Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 13 [1] December 2023 :286-292

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

The Interplay between Mitochondrial Dysfunction, pH, and Oxygen in Metabolic Disorders: A Holistic Review

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ABSTRACT
This in-depth review paper thoroughly examines the connection between dysfunctional Mitochondria, pH regulation, and oxygen levels within metabolic disorders. It sheds light on how impaired mitochondrial function affects the balance of pH and the utilization of oxygen ultimately leading to the development and progression of conditions like obesity type 2 diabetes and cardiovascular diseases. The article dives into the underlying mechanisms. Signalling pathways that contribute to these processes provide insights into therapeutic approaches for restoring mitochondrial function and enhancing metabolic well-being. Moreover, it emphasizes the importance of research to fully comprehend the relationships between mitochondrial dysfunction, pH regulation, and oxygen availability. This will ultimately help identify targets for strategies aimed at managing metabolic disorders.
Keywords: *Mitochondrial dysfunction, pH imbalance, oxygen levels, metabolic disorders, interplay, therapeutic strategies.*

Received 06.10.2023 Revised 21.10.2023 Accepted 18.12.2023

INTRODUCTION

Diseases such as type 2 diabetes, cancer, obesity neurodegenerative diseases, and cardiovascular diseases are metabolic disorders that form a big challenge for global health. As time progresses, evidence from published data suggests that dysfunctional mitochondria, which are responsible for energy production in cells, play a vital role in the development and progression of these disorders. Dysfunctional mitochondria are characterized by problems with oxidative phosphorylation and high production of reactive oxygen species. This dysfunction also disrupts the pH balance within the cells and impairs efficient oxygen usage, thereby worsening metabolic abnormalities. Knowledge of the interactions amidst mitochondrial dysfunction, pH regulation, and oxygen availability is crucial for unmasking the underlying mechanisms of metabolic disorders and identifying potential targets for treatment.

Mitochondrial Dysfunction in Metabolic Disorders:

Alteration of mitochondrial function is a key player in the development and progression of most metabolic diseases debilitating the human population [1,2]. These diseases are defined by abnormal mitochondrial oxidative capacity, such as; reduced respiratory chain activity, low ATP production, and impaired fatty acid oxidation [1,2]. Obesity, which is characterized by excessive adipose tissue, is closely associated with abnormal mitochondria. In obese individuals, the adipose tissue shows reduced mitochondrial content, abnormal oxidative phosphorylation, and compromised oxidative capacity [3]. These changes pitch into abnormal lipid metabolism, insulin resistance, and the development of obesity-related complications [3]. Impaired mitochondria trigger insulin resistance, which is a key identifier of type 2 diabetes. Skeletal muscle, a major site of insulin-mediated glucose uptake, shows reduced mitochondrial density, impaired oxidative phosphorylation, and compromised ATP synthesis in insulin-resistant individuals[4]. These abnormalities result in an alteration in glucose metabolism, which causes hyperglycemia and insulin resistance [4]. Moreover, cardiovascular disease is associated with abnormal mitochondria. With its high energy demand, the heart relies heavily on mitochondrial energy production. Cardiovascular conditions such as heart failure and ischemic heart disease, show abnormal mitochondrial function, which is defined by low oxidative phosphorylation efficiency and ATP production [5,6]. These abnormalities contribute to energy depletion, contractile dysfunction, and myocardial damage [7]. Dysfunctional mitochondria also generate high reactive oxygen species, which are by-products of oxidative phosphorylation (ROS). Excessive ROS production due to mitochondrial dysfunction overwhelms the antioxidant defence system,

leading to oxidative stress [8,9]. In metabolic disorders, such as obesity, insulin resistance, and cardiovascular diseases, mitochondrial dysfunction contributes to elevated ROS levels, resulting in oxidative damage to cellular components[7].Moreover, altered mitochondrial dynamics play an important role in metabolic disorders. Mitochondria undergo fusion and fission, a process that regulates their shape, distribution, and function [9]. Imbalances in these processes disrupt mitochondrial quality control and contribute to metabolic dysfunctions. Excess fission of mitochondria has been indicated with fragmented mitochondria in skeletal muscles of insulin-resistant individuals, resulting in abnormal oxidative phosphorylation, and low ATP production [9]. The impact of altered mitochondrial function on cellular bioenergetics is complex. Impaired mitochondrial oxidative capacity and ATP production disrupt cellular energy balance, reducing metabolic flexibility and impairing substrate utilization [10]. Additionally, altered mitochondrial function disrupts intracellular signalling pathways involved in metabolism and insulin action, contributing to metabolic dysregulation [10].

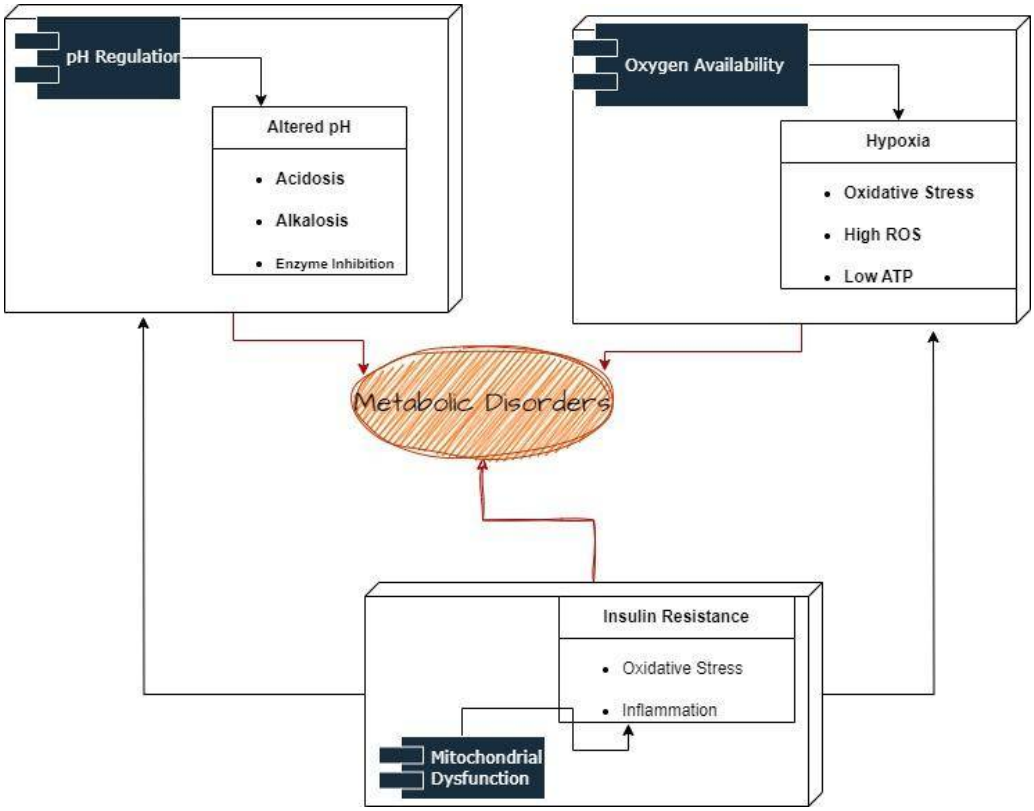

Fig. 1: The Sketch of Interconnectedness

1.2 pH Regulation and Metabolic Disorders:

The intricate relationship between pH regulation and metabolic disorders highlights the significant impact of pH alterations on cellular processes involved in metabolism, including glycolysis, insulin signaling, and lipid metabolism [11,12]. This section will explore how changes in intracellular and extracellular pH influence these processes, the role of acid-base transporters, proton pumps, and buffering systems in maintaining pH homeostasis, and the dysregulation of pH regulation observed in metabolic disorders. Intracellular and extracellular pH levels play crucial roles in regulating cellular metabolism. Alterations in pH can directly affect enzymatic activities and protein function, leading to profound effects on metabolic pathways. For example, intracellular acidification inhibits glycolytic enzymes and impairs glucose metabolism [11]. Acidic extracellular pH can also impact glycolysis by inhibiting the uptake and utilization of glucose by cells [12]. These pH-mediated changes in glycolysis have implications for metabolic disorders such as diabetes and cancer, where altered glucose metabolism is a hallmark. pH regulation is maintained by a complex interplay of acid-base transporters, proton pumps, and buffering systems. Acid-base transporters, such as sodium-proton exchangers (NHEs) and bicarbonate transporters, play essential roles in maintaining pH balance across cell membranes [13]. Proton pumps, such as the vacuolar-type H+-ATPase (V-ATPase) and the plasma membrane H+-ATPase, actively secrete protons to regulate intracellular and extracellular pH [14]. Buffering systems, including bicarbonate-carbon dioxide ($HCO3^-/CO2$) and intracellular pH buffering proteins, help stabilize pH levels within cells [15]. Dysregulation of pH regulation

has been observed in various metabolic disorders. In obesity and insulin resistance, alterations in pH regulation have been reported to contribute to metabolic dysfunction. Insulin signalling is highly sensitive to changes in pH, and intracellular acidification impairs insulin signalling pathways [16]. Acidic extracellular pH also affects insulin sensitivity and glucose metabolism [17]. Additionally, acid-base transporters, such as NHEs, have been implicated in obesity-related metabolic dysfunctions, suggesting a link between pH regulation and metabolic disorders [18]. Furthermore, dysregulation of pH homeostasis is observed in lipid metabolism disorders, including dyslipidemia and non-alcoholic fatty liver disease (NAFLD). Altered pH regulation affects lipid uptake, storage, and oxidation in hepatocytes [19]. Acidification of intracellular compartments, such as endosomes and lysosomes, disrupts lipid trafficking and impairs lipid degradation processes [20]. These pH-mediated disturbances in lipid metabolism contribute to the development of metabolic disorders.

Oxygen Utilisation and Metabolic Disorders:

Mitochondrial dysfunction in metabolic disorders has a profound impact on oxygen utilization, leading to cellular hypoxia and oxidative stress. This section will discuss how impaired mitochondrial respiration and altered oxygen consumption rates contribute to these conditions. Additionally, the role of hypoxia-inducible factors (HIFs) and oxygen-sensing mechanisms in metabolic regulation will be explored, along with their dysregulation in metabolic disorders. Impaired mitochondrial respiration and decreased oxygen consumption rates are characteristic features of metabolic disorders such as obesity, insulin resistance, and cardiovascular diseases. Mitochondrial dysfunction, including reduced electron transport chain (ETC) activity and ATP production, compromises cellular energy metabolism and impairs oxygen utilization [1,2]. These deficiencies lead to inadequate oxygen consumption, resulting in cellular hypoxia. Cellular hypoxia contributes to metabolic dysregulation and the pathogenesis of metabolic disorders. Hypoxia alters the expression and activity of key enzymes involved in glucose and lipid metabolism. For instance, hypoxia inhibits the activity of the pyruvate dehydrogenase complex, reducing glucose oxidation and promoting glycolysis [21]. This metabolic shift promotes the accumulation of lactate and contributes to insulin resistance and metabolic dysfunction. Oxidative stress is another consequence of mitochondrial dysfunction and impaired oxygen utilization in metabolic disorders. Mitochondrial dysfunction increases the production of reactive oxygen species and disrupts the cellular redox balance [1,2]. ROS can cause damage to cellular components, including lipids, proteins, and DNA, leading to oxidative stress [7,8]. Oxidative stress further exacerbates mitochondrial dysfunction, creating a vicious cycle of cellular damage and metabolic impairment. HIFs and oxygen-sensing mechanisms play critical roles in metabolic regulation, linking oxygen availability to cellular responses. HIFs are transcription factors that regulate the adaptive responses to hypoxia. Under normal oxygen conditions, HIFs are targeted for degradation through the action of oxygen-sensing enzymes called prolyl hydroxylases (PHDs) [21]. However, in hypoxic conditions or when mitochondrial dysfunction impairs oxygen utilisation, HIFs accumulate and activate genes involved in glycolysis, angiogenesis, and other adaptive responses to restore cellular oxygen balance. Dysregulation of HIFs and oxygen-sensing mechanisms is observed in metabolic disorders. In conditions such as obesity and insulin resistance, HIFs can be activated under normoxic conditions, a phenomenon known as pseudohypoxia [21]. Dysfunctional oxygen-sensing mechanisms, including increased PHD activity or altered HIF degradation pathways, can contribute to HIF activation in these disorders. Pseudohypoxia-induced activation of HIFs promotes metabolic alterations, including increased glucose uptake, glycolysis, and adipogenesis, which further contribute to the development of metabolic dysfunction. Alongside hypoxia-inducible factors (HIFs), various other mechanisms play a role in sensing oxygen levels and regulating metabolism. One such mechanism is the activation of the AMP-activated protein kinase (AMPK) pathway, which serves as an energy sensor triggered by reduced cellular energy levels, including diminished ATP production caused by impaired mitochondrial function [22]. Activation of AMPK fosters metabolic adjustments to restore energy equilibrium, such as increased glucose uptake, enhanced fatty acid oxidation, and the generation of new mitochondria. The disruption of oxygen-sensing mechanisms in metabolic disorders further disturbs the balance of metabolic processes. In conditions like obesity and insulin resistance, abnormal activation of HIFs and dysregulation of the AMPK pathway have been observed [23,24]. These changes contribute to metabolic dysfunction, including impaired glucose and lipid metabolism, insulin resistance, and inflammation. Moreover, the disturbance in oxygen-sensing mechanisms and impaired utilization of oxygen also impact the biology of adipose tissue. Oxygen deprivation occurs in adipose tissue, particularly in visceral adipose tissue, due to inadequate vascularization, leading to a hypoxic microenvironment [25]. Hypoxia in adipose tissue stimulates the production of adipokines, such as leptin, adiponectin, and pro-inflammatory cytokines, which contribute to metabolic dysfunction and insulin resistance [25].

Signalling Pathways and Mitochondrial Dysfunction:

The signalling pathways associated with mitochondrial dysfunction and metabolic disorders involve key regulators, such as AMP-activated protein kinase, mammalian target of rapamycin (mTOR), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-a1). These pathways play crucial roles in regulating mitochondrial biogenesis, oxidative stress, and energy metabolism. Additionally, there is a significant interplay between these signalling pathways and those related to pH and oxygen. This section explores the involvement of AMPK, mTOR, and PGC-1α in metabolic regulation and their interactions with pH and oxygen-related pathways. AMPK acts as a central regulator of cellular energy balance and becomes activated during periods of low energy availability or an increased AMP/ATP ratio [26]. Its activation promotes mitochondrial biogenesis by enhancing the expression of PGC-1α, a transcriptional coactivator that regulates genes involved in mitochondrial function and oxidative metabolism [27]. PGC-1α, in turn, increases the expression of nuclear respiratory factors and mitochondrial transcription factor A, promoting mitochondrial DNA replication and gene transcription [28]. Through this coordinated mechanism, AMPK and PGC-1α regulate mitochondrial biogenesis, leading to improved oxidative capacity and enhanced energy metabolism. mTOR, a critical sensor of nutrients and energy, governs cell growth, metabolism, and protein synthesis [29]. Its activity is inhibited under conditions of energy deprivation or during AMPK activation, resulting in the suppression of protein synthesis and cell growth. Dysregulation of mTOR signalling, often observed in metabolic disorders, can contribute to mitochondrial dysfunction and metabolic abnormalities. Activation of mTOR inhibits autophagy, a cellular process essential for maintaining mitochondrial quality control and turnover [30]. Dysfunctional autophagy results in the accumulation of damaged mitochondria and increased oxidative stress. Therefore, dysregulation of mTOR signalling can negatively impact mitochondrial function and contribute to the development of metabolic disorders. PGC-1α plays a critical role in coordinating mitochondrial biogenesis, oxidative metabolism, and antioxidant defences [28]. It activates transcription factors such as nuclear factor erythroid 2-related factor 2 (NRF2), which regulates the expression of antioxidant enzymes, providing protection against oxidative stress. Furthermore, PGC-1α promotes fatty acid oxidation and improves insulin sensitivity by activating genes involved in lipid metabolism, including peroxisome proliferator-activated receptors (PPARs) [31]. Dysregulation of PGC-1α signalling is associated with impaired mitochondrial function and metabolic disorders. Extensive cross-talk exists between these signalling pathways and those related to pH and oxygen. For example, AMPK can be activated by low intracellular pH and hypoxia, aiding in the restoration of energy balance and alleviation of metabolic stress [32,33]. Additionally, AMPK and PGC-1α signalling interact with hypoxia-inducible factors (HIFs), which are key regulators of the cellular response to hypoxia [34]. PGC-1α facilitates the degradation of HIF-1α under normoxic conditions, while HIFs can induce PGC-1α expression to modulate mitochondrial function and metabolic adaptations to hypoxia [35].

Table : Mitochondrial Dysfunction, pH, and Oxygen in Metabolic Disorders.

S N.	Headlines	Key Insights
1	Mitochondrial Dysfunction	• Impaired function contributes to obesity, insulin resistance, and cardiovascular diseases. • Reduced oxidative capacity, ATP production, and fatty acid oxidation are common disorders
2	pH Regulation	• Alters cellular metabolism such as glycolysis, insulin signalling, and lipid metabolism. • Maintained by acid-base transporters, proton pumps, and buffering systems. • Dysregulation observed in obesity, insulin resistance, and lipid metabolism disorders.
3	Oxygen Utilisation	• Mitochondrial dysfunction leads to cellular hypoxia and oxidative stress. • Impaired respiration and oxygen consumption contribute to metabolic disorders. • HIFs and oxygen-sensing mechanisms play crucial roles in metabolic regulation. • Dysregulation observed in metabolic disorders.
4	Signaling Pathways	• AMPK, mTOR, and PGC-1α are key regulators. • AMPK and PGC-1α regulate mitochondrial biogenesis, oxidative stress, and energy metabolism. • mTOR signaling affects mitochondrial function and autophagy. • Cross-talk exists between signaling pathways, pH regulation, and oxygen-related pathways.

5	Clinical Implications	• Targeting dysfunction, pH regulation, and oxygen availability could improve metabolic disorders. • Strategies to enhance function and restore pH show promise. • Enhancing oxygen availability and utilization may alleviate hypoxia. • Targeting oxygen-sensing pathways could restore metabolic regulation.
6	Climax	This review provides insights into the mutuality between dysfunctional Mitochondria, pH regulation, and oxygen and emphasizes the importance of understanding this interplay for therapeutic interventions. Additionally, it highlights the need for further research to fully unravel the connections and explore the potential of managing disorders in this context.

DISCUSSION

The literature review has shed light on the relationship between mitochondrial dysfunction, pH regulation, and oxygen utilization in metabolic disorders enhancing our understanding of these interconnected processes. Dysregulation of these factors plays a role in the development and progression of metabolic disorders. In this discussion, we explore mechanisms that connect mitochondrial dysfunction, pH regulation, and oxygen utilization while examining the clinical implications of targeting these processes for managing metabolic disorders. One potential mechanism that establishes a link between dysfunctional mitochondria and pH dysregulation is the production of reactive oxygen species. When mitochondria malfunction, they generate an increased amount of ROS overpowering the defense system and leading to stress [7,8]. ROS directly influences pH regulation by impacting acid-base transporters and ion channels [7]. This disruption of pH balance due to ROS-induced alterations in acid-base transporters intensifies dysfunction resulting in a cycle of metabolic impairment and oxidative stress. Another mechanism connecting dysfunctional mitochondria, pH dysregulation, and metabolic disorders is uncoupling. Uncoupling proteins (UCPs) play a role in regulating the proton gradient and their malfunction disrupts the equilibrium, between respiration and ATP synthesis [36]. The separation mentioned above hampers the effectiveness of ATP generation resulting in oxygen usage and potential disturbance of pH levels [36]. This diminished production of ATP and changes in pH contribute to the metabolic irregularities observed in conditions, like obesity, insulin resistance, and cardiovascular diseases. In addition, to the abovementioned factors it is worth considering the impact of oxygen-sensing mechanisms on the interplay between mitochondrial dysfunction, pH regulation, and metabolic disorders. Oxygen sensing pathways, including HIFs and AMPK play roles in maintaining metabolic homeostasis (Semenza, 2012; Hardie, 2011). When these pathways are dysregulated in metabolic disorders the body's adaptive responses to hypoxia are disrupted, resulting in pH regulation [23,37]. This further worsens dysfunction. This leads to changes in oxygen utilization ultimately causing cellular hypoxia. The implications of targeting dysfunction, pH regulation, and oxygen availability in managing metabolic disorders are significant from a standpoint. Promising therapeutic strategies involve improving function and restoring pH homeostasis. For instance, activating AMPK or modulating PGC 1Î± activity could enhance biogenesis and function thus restoring energy metabolism and alleviating metabolic dysregulation [38,39]. Similarly, interventions that focus on addressing pH dysregulation by modulating acid-base transporters or mitigating the effects of oxygen species may help mitigate the impact on mitochondrial function and metabolic processes [7,8]. Moreover, exploring strategies to increase oxygen availability and optimize its utilization holds the potential for benefiting individuals with metabolic disorders. Enhancing tissue oxygenation can be achieved by engaging in exercise using medications to improve oxygen transport or stimulating the growth of blood vessels, a process known as angiogenesis. These approaches have shown promise in relieving hypoxia and addressing metabolic disorders [40,41]. Furthermore, exploring oxygen sensing pathways, like HIFs or AMPK, holds potential as strategies for reestablishing oxygen-dependent metabolic regulation . This underscores the importance of understanding how various factors and interventions can influence our metabolism and overall well-being.

CONCLUSION

In a few words, this holistic review gives insights into the interplay between dysfunctional mitochondria, pH regulation, and oxygen availability in metabolic disorders. It highlights the role of mitochondrial function in disrupting cellular pH homeostasis and oxygen utilization contributing to various metabolic disorders such, as obesity, type 2 diabetes, and cardiovascular diseases. The review explores the underlying mechanisms. Signaling pathways involved in these processes uncover therapeutic interventions to restore mitochondrial function and improve metabolic health. It is necessary to conduct research to completely understand the interconnections between mitochondrial dysfunction, pH regulation, and oxygen

availability. Furthermore, investigating their potential as targets for approaches, in the treatment of metabolic disorders is essential.

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CITATION OF THIS ARTICLE

Hassan Nanbol Bawa, Adamu Abubakar, Muhammad Ahmad Gasma, Faizu Mohammed Shuaibu, Rajesh Prasad Jayaswal. "The Interplay between Mitochondrial Dysfunction, pH, and Oxygen in Metabolic Disorders: A Holistic Review". Bull. Env.Pharmacol. Life Sci., Vol 13 [1] December 2023: 286-292