Metabolomic and lipidomic approaches to identify biomarkers for bladder cancer and interstitial cystitis (Review)

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Abstract. The discovery, introduction and clinical use of prognostic and diagnostic biomarkers has significantly improved outcomes for patients with various illnesses, including bladder cancer (BC) and other bladder-related diseases, such as benign bladder dysfunction and interstitial cystitis (IC). Several sensitive and noninvasive clinically relevant biomarkers for BC and IC have been identified. Metabolomic- and lipidomic-based biomarkers have notable clinical potential in improving treatment outcomes for patients with cancer; however, there are also some noted limitations. This review article provides a short and concise summary of the literature on metabolomic and lipidomic biomarkers for BC and IC, focusing on the possible clinical utility of profiling metabolic alterations in BC and IC.

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1. Bladder cancer

Bladder cancer (BC) is the most common malignancy of the urinary tract. In 2018, there were ~549,000 new cases of BC and 200,000 deaths related to BC globally (1). BC is the eighth most common cancer among men in the US (2) and is reported to affect men more frequently than women, with a ratio of 3.2:0.9 (1,2). In addition, the incidence of BC increases with age (3). According to the European Association of Urology, BC can be classified into two divergent phenotypes: Non-muscle-invasive BC (NMIBC) and muscle-invasive BC (MIBC). Furthermore, BC can be categorized into the following subtypes: Urothelial carcinoma, squamous epithelial carcinoma and adenocarcinoma (1-3). Urothelial carcinomas account for an overwhelming 90% of worldwide BC cases (4). Risk factors for BC include occupational factors, age, sex, race, socioeconomic status, personal health, diet and infection by pathogens (5-7). It is well-established that the progression of a normal cell to a cancer cell is a multistep process involving the accumulation of genetic alterations, referred to as carcinogenesis. NMIBC generally involves the mutation of fibroblast growth factor receptor 3 (*FGFR3*), giving rise to low-grade cancer that frequently recurs but seldom becomes invasive or progresses. By contrast, MIBC and carcinoma *in situ* exhibit deletions or mutations of *TP53*, RB transcriptional corepressor 1 (*RB1*), erb-b2 receptor tyrosine kinase 2 or *PTEN*, leading to high-grade and metastatic cancer (8). The emergence of high-throughput transcriptome sequencing techniques has assisted in the identification of versatile BC biomarkers, including long non-coding RNAs (lncRNAs), the aberrant expression of which can contribute to tumorigenesis in bladder tissues (9). lncRNA abhydrolase-domain containing 11 antisense RNA 1 (ABHD11-AS1) and lncRNA hypoxia-inducible factor 1α antisense RNA 2 (HIF1A-AS2) have been reported to be upregulated in BC tissues and cells,

and their expression levels in tissues have been shown to be positively associated with advanced pathological grade and TNM classification (10,11).

2. Recently reported molecular subtype classification of BC

Classification systems for cancer are mainly based on pathological parameters, such as stage and grade. Such classification provides predictive prognostic information; however, for BC, recurrence and progression vary widely from patient to patient, greatly affecting monitoring and treatment (12). The development of advanced techniques, such as sequencing and mass spectrometry (MS), and their implementation in omics, has provided better diagnostic and therapeutic information for the treatment of BC (13-16). Molecular subtyping, which is based on genetic characteristics, has made particularly notable progress in BC and is of increasing interest (17). The current molecular subtypes of BC share various characteristics, such as molecular features. However, these classifications can also vary, with two to seven distinct subtypes (18-20). As a result of this diversity, molecular classifications are not feasible for use in the clinical setting. This also highlights the need for a consensus on a single set of molecular subtypes that is applicable to clinical use. Nevertheless, the understanding of the biology of BC has been substantially improved by key achievements in molecular classification; for example, associations have been identified between molecular subtypes and urothelial differentiation, and similarities have been noted between BC subtypes and other types of cancer.

The first study into BC subtyping using molecular signatures was conducted at the University of Lund. This previous study examined the transcriptomes from 308 BC samples, identifying five different subtypes: Urobasal A, genomically unstable, urobasal B, squamous cell carcinoma-like and infiltrated (2). In addition, two subtypes of high-grade MIBC were identified by examining published data from 262 BC samples (18). The expression levels of keratin and *CD44* were analyzed, which were found to be related to differentiation of the urinary epithelium. Owing to similarities with expression profiles in breast cancer, these two molecular subtypes were named luminal-like and basal-like. Case studies of the luminal-like subtype revealed that it had much higher disease-specific and overall survival rates compared with the basal-like subtype, and the following transcription factors were enriched: *FGFR3* and tubercular sclerosis 1. Specific changes were also noted in various pathways, including deletion mutations in the RB1 pathway and amplification of cyclin D1, E2F transcription factor 3 and cyclin E1 (18). In 2014, the MD Anderson Cancer Center analyzed mRNA expression patterns in 73 MIBC samples using molecular signatures identified from breast cancer studies. This led to the identification of three BC subtypes: Luminal, p53-like and basal (19). In addition to the aforementioned studies, The Cancer Genome Atlas (TCGA) has greatly improved biological databases and led to the updating of subtypes. Through genetic analysis of 129 patients with MIBC, TCGA identified four molecular BC subtypes: Clusters I, II, III and IV (20). This classification system was updated to include luminal, immune undifferentiated, luminal immune and basal subtypes based on genetic signatures, such as uroplakins and immune infiltration. Upon analysis of an additional 412 MIBC cases, TCGA classification of BC was further updated and consolidated into five subtypes: Luminal, luminal-infiltrated, basal-squamous, neural and luminal-papillary (21).

3. Interstitial cystitis

Interstitial cystitis (IC) is a chronic condition of unknown etiology with long-term notable pelvic/suprapubic pain and urinary storage symptoms, such as urgency, nocturia and frequency (22). The advent of cystoscopy led to major findings in IC, including bladder glomerulations during hydrodistention and Hunner's lesions (23). Although the epidemiology of IC is difficult to monitor due to its plethora of symptoms, recent studies have suggested an estimated prevalence of 100-300 per 100,000 women, and the prevalence rate is ≥10-20% lower in men (24,25).

IC is generally diagnosed through exclusion; however, several attempts have been made to define standard diagnostic criteria. Recent guidelines set by the European Society for the Study of Interstitial Cystitis and the American Urological Association are currently being used worldwide to treat IC (26). Although treatment options for IC are limited and include hydrodistention, several oral pharmaceutical drugs have been approved by the US Food and Drug Administration, including pentosan polysulfate (elmiron), antihistamines, tricyclic antidepressants and immune modulators (27).

Owing to its unknown etiology, and large variability in sites of occurrence and symptom severity, IC is difficult to subtype. However, there is still an urgent need for a well-established and precise subtyping system. A recent study revealed that IC with Hunner's lesions displayed completely different histology, gene expression and prognoses compared to other forms of IC (28). IC can also be defined as a distinct non-inflammatory disorder characterized by preservation of the urothelium layer and symptom spread beyond the bladder without lesions (29).

4. Metabolomics and lipidomics

Metabolomics. Metabolomics is defined as the large-scale study of small molecules and metabolites involved in the regulation of metabolic pathways and their networks. Compared with genomics and proteomics, metabolomics is more closely linked to phenotypes; therefore, it can detect subtle changes in biological pathways under different physiological conditions and abnormal pathological processes. For the purposes of this review, we will focus on the application of metabolomics and lipidomics to BC.

The aim of precision medicine is to create novel approaches to prevent disease and update clinical strategies to consider each individual's variability in terms of environment, lifestyle, genetics and molecular phenotypes (30). Metabolomics holds much promise for precision medicine and can be used to measure all metabolites in biological specimens (31). However, metabolomics presents significant analytical challenges over genomics and proteomics; it aims to measure molecules that range in polarity, from organic water-soluble acids to nonpolar lipids, which have disparate physical properties (32). As a complement to other omics techniques, metabolomics serves as a critical component of systems biology. Moreover, the study of

metabolites and molecules is closely related to phenotypes and can improve understanding of intracellular metabolic alterations (31). The main aim of metabolomics is to identify altered metabolic pathways and biomarkers (33). Recent developments in metabolomics and statistical capabilities have improved the ability to investigate cancer metabolism and better understand cancer-related changes in metabolism, such as the conversion of glucose into the macromolecules needed for tumor cell proliferation and vascularization (34-36).

Lipidomics. Lipids are essential building blocks in the body that have several critical cellular functions and can provide information regarding ongoing lipid metabolism. The lipidome is the total lipid content in a cell (37). The emergence of lipidomics allows for the complete characterization of the cellular metabolome. Lipidomics may be the potential key to numerous metabolic diseases and can be utilized in several research areas, as well as in the development of diagnostic tools, drugs and therapeutic strategies (38). Lipidomics combined with bioinformatics can serve as a powerful tool for better understanding the biochemical mechanisms underlying lipid-related diseases by quantifying alterations in the levels of individual lipids, subclasses and molecular species, and identifying changes in pathways and networks (37). The emergence of metabolomics and lipidomics has enabled improved definition of differential metabolites in pathological conditions. Over the past two decades, metabolomics and lipidomics have seen significant advances, facilitated by rapid developments in novel analysis strategies, approaches, instruments and techniques (39).

5. Emerging technologies

Current development of methodologies. The physicochemical properties of all metabolites add additional complexity to metabolomics studies. To overcome these restrictions, various methods have been applied to overcome this complexity and challenges. MS and nuclear magnetic resonance (NMR) are the most frequently applied analytical approaches in metabolomics studies.

NMR spectroscopy. NMR is a nondestructive, nonbiased, easily quantifiable, fast and reproducible spectroscopy technique based on the principle that nuclei absorb and emit electromagnetic signals based on changes in the external magnetic field. NMR has several unique advantages in metabolomics (40). Metabolomics profiling by NMR is a powerful tool that can be used to diagnose a variety of diseases. NMR is based on the fact that nuclei, such as ^1H, ^{13}C and ^{31}P, have nuclear spins and are able to exist at different energy levels in a magnetic field. Thus, these nuclei can generate valuable and identifiable information about metabolites. ^1H NMR is the most commonly used technique in metabolomics since ^1H is naturally abundant in biological samples. ^{13}C and ^{31}P NMR are used less frequently but can provide additional information on specific metabolites (40).

MS. MS-based metabolomics offers quantitative analysis of metabolites, ranging from measurement of a single molecule to thousands, with high selectivity and sensitivity. The combination of MS with separation techniques reduces the complexity of mass spectra by separating metabolites based on time, providing isobar separation and delivering additional information regarding physicochemical properties. To calculate the mass-to-charge ratio (m/z), MS acquires spectral data and relative intensity of the measured compounds. One potential drawback of MS-based techniques is the need for sample preparation, which can lead to potential loss of metabolites, changes in experimental conditions, discrimination of specific metabolite classes and other consequences (41,42).

MS can effectively analyze small molecules separated by techniques, such as gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis. LC-MS and GC-MS can provide large amounts of chemical information for metabolomics studies. GC-MS uses the gaseous phase and achieves better metabolite separation than LC; however, unlike LC, GC typically requires chemical derivatization of the metabolic species prior to analysis. GC-MS is widely used in metabolomics studies as it can detect a wide range of intact metabolites with no need for chemical modification. For the separation of nonpolar to slightly polar molecules, traditional reverse-phase chromatography is used. Hydrophilic interaction LC is the technique of choice for separating strongly to slightly polar metabolites (41,42).

Advantages and disadvantages. For metabolomics studies, each analytical technique has its own advantages and limitations. No single instrument or method can detect all metabolites accurately. Therefore, multiple methods and instruments are recommended to detect the greatest number of metabolites. For example, the Phenome Centre Birmingham utilizes LC-MS and NMR spectroscopy for metabolomic profiling and is able to detect a higher number of metabolites compared with using a single method alone (https://www.birmingham.ac.uk/ research/activity/phenome-centre/about/index.aspx). Owing to the complexity of the metabolome, no single analytical method can fully discern the metabolome. NMR and MS each have their own strengths and weaknesses, which are described in previous publications (41-43).

6. Applying metabolomics and lipidomics to BC

Applying metabolomics to BC. To diagnose initial or recurrent BC, two standard diagnostic procedures are used: Cystoscopy and urine cytology. However, there are several limitations (43). As a result, there is an urgent need for a noninvasive, highly-sensitive, specific and convenient method for BC diagnosis. Urine is particularly suited for diagnostic purposes due to its availability, easy sample collection and storage in the malignant bladder (42,44).

Both MS and NMR are used to analyze the metabolic profile and have become critical techniques for quantitatively and qualitatively measuring the metabolome. Both techniques allow for extensive and rapid analysis of small-molecule metabolites (45). Metabolomics can be useful in cancer research, demonstrating its potential for not only identifying candidate biomarkers but also elucidating the mechanisms underlying cancer pathogenesis. Metabolomics has already been applied to several cancer types with encouraging results, including breast, prostate, lung and liver cancer (46-50). Sahu *et al* (51) identified metabolic signatures, including those
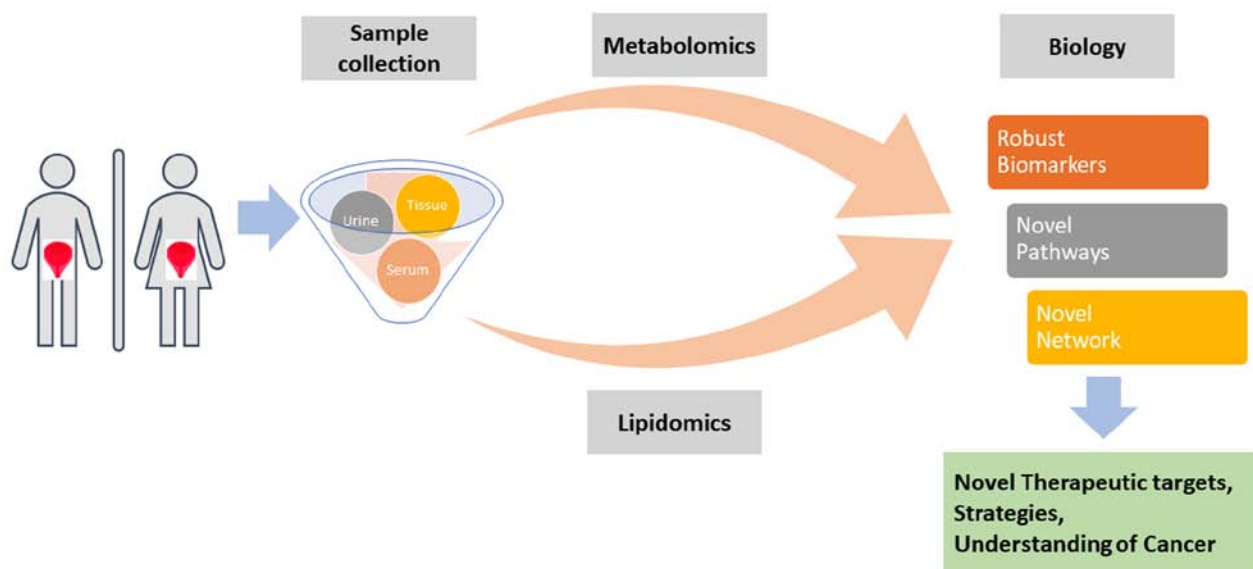
Figure 1. Biomarker discovery in the clinical setting. The field of metabolomics and lipidomics has advanced with respect to technological development. Large-scale datasets can help provide systems-scale information regarding diseases with inputs from metabolomics- and lipidomics-based analyses, which provide insightful biological data. This data can lead to robust and valid individual specific biomarkers for novel disease-specific pathways and networks. The application of new analytical technologies in omics studies should provide new information about promising drug therapeutics and improve understanding of the diseases.

for glucose, the tricarboxylic acid (TCA) cycle, lipids, amino acids and nucleotide pathways, by profiling the global metabolome using GC-MS and LC-MS. The results of this previous study revealed alterations in numerous pathways between normal urothelium and high-grade urothelial carcinoma at different stages. Recently, novel analytical methods have been developed using reverse-phase-high performance LC coupled with triple quadrupole MS for quantitatively determining and validating previously identified BC metabolites (52,53). Clinical validation has previously been performed using urine samples from 40 patients with BC and matched controls, and suggested that the recovery and precision values were within the ranges set by FDA guidelines (52). Jin *et al* (53) performed LC-MS-based profiling of metabolites and identified distinctive metabolites in 138 BC samples and 121 controls. This previous study identified 12 putative glycolysis- and β-oxidation-related markers. Multivariate regression analysis was then applied to confirm the association between the metabolic profiles and survival.

Applying lipidomics to BC. Current technologies allow for lipidomic analysis of a wide variety of biological specimens derived from animal models and clinical samples (54). The most appropriate analytical technique is selected based on the characteristics of the biological sample and the chemical properties of the targeted lipids. NMR and MS are accepted as the most powerful tools for phospholipid structure identification (55). Owing to structural diversity across phospholipid classes, analytical methods for lipidomics are continuously being improved. Notable progress has been made in lipid research by coupling MS with chromatographic separations. Soft ionization techniques, including matrix-assisted laser desorption/ionization and electrospray ionization (ESI), are good examples (56). Dill *et al* (57) used desorption ESI-imaging MS to investigate lipid species as diagnostic

biomarkers of human BC compared to adjacent normal bladder tissue samples. The results revealed significant differences in the levels of glycerophosphoinositols, glycerophosphoserines, and fatty acids in tumor tissues compared with those in normal samples. Our group previously used ultra-performance LC-MS (UPLC-MS) to identify 1,864 differentially expressed lipids in cisplatin-resistant BC cells (58). Another of our lipidomics studies on cisplatin resistance of BC demonstrated that acyl-CoA synthetase short chain family member 2 inhibition perturbed lipid metabolism, suggesting that cisplatin-resistant BC may have a specific lipidomic profile (58). Previously reported metabolomic biomarker candidates are summarized in Table I.

7. Applying metabolomics and lipidomics to IC

Applying metabolomics to IC. Chronic bladder pain is a hallmark of IC. Metabolomics studies can be used to analyze the characteristics of the disease state and identify novel approaches for reducing symptoms (41). Kind *et al* (59) performed global metabolomics profiling using various platforms, including NMR and LC-MS. Utilizing urine from patients with IC, this previous study profiled 490 metabolites, including histidine, erythronic acid and tartaric acid, and identified those with the highest fold changes. The identified metabolites were found to be associated with IC, suggesting its possible clinical use in urinary IC diagnosis. Using an MS-based metabolomics approach, the central clinical protocol of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, the Trans-MAPP Epidemiology and Phenotyping discovered urinary biomarkers in female patients with IC who underwent extensive urologic and non-urologic phenotyping (60). Parker *et al* (61) used LC-MS to identify molecular correlates of IC from urine obtained from female patients. This previous study identified a novel biomarker, etiocholan-3α-ol-17-one sulfate (Etio-S), a steroid metabolite,

Table I. List of metabolomic biomarkers in BC.

First author, year	Biomarker	Method	Sample size	Sensitivity (%)	Specificity (%)	AUC	Notes	(Refs.)
Pasikanti et al, 2013	2,5-furandicarboxylic acid, ribitol and ribonic acid	GCxGC/ TOFMS	38 BC, 61 Controls	71	100	-	Decreased	(70)
Wittmann et al, 2014	Taurine	MS	95 BC, 345 Controls	-	-	-	Increased	(68)
Srivastava et al, 2010	Taurine	NMR spectroscopy	33 BC, 37 Controls	-	-	-	Increased	(65)
Jin et al, 2014	Glycolysis and acylcarnitines	LC-QTOFMS	138 BC, 121 Controls	85-91.3	85-92.5	0.93	Increased	(53)

BC, bladder cancer; AUC, area under the curve; GC, gas chromatography; MS, mass spectrometry; LC-MS, liquid chromatography-MS; NMR, nuclear magnetic resonance; GCxGC/TOFMS, two-dimensional GC time-of-flight MS; LC-QTOFMS, LC-quadrupole time-of-flight MS.

as being associated with a phenotypic subgroup of highly symptomatic IC. To the best of our knowledge, there are no reports in the literature involving the use of lipidomics to identify lipid compounds associated with IC.

8. Human specimens-based metabolomics and lipidomics biomarkers for BC

Diagnosis of BC is dependent on several variables, including sensitivity and specificity of the methods, the invasiveness of the procedures and cost. Currently, cystoscopy and urine cytology are the most commonly used methods; however, both have several critical drawbacks, the most important being their limitations for detecting early BC (62). Overall survival in BC is highly dependent on early detection (62). The discovery of clinically relevant BC biomarkers will provide clinical value for prognostication, stratification, and identification of patients at higher risk for recurrence and progression. It is only through these outcomes that better management and treatment of patients with BC can be achieved (50). Zhang et al (63) compiled the results of previous metabolomics studies to discover BC biomarkers using urine, blood, tissue and cell lines. However, there is still a lack of consensus surrounding the pathophysiology of BC. Thus, there is a great need for noninvasive markers to differentially diagnose BC (64).

BC biomarkers
Human urine. Numerous studies have reported that biomarkers can be identified using metabolomics, and recent studies have identified biomarkers that are capable of detecting early BC and predicting response to chemotherapy or relapse (53,65-70). Some diagnostic biomarker studies have already compared the metabolic profiles of urine samples from patients with BC and healthy controls. Using ¹H NMR, Srivastava et al (65) revealed significant differences in the urine concentrations of hippurate, citrate and taurine in patients with BC compared with those in healthy controls. Jin et al (53) hypothesized that patients with BC could be distinguished from healthy controls

based on metabolic profiles. This previous study revealed that the metabolic components of glycolysis and acylcarnitines were increased in MIBC compared with those in NMIBC. Citrate levels, a key metabolite of the TCA cycle, are altered in BC (66). Other urinary metabolites, including citrate, succinate and hippurate, have also been shown to be reduced in BC compared with those in healthy controls (67,68). Shen et al (69) also identified three upregulated and downregulated metabolites in BC: Nicotinuric acid, trehalose and AspAspGlyTrp were upregulated, whereas inosinic acid, ureidosuccinic acid and GlyCysAlaLys were downregulated. Several other studies have confirmed these results (70). The major findings from these studies are listed in Table I.

Tissue samples. Putluri et al (71) identified LC-MS-based metabolomic signatures using BC tissue samples, benign adjacent tissues and healthy controls. This previous study aimed to identify potential biomarker candidates and identify biology-related processes in BC carcinogenesis. A total of 50 metabolites with significant differences between BC and healthy controls were detected. Tripathi et al (72) performed high-resolution magic angle spinning NMR analysis of benign and BC tissues. The results revealed that BC exhibited more metabolic abnormalities compared with benign or healthy samples. These results identified 22 clearly differentiated metabolites. Using the same tissue samples, these results were cross-validated via targeted GC-MS analysis, demonstrating the potential of these biomarkers in clinically diagnosing BC. Yang et al (73) examined 48 BC tissue samples treated with gemcitabine as well as adjacent normal tissues from 12 of those patients. Based on UPLC-Q-Exactive-MS analysis, 34 significantly altered metabolites were found to be associated with BC.

Blood serum samples. Blood serum-based studies have established ways of distinguishing patients with BC from healthy controls. Cao et al (74) examined the serum profiles of patients with high- or low-grade BC; in addition, patients with urinary calculi (hematuria) were included in the control group.

Table II. List of metabolomic biomarkers in IC.

First author, year	Biomarker	Method	Sample size	Sensitivity (%)	Specificity (%)	AUC	Notes	(Refs.)
Parker *et al*, 2016	Etiocholan-3α-ol-1 7-one sulfate	MS	40 IC, 40 Controls	87.4	0.92	0.92	Increased	(61)
Kind *et al*, 2016	Erythronic acid, histidine and tartaric acid	GC/MS	42 IC, 21 Controls	-	-	0.9	Increased	(59)
Wen *et al*, 2015	tyramine and 2-oxoglutarate	NMR	43 IC, 21 Controls	-	-	-	Increased	(76)
Shahid *et al*, 2018	Menthol	GC-TOF-MS	10 IC, 10 Controls	-	-	-	Decreased	(79)

IC, interstitial cystitis; AUC, area under the curve; GC, gas chromatography; MS, mass spectrometry; NMR, nuclear magnetic resonance; GC-TOFMS, GC time-of-flight MS.

Statistical analysis revealed that the serum profiles of patients with BC differed from those of healthy controls and those of patients with calculi. Serum metabolic profiles also allowed for classification of low- and high-grade BC. The levels of isoleucine/leucine, tyrosine, phenylalanine, choline, lactate, glycine and citrate were also shown to be significantly lower in patients with BC compared with those in healthy controls, whereas lipid and glucose levels were higher in patients with BC. Notably, additional comparisons of metabolite levels between patients with low- and high-grade BC revealed that the levels of tyrosine, phenylalanine, lactate and glycine were comparatively higher in low-grade patients, whereas glucose levels were lower. In addition, Bansal *et al* (75) used blood serum samples from patients with low-grade and high-grade BC and healthy controls. A total of six metabolites, dimethyl-amine, malonate, lactate, glutamine, histidine and valine, were significantly altered in BC samples compared with those in controls. Notably, external validation via a double-blind study consisting of 106 patients with suspected BC confirmed the utility of these metabolites for early diagnosis of BC.

9. Human specimens-based metabolomics markers in IC

IC can present as a long continuum of mild to severe symptoms. In recent years, novel metabolomic techniques have been applied to gain a better understanding of disease mechanisms and uncover novel biomarkers (76). A previous study applied UPLC-MS-based metabolomics to examine urine samples from 10 patients with IC and 10 healthy controls. Phenylacetylglutamine was identified as a urinary marker of IC and was revealed to be elevated in the urine of patients with mild-to-moderate IC (77). In a separate study, Parker *et al* (61) used LC-MS to profile the metabolomes of urine samples from 40 patients with IC and matched controls. The results identified six metabolites as being closely associated with IC pathogenesis; one of which was Etio-S. Further analysis demonstrated that elevated Etio-S was a good predictor of IC, with sensitivity of 91.2%, specificity of 87.4%, and area under the curve of 0.92. Longitudinal analysis of women

in this cohort demonstrated that the differences in Etio-S persisted, indicating that these changes were long-lasting.

Taking an untargeted comprehensive metabolomic profiling approach, Kind *et al* (59) performed GC-MS analysis on urine specimens from patients with IC and healthy donors, and identified a total of 490 differentially expressed metabolites. Furthermore, Lamale *et al* (78) used urine samples from 40 women with IC and 29 healthy controls collected within a 24-h time frame. They discovered higher expression of three inflammatory markers, histamine, methylhistamine and IL-6, in patients with IC compared with those in the controls. In our previous biomarker discovery study, NMR-based global metabolomics analysis was applied to urine samples obtained from female patients with IC and matched healthy controls. The levels of tyramine and 2-oxoglutarate were significantly elevated in the IC urine specimens (76). Furthermore, in another of our previous studies, comprehensive solid-phase microextraction-GC-time-of-flight-MS profiling combined with bioinformatics analysis revealed that levels of volatile urinary metabolites, including menthol, were significantly reduced in patients with IC compared with those in normal controls (79). Previously reported metabolomics-based IC biomarker candidates are presented in Table II.

10. Conclusion

The present review aimed to understand the current development of biomarkers for bladder diseases based on various bioresources. In recent years, metabolomics and lipidomics has been widely used to understand the clinicopathology of the bladder and to discover the key differentially expressed metabolites or lipids specifically associated with bladder diseases. To determine the biological implications of metabolomic lipidomic signatures, bioinformatics tools, such as network and pathway enrichment analyses have been applied. The present review provided an overall summary of the metabolomics and lipidomic-based biomarker candidates for IC and BC (Fig. 1).

Availability of data and materials

Not applicable.

Authors' contributions

Research conception and design: JK. Data acquisition, data analysis and interpretation: MS and AY. Drafting of the manuscript: MS and AY. Critical revision of the manuscript: JK. Supervision: JK. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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