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The Role of Hyperuricemia in Chronic Kidney Disease

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Abstract

The association between hyperuricemia and the onset and progression of chronic kidney disease (CKD) has been controversial. Several studies have shown an association while others show hyperuricemia being an effect of CKD rather than a cause. This literature review is constructed around a case report of a 46-year-old male who presented to the clinic with pain and swelling in his right great toe. After further evaluation, a diagnosis of gout was established. His kidney function was within normal limits at the time of evaluation. With his increased uric acid level, concerns over the potential of damage to the kidneys promoted further research. The literature review confirms the association between hyperuricemia and the onset of CKD. Many observation studies have been done looking at uric acid level and its relation to CKD. Lack of studies analyzing the benefits of urate-lowering therapy are a major barrier, although several small studies have shown promising results. This is clinically relevant because it aims to guide providers with patients that have hyperuricemia in the prevention of onset and progression of chronic kidney disease.

Keywords: hyperuricemia, chronic kidney disease, serum uric acid

The Role of Hyperuricemia in Chronic Kidney Disease

In recent years, the controversial topic of hyperuricemia's role in kidney disease has gained attention. Hyperuricemia was previously thought of as a consequence of renal insufficiency. Research is now revealing hyperuricemia may essentially be the cause. Chronic kidney disease (CKD) is a worldwide public health concern with high morbidity and mortality due to its progression and increased risk for cardiovascular events (Mallat, Kattar, Tanios, & Jurjus, 2016). CKD is characterized as an irreversible decrease in renal function that gradually progresses to end-stage renal disease (ESRD) and is the ninth leading cause of death in the United States (Arora, 2016).

The case report this paper is constructed around focuses on a 46-year-old male who was found to have hyperuricemia, which led to an acute gout flare. After obtaining a history from the patient, he was also found to have dyslipidemia, type 2 diabetes mellitus, hypertension, and history of nephrolithiasis. With his medical history alone, this patient is at increased risk for CKD. Currently his other health problems are controlled with medication. One of the first line treatments for gout is nonsteroidal anti-inflammatory drugs, which have the potential to cause injury to the kidney. This brought to light my topic choice of investigating if hyperuricemia is also a risk factor for CKD.

The purpose of this report is to determine if hyperuricemia increases the risk for kidney disease and progression of CKD. CKD prevalence is increasing in both developed and developing countries making it more important to identify modifiable risk factors and treat them effectively. Patients with other comorbidities are at greater risk for developing CKD. Several medications that are used to treat a variety of different diagnoses can also cause injury to the kidney. Thus, it is something providers need to be very cautious of.

Case Report

The case related to this review is a 46-year-old white male who presents to the clinic with pain and swelling in his right great toe. His past medical history includes, hypertension, dyslipidemia, nephrolithiasis, and type II diabetes (diagnosed at age 45). He reports his last A1C was within goal.

He came to the clinic with new symptoms he has not previously experienced. He reports pain in his right great toe, along with redness and swelling which began this morning. He has no known injury. He describes his pain as a throbbing, constant pain which he rates at a 6/10. Movement seems to exacerbate pain, and nothing seems to improve pain. He has not utilized any over the counter medication.

Exam and Treatment

The physical examination reveals right first metatarsophalangeal joint painful to touch, edema with erythema, warmth and decreased range of motion (ROM). No tophi present. All other joints with full ROM, no edema, warmth, or erythema. All other exam findings are within normal limits. Patient otherwise feels well.

The patient is diagnosed with acute gout attack after history is reviewed and lab work is obtained. Indomethacin is prescribed. Medication, dose, and side effects are discussed with patient. Hydrochlorothiazide (HCTZ) will be discontinued as it can contribute to worsening gout. Education is provided to patient including encouraging healthy diet, avoiding high purine food/drinks, increasing water intake, resting foot along with cool compression to help relieve symptoms, then encouraging light exercise as tolerated. Patient will follow-up in one week unless symptoms worsen. If symptoms do not improve, further lab work will be obtained and

arthrocentesis of synovial fluid will be performed. For complete case write-up/labs refer to appendix A.

Pathophysiology

Gout occurs in response to the presence of monosodium urate crystals (MSU) that form, then deposit in joints, bones and soft tissue; it may be acute or chronic (Becker, 2017). Hyperuricemia is diagnosed when there is excess of uric acid in the blood, typically defined as serum uric acid greater than 7mg/dL, at which point it begins to crystalize (Kuwabara, 2015). When urate concentration exceeds the solubility of urate in extracellular fluid, hyperuricemia occurs. This is a common necessary pathogenetic factor in the development of gout (Becker, 2017). The development of hyperuricemia can be caused by several different factors, such as, impairment of renal uric acid excretion, overproduction of uric acid, and/or overconsumption of purine-rich foods that are metabolized to urate (Becker, 2017). The majority of patients with hyperuricemia do not develop gout.

Episodes of gout are brought on when uric acid levels increase, which causes MSU crystals to form and deposit in a joint. When the crystals deposit, it triggers an inflammatory response that is mediated by neutrophils. In reaction to these crystals there is a release of proinflammatory cytokine and chemokine mediators that are critical to the development of the symptoms of gout. Episodes generally occur in the first metatarsophalangeal joint. There are a few risk factors such as obesity, ethanol ingestion and diuretic use, which increase the risk for gout at any given level of hyperuricemia (Becker, 2017).

Literature Review

CKD is a worldwide problem with increasing morbidity and mortality that is becoming more prevalent. The purpose of this literature review is to determine if hyperuricemia puts the

patient in the case study at greater risk for developing CKD. Numerous observational studies indicate that uric acid is independently associated with CKD (Yan et al., 2015). Many have theorized the association between hyperuricemia and kidney disease. Commonly it has been regarded as a marker rather than a risk factor.

A complete literature review will be conducted to establish if hyperuricemia is, in fact, a risk factor or just a consequence of worsening renal function. Determining if hyperuricemia leads to worsening kidney function may allow for treatment of it, in hopes to prevent further damage. Other risk factors such as hypertension, type 2 diabetes, metabolic syndrome and gout have also been proven to be associated with hyperuricemia. Therefore, whether an elevated uric acid level is an independent risk factor for CKD remains to be elucidated (Li et al., 2014).

Synthesis of Current Research

A systematic literature review of studies performed between 2009-2017 was conducted utilizing online databases including PubMed and CINAHL. In total, there were ten articles identified and reviewed for this literature review. Nine of the ten studies showed a correlation between rising uric acid levels and the development and/or progression of CKD. A table depicting information found in the studies can be viewed in Appendix B.

Madero et al. (2009) conducted a cohort study to investigate the relationship between uric acid levels and the long-term outcomes in CKD. The study evaluated the correlation between baseline uric acid levels and all-cause mortality, cardiovascular disease mortality, and kidney failure. The study utilized data from the Modification of Diet in Renal Disease Study looking at uric acid levels in patients with nondiabetic CKD stage 3 to 4.

The results showed uric acid levels were not associated with increased risk of kidney failure in patients with established renal disease. Our case study patient did not have established

renal disease so results were not completely relevant to his case. Data regarding the relationship between uric acid level and earlier stages of CKD are limited (Madero et al., 2009). This article pertained to the topic of the case study but was one of the oldest studies found. Since 2009 there has been a lot more research done in looking at the earlier stages of CKD and the role of hyperuricemia.

In 2014, Li et al., conducted a systematic review to evaluate if elevated serum uric acid level could be an independent risk factor for new-onset CKD. They looked at 13 different studies that showed a significant positive association between elevated serum uric acid levels and new onset CKD. The findings showed that treating hyperuricemia may delay or even prevent the onset of CKD. Hyperuricemia can be the consequence of decreased renal uric acid excretion, which could in turn further exacerbate kidney function, therefore results of the study should be interpreted with caution (Li et al., 2014). Li et al. (2014) results showed the prevalence of CKD was significantly elevated in hyperuricemia participants and the frequency increased as uric acid levels climbed.

Li et al. (2014) state there are many potential mechanisms to explain the relationship between hyperuricemia and CKD which include; "vascular smooth cell proliferation, endothelial dysfunction, increased synthesis of interleukin-6, impaired endothelial nitric oxide production and insulin resistance" (p. 122). When uric acid levels increase, there are intraluminal crystals that collect in the ducts of the nephrons. Once these crystals adhere to the epithelial cells it triggers an inflammatory response. This article is very relevant to our patient in the case study because he currently has normal kidney function. Treating hyperuricemia could delay or prevent the development of kidney problems in our case study patient. The more we know about possible modifiable risk factors and treatment options the better job we can do preventing CKD.

The next article looks at if uric acid has a role in the development of hypertension and renal dysfunction. This is relevant to the case study patient because he has controlled hypertension and elevated uric acid level. Dawson et al. (2013) analyzed longitudinal BP control, change in renal function, and long-term cause-specific mortality using data from the Glasgow Blood Pressure Clinic. Their study aimed to explore the clinical significance of serum uric acid levels in a cohort of 6984 patients with treated hypertension that met the criteria of the study. The study did not find evidence that increasing serum uric acid influences BP control. It did find a relationship between hyperuricemia and the decline in renal function in adults with treated hypertension. Hyperuricemia was shown to induce renal arteriopathy and renal damage. In patients with uric acid > 10mg/dL there was a significant decline in eGFR (Dawson et al., 2013). The patient in the case studies serum uric acid was 10.9 mg/dL which puts him at greater risk for kidney problems. Uric acid reduction has the potential to prevent the decline in renal function, however, larger studies are needed to support these suggestions.

In 2016, Mallat et al., looked at epidemiologic and experimental findings to support their hypothesis that there is an emerging association between hyperuricemia, hypertension, and CKD. The possible mechanisms behind their theory are that with increasing uric acid levels there is also an increase in the excretion of uric acid. This causes intraluminal crystals to deposit in the collecting duct of the nephron causing obstruction, inflammation, and oxidative stress. With this endothelial dysfunction and activation of the renin-angiotensin system there is the subsequent development and progression of CKD. Hyperuricemia can antedate the development of hypertension and may have a pivotal role in CKD by increasing risk twofold (Mallat et al., 2016). Our case study patient has controlled hypertension and an increased uric acid level putting him at great risk of new onset CKD. Available evidence suggests there may be benefit

to uric acid lowering therapy in the management of hypertension and slowing the progression of CKD. Large randomized controlled trials are needed to evaluate the safety and efficacy of such therapies (Mallat et al., 2016).

Rodenbach et al. (2015) conducted a prospective cohort over five years looking at hyperuricemia and progression of CKD in children and adolescents. Uric acid levels greater than 7.5mg/dL showed to be a significant risk factor for the fastest progression to ESRD. These findings bring up the importance of having a recommended target uric acid level in patients with CKD, which currently is not available. It also suggests that asymptomatic hyperuricemia has the capacity to cause disease in the absence of clinical symptoms. There is currently no screening or treatment recommendations available.

While the patient in the case study is not a child or adolescent the information provided in this article is relevant regarding hyperuricemia and its effect in the progression of CKD. It brings up the fact that we don't have any current screening recommendations or treatment goals. This study used a large sample of children and adolescents with a wide range of baseline kidney function and broad spectrum glomerular and non-glomerular disease causes (Rodenbach et al., 2015). It was a well-rounded study to analyze the different effects of hyperuricemia in a variety of different kidney problems.

Tsai, Lin, Kuo, and Huang (2017) conducted a longitudinal analysis looking retrospectively to evaluate if there is an association between uric acid level and CKD progression in a Chinese population. They looked at patients diagnosed with hyperuricemia (defined as >7 mg/dL) in a Taiwan medical center between 2003-2005. The analyses showed patients with hyperuricemia had a greater decline in eGFR during follow-up. It suggested there was an

increased risk for progression of kidney failure by 7% for every 1mg/dL increase in baseline uric acid level.

The study suggested hyperuricemia is a potential modifiable factor of CKD progression. There seems to be more of an association between hyperuricemia and decline in renal function in patients with diabetes, IgA nephropathy, and kidney transplant patients (Tsia et al., 2017). Even though it suggests hyperuricemia being a risk factor they did not observe a beneficial effect of allopurinol on CKD progression. This study is significant even though it only looked at patient in the Chinese population. Our case study patient's uric acid level is significantly elevated which puts him at increased risk per this study.

Tsia et al. (2017) suggest there may be several potential mechanisms in why uric acid may hasten the progression of renal function. When levels of uric acid increase, so does the secretion of uric acid. This causes more inflammatory cells which is thought to contribute to chronic interstitial inflammation and fibrosis. The precipitation of urate in the renal tubules causes uric acid nephropathy. "Hyperuricemia may also induce proliferation of vascular smooth muscle cells, increase COX-2 expression and renal renin, leading to arteriopathy and hypertension which may further aggravate kidney function" (Tsai et al., 2017, p. 12). This article was relevant to the case study because his uric acid level was above 7mg/dL. The case study patient also has diabetes, which also is a risk factor for renal function decline. The patient in the case study is at increased risk for kidney disease because of other comorbidities, if we can modify his risk factors we have the potential to minimize his risk of CKD.

Yan et al. (2015) looked to further investigate the effects of increased uric acid on patients with type 2 diabetes. A cross-sectional study of 3,212 type 2 diabetic patients in a Chinese population was done to determine the incidence of diabetic kidney disease (DKD) and

uric acid as a promoter. The prevalence of DKD correlated with elevated serum uric acid levels, increased BMI, systolic blood pressure, diastolic blood pressure, microalbuminuria, creatinine, and triglycerides (Yan et al., 2015). The increase in prevalence of DKD was also more obvious in male patients than in females (Yan et al., 2015). The limitations of this study are that the sample size is small and its findings may be specific to Chinese patients. Even though the patient in the case study is not of Chinese ethnicity this article still demonstrates the relationship between uric acid as an indicator and risk factor for DKD.

When looking more at patients with type 2 diabetes, Kumagai, Ota, Tamura, Chang, Shibata, & Uchida (2016) suggested there has always been a relationship between hyperuricemia and CKD. Most recently there was unexpected findings that sodium glucose transporter 2 inhibitors for type 2 diabetes management modestly decrease serum uric acid. This shed light on uric acid and its metabolism in the setting of CKD. This is very relevant to our case study patient as he is a type 2 diabetic. His current A1C is within goal on Metformin alone but if he ever did need additional medication one should consider a SGL2 as a good option not only for blood glucose control but to help decrease uric acid.

Research suggests that there are multiple mechanisms involved when hyperuricemia causes renal injury including; “renal vasoconstriction mediated by endothelial dysfunction, activation of the renin–angiotensin system (RAS), afferent arteriolopathy, and epithelial-to-mesenchymal transition (EMT) in renal tubular cells” (Kumagai et al., 2016, “Mechanisms,” para. 1). Most studies that were analyzed by Kumagia et al. (2016) show a positive relationship with hyperuricemia as an independent risk factor for the development and progression of renal disease in patients with diabetes. Early recognition and intervention is vital to improve renal outcomes in patients at increased risk such as the patient in the case study.

Nashar & Fried (2012) also looked at if uric acid was a marker or an independent risk factor by looking at animal studies and observational studies. In animal studies, they found uric acid is shown to be more of a risk factor for the initiation of CKD than its progression. Their findings suggest a role of increased uric acid levels and the incidence of CKD. This just helps to support the rest of the studies by suggesting that uric acid may actual be the cause of CKD rather than the effect of. The case study patient currently has normal kidney function despite many risk factors. It's important to recognize any modifiable risk and treating them to help prevent the onset of CKD in our case study patient. Nashar & Fried (2012) recommend to establish a causal relationship between hyperuricemia and CKD, longitudinal randomized controlled studies of decreasing uric acid level in patients at increased risk are needed.

In 2015, Uchida et al. conducted a retrospective CKD cohort to clarify the independent impact of uric acid on the subsequent risk of end-stage renal disease by a propensity score analysis. They conducted this research because of the controversial impact of uric acid and inconsistent results from other observational studies. The study focused on the primary endpoint of end stage renal disease leading to initiation of dialysis versus the risk of mortality. After using three different methods of the propensity score analysis, the study concluded that higher uric acid accelerates the progression to the subsequent ESRD and treatment target should be a serum uric acid of less than 6.5mg/dL (Uchida et al., 2015). This isn't entirely relevant to the case study patient but is still valuable information when looking at treatment target for serum uric acid levels.

Learning Points

All studies that were looked at found at least some type of relationship between hyperuricemia and the development or progression of CKD. We need to be especially vigilant in

patients with other comorbidities such as diabetes and hypertension to prevent the onset of CKD. By modifying risk factors, we can potentially prevent the onset of CKD. After reviewing all the literature these are a few take away points that were discovered.

- Hyperuricemia is a potential modifiable factor of CKD progression.
- Hyperuricemia causes endothelial dysfunction in the kidneys.
- There are currently no screening recommendations or recommended target uric acid level in patients with CKD.
- Treating hyperuricemia may delay or even prevent the onset of CKD.
- More studies are needed looking at the effects and safety of urate-lowering therapy on kidney function.

Project Recommendations

There have been several small studies done in the past few years looking at effects of urate-lowering therapy on kidney function. All results have shown positive kidney outcomes from slowing progression, reducing proteinuria, and reducing blood pressure (Mallat et al., 2016). Even though these trials have shown promising results they are far from convincing and therefore larger studies are needed. It is something that needs be better analyzed before practice changes can be made.

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Appendix A

Chief complaint

Pain and swelling to right great toe.

HPI

Mr. A is a 46-year-old male here today with complaint of right great toe pain, redness, and swelling. The pain starting this morning when he woke up. He did not remember any injury/trauma and usually wears shoes at most times. The pain is located in his right great toe and is described as throbbing, constant pain. The pain is localized to the right toe and denies it radiating or any other joints involved. Nothing seems to improve pain. The pain worsens with movement. He rates pain at a 6/10. He has not taken any OTC medication for pain.

He reports his blood glucose levels have been controlled. Currently checks blood glucose about once per week and they usually are less than 120. Per patient report last A1C was within goal.

He also reports history of kidney stones with last episode several years ago, unsure what type of stone.

Allergies

None

Medication

Hydrochlorothiazide 25mg PO QD

Lisinopril 20mg PO QD

Metformin 500mg PO QD

Simvastatin 20mg PO QHS

Aspirin 81mg PO QD

Past Medical History

Type II Diabetic diagnosed at age 45

Kidney stones

Hypertension

Dyslipidemia

Past Surgical History

Lithotripsy (2 years ago)

Family History

Mother: HTN, Type II Diabetes

Father: HTN, Nephrolithiasis

Social History

Reports drinking 3-4 beers per week. He reports drinking a few beers last night after curling. Denies tobacco or illicit drug use. He reports his family owns a butcher show so he eats a lot of red meat.

Review of Systems

General: Denies fever, chills, recent illness, or unintended weight changes. Otherwise feels well.

Musculoskeletal: See HPI. Denies any pain, redness, or swelling in any other joints.

Cardiovascular: Denies chest pain/pressure. History of hypertension and dyslipidemia.

Respiratory: Denies shortness of breath.

Integumentary: Redness/swelling to right great toe. Denies any skin disorders, lesions, or open areas.

Extremities: Reports sensation of feet has been within normal limits. Denies any numbness or tingling in extremities. Redness/warmth to right great toe. Denies any edema.

Physical Exam

Vitals: BP 126/78 | HR 72 | T 37.4 C | BMI 29 kg/m2

Constitutional: Alert and orientated, answers questions appropriately.

Cardiovascular: S1, S2. Regular rate and rhythm without murmur, click, rub or gallop.

Respiratory: Lung sounds clear to auscultation bilaterally.

Integument: Edema noted to right MTP joint. Nails without clubbing or cyanosis, capillary refill <3. No varicosities or stasis changes. Feet without open areas, blisters or callous. Sensation of feet within normal limits.

Musculoskeletal: Right first metatarsophalangeal joint painful to touch, edema with erythema, warmth and decreased ROM. No tophi present. All other joints with full ROM, no edema, warmth, or erythema.

Labs

CBC

WBC 9.0

RBC 4.8

Plt 163

Hgb 14.5

Hct 45

MCV 88

MCHC 34

MCH 32

Uric Acid 10.9

BMP

BUN 23

Na 140

K 3.9

Cl 105

C02 27

Glucose 139

Cr 1.15

Calcium 8.8

GFR >60

Assessment

Gout

Differentials include pseudogout, osteroarthritis, cellulitis, reactive arthritis, rheumatoid arthritis, and septic joint

Plan

Indomethacin 50mg PO TID for 5 days. Reviewed medication, dose and side effects with patient.

Discontinue HCTZ as it can contribute to gout.

Education

Rest extremity, elevate and use cool compression to affected area for comfort 20 minutes three times per day until symptoms improve.

Drink 8-10 glasses of water per day.

Encouraged healthy diet and exercise as tolerated.

Avoid high purine food/drinks including alcohol, red meat, seafood, and oatmeal.

Follow-up

Recheck foot and blood pressure in one week or sooner if pain increases, swelling and redness worsen and spreads up leg, or if patient develops fever. If patient does not improve will do sedimentation rate and perform arthrocentesis of synovial fluid. If patient continues to have gout flares will start Allopurinol.

Appendix B

Table 1

Literature Search

Author (year)	Design (follow-up, years)	Findings on uric acid levels and kidney function	Significant
Tsai (2017)	Retrospective cohort	Hyperuricemia is a potential modifiable factor of CKD progression	Yes
Kumagai (2016)	Prospective cohort	Hyperuricemia is an independent risk factor for the development and progression of renal disease in patients with diabetes	Yes
Mallat (2016)	Prospective cohort	Hyperuricemia can antedate the development of hypertension and increase risk for CKD twofold	Yes
Rodenbach (2015)	Prospective cohort (5 years)	Hyperuricemia is an independent risk factor for faster progression of CKD in children and adolescents	Yes
Uchida (2015)	Retrospective cohort (median 4.0 years), propensity score analysis	Propensity score analysis showed the effect of SUA [6.5 mg/dL in the follow-up on ESRD	Yes
Yan (2015)	Cross-sectional	SUA was an independent predictor of diabetic kidney disease	Yes
Li (2014)	Systematic review and meta-analysis based on observational cohort	A significant positive association was found between elevated serum uric acid levels and new-onset CKD	Yes
Dawson (2013)	Prospective cohort (median 29 years in men and 34 years in women)	Highest quartile of SUA associated with GFR decline	Yes
Nashar (2012)	Cross-sectional	Uric acid is associated with CKD and risk factors for kidney disease	Yes
Madero (2009)	Retrospective cohort	Uric acid levels were not associated with increased risk of kidney failure in patients with established renal disease	No