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EDITORIAL

Unleashing the pathological role of epithelial-to-mesenchymal transition in diabetic nephropathy: The intricate connection with multifaceted mechanism

Pitchai Balakumar

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Abstract

Renal epithelial-to-mesenchymal transition (EMT) is a process in which epithelial cells undergo biochemical changes and transform into mesenchymal-like cells, resulting in renal abnormalities, including fibrosis. EMT can cause diabetic nephropathy through triggering kidney fibrosis, inflammation, and functional impairment. The diverse molecular pathways that drive EMT-mediated renal fibrosis are not utterly known. Targeting key signaling pathways involved in EMT may help ameliorate diabetic nephropathy and improve renal function. In such settings, understanding precisely the complicated signaling networks is critical for developing customized therapies to intervene in EMT-mediated diabetic nephropathy.

Key Words: Diabetes mellitus; Epithelial-to-mesenchymal transition; E-cadherin; N-cadherin; Renal fibrosis; Diabetic nephropathy

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Core Tip: Measures to maintain epithelial integrity and prevent epithelial-to-mesenchymal transition (EMT) are being investigated as prospective therapeutic options for diabetic nephropathy. Understanding the role of EMT in diabetic nephropathy lays the door for potential therapeutic approaches. The use of transforming growth factor-β inhibitors, renal anti-inflammatory agents, antifibrotics, and antioxidants to target EMT-related pathways and renal fibrosis may have the potential to reduce the evolution of diabetic nephropathy and to prevent kidney damage.

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INTRODUCTION

Chronic kidney disease (CKD) is a prevalent debilitating disorder in which renal function gradually declines over time [1]. Cardiovascular diseases account for most noncommunicable disease deaths, followed by cancers, respiratory diseases and diabetes mellitus[2]. Moreover, nephropathy due to diabetes mellitus is a leading cause of end-stage renal failure, and its mortality rate is increasing globally. Diabetic nephropathy is thought to be mediated by a variety of signaling pathways. Despite the availability of current treatments for diabetic nephropathy, such as antidiabetics and antihypertensives, the majority of patients continue to experience progressive kidney deterioration. This indicates that the major pathogenic process involved in the initiation and progression of diabetic nephropathy is still alive and unaffected by current medications. In this article, the recent developments on the pathological role of epithelial-to-mesenchymal transition (EMT) in diabetic nephropathy are presented.

INTRICATE CONNECTION BETWEEN EMT AND DIABETIC NEPHROPATHY

The process of EMT causes epithelial cells to lose their polarity and cell-to-cell adhesion characteristics and gain mesenchymal-like characteristics instead, such as increased invasiveness and migration potential[3]. In addition to its physiological role, this intricate process plays a pivotal role in pathological events, including tissue fibrosis[4]. Recent investigations have revealed partial EMT in the kidney, suggesting that epithelial cells undergo "partial EMT" to acquire some of the phenotypic features of fibroblasts rather than transforming to a "fully fibroblastic phenotype"[4]. EMT has been linked to the etiology of diabetic complications such as diabetic nephropathy, which is a major cause of end-stage renal illness. Diabetes-mediated EMT includes complex cellular and molecular alterations. EMT plays a crucial role in the development and progression of diabetic nephropathy, a common and devastating consequence of diabetes mellitus that can lead to end-stage renal disease[5]. EMT primarily affects renal tubular epithelial cells in diabetic nephropathy, resulting in renal fibrosis, inflammation, and, eventually, kidney function loss[6,7].

As EMT progresses, renal tubular epithelial cells lose their epithelial properties, such as cell-cell adhesion and apical-basal polarization[8]. They develop mesenchymal-like characteristics such as enhanced motility, invasive potential, and secretion of extracellular matrix (ECM) proteins such as collagen and fibronectin. These alterations promote the accumulation of myofibroblasts and ECM deposition, resulting in renal interstitial fibrosis. Hyperglycemia and metabolic abnormalities in the diabetic kidney activate signaling pathways such as transforming growth factor-beta (TGF-β) and Wnt/β-catenin, which are known to trigger EMT[7]. This process transforms renal tubular epithelial cells into myofibroblasts, which release ECM components and contribute to progressive fibrosis in diabetic kidney disease[7].

Overall, EMT contributes to the pathophysiology of diabetic complications by inducing tissue fibrosis and vascular dysfunction. Targeting EMT-related pathways could be a promising therapeutic option for preventing diabetes complications and improving patient outcomes. However, more studies are required to completely understand the molecular pathways underlying EMT in diabetes mellitus and to identify effective targeted therapies. Chronic hyperglycemia, coupled with other metabolic and hemodynamic variables associated with diabetes, sets off a chain reaction of molecular processes in the kidney. Profibrotic cytokines such as TGF-β, and advanced glycation end products and reactive oxygen species are activated during these processes[7]. These variables could contribute to kidney damage and inflammation, paving the way for EMT. To initiate EMT in renal tubular epithelial cells, signaling pathways such as the TGF-β/Smad, Wnt/β-catenin, and Notch pathways need to be activated. TGF-β is a strong inducer of EMT and promotes fibrosis and tissue remodeling in diabetic kidney disease[7]. These pathways might activate various transcription factors, which may repress epithelial indicators such as E-cadherin while upregulating mesenchymal markers such as N-cadherin[9]. During EMT, cell-cell adhesion molecules such as E-cadherin are downregulated, whereas mesenchymal markers such as α-smooth muscle actin (α-SMA), fibroblast-specific protein 1, fibronectin, collagen, and vimentin are upregulated[7].

A recent study implicated the specific functional modulatory role of METTL3 in diabetic nephropathy[10], and silencing METTL3 was shown to prevent the proliferation, migration, EMT, and renal fibrosis of high glucose-induced human renal tubular cells (HK2 cells) by mediating WISP1 in m6A-dependent manner, suggesting that the METTL3/WISP1 axis might be a novel therapeutic target for diabetic nephropathy[10]. In addition to EMT, endothelial-to-mesenchymal transition (EndMT) in glomerular endothelial cells too appears to play a significant role in diabetic nephropathy. EndMT, being a subset of EMT, may involve EMT regulators in common. While Fascin has been found to mediate EMT, a recent study reported that high glucose treatment increases fascin levels and activates EndMT in human glomerular endothelial cells (HGECs), whereas silencing fascin inhibits EndMT in hyperglycemic HGECs. Moreover, SirT7 has been observed to be reduced in hyperglycemic cells and the kidneys of diabetic nephropathic mice. Furthermore, inhibiting SirT7 raises fascin levels and facilitates EndMT, demonstrating an interrelationship between SirT7 and fascin levels[11]. Increased SirT7 expression reduces fascin expression, inhibits EndMT, and improves renal function in hyperglycemic cells and diabetic nephropathic mice[11].

Measures for maintaining epithelial integrity and preventing mesenchymal transition are being studied as potential therapeutic options for diabetic nephropathy. Understanding the role of EMT in diabetic nephropathy paves the way for possible therapeutic treatments. Targeting EMT-related pathways and renal fibrosis factors with TGF-β inhibitors, anti-inflammatory medications, and antioxidants might have the potential to prevent kidney damage and slow the progression of diabetic nephropathy. This contention is supported by the fact that imperatorin, a naturally occurring furanocoumarin derivative with proven antioxidant and anti-inflammatory potential, has been reported to ameliorate kidney injury in diabetic mice by regulating the TGF-β/Smad2/3 signaling axis, renal inflammation and EMT, highlighting that imperatorin might be a potential candidate for the management of diabetic nephropathy[12]. Likewise, Schisandrin B, derived from *Schisandra chinensis* and known for its antioxidant and anti-inflammatory properties, has been attributed to reduced renal tubular cells' EMT and mitochondrial dysfunction in db/db mice. This is accompanied by the downregulation of TGF-β1[13]. In addition, Schisandrin B reduced TGF-β1, α-SMA, and fibronectin expression while increasing E-cadherin expression in glucose-stimulated HK2 cells, while Schisandrin B alleviated renal tubular cells' EMT and mitochondrial dysfunction by upregulating Kielin/Chordin-like protein[13]. Furthermore, several bench investigations have suggested that the renin-angiotensin-aldosterone system (RAAS) may play a key role in renal EMT, fibrosis, and related renal disorders[14]. EMT appears to be a key pathogenic mechanism for the adverse renal effects of angiotensin II and aldosterone, the two major RAAS components. The renal RAAS-TGF-β-Smad3 pathway contributes significantly to EMT-related renal problems. In bench studies, RAAS antagonists, including losartan, telmisartan, eplerenone, and spironolactone, have shown promise in preventing renal EMT[14].

A recent study unprecedentedly proposed the concept of "ecological pathology", which is meant to apply ecological principles and approaches to study the etiology, pathogenesis, pathological changes and outcomes of human diseases [15]. This means that the incidence and development of human diseases might be pathologically an ecological process. The concept of ecology mainly emphasizes the interaction between organisms and their surrounding environment, including biotic and abiotic interactions. Considering the pathological changes in the occurrence and development of diabetic nephropathy, this disease might also be associated with complex ecological processes. In this context, EMT-mediated CKD can be understood as a morphological and ecological adaptation of epithelial cells to external environmental stimuli.

CONCLUSION

EMT could contribute significantly to the development of diabetic nephropathy by promoting renal fibrosis, inflammation, and functional impairment. Targeting EMT pathways and associated mechanisms might hold potential for developing novel drugs to combat diabetic nephropathy and improve outcomes for patients afflicted with diabetes mellitus who are at risk of developing kidney issues. Understanding precisely the molecular pathways underlying EMT-mediated renal fibrosis in diabetic nephropathy is crucial for developing tailored therapies to minimize kidney damage and preserve renal function in diabetic patients. Therapeutic approaches that target vital signaling pathways involved in EMT might have the potential to arrest the course of diabetic nephropathy and lessen the burden of diabetes mellitus on kidney function. Finally, the signaling systems involved in EMT and diabetic nephropathy are complex and multifaceted. Understanding these signaling networks is critical for designing tailored therapeutics to intervene in EMT-mediated diabetic nephropathy and to prevent or delay kidney damage.

FOOTNOTES

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MINIREVIEWS

Obstructive uropathy: Overview of the pathogenesis, etiology and management of a prevalent cause of acute kidney injury

Xabier Pérez-Aizpurua, Ramiro Cabello Benavente, Gonzalo Bueno Serrano, José María Alcázar Peral, Blanca Gómez-Jordana Mañas, Jaime Tufet i Jaumot, Joaquín Ruiz de Castroviejo Blanco, Felipe Osorio Ospina, Carmen Gonzalez-Enguita

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Abstract

Obstructive uropathy is defined as the structural or functional interruption of urinary outflow at any level in the urinary tract. It is regarded as one of the most prevalent causes of acute kidney injury (AKI), accounting for 5%–10% of cases. Acute severe obstruction of the urinary tract is a potentially threatening situation for the kidneys and therefore requires prompt identification and management to relieve obstruction. The aim of the present article is to review and synthesize available evidence on obstructive uropathy, providing a clinical guideline for clinicians. A literature review on obstructive uropathy in the context of AKI was performed, focusing on the least clarified aspects regarding diagnosis and management. Recent literature searching was conducted in English and top-level evidence articles including systematic reviews, metanalyses and large series were prioritized. Acute obstruction of the urinary tract is a diagnostic and therapeutical challenge that may lead to important clinical complications together with direct structural and hemodynamic damage to the kidney. Early recognition of the leading cause and its exact location is essential to ensure prompt urinary drainage together with the most suitable drainage technique selection. A multidisciplinary approach, including urologists, nephrologists, and other medical specialties, is best suited to correctly manage concomitant hemodynamic changes, fluid and electrolyte imbalances, and other related issues. Obstructive uropathy is one of the leading causes of AKI. Recognition of patients suitable for early diversion and feasibility or adequate selection of the indicated technique is sometimes challenging. A thorough understanding of the physiopathology behind the development of urinary obstruction is vital for correct diagnosis and management.

Key Words: Obstructive uropathy; Urinary tract obstruction; Obstruction of the urinary

tract; Acute kidney injury; Urinary diversion; Renal recovery

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Core Tip: Obstructive uropathy is a prevalent cause of acute kidney injury that can potentially lead to death or irreversible and permanent tissue damage leading to chronic kidney disease. It is of vital importance to perform a correct initial assessment in order to identify patients that may benefit from early urinary diversion. Acute obstruction of the urinary tract leads to volume overload, electrolyte imbalances and infectious complications that need to be correctly addressed, therefore, a multidisciplinary team is key. Management of urinary tract obstruction does not end after urinary diversion. Timing and adequate management of such condition will determine renal recovery following obstruction.

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INTRODUCTION

Obstructive renal failure is defined by impaired urinary flow due to an obstruction along the urinary tract. It is important to clarify associated terminology as it is not uncommon to see different terms used indistinctively referring to urinary obstruction and the secondary kidney injury produced. Classically, *obstructive uropathy* has been considered the presence of structural or functional changes in the urinary tract altering the normal flow of urine. On the other hand, obstructive nephropathy has been regarded as the secondary renal disease to the alteration of the normal flow of urine that leads to renal failure[1]. Impaired renal function may then lead to potential long-term sequelae. Understanding the different mechanisms underlying obstructive renal failure is of vital importance, as it guides diagnostic strategies and therapeutic interventions required.

Despite acute kidney injury (AKI) being a very common condition observed both in the hospital and the outpatient setting, the incidence of urinary tract obstruction (UTO) as a main cause for AKI is not known with certainty. A global incidence of 1.7/1000 with an estimated proportion of 5%-10% of AKI secondary to UTO is often considered, however, a clear age-related incidence variation has been described with incidence peaks during infancy and in late life[2,3]. The largest series of elderly patients and AKI often show significantly higher rates of UTO as a leading cause for their condition, with incidence rates as high as 22% in some series[4]. AKI secondary to UTO is more common in men than women due to male-exclusive conditions, benign prostatic hyperplasia and prostate cancer predominantly[5]. This article aims to provide a comprehensive review of the current state of knowledge surrounding obstructive renal failure, focusing on the mechanisms contributing to its development and progression.

Although obstructive uropathy is a well-known condition, there is a notable deficiency in the literature concerning comprehensive exploration of the issue from a urological standpoint. Most published research emphasizes its pathophysiology, omitting a more systematic examination of diagnostic and therapeutic strategies based on existing evidence. UTO may occur at various levels, including the renal pelvis, ureter, or bladder outlet, each presenting unique challenges in both diagnosis and management. Recent advancements in imaging modalities, such as computed tomography (CT) urography and magnetic resonance imaging, have enhanced our ability to visualize and characterize obstructive lesions [6]. Additionally, molecular signaling studies have shed light on the underlying individual predispositions and signaling pathways involved in obstructive renal failure[7].

Furthermore, the consequences of urinary obstruction extend beyond the immediate threat to renal function. Complications may include electrolyte imbalances or infectious complications, together with potentially irreversible structural damage to the kidneys[8]. Therefore, such a condition urges the need for prompt recognition and intervention to mitigate adverse outcomes. In terms of therapeutic approaches, an understanding of obstructive mechanisms is crucial for tailoring effective interventions. Therefore, our aim was to compile and summarize the existing evidence on obstructive uropathy into a single article, spanning from its etiology to potential sequelae. This comprehensive approach is sought to guide clinicians in making informed decisions based on the unique characteristics and clinical circumstances of each patient.

PATHOPHYSIOLOGY OF UTO

Acute UTO results in a disruption of urine flow, causing an elevation in pressure within the urinary tract. Pressure increase is transmitted retrogradely, ultimately impacting renal intratubular flow and inflicting injury on the kidney leading to changes in the kidneys and urinary tract[9]. An initial compensatory hemodynamic response produces

functional changes in the kidney, which, in the absence of obstruction relief, may structurally affect the kidneys resulting in permanent damage[10]. These undesirable effects derived from urinary obstruction have been widely studied since the mid 1900s. However, not many advances have been made in the clinical understanding of obstruction since the first experimental studies were published[11,12].

Hemodynamic changes

Hemodynamics in UTO may vary depending on the degree and site of obstruction.

In unilateral UTO (UUO) three different stages may be observed[13,14].

The resulting elevation of intratubular pressure is compensated with increased renal blood flow secondary to the secretion of intrinsic prostaglandin-E2 by the kidneys to maintain an adequate glomerular filtration rate (GFR).

This compensatory mechanism lasts no longer than 1-2 h; renal blood flow starts to decrease. On the contrary, intratubular pressure keeps increasing.

After 3-4 h, a pronounced decrease in renal blood flow is observed as a consequence of increasing intratubular pressure. With this decrease in renal vascular supply, intratubular pressure also declines. Renal blood flow impairment produces a decrease of GFR and a redistribution of intrarenal blood circulation from the cortex to the medulla.

In bilateral UTO (BUO) only two phases are observed[15].

An initial increase in renal blood flow that lasts for 90 min approximately.

Accused renal blood flow impairment following the same mechanisms described above. Intrarenal blood circulation is redistributed in the opposite way from the medulla to the cortex.

These changes lead to vascular impairment of renal nephrons, resulting in acute tubular necrosis and, if maintained over time, may produce permanent damage to renal tissue[16].

Pathological (structural) changes

The establishment of renal injury starts with the retrograde transmission of the elevation of urinary tract pressure, which produces dilation of the urinary tract and consequently hydronephrosis. High intratubular pressure produces an interstitial expansion of the kidney extracellular matrix which triggers an inflammatory cascade with cellular infiltrates and interstitial fibrosis, finally producing tubular cell apoptosis[17]. The persistence of unrelieved obstruction results in tubulointerstitial necrosis with possible associated glomerulosclerosis[18].

Functional changes

The effects of UTO on the kidney mainly affect three aspects of tubular function; sodium transport, urinary concentrating ability and urinary acidification[19]. These changes are more pronounced in cases of BUO than in UUO. With the onset of obstruction, aquaporin tubular channels in charge of the transport of water are downregulated. *In vivo* studies show a 50% decrease of these channels, even 7 d after the relief of obstruction[20]. This mechanism has been proposed as one of the ultimate causes of post-obstructive polyuria and the inability to reabsorb water and concentrate urine of the obstructed kidney. Sodium channels are also affected by obstructive uropathy; diminished levels are observed 24 h after the onset of obstruction[21]. These alterations are translated into an increased natriuresis/salt-wasting syndrome due to the inability to reabsorb sodium by the obstructed kidney(s). Hyperkalemia is the most life-threatening ionic alteration derived from obstruction. First, the amount of potassium filtered by the glomerulus is diminished due to the decrease of GFR derived from impaired renal blood flow. This situation is aggravated by the lack of sodium at the distal tubule secondary to obstructive natriuresis, reducing its intraluminal concentration. Sodium-potassium exchange is therefore impaired and potassium cannot be excreted[22]. Finally, urinary acidification is also affected by the inability of the affected kidney to secrete hydrons in the distal tubule (type I distal tubular acidosis)[5].

ETIOLOGY AND DIAGNOSTIC CHALLENGES

Origin of obstruction

Establishing the site at which UTO occurs is of vital importance for diagnosis and posterior management. From a functional perspective, UTO can be divided into three main areas depending on the level at which it is produced (Figure 1):

Intrarenal: Translated as retrograde dilation of individual calyces or caliectasis. Kidney stones, infundibular stenosis secondary to infection or stones, urothelial tumors, blood clots or idiopathic causes can be possible causes. Treatment often involves, if necessary, drainage of the affected area proximally (stenting if feasible or nephrostomy).

Postrenal - intravesical: Produces ureterohydronephrosis proximally to the site of obstruction. May affect both kidneys in some cases, as in retroperitoneal fibrosis. The most common causes ca be *intrinsic;* ureteral stones, ureteral tumors, pelviureteric joint obstruction (UPJ syndrome), thrombi or *extrinsic;* retroperitoneal masses or fibrosis and in the female patient compression from gynecologic cancer. Intravesical causes, such as bladder tumors or prostate cancer with infiltration of the trigone may produce UUO or BUO depending on the specific affectation of ureteral orifices[1].

Post vesical: Causes BUO with bilateral ureterohydronephrosis. Bladder outlet obstruction often as a result of an alteration at the level of the prostate or urethra; prostatic enlargement/cancer, urethral stenosis or neurogenic bladder with associated contractility disorder[23].

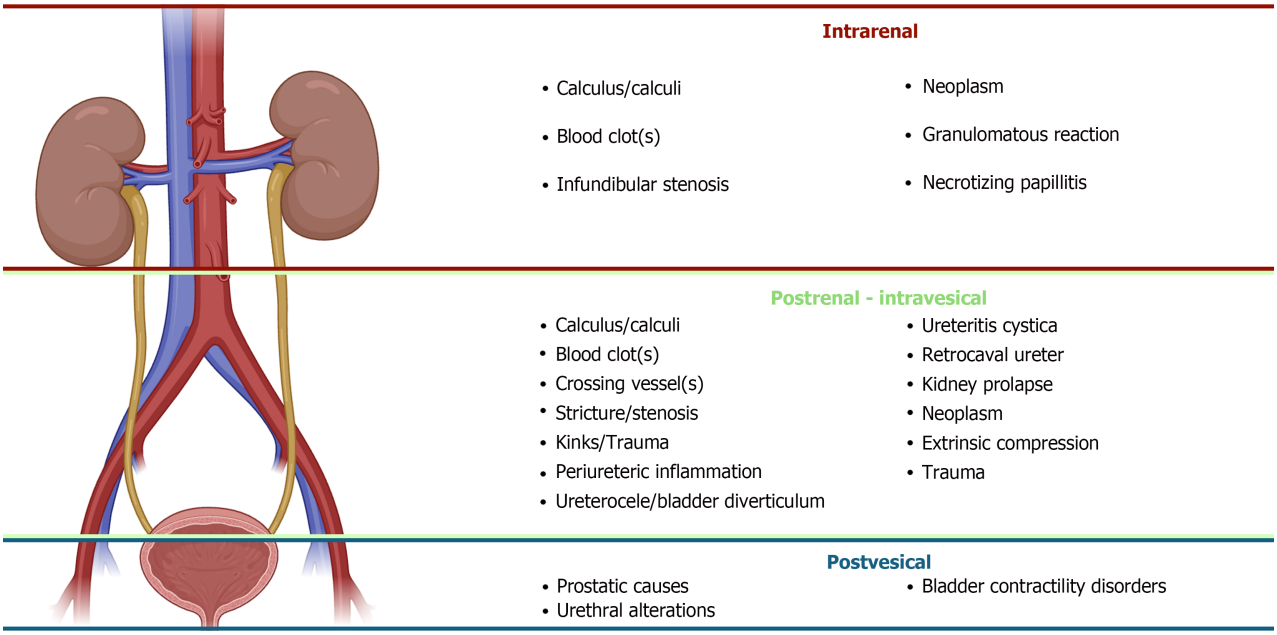

Figure 1 Overview of the different sites at which urinary tract obstruction may occur and their potential causes. A distinction is made based on the level of obstruction, categorizing them into three groups: Intrarenal, ureteral, or post-vesical. Each group includes common clinical, diagnostic, and therapeutic features.

Onset and degree of obstruction

The urinary tract is a peristaltic organ. Starting from the renal papillae, where the concentration of myoblastic interstitial cells is highest, it extends 25-30 cm cranially until its insertion in the urinary bladder at the level of the ureteral orifices. These cells are known for their pacemaker activity, allowing the ureter to work as a manometric multiplier, producing a constant pressure peristaltic wave along the ureter until it reaches the bladder[24]. This wave is transmitted at a speed of 2-5 cm/s, starting at a low resting pressure of 0-5 cm H_2O at its site of origin and progressively increasing to a maximum of 20-60 cm H_2O at the level of the ureteral orifices[25]. *In vivo* studies of ureteral peristalsis have revealed the presence of an anatomical structure, sometimes referred to as *"ureteral displacement sheath"*, inside which the ureter performs the action of peristalsis[26].

Partial or complete disturbance of such structure in *extrinsic* causes of UTO, such as retroperitoneal fibrosis, impairs the correct flow of urine from the kidneys to the bladder. On the other hand, *intrinsic* causes of UTO impair the correct flow of the peristaltic bolus due to a blockage of the normal flow of urine inside the urinary tract. The timing and degree of obstruction leads to differences in physiopathological pathways and consequently the clinical implications derived from the initial insult. Previously described hemodynamic changes are more notable when complete or bilateral obstruction occurs, leading to lower adaptability derived from compensatory mechanisms[13,14]. Similarly, complete and abrupt obstruction will more frequently lead to acute renal failure, while partial and progressive obstruction will permit the onset of compensatory mechanisms with a more gradual course as observed in cases of chronic obstructive uropathy.

Diagnosis of urinary obstruction

Physical examination is the initial approach to diagnosing obstructive uropathy. Depending on the location of obstruction, different related signs and symptoms may be observed. In cases of upper UTO, patients normally will present flank pain as in renal colic or physical impairment in case of established kidney injury. Infectious complications may also be present if obstruction leads to bacterial overgrowth in trapped urine, usually associating fever and other infectious signs such as positive kidney percussion. In the event of bladder outlet obstruction, patients may present with acute urinary retention and therefore a palpable and tender suprapubic mass might be present. After urinary catheterization with low urine output, suggesting absence of urinary retention or slight improvement of kidney function, further examination *via* digital rectal or vaginal assessment may reveal additional signs of the implicated causes[23]. The onset of signs and symptoms may also reveal additional information on the cause of obstruction; severe flank pain suggests a more acute onset being a urinary stone the most frequent underlying etiology. However, a more insidious onset may reveal extrinsic causes such as retroperitoneal fibrosis or malignancy. Anuria is usually observed in cases of bladder outlet obstruction more frequently, trigonal invasion by pelvic malignancy (mainly prostate and bladder tumors) and less frequently bilateral obstruction or obstruction in a solitary kidney.

Initial assessment after physical examination and a correct anamnesis includes laboratory testing and imaging. Regarding laboratory tests, it is important to check serum creatinine, potassium and acid-base balance to determine the functional effect of hydronephrosis[27]. Determining accurately the GFR, the hallmark of kidney function, is cumbersome and time-consuming with the available technology. Thus, it is usually assessed in a clinical setting by monitoring different solutes that are normally cleared by the kidney (mainly creatinine and others, such as cystatin C)[28]. Nevertheless, variations in creatinine levels lack sensitivity for AKI detection in an otherwise healthy individual. Approx-

imately 50% of GFR must be lost before detectable creatinine changes[29], thus new biomarkers such as cyclophilin are being investigated for improved diagnostic precision[30,31]. Creatinine is also a product of muscle catabolism and levels may vary. Interpretation in the context of AKI might be difficult in individuals with very high or very low levels of muscle mass[32]. Potassium should also be assessed; hyperkalemia is the main electrolyte imbalance derived from obstructive uropathy and represents one of the main indications for prompt urinary drainage. In cases of unclear etiology of AKI, other measurements as urinary sodium and fractional excretion of sodium (FeNa: Urine sodium/Serum sodium) may play a role. Typically, a urine sodium < 20 mEq/mol and FeNa < 1% are markers of a prerenal cause of AKI[33].

Initial radiologic assessment must include abdominal X-ray and, if no clear images of urinary stones are seen, a kidney-bladder ultrasound must be performed. Renal ultrasonography represents the main and less invasive imaging technique in the initial assessment of obstructive uropathy. It allows for visualizing the presence of ureterohydronephrosis or retrograde dilation of the ureterocallyceal system, and it also permits the diagnosis of reno ureteral stones, bladder tumors or the presence of acute urinary retention with a filled bladder[1]. It is important to remark that hydronephrosis indicates that the collecting system is dilated, therefore it is an anatomical finding, and it does not imply the cause of dilation or its nature. The cause of hydronephrosis can be obstructive or non-obstructive, as observed in cases of excessive hydration or a prominent extra-renal pelvis. Thus, hydronephrosis can be present in the absence of obstruction. In patients with a high clinical suspicion of obstructive uropathy, the finding of hydronephrosis has a positive predictive value of almost 70% and declines up to 6% in cases with a low clinical suspicion[34]. On the other hand, obstructive uropathy may also be present in the absence of hydronephrosis. A false negative rate of up to 35% has been recorded, usually in the event of acute ureteric colic. Diagnostic performance of ultrasound in the obstructive uropathy setting is therefore not perfect, and findings must be considered together with the previous degree of clinical suspicion. The main advantage of ultrasonography is the exclusion of obstruction in the absence of hydronephrosis with low clinical suspicion providing a negative predictive value of 98%[27]. Consequently, considering reno ureteral stones as the most prominent case of obstructive uropathy, initial ultrasonography has been proven to have a similar efficacy to initial abdominopelvic CT with less associated radiation in high-risk diagnosis[35]. Additionally, with the use of Doppler Ultrasound, it is possible to evaluate the presence of ureteral jets in the bladder; the absence or decreased frequency of these suggests the presence of urinary obstruction[36].

If initial assessment does not reveal a determined etiology, usually with the finding of urinary tract dilation in the absence of a specific obstructive cause, further imaging must be considered. Besides, ultrasonography has limited view of the middle part of the ureters and usually fails to correctly evaluate them, even if they are dilated. The following step in the diagnostic algorithm of obstructive uropathy after an undetermined ultrasound should be performing a non-contrast-enhanced CT scan[34]. It has long been proven that non-contrast CT is more effective than the long-time-gold-standard intravenous urography in the determination of the presence of ureteric obstruction[37]. Non-contrast CT is the initial most important diagnostic method following ultrasonography in obstructive uropathy. However, as we previously mentioned, despite urinary stones being the main cause for ureteric obstruction, there are many other causes which may not be detected by conventional non-contrast CT (blood clots, upper tract malignancy or other intraluminal causes…). Thus, the addition of an excretory phase in doubtful cases may reveal further information. Modern multidetector CT scans with additional excretory phase images offer a multiplanar imaging modality with good spatial resolution, allowing to locate the site and source of obstruction. Additionally, they offer further information on renal functioning due to the evaluation of the excretion of infused contrast by the kidneys[6]. Functional tests, such as diuretic isotopic renogram or other invasive tests such as Whitaker, usually do not have their place in the acute setting. They are time-consuming, difficult to interpret, and are often relegated to uncertain cases after initial stabilization or in the event of subacute/chronic onset of obstruction. It is important to highlight that these functional tests represent the sole diagnostic modality capable of diagnosing obstruction on their own[38].

MANAGEMENT OF URINARY OBSTRUCTION

The treatment of obstructive uropathy comprises three main factors. Firstly, a series of general measures should be considered. These include a general assessment of hemodynamic instability, mainly in the event of associated urosepsis, and the rapid approach of emergent life-threatening complications derived from obstruction. Once clinical stability is assured, attention should be directed towards symptomatic control which usually involves pain control. Finally, a decision on whether the patient should undergo urgent urinary diversion should be promptly made. Urinary diversion is the most important aspect of the treatment of obstructive uropathy and it should be considered as soon as diagnosis is confirmed and generally not be deferred.

General assessment, fluid management and treatment of electrolyte imbalance.

Early recognition of some obstruction-related aspects is vital. Firstly, the possibility of associated infectious complications should be assessed. There are a series of signs and symptoms (fever, malaise, chills) that suggest the presence of urosepsis and evidence-proven identification clinical scales can be used (qSOFA, SOFA, NEWS…) to aid with early recognition[39]. In case urosepsis is suspected, immediate antibiotic treatment should be started either empirically or pathogen-directed in case of previous positive cultures. If empirical treatment is started, it should consider the most common pathogens producing infection in the urinary tract in accordance with the different geographical patterns of antimicrobial resistance following the local antimicrobial stewardship recommendations[40]. Laboratory tests should be performed, acute phase reactants help both in the diagnosis and give prognostic information in cases when associated urosepsis is present. Other alterations, such as hyperkalemia, should also be addressed. If moderate-severe hyperkalemia is present (K > 6 mEq/L),

antihyperkalemic measures should be started. It is important to detect and suspend medications that elevate potassium plasma levels [beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), antimineralocorticoids] and consider the use of loop diuretics if eGFR < 30 mL/min and fluid overload is present[41]. If the patient fails to respond or develops anuria, additional measures should be considered. A solution to enhance transcellular potassium shift should be started (50% glucose solution + a maximum of 10UI of regular acting Insulin), and sodium bicarbonate intravenous infusion (1 mEq/kg for 10-15 min). Beta-adrenergic agonists (albuterol, salbutamol) are also quite effective but are perhaps somewhat more controversial and more likely to produce side effects. If EKG changes are present, a cardiac membrane stabilizing agent such as calcium gluconate 10% IV should be used[42]. In patients failing to these measures, further agents such as ion exchange resins may be employed; however, it is vital to remark the need for urgent urinary diversion consideration, as the relief of obstruction will normally lead to the resolution of the derived electrolyte imbalances. All of the previously mentioned measures should not defer the need for prompt urinary diversion[43].

Symptomatic control

The obstruction of the urinary tract results in the retrograde transmission of pressure dilating intrarenal cavities against a non-distensible capsule and producing pain. In the case of bladder outlet obstruction, both the bladder and upper urinary tract are dilated and progressively painful[26]. NSAIDs decrease pressure in the collecting system during obstructive uropathy secondary to the inhibition prostaglandin secretion and their vasodilating effect on the afferent renal arteriole, which increases renal blood flow[14]. Proinflammatory signals during the acute phase of urinary obstruction have shown to increase the medullar expression of COX-2 enzyme. Parecoxib, a COX-2 specific inhibitor NSAID, has shown to decrease the downregulation of AQP2 and AQP3 and other renal transmembrane transport channels if used during bilateral obstruction or in the post obstructive phase[19]. However, this *in vitro* observed effect has not been associated with less polyuria or urinary concentration inability reversal during the post obstructive phase[44]. Despite NSAIDs should be used with caution in patients with a certain degree of renal failure, they represent the first-line treatment for pain control in urinary obstruction[45].

Urinary diversion vs conservative management

Diversion of the urinary tract is the most important aspect in the treatment of obstructive uropathy. If a decision of urinary diversion is made, it should be performed as soon as possible. The chosen technique will vary depending on the site of obstruction, patient characteristics, and the treating team preferences. Upper tract obstruction is usually managed by retrograde diversion using a ureteral double-J stent. If not feasible, diversion with percutaneous nephrostomy should be considered. Extrinsic compression of the urinary tract causing urinary obstruction (retroperitoneal mass, fibrosis…) retrograde diversion with a ureteral stent is associated with up to 42% failure rates with 29% of these patients requiring a subsequent diversion with a nephrostomy tube. Other independent bad prognostic markers of urinary diversion with stents are cancer diagnosis, basal creatinine values > 1.3 mg/dL or the need for systemic treatment after diversion[46]. The use of metallic stents (*Resonance*®) may help in these particular cases, being able to successfully divert the urinary tract in cases of extrinsic compression more efficiently than conventional stents[47]. In the case of bladder outlet obstruction, urinary diversion with a urinary catheter should be performed. Following unsuccessful urinary catheterization, a decision to insert a suprapubic catheter should be considered.

The timing of urinary diversion is also substantially important to assess. A distinction between emergent need for urinary diversion and other deferrable situations should be made. Immediate need for emergent diversion include the presence of high-risk infectious complications (urosepsis, pyonephrosis), solitary kidney, upper tract bilateral obstruction, previously marked renal impairment or hyperkalemia. Bacteriemia without associated sepsis does not require emergent diversion but rather urgent; it could be safely deferred 6-8 h[23]. Assuming urolithiasis as the most prominent cause of upper UTO, early urinary diversion even in the absence of the previously mentioned indications has also been considered. A recent study by Innes *et al*[48] in a multicentric cohort of patients admitted to emergency departments throughout Canada explored early urinary diversion even in the absence of emergent diversion criteria *vs* a more conservative approach. Early diversion showed benefits for larger stones (> 7 mm) and medium-sized stones (5-7 mm) located in the proximal or mid-ureter, reducing emergency department admissions and/or the need for intervention within the first 60 d after diagnosis. In smaller (< 5 mm) or medium-size stones (5-7 mm) in the distal ureter, a conservative approach was found to be superior over early diversion.

In patients amenable to conservative management, medical expulsive therapy is often considered as the preferred treatment of choice. Spontaneous passage of urinary stones depends on stone size and their relative location within the urinary tract. Regarding their location, spontaneous passage rates of up to 68% at the distal ureter, 58% mid-ureter and 49% proximal ureter have been recorded. Smaller stones (< 5 mm) are prone to spontaneous passage in up to 75% cases. However, bigger stones (> 5 mm), are less likely to pass, in up to 62% cases[49]. Medical expulsive therapy (MET) involves the use of an alpha-adrenergic blocker (tamsulosin, silodosin) based on the smooth-muscle relaxation effect it enhances at the level of the ureteric wall[50]. This class effect of alpha-blockers has been demonstrated, although it is an off-label indication[51]. Other drug classes, such as phosphodiestarase-5 inhibitors, calcium channel inhibitors or corticosteroids have also been proposed in combination with alpha-blockers. However, based on small studies with contradictory evidence, no recommendations have been made in most clinical guidelines regarding their use. Regarding alpha-blockers, the available evidence is also contradictory. Several well-designed, double-blinded randomized controlled trials show limited or no efficacy, except for some advantage in treating distal ureteral stones larger than 5 mm[52,53]. A recent meta-analysis comparing the use of tamsulosin or tadalafil as MET for distal ureteral stones found a higher stone expulsion rate in the patients treated with tadalafil, with similar stone expulsion times[54]. Based on current evidence, European guidelines recommend the use of alpha-blockers, not other drug classes, as a treatment option for patients amenable to conservative treatment with distal > 5 mm ureteral stones[55].

Another matter of debate regarding urinary tract diversion is the risk of tumor seeding or metachronous tumor development in the presence of malignancy. Upper urinary tract carcinoma or bladder tumors with ureteral orifice invasion are another prominent cause of obstructive uropathy and sometimes require urinary diversion. The insertion of a ureteral stent may facilitate tumor spreading along the urinary tract or cause a reflux mechanism at the level of the ureteral orifice which may ease the translocation of bladder tumoral cells to the ureter or kidney[56]. A recent meta-analysis explored the association between prophylactic stenting of patients with bladder tumors involving the ureteral orifice during transurethral resection of bladder tumor (TURBT) or radical cystectomy, and the development of metachronous upper urinary tract urothelial carcinoma. Patients treated with ureteral stents were found to have a higher likelihood of metachronous upper tract urothelial carcinoma (UTUC) compared to non-derived patients. Among patients with urinary diversion, no difference regarding metachronous upper tract urothelial carcinoma was observed with the use of stent or nephrostomy. They concluded that stenting should be avoided as a preventive measure after resection of tumors involving the orifice. In cases where drainage is necessary, either nephrostomy or stent is recommended, as they do not differ in the risk of metachronous upper tract urothelial carcinoma[57].

COMPLICATIONS AFTER URINARY DIVERSION

Hematuria

Hematuria following urinary tract drainage is based on the assumption that rapid or sudden decompression of a high-pressure dilated cavity might lead to vessel breakdown and hemorrhage. To date, debate persists on whether decompression should be rapid or gradual. Hematuria *ex-vacuo*, as it is often referred to, occurs mainly after catheterization following bladder outlet obstruction, although it may also be observed following upper urinary tract diversion. It is more common to be observed in obstructive uropathy affecting the bladder due to its higher capacity and distensibility favoring the rapid and significant variation in volume and pressure that stresses bladder wall vascularization[58]. The first randomized clinical trial to study the need for gradual or rapid urinary decompression, found no differences between gradual and rapid emptying of the bladder for urinary retention[59]. A later meta-analysis confirmed these findings and concluded that currently available data suggest that rapid urinary decompression is an effective and safe method with a complication rate similar to that of gradual decompression[60].

Post-obstructive polyuria

Post-obstructive polyuria is a common finding after urinary tract drainage with an estimated prevalence of up to 50% in some studies[61]. Its physiopathological basis resides on fluid overload and AQP2-3 and sodium channel downregulation in the obstructed kidney leading to the inability of urinary concentration, resulting in the loss of water and solutes due to lack of reabsorption[20]. Similarly to hematuria *ex-vacuo*, it is more frequently observed in cases of bilateral or bladder outlet obstruction. Post-obstructive polyuria is often defined as a urinary output > 200 cc/h during the first 2 h following urinary tract drainage[62]. It can also be defined by other authors as a urinary output > 3000 cc during the first 24 h following drainage[63].

The polyuric phase following diversion often lasts about 48 h, during which strict monitoring is mandatory. Management often involves close monitoring of vital signs, urinary output, and electrolyte imbalances together with volume reposition. In stable patients, oral reposition is preferred over intravenous administration of fluids. The aim is to approximately replace 50%-75% of hourly urinary output with balanced solutions such as lactated Ringer's solution. In patients with sodium overload, compensation should be minimally applied (30%-50% on the first day) because polyuria already allows for sodium levels correction. In patients with dehydration, fluid compensation should be aggressively managed (125%-150% during the first day) because the initial output is negative[64].

RENAL RECOVERY

The functional recovery of the obstructed kidney following urinary decompression will depend on the degree of obstruction, total obstruction time and the presence of associated urinary infection. Renal recovery after obstruction has been studied in a variety of animal models, experimentally reproducing a range of scenarios comparing different types of obstruction based on their origin, time or onset[65]. Following a complete unilateral occlusion for a period of 7 d, classic studies in dogs found a 100% renal function recovery. If the obstructive period was prolonged for 14 d, renal recovery following decompression declined to 70% and to a further 30% if obstruction was maintained for 4 wk. After 6 wk of complete unilateral obstruction, absence of renal recovery was observed following drainage of the urinary tract[66]. Other studies in rat models, have observed a decline in GFR and renal blood flow following 7 d of complete unilateral obstruction which remains diminished to 40% up to 30 d following urinary drainage[67]. Other experimental human studies have demonstrated an even more rapid deleterious effect during the first 24-72 h and in the first 2 wk, which may be irreversible[11]. Therefore, even though renal recovery might be complete following treatment, there are several changes that may be unrecoverable following even a 3-d long unilateral obstruction. Damage to the kidney, which initially might not be reflected in renal function tests, might condition a worse response and recovery in subsequent obstructive episodes. A total period of 6 wk of obstruction is often considered the threshold for non-recoverable permanent kidney injury.

In addition to the previously mentioned causes of renal function loss, which respond to hemodynamic changes during obstructive uropathy resulting in impaired renal blood flow and acute tubular necrosis, there are other pathways that may hinder renal recovery following obstruction. A proinflammatory immune cellular response is triggered which results in interstitial expansion and fibrosis which may lead to tubulointerstitial necrosis. This fibrotic response leads to the deposition of elastin, collagen and other pro-fibrotic molecules which may lead to irreparable tissue damage in early phases of obstruction[17]. Collagen and elastin deposition leads to scarring and thinning of the renal parenchyma which can be radiologically assessed in order to determine the extent of damage and future prognosis[68]. Human studies on patients undergoing pyeloplasty, have also determined that higher concentrations of elastin[69] and collagen[70] in resected ureter specimens are associated with a slower functional and anatomical recovery following surgery.

Literature provides insights into therapies aimed at mitigating kidney damage in cases of chronic renal failure[23]. These treatment options serve as potential adjuncts following the management of obstructive uropathy. Among these, Angiotensin Receptor 1 Blockers (ARBs) emerge as nephroprotective agents in chronic kidney disease. Early initiation of ARB therapy holds promise in preserving renal function[71]. Furthermore, research has illustrated the advantageous impact of ARBs on glomerular injury. These benefits are attributed to the blockade of the AT1 receptor, and the amplified effects of angiotensin mediated through the AT2 receptor[72].

CONCLUSION

Obstructive uropathy is a prevalent cause of AKI. If incorrectly managed, it can potentially lead to death or irreversible permanent tissue damage leading to chronic kidney disease. It is of vital importance to perform a correct initial assessment in order to identify patients that may benefit from early urinary diversion to avoid potential complications. Acute obstruction of the urinary tract leads to volume overload, electrolyte imbalances and infectious complications that need to be correctly addressed, therefore, a multidisciplinary team is key. Management of UTO does not end after urinary diversion, there are several side effects and complications derived from the intervention that need to be early identified and corrected. Timing and adequate management of such condition will determine renal recovery following obstruction.

FOOTNOTES

Author contributions: Pérez-Aizpurua X revised the literature and wrote the manuscript; Gómez-Jordana B, Tufet i Jaumot J, Ruiz de Castroviejo J and Osorio F revised the literature and provided selected articles for inclusion; Cabello R, Bueno G, Alcázar JM and González-Enguita revised the manuscript; All authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Physico-chemical characterization of acid base disorders in patients with COVID-19: A cohort study

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Abstract

BACKGROUND

Acid-base imbalance has been poorly described in patients with coronavirus disease 2019 (COVID-19). Study by the quantitative acid-base approach may be able to account for minor changes in ion distribution that may have been over-looked using traditional acid-base analysis techniques. In a cohort of critically ill COVID-19 patients, we looked for an association between metabolic acidosis surrogates and worse clinical outcomes, such as mortality, renal dialysis, and length of hospital stay.

AIM

To describe the acid-base disorders of critically ill COVID-19 patients using Stewart's approach, associating its variables with poor outcomes.

METHODS
This study pertained to a retrospective cohort comprised of adult patients who experienced an intensive care unit stay exceeding 4 days and who were diagnosed with severe acute respiratory syndrome coronavirus 2 infection through a positive polymerase chain reaction analysis of a nasal swab and typical pulmonary involvement observed in chest computed tomography scan. Laboratory and clinical data were obtained from electronic records. Categorical variables were compared using Fisher's exact test. Continuous data were presented as median and interquartile range. The Mann-Whitney *U* test was used for comparisons.

RESULTS
In total, 211 patients were analyzed. The mortality rate was 13.7%. Overall, 149 patients (70.6%) presented with alkalosis, 28 patients (13.3%) had acidosis, and the remaining 34 patients (16.2%) had a normal arterial pondus hydrogenii. Of those presenting with acidosis, most had a low apparent strong ion difference (SID) (20 patients, 9.5%). Within the group with alkalosis, 128 patients (61.0%) had respiratory origin. The non-survivors were older, had more comorbidities, and had higher Charlson's and simplified acute physiology score 3. We did not find severe acid-base imbalance in this population. The analyzed Stewart's variables (effective SID, apparent SID, and strong ion gap and the effect of albumin, lactate, phosphorus, and chloride) were not different between the groups.

CONCLUSION
Alkalemia is prevalent in COVID-19 patients. Although we did not find an association between acid-base variables and mortality, the use of Stewart's methodology may provide insights into this severe disease.

Key Words: COVID-19; Physicochemical approach; Acid-base status; Critically ill patients; Acute respiratory syndrome

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Core Tip: In this retrospective study, alkalemia was the most prevalent acid-base disturbance in critically ill coronavirus disease 2019 (COVID-19) patients. It was mainly of respiratory origin. The results suggested that there was no association between acid-base disturbances and mortality. However, the physicochemical approach appeared to furnish supplementary information concerning the etiological factors involved in assessing metabolic acid-base imbalances in critically ill patients with COVID-19. Nevertheless, ascertaining their correlation with mortality remains pending.

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INTRODUCTION

Acid-base disorders are commonly found in the intensive care unit (ICU)[1]. Maintaining blood homeostasis and pondus hydrogenii (pH) regulation is crucial for normal physiology and cellular metabolism and function. The significance of this regulation is demonstrated by various physiological abnormalities that occur when plasma pH is either too high or too low. The body tightly controls acid balance through the respiratory and renal systems, both of which are essential for maintaining acid-base equilibrium[2].

The identification of severe acute respiratory syndrome coronavirus 2, the virus responsible for coronavirus disease 2019 (COVID-19), occurred in December 2019[3]. The pulmonary manifestations of COVID-19 are typically characterized by bilateral ground-glass opacities, with or without consolidations. Extensive pneumonia can be a serious infectious disease, as it impairs the exchange of respiratory gases and alters minute ventilation. Consequently, respiratory-related acid-base imbalances are expected complications in COVID-19 patients[4]. Additionally, acute tubular injury is a common complication of the disease. The pathophysiology of COVID-19 acute tubular injury involves local and systemic inflammatory and immune responses, endothelial injury, activation of coagulation pathways, and the renin-angiotensin system. There is also debate surrounding the possibility of direct viral infection with renal tropism. Therefore, renal involvement in COVID-19 may play a significant role in the development of acid-base disturbances[5].

The incidence and effects of acid-base disorders in COVID-19 patients have not been well studied thus far. Since these disorders serve as markers for underlying pathological conditions that can have severe consequences on multiple organs, it is crucial to accurately describe and assess acid-base disorders[6]. Small differences in correcting for anion gap, variations in analytical methods, and different approaches to diagnosing acid-base imbalances can result in significantly different interpretations and treatment strategies for the same disorder. By utilizing a quantitative acid-base approach, clinicians may be able to account for minor changes in ion distribution that may have been overlooked using traditional

acid-base analysis techniques[7].

Given that renal and pulmonary changes are commonly observed in COVID-19 patients, we hypothesized that these changes significantly affect acid-base status but may go unnoticed due to counteracting effects. Thus, the primary objective of this study was to analyze acid-base balance using the physicochemical method of Stewart. The secondary objective was to identify any potential association with outcomes such as dialysis need, vasopressor use, duration of hospital stay, and mortality.

MATERIALS AND METHODS

Population

This was a retrospective study conducted in a tertiary 600-bed hospital in Salvador, northeastern Brazil from March 2020 to December 2020. All adult patients who were more than 18 years of age at their first admission to the ICU at our hospital were screened for eligibility. The inclusion criteria were an ICU stay of more than 4 days, blood gas collection on the same day of ICU admission, a COVID-19 diagnosis by a positive test from a nasal swab, and a typical pulmonary involvement observed in the chest computed tomography scan. We excluded patients with chronic kidney disease stages 4 and 5, patients with acute kidney injury on dialysis, pregnant women, and patients with a kidney transplant. The swab was collected on the ICU admission day, and the viral RNA was detected by quantitative real-time-polymerase chain reaction (qRT-PCR) to confirm severe acute respiratory syndrome coronavirus 2 infection.

All patients were followed until discharge, death, or hospital transference. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee for Analysis of Research Projects of the Hospital São Rafael, Salvador, Brazil. A waiver of informed consent was granted by the Ethics Committee.

Data extraction and analysis

We obtained demographic (age, sex, simplified acute physiology score 3, sequential organ failure assessment, and Charlson's comorbidity index scores, hospital mortality), laboratory, radiological, treatment, and clinical outcome data from electronic medical records. Acute kidney injury was diagnosed by the kidney disease: Improving Global Outcomes criteria[8].

At ICU admission, an arterial blood sample was analyzed using a Siemens RAPID Point 500 blood gas analyzer (Siemens Health Care, Erlangen, Germany) to investigate acid-base disorders using both Henderson-Hasselbach and Stewart's methodologies. From these data, the base deficit, anion gap, apparent strong ion difference (SIDa) and effective SID (SIDe) respectively, and strong ion gap (SIG) were calculated as described previously[9]: (1) Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$; (2) SIDa = $(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate^-)$; (3) SIDe = $2.46 \times 10^{-8} \times$ partial pressure of carbon dioxide $(PCO_2)/10^{-pH} + Albumin \times (0.123 \times pH - 0.631) + PO_4^{2-} \times (0.39 \times pH - 0.469)$, and (4) SIG = SIDa – SIDe.

According to the physicochemical approach (Stewart's), we classified acidosis, alkalosis, and no pH disorder based on the partial PCO_2 and the electrolyte composition of blood as follows[10]: (1) A pH of less than 7.38 was categorized as acidosis, a pH of more than 7.42 was categorized as alkalosis, and a pH between 7.38 and 7.42, with PCO_2 between 38 mmHg-42 mmHg and SIDa between 38 mEq/L-42 mEq/L, was categorized as no disorder; (2) Respiratory acidosis: PH < 7.38, PCO_2 > 42 mmHg, and SIDa between 38 mEq/L-42 mEq/L; (3) Metabolic acidosis secondary to SIDa: PH < 7.38, PCO_2 between 38 mmHg-42 mmHg, and SIDa < 38 mEq/L; (4) Other metabolic acidosis: PH < 7.38, PCO_2 between 38 mmHg-42 mmHg, and SIDa between 38 mEq/L-42 mEq/L; (5) Respiratory alkalosis: PH > 7.42, PCO_2 < 38 mmHg, and SIDa 38 mEq/L-42 mEq/L; (6) Metabolic alkalosis secondary to SIDa: PH > 7.42, PCO_2 between 38 mmHg-42 mmHg, and SIDa > 42 mEq/L; (7) Other metabolic alkalosis: PH > 7.42, PCO_2 between 38 mmHg-42 mmHg, and SIDa between 38 mEq/L-42 mEq/L; and (8) Mixed disorder pH 7.38-7.42 with PCO_2 > 42, and SIDa > 42 mEq/L or PCO_2 < 38 and SIDa < 38 mEq/L.

Statistical analysis

Categorical variables were compared using Fisher's exact test. Continuous data were presented as median and inter-quartile range or mean ± SD, as appropriate. The Mann-Whitney *U* test or the Student's *t*-test was used for comparisons. $P < 0.05$ were considered significant. Data were analyzed with the PSPP® statistical package, version 1.2.1 (GNU Project, www.gnu.org/software/pspp/).

RESULTS

Clinical data

During the evaluation period, a total of 799 patients had a positive COVID-19 nasal swab by RT-PCR in our hospital, and 456 were admitted to the ICU. Among them, 254 patients had an ICU stay longer than 4 days. Forty-three patients were excluded due to age less than 18 years, advanced chronic kidney disease, and no arterial blood gas analysis at ICU admission.

Demographic, laboratory, and acid-base variables are shown in Table 1. The mean age of the population was 59.7 years ± 17.1 years with a higher predominance of males (60.0%). Overall, the non-survivors were older (79.0 years ± 9.0 years *vs* 58.6 years ± 16.0 years, $P = 0.000$) and had more comorbidities such as high blood pressure (74.0% *vs* 49.0%, $P = 0.040$), diabetes mellitus (50.0% *vs* 30.0%, $P = 0.050$), or chronic pulmonary disease (26.0% *vs* 12.0%, $P = 0.100$). We found higher

Table 1 Clinical and laboratory variables of 211 critically ill coronavirus disease 2019 patients, *n* (%)

Variable	All patients	Survivors	Non-survivors	*P* value
Age in years	59.7 ± 17.1	58.6 ± 16.0	79.0 ± 9.0	0.000
Male sex	99 (60.0)	84 (59.0)	15 (65.0)	0.650
T2DM	55 (33.4)	43 (30.0)	12 (50.0)	0.050
Hypertension	87 (53.0)	70 (49.0)	17 (74.0)	0.040
COPD or asthma	23 (14.0)	17 (12.0)	6 (26.0)	0.100
SOFA score	2 (1.0-3.0)	2 (1.0-3.0)	3 (1.5-4.0)	0.110
Charlson's score	3 (1.0-4.0)	2 (1.0-4.0)	5 (4.0-7.0)	0.000
SAPS 3	42.0 ± 19.0	42.0 ± 16.4	61.0 ± 15.0	0.000
Antimicrobial treatment	89 (54.0)	66 (46.8)	23 (100)	0.000
PO_2/FIO_2	296 ± 87	308 ± 94	264 ± 116	0.360
HFO_2/NIV	83 (50.6)	67 (47.5)	16 (69.5)	0.040
Lung involvement				0.360
< 25%	13.4	12.0	21.7	
25%-50%	44.5	46.8	30.4	
50%-75%	34.7	34.7	34.7	
> 75%	6.7	5.6	13.0	
VAD at admission	25 (15.0)	18 (12.0)	7 (30.0)	0.050
VAD any time	60 (37.0)	39 (27.0)	21 (91.0)	0.000
MV	65 (40.0)	43 (30.0)	22 (95.0)	0.000
AKI	50 (30.4)	28 (19.8)	22 (95.6)	0.000
KDIGO 1	18 (11.0)	17 (12.0)	1 (4.3)	0.000
KDIGO 2	7 (4.2)	5 (3.5)	2 (8.7)	
KDIGO 3	25 (15.2)	6 (4.2)	19 (82.6)	
Dialysis	19 (11.6)	2 (1.4)	17 (73.0)	0.000
Hospital stay in day	13 (10.0-21.0)	17 (9.0-20.5)	22 (13.0-32.0)	0.005
ICU stay in day	12.6 (5-17)	11.0 (9-14)	21.0 (18-25)	0.000
Illness day	7.0 (5.0-9.0)	10.1 (5.0-8.7)	8.2 (3.0-17.0)	0.003
Days in hospital	0 (0-1)	0 (0-1)	0 (0-1)	0.410
Ferritin (normal range: 12 ng/mL-300 ng/mL)	985 ± 1447	1088 ± 1529	679 ± 609	0.170
Leukocyte count (normal range: 3.6 × 10^9/L-11.0 × 10^9/L)	7.0 (5.5-9.1)	7.1 (5.1-9.4)	6.6 (4.3-8.9)	0.720
Lymphocyte count (normal range: 1 × 10^9/L-4 × 10^9/L)	0.86	0.92	0.78	0.040
Platelet count (normal range: 150 × 10^9/L-400 × 10^9/L)	179 (151-237)	191 (151-244)	169 (148-219)	0.290
Creatinine (normal range: 0.5 mg/dL-1.3 mg/dL)	0.83 (0.67-0.98)	0.83 (0.65-0.98)	0.84 (0.69-0.99)	0.770
D dimer (normal range < 250 ng/mL)	832 (563-1740)	880 (536-1651)	1512 (746-2151)	0.040
Fibrinogen (normal range: 200 mg/dL-400 mg/dL)	532 ± 185	555 ± 206	580 ± 179	0.580
Total bilirubin (normal range: 0.2 mg/dL-1.2 mg/dL)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.4-0.7)	0.930

Data are presented as median and interquartile range or mean ± SD. All laboratorial data were collected at admission to the intensive care unit (ICU). Lung involvement was determined by the percent of lung infiltrates on chest computed tomography. Illness day and days in hospital were counted at the intensive care unit admission. Data were analyzed using Fisher's exact two-tailed test, Mann-Whitney *U* test, or Student's *t*-test, as appropriate. AKI: Acute kidney injury; COPD: Chronic obstructive pulmonary disease; FIO_2: Fraction of inspired oxygen; HFO_2: High flow nasal oxygen; KDIGO: Kidney disease improving global outcomes; MV: Mechanical ventilation; NIV: Noninvasive ventilation; PO_2: Partial pressure of oxygen; SAPS 3: Simplified acute physiology score 3; SOFA: Sequential organ failure assessment; T2DM: Diabetes mellitus type 2; VAD: Ventilatory assist device.

Charlson's and simplified acute physiology score 3 scores in non-survivors. Secondary infections were diagnosed more frequently in this group of patients (100% *vs* 46.8%, $P = 0.000$). Vasoactive drugs, mechanical ventilation, acute kidney injury, and dialysis were associated with mortality. As expected, patients who did not survive had a longer hospital and ICU stay (median of 22.0 days *vs* 17.0 days and 21.0 days *vs* 11.0 days, respectively), but a shorter disease duration at hospital admission (8.2 days *vs* 10.1 days).

Laboratory data

The blood gas and acid-base variables are shown in Table 2. Overall, 149 patients (70.6%) presented with alkalosis, 28 patients (13.3%) had acidosis, and the remaining 34 patients (16.2%) had a normal arterial pH. From those presenting with acidosis, most had a low SIDa (20 patients, 9.5%). Within the group with alkalosis, 128 patients (61% of all patients) had respiratory origin. We found no statistically significant differences in pH, PCO_2, bicarbonate, or lactate levels between survivors and non-survivors. Serum sodium and chloride levels were slightly higher in survivors ($P < 0.010$ and $P < 0.030$, respectively). We also searched for differences in Stewart's variables between these two groups. The values of SIDe, SIDa, and SIG and the effect of albumin, lactate, phosphorus, and chloride were not different between the groups.

DISCUSSION

In this cohort of critically ill COVID-19 patients, the quantitative approach to acidosis demonstrated that the main acid-base disorder was alkalosis, with the majority of these being of respiratory origin. The remaining patients had either metabolic acidosis or alkalosis. Among patients with metabolic acidosis, the majority had low SIDa. The results of this study were consistent with other studies that addressed this topic. Alfano *et al*[6] described metabolic and respiratory alkalosis as the main acid-base disorders, but metabolic alkalosis was the most frequent finding without specification of the etiology. In patients with respiratory failure treated with noninvasive mechanical ventilation, the most frequent acid-base disorder described was alkalosis, also of metabolic or respiratory origin. As an additional finding, the patient's diagnosis was only possible through the quantitative method in 12% of patients[11]. This innovative methodology seems more suitable for studying the complex acid-base abnormalities in critically ill patients[12]. Some authors argue that this mechanistic approach may resolve several inconsistencies in the traditional model, give rise to novel clinical applications, and enhance understanding of pharmacological manipulation of electrolytes and clinical fluid management[13].

Respiratory alkalosis was the main acidosis-based disorder identified in our population. This disturbance involves an increase in respiratory rate and/or tidal volume. In patients admitted with respiratory failure, this finding has already been correlated with the presence of a greater extent of pulmonary inflammatory involvement identified by chest computed tomography. In this way, it can be a sign of greater severity and the need for a faster decision-making process [14]. Patient self-inflicted lung injury might be one of the many factors that can explain progression of lung disease in COVID-19. Patients who have injured lungs typically experience a heightened respiratory drive due to the impairment of gas exchange and respiratory mechanics. If the neuromuscular transmission is intact, this increased respiratory drive leads to powerful inhalations that may have physiological effects, such as a risk of over-distension, pendelluft, or atelectrauma, and an increase in vascular transmural pressure. Consequently, these effects are likely to worsen the existing lesions. This further deterioration of gas exchange and respiratory mechanics results in an even higher respiratory drive, which then exposes the lungs to the risks of even stronger inspiratory efforts. Therefore, the concept of patient self-inflicted lung injury incorporates a dynamic aspect that functions as a vicious circle[15]. The presence of respiratory alkalosis in these patients can be justified by excessive ventilatory effort and increased breath work. It can be used as a marker of underlying severity and should be approached with a sense of urgency and be judiciously corrected[16].

In our study, the diagnosis and variables involved in the quantitative assessment of acid-base disorders were not associated with mortality and other outcomes. The performance of the quantitative approach for determining the prognosis of critically ill patients has been questioned due to the impact of lactate, other measured ions, and even therapeutic interventions from the Stewart equation[17].

Bezuidenhout *et al*[18], in a single-center African retrospective observational study, found that most patients admitted to the ICU had alkalosis and a lower partial pressure of oxygen, which was associated with survival. They suggested that alkalosis could be caused by the activation of the traditional branch of the renin-angiotensin system and the resulting rise in the effects of aldosterone.

Aldosterone levels in critically ill patients are abnormally low despite an increase in plasma renin activity. This dissociation of aldosterone is not caused by a decrease in angiotensin II synthesis or alterations in plasma adrenocorticotropic hormone and potassium ions. This phenomenon has been linked to a higher mortality rate during critical illness.

Al-Azzam *et al*[19] found that mixed metabolic and respiratory acidosis were associated with increased mortality in COVID-19 patients. These findings may have been influenced by the higher prevalence of patients with diabetes mellitus,

Table 2 Physicochemical analysis of 211 critically ill coronavirus disease 2019 patients

Parameter	All patients	Survivors	Non-survivors	*P* value
PH (normal range: 7.38-7.42)	7.46 (7.42-7.53)	7.45 (7.40-7.47)	7.45 (7.40-7.50)	0.850
PCO2 (normal range: 36 mmHg-44 mmHg)	34.1 ± 5.6	34.0 ± 5.7	34.5 ± 4.8	0.660
Bicarbonate (normal range: 24 mEq/L ± 2 mEq/L)	23.3 (21.0-24.8)	23.3 (20.9-24.9)	23.1 (21.7-24.4)	0.630
Lactate normal range: (4 mg/dL-18 mg/dL)	12.1 (2.0-15.9)	11.5 (1.9-15.2)	13.9 (10.7-21.2)	0.130
Albumin (normal range: 4.0 g/dL-5.5 g/dL)	3.6 (3.2-3.8)	3.6 (3.3-3.8)	3.4 (3.2-3.8)	0.650
Phosphorus (normal range: 2.5 mg/dL–4.5 mg/dL)	3.57 ± 0.84	3.58 ± 0.86	3.44 ± 0.68	0.450
Sodium (normal range: 135 mEq/L-142 mEq/L)	135 (133-138)	136 (134-138)	135 (129-136)	0.010
Potassium (normal range: 3.5 mEq/L-5.2 mEq/L)	4.17 ± 0.51	4.17 ± 0.51	4.15 ± 0.52	0.820
Chloride (normal range: 96 mEq/L-106 mEq/L)	100 (97-103)	100 (98-103)	98 (94-100)	0.030
SIDa	37.96 ± 4.30	37.81 ± 4.33	37.86 ± 4.21	0.920
SIDe	35.35 ± 3.50	35.42 ± 3.64	34.94 ± 3.15	0.670
SIG	2.69 (-0.30 to 4.94)	2.67 (0.21-4.99)	2.71 (-0.40 to 4.88)	0.930
SBE	-0.35 (-2.90 to 1.30)	-0.33 (-3.00 to 1.40)	-0.84 (-2.30 to 0.28)	0.740
Chloride effect	-2.44 (-4.80 to 0.28)	-2.44 (-5.50 to 0.70)	-2.58 (-4.80 to 11.58)	0.580
Lactate effect	-1.47 (-1.90 to 1.20)	-1.45 (-1.86 to 1.20)	-1.69 (-2.34 to 1.30)	0.240
Albumin effect	1.51 (0.60-2.60)	1.49 (0.60-2.46)	1.82 (0.76-2.73)	0.730
Phosphorus effect	-0.02 ± 0.50	0 ± 0.52	0.10 ± 0.40	0.270

Data are presented as median with interquartile range or as mean ± SD. Data were analyzed using the Mann-Whitney *U* test or Student's *t*-test. PCO_2: Partial pressure of carbon dioxide; pH: pondus hydrogenii; SBE: Standard base excess; SIDa: Apparent strong ion difference; SIDe: Effective strong ion difference. SIG: strong ion gap.

chronic kidney disease, and severe respiratory failure with hypercapnia in this patient population.

Limits of the study

Our study was designed to investigate the acid-base and electrolyte disturbances in COVID-19 patients with severe pulmonary involvement admitted to the ICU unit and the complications that may occur following these disorders in the patients. Possible limitations were the retrospective nature of the study and the limited number of patients included. However, our study had several strengths. To date, it is the largest COVID-19 cohort to describe the acid-base status with Stewart's methodology and the first report of a search for mortality predictors using this innovative approach. Our study population included 211 patients in the year 2020 before vaccination was available. This represented an opportunity to study the clinical and metabolic effects of the virus in a non-immunized population. We also excluded chronic kidney patients and did not detect corticosteroid or alkaline fluid administration before blood gas collection in the ICU, eliminating these potential biases. As the median time from emergency department presentation to ICU admission was 0 d, another possible interference in the acid-base status was very unlikely. Thus, our cohort likely describes the effects of serious COVID-19 on acid-base status.

CONCLUSION

In summary, patients with COVID-19 who were admitted to the hospital had a high incidence of acid-base disorders. They had all types of acid-base changes that were not related to outcomes. The most common acid-base disorders in these patients were metabolic and respiratory alkalosis.

FOOTNOTES

Author contributions: de Souza SP, Caldas JR, Passos RDH, Coelho FO, and Silveira MAD designed the research study; de Souza SP, Silveira MAD, Coelho FO, Queiroz IO, and Cury PD performed the research; de Souza SP, Caldas JR, and Lopes MB provided statistical planning and analysis; de Souza SP, Caldas JR, Queiroz IO, Cury PD, and Lopes MB analyzed the data; de Souza SP, Queiroz IO, Cury PD, and Passos RDH wrote the manuscript; all authors read and approved the final manuscript.

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CASE REPORT

Severe acute kidney injury due to oxalate crystal induced severe interstitial nephritis: A case report

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Abstract

BACKGROUND

Acute kidney injury (AKI) due to interstitial nephritis is a known condition primarily attributed to various medications. While medication-induced interstitial nephritis is common, occurrences due to non-pharmacological factors are rare. This report presents a case of severe AKI triggered by intratubular oxalate crystal deposition, leading to interstitial nephritis. The aim is to outline the case and its management, emphasizing the significance of recognizing uncommon causes of interstitial nephritis.

CASE SUMMARY

A 71-year-old female presented with stroke-like symptoms, including weakness, speech difficulties, and cognitive impairment. Chronic hypertension had been managed with hydrochlorothiazide (HCTZ) for over two decades. Upon admission, severe hypokalemia and AKI were noted, prompting discontinuation of HCTZ and initiation of prednisolone for acute interstitial nephritis. Further investigations, including kidney biopsy, confirmed severe acute interstitial nephritis with oxalate crystal deposits as the underlying cause. Despite treatment, initial renal function showed minimal improvement. However, with prednisolone therapy and supportive measures, her condition gradually improved, highlighting the importance of comprehensive management.

CONCLUSION
This case underscores the importance of a thorough diagnostic approach in identifying and addressing uncommon causes of interstitial nephritis. The occurrence of interstitial nephritis due to oxalate crystal deposition, especially without typical risk factors, emphasizes the need for vigilance in clinical practice.

Key Words: Acute kidney injury; Interstitial nephritis; Oxalate crystal; Hydrochlorothiazide; Hypokalemia; Case report

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Core Tip: We have submitted a case report detailing a rare instance of acute kidney injury presenting as interstitial nephritis due to oxalate crystal deposition. While cases of thiazide-induced interstitial nephritis are documented, occurrences after 20 years of treatment are uncommon. This underscores the necessity of considering oxalate crystal deposition when evaluating patients on long-term thiazide diuretics without other risk factors for interstitial nephritis, emphasizing the importance of a comprehensive diagnostic approach.

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INTRODUCTION

Acute kidney injury (AKI) due to interstitial nephritis is a well-known entity. Interstitial nephritis can be acute or chronic, leading to AKI or chronic kidney disease depending on the duration of exposure to the offending agent and severity of insult[1,2]. Interstitial nephritis usually occurs due to exposure to various drugs. The list of drugs available for interstitial nephritis is quite large. However, interstitial nephritis due to causes other than medications is uncommon[2]. Here, we describe a case of severe AKI due to interstitial nephritis triggered by intratubular oxalate crystal deposition and its management.

CASE PRESENTATION

Chief complaints

Progressive weakness in lower extremities, intermittent slurring of speech, dementia, decreased appetite, severe fatigue.

History of present illness

A 71-year-old female presented with stroke-like symptoms including weakness, speech difficulties, and cognitive impairment. She reported a recent episode of diarrhea but denied urinary symptoms including dysuria, urinary frequency, urgency, or decreased urine output. She reported diarrhea for one week, 2 wk before admission, which was resolved without any medical intervention. She has been on 25 mg hydrochlorothiazide (HCTZ) daily (for more than 2 decades) and 100 mg metoprolol succinate daily for her blood pressure. She denied any exposure to nonprescription medication, such as proton pump inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs) and herbal agents, which can cause interstitial nephritis. She was on HCTZ and metoprolol for hypertension for more than 20 years. Because of her severe hypokalemia and AKI, HCTZ was discontinued. She started prednisolone (60 mg daily) for acute interstitial nephritis. She was discharged with trimethoprim-sulfamethoxazole for Pneumocystis pneumonia prophylaxis and calcium and vitamin D supplements for preventing osteoporosis from high-dose steroids.

History of past illness

History of obstructive sleep apnea, peripheral vascular disease, common iliac artery stenting, Gillian Barre syndrome, Long-standing hypertension managed with HCTZ and metoprolol succinate, and hyperlipidemia. No history of renal calculi.

Personal and family history

No relevant family history.

Physical examination

Afebrile, heart rate approximately 70 beats/min, respiratory rate 16 breaths per minute, blood pressure 153/128 mmHg, and weight 76 kg.

Laboratory examinations

She had normal kidney function at baseline as per the patient's previous baseline range, with a serum creatinine level of approximately 0.7 mg/dL and an estimated glomerular filtration rate (eGFR) greater than 60 mL/minute. The basic metabolic panel (BMP) on admission showed a creatinine concentration of 10 mg/dL and an eGFR concentration less than 15 mL/minute. She had moderate acidosis with an anion gap of 17, a serum bicarbonate concentration of 24 millimoles/L, a sodium concentration of 136 millimoles/L, a chloride concentration of 95 millimoles/L and a blood urea nitrogen concentration of 69 mg/dL (Table 1).

Urinalysis on admission revealed large blood, 30 mg/dL protein, 4-10 white blood cell (WBC) counts per high-power field, no red blood cell (RBC) count, and no granular casts. The creatinine kinase level was 862 U/L. Her complete blood count was 9.8 g/dL, her platelet count was 243000/mL, and her leukocyte count was 6000/mL. She had severe hypokalemia; her potassium concentration was 2.7 millimoles/L at admission, and she received IV and oral potassium chloride (KCl) supplements. The magnesium concentration was 2.3 mg/dL.

She underwent extensive serology investigations for cryoglobulins, antineutrophil cytoplasmic antibody vasculitis, anti-GBM antibody disease, antinuclear antibody screening, monoclonal protein studies to detect paraproteinemia, serum free light chains, viral hepatitis panels, and complement agents, which were all negative (Table 2).

Repeating BMP after one month showed that her serum creatinine concentration improved to 1.5 mg/dL, and her eGFR was close to 35 mL/minute. Her prednisolone dose slowly tapered over 6 wk (approximately 1 and a half months). Her potassium concentration stabilized, and she was given potassium supplements at the follow-up visit. Repeat urinalysis did not reveal any WBCs, RBCs, or proteins. Blood pressure had normalized and was hovering at approximately 120 to 130/70 to 80 mmHg during the clinic visits.

Kidney biopsy: (1) Final diagnosis: Acute onset of severe interstitial nephritis; (2) Light microscopy: The glomeruli were normal in size and had a normal mesangial matrix. There was no mesangial or endocapillary hypercellularity. Special stains do not demonstrate spikes, craters, or basement membrane remodeling; (3) Tubules and interstitium (Figures 1 and 2): Severe diffuse interstitial edema involving the cortex and medulla was observed. Severe tubular epithelial cell injury occurs with luminal ectasia, fraying of the brush border, and simplification of the lining epithelium. Tubular lumina contain necrotic debris, and some lumina contain hypereosinophilic ropy casts. The interstitium contains dense infiltrates of lymphocytes. Some areas contained aggregates of eosinophils. Mild tubulitis was observed. There are intratubular oxalate crystals (Figure 3); (4) Vessels: The visualized arteries show severe intimal fibrosis. There was no vasculitis, thrombi, or atheroembolic lesions; (5) Electron microscopy: Normal cellularity and mildly expanded mesangial regions were confirmed. No immune complex or paraprotein-related deposits were observed, and the glomerular basement membranes showed wrinkling of several of the segments; however, other regions showed no ultrastructural abnormalities. There was mild foot process effacement present. An examination of the tubulointerstitial compartment revealed interstitial edema, severe interstitial inflammation, and multifocal tubulitis. No tubular basement membrane deposits were observed; (6) Impression: Kidney, needle biopsy: Acute interstitial nephritis; and (7) Immunofluorescence: There was no significant glomerular staining for albumin, IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, or lambda light chains. The cast was observed to be stained equally with IgA, kappa, and lambda light chains.

Imaging examinations

Computed tomography of the abdomen pelvis did not reveal any hydronephrosis but showed a 3 mm (approximately 0.12 in) stone in the distal left ureter. A renal artery Doppler study revealed normal-sized kidneys bilaterally with normal velocities in both renal arteries and no occlusion in the renal arteries.

FINAL DIAGNOSIS

Severe acute interstitial nephritis with oxalate crystal deposits leading to AKI.

TREATMENT

She received normal saline and potassium chloride supplementation and had a normal urine output. However, her renal function did not significantly improve. HCTZ was discontinued due to hypokalemia and AKI. She was started on Nifedipine and continued to use metoprolol. After 48 h (approximately 2 d) of continuous IV fluid infusion, her creatinine level remained at approximately 9 mg/dL, and her eGFR level remained below 15 mL/minute.

OUTCOME AND FOLLOW-UP

Serum creatinine and eGFR improved with prednisolone treatment. Potassium stabilized, blood pressure normalized, and urinalysis normalized. Prednisolone tapered over 6 wk. Follow-up showed continued improvement in renal function and resolution of symptoms. Biopsy confirmed oxalate crystal deposits as the etiology of acute interstitial nephritis.

Table 1 Laboratory test results

Diagnostic test	Normal value	At presentation	Hospital day 2	Hospital day 6	On discharge	Follow-up
Hemoglobin, g/dL	11.6-15.0	9.0	7.6	9.1	7.3	
White blood cell count, × 10^9 /L	3.4-9.6	6.0	4.3	16.8	9.2	
Platelet count, × 10^9/L	157-371	243	207	168	124	
Serum urea nitrogen, mg/dL	6-21	69	62	55	34	23
Serum creatinine, mg/dL	0.59-1.04	10.15	9.10	8.03	5.03	1.6
Serum sodium	135-145 mmol/L	136	143	143	144	137
Serum potassium	3.6-5.2 mmol/L	2.7	3.6	3.9	3.4	3.9
Serum chloride	98-107 mmol/L	95	106	108	109	98
Serum calcium	8.8-10.2 mg/dL	9.4	8.8	8.6	8.4	9.7
Serum phosphorus	2.5-4.5 mg/dL	5.5	5.5	5.2	3.8	
Serum magnesium	1.7-2.3 mg/dL	2.3	2.0	1.6		
Serum bicarbonate	22-29 mmol/L	24	21	21	22	26
eGFR	≥ 60 mL/min/BSA	< 15	< 15	< 15	< 15	34
Anion gap	7-15	17	16	14	13	13
Serum albumin	3.5-5.0 g/dL	3.7				

eGFR: Estimated glomerular filtration rate.

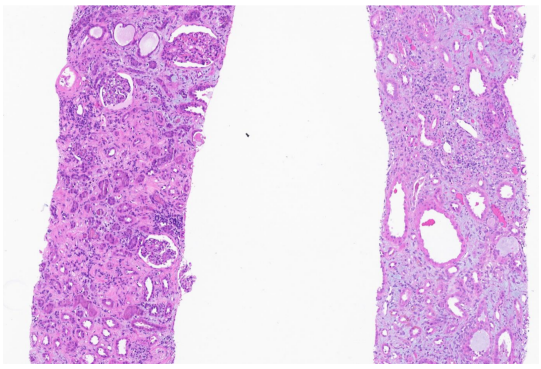

Figure 1 Oedema and marked diffuse mononuclear tubulointerstitial inflammation. The tubules had simplified epithelium with a lost brush border and reactive nuclear changes. There was no significant tubular vacuolization. The glomeruli appeared spared.

DISCUSSION

Interstitial nephritis is a renal disease characterized by inflammation and scarring of the kidney's tubular and interstitial components. It manifests in three primary types: immune-mediated, infection-mediated, and idiopathic. Immune-mediated interstitial nephritis can be caused by drug reactions or due to immunological diseases. Many drugs, including antibiotics, antacids, analgesics, immunotherapies, diuretics (including thiazide diuretics), antivirals, anticonvulsants, lithium, allopurinol, *etc*., have been linked to interstitial nephritis[2]. The mechanism through which drugs induce interstitial nephritis varies[3]. As mentioned, drug-induced interstitial nephritis is a well-documented entity associated with thiazide diuretics, and our case report adds a complex layer to this well-known entity[1,2,4].

In our patient, the complexity was enhanced when multiple oxalate crystals were identified *via* kidney biopsy along with interstitial nephritis. Oxalate nephropathy is a rare pathology that can be difficult to diagnose clinically and requires a biopsy. This presentation aligns with crystalline nephropathy, a condition marked by crystal precipitation in kidney tubules[2,3]. Crystalline nephropathy poses risks of both acute and chronic kidney injuries. Various factors contribute to the risk of crystal deposition, encompassing intravascular volume depletion, underlying kidney disease, and metabolic imbalances that alter urinary pH[2,3]. The intricate interplay of supersaturation, urine pH, and crystallization inhibitors influences intratubular crystal deposition. Drug-induced crystal precipitation, often associated with supersaturation in low urine volume or drug insolubility in acidic or alkaline urine pH, can exacerbate renal complications. Metabolic disturbances, including systemic acidosis or alkalosis and renal tubular acidosis, play a role in worsening intrarenal

Table 2 Summary of key diagnostic tests

Diagnostic test	Normal value	Result
HCV Ab screen, S	Negative	Negative
HBs antibody, S	Negative	Negative
HBs antigen, S	Non-reactive	Non-reactive
HBc total ab w/reflex, S	Negative	Negative
Complement, C3	75-175 mg/dL	143 mg/dL
Complement, C4	14-40 mg/dL	27 mg/dL
Cryoglobulins	Negative	Negative
GBM, IgG Ab	< 0.1 (Negative) U	< 0.2 U
MPO, Ab	< 0.4 (Negative) U	< 0.2 U
PR 3, Ab	< 0.4 (Negative) U	< 0.2 U
SPEP	No monoclonal protein	-
Haptoglobin, S	30-200 mg/dL	297
Kappa free light Chain, S	0.3300-1.94 mg/dL	13.7
Lambda free light chain, S	0.5700-2.63 mg/dL	8.08
Kappa/Lambda FLC ratio	0.2600-1.65	1.70
DNA double stranded Ab, IgG, S	≤ 4 (Negative) IU/mL	2
Sm. Ab, IgG, S	< 1.0 (Negative) U	< 0.2
CRP	≤ 8.0 mg/L	< 3.0 mg/L
Bilirubin, total	≤ 1.2 mg/L	0.8
ALT, S	7-45 U/L	11
AST, S	8-43 U/L	17
Alkaline phosphatase	35-104 U/L	60
Protein, total	6.3-7.9 g/dL	6.9 g/dL
Albumin	3.5-5.0 g/dL	3.7 g/dL

CRP: C-reactive protein; ALT: Alanine transaminase; AST: Aspartate aminotransferase; HCV: Hepatitis C virus; MPO: Myeloperoxidase; SPEP: Serum protein electrophoresis; GBM: Glomerular basement membrane.

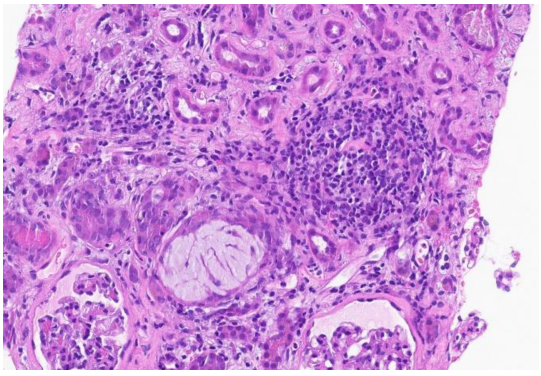

Figure 2 There is necrotic debris in two tubular lumens (lower left and upper right) and in the inspissated Tamm-Horsfall protein (center) on a severe inflammatory background.

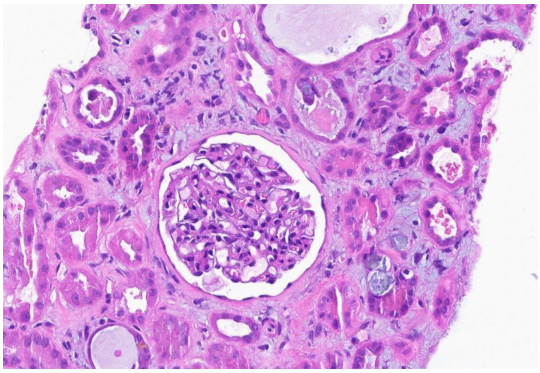

Figure 3 The background is inflammatory and there is an oxalate crystal in the center-right. Necrotic debris in 2-3 tubules.

crystal deposition. Patient characteristics linked to medication intake predispose individuals to intratubular crystal deposition and subsequent tubular obstruction[2,3].

Severe volume depletion, prevalent in conditions such as chronic diarrhea, anorexia, excessive diuresis, febrile illnesses, adrenal insufficiency, and renal salt wasting, is a crucial factor in the development of AKI. Conditions leading to effective intravascular volume depletion, such as pancreatitis, ascites, heart failure, pleural effusions, and nephrotic syndrome, contribute to renal hypoperfusion, heightening the risk of tubular crystal deposition[2,3]. Urine pH further modulates crystallization, with certain drugs exhibiting varying solubilities in acidic or alkaline urine. Crystal precipitation within the kidneys obstructs tubular lumens in the distal nephron, involving crystals mixed with cellular debris and proteinaceous material[4,5]. Gastrointestinal disorders involving small bowel dysfunction or defective fat and bile acid absorption contribute to enteric hyperoxaluria, which is characterized by increased gastrointestinal oxalate absorption and excessive urinary oxalate excretion[2,3]. In addition, certain case reports has shown an evidence, though rare, of food induced oxalte crystallopathy including excessive consumption of cashew nuts, vitamin C supplementation, spinach and peanuts.

Numerous case reports have described drug-induced crystallopathy[6-10]. In our case, the patient had been on a thiazide diuretic for more than two decades without any previous kidney injury or associated complications. The continued exposure to a thiazide diuretic throughout the period during which she had diarrhea raises the possibility of severe volume depletion and enteric hyperoxaluria as contributing factors to her crystal formation. Prolonged exposure to thiazide diuretics without any adverse events ruled out the possibility that interstitial nephritis was solely due to the thiazide diuretic. However, it is quite possible that thiazide diuretic use in the setting of diarrhea might aggravate volume depletion, leading to oxalate crystal deposition, which triggers the onset of interstitial nephritis.

Recommendations to reduce the risk of developing crystal nephropathy emphasize maintaining adequate volume status and avoiding concurrent use of diuretics, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and NSAIDs[2,3]. In cases where crystal nephropathy occurs, sustaining a high urine flow rate is crucial for minimizing further crystal precipitation and dislodging obstructing crystals. Early detection and withdrawal of the causative agent can be achieved through timely examination of urine sediment in individuals experiencing AKI, which can sometimes demonstrate crystals. Monitoring facilitates the implementation of supportive measures, including volume repletion, urine alkalinization and, rarely, hemodialysis, in severe cases of AKI[2,3]. Case reports have highlighted various treatments for oxalate crystallopathy, often tailored to underlying causes. For food-induced crystallopathy, a low-oxalate diet, high fluid intake, and calcium acetate have shown efficacy[11]. Treatment for oxalate disorders depends on whether they're primary or secondary. Enteric hyperoxaluria patients benefit from a low-fat, low-oxalate diet. Those with fat malabsorption may need calcium supplements or pancreatic enzyme supplementation (in case of pancreatic insufficiency). Lanthanum carbonate shows promise for secondary hyperoxaluria. Primary hyperoxaluria (PH) requires strategies to reduce endogenous oxalate production, with PH1 patients possibly benefitting from pyridoxine supplementation. Dialysis is essential if renal function declines, with transplantation preferred for severe systemic oxalosis in PH patients. In severe cases requiring dialysis, high flux or continuous hemodialysis is crucial for removing excess oxalate[12].

In this case, we treated the patient with a prolonged prednisolone tapering agent *via* a strategy targeting the inflammatory response associated with interstitial nephritis. There was a significant improvement in renal function, which provides insight into the role of corticosteroids in the treatment of oxalate crystallography-induced interstitial nephritis.

In addition, oxalate crystal deposition is associated with kidney epithelial cell damage, suggesting that crystals induce epithelial injury and progressive inflammation, leading to interstitial nephritis[13]. Our case study revealed that prolonged exposure to diuretics can lead to volume depletion, triggering oxalate crystal deposition, which can induce severe interstitial nephritis.

CONCLUSION

It is important to fully assess the impact of oxalate crystal deposition on renal function to provide comprehensive patient

care. The frequency of interstitial nephritis due to oxalate crystal deposition, especially in the context of long-term thiazide diuretic use in the absence of other risk factors for interstitial nephritis, highlights the importance of a comprehensive diagnostic approach. This case contributes to the expanding body of knowledge on renal pathology, highlighting the clinical importance of identifying and addressing uncommon causes of interstitial nephritis. Further research and case studies will play an important role in improving our understanding of such unusual presentations and optimizing treatment strategies.

FOOTNOTES

Author contributions: Lathiya MK and Errabelli P contributed to the investigation, coordination, writing (original and final draft), reviewing, and editing; Roy S and Mareedu N contributed to the reviewing, and editing.

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