

REVIEW ARTICLES

Beyond the Odour: Enhancing Primary Care for Trimethylaminuria Patients

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ABSTRACT

Trimethylaminuria (TMAU) is a rare, socially debilitating metabolic disorder, caused by an enzyme deficiency due to mutations in the flavin-containing mono-oxygenase 3 (FMO3) gene, resulting in excess excretion of trimethylamine in body fluids. Nevertheless, it may also occur due to a low processing capacity of the enzyme. TMAU is characterized by body odour that resembles rotting fish which can be intermittent, variable and influenced by diet, menstruation and medications.

A literary review of articles containing the keywords “trimethylaminuria” and “fish odour syndrome”, published between 2000 and 2024 in Portuguese, English and Spanish, was performed.

Diagnosis of trimethylaminuria is made by a combination of clinical, biochemical and genetic tests. It is also important to exclude other causes of fish odour, such as poor hygiene, gingivitis, bacterial vaginosis, urinary tract infections, chronic and advanced liver and kidney disease. Even though there are currently no effective treatments, patients may use products such as chlorophyllin and activated charcoal, riboflavin supplements and antibiotics. In addition, patients are advised to avoid foods such as shellfish, eggs, meat, certain vegetables, and mushrooms, which contain TMA precursors. These measures only temporarily reduce the bad smell, and more studies are being conducted to resolve these symptoms.

The psychosocial impact of trimethylaminuria is profound, often leading to low self-esteem, isolation, anxiety, depression and eventually suicidal thoughts. Patients may develop obsessive-compulsive behaviors to mitigate the unpleasant odour. Further research is required to improve diagnostic and treatment options, as well as enhance patients' quality of life.

Keywords: trimethylaminuria; fish odour syndrome

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INTRODUCTION

Trimethylaminuria (TMAU) is a rare metabolic condition of multifactorial origin that remains frequently underdiagnosed. Despite its low prevalence, it has a significant impact on the quality of life of affected individuals.

Reports of a persistent fish-like body odour date back centuries, with some scholars suggesting that Shakespeare may have been describing this condition in *The Tempest*, where he attributes such an odour to one of the characters. The first well-documented clinical case, however, was reported by Humbert and colleagues in 1970.⁽¹⁾ Since then, medical literature has expanded considerably, encompassing more than two hundred documented cases and providing a much deeper understanding of the disorder's underlying biochemistry and genetics. Consequently, TMAU has evolved from being regarded as a rare medical curiosity to a condition now considered uncommon.⁽²⁾

The etiology of TMAU is multifactorial but is generally associated with reduced or absent activity of the flavin-containing monooxygenase 3 (FMO3) enzyme and will be further explored throughout this article. This enzymatic deficiency leads to the excessive accumulation of trimethylamine, which is subsequently excreted through various bodily secretions, resulting in a strong and characteristic body odour.

Beyond its physical manifestations, TMAU is frequently associated with considerable social stigma and profound psychosocial consequences. Therefore, timely diagnosis is essential to enable the implementation of strategies aimed at mitigating both the physical and psychological burden of the disorder.

METHODS

A comprehensive literature review was conducted to identify relevant clinical guidelines and original research articles concerning trimethylaminuria.

The literature search was conducted between March 1 and March 20, 2025. The search was performed using the following electronic databases: National Guidelines Clearinghouse, National Institute for Health and Care Excellence (NICE), CMA Infobase, Cochrane Library, Clinical Evidence, BMJ, Directory of Open Access Journals (DOAJ), and PubMed. The keywords used for the search in the databases were “trimethylaminuria” and/or “fish odour syndrome”.

Inclusion criteria comprised articles published between January 1, 2000, and December 31, 2024, written in Portuguese, English, or Spanish. Only clinical guidelines, systematic reviews, original research articles and case reports were considered for inclusion.

Exclusion criteria included duplicate articles and studies involving animals or plants.

RESULTS

A total of 35 articles were initially retrieved using the selected keywords across the databases. Of these, 19 articles were excluded: three were duplicates, one involved an animal study, one involved a plant-based study, three did not meet inclusion criteria, and 11 did not meet the objectives of the present review. The remaining 12 articles were included for full-text analysis, presented in **table 1**, and four systematic reviews were mentioned along the article.

Table 1 - Full-text analysis (author; year; country; publication type; findings).

Author	Year	Country	Publication type	Findings
Mazón Ramos A, Gil-Setas A, Berrade Zubiri S, <i>et al.</i>	2003	Spain	Case Report	This article reports a 4-year-old girl who, from 9 months of age after the introduction of fish into her diet, developed a strong, unpleasant body odor resembling rotten fish, also noticeable in her urine. The family reported that the odor consistently appeared after the consumption of fish or seafood. Clinical and biochemical evaluation confirmed trimethylaminuria, and genetic analysis identified a mutation in the FMO3 gene associated with reduced enzyme activity. The identified mutation, R51G (c.151A>G), results in the replacement of arginine with glycine. The patient was homozygous for this mutation, while both parents were heterozygous carriers. The case highlights the importance of considering trimethylaminuria in patients with unexplained body odor and confirms a novel pathogenic mutation in the FMO3 gene.

Shimizu M, Cashman JR, Yamazaki H	2007	Japan	Observational longitudinal study	The study investigated the relationship between menstruation and transient trimethylaminuria in women with different FMO3 genotypes. Two women with self-reported malodor and three healthy controls were monitored over time through urinary trimethylamine and trimethylamine N-oxide measurements. Women carrying homozygous FMO3 variants associated with reduced enzyme activity showed significant decreases in FMO3 metabolic capacity during menstruation. Even healthy women with active FMO3 enzymes demonstrated temporary reductions in metabolic capacity around menstruation. The findings suggest that hormonal changes during menses can transiently impair FMO3 function, particularly in individuals with genetic susceptibility, contributing to temporary or mild TMAU symptoms.
Arseculeratne G, Wong AKC, Goudie DR, <i>et al.</i>	2007	United Kingdom	Case Report	The article described a 41-year-old male patient diagnosed with primary trimethylaminuria caused by a homozygous mutation in the FMO3 gene. The study highlighted the severe psychosocial burden associated with the disorder, including social embarrassment, anxiety, and isolation. Dietary modification and metronidazole therapy contributed to partial symptom improvement; however, psychosocial support, patient education, and communication with family and friends were identified as the most beneficial therapeutic strategies.
Mountain H, Brisbane JM, Hooper AJ, <i>et al.</i>	2008	Australia	Case Report	The article described the case of a 41-year-old woman with trimethylaminuria who experienced delayed diagnosis and severe psychosocial consequences throughout her life. The authors emphasized that trimethylaminuria is associated with profound psychosocial sequelae, including shame, anxiety, depression, low self-esteem, social isolation, and impaired interpersonal relationships. The study highlighted the importance of increased clinical awareness, early diagnosis, multidisciplinary management, dietary counselling, and genetic counselling to reduce the psychosocial burden associated with the condition.
Nanayakkara PW, Meijboom M, Kramer MH, <i>et al.</i>	2010	Netherlands	Case Report	The article described a 45-year-old man with primary trimethylaminuria who presented with severe fish-like body odour and substantial psychosocial impairment, including anxiety, depression, low self-esteem, marital difficulties, and occupational limitations. Diagnosis was confirmed through urinary biochemical analysis and genetic testing, which identified multiple FMO3 mutations. Dietary modification with restriction of choline- and lecithin-rich foods led to improvement in body odour and self-confidence.

Sabir N, Jones EA, Padmakumar B.	2016	United Kingdom	Case Report	The article described the case of a 9-year-old boy presenting with a persistent fishy odor affecting his hands, feet, saliva, breath, and urine. Biochemical urine analysis demonstrated elevated trimethylamine levels and an increased TMA/TMAO ratio, while genetic testing confirmed homozygosity for the p.Glu208X mutation in the FMO3 gene, establishing the diagnosis of trimethylaminuria. Management included multidisciplinary follow-up and dietary modification targeting foods rich in choline, lecithin, and trimethylamine precursors, resulting in substantial improvement in symptoms and quality of life. The authors highlighted the importance of early recognition of TMAU to reduce psychosocial burden and improve patient outcomes.
Kılıç M	2017	Turkey	Case Report	The study described a Turkish adolescent boy diagnosed with primary trimethylaminuria through molecular analysis after presenting with socially distressing malodor. The patient also had primary hypothyroidism, previously identified during the diagnostic investigation for odor complaints. The authors emphasized the psychosocial burden associated with TMAU and highlighted the importance of physician awareness. Although the coexistence of TMAU and hypothyroidism was explored, no definitive pathophysiological association was identified, suggesting that the coexistence might be coincidental.
Bouchemal N, Ouss L, Brassier A, <i>et al.</i>	2019	France	Retrospective observational study	The study evaluated 13 patients with suspected trimethylaminuria using proton nuclear magnetic resonance spectroscopy and FMO3 genetic testing. Two pediatric patients exhibited confirmed TMAU with pathogenic FMO3 variants, objective malodor, and abnormal urinary TMA/TMAO ratios. Riboflavin (vitamin B2) treatment significantly reduced trimethylamine excretion and improved body odor in these children. In contrast, adult patients mainly presented subjective odor complaints associated with psychological or psychiatric manifestations, without consistent biochemical confirmation of TMAU. The authors emphasized the importance of differentiating true TMAU from olfactory reference syndrome and highlighted the diagnostic value of combining biochemical and genetic analyses.
Schmidt AC, Hebels ER, Weitzel C, <i>et al.</i>	2020	Switzerland	Experimental Research Article	The study developed engineered poly(isoprene)-block-poly(ethylene glycol) polymersomes as a novel topical treatment approach for Trimethylaminuria, also known as fish odour syndrome. Researchers demonstrated that transmembrane pH-gradient polymersomes efficiently captured trimethylamine. The polymersomes were incorporated into a hydrogel suitable for skin application and showed rapid TMA sequestration in vitro. The study found that the polymersome-containing hydrogel significantly reduced perceived TMA odour intensity compared with control gels.

Zia S, Lasso RS, Wasim AU, <i>et al.</i>	2022	Pakistan	Case Report	The authors observed that fungal infections worsened after the onset of trimethylaminuria symptoms, suggesting a possible association between TMA accumulation and increased susceptibility to fungal infections. This disease has a severe psychosocial burden, including social isolation, anxiety, frustration, and stigma. Management strategies discussed included dietary modification, reduction of choline and carnitine intake, antibiotics such as metronidazole and neomycin, and symptomatic dermatological treatment.
Rua I, Ribau R, Silva MF, <i>et al.</i>	2022	Portugal	Case Report	The article presents a case of a 6-year-old girl with Trimethylaminuria, The child presented with a persistent fish-like body odor, especially after consuming certain types of fish, while otherwise being healthy. Diagnosis was confirmed through genetic testing, and management focused on dietary measures and psychosocial support. The case highlights that, if left undiagnosed, the condition may lead to significant psychosocial impact due to social stigma and misinterpretation of symptoms. For diagnosis to be possible, this condition must be recognized, especially in primary care, so that unpleasant body odor is not mistaken for poor hygiene.
Flaherty CC, Phillips IR, Janmohamed A, <i>et al.</i>	2024	United Kingdom	Cross-sectional online survey study	The study demonstrated that individuals living with trimethylaminuria and other body/breath malodour conditions experience substantial psychosocial burden, including bullying, social exclusion, workplace discrimination, anxiety, depression, loneliness, and suicidal ideation. Participants also reported significant barriers to diagnosis, largely due to limited awareness among healthcare professionals. The authors emphasized the need for improved clinical recognition, standardized diagnostic pathways, and greater societal awareness and support for affected individuals.

The data extracted from the selected literature were analyzed and synthesized according to the main clinical and scientific aspects of trimethylaminuria. For clarity and comprehensiveness, the findings are presented in four thematic categories: etiology, clinical presentation, diagnosis, and treatment. This structure was chosen to facilitate a systematic understanding of the condition based on the evidence available in the reviewed literature.

ETIOLOGY

Trimethylaminuria is a rare metabolic disorder characterized by the excessive excretion of trimethylamine (TMA), a volatile compound with a strong, unpleasant odour often compared to that of rotting fish.^(3,4) Although some epidemiological studies estimate a prevalence of approximately 1 in 40,000

individuals, the true extent of the condition remains uncertain due to significant underreporting and underdiagnosis.⁽⁵⁾

Production and Metabolism of TMA

TMA, a tertiary amine with an odour similar to that of rotting fish, is primarily produced in the gastrointestinal tract through the action of the gut microbiota on dietary precursors such as choline, carnitine, lecithin, betaine, and ergothioneine.^(6,7) These compounds are abundant in foods such as fish (especially saltwater and fatty fish), red meat, eggs, liver, vegetables and peanuts.⁽⁷⁾

In healthy individuals, TMA is efficiently converted in the liver by the enzyme flavin-containing monooxygenase 3 (FMO3) into its oxidized, odorless form, trimethylamine N-oxide (TMAO). However, when this conversion is impaired, TMA accumulates and is excreted, resulting in the characteristic body odour.⁽³⁾ In addition to the lack of intestinal conversion of

TMA into TMAO, TMA production can also occur to a lesser extent in the oral and vaginal cavities.⁽⁷⁾

In patients with TMAU, the higher concentration of TMA, along with its high solubility in both aqueous and lipid media, as well as its volatility at room temperature, gives

rise to intermittent episodes of the syndrome under specific conditions (**Figure 1**).^(7,8)

This failure in oxidation can result from various causes, allowing TMAU to be classified into three main forms: primary (genetic), secondary (acquired), and transient.

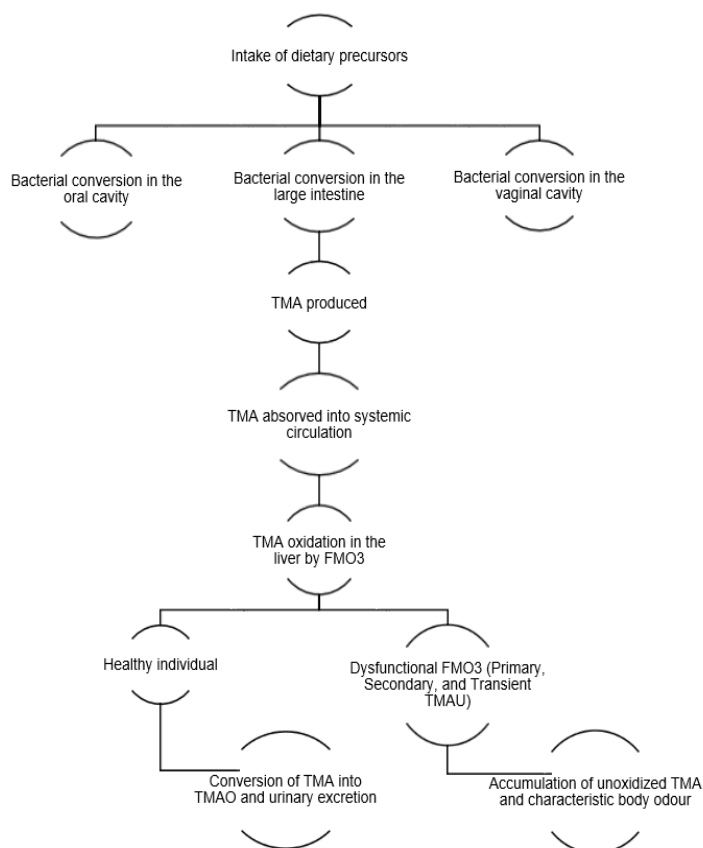


Figure 1 - Production and metabolism of trimethylamine and its association with trimethylaminuria.

CLINICAL FORMS OF TMAU

1. Primary (Genetic) TMAU

Primary TMAU, also known as type 1 TMAU, is of genetic origin and results from mutations in the *FMO3* gene, located on chromosome 1q24.3.^(3,7) This gene encodes the FMO3 enzyme, which is essential for the oxidation of TMA. In this form, the enzyme has absented or significantly reduced functional activity.⁽³⁾ The condition is inherited in an autosomal recessive manner and is considered an inborn error of metabolism.⁽⁷⁾ Most cases manifest in childhood, often coinciding with weaning, a period during which hepatic FMO3 expression is naturally low, and the intake of dietary TMA precursors increases.⁽⁸⁾

More than 300 variants of the *FMO3* gene have been

described, including over 90 directly associated with TMAU, each with varying impacts on enzymatic activity. Mutations such as p.Pro153Leu (c.458C>T) and p.Glu305 (c.913G>T)* are common in European populations, while p.Arg205Cys (c.613C>T) and p.Arg500 (c.1498C>T)* are more frequently found in Japanese individuals.^(7,8)

It is postulated that even combined polymorphisms and heterozygous variants may reduce the FMO3 activity, resulting in mild functional impact, as studies have reported that compound haplotypes like E158K/E308G, even in heterozygous states, may impair FMO3 activity and consequently lead to mild clinical manifestations.⁽⁹⁾

Additionally, variants in other genes of the FMO family (such as *FMO1*, *FMO2*, and *FMO5*), as well as in other oxidoreductases, have been studied as potential modulators of the phenotype, suggesting a more complex etiology than

initially thought.

2. Secondary (Acquired) TMAU

Secondary TMAU typically arises in adulthood and lacks a defined genetic cause. Family history is usually absent.^(4,7) It is associated with environmental factors such as:

- Hepatic or renal dysfunction, including some cases associated with viral hepatitis;⁽⁴⁾
- Pharmacological treatments involving TMA precursors (e.g., therapies for Alzheimer's and Huntington's disease);⁽⁴⁾
- Intestinal dysbiosis, the most frequent factor, is characterized by an imbalance in the gut microbiota.⁽³⁾

Several bacterial species - including *Clostridium*, *Desulfovibrio desulfuricans*, *Escherichia*, *Klebsiella*, *Proteus*, and *Streptococcus* - can convert dietary precursors into TMA. The main metabolic pathways involved are the CutC/CutD, CntA/B, and YeaW/X enzymatic systems, which exhibit high specificity for substrates such as choline, carnitine, and betaine. Overproduction of TMA via these pathways may exceed the liver's FMO3 oxidative capacity, even in individuals without genetic mutations, resulting in the manifestation of the phenotype.

Natural modulators such as allicin (from garlic), berberine, and resveratrol have shown beneficial effects in modulating the gut microbiota and reducing TMA production, representing potential adjunct therapeutic strategies.

3. Transient TMAU

The transient form manifests intermittently and depends on individual physiological and hormonal conditions. It is more commonly observed in:

- Women during menstruation, due to reduced FMO3 expression induced by sex hormones.^(4,7) Symptoms may be more pronounced in the presence of homozygous genetic variants that further decrease FMO3 expression.⁽¹⁰⁾ However, even healthy women may experience episodes of transient TMAU, highlighting that FMO3 expression and functionality can be modulated by epigenetic and hormonal mechanisms that are not yet fully understood;
- Infants during weaning, due to physiologically low hepatic enzymatic activity;⁽⁴⁾
- Stressful situations, fever, intense physical exercise, or oral contraceptive use.

CLINICAL PRESENTATION

The accumulation of TMA and its excretion through bodily fluids, such as urine, sweat, breath, saliva and vaginal secretions, is the cause for the unpleasant characteristic odour that patients with TMAU describe.^(7,11) This smell can occur transiently or persistently and be either intense or mild.⁽¹²⁾

Patients may develop these symptoms throughout different stages of life. In some patients, TMAU is suspected right at birth, however it often manifests when infants introduce foods with high choline content in their diets, such as eggs, fish, lean meat and liver, some nuts and beans. As such, it is reported that the ingestion of high choline foods may lead to a bout of unpleasant odour. It is also mentioned that some individuals can present an aggravated smell while sweating, either from exercising or stress induced. Moreover, while both men and women are affected by TMAU, women may also experience worsening odour during menstruation.^(8,13)

The malodour associated with the disease leads to a wide range of psychosocial symptoms that warrant serious attention and should not be underestimated. Due to social exclusion, isolation and loneliness, patients frequently present low self-esteem, anxiety, depression and even suicidal ideation. Low school and academic performance have also been reported.^(11,12) In a study by Flaherty, patients have reported bullying, harassment in both their work environment and social events, disadvantages regarding work offers and difficulty developing and maintaining friendships and relationships.⁽¹⁴⁾ Patients have also reported that their General Practitioners present a lack of knowledge regarding the disease.

DIAGNOSIS

The laboratory diagnosis primarily relies on quantifying TMA and TMAO in urine, as well as analyzing the ratio between these compounds.⁽³⁾ Biochemical diagnosis can be performed using mass spectrometry, ideally on two separate occasions, preferably fasting and after intake of a choline-rich meal, allowing assessment of the capacity to convert TMA into TMAO.⁽⁹⁾ Sample collection should be done at distinct times to increase diagnostic reliability. Analysis must be conducted by qualified personnel due to the volatile nature of TMA and the specific technical requirements, which are limited in availability.

Elevated urinary TMA levels accompanied by a reduced proportion of oxidized TMA indicate impaired FMO3 activity. A study by Flaherty et al. demonstrated that urinary levels of TMA at 14.7 µmol/mmol creatinine (reference: 1.5–11.0 µmol/mmol), TMAO at 34 µmol/mmol creatinine (reference: 17–147 µmol/mmol), and a TMA/TMAO ratio of 0.43, were compatible with primary TMAU.⁽¹⁴⁾

The proportion of TMAO relative to total TMA (TMAO / [TMAO + TMA] × 100) allows phenotypic stratification: proportions <70% indicate severe forms; 70–80% suggest mild phenotype; >80% are considered normal.⁽⁷⁾ Alternatively, the percentage of free TMA relative to total excreted TMA can also be used: ≥40% free TMA indicates a severe phenotype; 10–39% corresponds to mild phenotype; 0–9% is compatible with a normal phenotype.⁽¹⁴⁾

It is crucial to consider factors that may influence laboratory results and lead to false positives, such as urinary tract

infections, bacterial vaginosis, hepatic or renal dysfunction, or hormonal changes associated with menstruation.⁽⁷⁾

Molecular diagnosis consists of identifying pathogenic mutations in the FMO3 gene through DNA analysis extracted from peripheral blood. The presence of homozygous variants confirms the diagnosis of primary TMAU, while heterozygous individuals are typically asymptomatic. Multiple mutations associated with total or partial loss of enzymatic function have been described, including P153L (c.458C>T) in exon 4.⁽¹⁵⁾ and R51G (c.151A>G) in exon 3.⁽¹⁶⁾ Genetic testing is particularly useful in cases with ambiguous biochemical results or for genetic counseling.

Additionally, metagenomic analysis of the intestinal microbiota using next-generation sequencing (NGS) techniques has been explored as a complementary tool. Identifying an excess of bacteria capable of producing TMA may contribute to phenotypic severity, opening possibilities for therapeutic interventions based on modulation of the gut ecosystem.⁽⁷⁾

Despite the availability of sensitive analytical methods, the diagnosis of TMAU is limited by phenotypic variability, intermittent symptoms, and the absence of standardized clinical protocols, particularly within the National Health System. Currently, there are no specific guidelines for the investigation or referral of these patients, often resulting in significant diagnostic delays. The lack of self-perception of odour by patients and the limited awareness of the condition among many clinicians contribute to the underdiagnosis of this disorder.⁽¹⁴⁾

TREATMENT

To date, there is no treatment proven to be reliably effective for trimethylaminuria. However, there are strategies that help reduce the unpleasant odour, including the restriction of foods rich in choline and carnitine - precursors of trimethylamine (such as fish, seafood, eggs, liver, spinach, soy, peas, among others).⁽¹⁷⁾ Choline restriction is not recommended during pregnancy, breastfeeding, or childhood, as it is essential for neurodevelopment.^(7,8,18)

Furthermore, short-term use of antibiotics may be considered to reduce intestinal bacteria and consequently lower TMA production. Preferred antibiotics include metronidazole, neomycin, rifaximin, and amoxicillin.^(7,19) Caution is advised, as excessive antibiotic use may lead to microbial resistance and disruption of microbiota homeostasis.

Another less consensual approach involves the use of activated charcoal or chlorophyllin, which are intestinal absorbents intended to sequester TMA production in the gut.^(7,19) Urinary TMA levels in patients with trimethylaminuria have been shown to decrease following a regimen of 750 mg of activated charcoal taken twice daily for ten days.⁽⁷⁾

Riboflavin (vitamin B2) supplementation is used to enhance FMO3 enzymatic activity.^(7,8) According to Sidoti A.,

medications such as clozapine, deprenyl, and ranitidine are metabolized by FMO3 and should be avoided, as they may compete with TMA and potentially worsen the odor.⁽⁷⁾

The use of lotions, soaps, and fragrances can temporarily mask the odor in these patients. Since TMA is a basic compound, acidic products (pH 5.5–6.5) are preferred to help neutralize the odor.⁽⁷⁾

Several future therapeutic strategies are under investigation, including gene replacement therapy for defective FMO3 and the colonization of the human gut with genetically modified microorganisms that express human FMO3.⁽¹⁵⁾

Patients with trimethylaminuria should be referred for genetic counseling to receive essential information, psychological support, and testing options for other family members.^(15,17)

Finally, dietary follow-up by a registered dietitian or healthcare professional is recommended to ensure a diverse and nutritionally adequate diet.⁽¹⁷⁾

CONCLUSION

Trimethylaminuria is a complex and multifactorial metabolic disorder that, despite its low prevalence, exerts a profound impact on affected individuals' quality of life. This condition, primarily caused by impaired activity of the FMO3 enzyme, leads to the accumulation and excretion of malodorous trimethylamine, resulting in a strong and socially stigmatizing body odour. TMAU can manifest in genetic, acquired, or transient forms, influenced by both genetic predisposition and environmental factors, including hormonal fluctuations and gut microbiota imbalances.

Although biochemical and molecular tools for diagnosis exist, underdiagnosis remains common due to the condition's rarity, symptom variability, and limited clinical awareness. Early diagnosis is essential to initiate management strategies aimed at minimizing symptoms and supporting patients' psychosocial well-being. Current treatment is largely symptomatic, focusing on dietary modifications, antibiotic regimens, odour-neutralizing products, and supportive care, though emerging research offers promising avenues such as gene therapy and microbiota modulation.

Ultimately, increased clinical recognition, patient education, and multidisciplinary support, including genetic counseling and dietary guidance, are critical for improving outcomes and quality of life in individuals with TMAU.

AUTHORSHIP

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