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Metabolomics and oxidative stress assessment in diabetic patients

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Abstract

Metabolomics has emerged as a powerful tool in biomedical research, offering comprehensive insights into metabolic alterations associated with various diseases, including diabetes. One of the key aspects of diabetes pathophysiology is oxidative stress, which results from an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. This imbalance contributes significantly to insulin resistance, β-cell dysfunction, and the progression of microvascular and macrovascular complications.

This review explores the integration of metabolomics in assessing oxidative stress in diabetic patients, emphasizing the identification of metabolic biomarkers and their implications for early diagnosis and personalized treatment strategies. Key oxidative stress biomarkers, such as malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and F2-isoprostanes, have been identified through metabolomic studies, reflecting increased lipid, protein, and DNA oxidation. Furthermore, metabolic pathway alterations, including branched-chain amino acid (BCAA) dysregulation, polyol pathway activation, and lipid peroxidation, have been linked to diabetes onset and progression.

Beyond biomarker identification, metabolomics provides a foundation for targeted therapeutic interventions, such as modulation of metabolic pathways, dietary interventions, and antioxidant-based therapies aimed at restoring redox homeostasis. Future advancements in high-resolution mass spectrometry (HRMS), nuclear magnetic resonance (NMR), and artificial intelligence-driven data analysis promise to enhance the precision of metabolomic applications in diabetes research.

By integrating metabolomics into clinical practice, we can achieve a more refined understanding of oxidative stress-related metabolic disruptions, paving the way for improved diagnostic tools, patient-specific treatment strategies, and novel preventive approaches for diabetes management

Keywords: Metabolomics; Diabetes; Oxidative Stress; Biomarkers; Reactive Oxygen Species (ROS); Insulin Resistance; Metabolic Pathways; Antioxidant Therapy; Mass Spectrometry; Nuclear Magnetic Resonance (NMR)

1. Introduction

Metabolomics is a rapidly growing scientific discipline that aims to analyze the complete set of metabolites present in an organism, tissue, or biological fluid at a given moment. Thanks to technological advancements, particularly in mass spectrometry and nuclear magnetic resonance (NMR), this approach enables a better understanding of real-time biochemical processes and the identification of specific biomarkers for various pathologies, including diabetes (1).

At the same time, oxidative stress plays a major role in the progression of diabetes and its complications. It results from an imbalance between the production of free radicals (reactive oxygen species, ROS) and the body's antioxidant defense

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mechanisms. This excessive production of free radicals damages lipids, proteins, and DNA, promoting microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular diseases, atherosclerosis) complications associated with diabetes (2).

Recent studies have demonstrated a strong link between the metabolic profiles of diabetic patients and their level of oxidative stress. Specific alterations, such as variations in branched-chain amino acids, lipids, and glucose metabolites, have been identified as potential markers of oxidative stress in these patients. These findings suggest that metabolomics could be a powerful tool for assessing the impact of oxidative stress in diabetes and optimizing therapeutic strategies (3).

However, despite advancements in this field, many questions remain unanswered. The precise identification of metabolic signatures of oxidative stress in diabetic patients could open new avenues for early diagnosis and personalized treatment. Thus, this study aims to explore these complex interactions using metabolomics tools to better understand the underlying mechanisms and identify potential therapeutic targets.

2. Metabolomics and Its Application in the Study of Metabolic Diseases

2.1. Definition and Principles of Metabolomics

Metabolomics is a branch of systems biology that focuses on the comprehensive analysis of metabolites, which are small molecules (<1 kDa) derived from biochemical processes in cells, tissues, or biological fluids. Unlike genomics and proteomics, which study DNA and proteins respectively, metabolomics provides an instantaneous chemical snapshot reflecting the physiological and pathological state of an organism at a given time.

- The growing interest in metabolomics is due to its ability to capture the combined impact of genetic and environmental influences on metabolism. This approach enables the identification of disease-specific metabolic profiles, facilitating biomarker discovery and the identification of new therapeutic targets (4).

Metabolomic analysis relies on advanced technologies capable of identifying and quantifying a wide range of metabolites. The most commonly used techniques are :

2.1.1. Nuclear Magnetic Resonance (NMR):

- Enables non-destructive analysis of biological samples.
- Provides detailed information on metabolite molecular structures.
- Particularly suitable for longitudinal studies due to its high reproducibility (4).

2.1.2. Mass Spectrometry (MS) Coupled with Chromatography:

Gas Chromatography–Mass Spectrometry (GC-MS):

- Ideal for analyzing volatile and thermally stable compounds.
- Commonly used to study lipids and organic acids.

Liquid Chromatography–Mass Spectrometry (LC-MS):

- More suitable for polar and large metabolites.
- More sensitive than NMR, allowing the identification of thousands of metabolites at very low concentrations (5).

These tools help generate detailed metabolic profiles, improving our understanding of the underlying biological mechanisms in metabolic diseases such as diabetes, cancer, and neurodegenerative disorders.

The rise of metabolomics has revolutionized precision medicine by enabling:

- Early diagnosis: Specific metabolic signatures are detected before the onset of clinical symptoms.
- Prediction of treatment response: Therapies are tailored based on patients' metabolic profiles.
- Identification of new therapeutic targets: Exploration of metabolic dysregulations in various pathologies.

For instance, in type 2 diabetes, metabolomic analysis has identified early alterations in branched-chain amino acid (BCAA) metabolism, paving the way for new therapeutic strategies (6).

2.2. Metabolomics and Diabetes: A Key Tool for Diagnosis and Monitoring

In individuals with type 2 diabetes, significant alterations have been observed in several metabolite classes:

- Branched-chain amino acids (BCAA): Elevated levels of leucine, isoleucine, and valine have been associated with insulin resistance and an increased risk of developing diabetes (7).
- Fatty acids: Modifications in lipid metabolism, particularly an increase in free fatty acids, can contribute to pancreatic β-cell dysfunction and insulin resistance (7).
- Glucose and derivatives: Metabolites such as 1,5-anhydroglucitol are reduced in diabetic patients, reflecting chronic hyperglycemia (7).

These alterations provide insights into the metabolic imbalances present in diabetes and can help identify potential therapeutic targets.

One of the major contributions of metabolomics is the discovery of **predictive biomarkers** for diabetes before clinical symptoms appear. For example, studies have shown that elevated levels of certain amino acids and lipid derivatives precede the diagnosis of type 2 diabetes, suggesting their utility in early screening and prevention.

Notable biomarkers include:

- Branched-chain amino acids (BCAA): High concentrations of leucine, isoleucine, and valine have been correlated with insulin resistance and an increased likelihood of diabetes progression.
- 2-Aminoadipate (2-AAA): A study revealed that elevated 2-AAA levels precede type 2 diabetes diagnosis. Individuals with the highest 2-AAA concentrations had a fourfold increased risk of developing the disease. Moreover, experiments showed that 2-AAA can influence glucose homeostasis by modulating insulin secretion (8).
- Aromatic amino acids: Increased levels of phenylalanine and tyrosine have also been associated with a higher risk of diabetes, suggesting their potential role as early biomarkers.
- Lysophosphatidylcholine (LPC) 18:2: A decrease in this lipid metabolite has been observed in individuals with glucose intolerance, a prediabetic condition (9).
- Adiponectin: This hormone, secreted by adipose tissue, regulates insulin sensitivity. Reduced adiponectin levels have been observed in type 2 diabetes patients, particularly those with atherosclerotic complications (10).

3. Oxidative Stress and Diabetes: A Close Relationship

3.1. Mechanisms of Oxidative Stress in Diabetes

Oxidative stress plays a central role in the pathophysiology of diabetes, contributing to both the onset and progression of the disease. It results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. This imbalance leads to damage to cellular components, such as lipids, proteins, and DNA, thereby exacerbating diabetes-associated complications.

In diabetic patients, chronic hyperglycemia is a major source of excessive ROS production. Several mechanisms are involved:

- Glucose auto-oxidation: Excess glucose can undergo auto-oxidation, generating free radicals that damage cells (11).
- Polyol pathway activation: The enzyme aldose reductase converts glucose into sorbitol, consuming NADPH, an essential cofactor for glutathione regeneration, a major antioxidant. This process depletes the cell’s antioxidant capacity, increasing oxidative stress (11).
- Protein glycation and formation of advanced glycation end products (AGEs): Hyperglycemia promotes the non-enzymatic binding of glucose to proteins, leading to AGEs formation. These compounds alter protein function and enhance ROS production (11).

Under normal conditions, the body has antioxidant systems to neutralize ROS and maintain redox homeostasis. Among these systems are enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. In diabetics, these defense mechanisms are often impaired:

- Superoxide dismutase (SOD): This enzyme catalyzes the dismutation of superoxide anion into hydrogen peroxide, which is then broken down by catalase. Reduced SOD activity has been observed in diabetic patients, contributing to ROS accumulation (11).
- Catalase: This enzyme decomposes hydrogen peroxide into water and oxygen. Decreased catalase activity may lead to hydrogen peroxide accumulation, fostering the formation of highly reactive hydroxyl radicals (11).
- Glutathione peroxidase: This enzyme utilizes glutathione to reduce lipid peroxides and hydrogen peroxide. A decrease in its function, associated with reduced glutathione levels due to polyol pathway activation, exacerbates oxidative stress (11).

This imbalance between increased ROS production and weakened antioxidant defenses creates a pro-oxidant environment, leading to cell damage and diabetes complications such as cardiovascular diseases, neuropathy, and retinopathy.

3.2. Impact of Oxidative Stress on Diabetic Complications

Pancreatic β-cells, responsible for insulin secretion, are particularly vulnerable to oxidative stress. This increased sensitivity is due to their low expression of antioxidant enzymes. Excessive ROS production can lead to a decrease in insulin secretion and promote β-cell apoptosis, thereby contributing to diabetes onset and progression. Additionally, oxidative stress disrupts insulin signaling pathways in peripheral tissues, worsening insulin resistance (12).

Oxidative stress is closely linked to diabetes-related microvascular complications, including:

- Diabetic retinopathy: Increased ROS levels in the retina damage endothelial cells and pericytes, leading to increased vascular permeability, microaneurysms, and pathological neovascularization (12).
- Diabetic nephropathy: ROS contribute to glomerular dysfunction by inducing extracellular matrix alterations, mesangial cell hypertrophy, and interstitial fibrosis, ultimately leading to progressive renal function impairment (12).
- Diabetic neuropathy: Oxidative stress damages peripheral neurons and Schwann cells, disrupting nerve conduction and causing the sensory and motor symptoms characteristic of diabetic neuropathy (12).

Macrovascular complications of diabetes, such as atherosclerosis and myocardial infarction, are also influenced by oxidative stress:

- Atherosclerosis: ROS oxidize low-density lipoproteins (LDL), promoting their accumulation in the vascular walls and facilitating plaque formation. Additionally, oxidative stress activates pro-inflammatory and pro-thrombotic pathways, worsening atherosclerosis progression (12).
- Myocardial infarction: Increased oxidative stress in the myocardium impairs contractile function, promotes pathological remodeling, and increases susceptibility to ischemic damage, thereby raising the risk of heart attacks in diabetic patients (12).

Thus, oxidative stress is a key factor in the pathogenesis of diabetic complications, highlighting the importance of therapeutic strategies aimed at restoring redox balance to prevent or mitigate these complications.

4. Integration of Metabolomics in Assessing Oxidative Stress in Diabetic Patients

4.1. Identification of Oxidative Stress Biomarkers Using Metabolomics

Several metabolites have been identified as key indicators of oxidative stress:

- Malondialdehyde (MDA): A final product of lipid membrane peroxidation, MDA is commonly used as a marker of oxidative stress. Elevated MDA levels have been observed in type 2 diabetes patients, indicating increased lipid peroxidation (13).
- 8-Hydroxy-2'-deoxyguanosine (8-OHdG): Resulting from DNA oxidation, 8-OHdG is a marker of oxidative DNA damage. Increased 8-OHdG concentrations have been detected in the urine and plasma of diabetic patients, reflecting enhanced oxidative DNA lesions (13).

- F2-Isoprostanes: These derivatives of non-enzymatic peroxidation of polyunsaturated fatty acids are considered reliable in vivo biomarkers of oxidative stress. Elevated F2-isoprostane levels have been associated with increased oxidative stress in diabetic patients (13).

Oxidative stress is also characterized by alterations in the body's antioxidant defense systems:

- Vitamin C (Ascorbic Acid): A major water-soluble antioxidant, vitamin C neutralizes free radicals in plasma. Decreased plasma vitamin C levels have been observed in diabetic patients, suggesting increased consumption due to oxidative stress (13).
- Vitamin E (α-Tocopherol): A lipid-soluble antioxidant, vitamin E protects cell membranes from lipid peroxidation. Studies have reported reduced vitamin E levels in type 2 diabetes patients, indicating increased utilization to counteract oxidative stress (13).
- Glutathione (GSH): The primary intracellular antioxidant, glutathione plays a crucial role in detoxifying ROS. Reduced GSH levels in diabetic patients reflect a compromised antioxidant capacity and heightened vulnerability to oxidative damage (13).

The integration of metabolomics into oxidative stress evaluation in diabetic patients not only allows for biomarker identification but also enhances our understanding of underlying metabolic imbalances. This approach holds promising potential for the development of targeted therapeutic strategies aimed at restoring redox balance and preventing diabetes-associated complications.

4.2. Clinical Applications and Future Perspectives

Metabolomics is revolutionizing diabetes management by offering tools for early diagnosis, personalized therapeutic strategies, and the development of new antioxidant treatments.

- Use of Metabolomics for Early and Personalized Diagnosis: By analyzing patient metabolic profiles, metabolomics enables the identification of specific biomarkers associated with type 2 diabetes. This approach facilitates early disease detection—even before clinical symptoms appear—and helps tailor therapeutic interventions based on individual metabolic characteristics. Studies have shown that metabolomic profiling enhances type 2 diabetes prediction, complementing traditional clinical and biological risk factors (14).
- Targeted Therapeutic Strategies Based on Metabolomic Analysis: Metabolomics offers a deep understanding of metabolic disruptions associated with diabetes, paving the way for targeted therapeutic strategies. Identifying altered metabolic pathways allows for specific interventions to restore metabolic balance, including:
    - Modulation of the polyol pathway: In diabetic patients, excess glucose is partially metabolized via the polyol pathway, leading to the accumulation of sorbitol and fructose, which contribute to microvascular complications. Metabolomic analysis has highlighted this alteration, suggesting that inhibiting aldose reductase, the key enzyme in this pathway, could be an effective therapeutic strategy (15).
    - Targeting BCAA metabolism: Elevated BCAA levels have been linked to insulin resistance. Metabolomics has identified this association, suggesting that lowering BCAA concentrations could improve insulin sensitivity and prevent diabetes progression (15).

Regulation of lipid metabolism: Metabolomic analysis has identified lipotoxic alterations in diabetes, indicating that normalizing lipid metabolism could reduce lipotoxicity and improve β-cell function (15).

5. Conclusion

Throughout this analysis, it has become evident that metabolomics plays a crucial role in understanding the underlying mechanisms of oxidative stress in diabetic patients. Through this innovative approach, it is now possible to identify early biomarkers, track the progression of metabolic complications, and propose targeted therapeutic strategies.

The integration of metabolomics in biomedical research has helped establish clear links between metabolic disturbances and the development of diabetic complications. Specific biomarkers such as malondialdehyde (MDA), 8-hydroxy-2-deoxyguanosine (8-OHdG), and F2-isoprostanes have been identified as indicators of oxidative stress. Furthermore, alterations in antioxidant systems (vitamin C, E, and glutathione) confirm the significant role of oxidative stress in the progression of diabetes (13).

One of the main advantages of metabolomics lies in its ability to provide a dynamic and integrated view of metabolism. Unlike traditional approaches that focus on isolated biochemical parameters, metabolomics enables comprehensive mapping of metabolic dysregulations associated with oxidative stress. This approach, therefore, holds considerable diagnostic and prognostic potential, particularly in enabling personalized treatment strategies for diabetic patients based on their unique metabolic profiles.

The rise of new analytical technologies, such as high-resolution mass spectrometry (HRMS) and nuclear magnetic resonance (NMR), presents promising opportunities for the future. These advancements allow for the detection of metabolic alterations at very early stages, offering the potential for intervention even before clinical symptoms appear.

In the coming years, researchers will likely move toward a more integrated approach that combines genomics, transcriptomics, proteomics, and metabolomics to develop more precise and effective prevention and treatment strategies. The application of artificial intelligence (AI) and machine learning in the interpretation of metabolomic data could further enhance precision medicine, allowing for the identification of disease-specific metabolic signatures and the optimization of therapeutic protocols.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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