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Review

Ketamine-associated upper urinary tract dysfunction: What we know from current literature

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KEYWORDS
Ketamine;
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Pathologic mechanism

Abstract *Objective:* To review the current literature on ketamine-associated upper urinary tract (UUT) dysfunction and provide an overview of its pathogenesis and treatment principles.
Methods: A literature search was conducted using PubMed and Cochrane databases for relevant articles published in English between 2008 and 2023. Keywords used included "ketamine" and "upper urinary tract".
Results: A total of 22 papers were included. Relatively few studies have focused on ketamine-associated UUT dysfunction. Exclusion criteria included lack of hydronephrosis, or pathological findings. After careful screening and exclusion, we finally adopted 11 of these papers and analyzed them. Ketamine-associated UUT dysfunction may be a concern in this field.
Conclusion: Ketamine abuse can lead to UUT impairment and dysfunction, with symptoms such as bladder dysfunction and contracted bladder with vesicoureteral reflux, direct damage and barrier dysfunction, inflammation, apoptosis, fibrosis and stricture, and papillary necrosis. Oxidative stress, autophagy, and microvascular injury are also potential pathogenic mechanisms. The detection of these symptoms largely depends on laboratory and imaging examinations. The treatment principles of ketamine-associated UUT dysfunction are protecting the UUT, improving bladder dysfunction, and resuming normal social life. More investigations are needed to clarify the mechanisms and shed light on the treatment of ketamine-associated UUT damage.

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1. Introduction

Since its discovery in the 1960s, ketamine—a nonselective antagonist of the N-methyl-D-aspartate receptor—has been utilized as an anesthetic and analgesic in both human and veterinary medicine [1—5]. Since the 1990s, ketamine has been more and more popular among young people in clubs as a recreational drug due to its short-acting, hallucinogenic, and dissociative effects [1,4,5]. Epidemiological data show that among young individuals in the United States, and European and Asian countries, ketamine continues to rank highly among illicit substances [6—11].

Overdosing on ketamine for an extended length of time can have detrimental effects on many abusers' systems. The first report of ketamine-associated cystitis (KAC) was published in 2007 [12]. Lower urinary tract symptom (LUTS) manifestations, such as frequent urination, urgency, incomplete emptying, nocturia, dysuria, incontinence, and in some cases, hematuria, were the primary symptoms of KAC [12—14]. After almost 15 years of research on KAC, the pathophysiology of KAC has been explored using cell line tests, animal models, and clinical data. The following statements are the mechanisms of KAC: direct toxicity, disruption to the urothelial barrier, apoptosis and inflammation, microvascular injury, neuropathy, and oxidative stress [5,15]. Ketamine abstinence is the primary intervention prior to the systematic treatment. Anti-inflammatory, anticholinergic agent, cholinergic M-type receptor antagonist, analgesic, and other medications are used in the conservative treatment [5,15,16]. Bladder hydrodistension, intravesical instillation, cystoplasty, and other surgical procedures may be utilized based on the patient's condition [5,15,16].

Patients with bladder dysfunctions commonly experience upper urinary system lesions, such as hydronephrosis, hydroureter, and ureteral stricture [17]. Furthermore, certain animal models have indicated that ketamine can induce injury to the upper urinary system in addition to cystitis [18]. We have suggested that greater attention should be given to the upper urinary system in cases involving KAC [19]. However, there have been no reported systematic data or explanations regarding the mechanisms associated with ketamine-induced damage to the upper urinary system. Indeed, the upper urinary system plays a pivotal role in the formulation of treatment regimens. In this regard, we shall present clinical and experimental discoveries and elucidate the mechanisms underlying ketamine-related injuries to the upper urinary tract (UUT).

2. Clinical characteristics of ketamine-induced injuries to the upper urinary system

2.1. Clinical symptoms and epidemiological characteristics

Unlike LUTSs induced by ketamine, damages to UUT systems caused by ketamine are typically chronic, progressive, and asymptomatic, except in some emergency cases. While lumbago and abdominal pain may be potential symptoms of ketamine-associated hydronephrosis, they are often overshadowed by troubling LUTSs such as frequency, urgency, and dysuria. In cases of renal function failure, the symptoms are also not always identical. LUTSs may be accompanied by flank pain, and in some severe cases, even a change in consciousness [20—22].

Regarding the prevalence of upper urinary system involvement in ketamine abusers, the available data vary across different reports. A summary of UUT involvement in recent literature with total cases more than 30 is listed in Table 1 [17,23—29]. A univariate analysis revealed potential risk factors associated with hydronephrosis, including the age, duration of ketamine abuse, symptomatic score of pelvic pain, urine urgency or frequency, voiding volume, abnormal serum creatinine levels, and the activity of liver enzymes. These factors were found to be more relevant than abstinence status or the average weekly amount of ketamine assumption [17]. Furthermore, a multiple logistic regression analysis indicated significant associations between hydronephrosis and age, functional bladder capacity, abnormal serum creatinine, and the activity of liver enzymes [17].

Based on the table, we can observe that the occurrence of upper urinary system involvement in KAC ranged from 2.9% to 13.6% for abnormal serum creatinine levels, and from 4.7% to 50.8% for hydronephrosis. To gather a comprehensive understanding of ketamine-induced damage to the upper urinary system, it is necessary to involve multiple centers with a significant number of cases, as some cases had limited attendance and the sample size was small.

2.2. Laboratory examinations

Currently, the levels of the urine protein, blood creatinine, and the estimated glomerular filtration rate (eGFR) are measured in KAC to determine whether the upper urinary system is affected in patients. These laboratory tests are non-invasive and provide fast clinical monitoring. Several case reports have indicated the presence of urine protein in KAC, with some even showing renal function failure [21,30]. In a study involving 23 cases of KAC, urinary analysis revealed that five out of the 23 cases exhibited proteinuria (1^+); eight cases showed 2^+ proteinuria; and only one case had 3^+ proteinuria [31]. However, the authors did not provide additional data related to the upper urinary system, thus requiring further investigation into the diagnostic value of proteinuria in KAC. Creatinine, which is commonly used to assess renal function, was also included in Table 1. A study conducted on 53 ketamine abusers revealed that their creatinine levels were elevated to a mean of 1.25 (standard deviation 0.42) mg/dL [32]. However, Table 1 indicated that the UUT involvement is more likely to be detected by imaging examinations than creatinine. This suggests that creatinine has low sensitivity in distinguishing upper urinary system dysfunction caused by ketamine. To evaluate and monitor renal function in nephrology, the measurement of eGFR is considered a vital test [33,34]. Numerous studies have already utilized eGFR for clinical staging and monitoring renal function [20,27,35].

In animal models, several tests of measuring the urine protein, creatinine, and creatine clearance rate have been employed to assess renal function [18,36]. In a study in which Institute of Cancer Research (ICR) mice were injected intraperitoneally with ketamine at 30 mg/kg per day, the

Table 1 Epidemiological characteristics of ketamine-associated upper urinary tract injuries.

Study	Participant, *n*	Abnormal serum Cr	Hydronephrosis	Hydroureter	VUR
Chu et al., 2008 [23]	59	13.6% (8/59)	50.8% (30/59[a])	NA	12.8% (6/47)
Tam et al., 2014 [24]	318	7.2% (23/318)	8.1% (13/160[a])	NA	NA
Misra et al., 2014 [28]	34	2.9% (1/34)	11.1% (2/[13[a]+5[b]])	11.1% (2/[13[a]+5[b]])	NA
Lin et al., 2016 [29]	36	NA	22.2% (8/36[c])	NA	16.7% (6/36)
Yee et al., 2017 [17]	572	4.4% (25/572)	16.8% (96/572[a])	NA	NA
Jhang et al., 2018 [26]	38	NA	26.3% (10/38[c])	NA	NA
Sihra et al., 2018 [27]	44	NA	14.3% (4/28[b])	NA	11.1% (1/9)
Schifano et al., 2021 [25]	1758	NA	4.7% (82/1758[c])	0.2% (4/1758[c])	0.1% (2/1758)

Cr, creatinine; NA, not applicable; VUR, vesicoureteral reflux.
[a] The ultrasound was performed.
[b] The CT scan was performed.
[c] The detecting method was not reported.

urine protein was detected at 6 weeks, 16 weeks, and 28 weeks, respectively [37]. The urine protein was negative in the control group; however, 15%, 40% and 67% mice were positive in the ketamine-induced group at 6 weeks, 16 weeks, and 28 weeks, respectively [37]. When Sprague Dawley rats were injected intraperitoneally with ketamine at 25 mg/kg per day for 14 days or 28 days, the ratio of creatinine to urinary protein in the 14-day or 28-day groups was significantly higher than that in the control group injected with normal saline (both $p<0.01$), but the significant decrease in the creatine clearance rate was detected only in the 28-day group ($p<0.01$). Renal dysfunction was indicated in the experiment [18], and it was also consistent with our view that ketamine-associated UUT injury is chronic and progressive.

There are undoubtedly some limitations in the use of these almost non-invasive tests to predict renal function in ketamine users. High sensitivity with accepted specificity is needed in clinics. Further studies are needed with large sample sizes and epidemiological measures to guide early detection of the UUT injury.

2.3. Imaging examinations

Ultrasound is widely used for screening and diagnosis of ketamine-associated UUT injury. It is non-radioactive and easily accessible in clinics, especially in large-scale investigations and emergencies [17,20]. Some cases of hydronephrosis can be detected by ultrasound, but with a normal creatinine level [23]. Based on this phenomenon, ultrasound will provide earlier information on UUT damage. However, in a case series reported by Lai et al. [38], six cases of KAC were within the normal range of the creatinine level, with contracted bladder, bilateral upper ureteral stricture, and bilateral hydronephrosis on intravenous urography. Urography is used as a method to show the outline of the urinary system. Video cystometrogram would be used to check for vesicoureteral reflux (VUR) in addition to bladder structure and function [39]. Mercaptoacetyltriglycine renography can be used as a test to understand the drainage of each kidney [27].

In order to monitor the urinary system and reduce potential lesions in the urinary system as previous examinations, CT with enhancement will provide more information such as bladder thickness, ureteral stricture, hydroureter, and hydronephrosis. In a retrospective study by Huang et al. [40], the CT urography scans of 27 patients were reviewed. They reported the involvement of the UUT in their study as follows: 12 cases had hydronephrosis; nine had ureteral wall thickness; and two had ureterovesical junction involvement [40].

Although more information about the UUT can be obtained by imaging, especially CT, missed imaging appointments and loss to the follow-up are very common in these patients [28]. Proper combination of laboratory and imaging tests with patient compliance is a challenging problem for urologists.

3. Pathogenesis of ketamine-associated UUT injury

We have summarized the pathological mechanism of ketamine-associated UUT injury from previous literature, and made some assumptions and additions by referring to the pathological mechanism of ketamine cystitis (the corresponding chapter is 3.7), as shown in Fig. 1.

3.1. Direct damage and barrier dysfunction

Direct toxic damage and barrier dysfunction are important mechanisms in KAC. Denuded bladder urothelium and loss of cell–cell adhesion and junctional proteins (such as

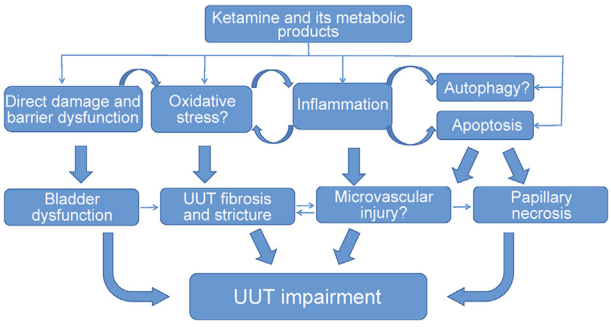

Figure 1 The pathological mechanism of UUT injury induced by ketamine. UUT, upper urinary tract. "?" Indicates a potential pathologic mechanism to be verified.

E-cadherin, claudin-4, and zonula occludens-1 [ZO-1]) are evidence of KAC [5,41]. In addition, bladder mucosa protectants showed significant effects of LUTSs on the ketamine abuser in clinical treatment and animal models [5,41]. As these presented in lower urinary tract, studies from upper urinary system also indicated similar results [26,42,43]. Histology from ureters showed the ulcer and denudation of the ureteral urothelium, partially with reactive regenerative changes [26,42,43]. We think ketamine-associated denuded urothelium, ketamine, urine metabolites, and irritating materials would infiltrate into ureter suburothelial layer then inducing inflammatory reactions and causing destructive changes. *In vitro* research in renal cell lines showed ketamine-induced morphology and cytoskeleton changes [44], accompanied by decreased of cell-to-cell junction markers (E-cadherin, occludin, and ZO-1) [45]. Ketamine could also disrupt barrier permeability in renal distal tubular cells [45]. Some degenerative changes have also been found in *in-vivo* studies, such as glomerular atresia, tubular hydropic degenerations, atrophy, distortion, and blocking [37,46]. These studies showed that ketamine caused changes in the structure and barrier function of the upper urinary system, leading to further disruption of the system.

3.2. Inflammation

Inflammation would be a key pathogenic process in ketamine-associated UUT injury. Inflammatory infiltrates were frequently seen in some ureteral biopsies and even in all layers of the ureter. We have summarized clinical cases with inflammatory infiltration in the UUT in Table 2 [23,26,39,42,43]. *In vivo* experiments from animal models had also presented some pathogenic information. A study by Yeung et al. [47] showed interstitial nephritis with normal appearance of glomeruli and tubules. a rat model induced with ketamine showed no significant histological changes in rat ureters [48]. This may represent a different stage of ketamine-associated UUT injury. A study by Li et al. [46] showed infiltration of large mononuclear cells in animal kidney specimens, in addition to structural changes in the renal tubules. The mouse model from Yeung et al.'s study [47] showed mononuclear dominant inflammatory cell infiltration near glomeruli and blood vessels in ketamine-associated kidney specimens, in addition to distal and collecting tubules, and even the papilla and ureter. An *in vitro* study in renal distal tubule cell lines showed increased secretion of inflammatory cytokines (tumor necrosis factor-α and interleukin) in a ketamine concentration-dependent manner [45].

Table 2 Histological results related to inflammatory infiltration in UUT from clinical cases.

Study	Type	Total participant, *n*	Patient with UUT, *n*	Histology description
Chu et al., 2008 [23]	Original article	59	1	• The histological feature of the ureter was fibrosis, secondary to an intense transmural inflammatory response
Chang et al., 2012 [39]	Original article	20	2	• Pathological results showed chronic inflammation of the ureter, with reactive changes of the urothelium and formation of granulation tissue with inflammatory exudates
Raison et al., 2015 [43]	Case report	1	1	• The ureteric biopsy showed focal mucosal ulceration with a mononuclear cell infiltrating of the urothelium and tunica propria
Wu et al., 2016 [42]	Case report	1	1	• Left ureteral histologic revealed denudation of most of the overlying urothelium, with reactive regenerative changes in the residual urothelium that showed mildly hyperchromatic nuclei; immunohistochemistry staining showed that the regenerative epithelium was positive for cytokeratin 7 and negative for p53; the stromal edema, diffuse chronic inflammatory infiltration, and active granulation tissue were observed in the subepithelial connective tissue; the granulation tissue also extended into the muscle layer; the inflammatory infiltrates were mainly composed of lymphocytes and only a few eosinophils; this morphology was compatible with ketamine ureteritis and negative for evidence of malignancy
Jhang et al., 2018 [26]	Original article	38	NA	• Ureter specimens from patients with severe ketamine-associated uropathy showed mucosal defects, including the infiltration of inflammatory cells in the mucosa, muscle, and subserosa

UUT, upper urinary tract; NA, not applicable.

The above studies indicate that inflammatory processes are involved in the pathogenesis of ketamine-associated UUT injury, which is associated with structural changes. Withdrawal of ketamine for 8 weeks could completely reverse the inflammatory process in the bladder but not in the kidney in animal experiments. Compared with animals in the ketamine group, animals in the ketamine and cyclooxygenase-2 inhibitor group had an increased creatinine clearance rate and a decreased urinary protein to creatinine ratio [36]. These experiments provided some insight into the treatment and inflammatory pathogenesis of ketamine-associated UUT injury. In some studies of KAC, mast cells, eosinophil infiltration, and IgE play important roles in the occurrence and development of inflammation [15,49]. The effects of these immune cells and protein on ketamine-associated UUT inflammation still need a further study.

3.3. Apoptosis

According to recent reports, apoptosis was found to be a key process in ketamine-associated damage in the neural, urological (mainly bladder), and male genital systems [50—53]. Apoptosis was also found to be regulated in the pathogenesis of renal injury and toxicity [54,55]. In a rat model of ketamine self-administration, a significant increase in renal injury and apoptosis was observed in the ketamine-associated group, which was partially reversed in the abstinence group [46]. Further studies and deeper investigations would clarify the effects of apoptosis and possible mechanisms in ketamine-associated UUT injury.

3.4. Bladder dysfunction and contracted bladder with VUR

Early clinical findings of KAC with hydronephrosis may be secondary to irreversible fibrotic changes in the lower urinary tract. As reported by Chu et al. [23] in 2008, most cases of hydronephrosis diagnosed by renal ultrasound were associated with hydroureter up to the vesicoureteral junction by intravenous urography. Video cystometrogram results also showed decreased bladder volume, and compliance and/or detrusor overactivity, while VUR was also detected in 13% of all cases. The authors suggest that the UUT damage was secondary to the decrease in bladder compliance and VUR over a long period of time [23]. Proof of concept can also be seen in other clinical studies.

Five cases with normal renal function in the study by Tsai et al. [56] presented with hydronephrosis, reduced bladder capacity, and detrusor overactivity. The "golf hole" alteration of the ureteral orifice was also found in a clinical case. Bladder contraction, reduced compliance in VUR, and bilateral hydronephrosis were also seen in the study by Yek et al. [57]. Hydronephrosis with ureteral thickening and stricture was also presented in a study [58]. Renal papillary necrosis and ureteral inflammatory changes were also found in a previous study [23]. Lamers et al. [58] reported an 18-year-old man who presented with acute kidney injury, UUT hydronephrosis, and ureterovesical reflux due to ketamine abuse.

Secondary to lower urinary tract damage is the etiology of UUT lesions. Other mechanisms have been proposed to explain the UUT injury. This view is inconsistent with other authors [28,35]. We will collect clinical data and try to clarify the potential mechanisms leading to the UUT injury through *in vivo* and *in vitro* experiments.

3.5. Fibrosis and stricture

Imaging evaluation by CT urography in 27 patients with KAC showed that the thickening of ureteral wall accounted for 33.3% patients, and the involvement of vesicoureteral junction accounted for 7.4% patients [40]. In another study, including 19 patients who underwent antegrade, retrograde pyelogram, or technetium-99m diethylenetriamine-pentaacetic acid scan, eight cases were found to have ureteral obstruction at either the pelvic-ureteric junction or the vesicoureteral junction [17]. In ketamine users, the ureteral stricture at various positions was found to be common in other reports [38,59]. Ureteral histology showed ureteral and periureteral fibrosis with extensive inflammation infiltrating the ureteral wall [23,60]. In an *in vitro* study in renal distal tubular cells, Ketamine could induce the secretion of inflammatory cytokines and transforming growth factor beta 1, as well as the expression of fibronectin in cells [45]. These studies indicated that inflammation and fibrosis constituted the pathogenesis of ketamine-associated UUT injury, with stenosis and obstruction occurring during this process.

The diffuse ureteral stricture was also noted in some cases, and some authors thought that retroperitoneal fibrosis might be the pathogenesis [60,61]. Ketamine induces transmural ureteral inflammation, inflammatory exudates, and periureteral fibrosis, which may stimulate an immunological response to induce retroperitoneal fibrosis [43,60,61]. The assessment of the presence, location, and length of ureteral stricture is an important factor in surgical management and prognosis.

3.6. Papillary necrosis

Renal papillary necrosis is associated with ischemic injury and infection of renal pyramids of the UUT [62—64]. Renal papillary necrosis can also be seen in ketamine-associated UUT injury. Four cases of papillary necrosis associated with inflammatory infiltration were identified by renal ultrasound in hospitalized patients with ketamine-associated LUTSs [23]. In addition, two cases of papillary necrosis with interstitial nephritis from ketamine-associated animal models were found on renal histological evaluation [23]. Inflammation is one of the pathogenesis of ketamine-associated uropathy, and microvascular injury is also associated with KAC [5]. Ketamine-associated renal infarction has also been reported, and the authors suggested that ketamine decreased nitric oxide synthesis, which then affected vascular contraction and relaxation [65]. From this evidence, it can be concluded that ketamine may induce inflammation and vascular ischemic changes leading to papillary necrosis.

3.7. Oxidative stress? Autophagy? Microvascular injury?

Many studies have shown that the toxic effects of ketamine abuse can activate oxidative stress [18,66]. This has been demonstrated in ketamine cystitis. Oxidative stress and inflammation are known to be closely related. Therefore, oxidative stress is very likely to be an important way in which ketamine damages renal function.

Autophagy plays a key role in the progression of ketamine cystitis [67—70]. Given the similarity of the urothelium in the renal pelvis, ureter, and bladder, it is very likely that autophagy plays an important role in ketamine-associated UUT injury; however, further basic studies are needed to clarify and confirm this.

Ketamine causes microvascular damage through a variety of inflammatory and angiogenic factors such as tumor necrosis factor alpha and vascular endothelial growth factors [29,71,72]. However, the effect of ketamine on the small vessels of the UUT and its specific mechanism remain unclear.

4. Signal pathways related to ketamine-associated injuries to the upper urinary system

Several *in vitro* studies have reported possible signaling pathways associated with UUT injury, providing some potential pathogenesis and therapeutic targets, as shown in Fig. 2.

4.1. Protein kinase B (AKT)/glycogen synthase kinase 3β (GSK-3β) signaling pathway

Ketamine induced phosphorylation of focal adhesion kinase, AKT and GSK-3β in a time- and concentration-dependent model in renal distal tubular cell lines [65]. Further investigation in the study revealed that ketamine might induce renal dysfunction through the phosphatidylinositol-3-kinase (PI3K)/AKT/GSK-3 beta signaling pathway [45]. Ketamine mediates the PI3K/AKT signaling pathway to inhibit GSK-3β activity through Ser-9 phosphorylation, and further reduces transepithelial resistance, and increases paracellular permeability and junction breakdown, accompanied by downregulation of apical junction (ZO-1, occludin, and E-cadherin) levels.

4.2. p38 mitogen-activated protein kinase (MAPK)/extracellular regulated protein kinases (ERK) or p38 MAPK/NF-κB signaling pathway

Ketamine can mediate the p38 MAPK/ERK signaling pathway to promote epithelial to mesenchymal transition, thereby accelerating the progression of proximal renal tubular epithelial fibrosis [44]. This process does not depend on transforming growth factor beta 1 function. After blocking p38 MAPK/ERK, the expression of epithelial markers (such as E-cadherin) was restored to some extent and fibrosis was improved. In addition, ketamine has been reported to affect the local inflammatory environment by increasing oxidative stress through extracellular vesicle-mediated p38 MAPK/NF-κB signaling pathways [66].

4.3. The inositol-requiring enzyme 1 (IRE1)/tumor necrosis factor receptor associated factor 2 (TRAF2)/apoptosis signal-regulating kinase 1 (ASK1)/c-Jun N-terminal kinase (JNK) signaling pathway

Ketamine enhanced autophagy and endoplasmic reticulum stress (ERS) *in vivo* and *in vitro* by inhibiting the IRE1/TRAF2/ASK1/JNK signaling pathway [73]. Ketamine and its metabolites can increase levels of reactive oxygen species, induce IRE1-TRAF2-ASK1 complex formation, and ultimately induce ERS-dependent autophagy and apoptosis. ERS inhibitors can reverse the effects of ketamine on cells, and similar results can be seen when the IRE1/TRAF2/ASK1/JNK signaling pathway is inhibited. It has been reported that ketamine can promote apoptosis and induce inflammation by regulating the upstream and downstream molecules of nucleotide-binding oligomerization domain-like receptor protein 3 [74].

4.4. The Ca^{2+}/ERK1/2 signaling pathway

Ketamine and its metabolite (norketamine) can induce mitochondrial dysfunction and ERS, accompanied by a significant increase in the intracellular Ca^{2+} level. The use of ERK1/2 inhibitors significantly improve cell viability and reduce apoptosis, ERS, and mitochondrial dysfunction. Ca^{2+} plays an important role in signaling in this process. Ketamine and norketamine exposure exerts urothelial cytotoxicity via Ca^{2+}-regulated ERK1/2 activation, which is involved in downstream mediation of the mitochondria-dependent and ERS-triggered apoptotic pathway, resulting in urothelial cell death [53].

Further studies are warranted to elucidate the complex molecular regulatory network to provide monitoring biomarkers and therapeutic targets in ketamine-associated UUT injury.

4.5. The Cav1.2-mediated signaling pathway

Cav1.2 is a potent L-type Ca^{2+} channel. In KAC, ketamine can inhibit signaling and regulate Ca^{2+} influx and smooth muscle contractility. Inhibition of Cav1.2 is an important pathway in KAC, and studies have confirmed that ketamine-associated smooth muscle dysfunction can be alleviated by reactivating this pathway [75].

4.6. The mammalian target of rapamycin (mTOR)/phospho-S6 ribosomal protein signaling pathway

The activation of the mTOR signaling pathway underlies ketamine-induced uropathy. mTOR phosphorylation levels increase after exposure to ketamine. As a product of the mTOR signaling pathway in bladder microvasculature, phospho-S6 ribosomal protein is significantly upregulated and involved in the transformation of bladder endothelium into mesenchymal cells [76].

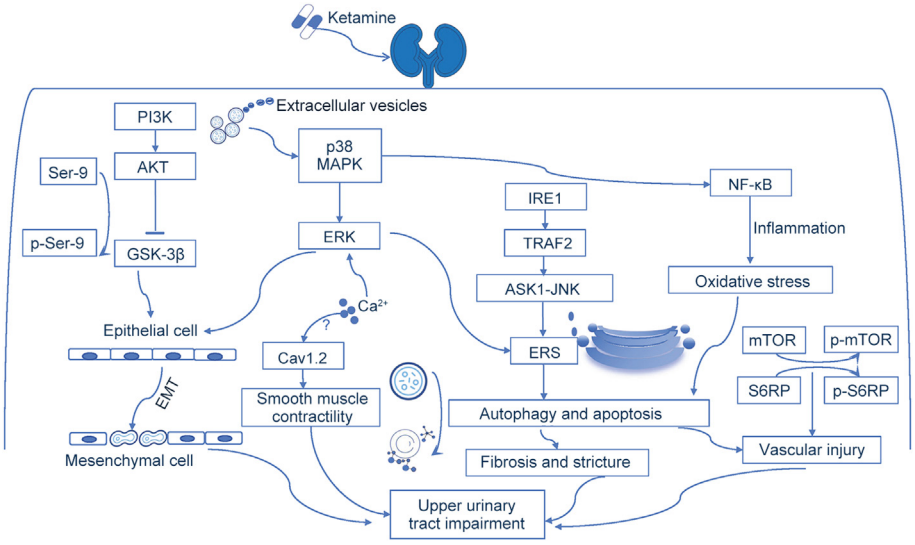

Figure 2 Signaling pathways of upper urinary tract injury induced by ketamine. PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; MAPK, mitogen-activated protein kinase; GSK, glycogen synthase kinase; ERK, extracellular regulated protein kinase; IRE1, inositol-requiring enzyme 1; TRAF2, tumor necrosis factor receptor associated factor 2; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; ERS, endoplasmic reticulum stress; mTOR, mammalian target of rapamycin; p-mTOR, phosphorylated mTOR; S6RP, ribosomal protein S6; p-S6RP, phosphorylated S6RP; p-Ser-9, phosphorylated Ser-9; EMT, epithelial–mesenchymal transition.

5. Treatment

The principles of treatment for ketamine-associated uropathy are to protect the UUT, improve bladder dysfunction, and return to normal social life. Ketamine withdrawal is the primary intervention. Conservative treatments to regulate inflammation and immunology, and to improve LUTSs are prescribed according to the patient's symptoms and severity. The surgery to improve bladder capacity and compliance is an option to reduce the possibility of hydronephrosis secondary to vesicopathy. Ureteral reimplantation is a surgical choice depending on the grade of VUR, bladder pressure, and the position and location of the ureteral obstruction [77,78]. Double-J tube implantation and/or nephrostomy are performed in patients with ureteral obstruction or renal insufficiency [35,60]. Clinical complexity, poor patient compliance, and poorly understood pathogenesis contribute to the difficulties in managing ketamine-associated UUT.

In line with the above pathways, potential future therapeutic targets include GSK-3β agonists, Cav1.2 agonists, ERS inhibitors, Ca^{2+} inhibitors, MAPK inhibitors, mTOR inhibitors, and ERK inhibitors. Reducing the level of autophagy, apoptosis, or fibrosis is also a direction worth considering. The next step is to promote the clinical translation and application of these targeted drugs and actually test their clinical efficacy. Perhaps the development of a protective agent that separates ketamine and urothelium is a good option.

6. Perspective

Firstly, more well-designed large prospective studies are needed to learn more about the prevalence and risk factors of UUT involvement in ketamine-associated uropathy. These details include the early stage of renal injury and ureteral changes, incidence of hydronephrosis, ureteral thickening or even stenosis, and renal dysfunction. Secondly, more clinical data are needed to explain the clinical presentation and the relationship of laboratory and imaging tests. This will provide some guidance to clinicians in selecting investigations in KAC to detect UUT injury earlier. Thirdly, histological studies are welcome to clarify the process of ketamine-associated UUT involvement. In addition, the results of histological studies will also provide research directions for ketamine-associated uropathy. Fourthly, studies on the mechanisms and pathogenesis of ketamine-associated UUT, especially in the kidney, will also shed light on how ketamine-associated renal injury occurs and facilitate further treatment to protect renal functions. Last but not least, the follow-up of current patients with UUT involvement will provide more information on the progression and guide the further making of treatment regimens.

In addition, more research is needed into the mechanism of UUT injury caused by ketamine. At present, there is a relative lack of targeted literature and evidence in this area. We need basic research to clarify the etiology and mechanism of ketamine on UUT injury and to explore feasible options to mitigate or even reverse the toxic effects of ketamine. The development of drugs that target specific pathways is also something to look forward to in the future. This will give doctors more tools to fight the disease.

7. Conclusion

According to the limited current literature, ketamine-associated UUT injury is a challenge for urologists. The prevalence is variable in different reports. Direct

damage, barrier dysfunction, and inflammation may be the basis of ketamine-associated UUT involvement; apart from the secondary injury to bladder dysfunction, apoptosis, oxidative stress, fibrosis, stricture, and papillary necrosis are further pathogenesis based on the former.

Author contributions

Study concept and design: Li Huang, Zhao Wang.
Data acquisition: Zhihuan Zheng.
Data analysis: Zhihuan Zheng.
Drafting of manuscript: Zhihuan Zheng.
Critical revision of the manuscript: Zhongyi Li, Jiazhe Yuan, Feng Han, Li Huang, Zhao Wang.

Conflicts of interest

The authors declare no conflict of interest.

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