OPEN ACCESS Freely available online

Biochemistry & Analytical Biochemistry

Review Article

The Management of Tyrosinemia

Peterchris Okpala*, Sandra Okpala

Department of Chanchellor's Office, Charisma University, Providenciales, Turks and Caicos Islands

ABSTRACT

Tyrosinemia is a rare autosomal recessive genetic metabolic disorder, which occurs due to the error of metabolism that affects the body's ability to breakdown tyrosine, an amino acid. Persons experience three types of tyrosinemia, which are tyrosinemia I, tyrosinemia II, and tyrosinemia III. In the United States, the incidence of tyrosinemia I am present in one in 100,000 live births. Individuals with tyrosinemia type I experience adverse signs and symptoms, including blood stools, vomiting, failure to thrive, fatigue, poor weight gain, diarrhea, and cabbage-like odor. The study offers detailed information on evidence-based treatment and prevention methods for tyrosinemia. The research's completion is based on empirical data and evidence from peer-reviewed articles with accurate and detailed information on tyrosinemia's pharmacological and non-pharmacological treatment methods. The study includes an analysis of psychosocial support, genetic counseling, nutritional therapy, liver transplantation, patient education, and nitisinone therapy that medical practitioners use to manage tyrosinemia appropriately. Even though the literature review has detailed information, the articles fail to provide information about the side effects of nutritional, liver transplantation, and gene therapies. Scholars should conduct more research to reveal the side effects of pharmacological and non-pharmacological treatment methods. Overall, the study encourages interprofessional healthcare workers to apply evidence-based pharmacological and non-pharmacological treatment methods in managing tyrosinemia.

Keywords: Tyrosinemia; Pharmacological; Non-pharmacological; Psychosocial support; Genetic counseling; Nutritional therapy; Liver transplantation; Patient education; Nitisinone therapy

INTRODUCTION

Mainly, tyrosinemia among the rare health complications that affect a significant number of people globally. According to the National Organization for Rare Disease tyrosinemia is a rare autosomal recessive genetic metabolic disorder, which occurs due to the error of metabolism that affects the body's ability to breakdown tyrosine, an amino acid. Persons experience three types of tyrosinemia, which are tyrosinemia I, tyrosinemia II, and tyrosinemia III.1 Globally, the National Organization for Rare Disease notes that tyrosinemia I affect one in 120,000 births.1 In the United States, the incidence of tyrosinemia I is present in one in 100,000 live births. Individuals with tyrosinemia type I experience adverse signs and symptoms, including blood stools, vomiting, failure to thrive, fatigue, poor weight gain, diarrhea, and cabbage-like odor [1]. Although tyrosinemia type I is a prevalent health complication, numerous individuals, patients, caregivers, and medical practitioners have limited knowledge about its evidence-based treatment and prevention methods. In this regard, the research aims to conduct a detailed literature review to reveal existing and new evidence-based management, treatment, and prevention strategies for tyrosinemia type I to improve the health and wellbeing of infants diagnosed with the rare disease.

LITERATURE REVIEW

The completion of the literature review is based on information and data from secondary research. According to Largan and Morris, secondary research involves identifying, reviewing, and using existing data to complete studies. Researchers conduct secondary research online or offline, including examining and

Correspondence to: Peterchris Okpala, Department of Chanchellor's Office, Charisma University, Providenciales, Turks and Caicos Islands
E-mail: peterchris.okpala@charisma.edu.eu

Received: June 17, 2021; **Accepted:** July 01, 2021; **Published:** July 08, 2021

Citation: Okpala P, Okpala S (2021) The Management of Tyrosinemia. Biochem Anal Biochem. 10:398.

using information from published reports, e-books, and peer-reviewed journals. The researcher reviewed and utilized information from peer-reviewed journals, government agencies, and reputable organizations in completing this study [2]. The researcher included only information published within the last seven years in the study. The researcher obtained secondary resources from Google Scholar, ProQuest, and Google search engine. Next, the researcher used vital phrases like "non-pharmacological treatment methods for tyrosinemia," "pharmacological treatment methods for tyrosinemia," "evidence-based treatment methods for tyrosinemia," and "ways of managing tyrosinemia" to get useful peer-reviewed articles to complete the study. The researcher spent minimum finances and time to complete the study due to the use of secondary research.

Management of tyrosinemia type I pharmacological and non-pharmacological treatment of tyrosinemia type I nitisinone therapy

Notably, nitisinone therapy is an evidence-based method for treating tyrosinemia type I. According to Al-Noaemi and Daghriri, scientists developed nitisinone, a herbicide family member, to break apart tyrosine in plants and animals. Scientists conducted numerous trials of the impact of nitisinone drug therapy on humans. Al-Noaemi and Daghriri reveal that clinical drug trials showed the effect of nitisinone drug therapy, which included reversible inhibition of 4-hydroxyphenylpyruvate dioxygenase. The inhibition of 4-hydroxyphenylpyruvate dioxygenase reduces or eliminates the formation of fumarylacetoacetic acid and maleylacetoacetate acid, which contribute directly to the liver and kidney damage in patients with tyrosinemia type I [3]. As a result, patients treated with nitisinone therapy have a significantly reduced risk of experiencing kidney or liver damage.

Likewise, Chinsky et al. examined the effectiveness of nitisinone therapy in managing the tyrosinemia type I's adverse symptoms. The researcher reviewed four studies that revealed the potential of nitisinone therapy in inhibiting 4-hydroxyphenylpyruvate dioxygenase and indicate that nitisinone therapy minimizes the formation of fumarylacetoacetic acid and maleylacetoacetate acid by blocking the proximal pathway of tyrosinemia. For example, Chinsky et al. note that the use of nitisinone therapy in five patients showed the drug's ability to reverse tyrosinemia's adverse symptoms in all of the patients. Also, Chinsky et al. add that the United States Food and Drug Administration conducted a clinical trial that involved 180 pediatrics from 25 countries to examine the effectiveness of nitisinone therapy. The study revealed the nitisinone therapy contributed to a 4-year survival probability of more than 85% of children under two years. Chinsky et al. state that the correct dosage of nitisinone drug therapy leads to improved renal and liver functioning in tyrosinemia patients. Consequently, medical practitioners should prioritize nitisinone therapy in treating persons with tyrosinemia [4].

Even though nitisinone therapy is exceptional in treating tyrosinemia, Van Ginkel et al. conducted a study to examine positive and negative long-term impacts of the evidence-based treatment strategy. Notably, the study revealed that nitisinone therapy leads to eye problems. Van Ginkel et al. argue that nitisinone therapy causes long-term eye problems, such as photophobia, transient itching, and burning, in roughly 5% to 10% of tyrosinemia patients. Van Ginkel et al. recommend that medical practitioners must ensure that tyrosinemia patients undergo ophthalmic follow-up care during and after nitisinone therapy. Also, nitisinone therapy leads to reduced plasma phenylalanine in tyrosinemia patients. Van Ginkel et al. state that limited plasma phenylalanine leads to skin problems, growth retardation, and neurological impairment among infants with tyrosinemia. Van Ginkel et al. add that medical practitioners prescribe phenylalanine supplements for infants with tyrosinemia to reduce their risks of nitisinone therapy's side effects [5]. Lastly, some tyrosinemia patients experience other adverse side effects like pruritus, exfoliative dermatitis, myoclonia, and constipation during or after nitisinone therapy. Hence, patients should review the adverse impacts of nitisinone therapy before accepting the evidence-based treatment approach.

Liver transplantation: Chinsky et al. researched the importance of liver transplantation in treating tyrosinemia patients. Medical practitioners use the liver transplantation method to treat tyrosinemia patients with malignancy or when nitisinone therapy is unavailable. The evidence-based treatment method minimizes hepatocellular carcinoma risk and restores the liver's normal functioning in tyrosinemia patients. Chinsky et al. add that liver transplantation leads to decreased urine and plasma SA in tyrosinemia patients. Chinsky et al. note that research showed that successful liver transplantation before 2008 contributed to the 5- year survivals of more than 90% of tyrosinemia patients [4]. Consequently, medical practitioners should use liver transplantation to treat tyrosinemia patients with malignancy.

Likewise, Al-Noaemi and Daghriri examined the viability of liver transplantation in treating tyrosinemia patients. The researchers state that liver transplantation was among the first treatment options for tyrosinemia before the introduction of nitisinone therapy. According to Al-Noaemi and Daghriri, medical practitioners only use liver transplantation to manage tyrosinemia in children with severe liver failure [3]. The treatment improves the normal functioning of the liver of children with tyrosinemia. Therefore, it improved their long-term health and wellbeing.

Dietary therapy: De Laet et al. completed a study to reveal the importance of dietary therapy in tyrosinemia management. The research indicates that medical practitioners require tyrosinemia patients to consume low tyrosine low phenylalanine diet to overcome the adverse complications of tyrosinemia. The dietary therapy goals for tyrosinemia patients include support normal intellectual development, adequate nourishment; prevent the neurological crisis, and liver and renal function issues. According to De Laet et al., medical practitioners collaborate with patients and caregivers to create low tyrosine diets to maintain tyrosine concentrations of tyrosinemia patients between 200–400 μmol/l. For example, nutritionists encourage tyrosinemia patients to avoid high protein food, such as nuts, eggs, cheese, beans, meat, and poultry, from their low tyrosine

low phenylalanine diets. Low-protein diets like vegetables and fruits help tyrosinemia patients to maintain tyrosine concentrations between 200–400 μmol/l for extended periods. De Laet et al. recommend that tyrosinemia patients complement low tyrosine low phenylalanine with phenylalanine and tyrosine-free amino acid supplements. Therefore, patients that adhere to the low tyrosine low phenylalanine diet have normal liver and renal functioning, growth, and intellectual development [6].

Likewise, Chinsky et al. completed a study to examine the nutritional management of tyrosinemia. The researchers indicate that the goal of tyrosinemia's nutritional management is to promote normal growth and development and restrict amino acids to healthy levels. Chinsky et al. state that medical practitioners prescribe medical foods, including Tyrex 1, Tyros 1, and Tyr coolers, to accomplish energy, protein, and nutrient requirements of tyrosinemia patients. Chinsky et al. note that medical practitioners complement medical foods with artificial low-phenylalanine and low-tyrosine nutrition sources. Nutritionists ensure that the nutritional intake of tyrosinemia patients meets the age-appropriate energy, protein, and nutrient requirements. Chinsky et al. state that exceptional nutritional management enables tyrosinemia patients to maintain tyrosine concentrations between 200–400 μmol/l for extended periods. Consequently, they avoid the adverse impacts of tyrosinemia [4].

Genetic therapy: Al-Noaemi and Daghriri completed a study to examine genetic therapy's viability in managing tyrosinemia. The researchers argue that studies have shown that Adeno-Associated Virus (AAV), a mediated gene repair, effectively treats mice and pigs with tyrosinemia. Al-Noaemi and Daghriri argue that gene therapy's use increased the survival time of mice with tyrosinemia by nine months. In contrast, mice with tyrosinemia that failed to undergo gene therapy succumbed to liver failure within six weeks [3]. The animal evidence indicates that clinicians should conduct more human trials to utilize gene therapy successfully to manage tyrosinemia.

Evidence-based management and prevention methods for tyrosinemia

Early diagnosis and treatment: Al-Noaemi and Daghriri note that medical practitioners should strive to diagnose and treat tyrosinemia early. Medical practitioners use DNA analysis and the detection of succinylacetone in amniotic fluids to complete prenatal diagnosis of tyrosinemia successfully [3]. Prenatal or early detection of tyrosinemia helps medical practitioners to utilize evidence-based methods to prevent the onset of symptoms among tyrosinemia patients and enhance their wellbeing.

Follow-up care: Medical practitioners should provide long-term follow-up care for tyrosinemia patients to improve their health and wellbeing. According to Al-Noaemi and Daghriri, medical practitioners should conduct neurocognitive, nutritional, physical, and psychosocial follow-up to ensure patients overcome the adverse effects of tyrosinemia. dela et al. note that medical practitioners should conduct liver functioning tests among tyrosinemia patients undergoing treatment to ensure they respond positively to their therapies. Nutritionists should visit tyrosinemia patients to ensure they consume low tyrosine low phenylalanine diets to overcome tyrosinemia's adverse complications. For example, nutritionists should ensure that patients consume only vegetables, fruits, and foods low in protein during their treatment processes.

Also, Al-Noaemi and Daghriri add that medical practitioners should offer psychosocial support for tyrosinemia patients. They should guide tyrosinemia patients on how to access low tyrosine low phenylalanine diets and medical foods. For example, nutritionists should inform patients about the names and locations of grocery stores with adequate and fresh vegetables and foods with low-protein content to ensure tyrosinemia patients access and consume healthy meals. Medical practitioners should connect tyrosinemia patients with interprofessional healthcare workers, such as social workers, physical trainers, and psychologists. Interprofessional healthcare workers will offer physical, social, and emotional support to patients to ensure they receive holistic care. Further, medical practitioners should guide tyrosinemia patients on accessing community-based and appropriate health services to enhance their recovery process. For example, nurses and physicians should inform patients about pharmacies to access original and affordable nitisinone drugs. As a result, psychosocial support will enable tyrosinemia patients to receive holistic care and overcome adverse tyrosinemia symptoms [3,6].

Genetic counseling: According to Al-Noaemi and Daghriri, genetic counseling is an evidence-based method, which involves educating individuals or families about inheritance and implications of genetic disorders. Medical practitioners provide genetic counseling to guide individuals or families in making informed medical and personal decisions to avoid or reduce their risks of genetic diseases. Based on this explanation, medical practitioners should offer genetic counseling to tyrosinemia patients or individuals at risk of tyrosinemia. Chinsky et al. indicate that medical practitioners should offer genetic counseling to women with 25% of recurrence risk of giving birth to children with tyrosinemia. Physicians use diagnosis information or results to provide evidence-based genetic counseling. The approach influence women to make informed medical and personal decisions to avoid pregnancies and giving birth to children with tyrosinemia [3,4].

Patient education: Medical practitioners should provide detailed patient education to tyrosinemia patients and their caregivers. According to the Medical Portal Home (2020), healthcare workers should educate tyrosinemia patients and their caregivers about tyrosinemia, signs and symptoms, risk factors, and evidence-based treatment and prevention methods. Information about the rare disease will enable patients and their caregivers to participate actively in the treatment plan and make informed decisions about evidence-based approaches to overcome tyrosinemia's adverse symptoms. The Medical Portal Home argues that medical practitioners should educate patients about healthy foods and drinks to enhance their physical and mental health [7]. The information will influence patients to adhere to low tyrosine low phenylalanine diets. As a result, patient education will reduce mortality rates and the prevalence of adverse symptoms among tyrosinemia patients.

Compare and contrast themes and gaps in literature

Mainly, the common theme in the literature reviewed in this project is the evidence-based treatment methods for tyrosinemia patients. Chinsky et al. discuss the pharmacological and non-pharmacological treatment methods for tyrosinemia patients. The peer-reviewed journal provides detailed information about genetic counseling, nutritional therapy, liver transplantation, and nitisinone therapy. Chinsky et al. indicate that nitisinone therapy minimizes the formation of fumarylacetoacetic acid and maleylacetoacetate acid by blocking the proximal pathway of tyrosinemia. Likewise, Al-Noaemi and Daghriri offer a detailed discussion of pharmacological and non-pharmacological treatment methods for tyrosinemia patients. Al-Noaemi and Daghriri discuss nitisinone therapy, liver transplantation, and dietary therapy to manage tyrosinemia's adverse symptoms.1 Also, Dela et al. provided empirical evidence about the positive impact of dietary treatment, liver transplantation, and medications for managing tyrosinemia. Consequently, the peer-reviewed articles are relevant for this literature review [3,4,6].

On the contrary, some articles provide positive outcomes, whereas another peer-reviewed article offers negative implications of nitisinone therapy in managing tyrosinemia's adverse symptoms. Chinsky et al. indicate that nitisinone therapy minimizes the formation of fumarylacetoacetic acid and maleylacetoacetate acid by blocking the proximal pathway of tyrosinemia. Al-Noaemi and Daghriri reveal that clinical drug trials showed the effect of nitisinone drug therapy, which included reversible inhibition of 4-hydroxyphenylpyruvate dioxygenase, which eliminates the formation of fumarylacetoacetic acid and maleylacetoacetate acid to protect the liver and kidney in tyrosinemia patients.1 On the other hand, Van Ginkel et al. argue that nitisinone therapy causes long-term eye problems, such as photophobia, transient itching, and burning, in roughly 5% to 10% of tyrosinemia patients [3-5]. The article adds that nitisinone therapy leads to reduced plasma phenylalanine in tyrosinemia patients. Some tyrosinemia patients experience other adverse side effects like pruritus, exfoliative dermatitis, myoclonia, and constipation during or after nitisinone therapy. As a result, medical practitioners and patients must consider the positive and negative effects of nitisinone therapy before using it.

The peer-reviewed journals have gaps that researchers should explore to contribute to evidence-based treatment and management of tyrosinemia.

Questions to further research

- What are the side effects of evidence-based treatment methods, especially liver transplantation, nutritional therapy, and gene therapy?
- Is there health informatics appropriate for providing follow-up care for tyrosinemia patients?
- Can medical practitioners use telemedicine to promote genetic counseling and patient education among tyrosinemia patients?

Researchers need to consider the three answered questions in completing studies on evidence-based treatment and management of tyrosinemia.

DISCUSSION

In the discussion, there is adequate information about the side effects of only nitisinone therapy. Researchers need to explore the side effects of other evidence-based treatment methods, such as liver transplantation, nutritional therapy, and gene therapy of patients. The peer-reviewed article also has limited information about the dosage of nitisinone therapy for patients of different age groups. The articles do not provide adequate information about the variety of foods that make up the low tyrosine low phenylalanine diets. tyrosinemia is a rare autosomal recessive genetic metabolic disorder, which occurs due to the error of metabolism that affects the body's ability to breakdown tyrosine, an amino acid. Persons experience three types of tyrosinemia, which are tyrosinemia I, tyrosinemia II, and tyrosinemia III. In the United States, the incidence of tyrosinemia I is present in one in 100,000 live births. Individuals with tyrosinemia type I experience adverse signs and symptoms, including blood stools, vomiting, failure to thrive, fatigue, poor weight gain, diarrhea, and cabbage-like odor.

CONCLUSION

In conclusion, Medical practitioners currently use evidence-based pharmacological and non-pharmacological methods, such as genetic counseling, nutritional therapy, liver transplantation, and nitisinone therapy, to reduce and eliminate tyrosinemia's adverse symptoms. The evidence-based techniques improve the health and wellbeing of tyrosinemia patients globally.

ACKNOWLEDGEMENT

The corresponding author sincerely thanks Sandra Okpala for her help and willingness to take part in this study.

CONFLICT OF INTEREST

The authors have no competing interests to declare.

REFERENCES

1. National Organization for Rare Disease. (2019, September 12). Tyrosinemia Type 1.
2. De Laet C, Dionisi-Vici C, Leonard JV, McKiernan P, Mitchell G, Monti L et al. . Recommendations for the management of tyrosinaemia type 1. Orphanet J Rare Dis. 2013;8(1):1-9.
3. Al-Noaemi MC, Daghriri HA. Successive Drug Therapy for a Very Rare Autosomal Diseases. In Drug Discovery and Development-New Advances. 2019.
4. Chinsky JM, Singh R, Ficicioglu C, Van Karnebeek CD, Grompe M, Mitchell G, et al. . Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. GENET MED. 2017;(12):1380.
5. Van Ginkel WG, Rodenburg IL, Harding CO, Hollak CE, Heiner-Fokkema MR, van Spronsen FJ. Long-term outcomes and practical

considerations in the pharmacological management of tyrosinemia Type 1. Paediatr Drugs. 2019;21(6):413-26.

6. Largan C, Morris T. Qualitative secondary research: A step-by-step guide. Sage; 2019.

7. Medical Home PortaL. Tyrosinemia Type 1. (2020).