

Oxidative Stress and Inborn Errors of Metabolism

Received: 3 August 2022, **Revised:** 8 September 2022, **Accepted:** 10 October 2022

Urvashi Midha,

Phd Scholar (medical biochemistry)Batch 2022,
Santosh Medical College and Hospital, Santosh deemed to be University,
Ghaziabad, Uttar Pradesh -201009

Mail id: urvashimidha28@gmail.com

Dr. Juhi Aggarwal,

Professor & Head, Department of Biochemistry,
Santosh Medical College and Hospital, Santosh deemed to be University,
Ghaziabad, Uttar Pradesh -201009

mail id- jaggarwal38@gmail.com

Dr Eram Hussain Pasha,

Assistant Professor, Department of Biochemistry,
Santosh Medical College and Hospital, Santosh deemed to be University,
Ghaziabad, Uttar Pradesh -201009.

Mail id- pasha.eram7@gmail.com

Dr. Jyoti Batra,

Professor, Department of Biochemistry,
Santosh Medical College and Hospital, Santosh deemed to be University,
Ghaziabad, Uttar Pradesh -201009.

Mail id- dean.research@santosh.ac.in

Corresponding author: Dr Jyoti Batra

Keywords

Oxidative stress; free radicals; reactive oxygen species (ROS), inborn error of metabolism (IEM)

Abstract

Oxidative stress has been demonstrated to be an underlying patho-physiologic process in various inborn errors of metabolism. Metabolic profiling of oxidative stress may provide a nonspecific measure of disease activity that may further enable physicians to monitor disease. In this study, we try to find the correlation between the oxidative stress and inborn. Quantifying oxidative stress offers a unique perspective to IEM. Certain measures may provide a means of addressing mitochondrial function in IEM and aid in the development of therapeutic targets and clinical monitoring in this diverse set of disorders.

1. INTRODUCTION

A wide variety of diseases known as inborn errors of metabolism (IEM) can be inherited or emerge from spontaneous mutation. In these diseases, the

metabolic processes that digest or store proteins, fatty acids, and carbohydrate are broken down improperly. Individual inborn metabolic mistakes are exceedingly rare, but overall, inborn faults are

Journal of Coastal Life Medicine

quite common, affecting 1 in every 2500 births. The emergency practitioner must have a thorough awareness of these conditions, their symptoms, and how to evaluate them because they can appear at any age.^[1-4]

The incidence of IEMs, collectively, is estimated to be as high as 1 in 800 live births,^[5] but it varies greatly and depends on the population. Phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency with respective incidences of 1 in 10,000 and 1 in 20,000 are among the most prevalent.^[6]

Oxidative stress is a phenomena brought on by an imbalance between a biological system's capacity to detoxify these reactive byproducts and the creation and buildup of reactive oxygen species (ROS) in cells and tissues. Although ROS are normally produced as by-products of oxygen metabolism and can play a variety of physiological roles, including cell signalling, environmental stressors like UV, ionising radiation, pollutants, and heavy metals, as well as, xenobiotics such as antitubercular medications and other factors dramatically boost the formation of ROS, which results in the imbalance that damages cells and tissues (oxidative stress). Although oxidative stress is frequently associated with being bad for the body, it is also true that it can be employed therapeutically to treat a number of diseases. The most recent research on oxidative stress and its impact on inborn errors metabolism will be discussed in this review.^[7]

As previously mentioned, free radicals and oxidants can cause oxidative stress if they are present in excess. This damaging process can disrupt various cellular structures, including membranes, lipids, proteins, lipoproteins, and

deoxyribonucleic acid (DNA).^[8-13] When there is an imbalance between the production of free radicals and cells' capacity to eliminate them, oxidative stress results.^[14] Proteins may also be harmed by oxidative stress, going through structural changes that could lead to a reduction in or loss of their enzymatic activity.^[12,14]

Numerous inborn errors of metabolism (IEM) have been linked to oxidative stress, including organic

aciduria, phenylketonuria, maple syrup urine illness, tyrosinemia, urea cycle defects, and homocystinuria^[15-22]. Numerous studies on oxidative stress in IEM have so far been published in the literature. In an effort to enhance the number of human inborn disorders for which oxidative stress may be patho-physiologic, we collected earlier research. Additionally, the accumulation of dangerous metabolites may change the way genes are expressed or cause the body to use other metabolic pathways, both of which may encourage the growth of cancer.

In this review, we will describe the most recent findings in the oxidative stress field, and its effect on inborn errors metabolism.

2. Discussion

Three factors—which are interconnected and frequently overlap—are involved in the pathophysiology of various IEM: 1) toxicity brought on by an accumulation of hazardous byproducts; 2) a lack of a crucial metabolic intermediate; and 3) diminished mitochondrial activity. It has been suggested that oxidative stress, which frequently originates from mitochondrial malfunction, is the main cause of the cellular damage that manifests in various IEM.^[23]

The results of the investigations conducted by Sharma, P. et al. provide a rare chance to investigate the incidence of inborn metabolic diseases in the current population (2018). Understanding the birth prevalence of these ailments in India's various zones can help the affected communities' immediate and long-term medical requirements.^[24]

Oxidative stress seems to play a role in the pathophysiology of several inborn errors of metabolism, such as phenylketonuria, (PKU) i.e. The results of study by Sirtoriet.al, 2005 showed a decrease of erythrocyte GSH-Px activity. Therefore, it is presumed that oxidative stress is involved in the pathophysiology of the tissue damage found in PKU.^[25]

Gabriele Pizzino et.al, 2017 reviewed in their study that, Oxidative stress and free radicals are generally known to be detrimental to human health. A large amount of studies demonstrates that in fact free

Journal of Coastal Life Medicine

radicals contribute to initiation and progression of several pathologies, ranging from CVD to cancer.^[7]

A study by e.ristoff and Larson 2002 stated that the role of oxidative stress in pathogenesis of inborn error of metabolism is discussed in the light of inborn error in the metabolism of glutathione.^[26]

In 2009 Peter J. Mc Guire, Aditya Parikh, and George A. Diaz explained in their theory that, quantifying oxidative stress offers a unique perspective to IEM. These measures may provide a means of addressing mitochondrial function in IEM and aid in the development of therapeutic targets and clinical monitoring in this diverse set of disorders.^[27]

Study by Cam, Veysel, et al in 2022 Metabolic control status and compliance with treatment are related to oxidative stress level, showing thiol/disulfide balance in ureacycle defects, phenylketonuria, and galactosemia patients.^[28]

Although the idea of reducing oxidative stress has been around for a while, more research is needed to demonstrate its effectiveness in promoting health and lessening the burden of disease. There may be a role for antioxidant therapy in various forms of IEM, according to several research,^[29-33]. With the use of tocopherol, ascorbate, melatonin, and glutathione, oxidative stress has been reduced and harmful effects have been avoided in a number of animal models, including organic acidemias, PKU60, tyrosinemia type I64, and MSUD. The efficacy of this strategy may be increased by addressing respiratory chain malfunction particularly with more recent mitochondrial-targeted antioxidants.^[34]

3. Conclusion

Management of many IEM is complicated by the fact that the currently available biomarkers may not reliably reflect the patient's current clinical status or disease progression and have limited prognostic value. Evaluating mitochondrial activity in IEM and developing treatment targets and clinical monitoring in this varied range of illnesses may be made possible by quantifying oxidative stress.

We also have come to the conclusion that although oxidative stress is a phenomenon that significantly

hurts individual's wellness and health, it may also be used as a treatment tool when and if we are able to fine-tune this process within the human organism.

Reference:

1. Stenton SL, Kremer LS, Kopajtich R, Ludwig C, Prokisch H. The diagnosis of inborn errors of metabolism by an integrative "multi-omics" approach: A perspective encompassing genomics, transcriptomics, and proteomics. *J Inherit Metab Dis*. 2020 Jan;43(1):25-35.
2. Marques EP, Wyse ATS. Creatine as a Neuroprotector: an Actor that Can Play Many Parts. *Neurotox Res*. 2019 Aug;36(2):411-423.
3. Guerrero RB, Kloke KM, Salazar D. Inborn Errors of Metabolism and the Gastrointestinal Tract. *Gastroenterol Clin North Am*. 2019 Jun;48(2):183-198.
4. Canton M, Gall DL, Feillet F, Bonnemains C, Roy A. Neuropsychological Profile of Children with Early and Continuously Treated Phenylketonuria: Systematic Review and Future Approaches. *J Int Neuropsychol Soc*. 2019 Jul;25(6):624-643.
5. Mak CM, Lee HC, Chan AY, Lam CW. Inborn errors of metabolism and expanded newborn screening: review and update. *Crit Rev Clin Lab Sci*. 2013 Nov. 50 (6):142-62.
6. Argmann CA, Houten SM, Zhu J, Schadt EE. A Next Generation Multiscale View of Inborn Errors of Metabolism. *Cell Metab*. 2016 Jan 12. 23 (1):13-26.
7. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. *Oxid Med Cell Longev*. 2017;2017:8416763. doi: 10.1155/2017/8416763. Epub 2017 Jul 27. PMID: 28819546; PMCID: PMC5551541.
8. W. Droge, "Free radicals in the physiological control of cell function," *Physiological Reviews*, vol. 82, pp. 47-95, 2002.
9. J. K. Willcox, S. L. Ash, and G. L. Catignani, "Antioxidants and prevention of chronic disease," *Critical Reviews in Food Science and Nutrition*, vol. 44, pp. 275-295, 2004.
10. P. Pacher, J. S. Beckman, and L. Liaudet, "Nitric oxide and peroxynitrite in health and

Journal of Coastal Life Medicine

- disease," *Physiological Reviews*, . 87, pp. 315–424, 2007.
11. M. Genestra, "Oxyl radicals, redox-sensitive signaling cascades and antioxidants," *Cellular Signalling*, vol. 19, pp. 1807–1819, 2007.
12. B. Halliwell, "Biochemistry of oxidative stress," *Biochemical Society Transactions*, vol. 35, pp. 1147–1150, 2007.
13. I. Young and J. Woodside, "Antioxidants in health and disease," *Journal of Clinical Pathology*, vol. 54, pp. 176–186, 2001.
14. Bird S, Miller NJ, Collins JE, Rice-Evans CA. Plasma antioxidant capacity in two cases of tyrosinaemia type 1: one case treated with NTBC. *J Inherit Metab Dis* 1995;18:123–126.
15. Ercal N, Aykin-Burns N, Gurer-Orhan H, McDonald JD. Oxidative stress in a phenylketonuria animal model. *Free Radic Biol Med* 2002;32:906–911.
16. Streck EL, et al. Inhibition of rat brain Na⁺, K⁺-ATPase activity induced by homocysteine is probably mediated by oxidative stress. *Neurochem Res* 2001;26:1195–1200.
17. Wyse AT, et al. Nitric oxide synthase inhibition by L-NAME prevents the decrease of Na⁺,K⁺-ATPase activity in midbrain of rats subjected to arginine administration. *Neurochem Res* 2001;26:515–520.
18. Wyse AT, et al. Inhibition of Na⁽⁺⁾,K⁽⁺⁾-ATPase activity in hippocampus of rats subjected to acute administration of homocysteine is prevented by vitamins E and C treatment. *Neurochem Res* 2002;27:1685–1689.
19. Barschak AG, et al. Oxidative stress in plasma from maple syrup urine disease patients during treatment. *Metab Brain Dis* 2008;23:71–80. [PubMed: 18026828]
20. Barschak AG, et al. Evidence that oxidative stress is increased in plasma from patients with maple syrup urine disease. *Metab Brain Dis* 2006;21:279–286.
21. Bridi R, et al. Induction of oxidative stress in rat brain by the metabolites accumulating in maple syrup urine disease. *Int J Dev Neurosci* 2003;21:327–332.
22. Bridi R, et al. alpha-keto acids accumulating in maple syrup urine disease stimulate lipid peroxidation and reduce antioxidant defences in cerebral cortex from young rats. *Metab Brain Dis* 2005;20:155–167.
23. Wajner M, Latini A, Wyse AT, Dutra-Filho CS. The role of oxidative damage in the neuropathology of organic acidurias: insights from animal studies. *J Inherit Metab Dis* 2004;27:427–448. [PubMed: 15303000]
24. Sharma P, Kumar P, Tyagi MS, Sharma R, PS D. Prevalence of Inborn Errors of Metabolism in Neonates [Internet]. *Journal of clinical and diagnostic research. JCDR Research and Publications*; 2018.
25. L.R. Sirtori, C.S. Dutra-Filho, D. Fitarelli, A. Sitta, A. Haeser, A.G. Barschak, M. Wajner, D.M. Coelho, et al. Oxidative stress in patients with phenylketonuria, *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, Volume 1740, Issue 1, 2005, Pages 68-73, ISSN 0925-4439, <https://doi.org/10.1016/j.bbadis.2005.02.005>
26. Ristoff, E. and Larsson, A. (2002), Oxidative stress in inborn errors of metabolism: Lessons from glutathione deficiency. *J Inherit Metab Dis*, 25: 223-226. <https://doi.org/10.1023/A:1015634032042>
27. Artuch R, et al. A longitudinal study of antioxidant status in phenylketonuric patients. *Clin Biochem* 2004;37:198–203. [PubMed: 14972641]
28. Cam, Veysel, et al. "Oxidative Stress in Intoxication Type Inborn Errors of Metabolism using Thiol-Disulfide Ratio." *Journal of the College of Physicians and Surgeons Pakistan*, vol. 31, no. 6, June 2021, pp. 663+. Gale Academic OneFile
29. McGuire, Peter & Parikh, Aditya & Diaz, George. (2009). Profiling of Oxidative Stress in Patients with Inborn Errors of Metabolism. *Molecular genetics and metabolism*. 98. 173-80. 10.1016/j.ymgme.2009.06.007.
30. Colome C, et al. Lipophilic antioxidants in patients with phenylketonuria. *Am J Clin Nutr* 2003;77:185–188. [PubMed: 12499340]
31. Delwing D, et al. Alpha-tocopherol and ascorbic acid administration prevents the impairment of brain energy metabolism of hyperargininemic rats. *Cell Mol*

Journal of Coastal Life Medicine

- Neurobiol 2006;26:177–189.[PubMed: 16619133]
32. Kosenko E, et al. Superoxide production and antioxidant enzymes in ammonia intoxication in rats. Free Radic Res 1997;27:637–644. [PubMed: 9455699]
33. Martinez-Cruz F, et al. Oxidative stress induced by phenylketonuria in the rat: Prevention by melatonin, vitamin E, and vitamin C. J Neurosci Res 2002;69:550–558. [PubMed: 12210848]
34. Ribeiro CA, et al. Inhibition of brain energy metabolism by the branched-chain amino acids accumulating in maple syrup urine disease. Neurochem Res 2008;33:114–124. [PubMed: 17680360]