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REVIEW

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Metabolomics and biomarkers for lupus nephritis – a systematic review

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Abstract

Background The development of personalized medicine using high-throughput methods, such as metabolomics profiling, in discovering and validating biomarkers, may play a key role in the development of new and non-invasive methods for diagnosis and understanding of lupus nephritis (LN).

Objectives The aim of this systematic review was to present the current status of metabolomics discovery of biomarkers applied to diagnosing, staging, understanding and treating LN.

Methods The review was made according to PRISMA guidelines, searching for keywords associated to "Lupus", "Lupus nephritis", "Metabolomics" and their variants, with no language restriction, in PUBMED, MEDLINE and EMBASE databases. Full-texts and primary studies in humans including the topics of lupus erythematosus and/or lupus nephritis and used metabolomics in urine and serum as a research method, were included and data analysis was performed individually.

Results The search revealed multiple candidates for the diagnosis, staging and prognosis of lupus nephritis, such as citrate, acetate, N-acetyl glycoproteins and various amino acids, as their level in the biofluids of LN patients found in the studies are consistent with the known pathophysiology of LN and inflammatory processes.

Conclusions The study of metabolomics associated with LN still needs further investigation concerning metabolic pathways and pathogeny. As the community building the databases for the research and annotation of metabolites grow, the use of serum, urine, and saliva in metabolomic profiling, may become a potential non-invasive method in translational medicine studies.

Keywords Lupus nephritis, Metabolomics, Chronic kidney disease, Research, Review

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune and multifactorial disease, with a prevalence of 10 to 400 per 100,000 in the United States of America. It occurs predominantly in women of childbearing age and, although its aetiology is not thoroughly known, its genesis involves genetic, hormonal, environmental and immunologic factors, with the activity of autoantibodies directed especially against nuclear antigens – some of which participate in tissular lesions immunologically mediated. Extrinsic factors such as ultraviolet radiation and drugs can also trigger

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manifestations of the disease. In most patients, the autoimmune reaction begins years before the first clinical symptoms, which emerge in different ways, affecting multiple systems (Ghodke-Puranik and Niewold 2015; Louis and Fernandes 2001).

A most severe and threatening manifestation of SLE is kidney involvement, which characterizes lupus nephritis (LN). Around 50% of SLE patients present with renal manifestations, such as oedema, hypertension, proteinuria, urinary sediment abnormalities and compromised renal function. If not properly treated, this condition can lead to end-stage kidney disease, requiring renal replacement therapy (Kalantari et al. 2019; Romick-Rosendale et al. 2011; Li et al. 2017; Guleria et al. 2016). Concerning the pathogeny of LN, it involves antibodies binding to intrarenal autoantigens, immune complexes deposing in the glomeruli and inflammatory cells infiltrating in the renal parenchyma. Nevertheless, the immune-pathological pathways involved in the disease are not completely unravelled (Kalantari et al. 2019; Klocke et al. 2017).

The evaluation of LN disease activity is currently based on clinical, laboratory and imaging features, upon which a score is defined. This method has considerable limitations, once it relies on unspecific and subjective variables (Julià et al. 2016). The gold standard for its diagnosis, staging and prognosis is kidney biopsy. However, this procedure, due to its invasiveness and intrinsic risk of complications, presents restrictions for serial monitoring of patients (Li et al. 2017). Therefore, novel less invasive diagnostic and staging methods for LN might engender new horizons for better prognosis and more effective and well-aimed treatment options and research, improving the quality of life and diminishing the risks for LN patients. In this scenario, metabolomics offers a new technical framework for the identification of biomarkers, establishing additional bases for the evaluation of the disease (Yan et al. 2016).

Metabolomics is the quantification of small molecules, metabolites, in biological specimens, including fluids such as blood, urine and saliva. It appertains to the "omics" methods, beside genomics, transcriptomics, and proteomics. It permits the assessment of bodily components through non-invasive methods, and its analyses generally involve liquid or gas chromatography, and mass spectrometry (MS) or nuclear magnetic resonance (NMR). Concerning the latter, for the analysis of biological fluids NMR does not require chemical manipulation of a sample, whereas MS usually demands previous ionization. MS is more sensitive and its analyses encompass a wider range of metabolites (Shah et al. 2012).

Metabolomics has already been used for the diagnosis of various diseases, and could represent an auspicious method for assessing LN as it may suggest biomarkers for the disease and help to understand the metabolic pathways involved in its pathogenesis through the analysis of biofluids (Kalantari et al. 2019). Both urine and serum are biofluids whose collection is simple and minimally invasive, turning them into good choices for metabolomics applied to LN (Julià et al. 2016).

In this review, we present the current status of metabolomics applied to diagnosing, staging, understanding and treating LN.

Methods

The review was made according to PRISMA guidelines (Moher et al. 2009) [see Additional file 1]. The search strategy comprehended the keywords associated to "Lupus", "Lupus nephritis", "Metabolomics" and their variants, with no language restriction. The search was conducted in PUBMED and EMBASE databases [see section Declarations - Availability of data and materials] and comprised studies published until February 28, 2023. The relevant articles were assessed in full text.

The inclusion criteria comprehended primary studies in humans including the topics of lupus erythematosus and/or lupus nephritis and used metabolomics in urine and serum as a research method. Single case reports, reviews and articles concerning gut microbiota metabolomics in lupus patients were excluded.

To evaluate the quality of the studies, a Critical Appraisal Skills Programme (CASP) checklist for case-control studies was used (Critical Appraisal Skills Programme 2019). Data from the included studies were collected in an independent form by two independent investigators and summarized together; the general items collected were country, year and type of study.

Results

The database searching yielded 367 results, as shown in PRISMA flow diagram [see Fig. 1 – Appendix], 98 duplicates and 269 records based on their titles, abstract, and/or keywords. Both reviewers examined 14 full-text records, with a third author available to independently mediate disputes, if required. Finally, 7 studies satisfied the inclusion criteria and quality assessment [See Table 1 - Appendix].

The studies presented data regarding 453 patients. Among them: (a) 191 patients were diagnosed with lupus nephritis, whose average age was 34.21 ± with a standard deviation (SD) of 4.67, 157 patients (82.20%) females and 34 (17.80%) males; (b) 84 patients were diagnosed with SLE without renal involvement (thus without LN), with an average age of 37.33 with an SD of 3.07, 82 patients (97.62%) females and 2 (2.38%) males; (c) 138 were healthy controls, with an average age of 36.07 with an SD of 7.40, 113 (81.88%) females and 25 (18.12%) males; (d)

40 were diagnosed with other conditions than LN, such as primary focal segmental glomerulosclerosis (FSGS) and proteinuria, and idiopathic nephrotic syndrome (INS), whose average age was 33 years, being 18 females and 22 males. Patients from groups (b), (c) and (d) were treated as control groups in the studies.

The inclusion of patients in LN groups in the studies analysed was based on confirmation of kidney involvement in SLE patients, defined by kidney biopsy and/or proteinuria in 24-hour urine, daily proteinuria greater than 0.5g, haematuria greater than 5/hpf, pyuria greater than 5/hpf, urinary casts (hemoglobin, granular casts, or erythrocyte casts), increase in serum creatinine greater than 0.3 mg%, active urinary sediment, and Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) criteria or American College of Rheumatology (ACR) criteria (Fortuna and Brennan 2013). One of the studies subdivided LN patients into stage-related groups: through kidney biopsy results, SLE patients were allocated to class III or IV LN without membranous features (class III/IV), or to pure membranous class V LN, using the International Society of Nephrology/Renal Pathology Society classification. Another study separated SLE patients between active SLE and inactive SLE, and SLE patients in 4 groups, namely: with only kidney involvement (KI), with only skin involvement, with only blood system involvement and with multisystem involvement (Zhang et al. 2022). We considered the KI group as LN, and included in this review only the groups KI and HC, as KI was compared only with HC patients.

Patients in the SLE group fulfilled the criteria for SLE diagnosis; these criteria included decreased serum complement factors, positive antinuclear antibodies and positive anti-double-stranded DNA antibody (anti-dsDNA) but did not present renal injury signs. FSGS and proteinuria patients were allocated to this group based on the result of kidney biopsy. Finally, healthy control groups (HC) criteria, when described, consisted of presenting normal clinical tests, no active systemic diseases or history of diseases, and no renal history.

Exclusion criteria for patients, when mentioned, consisted of infections, critical illness, pregnancy, cancerous tumors, primary nephrosis, diabetes, cardiovascular diseases, other rheumatic immune diseases and respiratory diseases, or patients unable to give consent.

Concerning sample collection, the studies involved both blood (4 studies, 57%) and urine (3 studies, 43%). Overall, the protocol used for obtaining the urine samples was the collection in the morning, second-pass urine, and stored immediately after collection at -80°C. One study mentions that the urine samples were centrifuged before storage (Kalantari et al. 2019). The amount of urine per sample varied from 640µl to 1ml. As for blood, two of the studies describe the collection of venous blood samples after an overnight fasting, with subsequent centrifugation and storage at -80°C (Guleria et al. 2016; Zhang et al. 2022). One of them mentions that the samples were reversed and mixed for 10 times before centrifugation (Zhang et al. 2022). The amount of serum used in the analyses varied from 10µl to 250µl.

Regarding the method applied, all studies analysing urine used nuclear magnetic resonance (NMR) spectroscopy-based metabolic profiling. One of the studies analysing blood samples also used NMR, and the others applied liquid chromatography and mass spectrometry to identify the molecules.

The biomarker candidates for the disease are described with the assumed variation, area under the curve (AUC) and the variable importance in projection (VIP) in Table 2 [See Appendix].

Discussion

The field of analytic assays such as metabolomics to identify biomarkers for LN remain as an open avenue. As we intended to compile and summarize studies with similar methods, for comparability reasons, our remarks are limited to published data on metabolomics only, as other methods could represent confounding factors in this focused analysis.

When leukocytes are inactive, their energetic metabolism relies on the production of adenosine-3-phosphate (ATP) through glycolysis, which transforms glucose into pyruvate, then metabolized into ATP via oxidative phosphorylation in the tricarboxylic acid cycle (TCA) in the mitochondria. Under anaerobic conditions, cells perform anaerobic glycolysis, which results in the production of NADH and lactate. In activated T cells, however, the necessity of cell biomass availability to support clonal expansion, polarisation, and effector functions such as the secretion of cytokines leads to a change in the energetic metabolism, favouring aerobic glycolysis, when cells are dependent on glycolysis even in the presence of oxygen. In aerobic glycolysis, pyruvate does not enter the TCA, and lactate continues to be produced. The activation of immune cells leads to the secretion of nitric oxide (NO), which inhibits the oxidative phosphorylation until no oxygen is absorbed by mitochondria (Alberts et al. 2014; Vander Heiden et al. 2009; Pearce and Pearce 2013).

In two of the studies analysed (Guleria et al. 2016; Ganguly et al. 2020), a significant reduction in serum or urine levels of citrate was observed, when compared to healthy controls. The behaviour of citrate in urine and serum are similar since it passes freely through the

glomerulus, 60% of it being reabsorbed in the proximal tubule. Citrate is a tricarboxylic acid synthetized in the mitochondria that plays a key role in the TCA – therefore, it is reasonable to expect that when immune cells are activated and their energetic metabolism shifts, its levels in serum decrease, as the oxidative phosphorylation diminishes (Ganguly et al. 2020).

Acetate also showed significant changes in two studies (Guleria et al. 2016; Ganguly et al. 2020). Hyperlipidaemia may be a manifestation of LN and represents an associated cause of cardiovascular complications and mortality in LN patients. As acetate is a product of the oxidation of fatty acids, the changes in its serum levels indicate disturbed lipid metabolism in LN patients, as pointed in the study conducted by (Guleria et al. 2016) when the serum acetate levels were lower than HC. Regarding urine, (Ganguly et al. 2020) found higher levels of acetate in the samples of LN patients, with a trend of decreasing after treatment, probably as a result of tubular repair. The oxidation of fatty acids seems to occur mainly in the mitochondria and peroxisomes of the nephron tubules, especially the proximal. Moreover, toxins that damage the proximal tubules may cause an increased excretion of acetate in urine. This could explain the distinct behaviour of acetate in serum and urine.

The increased levels of N-acetyl glycoproteins (NAGs) in the serum of LN patients, as observed by (Guleria et al. 2016) and (Zhang et al. 2022) could be expected as they are proteins with anti-inflammatory properties expressed in inflammation and immune responses. On the other hand, choline, which participates in the synthesis of phosphorylcholine (a key component of membrane structure), appeared in lower levels in the serum of these patients– possibility indicating that in LN there is an increased use of phosphorylcholine for repairing the damage caused by inflammation and oxidative stress.

Amino acids were also found in decreased levels in the serum of LN patients: valine, leucine, alanine, proline, histidine, glycine and glutamate (Guleria et al. 2016); norvaline (Li et al. 2017) and; beta-alanine (Kalantari et al. 2019). Norvaline may be obtained in the branched chain amino acid pathway, derived from glycolysis – thus, lower levels of norvaline in LN patients may be a result of the impaired glycolysis. The diminished levels of glucose-6-phosphate might corroborate this hypothesis. The reduced levels of glucogenic amino acids (like valine, alanine and glycine), and the augmented level of glucose and lactate in the serum of LN patients may also confirm the shift in energetic metabolism. In a general concept, the altered level of amino acids mirror abnormal amino acid catabolism and protein biosynthesis in these patients, in an effort to control gene transcription and cell cycle progression, as well as immune and inflammatory responses.

Besides the significantly differential metabolites between SLE and LN identified by (Zhang et al. 2022) [see Table 2 – Appendix], the authors found SM d34:2 (higher in LN patients) and Cer-NS d27:4 (lower) to be efficient in discriminating LN from SLE (AUC 0.798 and 0.758 in a 95% confidence interval, respectively). Ceramide seems to be linked to oxidative stress by lipid peroxidation, and oxidative stress has implications in cell apoptotic signaling. In addition, ceramide could also induce the dilation of vessels. As for sphingomyelin, it has significant signaling properties and its metabolites are potential biomarkers for renal diseases – sphingosine phosphate choline, for example, can reduce the mesenteric and renal blood flow in rats. Thus, reduced renal blood flow can be attributed to both metabolites changing (Zhang et al. 2022).

Concerning LN staging, only one of the five studies included in this review correlated the histological classification of LN with the metabolites studied, by analysing the different levels of metabolites found in distinct LN classes (Romick-Rosendale et al. 2011).

Implications for clinical practice

The discovery and validation of these potential biomarkers could play a key role in translational medicine research by using non-invasive methods of sample collection and individualized planning of treatment, therefore improving the comfort and quality of care for patients with renal chronic diseases.

Conclusions

As these studies have shown so far, several metabolites are important candidates for representing biomarkers for the diagnosis, staging and prognosis of lupus nephritis.

Besides serum and urine, saliva is a biofluid whose collection for examination is non-invasive and pragmatic, which turns it into a highly promising source of information for future research. Currently, some studies have searched for lupus biomarkers in saliva, and the extension of such analyses to encompass LN could add new possibilities for better understanding and clinical management of lupus patients.

The study of the metabolome is considered recent, when compared to well stablished omics methods such as proteomics. The growing databases with metabolites annotation, metabolic pathways and interactions with drugs and diseases may become an important tool in future bench-to-bedside approaches of medical care.

Appendix

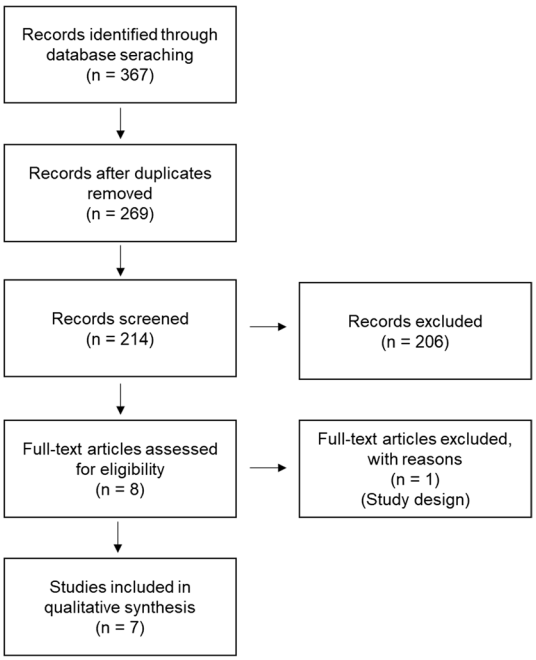

Fig. 1 Flow diagram from the selection of the studies

Table 1 Origin and sample size of metabolomics studies for LN

Author, year	Country	LN *n*=191	Control *n*=262
(Kalantari et al. 2019)	Iran	14	21
(Romick-Rosendale et al. 2011)	USA	14	10
(Li et al. 2017)	China	32	58
(Guleria et al. 2016)	India	40	52
(Zhang et al. 2022)	USA	30	30
(Zhang et al. 2022)	USA	43	73
(Ganguly et al. 2020)	India	18	18

Table 2 Candidate biomarkers for LN versus HC and SLE

	Biomarker	LN versus HC			LN versus SLE		
		Variation	AUC	VIP	Variation	AUC	VIP
Ganguly et al., 2020	Citrate/creatine	↓	0.9136				
	Acetate/creatinine ratio	↑	0.6883				
Li et al., 2017	Theophylline	↓	0.77	0.277			
	Oxidized glutathione	↓	0.77	1.473			
	Capric acid	↑	0.74	1.486			
	3-Indolepropionic acid	↓	0.72	0.650			
	Norvaline	↓	0.75	0.630			
	Hippuric acid	↓	0.72	0.531			
	Sphingosine	↓	0.72	0.533			
	Sorbitol	↑	0.75	5.077			
	Cortisol	↓	0.73	0.486			
	N-acetylglutamine	↓	0.72	0.158			
	Glucose 6-phosphate	↓	0.70	0.124			
	Riboflavin	↓	0.70	0.738			
	Taurine	↓	0.67	0.368			
	Creatinine	↓	0.75	0.762			
Guleria et al., 2016	Leucine	↓	0.82	1.1	—	-	—
	Valine	↓	0.93	1.8	—	-	—
	Alanine	↓	0.87	3.22	—	-	—
	Acetate	↓	0.81	0.62	↓	1	1.44
	NAG	↑	0.95	2.65	—	-	—
	Glutamate	↓	0.98	1.42	—	-	—
	Citrate	↓	0.99	0.89	-	-	-
	Choline	↓	0.76	2.72	↑	0.82	4.53
	Proline	↓	0.82	1.68	—	-	—
	Glycine	↓	0.89	3.33	—	-	—
	Lactate	↓	0.96	8.98	↑	0.75	3.13
	Glucose	↑	0.80-0.99	1.00–6.30	↓	0.75-0.92	1.00–6.09
	Histidine	↓	0.85	0.72	—	-	—
	L1\L2	↑	0.94	1.00–2.96	↑	0.98	1.00–2.59
	L3\L4	↑	0.98	2.00–10.1	↑	0.99	2.00–9.70
	L5	↑	0.87	0.78	↑	0.96	0.81
	L6	↑	0.92	1.5	↑	0.96	1.65
	L7	↑	0.88	1.06	↑	0.96	1.1
	L8	↑	0.83	0.37	↑	0.93	0.42
	L9	↑	0.96	1.4	↑	0.98	1.32
Kalantari et al., 2019	4-Methylcatechol	↑	0.73	1.4	-	0.61	-
	DOPAL	↑	0.72	1.3	↑	0.71	1.2
	Unknown	↑	0.72	1	-	0.88	-
	2,2-DMS	↓	0.87	1.3	↓	0.85	2.1
	Beta-alanine	↓	0.9	1.3	↓		1.8
	Nicotinamide ribotide (NMN)	-	0.73	-	↑		1.13
	Nicotinamide	-	0.74	-	↑		1.16
	Nicotinamide adenine dinucleotide (NAD)	-	0.79	-	↑		1.5
	Nicotinic acid	-		-	↑		1.1
	Guanosine triphosphate (GTP)	-	0.73	-	↑		1.2
	Epi-coprostanol	-	0.74	-	↓		1.3
	Pyridoxine	-	0.68	-	↓		1.7

Table 2 (continued)

	Biomarker	LN versus HC			LN versus SLE		
		Variation	AUC	VIP	Variation	AUC	VIP
	Hippuric acid	-	0.8	-	↓		1.5
	Anthranilic acid	-	0.76	-	↓		1.8
	Unknown	-	0.74	-	↓		1.3
W. Zhang et al., 2022[a]	(10E,12Z)-(9S)-9-Hydroperoxyoctadeca-10,12-dienoic acid	↓		1.424			
	5,8,11-Eicosatrienoic acid	↑		1.194			
	cis-p-Coumaroylcorosolic acid	↓		1.532			
	Dolichosterone	↓		1.865			
	Ganoderiol H	↓		1.702			
	L-Hexanoylcarnitine	↑		1.811			
	Lycoperoside D	↑		1.061			
	Malonylcarnitine	↑		1.403			
	PS(14:1(9Z)/14:0)	↓		1.078			
	5′-Methylthioadenosine	↑		1.119			
	Orotidine	↑		1.083			
	2-Hydroxyethanesulfonate	↑		1.997			
	4-Hydroxy-2-oxobutanoic acid	↓		1.373			
	Alanyl-Leucine	↑		1.998			
	apo-[3-methylcrotonoyl-CoA:carbon-dioxide ligase (ADP-forming)]	↑		1.733			
	Asymmetric dimethylarginine	↑		1.742			
	Creatinine	↑		1.598			
	gamma-Glutamylleucine	↑		1.453			
	Homocysteine thiolactone	↓		1.507			
	Leucyl-Valine	↓		1.816			
	Serylcysteine	↑		1.346			
	Aldehydo-D-xylose	↑		1.709			
	myo-Inositol	↑		1.407			
	Threonic acid	↑		1.377			
	2,4,6,8-Decatetraenoic acid dehydropiperidide	↑		1.642			
	4-Amino-1-piperidinecarboxylic acid	↑		1.558			
	Allantoin	↑		1.118			
	Aloesol	↓		1.546			
	Mercaptopurine	↑		1.767			
	2,4,6,8-Decatetraenoic acid dehydropiperidide	↑		1.642			
	4-Amino-1-piperidinecarboxylic acid	↑		1.558			
	Allantoin	↑		1.118			
	Aloesol	↓		1.546			
	Mercaptopurine	↑		1.767			
	Methylimidazole acetaldehyde	↑		1.577			
	Methylimidazoleacetic acid	↑		1.587			
	N1-Methyl-4-pyridone-3-carboxamide	↑		1.289			
	Pyrazine	↑		1.380			
	Xanthine	↑		1.604			

Table 2 (continued)

	Biomarker	LN versus HC			LN versus SLE		
		Variation	AUC	VIP	Variation	AUC	VIP
Y. Zhang et al., 2022	DG (18:3(9Z,12Z,15Z)/20:5(5Z,8Z,11Z,14Z,17Z)/0:0)				↑		2.45
	SM d34:2				↑		2.31
	1,5-Anhydro-4-deoxy-D-glycero-hex-3-en-2-ulose				↑		2.04
	8-(4-Methoxy-2,3,6-trimethyl-phenyl)-6-methyl-octa-3,5-dien-2-one				↑		2.00
	Cer-BDS d38:5				↑		1.90
	Phenylacetyl-L-glutamine				↑		1.82
	a-Amino-g-cyanobutanoate				↑		1.77
	Pro-Leu				↑		1.75
	lysoDGTS 15:2				↑		1.73
	LDGTS 15:1				↑		1.64
	Glycidyloleate				↑		1.53
	PE 34:1				↓		2.26
	1-Hexadecylthio-2-hexadecanoylamino-1,2-dideoxy-sn-glycero-3-phosphocholine				↓		2.21
	SM 24:1				↓		2.02
	PC (18:3(6Z,9Z,12Z)/18:3(6Z,9Z,12Z))				↓		2.01
	Cer-NS d27:4				↓		1.95
	PC (14:0/20:3(5Z,8Z,11Z))				↓		1.90
	PC 38:6				↓		1.88
	PC (13:0/19:0)				↓		1.86
	Diisononyl phthalate				↓		1.73
	DG 35:5				↓		1.65
	PC 40:6				↓		1.64
	Serylisoleucine				↓		1.58
	SM d36:2				↓		1.51
	PC (18:1(9Z)/22:5(7Z,10Z,13Z,16Z,19Z))				↓		1.51
	CAY10449				↓		3.48
	Nervonic acid				↓		1.96

[a] The metabolites from the study of W. Zhang et al., 2022 are specific to KI, when compared with HC

Abbreviations

ACR	American College of Rheumatology
ATP	Adenosine-3-phosphate
AUC	Area under the curve
CASP	Critical Appraisal Skills Programme
FSGS	Focal segmental glomerulosclerosis
HC	Healthy control groups
INS	Idiopathic nephrotic syndrome
KI	Kidney involvement
LN	Lupus nephritis
MS	Mass spectrometry
NAG	N-acetyl glycoproteins
NMR	Nuclear magnetic resonance
NO	Nitric oxide
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
TCA	Tricarboxylic acid cycle
VIP	Variable importance in projection

Supplementary Information

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Additional file 1.

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Authors' contributions
FPB: Participated in design and coordination, analysed the data, helped to draft manuscript, read and approved the final manuscript. SVL: Participated in design and coordination, analysed the data, helped to draft manuscript, read and approved the final manuscript. LSA: Analysed the data, helped to draft manuscript and approved the final manuscript. MNS: Analysed the data, read and approved the final manuscript. CMCC: Analysed the data, read and approved the final manuscript. GPF: Principal Project Leader, conceived study, participated in design and coordination, analysed the data, read and approved the final manuscript.

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Availability of data and materials
The data used in this article can be found in the studies included in the review. The search history in the databases are as follows:
PUBMED (https://pubmed.ncbi.nlm.nih.gov/):
(((((metabolom*[Text Word]) OR (metabolomics[Text Word])) OR (metabolomic[Text Word])) OR (metabolome[Text Word])) AND ((((lupus[Text Word]) OR (SLE[Text Word])) OR (""systemic lupus erythematosus""[Text Word])) OR (""lupus erythematosus""[Text Word]))) NOT ((""Canis lupus"") OR (""lupus familiaris""))
EMBASE (https://www.embase.com):
'systemic lupus erythematosus'/exp AND ('metabolomics'/exp OR 'metabolome'/exp OR 'metabolites'/exp OR 'metabolic fingerprinting'/exp)

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

Alberts B, Johnson A, Lewis J, Morgan D, Raff M, Roberts K, et al. Molecular Biology of The Cell. 6th ed. New York: Garland Science; 2014. p. 1464.
Critical Appraisal Skills Programme. CASP Case Control Study Checklist. 2019. p. 1–7.
Fortuna G, Brennan MT. Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. Dent Clin North Am. 2013;57(4):631–55.
Ganguly S, Kumar U, Gupta N, Guleria A, Majumdar S, Phatak S, et al. Nuclear magnetic resonance–based targeted profiling of urinary acetate and citrate following cyclophosphamide therapy in patients with lupus nephritis. Lupus. 2020;29(7):782–6.
Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: a comprehensive review. J Autoimmun. 2015;64:125–36.
Guleria A, Pratap A, Dubey D, Rawat A, Chaurasia S, Sukesh E, et al. NMR based serum metabolomics reveals a distinctive signature in patients with Lupus Nephritis. Sci Rep. 2016;6:35309.
Julià A, Vinaixa M, Domènech E, Fernández-Nebro A, Cañete JD, Ferrándiz C, et al. Urine metabolome profiling of immune-mediated inflammatory diseases. BMC Med. 2016;14(1):133.
Kalantari S, Chashmniam S, Nafar M, Zakeri Z, Parvin M. Metabolomics approach reveals urine biomarkers and pathways associated with the pathogenesis of lupus nephritis. Iran J Basic Med Sci. 2019;22(11):1288–95.
Klocke J, Kopetschke K, Grießbach AS, Langhans V, Humrich JY, Biesen R, et al. Mapping urinary chemokines in human lupus nephritis: potentially redundant pathways recruit CD4 + and CD8 + T cells and macrophages. Eur J Immunol. 2017;47(1):180–92.
Li J, Xie XW, Zhou H, Wang B, Zhang MJ, Tang FY. Metabolic profiling reveals new serum biomarkers of lupus nephritis. Lupus. 2017;26(11):1166–73.
Louis PJ, Fernandes R. Review of systemic lupus erythematosus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001;91(5):512–6.
Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38(4):633–43.
Romick-Rosendale LE, Brunner HI, Bennett MR, Mina R, Nelson S, Petri M, et al. Identification of urinary metabolites that distinguish membranous lupus nephritis from proliferative lupus nephritis and focal segmental glomerulosclerosis. Arthritis Res Ther. 2011;13(6):R199.
Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. Circulation. 2012;126(9):1110–20.
Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029–33.
Yan B, Huang J, Zhang C, Hu X, Gao M, Shi A, et al. Serum metabolomic profiling in patients with systemic lupus erythematosus by GC/MS. Mod Rheumatol. 2016;26(6):914–22.
Zhang W, Zhao H, Du P, Cui H, Lu S, Xiang Z, et al. Integration of metabolomics and lipidomics reveals serum biomarkers for systemic lupus erythematosus with different organs involvement. Clin Immunol. 2022;241:109057.
Zhang Y, Gan L, Tang J, Liu D, Chen G, Xu B. Metabolic profiling reveals new serum signatures to discriminate lupus nephritis from systemic lupus erythematosus. Front Immunol. 2022;13:967371.

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