so great that FMO3 oxidation is not enough to convert all the TMA. This problem may be exacerbated by intestinal structural problems such as 'blind loops' or post operative complications. TMAU2 usually presents in adulthood although children have been known to acquire excessive TMA-producing bacteria with the resultant odour.

The diagnosis of TMAU2 depends on the detection of increased urinary TMA and TMO with a normal TMA/TMO ratio indicating normal oxidation by FMO3.

Some TMAU2 patients may have liver or kidney disease which results in a TMAU1-like pattern of excretion. Importantly this may also occur with a urinary tract infection (UTI) which results in TMA being produced directly into the urine giving a false positive result. Whenever results suggest TMAU1, therefore, UTI must always be excluded by microbial analysis before a TMAU1 diagnosis is confirmed in a follow-up sample.

### Therapy

Treatment of both TMAU1 and TMAU2 is based on diet to restrict the sources (precursors) of TMA and antibiotics to eliminate the TMA-producing bacteria. TMAU2 can in fact be cured by eradication of the excess bacteria, although stubborn colonies may regrow to excess and require further courses of treatment.

TMAU1, as a genetic defect, cannot be completely cured although therapy (dietary and antibiotic) can successfully control the patient's TMA to a less odourous level. Patient's residual enzyme activity is variable depending on the specific mutation and as such trials with the cofactor riboflavin have been tried with some success. Milder TMAU1 patients can, however, reduce their TMA to almost normal values with just diet and periodic antibiotic therapy. Other forms of therapy are based on the neutralisation of TMA chemically. Skin creams with a comparatively low pH (5.0) may neutralise TMA which is alkaline. This creates a non-volatile salt of TMA which lessens any odour and can be washed off by the patient later. The other solution lies in deodorising tablets such as 'activated charcoal' or copper-chlorophyllin complex (marketed as 'Nullo'). These 'internal deodorants' have been successfully used for many years and would be ideal for more severely affected TMAU1 patients.

### Testing for TMAU

We offer a urine test for trimethylamine (TMA) and the oxide of TMA. The technique used is gas chromatography – mass spectrometry. This enables us to diagnose TMAU1 and TMAU2. A positive result is always followed up – with a routine second test after a report of the initial findings. The turnaround time for the test is currently 4 weeks or less. A GP or physician referral is essential, but we can offer advice by phone or email about how to start the process.