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Review Article

Precision Medicine in Urolithiasis: A Review

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ABSTRACT

Urolithiasis commonly known as kidney stone is the accumulation of hard, solid, and nonmetallic materials in the urinary tract. Medical treatments for hypercalciuric urolithiasis include sodium cellulose phosphate, thiazide, and orthophosphate; for hypocitraturia calcium urolithiasis, potassium citrate; for infection stones, acetohydroxamic acid; and for cystinuria, d-penicillamine and α-mercaptopropionylglycine. Recently noncoding RNAs, particularly microRNAs (miRNAs) and small interfering RNAs (siRNAs) are being used in the studies related to the development of stone induced kidney damage and anti-urolithiasis therapies. MicroRNAs (miRNAs) are a class of non-coding RNAs that have a role in regulating gene expression. Double-stranded siRNAs attach to target messenger RNA sequences, cleaving and degrading the target RNA and blocking translation, gene expression, and function. This review article provides a comprehensive overview of urolithiasis and the recent advancement of miRNAs and siRNAs related therapies in urolithiasis.

INTRODUCTION

Urolithiasis is a chronic kidney disease more common in men than in women is the retention of crystals within the kidney. Calcium oxalate is the main component of most stones, often accompanied by calcium phosphate. Women are more likely to experience stones composed of calcium phosphate. Recurrence is common after a first stone, with idiopathic stones a higher recurrence rate. Insoluble drugs may also cause stones.[1] Nucleation, growth and aggregation are the physiochemical aspects of urolithiasis.[2] Reduced urine citrate is linked to thiazide prescriptions; this is because thiazide induces hypokalemia, which would encourage citrate reabsorption in the shortest tubules. To treat recurrent hypercalciuric nephrolithiasis, potassium citrate is frequently used with a thiazide diuretic. Unless there is severe hyperuricosuria or clinical gout, xanthine oxidase inhibitors such as allopurinol should not be used to treat uric acid stone formers. Antidiuretic hormone (ADH)

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antagonist like tolvaptan would increase urine flow rates in patients with cystinuria.[3] Medical expulsive therapy in urolithiasis particularly alpha blockers, is weak especially for stones larger than 5mm.[4] Another treatment for urolithiasis include extracoroporeal shock wave lithotripsy, it is minimally invasive and has a favorable safety profile.[5] Small non-coding RNAs (miRNAs) with a length of 21–24 nucleotides are important for cell formation, differentiation, control of the cell cycle, and apoptosis.[6] Since siRNAs may be specifically engineered to target particular mRNA sequences, RNA interference, or RNAi, it is a potentially effective treatment strategy for disorders caused by overexpressed genes or "undruggable" proteins. When compared to conventional procedures, the siRNA drug discovery process is typically speedier, and continual advancements have improved both safety and efficacy.[7] Three claudin genes claudin-14, claudin-16, and claudin-19—have been connected to renal disorders like hypercalciuria, kidney stones, and bone mineral loss. These genes are involved in calcium ion transport in the thick ascending limb of Henle. Extracellular calcium ions control the amounts of miR-9 and miR-374; their suppression raises the production of claudin-14 and thus depletes the kidney's supply of calcium and magnesium.[8] Recent advancement in urolithiasis treatment showed that overexpression of miR-34a reduced the expression of CD44 and the adherence of cell crystals, while overexpression of CD44 had the opposite effect.[9] The phase 1, 2, and 3 clinical trials of nedosiran a siRNA candidate have successfully achieved the primary end point of lowering urinary oxalate levels in patients with primary hyperoxaluria 1 by specifically inhibiting lactate dehydrogenase enzyme, which is the key enzyme in the manufacture of oxalate in the liver.[10]

Mechanism of urolithiasis

The process of kidney stone production is intricate and multi-step, involving supersaturation of urine, nucleation of crystals, growth and aggregation.[11] The nucleation of the crystals that make up the stone, their growth or aggregation to a size where they can interact with an intrarenal structure, their retention inside the kidney or renal collecting system, and additional aggregation and/or secondary nucleation to form the clinical stone are the mechanisms involved in the formation of stones.[12] Colic of the kidneys starts out abruptly and builds up gradually over 15 to 30 minutes into an excruciating ache that makes you feel sick to your stomach and vomit up. Similar to the stone, the discomfort frequently travels from the flank downwards and then twists anteriorly into the groin. The stone may cause dysuria along with frequent urination as it approaches the ureterovescile junction. The pain may suddenly stop when the stone enters the bladder or most of the ureter, decompressing the urinary tract.[13] Calcium stone former urine is often more supersaturated with calcium oxalate and calcium phosphate than normal individuals. However, nucleation of these crystals usually doesn't occur, and even if it does, they don't grow or aggregate large enough to be retained in the kidney. This inhibitory property is defective in some stone formers.[12] In kidney stone disease inhibitory crystallization deficit plays an important role together with supersaturated levels of different salts, promoters and inhibitors of crystallization.[14] Inhibitors of calcium oxalate (CaOx) crystal formation, such as proteins, peptides, and small compounds, have been created recently and are essential for avoiding pathological crystallization. By interacting with Ca2+ ions, compounds containing acidic moieties, as well as synthetic peptides and polymers, efficiently inhibit the development of calcium oxalate monohydrate (COM) crystals.[15] Glycosaminoglycans (GAGs) have a complicated role in the development of

stones, which is impacted by their acidic characteristics, urine oxalate levels, and possible side effects from nonsteroidal anti-inflammatory medications. According to long-term studies, adjusting GAG levels may help avoid urolithiasis, and some GAGs may be able to prevent the production of stones.[16]

Lifestyle modification

Steer clear of milk, yogurt, and cheese to limit daily calcium intake to a few hundred milligrams. Compared to those on a low-calcium diet, people with a history of kidney stones were less likely to develop kidney stones if they consumed less animal protein and sodium and had a normal calcium consumption. Although calcium oxalate stone formers are frequently advised to limit their consumption of certain foods that contain oxalate, current findings indicate that this is not necessary in some situations since it could potentially lead to a lesser consumption of fruits, vegetables, and whole grains.[17] Exercise and dietary restriction may lower the chance of developing calcium and uric acid stones.[35] A higher body mass index has been linked to a higher incidence of kidney stones and higher fluid intake has been linked to a decreased risk of stones.[18] In comparison to normal-weight individuals, overweight stone patients exhibited greater 24-hour excretion levels of calcium, oxalate, uric acid, and sodium, as well as lower urine pH, according to a systematic review with meta-analysis. These variables raise the incidence of kidney stones caused by calcium oxalate and uric acid. Patients with stones should have their weight loss plans tailored to their particular stone types, comorbidities, and cardiometabolic disorders. To find any underlying clinical and biochemical problems, anthropometric data, dietary practices, and metabolic parameters must be carefully evaluated.[19] Urolithiasis can be avoided by consuming vegetables such as celery, asparagus, parsley, and carrots, which have diuretic and urinary-tract tonic properties. Because a low magnesium-to-calcium ratio in the diet is associated with an increased risk of kidney stone formation, foods high in magnesium compared to calcium, such as avocados, bananas, and oats, are also advised.[20]

Surgical Removal Of Kidney Stone:

Using the following procedures, a urologist can either remove the kidney stone or break it up into smaller pieces:

Shock wave lithotripsy:

The kidney stone can be broken up into tiny fragments by the doctor using shock wave lithotripsy. The kidney stone's smaller fragments then travel through your urine tract. You may receive anesthesia from a doctor for this outpatient treatment.[21]

Cystoscopy and ureteroscopy:

A tiny telescope known as a ureteroscope is passed through the urethra, the bladder, and up the ureter to the location of the stone during ureteroscopy, a treatment used to treat kidney stones. Usually carried out under general anesthesia, ureteroscopy takes one to three hours to complete.[22]

Percutaneous nephrolithotomy:

The kidney stone is located and removed by the physician using a narrow viewing instrument known as a nephroscope. The doctor inserts the device directly into your kidney through a little incision on your back. To break larger kidney stones into smaller fragments, the physician could potentially use a laser.. Under anesthesia, the physician conducts percutaneous nephrolithotomy in a hospital.[21]

Use of targeted therapies in urolithiasis management

- **MicroRNAs**

A class of non-coding RNAs known as microRNAs (miRNAs) is involved in controlling gene expression. Most miRNAs originate from DNA sequences and are transcribed into primary miRNAs, which are then processed into precursor

miRNAs and mature miRNAs. RNA polymerase II/III transcripts are processed post- or co-transcriptionally in the process of miRNA synthesis. The remaining miRNAs are intergenic, produced independently and controlled by their own promoters, while around half of the discovered miRNAs are intragenic, processed from introns and exons.[23] miRNAs govern several important cellular processes, including development, differentiation, growth, and metabolism. It has been estimated that the mammalian genome has about 2200 miRNA genes. It is believed that miRNAs govern about one-third of the human genome.[24] miRNAs have the ability to control 31% of target genes in eukaryotic cells and are involved in a variety of biological development and disease processes. According to recent research, some miRNAs may be significantly up or down regulated in the development of hypercalciuria, a significant risk factor for calcium urolithiasis. Real-time PCR confirmed, in line with the microarray data, that in stone-forming rat kidneys, there was a significant decrease in rno-miR-192-3p, rno-miR-194-5p, rno-miR-29c-3p, rno-miR-185-5p, and rno-miR-30c-5p, while there was a significant increase in rno-miR-132-3p, rno-miR-181a-1-3p, rno-miR-222-3p, and rno-miR-351-5p. [25]

MicroRNAs and its relevance in urolithiasis

- **miRNA 34a**

Experimental results show that miR-34a suppresses cell-crystal adhesion in HK-2 cells by targeting CD44 in both vitro and in vivo settings. These findings suggest that miR-34a could be a useful treatment target for kidney stones. CD44 is a transmembrane glycoprotein which is involved in many cellular processes such as adhesion and infammation.HK-2 cells were used in a dual-luciferase reporter test to confirm whether CD44 was the intended target of miR-34a. Western blot results also showed that the expression of CD44 signifcantly decreased with miR-34a [26] According to various researches, miR-34a could potentially target CD44 in various renal disease like renal cancer cells to inhibit the proliferation, formation of tubes, and metastasis of renal cancer cells in vitro or in vivo. As a result, miR-34 may be a promising molecular target for innovative treatment approaches.[27]

- **miRNA-30c-5p**

Mitochondrial membrane potential (MMP) and apoptotic rates using flow cytometry and discovered that miR-30c-5p was implicated in the oxalate-induced apoptosis process. Oxidative stress markers such as LDH, MDA, SOD, and CAT were examined and it was discovered that miR-30c-5p mimic might reduce oxidative damage brought on by oxalate. MiR-30c-5p's inhibition of ATG5 was linked to lower levels of oxidative stress and crystal-cell adhesion, which may have a preventive effect on the development of kidney stones. The RT-qPCR results also showed that HK-2 cells treated with oxalate had downregulated miR-30c-5p expression.[28]

- **miRNA-484**

Dual-luciferase reporter gene assays were used to confirm the link between miR-484 and vitamin D receptor(VDR) in rats with kidney stones, downregulation of miR-484 and forkhead box protein 01 (FoxO1) and overexpression of VDR were seen. In vitro RTEC cytotoxicity and crystal attachment were reduced by overexpressing miR-484 or suppressing vitamin D receptor, and in vivo CaOx crystallization was likewise reduced. The findings indicate that miR-484 may have potential therapeutic value by blocking the VDR/FoxO1 axis, which in turn prevents RTEC proliferation and CaOx crystallization. [29]

- **miRNA-204**

To identify the miRNAs interaction involved in calculus, in silico analysis were conducted and a dual-luciferase reporter assay was used for validation. By inducing H_2O_2 in RTEC HK-2 cells, a model of calcium oxalate kidney stones

was created, and miR-204 expression was investigated. Excessive expression of MiR-204 reduces oxidative stress damage and kidney stone development by targeting MUC4, blocking the ERK pathway, and increasing RTEC proliferation. It also decreases ROS levels, apoptosis, and calcium oxalate crystallization.[30]

- **miRNA-20b-3p**

miR-20b-3p's have inhibitory effect on ATG7. miR-20b-3p-enriched exosomes reduced CaOx crystal adhesion and decreased levels of autolysosomes and autophagosomes. [31] In rats with EG-induced hyperoxaluria, the study examined the protective benefits of miR-20b-3p-enriched exosomes from adipose-derived stromal cells (ADSCs). By suppressing the expression of ATG7 and TLR4, co-culturing renal tubular epithelial cells (RTECs) with these exosomes was reported to decrease oxalate-induced autophagy and inflammation. According to these findings, miR-20b-3p-enriched exosomes may be a useful treatment strategy for preventing kidney stones.[32]

2. Small interfering RNAs (siRNA)

Double-stranded siRNAs attach to target messenger RNA sequences, cleaving and degrading the target RNA and blocking translation, gene expression, and function. Their binding sets off a chain of events that leads to the target mRNA's breakage and destruction, blocking translation as well as any further stages of gene expression and function. siRNAs have a significant therapeutic potential because they make it possible to specifically target and silence the mRNA products of genes that were previously thought to be "undruggable" targets.[33] The targets of recent research on siRNA therapy for primary hyperoxaluria (PH1) include hydroxyproline dehydrogenase (HYPDH) and glycolate oxidase (GO). RNAi targeting GO has been successful in animal models, especially when lipid nanoparticle administration is used. Animal oxalate levels were similarly lowered by targeting HYPDH, but more effective ways to deliver specific organs are still required.[34] Two of the examples of the siRNA therapy licensed by the FDA for primary hyperoxaluria type 1 is lumasiran and nedosiran.[35]

- **Dicer substrate siRNA**

The lead Hydroxyacid oxidase (HA01) targeted by DsiRNA, delivered via lipid nanoparticles (LNP), effectively reduced target gene expression in hepatocytes of mice and monkeys. In mice, this suppression of glycolate oxidase (GO) led to decreased urinary oxalate levels, increased glycolate, and eliminated calcium oxalate deposition in a model mimicking human primary hyperoxaluria type 1 (PH1). No adverse health effects were observed in HA01-deficient mice or those receiving multiple doses of Hydroxyacid oxidase 01 DsiRNA over 150 days. These findings suggest that targeting HAO1 with DsiRNA is a potentially safe and effective approach for treating PH1.[34]

- **Nedosiran**

The hypothesized enzyme mediating the last stage of oxalate formation in all three genetic subtypes of primary hyperoxaluria (PH), hepatic lactate dehydrogenase (encoded by the LDHA gene), is the target of Nedosiran, a N-acetyl-D-galactosamine (GalNAc)–conjugated RNA interference agent.[36]Nedosiran is a potentially useful therapy option for PH1, as evidenced by its ability to lower plasma oxalate levels in preclinical and early clinical investigations. Even if it worked, more research needs to be done on the long-term safety and effects of nedosiran in ESRD patients. These results point to the possibility that Nedosiran could alter the way PH1 is clinically managed, particularly for individuals with severe conditions who are frequently turned away from ongoing clinical studies.[37]

- **Lumasiran**

The illuminate trials of lumasiran sinificantly lowered urine and plasma oxalate levels over a period of 24 to 36 months, while also effectively preserving kidney function in PH1 patients. The medication only causes modest, temporary adverse effects that are readily tolerated. To validate its influence on the course of the disease, long-term data are required. [38]

CONCLUSION

Urolithiasis is a complicated disorder involving buildup of minerals and changes in the content of the urine, among other biochemical and physiological causes. The underlying pathophysiology that causes crystal formation and stone development involves abnormalities in calcium, oxalate, and other components of the urinary system.

MicroRNAs (miRNAs) play a crucial role in regulating gene expression associated with urolithiasis. These small non-coding RNAs influence various pathways involved in stone formation, such as those regulating calcium and oxalate metabolism. By modulating the expression of key genes, miRNAs have the potential to impact the formation and progression of kidney stones, making them valuable biomarkers and therapeutic targets. By specifically targeting and suppressing particular mRNAs implicated in stone formation, small interfering RNAs (siRNAs) present a possible therapeutic option. By lowering the expression of genes involved in the pathophysiology of urolithiasis, siRNAs can slow the development of the disease by reducing the synthesis of substances that lead to stone formation.

Combining siRNA and miRNA-based treatments provides urolithiasis patients with a fresh, focused approach to treatment. By treating kidney stones at the molecular level, these RNA-based methods have the potential to completely change how the ailment is managed. Although research is still in progress, these medicines have a significant potential to enhance patient outcomes and offer efficacious treatments for urolithiasis. As they validate their safety and efficacy, more research and clinical trials will be necessary to open the door for more sophisticated treatment choices.

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