Lactate and lactylation in the kidneys: Current advances and prospects (Review)

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Abstract. Lactate, traditionally overlooked as a glycolytic byproduct, has recently been recognized for its significant biological roles. The normal kidney plays an essential role in maintaining systemic glucose and lactate homeostasis. Lactylation, as a new epigenetic modification, influences the initiation and progression of kidney diseases through the regulation of gene transcription and cellular metabolism. The present review summarizes current perspectives on the physiological functions of lactate and its renal metabolism, analyzes the roles of lactate and lactylation in acute kidney injury, diabetic nephropathy and chronic kidney disease, and proposes that targeted modulation of lactate metabolism may represent a promising therapeutic strategy for kidney disorders, thereby providing a foundation for future investigations.

Contents

1. Introduction

The kidney plays a vital role in numerous physiological processes, including the excretion of metabolic waste, the regulation of fluid balance and the secretion of endocrine hormones, which are all fundamental to maintaining internal homeostasis (1). In sugar metabolism, the kidneys contribute to acid-base equilibrium and energy supply by excreting and metabolizing lactate, thereby supporting glucose and lactate homeostasis (2). The involvement of lactate in kidney diseases includes intricate metabolic regulation, cellular injury and clinical monitoring. As a glycolytic product, lactate accumulates excessively under conditions of impaired clearance in renal dysfunction, potentially precipitating metabolic acidosis and directly impacting the function of renal tubular epithelial cells (3,4). During renal fibrosis, lactate accelerates fibrotic progression by inducing histone lactylation. For instance, in advanced glycation end product (AGE)-induced renal tubular epithelial cells, increased lactate levels enhance histone H3 lysine 14 lactylation (H3K14la) in diabetic nephropathy (DN), thereby promoting Krüppel-like factor 5 (KLF5) expression and driving the epithelial-mesenchymal transition (EMT) in DN (5). In chronic kidney disease (CKD), the expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) is positively correlated with the severity of renal fibrosis. PFKFB3-mediated glycolytic reprogramming in renal tubules generates lactate, which enhances H4K12la, facilitating gene transcription and activation of nuclear factor-κB (NF-κB), thus subsequently promoting inflammatory responses and exacerbating renal fibrosis (6). Furthermore, in acute kidney injury (AKI), DN and CKD, lactate concentrations and the activity or expression of glycolytic enzymes may exhibit alterations (4,7). Such metabolic shifts establish lactate-associated enzymes and lactate kinetics as emerging biomarkers for disease progression assessment. Consequently, lactate is not only a significant participant in renal metabolism but also a potential pathological driver in kidney disease evolution. Dynamic lactate monitoring offers valuable diagnostic and therapeutic insights, and targeting lactate metabolism may represent an innovative approach to renal protection.

Lactate, historically regarded as a negligible glycolytic byproduct with limited physiological relevance (8), has now

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emerged as a molecule of significant biological importance. Beyond its role as a ubiquitous metabolite, lactate functions as a substrate for epigenetic modifications, regulating gene transcription and protein function through lactylation of histone and non-histone proteins (9,10). This discovery illustrates the capacity of metabolites to regulate gene expression via post-translational modifications. Lactate, acting as a metabolic intermediate and signaling molecule, regulates diverse physiological and pathological processes, including osteoblast differentiation, inflammatory signal transduction, angiogenesis and myogenesis, among others (11-14). Notably, targeting the roles of lactate offers a promising therapeutic strategy for addressing chronic diseases. An expanding body of research highlights the relevance of lactate in various cellular functions, with particular attention on its emerging role in kidney disease.

The present review offers an in-depth evaluation of lactate and its associated metabolic pathways, providing a foundation to comprehending its role in renal physiology. Advances in delineating the involvement of lactate and lactylation in kidney disorders, specifically AKI, DN and CKD, are thoroughly evaluated. Moreover, an analysis of therapeutic targets and strategies focused on lactate metabolism and lactylation is performed, presenting innovative perspectives for the prevention and treatment of renal diseases.

2. Lactate and lactate metabolism

Generation and clearance of lactate. Glycolysis constitutes the primary pathway for lactate generation in organisms (15) (Fig. 1). Under hypoxic conditions, such as those experienced during intense physical exertion or within certain pathological environments, the entry of pyruvate into the mitochondria for aerobic metabolism is hindered. As a result, glucose in the cytoplasm undergoes enzymatic reactions leading to pyruvate formation, which is subsequently reduced to lactate through lactate dehydrogenase-A (LDHA). Notably, the glycolysis pathway can generate lactate even under aerobic conditions. This oxygen concentration-independent process represents a distinct metabolic mode known as aerobic glycolysis (16). The regulation of glycolysis is mediated by various enzymes, including LDH, pyruvate kinase M2 (PKM2), glucose transporters (GLUT) and hexokinase 2 (HK2) (17-20).

Lactate exists in two isomeric forms: L-lactate and D-lactate. L-lactate, the dominant isomer, is integral to immune regulation, acid-base balance and signal transduction within various physiological contexts (21). In eukaryotic cells, L-lactate represents the chief glycolytic end-product, whereas D-lactate is present only in trace amounts (22). D-lactate arises predominantly from intestinal microbiota metabolism, notably by *Lactobacillus* and *Escherichia coli*. In humans, lactate metabolism primarily depends on L-lactate dehydrogenase, while D-lactate dehydrogenase activity remains limited, resulting in slower D-lactate clearance (21,23).

Excessive lactate accumulation correlates with a heightened risk of lactic acidosis (24). Metabolic homeostasis necessitates the efficient clearance of lactate from tissues and the bloodstream (25,26). The primary mechanism for lactate clearance is its oxidation to pyruvate by LDHB in the presence of adequate oxygen, followed by mitochondrial entry for participation in the tricarboxylic acid cycle, yielding CO_2, water and energy (27,28). Elevated lactate concentrations are also redirected to the liver and kidneys, where lactate undergoes conversion to glucose via gluconeogenesis. Notably, renal gluconeogenesis contributes ~40% of total gluconeogenesis during fasting, a function markedly compromised in CKD, leading to systemic metabolic imbalances manifesting as hypoglycemia and hyperlactatemia (7). Additionally, lactate is enzymatically transformed into fatty acids, cholesterol, and ketone bodies, or eliminated through the excretion of urine and sweat (Fig. 2).

Biological roles of lactate shuttle and lactate in the kidneys. The lactate shuttle theory systematically characterizes the intercellular transfer of lactate, highlighting its function as both an oxidative and gluconeogenic precursor, as well as a signaling molecule (29,30). This mechanism regulates the exchange of energy substrates between active cells, such as skeletal muscle, and recipient cells, including the brain, heart, liver and kidney, a process governed by the concentration gradients generated through mitochondrial respiration within recipient cells (30).

Monocarboxylate transporters (MCTs) are essential to the lactate shuttle mechanism, mediating lactate transport. The MCT family comprises 14 distinct members, each characterized by specific transport properties and tissue-specific expression. Among them, MCT1 and MCT4 are central to lactate dynamics: MCT1 promotes lactate flux in accordance with cellular metabolic needs, while MCT4 predominantly handles lactate efflux (31-33). Acting synergistically, these transporters maintain lactate homeostasis, pH balance and intracellular metabolic stability.

In murine kidneys, MCTs mediate the transport of monocarboxylates between renal tubular cells and the circulatory system (34). MCT1, MCT2, MCT7 and MCT8 are specifically localized on the basolateral membranes of the epithelial cells lining the nephron, with MCT1 and MCT8 expressed in proximal tubule cells, and MCT7 and MCT2 in the thick ascending limb and distal tubule (35). Concurrently, LDHA is predominantly expressed in the proximal nephron, functioning as a lactate producer, whereas LDHB is primarily localized to the distal nephron, serving as a lactate consumer, with both exhibiting spatial and temporal shifts in response to ischemic injury (36). Collectively, this spatial distribution supports the hypothesis that lactate shuttles from the proximal to the distal nephron, acting either as an energy substrate or a signaling mediator.

In addition, lactate exerts essential biological functions within the kidney. Podocytes and their foot processes constitute critical components of the renal filtration barrier, governing glomerular permeability. Podocyte injury is widely recognized as a central pathological mechanism in various kidney diseases, particularly DN and primary tubular disorders (37,38). Emerging evidence indicates that podocytes utilize lactate as an energy substrate and possess intrinsic regulatory systems to maintain lactate homeostasis. Under glucose-deprived conditions, L-lactate exposure preserves cellular viability and sustains glycolytic flux, mitigating glycogen depletion and highlighting the indispensable role of lactate in supporting podocyte metabolism during metabolic stress (39). Additionally, lactate stimulation modulates

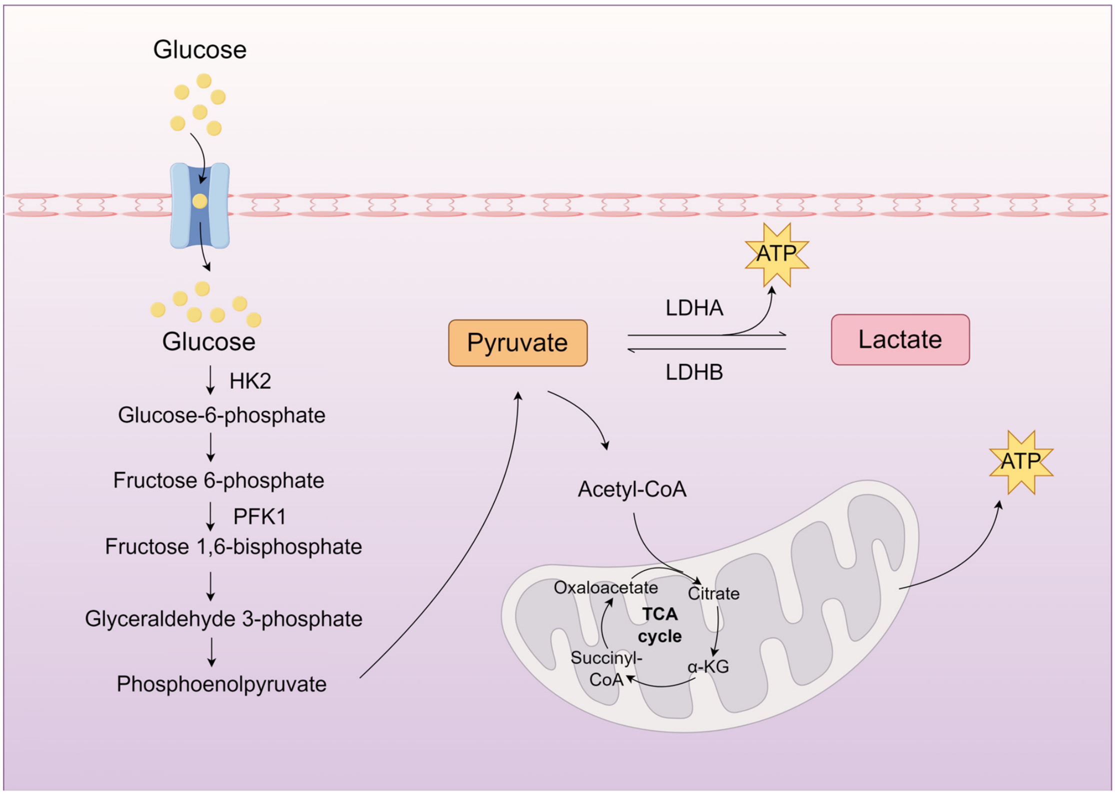

Figure 1. Primary pathways of lactate production. In the cytoplasm, glucose undergoes sequential glycolytic enzyme-mediated reactions to generate pyruvate. Under normoxic conditions, pyruvate translocates into mitochondria to enter the TCA cycle. By contrast, hypoxic environments promote the LDHA-catalyzed conversion of pyruvate into lactate. TCA, tricarboxylic acid; LDHA, lactate dehydrogenase-A; LDHB, lactate dehydrogenase-B; HK2, hexokinase 2; PFK1, phosphofructokinase-1; α-KG, α-ketoglutarate; ATP, adenosine triphosphate. The figure was drawn using Figdraw (figdraw.com).

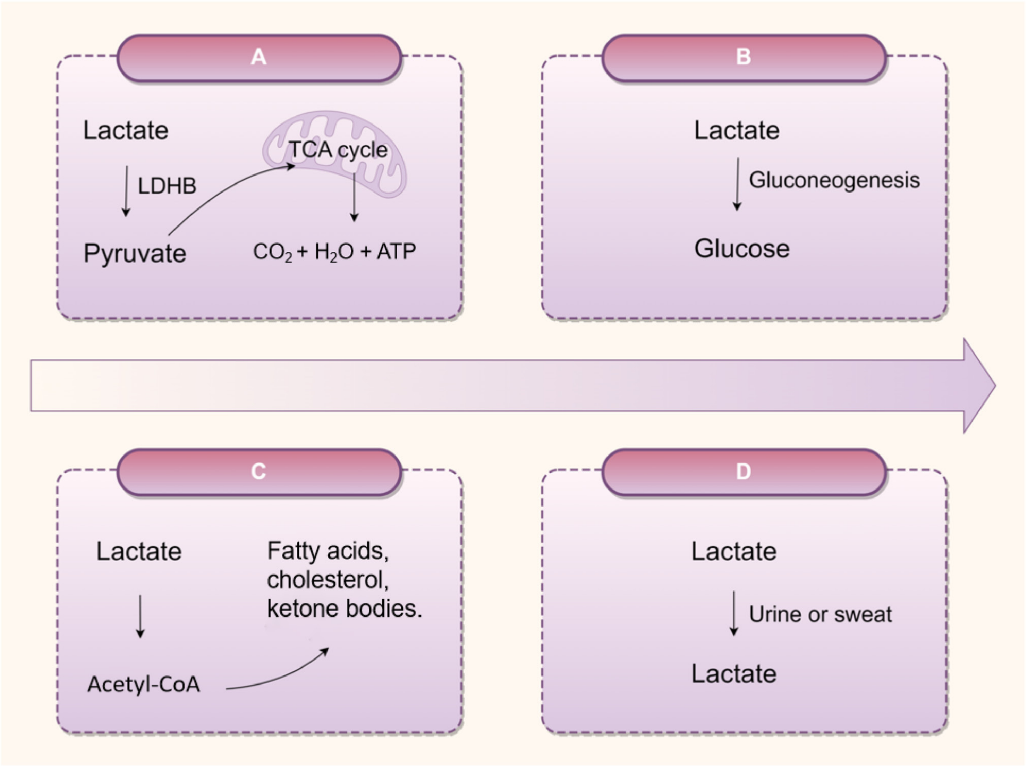

Figure 2. Lactate metabolism. (A) Under conditions of sufficient oxygen supply, lactate is oxidized to pyruvate by LDHB, which subsequently enters the mitochondria to participate in the TCA cycle, generating CO_2, H_2O and ATP. (B) Lactate is converted into glucose via the gluconeogenic pathway. (C) Lactate indirectly participates in the synthesis of fatty acids, cholesterol or ketone bodies through the metabolic intermediate acetyl-CoA. (D) When blood lactate levels are abnormally elevated, lactate may be excreted through urine; sweat gland cells can secrete trace amounts of lactate, which is subsequently eliminated via sweat. TCA, tricarboxylic acid; LDHB, lactate dehydrogenase-B; ATP, adenosine triphosphate. The figure was drawn using Figdraw (figdraw.com).

mitochondrial dynamics and respiratory efficiency; exposure to lactate elevates the mitochondrial DNA-to-nuclear DNA ratio, thereby enhancing mitochondrial biogenesis and regulating LDH subtype expression and activity in podocytes (40).

In renal cells, lactate not only undergoes catalysis to pyruvate, serving as a key intermediary in energy metabolism, but also functions as a gluconeogenic precursor for endogenous glucose synthesis. Renal gluconeogenesis predominantly occurs in the renal cortex, particularly within the proximal tubules, where the key enzymes required for the gluconeogenic pathway are expressed (41,42). Renal and hepatic gluconeogenesis collectively regulate systemic glucose homeostasis, critically contributing to the regulation of blood glucose levels and whole-body energy metabolism (43).

In clinical contexts, renal insufficiency impairs the lactate clearance capacity of the kidney, resulting in lactate accumulation and subsequent metabolic acidosis (44). This elevation serves as an indirect marker of renal dysfunction, particularly after excluding confounding factors such as hypoxia and infection. Therefore, monitoring lactate levels can indirectly help to assess the compensatory status of kidney function in patients with kidney disease. In diabetic populations, urinary lactate levels can predict clinical outcomes such as doubling of serum creatinine or the development of kidney failure, and elevated urinary lactate levels may be a potential biomarker for the risk of kidney disease progression (4). Thus, the role of lactate in kidney function not only reflects the metabolic and excretory capacity of the kidney but is also related to acidosis and disease prognosis. In clinical practice, a comprehensive analysis combining lactate levels, kidney function indicators and etiology should be conducted to optimize intervention strategies for kidney diseases.

In conclusion, lactate constitutes an essential metabolic substrate sustaining the energetic demands of renal cells. Beyond its fundamental bioenergetic contribution, lactate operates as a central regulator within cellular metabolic and signaling networks, critically supporting physiological stability and systemic metabolic balance.

3. Discovery of lactylation and its regulation

Lactate metabolism, homeostasis and the lactate microenvironment significantly regulate cellular and biomolecular functions. Recent studies have identified lactate as an epigenetic modulator (11,45,46), capable of inducing post-translational modifications and influencing gene expression, thereby causing diverse biological outcomes. Zhang *et al* (45) demonstrated that lactate facilitates transcriptional regulation through lactylation, an epigenetic mechanism wherein lactate-derived modifications of histone lysine residues directly promote gene transcription within chromatin, marking the initial discovery of histone lysine lactylation. Consequently, lactylation establishes a direct nexus between cellular metabolic activity and epigenetic governance.

Following the identification of histone lactylation, the emergence of non-histone lactylation has highlighted its wider prospects beyond chromatin modification (47). Current evidence implicates protein lactylation in a range of renal pathologies, including AKI (48) and DN (49), along with a variety of other diseases. For instance, H3K18la has been associated with the progression of arsenite-induced idiopathic pulmonary fibrosis (50), whereas glutamine mitigates intervertebral disc degeneration by inhibiting adenosine-5'-monophosphate-activated protein kinase α (AMPKα) lactylation through suppression of glycolytic pathways (51). Moreover, lactylation exerts regulatory effects on critical physiological processes, such as autophagy, macrophage activation and osteoblast differentiation (13,52,53). Accordingly, lactylation emerges as a central mechanism within both renal pathophysiology and systemic disease contexts.

The regulation of lactylation is modulated by a network of enzymes and regulatory proteins. Emerging evidence reveals that, analogous to acetylation, lactylation is controlled by 'writer' proteins such as P300/ CREB binding protein and 'eraser' proteins, including histone deacetylases (HDACs) (13,54,55), and that these proteins are integral to the dynamic modulation and reversibility of lactylation (Fig. 3). P300, a major writer protein, catalyzes lysine lactylation by transferring lactate groups onto lysine residues. The P300/ASF1A complex integrates metabolic reprogramming with epigenetic modulation via H3K18la during atherogenesis driven by endothelial-to-mesenchymal transition (56). Eraser proteins, such as HDACs, counteract lactylation by enzymatically removing lactate groups. Notably, the feedback loop between H3K9la and HDAC2 in endothelial cells modulates vascular endothelial growth factor-induced angiogenesis; glycolysis inhibition reduces H3K9la levels and consequently attenuates neovascularization (11).

The identification of protein lactylation introduces a new framework for linking nutrient metabolism to gene expression. Continued investigation into lactylation and its regulatory pathways is anticipated to enhance the understanding of cellular dynamics and disease mechanisms. Expanding research efforts may clarify the functional roles of this post-translational modification and reveal novel therapeutic targets for related pathologies. Future studies should delineate the interplay between lactylation, cellular metabolism and other post-translational modifications, and systematically define the regulatory architecture of lactylation in kidney disease initiation and progression. Such advances would substantially enrich the mechanistic insight into lactate metabolism in kidney disease.

4. Detection methods of lactylation

Elucidating the biological significance of lactylation necessitates the development and implementation of precise detection methodologies.

Mass spectrometry (MS) is currently one of the most commonly used techniques for detecting lactylation, leveraging high-resolution instruments to identify mass shifts in proteins or peptides and thereby accurately pinpointing lactylation sites on proteins (57). As demonstrated by Li *et al* (58) in an AKI model, MS was successfully employed to identify lactylation sites on aldehyde dehydrogenase 2 (ALDH2), followed by immunoprecipitation-MS (IP-MS) analysis to characterize the interaction between ALDH2 and prohibitin 2 (PHB2). The study established that ALDH2 lactylation exacerbates mitochondrial dysfunction in AKI by impairing PHB2-mediated mitophagy (58).

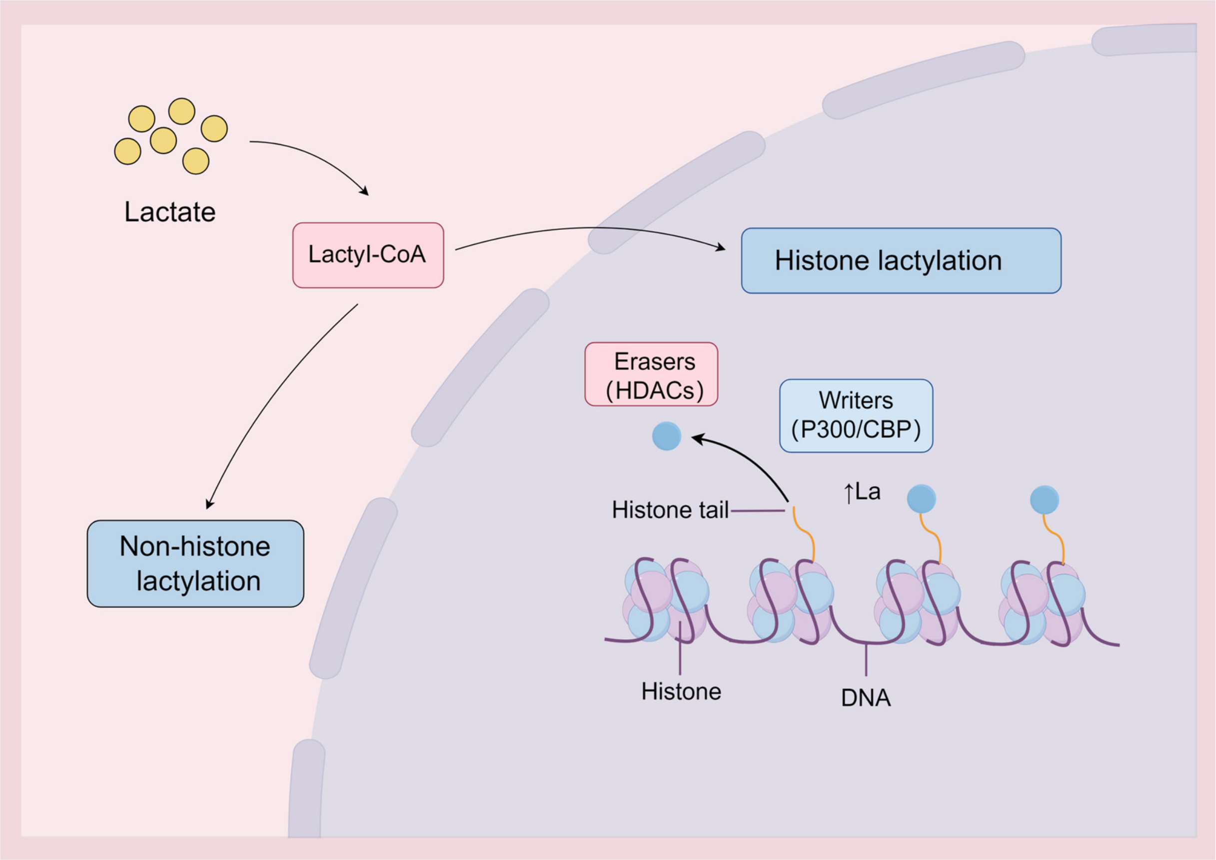

Figure 3. Protein lactylation. Lactate participates in histone lactylation and non-histone lactylation by conversion to lactoyl-CoA. Writer proteins (such as P300/CBP) and eraser proteins (such as HDACs) can regulate the histone lactylation. HDAC, histone deacetylase; CBP, CREB binding protein; La, lactyl. The figure was drawn using Figdraw (figdraw.com).

Specific antibodies targeting lactylated lysine residues constitute indispensable tools for detecting lactylation, enabling the application of western blotting and IP assays to assess lactylation expression in cellular and tissue contexts. In a hypoxia/reoxygenation cell model in the human proximal tubular HK-2 cell line, Zhou *et al* (59) employed western blotting to detect histone lactylation and performed chromatin IP (ChIP) to assess its association with hexokinase 2 (HK2). The results demonstrated significant enrichment of H3K18la at the HK2 promoter region, which upregulated HK2 expression and consequently exacerbated renal ischemia/reperfusion injury. In renal tubular epithelial cells, An *et al* (48) demonstrated through western blot analysis that lactate overproduction mediates lactylation of mitochondrial fission 1 protein (Fis1) lysine 20 (Fis1 K20la), which subsequently induces mitochondrial dysfunction and exacerbates sepsis-associated AKI (SA-AKI).

Techniques such as immunofluorescence (IF) and immunohistochemistry (IHC) further allow for the visualization of the spatial distribution of lactylation within cells and tissues, providing an intuitive localization tool for studying lactylation. Qiao *et al* (60) employed western blotting and IF to assess H3K18la expression in the renal tubular epithelial cells of SA-AKI mice, combined with Cleavage Under Targets and Tagmentation technology to identify H3K18la-regulated target genes. The study revealed significant enrichment of H3K18la at the promoter region of Ras homolog gene family member A (RhoA), demonstrating that H3K18la upregulation activates the RhoA/Rho-associated protein kinase/Ezrin signaling pathway, thereby promoting renal dysfunction (60).

ChIP sequencing (ChIP-seq), a high-throughput method for analyzing protein-DNA interactions (61), facilitates genome-wide mapping of lactylation sites. Integration of RNA-seq data provides a complementary strategy to elucidate transcriptional regulatory networks influenced by lactylation modifications (62). As demonstrated by Zhang *et al* (5) in AGE-induced renal tubular epithelial cells, IHC and IF analyses of pan-lysine lactylation (pan-Kla) and H3K14la, combined with integrated ChIP-seq and RNA-seq profiling, revealed that H3K14la promotes the EMT process through upregulation of downstream KLF5 expression (5).

However, research on lactylation modifications remains in its nascent stages, with methodologies undergoing continuous refinement. Integrating multiple analytical approaches can significantly improve the reliability of findings. As technological advancements progress, future detection methods for lactylation modifications are expected to achieve greater sensitivity and efficiency, providing robust support for elucidating their significant roles in biology.

5. Function of lactylation in renal cells

The kidney has unique anatomical and physiological characteristics, with various renal cell types displaying specialized metabolic adaptations tailored to their specific functions and microenvironments (63). Consequently, the functional of lactylation in renal cells is likely determined by cell type-specific metabolic properties and pathological status, particularly in injury repair, metabolic regulation and fibrosis progression.

In AKI, the lactylation of renal tubular epithelial cells modulates kidney functional by regulating cellular proliferation and reparative pathways. For instance, heat shock protein A12A augments the proliferative capacity of renal tubular epithelial cells by enhancing c-Myc lactylation, thereby promoting functional restoration following AKI (64). Furthermore, lactylation influences the progression of SA-AKI, wherein lactate modifies inflammatory metabolism in renal proximal tubular epithelial cells via lactylation at H3K18 and Ezrin-K263 residues, consequently affecting SA-AKI recovery (60). Excessive lactate accumulation in renal tubular epithelial cells drives Fis1 K20la. Elevated Fis1 K20la levels promote aberrant mitochondrial fission, leading to ATP depletion, mitochondrial reactive oxygen species (ROS) overproduction and mitochondrial apoptosis, ultimately intensifying SA-AKI pathology (48). Thus, lactylation may regulate renal tubular epithelial cell survival and functional restoration in AKI through epigenetic mechanisms.

In DN, lactate derived from renal tubular epithelial cells promotes KLF5 expression via H3K14la, thereby upregulating Vimentin and α-smooth muscle actin (α-SMA) expression and accelerating the EMT process (5). In the CKD model, lactate stimulates transforming growth factor (TGF)-β1 expression in mouse renal tubular epithelial cells via H3K18la, which subsequently activates the Smad3 pathway in macrophages, driving macrophage-myofibroblast transition and renal fibrosis (65). Furthermore, in DN mice, lactate accumulation promotes histone pan-lactylation in podocytes, which downregulates nephrin and zonula occludens-1 levels while upregulating collagen IV, fibronectin and α-SMA, ultimately inducing EMT in podocytes (66).

These findings demonstrate that during AKI, renal tubular epithelial cells are susceptible to lactylation-induced disturbances in energy metabolism and oxidative stress. By contrast, under DN or CKD conditions, tubular lactylation appears to promote renal fibrogenesis. In podocytes, lactylation primarily drives fibrotic progression. Current evidence reveals the complex regulatory roles of lactylation in renal cells. However, its effects in other renal cells, including interstitial fibroblasts, glomerular mesangial cells, immune cells and pericytes, remain largely unexplored. The functional heterogeneity of lactylation among different renal cell populations warrants further investigation.

6. Lactate metabolism and lactylation in kidney diseases

AKI. AKI, a common and severe renal disorder, involves a sudden decline in renal function, evidenced by decreased glomerular filtration rate (GFR) and/or diminished urine output, resulting in metabolic waste accumulation, acid-base disturbances and electrolyte imbalances. Integrating prognostic biomarkers with clinical risk factors remains essential for early evaluation and management of AKI (67).

Clinical evidence has revealed an association between AKI and impaired gluconeogenesis, along with diminished lactate clearance (68). Elevated lactate levels have emerged as reliable predictors for both the onset and prognosis of AKI (69,70). Gong *et al* (71) identified increased serum lactate as an independent risk factor for SA-AKI, where concentrations ≥2.75 mmol/l were linked to a 1.772-fold escalation in AKI risk. In the postoperative setting, particularly after cardiac surgery, serum lactate levels independently predict AKI development (72). Early dynamic monitoring of lactate trajectories also enables the prediction of continuous renal replacement therapy requirements following acute type A aortic dissection surgery (73). Furthermore, in conditions such as acute decompensated heart failure (74), ST-segment elevation myocardial infarction (75) and traumatic brain injury (76), lactate levels serve as key indicators for assessing AKI risk, thereby strengthening opportunities for early diagnosis.

Clinical studies have highlighted the potential of lactate levels as biomarkers in AKI, prompting further exploration of the regulatory mechanisms of lactate in this condition. In a suppurative AKI model induced by cecal ligation and puncture in C57/B6 mice, lactate-mediated activation of the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway triggered lymphocyte apoptosis and subsequent immunosuppression (Fig. 4), indicating that blockade of lactate receptors or inhibition of the PD-1/PD-L1 axis may offer innovative therapeutic strategies for septic AKI (77). Sepsis-induced aerobic glycolysis, characterized by increased lactate production and upregulation of glycolysis-associated genes in renal tissues, further implicates lactate in AKI pathology. In lipopolysaccharide-stimulated HK-2 cells, lactate treatment suppressed sirtuin 3 (SIRT3) and phosphorylated-AMP-activated protein kinase (p-AMPK) expression, decreased the microtubule-associated protein 1A/1B-light chain 3-II/microtubule-associated protein 1A/1B-light chain 3-I ratio and elevated p62 levels, thereby inhibiting autophagy, promoting apoptosis and intensifying sepsis-induced AKI (SI-AKI) progression (78) (Fig. 4). Intervention with the aerobic glycolysis inhibitor 2-deoxy-D-glucose attenuated glycolysis, with underlying mechanisms likely involving the restoration of autophagy via modulation of the lactate/SIRT3/AMPK signaling axis, thereby mitigating SI-AKI (78). Renal fibroblasts play a crucial role in the regulation, repair and recovery of renal tubular injury after AKI. The proliferation of fibroblasts follows the proliferation of renal tubular epithelial cells. Proliferating renal tubular epithelial cells preferentially utilize aerobic glycolysis as the primary metabolic pathway during AKI progression. In the later stages of AKI, lactate generated by injured tubular epithelial cells is absorbed by interstitial fibroblasts, promoting fibroblast activation and proliferation (79). Consequently, glycolysis-derived lactate from tubular epithelial cells modulates fibroblast activation and proliferation.

The discovery of lactylation has substantially advanced the understanding of its involvement in AKI. Elevated lactate levels are established as an independent risk factor for SA-AKI. Evidence suggests that H3K18la may serve as a biomarker for diagnosing and gauging the severity of septic shock (80). A recent investigation has reveal that increased H3K18la expression in SA-AKI contributes to the progression of renal insufficiency associated with this condition (60). Moreover, hyperacetylation and inactivation of pyruvate

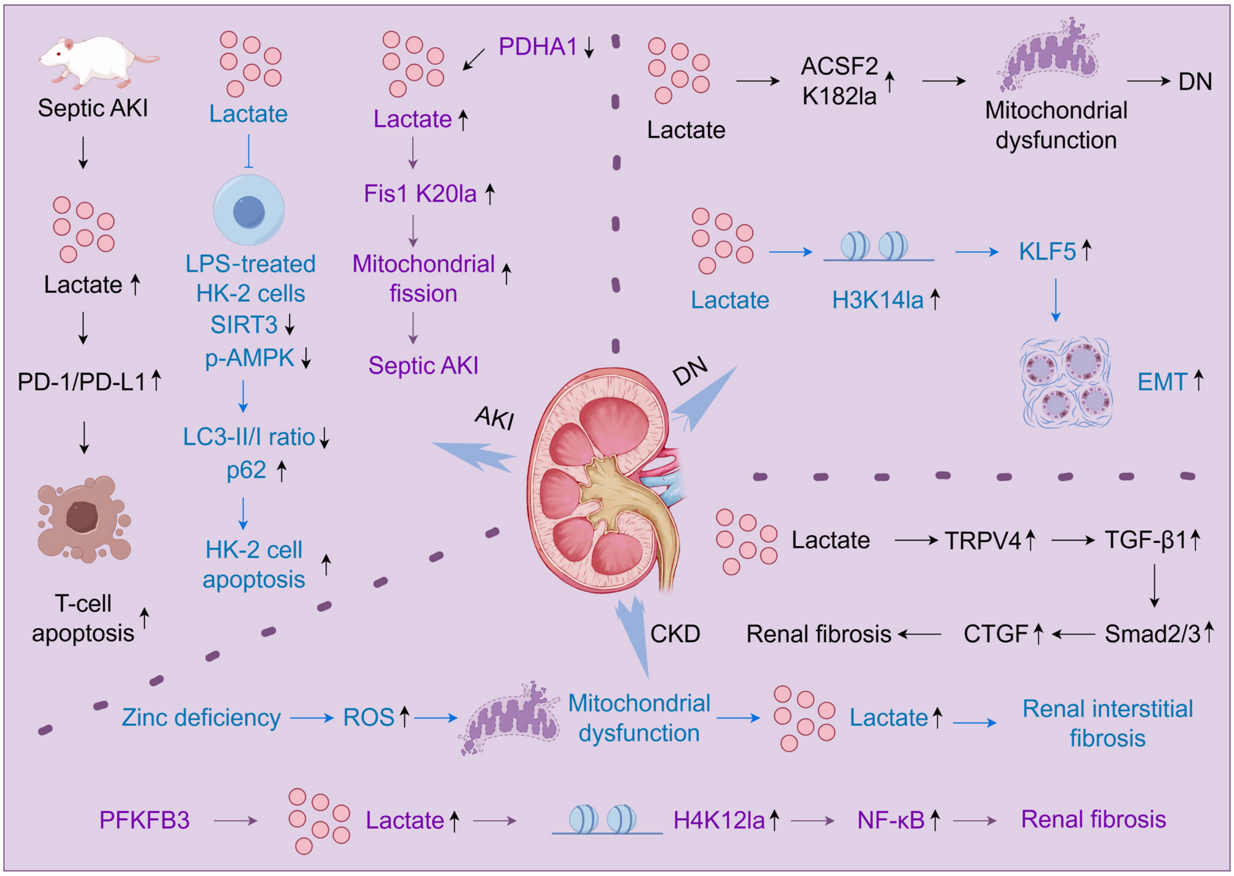

Figure 4. Mechanisms of lactate and lactylation in renal diseases. In a septic AKI mouse model, lactate activates the PD-1/PD-L1 pathway, inducing T lymphocyte apoptosis and contributing to immunosuppression during septic AKI. In LPS-stimulated HK-2 cells, lactate inhibits autophagy by downregulating SIRT3 and p-AMPK expression, reducing the LC3-II/I ratio and elevating p62 levels, thereby promoting HK-2 cell apoptosis and worsening SI-AKI. High acetylation and inactivation of PDHA1 in renal tubular epithelial cells drive lactate accumulation, mediate Fis1 K20la, impair mitochondrial function and aggravate SI-AKI. In human proximal tubular epithelial cells, increased lactylation at K182 of ACSF2 induces mitochondrial dysfunction, accelerates renal tubular injury and advances DN progression. Elevated lactate concentrations in renal tubular epithelial cells promote H3K14la, upregulating KLF5 expression and driving EMT in DN. In spontaneous hypertension, excessive lactate mediates renal fibrosis through activation of the TRPV4-TGFβ1-SMAD2/3-CTGF signaling cascade. ROS stress resulting from zinc deficiency also disrupts mitochondrial function, causing metabolic stress characterized by abnormal lactate metabolism and promoting the development of renal interstitial fibrosis. Moreover, lactate accumulation driven by PFKFB3 activation enhances H4K12la, augments NF-κB gene transcription and activation, intensifies inflammatory responses, and accelerates renal fibrosis. LPS, lipopolysaccharide; SIRT3, sirtuin 3; p-AMPK, phosphorylated-AMP-activated protein kinase; PDHA1, pyruvate dehydrogenase E1 component subunit α; Fis1 K20la, mitochondrial fission 1 protein lysine 20 lactylation; ACSF2, Acyl-CoA synthetase family member 2; K182la, lysine 182 lactylation; H3K14la, histone H3 lysine 14 lactylation; EMT, epithelial-mesenchymal transition; TRPV4, transient receptor potential vanilloid 4; TGF-β1, transforming growth factor β1; p-Smad2/3, phospho-Smad2/3; TRPV4, transient receptor potential cation channel subfamily V member 4; CTGF, connective tissue growth factor; ROS, reactive oxygen species; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; SI-AKI, sepsis-induced acute kidney injury; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1; HK-2, hexokinase 2; LC3-II/I, microtubule-associated protein 1A/1B-light chain 3-II/microtubule-associated protein 1A/1B-light chain 3-I ratio; KLF5, Krüppel-like factor 5; diabetic neuropathy; CKD, chronic kidney disease. The figure was drawn using Figdraw (figdraw.com).

dehydrogenase E1 component subunit α in renal tubular epithelial cells promote excessive lactate production, subsequently inducing Fis1 lactylation and accelerating the deterioration of SI-AKI (48) (Fig. 4). These findings elucidate the epigenetic pathways implicated in AKI pathogenesis.

Although lactate is recognized as a biomarker for AKI prediction and prognosis assessment, the mechanisms underlying AKI progression and the specific contributions of lactate require further elucidation. While H3K18la involvement in SA-AKI has been characterized, the impact of lactylation in AKI resulting from other etiologies remains poorly defined. Future research should focus on delineating the roles and mechanistic pathways of lactate and lactylation across diverse AKI models.

DN. DN, a severe microvascular complication of diabetes characterized by proteinuria and progressive GFR decline, is a leading global contributor to CKD (81). Effective early detection and intervention depend on the development of robust predictive models and biomarkers. Accumulating evidence positions lactate as a promising non-invasive biomarker for early DN diagnosis (82). Jiang *et al* (83) proposed a DN risk prediction model incorporating serum lactate levels through a nomogram, offering a straightforward, economical and highly sensitive method for DN risk stratification.

Investigations into the role of LDH in DN have yielded significant insights. Tang *et al* (84) analyzed data from type 2 diabetes (T2DM) patients collected between 2009 and 2018 in the National Nutrition and Health Examination Survey database, utilizing restricted cubic spline plots to delineate a dose-response relationship between LDH levels and DN risk, thereby establishing LDH as a relevant biomarker for DN screening in T2DM populations. In parallel, Azushima *et al* (4) applied targeted metabolomics in a DN mouse model, revealing elevated renal lactate concentrations, impaired energy metabolism, and increased expression levels of LDHA and LDHB isoforms. Administration of angiotensin receptor blockers attenuated albuminuria, suppressed LDH expression, mitigated renal injury, restored metabolic homeostasis, normalized lactate concentrations and improved renal ATP content, implicating metabolic dysregulation and excessive lactate accumulation in the pathogenesis of DN.

Research into the mechanisms of lactate and lactylation in DN has demonstrated that enhanced lactylation at lysine 182 (K182) of ACSF2 in human proximal tubular epithelial cells induces mitochondrial dysfunction, thereby promoting renal tubular injury and accelerating DN progression (49) (Fig. 4). Moreover, EMT is widely recognized as a central contributor to DN development. In renal tubular epithelial cells exposed to AGEs, a metabolic shift from oxidative phosphorylation to glycolysis elevates renal lactate levels. Elevated lactate levels also increase H3K14la, subsequently upregulating KLF5 expression and further driving EMT in DN (5) (Fig. 4).

Advances in lactylation research have substantially expanded the understanding of the epigenetic regulation of DN. Modulation of the lactate-mediated H3K14la/KLF5 axis or adjustment of lysine lactylation levels offers a potential pathway for therapeutic innovation in DN. Although current evidence identifies lactate and LDH as candidate biomarkers for DN, further investigations are required to clarify the underlying mechanisms and enhance their clinical translation.

CKD. CKD constitutes a major global public health concern, characterized by chronic structural and functional renal impairments originating from diverse etiologies, including primary and secondary glomerulonephritis, tubular injury and renovascular pathologies (85,86).

Lactate metabolism holds clinical relevance in CKD across several dimensions, including metabolic dysregulation, prognostic evaluation and complication management. Impaired renal function, particularly tubular dysfunction, diminishes lactate clearance in patients with CKD. Evidence indicates that defective renal gluconeogenesis in CKD alters systemic metabolism, typified by reduced glucose and elevated lactate levels, increasing susceptibility to hyperlactatemia. This metabolic disturbance not only predisposes patients to metabolic acidosis but also correlates with adverse renal outcomes (7,87). Consequently, abnormal lactate metabolism is a manifestation of metabolic imbalance in patients with CKD. Monitoring blood lactate levels may help assess the status of lactate metabolism in patients with CKD and could potentially assist in evaluating the prognosis of the disease. However, its specific clinical application value in monitoring disease progression, managing complications and assessing prognosis in CKD still requires further evaluation.

The hallmark pathology of CKD is renal fibrosis, encompassing glomerulosclerosis, tubular atrophy and interstitial fibrosis. Dysregulated lactate metabolism has been implicated in fibrotic progression. In spontaneous hypertension, elevated lactate concentrations aggravate renal fibrosis via activation of the transient receptor potential cation channel subfamily V member 4-TGFβ1-SMAD2/3-connective tissue growth factor (CTGF) signaling cascade (88) (Fig. 4). Zinc, a critical micronutrient for mitigating oxidative stress and promoting tissue repair, is essential for maintaining systemic homeostasis. Markedly reduced plasma zinc concentrations have been reported in patients with CKD (89), where ROS stress resulting from zinc deficiency also disrupts mitochondrial function, causing metabolic stress characterized by abnormal lactate metabolism and promoting the development of renal interstitial fibrosis (90) (Fig. 4).

Enhanced renal glycolysis contributes to CKD progression (91), with PFKFB3 acting as a critical modulator of this metabolic shift (92). PFKFB3 expression is markedly upregulated in renal proximal tubular cells following ischemia-reperfusion injury in mice, displaying a positive correlation with the extent of renal fibrosis (6). Mechanistically, lactate accumulation driven by PFKFB3-mediated glycolytic reprogramming significantly elevates histone lactylation, particularly H4K12la, which is enriched at the promoters of NF-κB signaling genes, thereby initiating their transcription and intensifying inflammatory responses (6) (Fig. 4). Thus, targeting PFKFB3-mediated NF-κB signaling in tubular cells represents a potential therapeutic avenue for CKD. During renal fibrosis, cellular metabolic reprogramming occurs, with enhanced glycolysis constituting a major feature of disease progression (93,94). Suppressing glycolytic flux may, therefore, mitigate fibrosis advancement. However, glycolysis exerts divergent effects across different renal cells; for instance, dichloroacetic acid and shikonin inhibit fibroblast activation while eliciting distinct responses in renal epithelial cells (95), suggesting that cell type-specific metabolic modulation could open new therapeutic possibilities.

Recent investigations further implicate lactate metabolism in CKD progression, although the underlying mechanisms and clinical relevance require deeper exploration. Future research should prioritize identifying specific cell types affected by lactate dynamics, and delineating the gene networks and regulatory pathways modulated by lactate. Expanding this area of study could establish a theoretical framework for innovative therapeutic strategies and ultimately enhance clinical outcomes.

7. Prospects and limitations of lactate and its related biomarkers in nephropathy

Clinical application prospects of lactate-related biomarkers. The application prospects of lactate and its related biomarkers in samples of patients with kidney disease include the potential as diagnostic markers, prognostic assessment tools and therapeutic targets.

Evidence from a cohort of patients with T2DM demonstrated that urinary lactate levels maintained a statistically significant association with end-stage renal disease risk, even after adjustment for conventional risk factors such as estimated glomerular filtration rate and urine albumin-to-creatinine ratio, highlighting their value as predictive biomarkers for disease advancement (4). Notably, urinary lactate levels show a significant correlation with established biomarkers of tubular injury and epithelial stress, namely kidney injury molecule-1 and Dickkopf-3, suggesting its potential as a predictive biomarker for disease progression (4). These findings underscore the utility of urinary lactate as a potent tool for risk stratification in DN, where it is particularly adept at identifying patient populations who, despite presenting with seemingly acceptable conventional indicators, are actually at a high risk.

Beyond quantifying lactate concentrations, molecules involved in lactate metabolism have emerged as promising biomarkers. H3K14la, a lactate-mediated epigenetic modification, has been identified as a key participant in EMT progression in DN through activation of KLF5 expression (5). Theoretically, measuring H3K14la levels in renal tissues or urinary exosomes could serve as an indicator of renal fibrosis activity. However, standardized detection methodologies for this purpose remain unavailable.

The application of lactate-related biomarkers extends beyond diagnosis and prognosis, offering potential for therapeutic target identification. The elucidation of the H3K14la/KLF5 axis introduces new avenues for anti-fibrotic drug development, with interventions targeting this pathway representing a potential strategy to delay DN progression (5). In parallel, therapeutic approaches aimed at modulating lactate production or clearance, such as adjusting LDH activity or promoting lactate utilization, may offer new opportunities for kidney disease management. The refinement and implementation of these therapeutic strategies will inevitably rely on the guidance and monitoring of corresponding biomarkers.

Limitations of clinical application. Despite significant progress, current research and technological applications encounter multiple limitations that obstruct the clinical translation of biomarkers. Obstacles span the entire workflow, from sample collection and data analysis to mechanistic interpretation and clinical validation, demanding prompt and systematic resolution.

A primary technical barrier lies in the absence of standardized detection protocols. Studies utilize a wide range of lactate measurement techniques, including enzymatic electrode assays, gas chromatography-MS, and high-performance liquid chromatography, each differing in sensitivity, specificity and reproducibility, thereby complicating cross-study comparisons (96,97). Variations in sample types and analytical strategies further impede the definition of unified cutoff thresholds.

The invasive nature of sample collection constrains the clinical applicability of certain biomarkers. Although urinary lactate measurement offers a relatively non-invasive alternative, analyses of kidney tissue-specific modifications, such as H3K14la, continue to rely on renal biopsy specimens, limiting practicality for routine diagnostics. Even blood-based assays, while less invasive than tissue sampling, impose additional burdens due to the need for frequent collection, potentially compromising patient adherence. While microneedle sensors present a novel approach for minimally invasive monitoring, their long-term stability and reusability require further validation (98,99).

Regarding biomarker specificity, elevated lactate levels commonly arise under diverse pathophysiological conditions, including tissue hypoxia, hepatic dysfunction, systemic inflammatory responses and pharmacological influences (78,100). Such conditions may overlap in patients with renal disease, thereby limiting the utility of lactate quantification alone to accurately distinguish renal-specific injuries from systemic disturbances. Moreover, distinct kidney pathologies, such as DN and ischemic renal injury, may drive lactate metabolism alterations via different molecular mechanisms (63). However, the majority of current studies focus on specific disease types and lack systematic data for cross-disease comparisons.

Limitations in dynamic monitoring technologies constrain the clinical implementation of lactate-related biomarkers. Kidney disease progression often involves dynamic metabolic fluctuations that single-time-point measurements fail to capture. Although wearable devices theoretically support continuous monitoring, practical application remains hindered by challenges such as signal instability, skin irritation and acquisition efficiency (99,101).

The translational gap between mechanistic research and clinical application remains a major obstacle. Findings derived from basic studies often lack reproducibility in clinical cohorts. Additionally, current clinical investigations predominantly employ observational designs. Interventional trials are required to substantiate the clinical relevance of lactate-related biomarkers.

Research on lactate is evolving beyond its characterization as a metabolic byproduct toward its recognition as a multifunctional signaling molecule. Addressing existing challenges is essential for refining future research priorities, advancing detection methodologies and optimizing the clinical integration of current technologies. These efforts may offer novel perspectives for the early diagnosis and precision management of kidney diseases.

8. Management strategies of kidney diseases based on lactate metabolism

According to the present review, lactate has demonstrated predictive utility as a biomarker in kidney disease and contributes to disease progression; its production is regulated by critical glycolytic enzymes, including LDH, GLUT, HK2 and PKM2. Modulation of lactate metabolism through targeting these enzymes, altering its synthesis, transport and conversion, represents a potential therapeutic approach for the treatment of kidney diseases.

PKM2, a key isomer of the pyruvate kinase family, serves a fundamental role in glycolysis; its expression is markedly diminished in podocytes from patients with hypertensive nephropathy and DN (102). Urinary PKM2 has also emerged as a potential biomarker for predicting SA-AKI (103), highlighting PKM2 as an attractive therapeutic target for kidney diseases. TEPP-46, a small-molecule activator of PKM2, enhances glycolytic flux in healthy renal tissue (104). In diabetic mouse models, TEPP-46 restores tubular epithelial integrity by suppressing EMT and abnormal glycolysis, thereby attenuating diabetic renal fibrosis (105). Additionally, TEPP-46 restricts pericyte proliferation, migration and pericyte-myofibroblast transdifferentiation by limiting nuclear translocation of PKM2, offering a new approach to preventing the transition from AKI to CKD (106). Microcystin-RR (MC-RR), which demonstrates anti-pulmonary fibrosis properties (107), also exhibits renal protective effects. Using unilateral ureteral obstruction (UUO) mouse models and *in vitro* cell models, Ren *et al* (108) demonstrated that MC-RR directly bound to PKM2, modulated the PKM2-HIF-1α signaling axis, restored suppressed MMP-7 and MMP-13 expression, and reduced elevated MMP-9 levels in UUO renal tissue, thereby mitigating renal fibrosis. Furthermore, several Chinese herbal compounds exert nephroprotective effects through PKM2 targeting. For instance, modified Hu-lu-ba-wan ameliorates glomerular injury and podocyte apoptosis by maintaining PKM2-mediated mitochondrial homeostasis in DN (109). Similarly, Qian Yang Yu Yin granules improve hypertensive nephropathy by reprogramming metabolism through the HIF-1α/PKM2 positive feedback mechanism (110).

HK2, the principal rate-limiting enzyme of glycolysis, serves a central function in metabolic regulation. Evidence indicates that ceria nanoparticles attenuate metabolic disturbances in renal fibrosis models by diminishing ROS, enhancing mitochondrial ATP production, and suppressing HK1 and HK2 expression, thereby conferring renal protection (111). LDHA, responsible for catalyzing the conversion of pyruvate to lactate during glycolysis, is integral to maintaining cellular energy equilibrium. Curcumin, the primary curcuminoid in turmeric, mediates renoprotective effects by inhibiting aerobic glycolysis through the miR-489/LDHA axis, thereby alleviating glucose fluctuation-induced renal injury in the 293 cell model (112). Moreover, the glycolysis inhibitor 3-bromopyruvate restrains TGF-β1-induced fibroblast proliferation in a time- and dose-dependent manner, significantly downregulating the expression of aerobic glycolysis-related enzymes, such as HK2, LDHA and PKM2, while modulating the IL-1 receptor-associated kinase 4/MYC signaling pathway to mitigate renal fibrosis (113).

Modulating glucose entry into glycolysis represents a promising therapeutic strategy. The membrane protein GLUT is integral to the transport of glucose and related substrates across cell membranes. In HK-2 cells treated with high glucose, the expression level of GLUT-1 was upregulated (114), and in a streptozotocin-induced DN rat model, the expression level of GLUT-2 was downregulated (115). p-Coumaric acid nanoparticles have been shown to attenuate DN in rats by controlling hyperglycemia, suppressing inflammation and enhancing GLUT-2 mRNA expression in nephropathic models (115). Similarly, Huangqi decoction restores GLUT expression in diabetic kidneys, elevating GLUT4 levels while reducing GLUT1 expression in a dose-dependent manner (116). A bioflavonoid combination has further demonstrated renal function improvement in DN by regulating MMP-9/TIMP-1 expression, upregulating GLUT-4 and downregulating TGF-β (117). Regulation of glycolytic enzymes through these interventions may influence lactate production, transport and metabolism, offering therapeutic advantages in kidney disease management.

Clinical research into drugs targeting lactate metabolism or modulating lactylation mechanisms for kidney disease treatment remains an emerging and promising domain. Pharmacological or metabolic interventions designed to reduce lactate accumulation may potentially slow disease progression. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as dapagliflozin, currently in clinical use, appear to indirectly decrease lactate levels by enhancing energy metabolism and exert renal protective effects in patients with DN (118). Levocarnitine mitigates oxidative stress and attenuates lactate accumulation in patients with kidney disease, particularly benefiting individuals with chronic renal failure and L-carnitine deficiency secondary to hemodialysis (119,120). However, most agents intended to regulate lactate metabolism or influence lactylation pathways remain at experimental stages, with clinical validation of their therapeutic potential still limited. Further research is warranted to clarify their mechanisms of action, assess safety profiles and establish therapeutic efficacy to support clinical translation in kidney disease management.

In clinical practice, dysregulation of lactate metabolism and lactate-mediated modifications in the kidney constitute a shared pathophysiological basis for multiple renal disorders. Effective monitoring requires an integrated evaluation of blood lactate concentrations, urinary lactate levels and biomarkers of lactate modifications in renal biopsy specimens. Management of patients with lactic acidosis emphasizes the aggressive treatment of underlying conditions, correction of hypoxic states and amelioration of metabolic perturbations. In the medication of certain populations, particular caution is warranted in patients with CKD to avoid nephrotoxins that may enhance lactate production, such as metformin (121), alongside monitoring of serum lactate and acid-base status. In the context of SA-AKI, early goal-directed therapy combined with infection source control can mitigate lactate accumulation. Pharmacological strategies targeting lactification currently remain under investigation. Future progress will depend on interdisciplinary efforts to integrate lactate metabolic regulation with epigenetic modification mechanisms, thereby enhancing their translational potential.

Targeting glycolytic enzymes to regulate lactate metabolism offers a promising therapeutic approach for kidney diseases but faces multiple substantive challenges. Low target specificity remains a major concern, as glycolytic enzymes such as PKM2 and HK2 are extensively involved in systemic metabolism, raising the risk of unintended metabolic disturbances. The pronounced heterogeneity among kidney diseases further complicates therapeutic outcomes, with the same target having variable effects across different pathological contexts. Insufficient drug delivery efficiency also limits therapeutic success, particularly for natural compounds such as curcumin, which exhibit poor renal targeting due to hepatic first-pass metabolism and systemic distribution. Additionally, inhibition of a single glycolytic enzyme may provoke compensatory metabolic pathways, introducing further complexity into therapeutic modulation. Clinical translation remains constrained by the reliance on animal and *in vitro* models, with minimal validation in human kidney tissues. Future strategies require the development of highly specific renal delivery technologies. Integrating multi-omics approaches to delineate the metabolic-immune-epigenetic networks, alongside the construction of dynamic biomarker systems through spatial metabolomics, will be instrumental in mapping the spatiotemporal heterogeneity of lactate metabolism throughout kidney disease progression. Furthermore, advancing personalized therapeutic strategies through clinical trials guided by dynamic biomarkers may shift the paradigm from merely correcting metabolic imbalances to reconstructing renal microenvironmental homeostasis.

9. Conclusion

Lactate and its metabolic pathways exert multifaceted roles in renal physiology and pathology, functioning not only as central mediators of energy metabolism but also through lactylation-driven epigenetic modifications that influence renal cell inflammation, fibrosis and reparative processes. Current research has preliminarily established the association between dysregulated lactate metabolism and kidney diseases, with interventions targeting lactate pathways exhibiting therapeutic potential in preclinical models. Nevertheless, prevailing conclusions largely derive from broad-spectrum metabolic regulation studies, lacking precise delineation of cell-type specificity, spatiotemporal dynamics and the molecular network underlying lactylation-mediated pathological mechanisms, which remain to be systematically elucidated.

Future research priorities should address the following areas: i) Development of precision intervention tools, engineering tissue-specific modulators of lactylation, such as LDHA inhibitors or lactylation enzyme regulators targeting renal tubular epithelial cells, to enable selective intervention within renal parenchymal cells while minimizing systemic metabolic perturbations. ii) Construction of dynamic models, establishing animal models capturing the temporal dynamics of lactylation alterations during kidney disease progression, including cell-specific lactate sensor transgenic mice to characterize metabolic heterogeneity across pathological stages. iii) Integration of interdisciplinary technologies, applying multi-omics approaches such as metabolomics and spatial transcriptomics to unravel the interaction networks linking the glycolysis-lactate axis with immune microenvironmental remodeling and fibrotic pathways, and identifying key regulatory nodes. Concurrently, clinical translation challenges must be addressed by developing non-invasive detection tools for lactate metabolism markers and validating the safety profiles of therapeutic strategies using models such as organoids, thereby providing a basis for personalized treatment. Comprehensive, multidimensional analyses of cell-specific mechanisms and dynamic lactate metabolic networks are anticipated to drive the evolution from biomarker discovery to targeted therapies in kidney disease management.

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Authors' contributions

XL wrote the manuscript text. HJ conceived and designed the review. LH and QH edited and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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