ISSN: 2378-3419

Kumar and Mewar. Int J Cancer Clin Res 2024, 11:189
DOI: 10.23937/2378-3419/1410189
Volume 11 | Issue 1
Open Access

International Journal of
Cancer and Clinical Research

REVIEW ARTICLE

NMR Spectroscopy-Based Metabolomics Profiling: A Clinically Helpful Approach for Prostate Cancer Early Detection

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Abstract

PCa diagnosis is difficult since there is/are no acceptable, sensitive, and specific tumor biomarkers. The most common cancer in the world to be diagnosed in males over 50 is prostate cancer (PCa). In its early stages, there are no symptoms, and the cancer grows slowly. Measuring a predetermined list of certain metabolites is the goal of metabolomics. Understanding metabolites and their metabolic pathways is essential for finding new biomarkers, and the most significant pattern may have a big impact on how PCa is treated. Due to their low sensitivity and specificity, current non-screening diagnostic techniques have certain limitations when it comes to diagnosing PCa. They can also yield false negative results, which can result in overdiagnosis and overtreatment. Consequently, the purpose of this review is to present an overview of recent findings about NMR-based metabolomics in blood and urine biomarkers for PCa improvement, diagnosis, and prediction.

Keywords

Prostate cancer, BPH, NMR, Multivariate analysis, Metabolites, Metabolomics

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy in men over the age of 50-years-old worldwide [1]. In its early stages, there are no symptoms, and the cancer grows slowly. The main risk factors for the development of cancer, such as age, race, and family history, are not well known in the pathogenesis of PCa. Furthermore, environmental, dietary, and lifestyle choices might alter genes and start cancer processes [1,2]. The mainstream of PCa screening is abnormal levels of serum prostate-specific antigen (PSA) and/or digital rectal examination (DRE) followed by transrectal ultrasound (TRUS) guided biopsy. These methods have some limitations in the diagnosis of PCa because of the lack of specificity and sensitivity and also provide false negative findings leading to over-diagnosis and overtreatment. The diagnosis of PCa is difficult due to the lack of potential, sensitive, and specific tumor biomarkers [3].

Two major medical conditions are PCa and benign prostatic hyperplasia (BPH), both of which are predicted to become more common as the population ages. The subject of these two clinical disorders' relationship is brought up due to their similarities and frequent intimate relationships. According to epidemiological research, there is a strong age correlation between PCa and BPH incidence [4]. Both are likewise dependent on hormones; for example, androgens are necessary for both the development of PCa and BPH and for the normal growth of the prostate. In perspective simply, two isozymes called 5-α reductase type 1 and type 2 are responsible for converting testosterone into dihydrotestosterone (DHT), which attaches to androgen receptors and promotes the proliferation and differentiation of cells in the prostate. The disturbance of DHT-supported equilibrium between cell death and proliferation is thought to be responsible for the aberrant development of the prostate [4,5]. This leads to a suppression of apoptotic activities and a predominance of proliferative processes. Research using blood, urine, and NMR metabolomics as well as comparisons with healthy controls has been reported in the literature about PCa patients with BPH [5]. Transcriptomics and proteomics can be analyzed downstream by the "omics" discipline of metabolomics. This method allows

Citation: Kumar P, Mewar SK (2024) NMR Spectroscopy-Based Metabolomics Profiling: A Clinically Helpful Approach for Prostate Cancer Early Detection. Int J Cancer Clin Res 11:189. doi.org/10.23937/2378-3419/1410189

Accepted: August 01, 2024: **Published:** August 03, 2024

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it possible to simultaneously identify and track a broad variety of low molecular weight metabolites, facilitating the classification of distinct diseases and the tracking of their therapeutic outcomes [6,7]. Blood and urine samples subjected to NMR-based metabolic profiling may aid in the identification of metabolic biomarkers that might lead to improved PCa diagnostic and prognostic.

Consequently, a growing number of researches have been conducted in the past ten years to identify metabolomic biomarkers for PCa; they were most recently covered in several narrative review publications [8-14]. None of these were systematic, though. Consequently, the purpose of this review is to present an overview of the most recent data about NMR-based metabolomics in blood and urine biomarkers for PCa prediction, progression, and diagnosis [8-14]. Metabolomics has the potential to fulfill a significant therapeutic need by providing biomarkers that help identify PCa in its early stages.

Role of NMR in Metabolomics Study

Nuclear magnetic resonance (NMR) spectroscopy and Mass spectroscopy (MS) are the two analytical techniques that are most frequently utilized in metabolomics for metabolic profiling. This review focuses on NMR spectroscopy-based metabolomic profiling investigation in the blood and urine of PCa [15]. Because of its high degree of repeatability, non-destructiveness, and ease and speed of sample preparation, NMR plays a significant role in metabolomics. Drug toxicity investigations, environmental evaluation, pharmacological drug development, and nutrition research have all made substantial use of NMR-based metabolomics. Measuring an established set of certain metabolites is the goal of targeted metabolomics [15]. The identification of new biomarkers depends critically on our understanding of metabolites and the metabolic processes leading to compounds. A potent method called non-targeted metabolomics, also known as global metabolome analysis, seeks to find and identify a broad spectrum of metabolites in a biological sample, both known and unknown [15,16]. As a result, non-targeted metabolomics may be used to analyze metabolic pathways and biologically complex systems, as well as to find new metabolite types. Metabolomics is a quick method that can offer a comprehensive understanding of complicated conditions, such as PCa. Furthermore, complete metabolite integration will eventually result in individualized molecular diagnosis and illness therapy since metabolomics complements transcriptomics, proteomics, and genomes [15,16].

The study of metabolomics in diseases is a new and active field. To better understand the pathophysiology of the diseases, the primary goals of the metabolomics study of the diseases are to discover the distinct biomarkers or biomarkers for diagnosis and associated metabolic pathways. Typically, metabolomics involves tissue, cell, or organ and profiling every molecule (or a subset) in that biofluid (blood and urine). Studies on metabolomics using NMR have been used to treat a wide range of illnesses, such as diabetes, cancer, heart disease, neurological disorders, etc. Below is a discussion of a few NMR-based metabolomics research related to PCa.

A sample's metabolite profile, which is often a combination of many metabolites, is produced using NMR spectra. To identify a pattern or trend in the population being studied, it is intended to compare many profiles of this type [8-14]. The general NMR spectroscopy approach is explained, and then the critical parameters for NMR-based metabolomics are defined [8-14]. An explanation of unique protocols and acquisition methods used for particular sample kinds follows in various NMR metabolomic studies in blood and urine in PCa reported in literature and study. Univariate and multivariate statistical approaches can be used to obtain statistical patterns and validation analysis for NMR data [8-14]. The principal essential tools included variable importance in projection (VIP) evaluations, principal component analysis (PCA), and partial least squares-discriminant analysis (PLS-DA). A simple statistical explanation of metabolites has been presented, which includes an outline of the principles of both of these methods [17]. The diagnostic performance of this reduced set of biomarkers in the training set was further assessed using a ROC curve analysis, and the test set was defined according to the literature reviewed in the section below on blood and urine metabolites. A description is given of the many univariate and multivariate statistical instruments used in this thesis. In this case, the four most often utilized tools were route analysis, PCA, PLS-DA, OPL-DA, and VIP score [17]. An overview of the 1H-NMR metabolomics-based study using data processing, statistical analysis, and samples of blood and urine is given in Table 1 and Figure 1.

Metabolomics Study in Prostate Cancer

One of the most serious diseases that kills a great deal of people worldwide is cancer. The phospholipid metabolites level and the glycolytic and glutaminolysis pathways are two of the well-characterized metabolomes of malignant growths. However, the metabolomes of various tumor groupings differ greatly from one another. NMR spectroscopy is particularly useful for cancer metabolomics since it can handle samples of biofluids, such as blood and urine, as well as intact tissue biopsies [18,19].

Different metabolite profiles were seen in prostatic tissue, prostatic fluid, seminal fluid, plasma, and urine when high-resolution NMR spectroscopy was reviewed. The identification or measurement of as many metabolites as possible, which may be

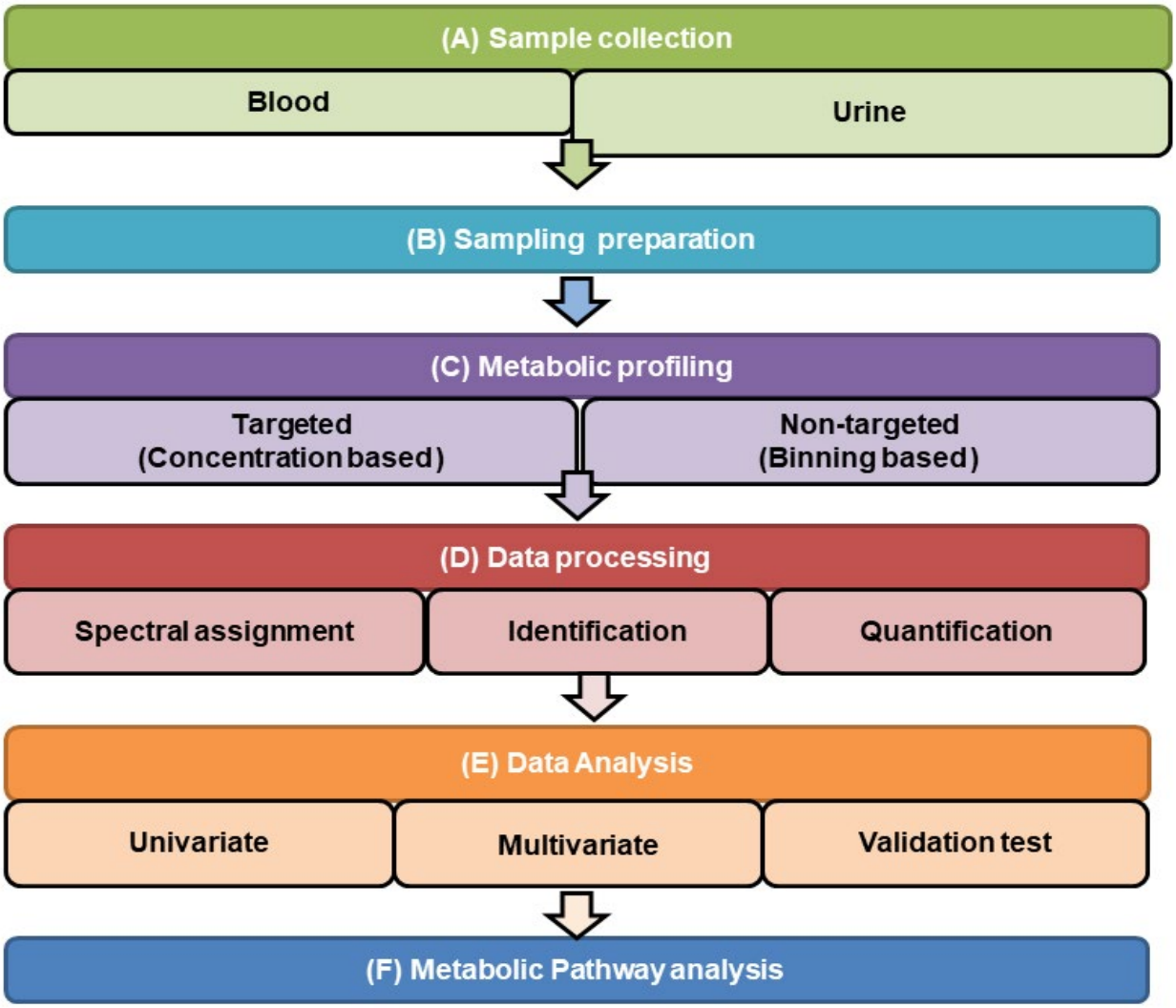

Figure 1: General overview of the ^{1}H-NMR metabolomics-based study based on blood and urine samples and data processing and statistical analysis.

Table 1: List of some important studies of NMR-based metabolomics profiling and identified metabolites and related significant patterns in blood and urine samples in PCa patients as compared to BPH and healthy controls.

Samples	Subjects (Comparison)	Altered metabolites	References
Blood	PCa vs. BPH vs. healthy controls	Alanine, glycine, sarcosine, citrate, and creatinine	[8]
Blood	PCa patient vs. BPH	Acylcarnitines, glycerophospholipids, and arginine	[9]
Blood	PCa patients vs. BPH	Glutamate and formate	[10]
Blood	PCa Patient low-grade (LG and HG) vs. healthy controls	Alanine, pyruvate, glycine, and sarcosine	[11]
Urine	PCa patients vs. BPH	Branched-chain amino acids (BCAA), glutamate, glycine, pseudouridine, dimethylglycine, 4-imidazole-acetate and fumarate	[12]
Urine	PCa patients vs. non-cancerous (control group)	Lactate, alanine glycine guanidinoacetate and phenylacetylglycine	[13]
Urine	PCa patients vs. BPH	Glycerol, acetone, levulinic acid, saccharic acid, alpha hydroxybutyric acid, and hippuric acid	[14]

BCAA: Branched-Chain Amino Acids; PCa: Prostate Cancer; BPH: Benign Prostatic Hyperplasia

compared with controls, might yield valuable diagnostic information. Sreekumar, et al. use urine, blood, and tissue samples from the same individuals to explain the correlation between changes in sarcosine levels and PCa development. Since then, sarcosine has been the subject of much research as a potential novel PCa biomarker, and it is a metabolite that is elevated as the disease becomes more aggressive. Urine sarcosine is ineffective as a biomarker for PCa detection or aggressive tumor identification. Sarcosine was not identified as

a novel non-invasive diagnostic biomarker for PCa; still, their work paved the way for other investigators to investigate the possible involvement of those metabolites in PCa diagnosis. The use of urine sarcosine as a marker for PCa detection was not supported by the research. Sarcosine and other metabolomic studies serve as examples of how metabolites are an especially fascinating class of metabolites to investigate in PCa. One attractive method in the hunt for a PCa diagnostic and prognostic Metabolites or biomarkers is the examination of their patterns in bodily fluids, such as blood and urine.

Blood Metabolites in PCa Patients

NMR analysis has been utilized in the metabolic profiling of plasma and serum samples from PCa and BPH patients. Univariate and multivariate statistical analyses were used to look at variations in blood metabolic profile patterns [9]. In addition to effectively differentiating patients with PCa and BPH, the combined analysis of blood plasma and serum samples by various metabolomics measurement techniques also produced metabolic biomarker(s) and insight into the mechanisms specific to PCa [9]. The findings of this study point to acylcarnitines, glycerophospholipids, and arginine as potential biomarker(s) for PCa patients in contrast to BPH patients [9].

Using NMR spectroscopy, Kumar, et al., investigated the PCa biomarkers in serum that were obtained from metabolomics. Four biomarkers such as alanine pyruvate, glycine, and sarcosine have been found in previous research to be useful in distinguishing between PCa patients and healthy controls [11]. Moreover, Kumar, et al. developed a model based on five metabolites alanine, sarcosine, creatinine, glycine, and citrate using blood serum samples, which allowed for the distinction between PCa and BPH patients as compared to healthy controls [8]. Fan, et al. used random forests to find changes in serum metabolites for PCa staging and detection [10]. Nine metabolites have been identified by NMR analysis in blood samples from men with BPH and PSA follow-up for 4-5 years, as well as patients with PCa who had Gleason scores of 5 and 7 [10]. Glutamate and formate were two of the NMR-detected metabolites that were much higher in PCa patients than in BPH patients. However, only a small number of large-scale NMR-based investigations have used blood and urine samples to compare the metabolic profiles of patients with PCa, BPH, and healthy controls [10]. Table 1 provides a summary of a few significant researches using NMR-based metabolomic analysis to identify metabolites and associated significant patterns in urine and blood samples from PCa patients compared to BPH and healthy controls.

Urinary Metabolites in PCa Patients

Sarcosine is an N-methyl derivative of glycine, and it was shown to be elevated in urine samples studied by Sreekumar, et al. when PCa progressed to a metastatic state [20]. The promise of NMR spectroscopy as a non-invasive diagnostic method for PCa detection has been established by this investigation. Changes in eight metabolites, including fumarate, branched-chain amino acids (BCAA), glutamate, pseudouridine, glycine, dimethylglycine, fumarate, 4-imidazole-acetate, and one unidentified molecule, have been observed in the urine metabolomic profile of PCa patients in comparison to those diagnosed with BPH [12].

According to this study, significant metabolites have been identified in urine samples from PCa patients and non-cancerous patients (the control group) using NMR analysis. Multivariate analysis can then be used to identify metabolites that may differentiate PCa from the control group. According to their study, glycine, phenylacetylglycine, and guanidinoacetate considerably increased in PCa, although L-lactate and L-alanine were dramatically reduced [13]. Moreover, the library's Pathway enrichment analysis revealed that PCa may include glycine, serine, and threonine metabolism. They found that glycine, phenylacetylglycine, and guanidinoacetate are potential PCa candidate biomarkers [13].

According to a recent study, NMR urine metabolomics may effectively differentiate between different degrees of PCa and separate it from BPH. This non-invasive diagnostic method could improve patient-specific treatment plans and early identification. The research showed that ^{1}H NMR urine metabolomics may identify different metabolic patterns between BPH and PCa as well as between Gleason grade groups [14]. Additionally, this approach was better than the PSA test at differentiating between PCa and BPH. Six metabolites (glycerol, acetone, hippuric acid levulinic acid, alpha hydroxybutyric and saccharic acid) have been reported to have variable relative quantities across PCa and BPH patients by untargeted metabolomics research, pointing to possible biomarkers for both diseases [14]. Furthermore, NMR metabolomics has demonstrated potential in tracking PCa growth. It is particularly appealing as a screening tool for cancer since it is non-invasive, inexpensive, and takes little time or effort for data collection and processing. Alternatively, invasive, possibly dangerous, or costly diagnostic methods would be needed.

Conclusion and Prospective Future

In conclusion, over the years, a limited amount of NMR-based metabolomics research has been done on PCa. Thus, metabolomics research has made it easier to identify biomarkers for PCa and BPH when compared to healthy controls, which raises the possibility of using metabolomic profiling in cancer therapy and preventive initiatives. While several metabolites have been found in PCa blood and urine samples, there

hasn't been enough research done to identify potential metabolomic indicators. The biological importance of important metabolites and metabolic pathways may be revealed by using metabolomic profiling in molecular epidemiologic research on PCa, although the underlying processes remain unknown. Finding metabolic biomarkers linked to early and later stages of PCa is essential given the multiple stages course of PCa carcinogenesis. This will help with early detection and high-risk population screening. Metabolomic profiling for the cascade of subsequent PCa stages and grades has been the subject of just a few research too far. To find metabolomic biomarkers and characterize the important metabolomic pathways and patterns, studies with high sample numbers, well-defined study populations, and independent validation samples are necessary. To effectively find metabolomics biomarkers for the evaluation of PCa risk, prospective follow-up of patients with a history of benign or negative biopsy results and future malignancies would be beneficial. Blood and urine samples subjected to NMR-based metabolic profiling may aid in the identification of metabolic biomarker(s) that might lead to improved PCa early diagnosis and prognostic tools.

Declarations

This work was not supported by any funding.

All of the above authors have seen and approved the manuscript.

The authors do not have any conflict of interest to declare.

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