## INTRODUCTION TO TRIMETHYLAMINURIA [TMAU]

Also known as:
- 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 metabolic 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.

## PRIMARY TRIMETHYLAMINURIA (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 oxidizes 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 in the sweat, urine, reproductive fluids, and breath. 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.

## SECONDARY TRIMETHYLAMINURIA (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.

## ODOR MANAGEMENT PROTOCOL

- **DIET:** Treatment of both TMAU1 and TMAU2 is based on diet to restrict the sources (precursors) of TMA. Treatment of manifestations: Dietary restriction of: (1) trimethylamine (present in milk obtained from wheat-fed cows) and its precursors including choline (present in eggs, liver, kidney, peas, beans, peanuts, soya products, and brassicas [Brussels sprouts, broccoli, cabbage, cauliflower]), lecithin and lecithin-containing fish oil supplements, (2) trimethylamine N-oxide (present in seafood [fish, cephalopods, and crustaceans]), (3) inhibitors of FMO3 enzyme activity such as indoles (found in brassicas)

- **ANTIBIOTICS: (neomycin, amoxicillin metronidazole)** to eliminate the TMA-producing bacteria, and thus suppress production of TMA. TMAU2 can well controlled by eradication of the excess bacteria, although stubborn colonies may regrow to excess and require further courses of treatment.

- **LAXATIVES:** The use of decrease intestinal transit time. Lactulose adsorbs and eliminates ammonia from the gut.

- **Riboflavin (Vit B2) supplements** to enhance residual FMO3 enzyme activity. Recommended intake is 30-40mg taken 3-5 times per day with food.

- **ACID SOAPS:** The use of acid soaps and body lotions are helpful to neutralize TMA chemically while removing secreted alkaline trimethylamine by washing. Trimethylamine is a strong base (pH 9.8), thus soaps with pH closer to that of normal skin help remove the secreted trimethylamine.

- **Odor effects may also be mitigated** with the administration of Activated charcoal taken at a dose of 750mg twice daily for ten days. Copper chlorophyllin taken at a dose of 60mg three times a day after meals for three weeks.to sequester trimethylamine produced in the gut, and copper chlorophyllin complex deodorizing tablets.

TMAU1, as a genetic defect, cannot be completely cured although therapy (dietary and antibiotic) can frequently successfully control the patient's TMA to a less odorous 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.

## ADDITIONAL TMAU INFORMATION

Trimethylaminuria. NCBI Bookshelf, A service of the National Library of Medicine, National Institutes of Health Web site. 2011 Available at: http://www.ncbi.nlm.nih.gov/books/NBK1103/#trimethylaminuria. Accessed May 31, 2011.

Trimethylaminuria. National Institutes of Health, Office of Rare Diseases Research, Genetic and Rare Diseases Information Center (GARD) Web site. 2010 Available at http://rarediseases.info.nih.gov/GARD/QnA.aspx?PageID=4&CaseID=20839&DiseaseID=6447#78. Accessed May 31, 2011.
Learning about Trimethylaminuria. National Human Genome Research Institute Web site. 2009 Available at: http://www.genome.gov/11508983 . Accessed May 31, 2011.
Trimethylaminuria. Genetics Home Reference Web site. April 2007 Available at: http://ghr.nlm.nih.gov/condition=trimethylaminuria. Accessed May 31, 2011.
Trimethylaminuria. MEBO Research, A Patient Advocacy International Campaign Web site. 2011 Available at http://www.meboresearch.org/trimethylaminuria.html.

## Suggested Reading


- Chalmers RA, Bain MD, Michelakakis H, Zschocke J, Iles RA. Diagnosis and management of trimethylaminuria (FMO3 deficiency) in children. 2006. Available online. Accessed 4-12-11.
- Cashman JR, Camp K, Fakharzadeh SS, Fennessey PV, Hines RN, Mamer OA, Mitchell SC, Nguyen GP, Schlenk D, Smith RL, Tjoa SS, Williams DE, Yannicelli S. Biochemical and clinical aspects of the human flavin-containing monooxygenase form 3 (FMO3) related to trimethylaminuria. Curr Drug Metab. 2003;4:151–70. [PubMed]
- Mamer OA, Choiniere L, Lesimple A. Measurement of urinary trimethylamine and trimethylamine oxide by direct infusion electrospray quadrupole time-of-flight spectrometry. Anal Biochem. 2010;406:80–2.[PubMed]
- Mamer OA, Choiniere L, Treacy EP. Measurement of trimethylamine and trimethylamine N-oxide independently in urine by fast atom bombardment mass spectrometry. Anal Biochem. 1999;276:144–9.[PubMed]
- Mitchell S. Trimethylaminuria (fish-odour syndrome) and oral malodour. Oral Dis. 2005;11 Suppl 1:10–3.[PubMed]
- Mitchell S, Ayesh R, Barrett T, Smith R. Trimethylamine and foetor hepaticus. Scand J Gastroenterol. 1999;34:524–8.[PubMed]
- Mitchell SC, Smith RL. Trimethylaminuria: the fish malodor syndrome. Drug Metab Dispos. 2001;29:517–2.
- Mitchell SC, Zhang AQ, Barrett T, Ayesh R, Smith RL. Studies on the discontinuous N-oxidation of trimethylamine among Jordanian, Ecuadorian and New Guinean populations. Pharmacogenetics. 1997;7:45–50.[PubMed]
- Pardini RS, Sapien RE. Trimethylaminuria (fish odor syndrome) related to the choline concentration of infant formula. Pediatr Emerg Care. 2003;19:101–3.[PubMed]
- Phillips IR, Francois AA, Shephard EA. The flavin-containing monoooxygenases (FMOs): genetic variation and its consequences for the metabolism of therapeutic drugs. Curr Pharmacogenet Pharmacogenom. 2007;5:292–313.
- Phillips IR, Shephard EA. Trimethylaminuria. GeneReviews Web site. March 18, 2008 Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=trimethylaminuria. Accessed July 21, 2010.
- Shimizu M, Cashman JR, Yamazaki H. Transient trimethylaminuria related to menstruation. BMC Med Genet. 2007;8:2.[PubMed]
- Treacy EP, Akerman BR, Chow LM, Youil R, Bibeau C, Lin J, Bruce AG, Knight M, Danks DM, Cashman JR, Forrest SM. Mutations of the flavin-containing monooxygenase gene (FMO3) cause trimethylaminuria, a defect in detoxication. Hum Mol Genet. 1998;7:839–45.[PubMed]
- Yamazaki H, Fujieda M, Togashi M, Saito T, Preti G, Cashman JR, Kamataki T. Effects of the dietary supplements, activated charcoal and copper chlorophyllin, on urinary excretion of trimethylamine in Japanese trimethylaminuria patients. Life Sci. 2004;74:2739–47.[PubMed]
- Mayatepek E, Kohlmuller D. Transient trimethylaminuria in childhood. Acta Paediatr. 1998;87:1205–7. [PubMed]
- Koukouritaki SB, Simpson P, Yeung CK, Rettie AE, Hines RN. Human hepatic flavin-containing monooxygenases 1 (FMO1) and 3 (FMO3) developmental expession. Pediatr Res. 2002;51:236–43. [PubMed]