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Review Article

Understanding the link between kidney stones and cancers of the upper urinary tract and bladder

Meredith Mihalopoulos[1], Alan Yaghoubian[1*], Shirin Razdan[1*], Johnathan A Khusid[1*], Reza Mehrazin[1,2], Ketan K Badani[1,2], John P Sfakianos[1,2], William M Atallah[1], Ashutosh K Tewari[1,2], Peter Wiklund[1,2], Mantu Gupta[1], Natasha Kyprianou[1,2,3,4]

[1]Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [3]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [4]Department of Pathology and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. [*]Equal contributors and co-second authors.

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Abstract: Kidney stones are one of the most common renal pathologies. While emerging evidence has implicated a potential association between kidney stones and upper urinary tract cancers (including renal cancer), there is limited understanding as to the common underlying biological pathways functionally linking the etiology of kidney stone formation and the incidence, development, and progression of urinary tract cancers. From a clinical perspective, kidney stone disease can be a barrier to oncologic care due to renal obstruction. From the epidemiological perspective, risk factors associated with both conditions include smoking, alcohol consumption, diet, and gender. Herein, we review the association between renal calculi and malignancy of the upper urinary tract and discuss the current understanding of (a) potential shared mechanisms, and (b) the impact this has on shared therapeutic management of both conditions.

Keywords: Kidney stone formation, mechanisms of pathogenesis, renal cancer, bladder cancer

Introduction

Urinary tract stones are one of the most common urinary tract pathologies in the United States. The prevalence of kidneys stones increased from 3.2% in 1980 to 10.1% in 2016 [1], affecting nearly 11% of men and 7% of women [2]. Nephrolithiasis is often a lifelong, recurrent burden for affected patients, with a 50% five-year recurrence rate [3]. The pathophysiology and mechanisms of stone formation are extremely diverse and depend largely on chemical composition of the stone. Recently, there has been an interest in both the mechanistic and clinical links between nephrolithiasis and genitourinary cancers [4]. Despite the prevalence of kidney stones, there is limited knowledge as to the potential association between the presence of nephrolithiasis and the incidence of cancers of the upper urinary tract and the urothelium.

The vast majority of kidney stones (> 70-80%) are calcium containing [5]. Elemental calcium is a crucial intracellular signaling molecule of which excess stores are normally contained within the human skeletal system. Thus, stone disease can abstractly be thought of as a disease of extraosseous calcification (i.e. calcium salt precipitation outside of the skeletal system). Extraosseous calcification also occurs in association with several forms of malignancy. This may occur secondary to paraneoplastic syndromes in which parathyroid-hormone-related-protein (PTHrP) is secreted resulting in bone resorption (this occurs most commonly with lung cancer) [6]. However, malignancy-related dystrophic calcifications may also occur in absence of paraneoplastic syndromes. For example, the Bosniak grading system is utilized to radiographically evaluate the malignancy risk of a complex renal mass and the presence of calcifications within the mass are a criteria for a

higher Bosniak score, which in turn predicts a higher risk of underlying renal cell carcinoma [7]. As another example from the realm of genitourinary malignancy, dystrophic calcifications of the urinary bladder wall can also be associated with bladder cancer [8]. Thus, it is intuitive that common pathophysiologic pathways associated with calcium processing and metabolism may underlie both genitourinary malignancy and urolithiasis.

According to the Center for Disease Control (CDC), prostate, urinary bladder, and kidney/renal pelvis cancers are part of the top 10 most prevalent malignancies in the US and cause significant cancer-related death globally [9]. Given the high prevalence of both nephrolithiasis and urinary tract malignancies, it is critically important to gain a better understanding of the biochemical link between the two pathological and clinical conditions. While chronic inflammation, urinary tract infection, and metabolic derangements are found to be associated with squamous cell and adenocarcinoma of the bladder and upper tracts [10, 11], there are additional biological pathways by which other forms of urinary tract cancers and renal stones may arise. It is thus of major significance to not only understand the association between renal stones and renal cancer but also the potential link between stones and ureteral and bladder cancers. In this review, we provide insights into the current understanding of the shared mechanisms linking the development of kidney stones and upper urinary tract and bladder cancers.

Cancers of the upper urinary tract and bladder: incidence and pathobiology

Renal cell carcinoma (RCC) is one of the most aggressive urologic malignancies, with a 76% 5-year overall survival rate. This rate drops precipitously for more advanced cancer, with 72.5% for stage II/III regional disease and only 12% for stage IV disease [12]. Most are derived from the proximal tubule, with clear cell carcinoma being the most common variant. RCC may also arise from the collecting ducts or renal medulla [13]. The majority of RCC is diagnosed while still localized, due to the increasing prevalence of abdominal imaging in emergency and urgent care settings [14]. In Europe and North America, the lifetime risk for developing RCC ranges between 1.3% and 1.8% [15]. According to the World Health Organization, there are more than 140,000 RCC-related deaths yearly, with RCC ranking as the 13th most common cause of cancer death worldwide [15]. The incidence is almost double in men compared to women, with a cumulative global risk of developing RCC of 0.69% and 0.35%, respectively [12].

The most commonly cited risk factors for RCC development include smoking and hereditary renal cell carcinoma syndromes [16, 17]. Obesity and hypertension are debated risk factors for RCC, with the former being associated with an increased risk of developing low grade disease [18-20]. Acquired kidney cystic disease and, specifically, time on dialysis are independently associated with development of RCC, and screening is often recommended for those patients on dialysis for more than 3 years [21]. Other risk factors include alcohol consumption, diets high in animal protein, chronic kidney disease, and environmental exposures [12, 15]. The most well-known gene mutation is loss of the *VHL* tumor suppressor gene and was first described in individuals with Von Hippel Lindau syndrome [22]. Mechanistically VHL is a component of an E3 ligase complex that ubiquitylates HIF1α and HIF2α for proteasome-mediated degradation [23, 24]. Thus, loss of VHL leads to aberrant accumulation of HIF proteins despite adequately oxygenated tissue microenvironment. This results in uncontrolled activation of HIF target genes, which mediate downstream angiogenesis, glycolysis, and apoptosis through expression of vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and fibroblast growth factor (FGF), amongst others [25]. As such, ccRCC is notoriously hypervascular in nature, and VEGF inhibitors are commonly used in treatment of patients with metastatic ccRCC [26]. While *VHL* mutation is considered the sentinel event in pathogenesis of and predisposition to ccRCC, subsequent mutational changes contribute to penetrance of the disease [27]. The reported gene mutations include in *PBRM1* (29-41% of tumor samples), *SETD2* (8-12%), *BAP1* (6-10%), *KDM5C* (4-7%) and *MTOR* (5-6%) [25, 28, 29]. *VHL* is then considered the "founder" mutation, with the subsequent gene mutations determining aggression of disease and contributing to tumor progression to metastasis [27].

The obesity paradox: As discussed above, obesity is an established risk factor for RCC. Moreover, obesity and, specifically, central adiposity contribute to lower grade tumors compared to de novo RCC in nonobese individuals. This is known as the "obesity paradox" and describes the phenomenon of obese RCC patients ultimately having longer progression free and overall survival compared to their nonobese cohorts [30, 31]. The pathogenesis of RCC in obese patients involves resistance to insulin and insulin-like growth factor, release of inflammatory cytokines, and disruption of metabolic homeostasis, resulting in the over-production of DNA damaging free radicals at the cellular level [32, 33]. Leptin is overexpressed in obese individuals and can stimulate the proliferation and promote cancer cell survival through mitogen-activated protein kinase (MAPK), Jak/Stat, and PI3K/AKT pathways, which are involved in oncogenic signaling, angiogenesis, and immunomodulation. Downregulation of adiponectin, which antagonizes leptin, results in increased angiogenesis and activation of mTOR and Stat3 pathways [34, 35]. Albiges et al. found that FASN gene expression was downregulated in obese patients compared with patients with normal BMI, and higher FASN expression was associated with worse survival in RCC patients [36].

Upper tract urothelial carcinoma (UTUC): Renal cell carcinoma represents over 90% of all tumors of the kidneys; the remainder arises from the urothelium [27]. As such, tumors of the renal pelvis and ureter behave more like urothelial carcinoma of the bladder, even though they only account for 5% of all tumors of urothelial origin [37-39]. UTUC has a peak incidence between ages 70-90, and the mean age of diagnosis has increased over the past 30 years, with an overall increase of 5 years from 68 to 73 [38, 40]. UTUC is more common in men than women, and Caucasians are most commonly affected [41, 42]. Pelvicalyceal tumors are more common than ureteral tumors [43]. Risk factors for UTUC are similar to risk factors of bladder cancer: smoking and aromatic amines. A unique risk factor to UTUC is aristolochic acid, a nitrophenanthrene carboxylic acid produced by Aristolochia plants [44].

Pure nonurothelial histology for upper tract disease is rare. However, variants exist in up to 25% of cases [43]. Pure squamous cell carcinoma of the upper tract has been associated with chronic inflammation either due to infection or stone disease [45, 46]. UTUC with variant histology is typically high grade and has a worse prognosis compared with pure urothelial carcinoma [45, 46]. Collecting duct carcinoma can have similar characteristics to UTUC due to its common embryological origin from the ureteric bud (branch of mesonephric duct) [44]. There is much overlap in the pathogenesis of UTUC and urothelial carcinoma of the lower urinary tract. Urothelial carcinoma of both the upper and lower urinary tracts is considered a "field defect", with multiple cells exhibiting genomic changes in response to a shared insult or carcinogen. As a result, recurrence after definitive treatment is notoriously common [47].

Extensive genomic analyses identified the most common gene mutations leading to development of UTUC and disease progression. The most frequently mutated genes in UTUC are *FGFR3, KDM6A, KMT2D, CDKN2A,* and *p53* [48]. Sfakianos et al. found that *FGFR3, HRAS*, and *CDKN2B* were more frequently altered in UTUC (35.6% vs. 21.6%, P = 0.065; 13.6% vs. 1.0%, P = 0.001; and 15.3% vs. 3.9%, P = 0.016, respectively), whereas *TP53* and *ARID1A* were more frequently altered in bladder cancer (57.8% vs. 25.4%, P < 0.001 and 27.5% vs. 13.6%, P = 0.050, respectively). They found no *RB1* mutations in their UTUC cohort compared with an 18.6% frequency in bladder cancer tumors (P < 0.001) [48]. The implications of these genomic analyses suggest that while there may be common founder mutations that lead to urothelial carcinoma, there is variability in driver mutations that result in divergent phenotypic expression of disease-either UTUC or bladder cancer.

Bladder cancer: Bladder cancer is the sixth most diagnosed cancer in the United States, with median age of diagnosis 73 [49]. There is a strong gender difference, with 75% of all bladder cancer cases occurring in men [50]. Use of tobacco products and smoking is the main risk factor for development of bladder cancer; however, infection with the parasite *Schistosoma haematobium* reflects the high burden of the disease in parts of Northern and sub-Saharan Africa [51]. Similar to UTUC, bladder cancer is

typically urothelial in histology, but variants are common [52]. These variants, for example squamous, micropapillary, plasmcytoid, sarcomatoid, nested, are typically more aggressive than pure urothelial and often do not respond to neoadjuvant chemotherapy [53]. Pure squamous cell carcinoma and adenocarcinoma histologies also exist, with small cell carcinoma of the bladder an even rarer histology [54]. The pathways that lead to urothelial tumorigenesis include inactivation of tumor suppressor genes such as *TP53* and *RB1*, as well as activation of proto-oncogenes such as *HRAS* and *PI3K*, which result in angiogenesis, tumor proliferation, cellular immortality, and metastasis [54]. The Cancer Genome Atlas Project (TCGA) described two distinct subtypes of bladder cancer, one leading to predominance of noninvasive disease and the other to muscle invasive and metastatic disease [54]. Tumors derived from the basal phenotypic landscape are more likely to be aggressive and invasive, often expressing sarcomatoid differentiation [55]. Those tumors of the luminal subtype that do progress to muscle invasive and metastatic disease are highly chemoresistant [56]. There is an environmental and molecular interactive milieu, predisposing one to the development of bladder cancer secondary to chronic irritation, either from tobacco products, aromatic amines and dyes, infections, or even stone formation, as primary drivers of mutagenic changes [57]. This is an example of gene-environment interactions where genetic polymorphisms in individuals predisposed to bladder cancer (including *GSTM1, UGT1A, NAT2*) are triggered by exposure to environmental toxins and can lead to the development of bladder cancer.

A clinical association

Evidence derived from the national Swedish Inpatient Registry (between 1965-1983) investigated patterns of cancer incidence in patients with urinary calculi, compared to those of the general population through standardized incidence ratios (SIR). After 1-25 years of follow-up, investigators found that of 61,144 patients hospitalized for urinary tract stones, there was a significantly increased risk of renal pelvis/ureteral cancer (SIR 2.5; 95% CI 1.8-3.3) and bladder cancer (SIR 1.4; 95% CI 1.3-1.6), with the risk higher among women. The majority of tumors were transitional cell carcinoma (TCC) (71.7% for renal pelvis/ureter cancer and 90.3% for bladder cancer), followed by squamous cell carcinoma (17.4% for renal pelvis/ureter cancer and 5.3% for bladder cancer) [58].

Shih et al. conducted a nationwide population-based cohort study using Taiwan's National Health Insurance Research Database from 2000 and 2009 [59]. A total of 43,516 patients with urinary calculi were included. After a median follow-up of 5.3 years, 1,891 patients developed cancer, and the risk of any cancer was significantly increased in these patients (SIR 1.75; 95% CI 1.68-1.83). The authors observed that urinary calculi were associated with a higher risk of kidney cancer (SIR 4.24; 95% CI 3.47-5.13) and bladder cancers (SIR 3.30; 95% CI 2.69-4.00), although specific pathologic subtypes were not specified. Urinary calculi are associated with a higher risk of other cancers outside the urinary tract, such as cancers of the thyroid, breast, lung, and digestive tract [59]. Another study of Taiwan's National Health Insurance Program from a similar time found an association between kidney cancer (of unspecified type) and prior urinary calculi (OR 3.18; 95% CI 2.75-3.68, $P < 0.001$) [60]. In addition, the magnitude of the observed associations was stronger among females (females OR 3.59; 95% CI 2.87-4.48 vs. males OR 2.93; 95% CI 2.42-3.55) and those with transitional cell carcinoma (OR 3.96; 95% CI 3.23-4.86) vs. renal cell carcinoma (OR 2.76; 95% CI 2.31-3.29) [60]. In addition, a meta-analysis of controlled cohort studies found a significant increase in the risk of RCC and TCC in patients with prior kidney stones, though this association was detected only in male patients [4], contrary to earlier studies of the Swedish Inpatient Registry and the Taiwan National Health Registry showing a stronger association in women.

Compelling evidence emerges from studies by Van de Pol et al. who examined the Netherlands Cohort Study on diet and cancer and found 120,852 participants aged 55-69 who completed a self-administered questionnaire on diet, medical conditions, and other risk factors for cancer [61]. After 20.3 years of cancer follow-up, 544 RCC cases and 140 upper tract urothelial carcinoma (UTUC) cases were eligible for case-cohort analysis. Kidney stones were

associated with an increased risk of RCC (HR 1.39; 95% CI 1.05-1.84), specifically papillary RCC (HR 3.08; 95% CI 1.55-6.11) but not clear-cell RCC (HR 1.14; 95% CI 0.79-1.65). UTUC risk was also increased for participants with kidney stones (HR 1.66; 95% CI 1.03-2.68) [61]. Further studies have shown patients diagnosed with squamous cell carcinoma (SCC) of the renal pelvis were associated with renal calculi [62, 63]. CT and MRI of the kidney showed renal masses and nephrolithiasis in one case, but all patients had a history of renal calculi. This evidence implicates chronic irritation, inflammation, and infection in the induction of squamous metaplasia of the renal collecting system, predisposing patients to dysplasia and ultimately carcinoma. Whether calculi cause tumor development or the presence of SCC results in calculi formation remains to be defined [62, 63].

Contributors to stone formation and cancer development and progression: shared cellular pathways

Renal stones create an inflammatory landscape for malignant progression

The potential link between kidney stones and urinary tract malignancies has not been fully investigated clinically, but there are several biochemical explanations for the association of cancer with chronic calculi. The inflammatory reaction caused by irritation of calculi and any superimposed infection drives hyperplasia in the renal epithelia. These cellular changes can progress into frank carcinoma or become dysplastic due to further irritation and dedifferentiate into squamous cell carcinoma or adenocarcinoma [64]. An array of key proteins produced during stone formation, could also functionally contribute to cancer development. Persistent hyperoxaluria leads to tubular epithelial injury, resulting in release of anti-inflammatory proteins, such as myeloperoxidase chain A (MPO-A), α-defensin and calgranulin, which are typically expressed in neutrophils in response to inflammation [65-67]. These proteins are thought to be first absorbed in calcium oxalate crystals and play a role in the nucleation process of inner matrix formation [68]. Exposure of renal epithelium to both calcium oxalate and calcium phosphate crystals has also been shown to stimulate the production of monocytes chemoattractant protein-1 (MCP-1), another protein associated with inflammation [69]. Though there is limited data on the association of inflammatory proteins and their relation to renal cancer, there is evidence implicating an association with GU malignancies. Mass spectrometry-based proteomic analysis of 23 patients with prostatic corpora amylacea and calculi found these prostate samples to include inflammatory proteins, such as lactoferrin, myeloperoxidase, α-defensin and calprotectin [70]. This suggests that acute inflammation has a role in the biogenesis of prostatic corpora amylacea and calculi. Because of the high rate of co-occurrence between corpora amylacea and prostate cancer, it is hypothesized that inflammatory processes involving the aforementioned protein components contribute to prostate carcinogenesis [67, 71]. These findings lay the foundation that renal calculi induce inflammatory changes that increase the risk of cancer development.

Additional evidence suggests a connection between renal stones and the progression of renal fibrosis, which predisposes patients to worse renal function and a higher risk of renal cancer [72]. Specifically, large stone-induced fibrosis may be a result of disruption of the epithelial-mesenchymal transition (EMT), an embryological process by which ectoderm transforms into mesenchymal tissue and that also plays a role in tumor cell dispersion, invasion, and metastasis [73]. The EMT phenotype has been found in tubular epithelial cells of the kidney [74], and markers of EMT (vimentin and E-cadherin) have been identified in biopsies of kidney grafts of transplanted patients, predictive of the progression of interstitial fibrosis over time [75]. An important effector of this process is *Twist*, a transcription factor for regulation of mesoderm differentiation but also an important player in cancer progression and metastasis through the modulation of tumor cell EMT [76]. Liu et al. found that activated Twist was strongly expressed in tubular epithelial cells in kidneys of nephrolithiasis patients, whereas little positive staining of Twist was found in normal kidneys [76]. Conversely, the expression of E-cadherin was significantly suppressed in kidneys of nephrolithiasis patients, suggesting that high Twist expression may induce EMT by dysregulation of the E-cadherin expression pattern and predispose patients of

nephrolithiasis to renal fibrosis [76]. This inverse correlation between Twist and E-cadherin found in stone-induced renal fibrosis, has also been detected in GU cancers, including bladder and prostate cancer, and renal cell carcinoma [77, 78].

Convergence of biochemical pathways for divergent diseases

There are several potential mechanisms by which aberrant signaling pathways may lead to the progression of not only renal calculi but also renal cancer and contribute to its progression. Studies have found bikunin, a Kunitz-type protease inhibitor found in human amniotic fluid and urine, to be important in the inhibition of stone formation. Found in the proximal tubules and thin descending segment near the Loop of Henle, bikunin may contribute to the regulation of crystal adhesion and retention within tubules to prevent stone formation [79, 80]. In addition to its anti-stone properties, bikunin also has been found to exhibit anti-inflammatory and anti-metastatic functions in human tumor cells [81]. A decreased bikunin mRNA level in renal cells is proposed as a poor prognostic marker in renal carcinoma [82]. Therefore, the dysregulation of bikunin and a potential decrease in this protease may increase the likelihood of developing renal calculi tumor progression alike, though further investigation is necessary to confirm this hypothesis.

Additional investigative studies have focused on hepsin, a transmembrane serine protease in renal endothelial cells and a promising therapeutic target previously studied in several cancers, including prostate cancer [83]. Hepsin exhibits oncogenic properties through disruption of the epithelium and influencing cell proliferation, EMT phenotypic interconversion (to mesenchymal-epithelial-transition, MET) for metastasis, inflammatory cascades and tyrosine-kinase-signaling pathways [84]. This protease is also involved in the release and polymerization of uromodulin in the urine [85]. Uromodulin plays a role in protection against nephrolithiasis formation by reducing luminal calcium concentration and increasing calcium reabsorption in the distal convoluted tubule via activity of TRPV5/6 channels [86]. Hepsin inhibitors are then important to increase the amount of uromodulin in the renal tubules to reduce calcium mineralization. There is currently work in developing small-molecule hepsin inhibitors that are showing promise in early stages of research to not only minimize stone formation but also prostate cancer progression [83].

Other targets for investigation have been isoforms of nephrocalcin, an acidic glycoprotein produced by the proximal tubules, present in urine, and an inhibitor of kidney stone formation. Alterations in the protein structure of nephrocalcin may predispose one to stone formation [87]. The differential expression of this glycoprotein in those with RCC compared to controls suggests there is an increased expression of nephrocalcin derived from cells of the primary tumor in patents with RCC and nephrocalcin levels increase with disease progression [88-90]. The majority of patients also return to normal levels of neprhocalcin after nephrectomy [88, 90]. The functional relationship of nephrocalcin and tumor behavior has yet to be defined. Because of its effect on kidney stone formation, there seems to be a relationship between aberrant nephrocalcin signaling, kidney stone formation, and the progression of renal tumors.

In addition to these proteins found in renal tubules, a specific gene mutation in Mucin-1 (MUC1) has also been found to cause tubulointerstitial kidney disease and nephrolithiasis. Nie et al. found that MUC1 forms a lattice with the N-glycan of the renal calcium channel TRPV5 via galectin-3. This impairs TRPV5 endocytosis, thereby upregulating urinary calcium reabsorption activity of the channel, ultimately increasing the incidence of calcium stone formation [91]. In addition to increasing the formation of urinary calculi, modifications of MUC1, by also binding to galectin-3, have been found to significantly increase cancer progression and metastasis through MUC1 clustering on the surface of tumor cells [92, 93]. Thus, aberrant changes in the level of activity of bikunin, hepsin, nephrocalcin, and MUC1 have been found to increase the formation of renal stones but also play a role in tumor progression and metastasis (**Figure 1**). These proteins must be investigated further in order to better understand their functional contribution to carcinogenesis and their therapeutic targeting value for future drug discovery.

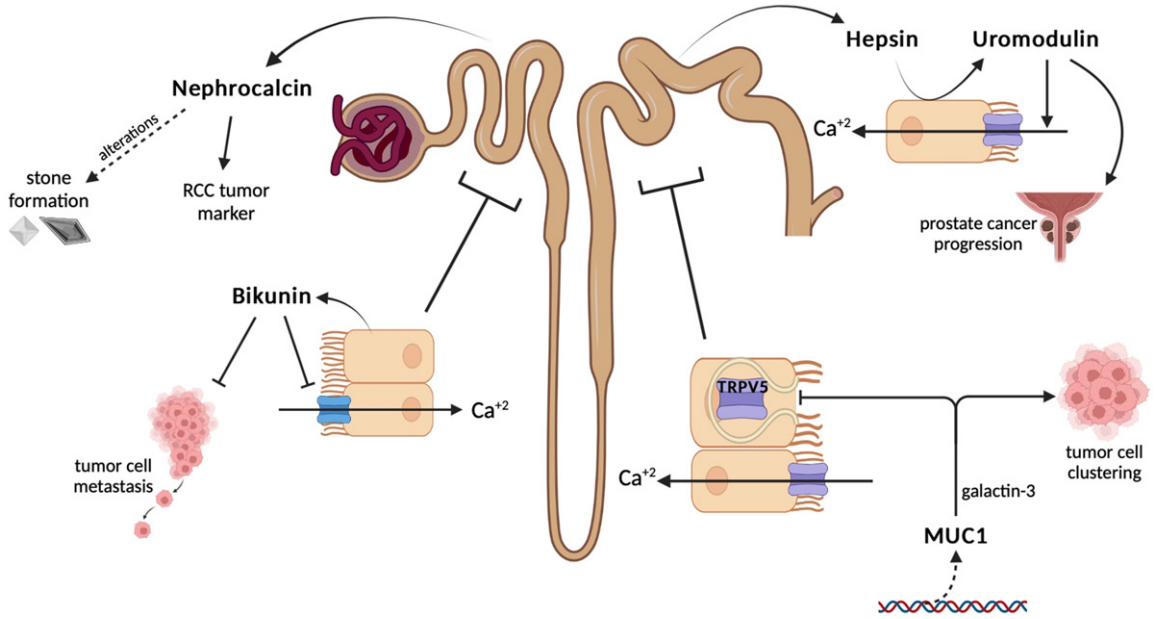

Figure 1. Summary of cellular mechanisms involved in stone formation and cancer progression. The proximal tubules produce the glycoprotein nephrocalcin, alterations to which can reverse its inhibitory effects and predispose one to stone formation as well as increase its production in cells of primary RCC tumors [87-90]. Bikunin, found in the proximal tubules and descending segment near the Loop of Henle, usually inhibits stone formation and has anti-inflammatory and anti-metastatic functions of human tumor cells [79-81]; thus, its dysregulation can predispose one to both stone formation and cancer progression. The transmembrane serine protease hepsin is produced in renal endothelial cells and induces the release of uromodulin in urine, which increases calcium reabsorption in the distal convoluted tubules by inducing TRPV5/6 channels while also affecting the progression of prostate cancer, though the mechanisms are still not fully understood [85, 86]. Lastly, the product of the MUC1 gene mutation interacts with galactin-3 to form a lattice with the N-glycan of the renal calcium channel TRPV5, impairing endocytosis of the channel and increasing calcium reabsorption while also increasing renal cancer progression and metastasis through MUC1 clustering on the surface of tumor cells [91-93].

Earlier studies established additional biochemical patterns that may suggest certain stone-promoting proteins may actually inhibit tumor formation. When comparing expression levels of matrix G1a (MGP) and bone morphogenetic protein 2 (BMP-2) in Randall's plaques of renal papillary tissues in patients with calcium oxalate kidney stones, a study of 30 samples found that the expression of BMP-2 was increased while the expression of MGP was decreased in renal papillary tissues of patients with calcium oxalate stones [94]. The study suggests that BMP-2 promotes an osteogenetic reaction or ectopic calcification. While BMP-2 induces osseous bone formation, the protein also inhibits tumor-initiating ability and may provide a beneficial strategy for RCC treatment by targeting cancer stem cell-enriched populations [95].

The role of extracellular vesicles in the pathogenesis of the two urologic conditions

The role of extracellular membrane vesicles (EVs), or "exosomes", is important in the discussion of stone formation and potential cancer progression. Tumor cell-generated microvesicles (TCMVs), a type of exosome, are very important for cellular interactions in the tumor microenvironment of renal cancer [96]. These exosomes promote cancer cell growth, evasion of host immunity and host immunosuppression, tissue invasion, and induction of the epidermal-mesenchymal transition (EMT) for metastasis [97]. TCMVs specifically aid cell invasion into the blood stream through activation of local blood coagulation, allowing tumor cells to adhere to the endothelium of vessels and promote tissue invasion at the stie of adherences [98]. Subsequently, to activate neoangiogenesis at ectopic sites of invasion, tumor cells release MVs enriched in epithelial growth factor receptor (EGFR), transcription factors, and developmental endothelial locus-1 protein [99, 100]. The released exosomes then fuse with local endothelial cells and stimulate the expression and release of vascular endothelial growth factor (VEGF), which stimulates angiogenesis

[99]. In regard to immune escape, exosomes secreted by kidney cancer cells can induce immune responses to trigger apoptosis of activated T lymphocytes through activating the caspase pathway. These vesicles can also can diminish the cytotoxicity of natural killer cells and reduce the production of IL-2, IL-6, IL-10, and IFN-γ, further down-regulating the host immune response and promoting the development of kidney cancer [101]. Specifically, exosomes from primary RCC cells of patients with clear cell RCC (ccRCC) and from RCC cell lines were found to have increased levels of TGF-β1 that further mediated natural killer cell dysfunction [102].

The function of urinary exosomes is mainly dependent on the proteins, RNA, and DNA they contain. These vesicles are cell-specific to every segment of the nephron, which makes exosomes a potential source of valuable urinary biomarkers for diseases of the kidney and urinary tract, particularly cancers [103]. One study exploring urinary exosomes derived from RCC patients found matrix metalloproteinase 9, ceruloplasmin, podocalyxin, Dickkopf-related protein 4, and carbonic anhydrase IX to be increased, whereas AQP-1, extracellular matrix metalloproteinase induce, neprilysin, dipeptidase-1, and syntenin-1 were decreased in these exosomes [104]. However, the majority of exosomes biomarker studies in RCC have focused on miRNAs in distinguishing those with RCC [105]. It was also reported that CD103-positive exosomes served as the biomarker of metastatic ccRCC [106]. We must also consider the recent advances in understanding the role of exosomes in stone formation. *In vitro* studies have demonstrated renal brush border membrane vesicles that induce calcium oxalate stone crystallization [107, 108]. In the absence of membrane vesicles, there is no crystallization in any artificial solutions simulating parts of the nephron within the time urine spreads in the renal tubules. The highest rate of crystallization and stone formation is in the collecting ducts, and this nucleation is dependent upon brush border membrane vesicles [108].

A functional analysis of proteome changes in exosomes derived from macrophages after exposure to CaOx monohydrate (COM) crystals [109], revealed that exosomes derived from COM-exposed macrophages had changes in levels of proteins involved in immune regulation, i.e., T-cell activation and homeostasis, Fcg receptor-mediated phagocytosis, IFN-γ regulation, and cell migration [109, 110]. Functional assays revealed an increase in production of IL-1b (a marker for inflammasome activation) in exosomes derived from the COM-exposed macrophages. Additionally, these exosomes activated several functions of inflammatory cells, including monocytes, macrophages, and T-cells. This data suggests that macrophage-derived exosomes are involved, at least in part, in immune process and inflammatory cascade frequently found in kidney stone pathogenesis [105, 109]. In addition to inflammasome activation, a label-free, gel-free, quantitative proteomic approach identified 26 proteins whose levels were significantly changed in exosomes derived from the COM-exposed macrophages as compared to other control exosomes derived from the untreated macrophages [110]. These proteins with significantly altered levels were involved in cytoskeleton and actin binding, calcium binding, stress response, transcription regulation, immune response, and extracellular matrix (ECM) disassembly [110].

The potential role of macrophage-derived exosomes in the inflammatory cascade of kidney stone disease induced by COM crystals in the renal interstitium, becomes critical as supported by evidence [105]. A better understanding of the contribution of macrophage-derived exosomes to stone formation, will lead to exploitation of new biomarker signatures for stone formers. A proteomic analysis of 960 proteins comparing protein composition of urinary exosomes in three kidney stone patients and three age-/sex-matched healthy controls showed dysregulated inflammatory proteins played a role in calcium binding [111]. Specifically, calgranulin proteins (S100A8, A100A9, A100A12) were enriched in the urinary exosomes but not in the urine of kidney stone patients, suggesting that urinary exosomal S100 proteins may provide potential biomarkers for nephrolithiasis [111]. While this information is important for understanding the pathogenesis of nephrolithiasis, there are stark differences in the contribution of exosomes to cancer progression and stone formation. One could argue the dysregulation of the immune response could alter the predisposition of cancer progression in those

who develop stones, though this potential hypothesis awaits exploration.

A potential genetic link

The genetic influence on stone formation has been widely studied. Twin studies estimate heritability of nephrolithiasis and hypercalcuria to be 45%-57% [112-114]. Several genes and molecular pathways contribute to stone formation according to genome-wide and candidate gene studies [115]. These genetic studies have revealed the following to have important roles in the predisposition of nephrolithiasis: transporters and channels; ions, protons and amino acids; the calcium-sensing receptor (G protein-coupled receptor) signaling pathways; and the metabolic pathways for Vitamin D, oxalate, cysteine, purines, and uric acid [115].

In particular, investigative efforts led to the identification of particular genotypes that may increase nephrolithiasis risk. For example, the single nucleotide polymorphism (SNP) rs755-622 within exon of anitsense lncRNA *MIS-AS* and promotor of *MIF* may affect the stability and splicing processes of mRNA formation and be implicated in renal disease risk [116]. A case-control study of 480 participants within a Chinese population found that rs755622 CG and CC genotypes had significantly increased nephrolithiasis risk compared with the CG genotype (adjusted OR 1.65, P = 0.016) [117]. The proposed mechanism of this increased risk is abnormal function of *MIF-AS* through modification of its folding structures as well as aberrant methylation of the *MIF* promotor, though the exact phenotypic implications are still under investigation [117]. A separate search of 380 polymorphic microsatellite markers of 18 individuals from a Spanish population found a new gene locus (NPL1) for autosomal dominant nephrolithiasis. The locus is located on chromosome 9q33.2-q34.2. Two recombination events define D9S1850 as the centromeric flanking marker and D9S1818 as the telomeric flanking marker restricting the NPL1 locus to a 14 Mb interval [118]. These provide just a sampling of the extensive research that is been done to uncover the genetic influence on nephrolithiasis [115].

Others have sought to uncover a potential genetic link in the association of urinary stones and cancer development. Hemminki et al. identified urolithiasis patients from inpatient and outpatient records organized by families and linked the information to national cancer data [119]. The study stratified cases of cancer in the offspring generation when parents were diagnosed with urolithiasis and cases of urolithiasis when parents were diagnosed with cancer. There was no significant genetic support linking urolithiasis and cancer risk. However, the investigators found a weak association between bladder urolithiasis with prostate cancer, while ureter and bladder urolithiasis were associated with salivary gland cancer, though the underlying mechanisms are poorly understood [119]. Though the evidence is limited for a genetic link between stone formation and cancer progression, it is important to get a better understanding of genomic and molecular landscape of nephrolithiasis in order to further survey those who are more predisposed to stone formation and could by nature be more at risk for carcinogenesis, as established in this review.

Contribution of metabolic health on stone formation and cancer risk

There are other medical reasons that could explain the association between kidney stones and urinary tract cancers (**Table 1**). Certain comorbidities, such as obesity, hypertension, diabetes, dyslipidemia, and metabolic syndrome have been linked to increased risk of renal cancer [120, 121] and have also been shown to be predisposing factors for kidney stone formation [122-124]. The hazardous effect of the SNP rs755622 was more pronounced in the subgroup of patients with age > 46, BMI > 24, hypertension, smoking history, and history of alcohol consumption [117], suggesting certain demographic and comorbid characteristics may have a confounding effect on those who are already genetically predisposed to stone formation. The diverse underlying mechanisms that drive the pathophysiology of tumor development and stone formation may potentially converge. It will thus be critical to address potential confounding variables in the biological link and overlapping functional signaling pathways in the clinical incidence of kidney stones and cancer.

There may be a reciprocal relationship between the development of stones and “metabolic syn-

Table 1. Shared contributors to renal stone formation and risk of urinary tract cancer

Type	Contributor	Stone Risk	Cancer Risk
Genetic	*Combined Heritability*	Heritability of stone formation 46% for women, 57% for men [112]	Kidney Cancer SIR 1.04 (95% CI 0.89-1.20) for those with family history of urolithiasis [119]
Genetic	*Gender*	Prevalence of stones in males 10.6% vs. 7.1% in females [2]	In males, RCC twice as common [4], TCC three times as common [179]
Comorbidity	*Obesity*	Incidence increase 20% to 42% with increasing BMI [185]	RR 1.77 for developing RCC in obese patients compared to non-obese patients [144]
Comorbidity	*Diabetes*	OR 6.9 (95% CI 5.5-8.8) for uric acid stone formation in patients with type 2 diabetes [186]	1.5 increase in incidence of diabetes in patients with RCC versus non-RCC patients [145]
Comorbidity	*Hypertension*	Incidence of stone formation 14% in patients with HTN vs. 3% in those with normal blood pressures [149]	10-22% increase risk in kidney cancer with each 10-mmHg increase in systolic or diastolic blood pressure [155]
Environmental	*Smoking*	OR 1.66 (95% CI 1.11-2.50) for calcium urolithiasis in patients who smoke [168]	52% increased risk developing RCC in current smokers and 25% in former smokers [162]
Environmental	*Alcohol**	HR 0.79 (95% CI 0.72-0.87) for risk of nephrolithiasis in those who drank > 1 drink per day compared to non-alcohol consumers [175]	28% reduction in risk of RCC in those who drink > 1 drink per day [172]

SIR: Standard Interval Ratio; CI: Confidence Interval; RR: Relative Risk; OR: Odds Ratio; HR: Hazard Ratio; RCC: Renal Cell Carcinoma; TCC: Transitional Cell Carcinoma; HTN: Hypertension. *These studies demonstrate that higher alcohol consumption lowers the risk of both stone formation and renal cancer risk; however, the evidence has been contradicted in other studies, and this relationship must be further explored.

drome", as defined here as a co-occurrence of several cardiovascular risk factors, such as insulin resistance, obesity, dyslipidemia and hypertension [125]. Patients with metabolic syndrome have been found to have an increased chance of developing urinary tract stones [126, 127], though patients with stones also seem to harbor metabolic syndrome at higher rates, as the diet, lifestyle and other medical conditions that predispose one to developing stones may also overlap with those contributing to metabolic syndrome [128, 129].

Metabolic syndrome has been identified as a contributor to kidney stone formation by causing impaired ammoniagenesis in the proximal convoluted tubule, thereby contributing to acidic urine and thus uric acid stones [130, 131]. It has also been known to be a powerful driver of malignancy [132, 133]. Prostate tumorigenesis has been shown to correlate with the metabolic syndrome, and lifestyle changes including diet and exercise have been advocated as a means for primary prevention or even to mitigate disease progression [134, 135]. A recent systematic review supports that this interaction is bidirectional, with prostate cancer and its inherent treatment (often involving systemic androgen deprivation therapy) contributing to the metabolic syndrome [136]. The interplay between renal cell carcinoma (RCC) and metabolic syndrome is an interesting case study of the paradoxical effect of adiposity and tumorigenesis [137]. While metabolic syndrome and increased central adiposity have been shown to increase the risk of RCC, the severity of disease is often less compared to RCC in individuals without the metabolic syndrome. This is hypothesized to occur due to the increased inflammatory milieu and cytokine production by adipose cells that serve as procarcinogenic mediators.

Uric acid stones and calcium oxalate stones are observed frequently in diabetic patients, and the underlying pathophysiology of stone formation is thought to be related to insulin resistance, a lithogenic urinary profile, and dietary factors [122]. Insulin typically increases the renal fractional excretion of calcium, suggesting insulin resistance leads to increased calcium excretion and subsequent calcium stone formation [138]. Insulin resistance has also been found to alter the acid-base metabolism of the renal tubules by reducing renal ammoniagenesis and urinary ammonium excretion, resulting in lower urine pH and a more favorable environment for uric acid and mixed urate-calcium oxalate stone formation [139, 140]. Higher urine glucose levels increase urinary tract infection incidence, further predisposing one to stone development [141]. Lastly, obesity is also associated with excess nutritional

intake of lithogenic substances, such as calcium, oxalate, sodium, and byproducts of animal proteins [124]. While a widespread intervention for obesity management is gastric bypass surgery (the Roux-en-Y specifically), this procedure increases the risk of stone development due to "enteric hyperoxaluria" caused by disturbed enterohepatic bile circulation. This leads to a loss of calcium, which binds to fatty acids as opposed to normally binding to dietary oxalate with excretion [124, 142]. Conversely, hyperoxaluria and stone formation have not been associated with restrictive management techniques, such as sleeve gastrectomy and adjustable lap banding. Therefore, one must not only consider the risks of stone formation in those with predisposing conditions like obesity but also must deliberate the risks associated with each treatment option for these patients.

Obesity in particular is one of the well-established risk factors for RCC [143]. Meta-analyses including multiple cohort and case-control studies have found a consistent positive association between obesity and RCC [143]. One meta-analysis of 21 cohort studies including 15,444 obese patients found the relative risk of 1.77 for developing RCC in obese compared to non-obese patients, and the risk increased by 4% for each 1 kg/m^2 increase in BMI [144]. An independent team of investigators found similar results in that a BMI of at least 35 had a 71% increased risk of RCC compared with non-obese patients [17]. Moreover, a prospective study found a significant incidence of diabetes mellitus in RCC (19.7%) versus non-RCC (12.8%) patients [145], and others have found higher rates of cancer recurrence and metastases in patients with diabetes [146, 147]. The mechanisms by which obesity and diabetes influence renal carcinogenesis have been under-explored but it is thought to involve insulin resistance and certain growth factors including insulin-like growth factor (IGF-1), sex steroid hormones, and biochemical markers such as adiponectin [148].

Hypertension is another condition reported to increase the risk of both nephrolithiasis and RCC development. An 8-year prospective study of 280 participants in Northern Italy found that patients with hypertension experienced a significantly increased incidence of stone episodes compared to those with normal blood pressures (14% vs. 3%) [149], with the majority forming calcium-based stones and few with uric acid stones. Hypertension has also been found to be a predictive determinant of recurrence of stone formation [150]. There are several potential explanations for such an association, mainly ascribed to hypertension-induced hypercalciuria [151]. The increased urine calcium excretion noted in hypertensive patients [149] may be due in part to primary renal tubular defects caused by the increased vascular pressure of hypertension [152]. Alternatively, expansion of the effective circulating volume decreases sodium reabsorption in the proximal tubule and thick ascending loop, subsequently decreasing calcium reabsorption and increasing its excretion [153]. Lastly, high dietary salt intake can favor hypertension by volume expansion and stone formation by increasing of urinary calcium and uric acid excretion while decreasing the excretion of citrate, a chelator calcium [152].

A large prospective study using data from the Korean National Health Insurance System found that those with hypertension were at higher risk for any kind of kidney cancer, and that those with hypertension and using medication were at higher risk than those not on any medication [154], though the types of medication that could increase the risk of renal cancer must be further explored. The risk of kidney cancer significantly increased with higher systolic or diastolic blood pressure, in a dose-dependent manner, even after adjusting for antihypertensive medication use [154]. The risk of each 10-mmHg increase in systolic or diastolic blood pressure is thought to be associated with a 10 and 22% increased risk of kidney cancer, respectively [155]. Despite the high correlation between obesity and hypertension, their associations with renal cancer risk have been shown to be independent of each other. The risk of cancer is higher among individuals who are both obese and hypertensive than those who have only one of these conditions [19, 156, 157]. The biologic mechanisms underlying the association between hypertension and renal cell cancer are unclear but are hypothesized to include chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species [158, 159].

It is well established that smoking is a risk factor for developing renal cell carcinoma [160, 161]. Studies have shown an 52% increased

risk of developing RCC in current smokers, and a 25% increased risk in former smokers [162]. This relationship has been found to be dose-dependent, with an increased risk with longer duration of smoking, as well as associated with poorer survival of RCC in current smokers [163-165]. Cigarette smoking is hypothesized to increase cancer risk through chronic tissue hypoxia due to carbon monoxide exposure and smoking-related conditions such as chronic obstructive pulmonary disease [166]. Additionally, deletions in chromosome 3p, a frequent site of genetic alterations in RCC, were shown to be more common in peripheral blood cells of RCC patients than control subjects after being treated with benzo[α]pyrene diol epoxide, a major constituent of cigarette smoke [167].

Smoking may also predispose one to stone formation, particularly as an independent risk factor for calcium urolithiasis development (OR 1.66; 95% CI 1.11-2.50, P = 0.014) [168]. A survey study of a convenience sample of stone clinic patients at a tertiary hospital showed that those patients with kidney stone development had higher rates of smoking as compared to those without a history of kidney stone (21% vs. 7%, P = 0.02) [169]. At the biological level, smoking increases vasopressin levels, which leads to poor urinary flow and low urine output through its antidiuretic properties, ultimately increasing the risk of stone formation [170]. Cigarettes also raise the plasma concentration of cadmium, which may also increase the risk of stone formation [171]. Another potential functional link potential link between stones and cancer progression, smoking causes the release of reactive oxygen species with subsequent oxidative stress on the kidneys that was found to not only increase the risk of developing RCC but also urinary tract stones [158, 161].

Alcohol consumption takes a paradoxical role as a contributing factor to both cancer and stone formation. One pooled analysis of 12 prospective studies that included 530,469 women and 229,575 men demonstrated that those with higher consumption of alcohol (≥ 15 gram/day) have an estimated 28% *reduction* in renal cell cancer risk [172]. This inverse relationship was observed for all types of alcoholic drinks, including beer, wine, and liquor [172]. This was corroborated by two meta-analyses that showed alcohol consumption was associated with lower risk of developing RCC compared with no lifetime alcohol consumption (RR 0.85; 95% CI 0.80-0.92) and was not altered after adjustment for smoking, BMI, or hypertension [173, 174]. These trends have also been observed in assessing nephrolithiasis risk. In a large prospective study from the China Kadoorie Biobank, Wang et al. concluded that participants who drank 30-59.9 g of alcohol per day had a lower risk of nephrolithiasis as compared to non-alcohol consumers (HR 0.79; 95% CI 0.72-0.87) [175]. A twin study also found that alcohol consumption in the past 2 weeks was associated with decreased risk of kidney stones (OR 2.7; 95% CI 1.0-7.7) [176]. However, there was no association with lifetime drinking habits and alcohol consumption with stone formation [161, 176]. Other independent investigative efforts found an increased risk of urinary tract urothelial caner in those who had ever drank alcohol compared to never-drinkers (OR 1.23; 95% CI 1.08-1.40; P = 0.001) [177]. Thus, the potential associations between alcohol consumption and cancer/stone risk require further investigation.

In addition to medical conditions and substance use, gender may also play a role in stone development risk. Metanalysis data found men with kidney stones in particular to have an increased risk of RCC [4]. In general, the prevalence of kidney stones is higher in males than females (10.6% vs. 7.1%, respectively) [2], and this trend is also seen in kidney cancers, both RCC and TCC (RCC twice as common in males [4, 178], TCC three times as common [179]). The underlying pathophysiology is unclear, though it is proposed that males may be more exposed to dietary or environmental factors that could increase their risk for renal cancer. Though this generalizes gender habits, males are more likely to be smokers than females, a potential risk factor for the development of kidney stones and cancer [180, 181]. Males may have different eating habits, with more lithogenic and carcinogenic foods that increase their risk of both stones and cancer [182]. As discussed in this review, stones may lead to the development of malignancy through diverse molecular mechanisms. Be that as it may, it is also critically important to recognize that there are certain demographic and comorbid characteristics that can predispose one to developing

both stones and cancer independently, transcending any pathological association.

Conclusions and future directions

From a clinical perspective, kidney stone disease can be a barrier to oncologic care due to renal obstruction. Stones can become lodged in the ureter and obstruct the flow of urine from the kidney resulting impaired renal function [183]. Given that many chemotherapeutic agents are renally cleared, impaired renal function can prevent the safe administration of chemotherapy resulting in disruptions and delays in oncologic care. Further complicating matters is that the stagnant urine upstream from the obstructing stone is prone to infection which can be particularly dangerous in an immunocompromised chemotherapy patient. Kidney stone disease is extremely common in the general population with a prevalence of 8.8% among American adults [2] making concurrent nephrolithiasis and malignancy a commonly encountered scenario in urologic practice. In such cases, it is crucial to promptly unobstructed the afflicted renal unit either through ureteral stenting or lithotripsy of the offending stone. Additionally, chemotherapy can itself be lithogenic, as the apoptosis-driven therapeutic response induced by chemotherapeutic antitumor agents in the treatment of kidney and bladder cancer, can result in the spillage of intracellular contents such as uric acid into circulation. Buildup of such substances secondary tor rapid cell death results in several adverse physiologic sequelae known collectively as the tumor lysis syndrome [184]. One of the classic presenting symptoms of tumor lysis symptoms is renal obstruction secondary to uric acid nephrolithiasis brought on large amounts of uric acid released following cell death [184].

In view of the complexity of the clinical conditions, one must also consider the potential mixture of comorbid environmental and genetic factors, as well as mechanical factors such as urinary stasis and chronic inflammation that can contribute to both diseases. Evidence derived from cellular and molecular studies supports the potential role of macrophage-derived exosomes in the inflammatory cascade of kidney stone disease induced by COM crystals in the renal interstitium. We recognize the limitations of the present review, pertaining predominately to the limited evidence-based understanding of an association between stone formation and cancer development. Imaging-defined approaches are critically important in detecting both conditions, yet interrogation of the pathophysiology of metabolic syndrome is emerging as instrumental in understanding the relationship between stone formation, particularly uric acid stones, and urinary tract cancer development. Ongoing technology-driven research in the exploration of shared biomechanical pathways of stones and cancers of the upper ureter, particularly in the context of inflammatory markers and dysregulation of calcium reabsorption, will provide valuable insights advancing our knowledge of the field. It is our opinion that the mechanisms linking stone formation and oncogenesis are multifactorial and quite variable, depending largely on the type of cancer and type of stone. While we treat each patient as an individual, it is important to continue to pursue the identification of overlapping biological pathways that can be exploited to further our understanding of the simultaneous detection (using molecular signatures) and therapeutic/medical management of both diseases.

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None.

Abbreviations

ADT, androgen deprivation therapy; BMI, body mass index; BMP-2, bone morphogenetic protein 2; ccRCC, clear cell renal cell carcinoma; CDC, Center for Disease Control; CI, confidence interval; COM, calcium oxalate monohydrate; ECM, extracellular matrix; EGFR, epithelial growth factor receptor; EMT, epithelial-mesenchymal transition; EV, extracellular membrane vesicle; HIFU, high intensity focused ultrasound; IGF, insulin-like growth factor; MCP-1, monocytes chemoattractant protein-1; MGP, matrix G1a; MPO-A, myeloperoxidase chain A; MUC1, Mucin-1; NCCN, National Comprehen-

sive Cancer Network; OR, odds ratio; PARP, Poly (ADP-ribose) polymerase; RCC, renal cell carcinoma; RNU, radical nephroureterectomy; RR, relative risk ratio; SCC, squamous cell carcinoma; SIR, standardized incidence ratio; SNP, single nucleotide polymorphism; TCC, transitional cell carcinoma; TCMV, tumor cell-generated microvesicle; TRVP, transient receptor potential vanilloid; UTUC, upper tract urothelial carcinoma; VEGF, vascular endothelial growth factor.

Address correspondence to: Drs. Natasha Kyprianou and Mantu Gupta, Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. E-mail: natasha.kyprianou@mountsinai.org (NK); mantu.gupta@mountsinai.org (MG)

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