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NEPHROLOGY – REVIEW

Metabonomic biomarkers for risk factors of chronic kidney disease

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Abstract
Purpose Chronic kidney disease, characterized by gradual loss of renal function and irreversible progression, is becoming a major public health problem worldwide. Chronic kidney disease may lead to end-stage renal disease, as well as increase the morbidity and mortality associated with cardiovascular disease.
Methods This review focuses on identifying risk factors indicating the need for intervention in early stages of chronic kidney disease, as well as determining factors that may improve patient prognosis. However, all the risk factors giving rise to the progression of chronic kidney disease have not yet been identified.
Results Metabonomics is a new type of omics that reflects the real-time pathophysiology of disease and focuses on endogenous metabolites of low molecular weight. This new and powerful tool has recently been used to explore metabonomic biomarkers of chronic kidney disease, enabling early diagnosis and timely intervention and treatment to slow the progression of chronic kidney disease.
Conclusions This review summarizes recent findings on the identification, using a metabonomic approach, of biomarkers associated with risk factors for the development and progression of chronic kidney disease.

Keywords Chronic kidney disease · Metabonomics · Risk factor · Biomarker

Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure and/or function that are present for >3 months, or as an unexplained reduction in glomerular filtration rate (GFR) to less than 60 mL/1.73 m^2 over 3 months. CKD has been categorized into five stages (CKD 1–5) based on estimated GFR (eGFR) [1, 2]. CKD often progresses to end-stage renal disease, requiring renal replacement with dialysis therapy or renal transplantation [3]. At present, over 1.4 million patients worldwide are receiving renal replacement therapy [4]. In addition, CKD is a strong risk factor for various cardiovascular diseases, with progression of CKD stage leading to increased cardiovascular morbidity and mortality [3–5]. The prevalence of CKD is estimated to be 8–16 % worldwide [6]. In the USA, CKD affects approximately 13 % of the adult population, and its prevalence is increasing [7]. In China, the overall prevalence of CKD is 10.8 % [8]. Because of the cost of renal replacement therapy and a shorter life expectancy, now, CKD is becoming a major public health problem worldwide, with a large impact on national healthcare budgets and individual patients [9–11]. The identification of risk factors for the progression of CKD may result in methods that prevent deterioration and improve prognosis.

Metabonomics

Metabonomics has been defined as "the quantitative measurement of the dynamic multiparametric metabolic

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response of living systems to pathophysiological stimuli or genetic modification" [12]. A similar term metabolomics was later coined [13], with the two methods and approaches being highly convergent and in effect synonymous [14–16]. In omics research, genomics reflects what is possible; transcriptomics reflects what appears to be happening; proteomics is used to determine what makes it happen; and metabonomics represents what is happening [17]. Metabonomics analyzes endogenous metabolites in the body, defined as small molecules of molecular weight less than 1 kDa [18]. Metabonomic samples generally include biofluids (such as urine and serum), tissue extracts, and intact tissues [19]. The workflow of metabonomic studies includes experimental design, sample collection and handling, metabolite extraction, data acquisition, data variability, pre-processing of data, statistical analysis, metabolite identification, metabolite quantitation, and pathway analysis [15]. As no current single-instrument platforms can cover all metabolites, the two main analytical techniques consist of nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). NMR is a nondestructive technique that provides detailed information on molecular structure and requires no sample preparation. However, NMR equipment is expensive and relatively insensitive compared with MS-based techniques. MS methods may therefore detect metabolites below the NMR detection limit and show superior separation of complex mixtures of chemicals. However, MS requires many preparation steps, including ionization and derivatization, both of which can result in metabolite losses [19–21]. Metabonomic studies yield huge amounts of data, making the application of pattern-recognition methods (also known as chemometrics or multivariate statistical analysis) important in interpreting complex data and identifying metabolites as potential biomarkers. Multivariate statistical analysis can be further categorized into unsupervised and supervised methods, in which principal component analysis and partial least squares discriminant analysis are the most widely used tools [15, 16, 21, 22].

Application of metabonomics to CKD

Most people with CKD are asymptomatic until renal function is severely damaged. Because healthy kidneys have a large reserve capacity, early stages of CKD are difficult to identify by subjective symptoms [3, 23]. Serum creatinine, a low molecular weight muscle breakdown product, is the biomarker most commonly used in clinical practice to detect and diagnose CKD [7]. Creatinine concentration is used to eGFR, an indicator of renal function [1, 2]. However, creatinine-based eGFR is not optimal for early diagnosis of CKD, because serum creatinine is a later marker of this disease and creatinine levels are affected by muscle mass, age, race, diet, exercise, and catabolic rate [3, 9, 24]. In addition, CKD shows irreversible progression, indicating a need for novel reliable biomarkers of early CKD and predictors of disease progression [9, 23, 24]. Metabonomic research on CKD can be classified into two categories.

Metabonomic biomarkers for early diagnosis of CKD

A liquid chromatography–mass spectrometry analysis of plasma from 10 rats with adenine-induced early CKD and five normal rats showed alterations in the plasma levels of N6-succinyl adenosine, lysophosphatidylethanolamine 20:4, and glycocholic acid [3]. These changes during early CKD were more sensitive markers than creatinine level. Moreover, the increase in plasma indoxyl sulfate level occurred earlier than increases in phenyl sulfate and *p*-cresol sulfate levels, indicating that these novel metabolites may serve as biomarkers for early-stage CKD [3].

^{1}H NMR-based metabonomics was also used to investigate altered metabolic patterns in 10 rats with CKD induced by surgical reduction of renal mass (5/6 nephrectomy), particularly to identify specific metabolic biomarkers associated with early-stage CKD [25]. Compared with 10 sham-operated rats, the plasma of the 5/6 nephrectomized rats showed significantly higher concentrations of organic anions, including citrate, β-hydroxybutyrate, lactate, acetate, acetoacetate, and formate, as well as significantly higher levels of alanine, glutamine, and glutamate. In contrast, the plasma levels of VLDL/LDL $(CH_2)_n$ and *N*-acetylglycoproteins were lower in nephrectomized rats. These changes in plasma metabolite profiles may provide insights into the disturbed metabolism occurring in patients with early-phase CKD [25].

In a clinical trial using a combined epidemiologic and metabonomic approach, liquid chromatography–mass spectrometry was used for metabolite profiling of plasma obtained from 1434 participants in the Framingham Heart Study who did not have CKD at baseline [26]. During the following 8 years, 123 individuals developed CKD, defined as an eGFR <60 mL min/1.73 m^2. Sixteen metabolites, including xanthosine, citrulline, isocitrate, aconitate, choline, kynurenine, β-aminoisobutyric acid, kynurenic acid, trimethylamine-*N*-oxide, adenosine, 5-hydroxyindoleacetic acid, quinolinic acid, LPC18:2, sucrose, LPC18:1, and inositol, were associated with incident CKD. Nine of these metabolites, citrulline, choline, kynurenic acid, kynurenine, 5-hydroxyindoleacetic acid, aconitate, isocitrate, xanthosine, and β-aminoisobutyric acid, were identified as potential markers of CKD risk. The addition of metabolite profiling to clinical data may significantly improve the ability to

Table 1 Metabonomic biomarkers for early diagnosis of CKD

Study	Study population/rats	Sample source	Method	Biomarker
Kobayashi et al. [3]	10 Rats with adenine-induced CKD versus 5 normal rats	Plasma	LC–MS	N6-succinyl adenosine, glycocholic acid, lysophosphatidylethanolamine 20:4, indoxyl sulfate
Kim et al. [25]	10 Rats with CKD induced by 5/6 nephrectomy versus 10 sham-operated rats	Plasma	NMR	Citrate, β-hydroxybutyrate, lactate, acetate, acetoacetate, formate, alanine, glutamine, glutamate, VLDL/LDL $(CH_2)_n$, *N*-acetylglycoproteins
Rhee et al. [26]	123 Individuals with vs. 1311 without CKD	Plasma	LC–MS	Xanthosine, citrulline, isocitrate, aconitate, choline, kynurenine, β-aminoisobutyric acid, kynurenic acid, trimethylamine-*N*-oxide, adenosine, 5-hydroxyindoleacetic acid, quinolinic acid, LPC18:2, sucrose, LPC18:1, inositol
Qi et al. [27]	20 Patients at each of the four stages of CKD versus 28 healthy controls	Serum	NMR	Glucose, lactate, valine, alanine, glutamate, glycine, betaine, myo-inositol, taurine, glycerophosphocholine, scyllo-inositol, choline, lipid, phosphorylcholine

CKD chronic kidney disease; *LC–MS* liquid chromatography–mass spectrometry, *NMR* nuclear magnetic resonance

predict whether an individual will develop CKD by identifying risk predictors independent of eGFR [26].

In another clinical study, NMR was used to assess the serum metabolic profiles of 80 patients with four stages of CKD and 28 healthy controls [27]. Endogenous metabolites that significantly contributed to distinguishing the different stages of CKD included glucose, lactate, valine, alanine, glutamate, glycine, betaine, myo-inositol, taurine, glycerophosphocholine, scyllo-inositol, choline, lipid, and phosphorylcholine. These metabolic biomarkers may provide useful information for the diagnosis of CKD, especially in the early stages [27].

The metabolites identified in experimental and clinical studies as markers for early diagnosis of CKD are presented in Table 1.

Metabonomic biomarkers for the progression of CKD

Several studies have analyzed potential biomarkers of CKD progression. One study analyzed urine samples from 16 patients with advanced-stage CKD (3–5) and 15 controls by liquid chromatography–triple quadrupole mass spectrometry [9]. Seven of the urinary metabolites, 5-oxoproline, glutamate, guanidoacetate, α-phenylacetylglutamine, taurine, citrate, and trimethylamine *N*-oxide, differed in the CKD and non-CKD urine samples, suggesting that these metabolites may help identify patients with early CKD and monitor disease progression [9]. In another study, ^{1}H-NMR spectroscopy was used to determine differences in plasma metabolites in 10 patients with CKD stages 3–4 and four healthy controls [28]. Fourteen metabolites were elevated in uremic plasma, including 1-methylhistidine, 3-methylhistidine, hippuric acid, *p*-cresyl sulfate, creatinine, dimethyl sulfone, 2-hydroxyisobutyric acid, *N,N*-dimethylglycine, trigonelline, pseudouridine, betaine, myo-inositol, dimethylamine, and trimethylamine *N*-oxide. In addition to confirming the retention of several previously identified uremic toxins, two novel uremic retention solutes were detected, dimethyl sulfone and 2-hydroxyisobutyric acid. These uremic retention solutes were associated with disease progression, suggesting that these may be new biomarkers for CKD and may contribute to a better understanding of the progressive character of renal disease [28].

In another study using gas and liquid chromatography coupled to mass spectrometry, plasma metabolites from 30 nondiabetic men aged 40–52 years, 10 each having CKD stages 2, 3, and 4 based on eGFR, were analyzed [29]. Comparisons of the groups with stage 3 and stage 2 CKD identified 62 metabolites that differed, with 39 higher and 23 lower in stage 3 than in stage 2. Similarly, comparisons of the groups with stage 4 and stage 2 identified 111 metabolites that differed, with 66 higher and 45 lower in stage 4, whereas comparisons of stage 4 with stage 3 identified 11 metabolites that differed, with seven higher and four lower in stage 4. As CKD stage increased, major differences were observed in metabolite profiles, including dimethylarginine, citrulline, ornithine, fibrinopeptide-A, phosphorylated fibrinopeptide-A, proline-hydroxyproline, dehydroisoandrosterone sulfate, 4-androsten-3-β,17-β-diol disulfate, γ-glutamylglutamine, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoate. These differences may reveal CKD stage-specific biomarkers, as well as provide insight

Table 2 Metabonomic biomarkers for the progression of CKD

Study	Study population	Sample source	Method	Biomarker
Posada-Ayala et al. [9]	16 Patients with advanced-stage CKD (3–5) versus 15 controls	Urine	LC–(QQQ) MS	5-Oxoproline, glutamate, guanidoacetate, α-phenylacetylglutamine, taurine, citrate, trimethylamine *N*-oxide
Mutsaers et al. [28]	10 Patients each with CKD stages 3–4 versus 4 healthy controls	Plasma	NMR	1-Methylhistidine, 3-methylhistidine, hippuric acid, *p*-cresyl sulfate, creatinine, dimethyl sulfone, 2-hydroxyisobutyric acid, *N,N*-dimethylglycine, trigonelline, pseudouridine, betaine, myo-inositol, dimethylamine,trimethylamine *N*-oxide
Shah et al. [29]	30 Nondiabetic men aged 40–52 years; 10 each with CKD stages 2, 3, and 4	Plasm	GC–MS, LC–MS	Dimethylarginine, citrulline, ornithine, fibrinopeptide-A, phosphorylated fibrinopeptide-A, proline-hydroxyproline, dehydroisoandrosterone sulfate, 4-androsten-3-β,17-β-diol disulfate, γ-glutamylglutamine, 3-carboxy-4-methyl-5-propyl-2-furanpropanoate
Toyohara et al. [30]	41 Patients with CKD	Plasma	CE–MS	Creatinine, symmetric dimethylarginine, guanidinosuccinate, citrulline, 1-methyladenosine, *N*-acetylglucosamine, γ-butyrobetaine, ophthalmate, 3-methylhistidine, hydroxyproline, trimethylamine *N*-oxide, allantoin, asymmetric dimethylarginine, *N*-ε-acetyllysine, kynurenine, cytosine, indole-3-acetate, hypotaurine, *N,N*-dimethylglycine, 7-methylguanine, methionine sulfoxide, Asn, Trp, Val, Tyr, 2-aminobutyrate, guanidoacetate, Glu, Leu, isethionate, gluconate, trans-aconitate, pimelate, 3-indoxyl sulfate, isocitrate, *N*-acetyl-b-alanine, *N*-acetylglutamate, sebacate, 4-oxopentanoate, *cis*-aconitate, homovanillate, adipate, citramalate, 2-isopropylmalate, threonate, hippurate, *N*-acetylaspartate, 4-hydroxy-3-methoxymandelate, oxamate, glutarate, azelate, phthalate, citrate, malonate, citraconate, quinate, succinate, cysteine s-sulfate, 4-hydroxy-3-methoxybenzoate, 4-methyl-2-oxopentanoate, 2-oxoisopentanoate, lactate, octanoate, 2-oxoglutarate
Boelaert et al. [31]	40 Patients, 20 each with CKD stages and 5 on hemodialysis vs. 20 healthy controls	Serum	LC–Q-TOF MS, GC–MS	Alanine, cinnamoylglycine, creatinine, dehydroisoandrosterone sulfate, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, dimethylguanosine, disaccharide, glutamic acid, glutamine, glutamylphenylalanine, hippuric acid, 4-hydroxyhippuric acid, 3-hydroxyhippuric acid, 2-hydroxyhippuric acid, hydroxyindole, indole-3-lactate, indoxyl sulfate, kynurenic acid, kynurenine, lysine, methionine, methyladenosine, methylinosine, *N*-methylpyridone-carboxamide, oleic acid, pantothenic acid, 4-pyridoxic acid, *N*-threonylcarbamoyladenosine, *p*-cresol glucuronide, *p*-cresol sulfate, phenylacetylglutamine, proline, pseudouridine, pyroglutamic acid, quinic acid, quinolinic acid, tryptophan, urea, uric acid and xanthosine, 4-acetamidobutanoate, acetylhomoserine, aminohydroxyhippuric, Asp Leu, tetrasaccharide, trihydroxypentenoic acid, 2-/3-hydroxyhippuric acid sulfate, succinoadenosine, 2-hydroxyhippuric acid glucuronide, oxoprolylproline, Phe Phe, methoxyhydroxyphenylglycol glucuronide, sialyllactose, monosaccharide, *N*-acetylneuraminic acid, gluconic acid, $C_{5:0}$–glycine, Dimethyluric acid, hexacosanedioic acid, 3-methyluridine/ribothymidine, methylglutarylcarnitine, methyluric acid, a-*N*-acetylneuraminyl-2,6-b-D-galactosyl-1,4-*N*-acetyl-b-D-glucosamine, hydroxypyridine, D-glucuronic acid-*N*-acetyl-D-glucosamine, alacturonic acid/glucuronic acid, 5-methoxysalicylic acid, methylglutarylcarnitine, mercaptolactic acid, lactose, maltose, $C_{10:0}$–OH, $C_{12:0}$–OH, $C_{14:0}$–OH, $C_{18:0}$–2OH, $C_{22:4}$, $C_{22:5}$, hexacosanedioic acid, keto-$C_{5:0}$, keto-$C_{6:0}$, palmitic acid ($C_{16:0}$)

CKD chronic kidney disease, *LC–(QQQ) MS* liquid chromatography–triple quadrupole mass spectrometry, *NMR* nuclear magnetic resonance, *GC–MS* gas chromatography to mass spectrometry, *LC–MS* liquid chromatography–mass spectrometry, *CE–MS* capillary electrophoresis with mass spectrometry, *LC–Q-TOF MS* liquid chromatography coupled to quadrupole time-of-flight mass spectrometry

into the possible pathophysiologic process that may contribute to the progression of CKD [29].

Renal function was assessed by using capillary electrophoresis with mass spectrometry to examine the retention of uremic solutes of plasma in 41 CKD patients [30]. As eGFR decreased, 22 cations and 30 anions accumulated significantly, while seven cations and five anions decreased significantly. These compounds included creatinine, symmetric dimethylarginine, guanidinosuccinate, citrulline, 1-methyladenosine, *N*-acetylglucosamine, γ-butyrobetaine, ophthalmate, 3-methylhistidine, hydroxyproline, trimethylamine *N*-oxide, allantoin, asymmetric dimethylarginine, *N*-ε-acetyllysine, kynurenine, cytosine, indole-3-acetate, hypotaurine, *N,N*-dimethylglycine, 7-methylguanine, methionine sulfoxide, Asn, Trp, Val, Tyr, 2-aminobutyrate, guanidoacetate, Glu, Leu, isethionate, gluconate, transaconitate, pimelate, 3-indoxyl sulfate, isocitrate, *N*-acetyl-b-alanine, *N*-acetylglutamate, sebacate, 4-oxopentanoate, *cis*-aconitate, homovanillate, adipate, citramalate, 2-isopropylmalate, threonate, hippurate, *N*-acetylaspartate, 4-hydroxy-3-methoxymandelate, oxamate, glutarate, azelate, phthalate, citrate, malonate, citraconate, quinate, succinate, cysteine s-sulfate, 4-hydroxy-3-methoxybenzoate, 4-methyl-2-oxopentanoate, 2-oxoisopentanoate, lactate, octanoate, and 2-oxoglutarate. Any or all of these may serve as markers of CKD progression [30].

Another study assayed serum samples from 40 patients, 20 with CKD stage 3 and 20 with CKD 5 on hemodialysis, along with 20 healthy controls, using liquid chromatography coupled to high-resolution quadrupole time-of-flight mass spectrometry and gas chromatography coupled to quadrupole mass spectrometry [31]. Eight-five metabolites differed, suggesting their association in CKD progression. Forty-three of these metabolites had previously been identified: alanine, cinnamoylglycine, creatinine, dehydroisoandrosterone sulfate, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, dimethylguanosine, disaccharide, glutamic acid, glutamine, glutamylphenylalanine, hippuric acid, 4-hydroxyhippuric acid, 3-hydroxyhippuric acid, 2-hydroxyhippuric acid, hydroxyindole, indole-3-lactate, indoxyl sulfate, kynurenic acid, kynurenine, lysine, methionine, methyladenosine, methylinosine, *N*-methyl-pyridonecarboxamide, oleic acid, pantothenic acid, 4-pyridoxic acid, *N*-threonylcarbamoyladenosine, *p*-cresol glucuronide, *p*-cresol sulfate, phenylacetylglutamine, proline, pseudouridine, pyroglutamic acid, quinic acid, quinolinic acid, tryptophan, urea, uric acid, and xanthosine. An additional 31 metabolites were found to increase with CKD progression: 4-acetamidobutanoate, acetylhomoserine, aminohydroxyhippuric, Asp Leu, tetrasaccharide, trihydroxypentenoic acid, 2-/3-hydroxyhippuric acid sulfate, succinoadenosine, 2-hydroxyhippuric acid glucuronide, oxoprolylproline, Phe Phe, methoxy-hydroxyphenylglycol glucuronide, sialyllactose, monosaccharide, *N*-acetylneuraminic acid, gluconic acid, $C_{5:0}$–glycine, dimethyluric acid, hexacosanedioic acid, 3-methyluridine/ribothymidine, methylglutarylcarnitine, methyluric acid, a-*N*-acetylneuraminyl-2,6-b-D-galactosyl-1,4-*N*-acetyl-b-D-glucosamine, hydroxypyridine, D-glucuronic acid-*N*-acetyl-D-glucosamine, alacturonic acid/glucuronic acid, 5-methoxysalicylic acid, methylglutarylcarnitine, mercaptolactic acid, lactose, and maltose. In addition, 11 metabolites were found to decrease as CKD progressed: $C_{10:0}$–OH, $C_{12:0}$–OH, $C_{14:0}$–OH, $C_{18:0}$–2OH, $C_{22:4}$, $C_{22:5}$, hexacosanedioic acid, keto-$C_{5:0}$, keto-$C_{6:0}$, keto-$C_{6:0}$, and palmitic acid ($C_{16:0}$) [31].

The metabolites associated with the progression of CKD in clinical studies are presented in Table 2.

Conclusions

No biomarker for the early diagnosis of CKD was identical in animal models and clinical studies. In the two clinical studies, however, one biomarker, choline, was identical. Nevertheless, additional clinical studies are needed to determine whether choline is a biomarker for early-stage CKD.

A comparison of biomarkers for progression of CKD identified in clinical studies showed that none was identical. These studies used different analytical methods, liquid chromatography–mass spectrometry, NMR, gas chromatography to mass spectrometry, capillary electrophoresis with mass spectrometry, and liquid chromatography–triple quadrupole mass spectrometry MS, and different sample sources, urine, plasma, and serum. In addition, using some of these metabolites as biomarkers is impractical in clinical studies. Additional clinical studies, including more participants and uniform analytical methods and sample sources, as well as multicenter clinical trials, are required to detect biomarkers of CKD progression. Improving the sensitivity of technological and analytical tools may lead to the identification of novel, reliable, and objective biomarkers for the early diagnosis and progression of CKD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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

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