Clinica Chimica Acta 499 (2019) 54–63

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Chronic kidney disease: Biomarker diagnosis to therapeutic targets

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ARTICLE INFO

Keywords:
Chronic kidney disease
Metabolomics
Biomarker
Glomerular filtration rate
Ultra-performance liquid chromatography
Mass spectrometry

ABSTRACT

Chronic kidney disease (CKD), characterized as renal dysfunction, is recognized as a major public health problem with high morbidity and mortality worldwide. Unfortunately, there are no obvious clinical symptoms in early stage disease until severe damage has occurred. Further complicating early diagnosis and treatment is the lack of sensitive and specific biomarkers. As such, novel biomarkers are urgently needed. Metabolomics has shown an increasing potential for identifying underlying disease mechanisms, facilitating clinical diagnosis and developing pharmaceutical treatments for CKD. Recent advances in metabolomics revealed that CKD was closely associated with the dysregulation of numerous metabolites, such as amino acids, lipids, nucleotides and glycoses, that might be exploited as potential biomarkers. In this review, we summarize recent metabolomic applications based on animal model studies and in patients with CKD and highlight several biomarkers that may play important roles in diagnosis, intervention and development of new therapeutic strategies.

1. Introduction

Chronic kidney disease (CKD) is characterized by a decrease in renal function, a glomerular filtration rate (GFR) of < 60 mL/min/per 1.73 m^2 or the presence of markers of renal injury, or both, for a duration of more than one trimester regardless of aetiology [1,2]. CKD is usually diagnosed by GFR, which is measured by biomarkers or estimated using equations. CKD is divided into 5 stages based on estimated glomerular filtration rate (eGFR) or albuminuria (Table 1) [2]. Global morbidity from CKD is as high as 11% to 13%, causing at least 10-fold higher cardiovascular mortality than the general population, making CKD a major public health problem worldwide, especially in high-income countries [3–5]. The irreversible progression of CKD frequently results in end-stage renal disease (ESRD), which contributes to poor clinical outcomes. In addition, metabolites change with the development of renal injury, providing new insight into sensitive biomarkers. The cause of CKD is complex and uncertain and the progression is multivariate, which leads to different prognoses [6–8].

Current medical intervention aimed at delaying the progression of CKD and preventing negative outcomes is greatly limited. The illumination of underlying mechanisms could help us discover new diagnostic approaches [9–14]. Renal histopathology, serum creatinine (Scr) and clinical manifestations are commonly used to diagnose CKD. Scr has been used to classify CKD and determine its different stages, but its role is very limited. The concentration of Scr is not changed until kidney failure occurs, indicating kidney damage occurs prior to Scr alterations. In addition, based on gender, age, muscle metabolism, muscle mass, overall body weight, hydration status and nutritional status, the concentration of Scr varies greatly [15]. However, existing diagnostic tools are unpractical for clinical use or seriously flawed, which hinders

Abbreviations: ^{1}H NMR, porton nuclear magnetic resonance; 5-MTP, 5-methoxytryptophan; AAN, aristolochic acid nephropathy; ADMA, asymmetric dimethylarginine; ANOVA, analysis of variance; CKD, chronic kidney disease; CLASSY, cluster analysis statistical spectroscopy; Cys-C, cystatin C; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HCA, hierarchical cluster analysis; HILIC-TOF/MS, hydrophilic interaction liquid chromatography time-of-flight mass spectrometry; HPLC, high performance liquid chromatography; LC-MS, liquid chromatography mass spectrometry; NMMA, N-mono-methylarginine; Nx, 5/6 nephrectomized; OPLS-DA, orthogonal partial least squares discriminant analysis; PCA, principal component analysis; PLS-DA, partial least squares discriminant analysis; Scr, serum creatinine; SDMA, symmetric dimethylarginine; TIF, tubulointerstitial fibrosis; TPH-1, tryptophan hydroxylase-1; UPLC-HDMS, ultra-performance liquid chromatography coupled with high-definition mass spectrometry; UUO, unilateral ureteral obstruction

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https://doi.org/10.1016/j.cca.2019.08.030
Received 10 July 2019; Received in revised form 29 August 2019; Accepted 29 August 2019
Available online 30 August 2019
0009-8981/

Table 1
Stages of CKD as defined by GFR/eGFR or ACR.

Stage	GFR ml/min/per 1.73 m^2	Descriptors	UACR range (mg/g)		
			A1 Normal to mildly increased (< 30)	A2 Moderately increased (30 − 300)	A3 Severely increased (> 300)
G1	≥ 90	Normal or high	1(CKD)	1	2
G2	60–89	Mildly decreased	1(CKD)	1	2
G3a	45–59	Mildly to moderately decreased	1	2	3
G3b	30–44	Moderately to severely decreased	2	3	3
G4	15–29	Severely decreased	3	3	≥ 4
G5	< 15	Kidney failure	≥ 4	≥ 4	≥ 4

effective disease management for CKD patients despite optimized treatment strategies and proven patient interest [16,17]. Therefore, it is urgent to find novel biomarkers to improve diagnostic efficiency and surveillance and treatment of CKD, and metabolomics has identified potential metabolites that can be used as biomarkers in clinical practice [18,19].

Metabolomics is a measure of dynamic changes in low-molecular-weight metabolites in biofluids and/or tissues [20–24]. We can quantitatively or qualitatively measure multi-parameter metabolic reactions of a biosystem to pathophysiological stimuli [25–27]. Metabolites are considered the final products of gene-environment interactions and physiological steady-state [28,29]. The measurement of metabolites can be combined with available clinical biochemistry indexes that have potential for clinical diagnosis, patient stratification and therapeutic response monitoring [30].

Metabolomics for progressive CKD provides new insights into biomarker discovery and dramatically widens our appreciation of pathological mechanisms [15,31,32]. The gradual loss of kidney function is one of the hallmarks of CKD, accompanied by uremic retention fluid accumulation in patients with CKD or ESRD [33]. The progression of CKD can be halted or alleviated if CKD is diagnosed in an early stage. Proteomics and genomics analysis cannot provide a full picture of what is occurring in cells, but metabolomics can provide immediate, candid snapshots of physiology [21]. New analytical tools with high throughput and sensitivity have made metabolomics easier and quantifiable to allow exploration of information from biological samples [22,34–36]. Moreover, our latest study demonstrated that 5 metabolites, including canavaninosuccinate, 5-methoxytryptophan (5-MTP), acetylcarnitine, taurine and tiglylcarnitine, were strongly correlated with the development of CKD [37]. 5-MTP decreased with the progression of CKD, and tryptophan hydroxylase-1(TPH-1) may be a target for CKD treatment [37].

2. Metabolomic techniques

2.1. Metabolomic analytical technologies

Metabolomic study generally include metabolome data collection, data preprocessing, multivariate analysis, biomarker identification and biological pathway analysis [38]. The metabolites are detected by advanced analytical platforms, such as high-performance liquid chromatography (HPLC), mass spectrometry (MS) and proton nuclear magnetic resonance (^{1}H NMR), to obtain a large amount of original experimental data reflecting information from biological samples [15,21].

Liquid chromatography (LC) is the most widely used technique due to its high-throughput and sensitivity. However, there is no single method that can effectively quantify and detect great quantities of metabolites that may have potential implications for metabolomics. Therefore, multiple orthogonal or complementary metabolomics platforms are strongly recommended [39]. LC-MS is the preferred analytical method for biological samples. Furthermore, evidence has suggested that ultra-performance liquid chromatography coupled with high-definition mass spectrometry (UPLC-HDMS) is suitable for studies of metabolic profiles and identification of metabolites, particularly untargeted metabolomics due to its improved reproducibility of retention time [40,41]. In addition, a hydrophilic interaction liquid chromatography time-of-flight mass spectrometry (HILIC-TOF/MS) can be optimized to find new uremic retention solutes and/or CKD biomarkers [42].

NMR is another important tool in metabolomics. Although ^{1}H NMR is currently overshadowed by MS in number of compounds, it has advantages both by itself and in combination with MS. ^{1}H NMR data are highly quantitative and repeatable over a large dynamic range, which is unparalleled in determining unknown structures [43]. ^{1}H NMR is considered suitable for tracing metabolic pathways and flows with isotope markers [44]. Moreover, ^{1}H NMR is nondestructive and can be used in vivo [44]. In addition, ion mobility-mass spectrometry and supercritical fluid chromatography-mass spectrometry are two complementary technologies for metabolomics applications [45–48].

2.2. Data analysis for metabolomics

Typical data processing in metabolomics has several phases: baseline correction, alignment and normalization, feature detection and filtering. A number of usable software platforms, including XCMS, MetAlign and MZmine, have been used to manage raw data from MS [49]. To analyse and maximize information retrieval from raw data, both unsupervised and supervised methods, such as principal component analysis (PCA), hierarchical cluster analysis (HCA), orthogonal partial least squares discriminant analysis (OPLS-DA) and partial least squares discriminant analysis (PLS-DA), have been applied for metabolomics data analysis [50]. PCA is frequently used for multivariate analysis by converting the multidimensional data space to a low-dimensional model. In addition, HCA groups samples according to their similarity. However, HCA cannot provide detailed information about a colony. Recently, cluster analysis statistical spectroscopy (CLASSY) formed by a combination of statistical correlation spectroscopy and HCA has been developed for metabolomics data analysis [51]. This method is better than statistical correlation spectroscopy because correlations between the same molecular peaks are detected with higher accuracy.

Supervised techniques are widely used in the discovery of biomarkers by utilizing a priori known structures. PLS-DA is a widely used method with advantages in metabolite classification and is suitable for highly correlated variables. In general, OPLS-DA is analogous to PLS-DA in prediction but superior to PLS-DA in interpretability [52].

2.3. Biomarker identification and metabolic pathway analysis

Biomarker identification is the most important process of metabolomics studies, and metabolites can be identified by using a number of metabolite databases, such as Kyoto Encyclopedia of Genes and Genomes, Biochemical Genetic and Genomic knowledgebase, PubChem Compound, Human Metabolome Database, LIPID MAPS and MetaCyc

Table 2
Metabolites and metabolic pathways in CKD.

Metabolites	Trend	Samples	Methods	Related metabolic pathways	References
ADMA[b]	Increased	Serum, plasma	LC-MS	Arginine metabolism	[97]
Arginine[b]	Increased	Serum, plasma	LC-MS	Arginine metabolism	[97]
Cadaverine putrescine[c]	Increased	Urine	GC–MS	Arginine metabolism	[106]
Citrulline[b]	Increased	Serum, plasma	LC-MS	Arginine metabolism	[97,103]
Myo-inositol[c]	Increased	Serum, tissue	NMR	Arginine metabolism	[104]
NMMA[b]	Increased	Serum, plasma	LC-MS	Arginine metabolism	[97]
Nitric oxide[a]	Increased	Plasma	HPLC	Arginine metabolism	[60]
SDMA[b]	Increased	Serum, plasma	LC-MS	Arginine metabolism	[97]
Alanine[c]	Decreased	Serum	NMR	Alanine, aspartate and glutamate metabolisms	[107]
Glutamate[b,c]	Increased	Serum, tissue	MALDI MSI	Alanine, aspartate and glutamate metabolisms	[105]
L-glutamate[c]	Increased	Plasma, urine	UPLC-QTOF/MS, NMR	Alanine, aspartate and glutamate metabolisms	[34]
Succinate[c]	Increased	Serum	MALDI MSI	Alanine, aspartate and glutamate metabolisms	[105]
Cholicacid[d]	Increased	Serum, plasma	UPLC-MS	Bile acid metabolism	[89]
Chenodeoxycholicacid[d]	Increased	Serum, plasma	UPLC-MS	Bile acid metabolism	[89]
Cys-C[a]	Increased	Plasma	HPLC	Cysteine metabolism	[54,60,85]
Adrenicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Docosahexaenoicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Docosapentaenoicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Hippuricacid[a]	Decreased	Urine	UPLC-QTOF/HDMS	Fatty acid oxidation	[78]
Hippuricacid[a]	Increased	Tissue, serum	UPLC-QTOF/MS	Fatty acid oxidation	[62]
Linoleicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Linolenicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Octacosanoicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Palmiticacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Palmiticacid[a]	Decreased	Serum	UPLC-QTOF/HDMS	Fatty acid metabolism	[82]
Stearicacid[a]	Increased	Tissue	UPLC-QTOF/HDMS	Fatty acid oxidation	[79]
Betaine[c]	Decreased	Serum, tissue	NMR	Glycine, serine and threonine metabolisms	[104]
Homocysteine[a]	Decreased	Urine	UPLC-QTOF/HDMS	Glycine, serine and threonine metabolisms	[78]
NGAL[b]	Increased	Plasma	HPLC	Glycolipid metabolism	[60,85]
Phenylacetylglycine[a]	Increased	Serum, tissue	UPLC-HDMS	Glycine metabolism	[78]
Glucose[c]	Increased	Serum	MALDI MSI	Glycolysis, gluconeogenesis	[105]
Pyruvicacid[c]	Increased	Serum	MALDI MSI	Glycolysis, gluconeogenesis	[105,107]
P-cresolglucuronide[a]	Increased	Tissue, serum	UPLC-QTOF/MS	Gut bacteria metabolism	[62]
Equol 7-glucuronide[a]	Increased	Tissue, serum	UPLC-QTOF/MS	Gut bacteria metabolism	[62]
4-ethylphenyl sulfate[a]	Increased	Tissue, serum	UPLC-QTOF/MS	Gut bacteria metabolism	[62]
3-methylhistidine[a]	Decreased	Urine	UPLC-QTOF/HDMS	Histidine metabolism	[78]
Histidine[a]	Decreased	Urine	UPLC-QTOF/HDMS	Histidine metabolism	[78]
L-histidine[a]	Decreased	Urine	UPLC-QTOF/HDMS	Histidine metabolism	[78]
Urocanicacid[a]	Increased	Urine	UPLC-QTOF/HDMS	Histidine metabolism	[78]
Isoleucine[c]	Increased	Serum	NMR	Leucine metabolism	[107]
Leucine[c]	Decreased	Serum, tissue	NMR	Leucine metabolism	[104]
Methionine[c]	Decreased	Serum, tissue	NMR	Methionine cycle	[104]
TMNO[b,c]	Increased	Serum, urine	NMR, MS	Methylamine metabolism	[103,104]
Phenylalanine[a,c]	Decreased	Urine	UPLC-QTOF/HDMS	Phenylalanine metabolism	[78,104]
P-cresol[a]	Decreased	Urine	UPLC-QTOF/HDMS	Phenylalanine metabolism	[78]
P-cresylsulfate[a]	Increased	Serum, tissue	UPLC-QTOF/HDMS	Phenylalanine metabolism	[62]
Tyrosine[c]	Decreased	Serum, tissue	NMR	Phenylalanine metabolism	[104]
Acetoacetate[c]	Increased	Serum	NMR	Tryptophan metabolism	[107]
Hypotaurine[a]	Decreased	Tissue	UPLC-QTOF/HDMS	Taurine and hypotaurine metabolisms	[79]
Indoxylsulfate[a]	Increased	Tissue, urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[62,86]
Indole[a]	Increased	Urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[78]
Kynurenine[a,b]	Decreased	Urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[78,103]
Kynurenicacid[a,c]	Decreased	Urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[34,78]
Tryptophan[a]	Increased	Tissue, urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[78,79]
Tyramine[a]	Increased	Urine	UPLC-QTOF/HDMS	Tyrosine metabolism	[78]
Taurine[b]	Decreased	Tissue	NMR	Taurine and hypotaurine metabolisms	[104]
Xanthurenicacid[a]	Decreased	Plasma, urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[78]
Valinea[c]	Decreased	Serum, tissue	NMR	Valine metabolism	[82,104,107]
Malate[b]	Increased	Tissue	NMR	TCA cycle	[98]
Citricacid[c]	Increased	Serum	MALDI MSI	TCA cycle	[105,107]
Inosine[c]	Increased	Serum	MALDI MSI	Nucleotide metabolism	[105]
Xanthine[c]	Decreased	Serum	MALDI MSI	Purine metabolism	[105]
Hypoxanthinec	Decreased	Serum	MALDI MSI	Purine metabolism	[105]
Allantoin[c]	Increased	Plasma, urine	UPLC-QTOF/MS	Purine metabolism	[34]
Uricacid[a]	Increased	Serum, urine	UPLC-QTOF/HDMS	Purine metabolism	[60,78,79]
LPC (18:0)[a]	Increased	Serum	UPLC-QTOF/HDMS	Phospholipid metabolism	[82]
LPC (20:4)[a]	Decreased	Serum	UPLC-QTOF/HDMS	Phospholipid metabolism	[82]
LPC (18:2)[a]	Increased	Serum	UPLC-QTOF/HDMS	Phospholipid metabolism	[82]
LPC (16:0)[a]	Decreased	Serum	UPLC-QTOF/HDMS	Lipid metabolism	[82]
LPE (20:2)[d]	Increased	Serum, plasma	UPLC-MS	Lipid metabolism	[89]
LPC (17:0)[d]	Decreased	Serum, plasma	UPLC-MS	Lipid metabolism	[89]

[a] Adenine-induced.
[b] NX.
[c] UUO.
[d] Aristolochic acid I-induced.

Table 3
Metabolites and metabolic pathways in CKD.

Metabolites	Trend	Smples	Methods	Related metabolic pathways	References
Arginine[a]	Increased	Plasma	UPLC-HDMS	Arginine metabolism	[17,109]
Citrulline[a]	Increased	Plasma	HPLC-QTOF/MS	Arginine metabolism	[111,112]
Creatinine[a,b]	Increased	Plasma, serum	LC-QTOF/MS	Arginine and proline metabolisms	[133]
Spermidine[a]	Increased	Serum	LC-MS	Arginine and proline metabolisms	[117]
L-asparticacid[b]	Decreased	Plasma	GC–MS	Alanine, aspartate and glutamate metabolisms	[136]
Glycoursodeoxycholicacid[a]	Decreased	Plasma, urine	HILIC/ESI-MS	Bile acid metabolism	[42]
Cinnamoylglycine[a]	Increased	Plasma,urine	HILIC/ESI-MS	Cinnamic acid metabolism	[42]
D-serine[a]	Increased	Plasma	2D-HPLC	D-amino acid metabolism	[113]
D-proline[a]	Increased	Plasma	2D-HPLC	D-amino acid metabolism	[113]
D-asparagine[a]	Increased	Plasma	2D-HPLC	D-amino acid metabolism	[113]
D-alanine[a]	Increased	Plasma	2D-HPLC	D-amino acid metabolism	[113]
Methylhexadecanoicacid[a]	Increased	Serum	UPLC-QTOF/HDMS	Fatty acid metabolism	[123]
Total free fattyacid[a]	Increased	Serum	UPLC-QTOF/HDMS	Fatty acid metabolism	[123]
Glycolicacid[a]	Decreased	Urine	NMR	Glycolate pathway	[114]
Homocysteine[a]	Decreased	Plasma, urine	UPLC-HDMS	Glycine, serine and threonine metabolisms	[111]
2-hydroxyethane sulfonate[a]	Decreased	Plasma, urine	HILIC/ESI-MS	Taurine and hypotaurine metabolisms	[42]
3-methylhistidine[a]	Increased	Plasma	UPLC-QTOF/HDMS	Histidine metabolism	[17]
Indole-3-lactate[b]	Increased	Plasma	GC-TOF/MS	Microbial metabolism	[131]
Pseudouridine[b]	Increased	Serum	CG/LC-MS	Pyrimidine metabolism	[131,134]
P-cresol sulphate[a]	Decreased	Urine	NMR	Phenylalanine metabolism	[114]
Uricacid[b]	Increased	Plasma, serum	NMR/GCTOF/MS	Purine metabolism	[131,133]
Sphingomyelin[a]	Decreased	Tissue	HPLC-QTOFMS	Sphingomyelin metabolism	[124]
Glycine[b]	Decreased	Urine	LC-MS	Serine metabolism	[132]
Serine[b]	Decreased	Urine	LC-MS	Serine metabolism	[132]
Threonine[a]	Decreased	Urine	NMR	Threonine metabolism	[114]
Kynurenicacid[a]	Increased	Plasma	LC-MS	Tryptophan metabolism	[112]
Indoxyl sulphate[a]	Decreased	Urine	NMR	Tryptophan metabolism	[114]
Tryptophan[a]	Increased	Plasma	LC-MS/MS	Tryptophan metabolism	[110]
5-Methoxytryptophan[a]	Increased	Plasma, urine	UPLC-QTOF/HDMS	Tryptophan metabolism	[111]
Tyrosine[b]	Decreased	Urine	LC-MS	Tyrosine metabolism	[132]
Dopamine[b]	Decreased	Urine	LC-MS	Tyrosine metabolism	[132]
Glycerolipids[a]	Increased	Serum	UPLC-QTOF/HDMS	Triglyceride metabolism	[123]
Glycerophospholipids[a]	Increased	Serum	UPLC-QTOF/HDMS	Triglyceride metabolism	[123]
Triglyceride[a]	Increased	Tissue	HPLC-QTOF/MS	Triglyceride metabolism	[124]
Norvaline[b]	Decreased	Plasma	GC/MS	Valine metabolism	[136]
Uracil[a]	Decreased	Urine	NMR	Nucleotide metabolism	[114]
Citrate[a,b]	Decreased	Plasma, serum	NMR/GC–MS	TCA cycle	[114,118,133,135]
Fumarate[b]	Increased	Serum, urine	GC–MS	TCA cycle	[135]
Malate[b]	Increased	Urine	GC–MS	TCA cycle	[135]
Ribonate[b]	Increased	Serum	MS	TCA cycle	[131]
Cis-aconitate[a]	Decreased	Plasma, serum	GC–MS	TCA cycle	[118]
Isocitrate[a]	Decreased	Plasma, serum	GC–MS	TCA cycle	[118]
2-oxoglutarate[a]	Decreased	Plasma, serum	GC–MS	TCA cycle	[118]
Succinate[a]	Decreased	Plasma, serum	GC–MS	TCA cycle	[118]
Ricinoleicacid[a]	Decreased	Plasma	UPLC-QTOF/HDMS	Lipid metabolism	[17]
Stearicacid[a]	Decreased	Plasma	UPLC-QTOF/HDMS	Lipid metabolism	[17]
LPA (16:0)[a]	Increased	Plasma	UPLC-QTOF/HDMS	Lipid metabolism	[17]
LPA (18:2)[a]	Increased	Plasma	UPLC-QTOF/HDMS	Lipid metabolism	[17]
LPC (24:1)[a]	Increased	Serum	UPLC-QTOF/HDMS	Lipid metabolism	[123]
PC (20:2/24:1)[a]	Decreased	Serum	UPLC-QTOF/HDMS	Lipid metabolism	[123]
Ethanolamine[a]	Decreased	Urine	NMR	Lipid metabolism	[114]
Acylcarnitines[b]	Decreased	Plasma	LC-MS	Lipid metabolism	[128]
Phosphatidylcholine[a]	Increased	Tissue	HPLC-QTOF/MS	Phospholipid metabolism	[124]
Choline[a]	Decreased	Plasma	LC-MS	Phospholipid metabolism	[112]
Pregnenolone sulfate[a]	Decreased	Plasma, urine	HILIC/ESI-MS	Steroid metabolism	[42]

[a] CKD.
[b] CKD complication.

Encyclopedia of Metabolic Pathways [53], which are time-consuming and challenging.

3. Recent advances in metabolomics in CKD

Metabolomics has been widely used for identifying metabolites in CKD and its complication in serum, plasma, urine and tissues from both animal models (Table 2) and CKD patients (Table 3). These studies provide new insight into novel biomarker discovery and disease diagnosis.

3.1. Metabolomics in animal models with CKD

Metabolomics has shown great potential in clarifying biomarkers associated with early CKD in animal models, including adenine-induced CKD, aristolochic acid nephropathy (AAN), 5/6 nephrectomized (Nx)-induced CKD and unilateral ureteral obstruction (UUO)-induced renal fibrosis. We revealed metabolic aberrations in the above-mentioned models that might improve CKD diagnosis.

3.1.1. Adenine-induced CKD

Purine metabolism is closely associated with CKD, and adenine plays crucial roles in purine metabolism (Fig. 1). A recent study

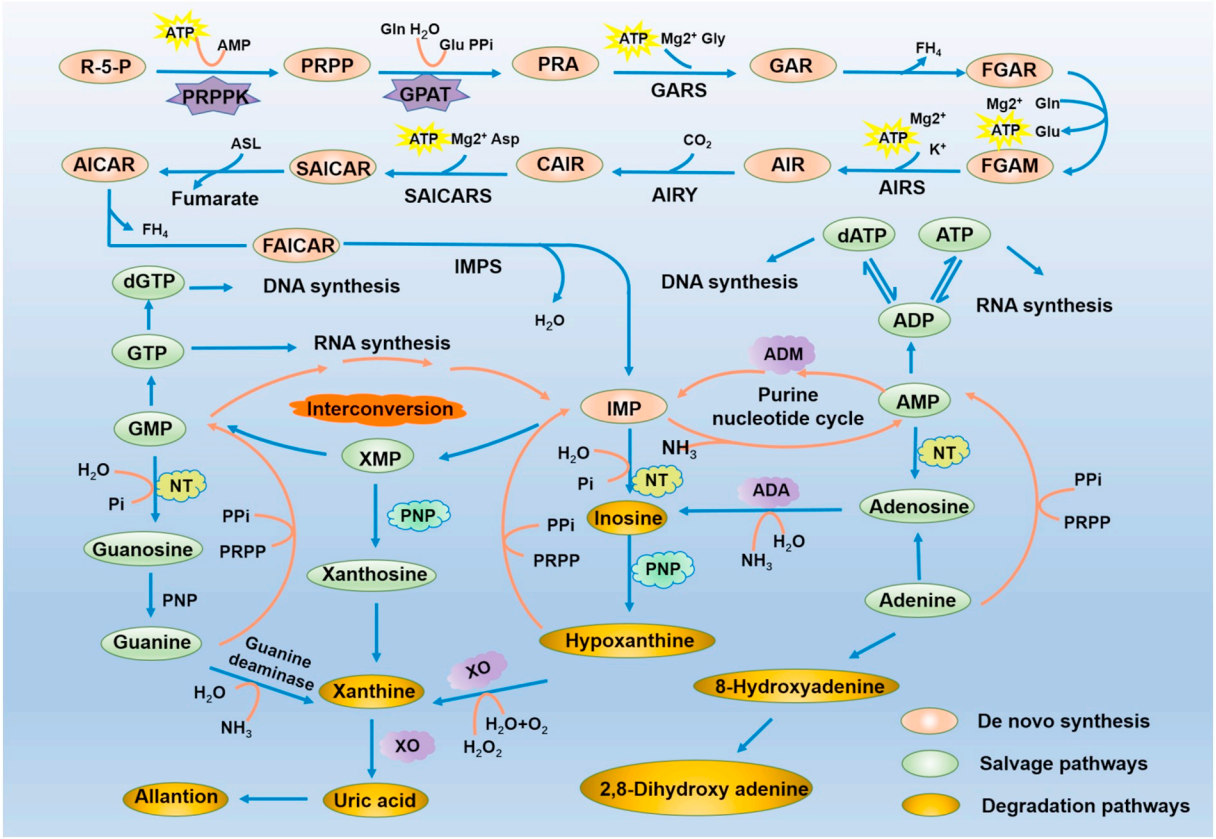

Fig. 1. Abnormal purine metabolism is related to CKD inducedby a variety of factors. Adenine and guanine are metabolized to xanthine via a series of reactions, and ultimately degraded to uric acid to excrete in urine. R-5-P, ribose-5-phosphate; PRPP, 5-phosphoribosyl 1-pyrophosphate; PRA, ribosamine 5-phosphate; GAR, glycinamide ribonucleotide; FGAR, formylglycinamideribotide; FGAM, formylglycinamide nucleotide; AIR, 5-amino-imidazole ribotide; CAIR, 5-amino-imidazole-4-carboxyl ribotide; AICAR, 5-aminoimidazole-4-carboxamide ribotide; SAICAR, N-succinyl 5-aminimidazole-4-carboxamide ribotide; FAICAR, 5-formamidoimidazole-4-carboxamide ribotide; IMP, inosine monophosphate; XMP, xanthosine monophosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; AMP, adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate; PRPPK, PRPP synthase; GPAT, glutamine PRPP amidotransferase; GARS, GAR synthase; AIRS, AIR synthase; AIRY, AIR carboxylase; SAICARS, SAICAR synthase; ASL, adenylate succinate lyase; IMPS, IMP synthase; NT, nucleotidase; PNP, purine nucleotide phosephorylase; XO, xanthine oxidase; ADA, adenosine deaminase.

revealed that adenine-induced CKD was more similar to patients with CKD [54]. Adenine is metabolized to 2,8-dihydroxy adenine in vivo and is insoluble in water and ultimately affects renal function by mediating the excretion of nitrogen compounds and the balance of electrolytes [55]. In adenine-induced CKD rats, UPLC-HDMS was employed for metabolic profiling of urine, plasma, serum, faeces and kidney tissue samples. The findings suggested that CKD was associated with metabolic dysfunction in taurine, choline, purine, amino acid and fatty acid metabolisms [56–59]. Many drugs were used to intervene, and the metabolic aberrations were partially reversed by sitagliptin [60] and AST-120 [61,62]. AST-120, an adsorbent uremic toxin, decreased metabolites in adenine-induced CKD rat tissue and plasma by 55%. Moreover, natural products are also widely used to treat CKD in the clinic [63–73]. Treatment with ergone [74–77], rhubarb [78–81] and *Poria cocos* [82–84] mitigated kidney damage and completely or partially reversed these abnormal changes in metabolites. Significant differences in p-cresyl sulfate and indoxyl sulfate were observed in CKD compared with control rats [85,86]. Compared with control rats, indoxyl sulfate in urine and serum were significantly reduced by 66% and 36%, respectively, and urine paracresol was significantly decreased by 47% in high amylose-starch resistant starch type 2-fed adenine-induced CKD rats [86], suggesting metabolomics is of great significance for exploring abnormal metabolism in CKD induced by adenine.

3.1.2. Aristolochic acid nephropathy

AAN is a progressing tubulointerstitial nephritis that results in ESRD and urothelial malignancy [87,88]. Progressive tubulointerstitial fibrosis (TIF) is one of the pathological characteristics of CKD, which is intimately related to fatty acid metabolism and amino acid metabolism in AAN [89–91]. Metabolomics has been used to identify LPC (15:0), taurochenodesoxycholic acid, docosahexaenoic acid and 12-ketodeoxycholic acid as potential biomarkers of TIF in rats with CKD induced by aristolochic acid I [89]. With the progression of aristolochic acid I exposure, LPC (17:0), chenodeoxycholic acid, LPE (20:2) and cholic acid were recognized as potential biomarkers for the progression of early AAN to late AAN. Furthermore, creatinine, uric acid, indoxyl sulfate and LPE (22:5) were recognized as advanced AAN biomarkers [89]. Collectively, metabolite alterations can be used as potential biomarkers and provide clues that elucidate the underlying mechanism of TIF development. Moreover, these abnormalities were restored by ergone and irbesartan in adenine-induced CKD rats and AAN rats [89], indicating metabolic dysfunction may be a possible therapeutic target for CKD treatment.

3.1.3. Nx-induced CKD

Nx is one of the classic animal models of progressive renal failure created by reducing the nephron [92,93]. The renal mass is reduced by surgically removing both poles, and the contralateral kidney is removed. The remnant nephron undergoes compensatory function and structural adaptation. Glomerular hypertension is one of the main factors leading to kidney injury [94]. Choline metabolism, amino acid metabolism, energy metabolism and oxidative stress play pivotal roles

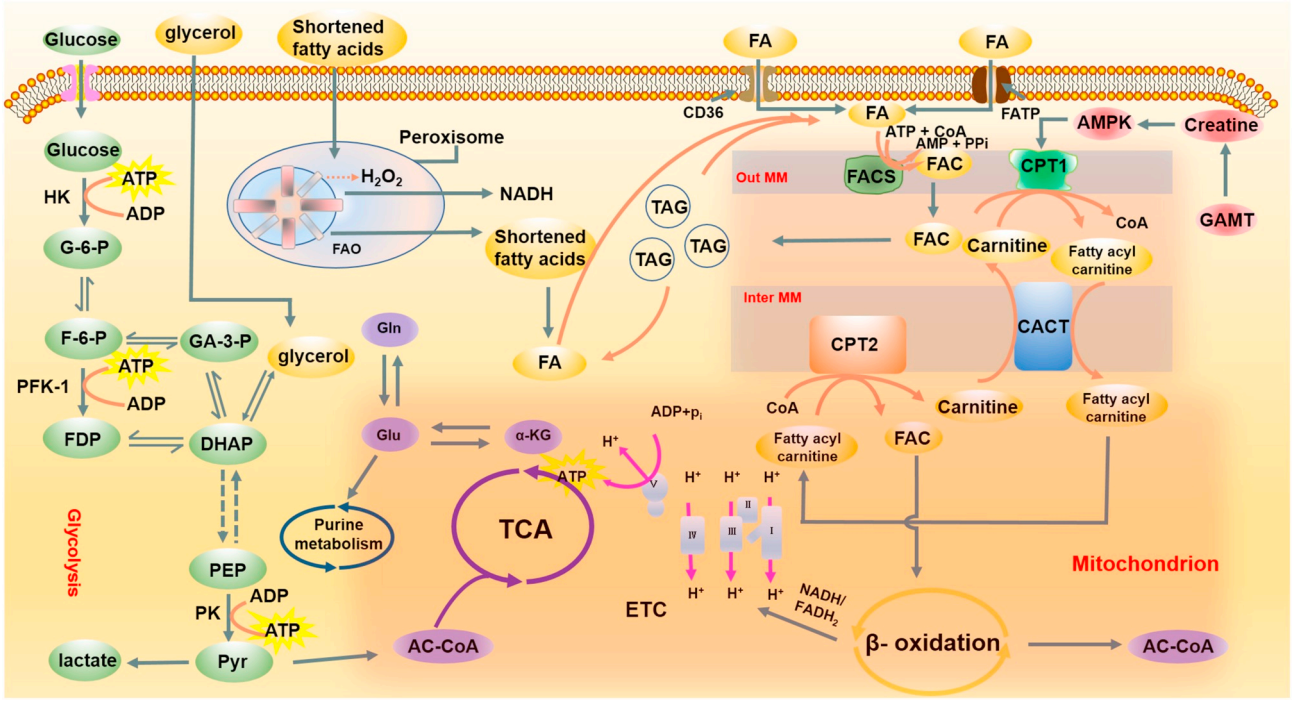

Fig. 2. Progression of CKD was associated with the disorders of fatty acid, glycolysis and purine metabolism as well as TCA cycle. Glycolysis involve in glucose, glyceraldehyde-3-phosphate, pyruvate, lactate etc. The key enzymes in glycolysis pathway are HK, PK and PFK-1, while the key enzymes in β-oxidation are CPT1. Pyruvate is a key metabolite linking glycolysis and TCA. AC-CoA, acetyl CoA;α-KG, α-ketoglutarate; Pyr, pyruvate; Glu, glutamate; α-KG, α-ketoglutarate dehydrogenase complex; G-6-P, glucose-6-phosphoric acid; F-6-P, fructose-6-phosphoric acid; DHAP, dihydroxy acetone phosphate; GDP, glyceraldehyde-3-phosphate; PEP, Phosphoenolpyruvate; GA-3-P, glyceraldehyde-3-phosphate; HK, hexokinase; PFK-1, phosphofructokinase; PK, pyruvate kinase; FA, fatty acid; FATP, fatty acid transport protein; FACS, fatty acyl CoA synthase; FAC, fatty acyl CoA; CPT1, carnitine acyl transferase I; CPT2, carnitine acyl transferase II; CACT, carnitine acylcarnitine translocase; ETC, electron transport chain; TAG, triacylglycerol; AMPK, adenosine monophosphate-activated protein kinase; GAMT, guanylate methyl ester transferase; Out MM, outer mitochondrial membrane; Inter MM, inter mitochondrial membrane.

in CKD and organ dysfunction [15,95,96]. Metabolomics was used to characterize the altered metabolites in Nx-induced CKD rats, particularly to identify specific biomarker associated with early CKD. The latest study demonstrated that significant decline in microbial diversity and richness was accompanied by significant alterations in 291 serum metabolites, which were associated with altered enzymatic activity and dysregulation of lipid, amino acid, bile acid and polyamine metabolisms [94]. Interestingly, the creatinine clearance rate was directly related to several microbial genera and polyamine metabolism. However, systolic blood pressure was directly related to certain microbial genera and glycine-conjugated metabolites in CKD rats [94]. In addition, plasma metabolites, including citrulline, arginine, N-mono-methylarginine (NMMA), symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA), were analysed by isotope dilution LC-MS. Only higher ADMA levels were related to degree of atherosclerosis. CKD mice had high levels of arginine and citrulline. Alterations in accumulation of ADMA and arginine methylation may accelerate atherosclerosis and partly lead to CKD [97], which suggests that the inhibition of pathways in charge of ADMA production or enhancement of its metabolism may have therapeutic potential for reducing atherosclerosis. In addition, metabolomic analyse indicated that glucose 1-phosphate and glucose 6-phosphate were decreased, and the ratio of malate to aspartate was 1.6 times higher than that of sham rats [98]. Therefore, improving glucose 6-phosphate and glucose 1-phosphate levels and malate/aspartate ratio may alleviate the progression of CKD.

3.1.4. UUO-induced renal fibrosis

UUO, a typical TIF model, induces tubulointerstitial inflammation and fibrosis in rats and mice [99–101], which is consistent with the characteristics of obstructive uropathy in humans. The latest study indicated that UUO was related to dysregulation of 219 metabolites in plasma, including lipid, amino acid and bile acid metabolisms [102]. 5-hydroxytryptamine, tryptophan and kynurenine levels were associated with TIF in UUO [102]. Tryptophan in plasma was positively related to *Lactobacillus*, *Pseudomonas*, *Turicibacter* and *Clostridium IV*, but it was negatively related to *Intestinimonas*, *Blautia*, and *Oscillibacter*, which were regulated by genes encoding indoleamine 2,3-dioxygenase, tryptophan synthase, tryptophan 2,3-dioxygenase and their corresponding enzymes (EC:1.13.11.11 and EC:1.13.11.52) that worsen TIF [102]. These findings indicated that metabolites were changed in animal models of UUO, further promoting inflammation and TIF. Moreover, many metabolites have been identified as potential biomarkers, such as citrulline, kynurenine and trimethylamine N-oxide [103]. Evidence revealed that methionine was upregulated and phenylalanine was downregulated [104]. Significant decreases in valine, leucine, phenylalanine and tyrosine were also observed in rats with UUO [104]. The metabolism of UUO in TIF was studied by laser desorption/ionization mass spectrometry, and several specific metabolites were obtained [105]. Zhang et al. demonstrated a panel of biomarkers may perform better than individual biomarkers, among which a combination of L-glutamate, allantoic acid, TG (24:0) and kynurenic acid were recognized to be effective biomarkers [34]. After treatment, UUO-induced metabolic disorders were reversed, and total aglycone extracts of *Scutellaria baicalensis* had a dose-dependent therapeutic effect on TIF. In addition, a panel of TIF-related biomarkers involved in proline, arginine, retinol, threonine and serine, glycine, mannose and fructose metabolisms were identified [106]. Altered metabolites, such as glutamate, acetate, alanine, 3-hydroxybutyrate, isoleucine, pyruvate, acetoacetate, lactate and valine, were observed in UUO rats. Increased ketone body synthesis and lipid metabolic pathways were the main pathways in TIF rats [107]. These metabolites could be used to

diagnose and detect the development of CKD.

3.2. Metabolomics in patients with CKD

Early monitoring of CKD can improve clinical prognosis and ameliorate progression to ESRD. This review presents several potential biomarkers that may be beneficial for diagnosis and prognosis of CKD, including amino acids (valine, alanine, glutamine, glycine, proline, arginine), glycolysis metabolites (glucose, lactate), tricarboxylic acid (TCA) cycle intermediates (succinate, fumarate), organic osmolytes (betaine, myo-inositol, taurine, glycerophosphcholine, TMAO, indoxyl sulfate) and purine metabolites (adenosine monophosphate (AMP), inosine monophosphate (IMP), guanosine monophosphate (GMP)) [15,87,108] (Fig. 2). Based on untargeted metabolomics, five metabolites, including taurine, acetylcarnitine, canavaninosuccinate, 5-MTP and tiglylcarnitine were identified in serum samples from large-scale studies including healthy controls and stage 1-5 CKD patients [37]. 5-MTP was closely related to the development of kidney disease, and its level was significantly decreased with progressive CKD. Furthermore, therapeutic treatment with 5-MTP slowed TIF, enhanced the Keap1/Nrf2 signalling pathway in UUO mice and cultured human kidney cells, and suppressed the IκB/NF-κB signalling pathway [37]. TPH-1 is one of enzymes that participates in 5-MTP synthesis. In the absence of TPH-1, the activation of NF-κB and inhibition of the Nrf2 pathway aggravate kidney damage and fibrosis, whereas overexpression of TPH-1 inhibits renal inflammation and fibrosis to prevent renal injury [37], indicating TPH-1 could be a target for CKD treatment. Moreover, dysfunctional arginine metabolism on adrenal steroid production in plasma was related to CKD stage [109]. Collectively, these findings demonstrated that the metabolites were closely associated with progression of CKD.

CKD results in reduced sensitivity to insulin. Roshanravan et al. studied the metabolomes of plasma from 95 non-diabetic adults who underwent a hyperinsulinaemic-euglycaemic clamp [110]. Differences between CKD and controls included abnormal tryptophan metabolism, TCA cycle and ubiquinone biosynthesis [110]. Significantly increased metabolites in CKD were intermediates of the TCA cycle, such as oxaloacetate and fumarate [110]. Using UPLC-HDMS-metabolomics, Zhang et al. defined 7 metabolites that were able to distinguish CKD patients from healthy subjects, including lysophosphatidic acid (LPA) (18:2), cytosine, stearic acid, ricinoleic acid, arginine acid, LPA (16:0) and 3-methylhistidine. Their specificity and sensitivity ranged from 96.7% to 83.3% [17]. Other studies showed that serum canavaninosuccinate, homocysteine, 5-MTP and leucine were related to both Scr and eGFR [111]. Nine metabolites predicted CKD better than to creatinine, indicating they may act independently of GFR [112]. Choline and citrulline were determined to be markers of kidney metabolism through urine isotope dilution studies, even adjusting for age, eGFR, gender, proteinuria and diabetes at baseline [112]. Chiral amino acids can be used as potential biomarkers for CKD [113]. Enantioselective analysis of all chiral amino acids revealed 16 of the 21 D-amino acids were in plasma from 108 CKD patients. In patients with higher plasma D-serine and D-asparagine levels, the risk of composite endpoints increased from 2.7-fold to 3.8-fold, suggesting that D-asparagine and D-serine were significantly correlated with CKD progression [113].

The imbalance of renal osmotic pressure regulation leads to increasing renal cell damage, which aggravates CKD. Increased urinary renal osmolar concentration could serve as a marker for declining eGFR. For example, increased urinary inositol and betaine levels are important prognostic indicators of the progression of CKD [114]. 3-indoxyl sulfate and creatine are positively and negatively associated with eGFR, respectively. In addition, higher levels of 5-oxoproline and 1,5-anhydroglucitol were robustly correlated with lower risk of CKD, even when they were adjusted for each other [115].

The complex pathological mechanisms of CKD cannot be explained by a single marker due to limited efficiency, such as ADMA and SDMA [116]. Spermidine and the ratio of two metabolites (the kynurenine-to-tryptophan ratio and the phosphatidylcholine acyl-alkyl C36:0-to-phosphatidylcholine diacyl C42:5 ratio) were robustly correlated with annual changes in eGFR [117]. The ratio of kynurenine-to-tryptophan was related to significantly increased CKD incidence [117]. The TCA cycle has the most severe impact on metabolic pathways in CKD patients. Urinary excretion of succinate, 2-oxoglutarate, isocitrate, cis-aconitate and citrate was decreased by 40–68%, while 2-oxoglutarate and urine citrate excretion were significantly increased in patients with CKD receiving a vitamin-D receptor agonist [118]. The above-mentioned findings indicated that these biomarkers promoted diagnosis of CKD and provided a new approach for monitoring the progression of CKD and choosing a therapeutic intervention.

The application of lipidomics in the identification of lipid metabolites also provides novel chances for the detection, classification and prognosis of a myriad of diseases [119–122]. Chen et al. demonstrated that the levels of glycerophospholipids, glycerolipids and total fatty acids in serum were positively related to the increase in serum triglycerides and negatively associated with eGFR by logistic regression analysis [123]. Renal tubular epithelial cells were the main site of toxin-induced lipid accumulation, and lipidomics showed that troxerutin effectively reduced the levels of phosphatidylcholines, triglycerides and phosphatidylethanolamines in nephropathy [124], providing novel insights into the underlying mechanism of toxin-induced lipotoxicity in renal tubular epithelial cells.

3.3. Metabolomics in patients with CKD complications

Metabolomics is promising for the investigation of CKD complications, including CKD with cardiovascular disease and diabetic kidney disease (DKD), which facilitates understanding of disease pathogenesis.

3.3.1. CKD patients with cardiovascular disease

The high and increasing incidence of early-stage CKD contributes to increasing risk for cardiovascular diseases [125–127]. It has been reported that plasma medium-chain acylcarnitines are independently related to cardiovascular events in patients with CKD, which may be used to predict the occurrence of cardiovascular disease in CKD patients [128]. In addition, other studies demonstrated that uremic toxins were significantly increased rather than simply passively accumulated in CKD and coronary artery disease [129]. The urinary metabolites and follow-up for atherosclerosis risk confirmed the association between urinary glycine and CKD.

Hypertension is the main risk factor that causes the decline of renal function. It is the most common complication of CKD [130]. Kim et al. determined the metabolic profile of plasma from patients with polycystic kidney disease [131]. Specific metabolites, such as creatinine, pseudouridine, uric acid (Fig. 1) and isothreonic acid indole-3-lactate, were significantly increased in urine and/or plasma of patients with advanced renal insufficiency in cystic renal diseases and diabetes [131]. Moreover, metabolomics showed that there were significant differences in the distribution of 11 amino acids and urinary excretion in hypertensive nephrosclerosis [132].

3.3.2. Diabetic kidney disease

Compared with patients with advanced CKD, diabetes has a more serious effect on patients with early stage CKD. Metabolites in the serum of pre-dialysis patients with CKD and healthy volunteers were identified by ^{1}H NMR-based metabolomics. DKD was associated with amino acid metabolism, dyslipidaemia and uremic toxin accumulation [133]. In addition, it has been reported that a panel of serum metabolites, including N6-carbamoylthreonyladenosine, *N*-acetyl-serine, pseudouridine, *N*-acetyl-threonine, N6-acetyllysine, O-sulfo-tyrosine, and C-glycosyl-tryptophan, were related to reduced incidence of ESRD in patients with CKD and type 1 diabetes [134]. Urinary citrate was significantly reduced, and malate, fumarate and lactate were robustly elevated in patients with CKD [135]. Malate and fumarate both can

predict progression of CKD (independent of eGFR and albuminuria) [135]. In particular, fumarate may participate in pathophysiological pathways apart from risk factors for traditional heart and kidney diseases, resulting in progressive CKD in type 2 diabetes mellitus patients [135]. Moreover, the declines in l-aspartic acid, norvaline and 1,5-anhydroglucitol were related to the progression of macroalbuminuric DKD [136]. These hyperglycaemia-associated biomarkers will provide further information DKD diagnosis.

4. Conclusion

With advances in analytical technology, metabolomics has been widely used with many renal diseases in recent years. Metabolomics in CKD and its complications revealed that the development of CKD was closely correlated with dysfunction of lipid, carbohydrate, amino acid and nucleic acid metabolisms and the TCA cycle, which offers a powerful implement in understanding the pathogenesis of CKD and developing new therapeutic strategies. Numerous studies demonstrated that metabolomics was of great significance and had high accuracy, specificity and sensitivity for biomarker identification for CKD diagnosis. Of note, single biomarkers were incapable of diagnosing disease and clarifying mechanisms. Therefore, a panel of biomarkers is strongly recommended. In addition, a combination of biomarkers with clinical indexes could improve CKD prediction. Unfortunately, metabolites in patients at different stages of CKD need to be further determined due to the limited number of studies. Notably, although metabolomics has made breakthroughs in biomarker validation, clinical application is still in its infancy. Once obstacles have been removed, utilizing metabolites to monitor the progression of CKD will be possible.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Nos. 81673578, 81872985).

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