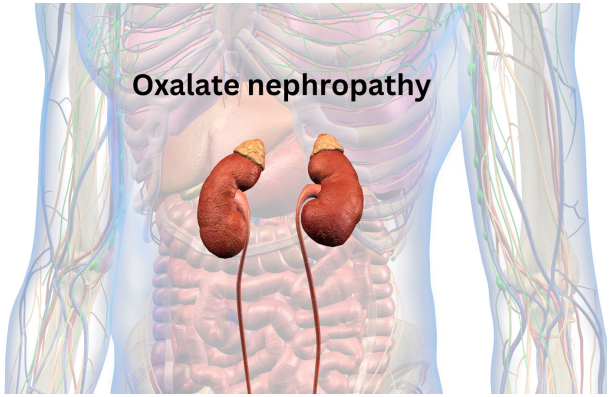
Acute oxalate nephropathy and diabetes mellitus

Mojgan Mortazavi

Professor of nephrology

Isfahan Kidney Diseases Research



Case presentation

- Female 63 years old came with cr rising
- PMH:

DM from 40 years ago

IHD from 15 years ago

Cholesyctectomy 9 years ago

Hypothyroidism from 10 years ago

FH:

Renal stone in her brothers

Case presentation

Date	Serum Cr	Serum BUN
1401/3/10	1.34	18
1401/7/6	1.52	20
1401/11/10	2.53	43
1401/11/25	5.9	78

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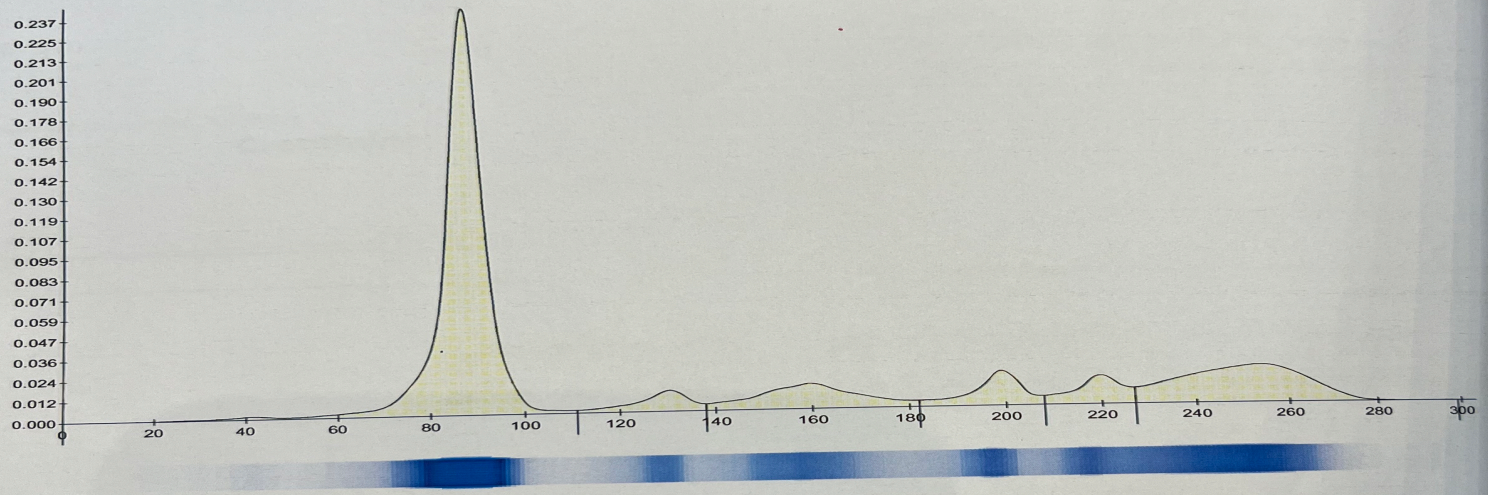
Name: S-SALIMIAN
ID : 14010410681
Sex: F
Age: 63

Capillary Serum Protein Electrophoresis



Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	59.0	55.8 - 66.1	4.6	4.0 - 4.8
Alpha 1	3.9	2.9 - 4.9	0.3	0.2 - 0.4
Alpha 2	8.8	7.1 - 11.8	0.7	0.5 - 0.9
Beta 1	5.8	4.7 - 7.2	0.5	0.3 - 0.5
Beta 2	4.9	3.2 - 6.5	0.4	0.2 - 0.5
Gamma	17.6	11.1 - 18.8	1.4	0.8 - 1.4
Total Protein :			7.8	6.8 - 8.7

Albumin / Globulines: 1.44

Comments:

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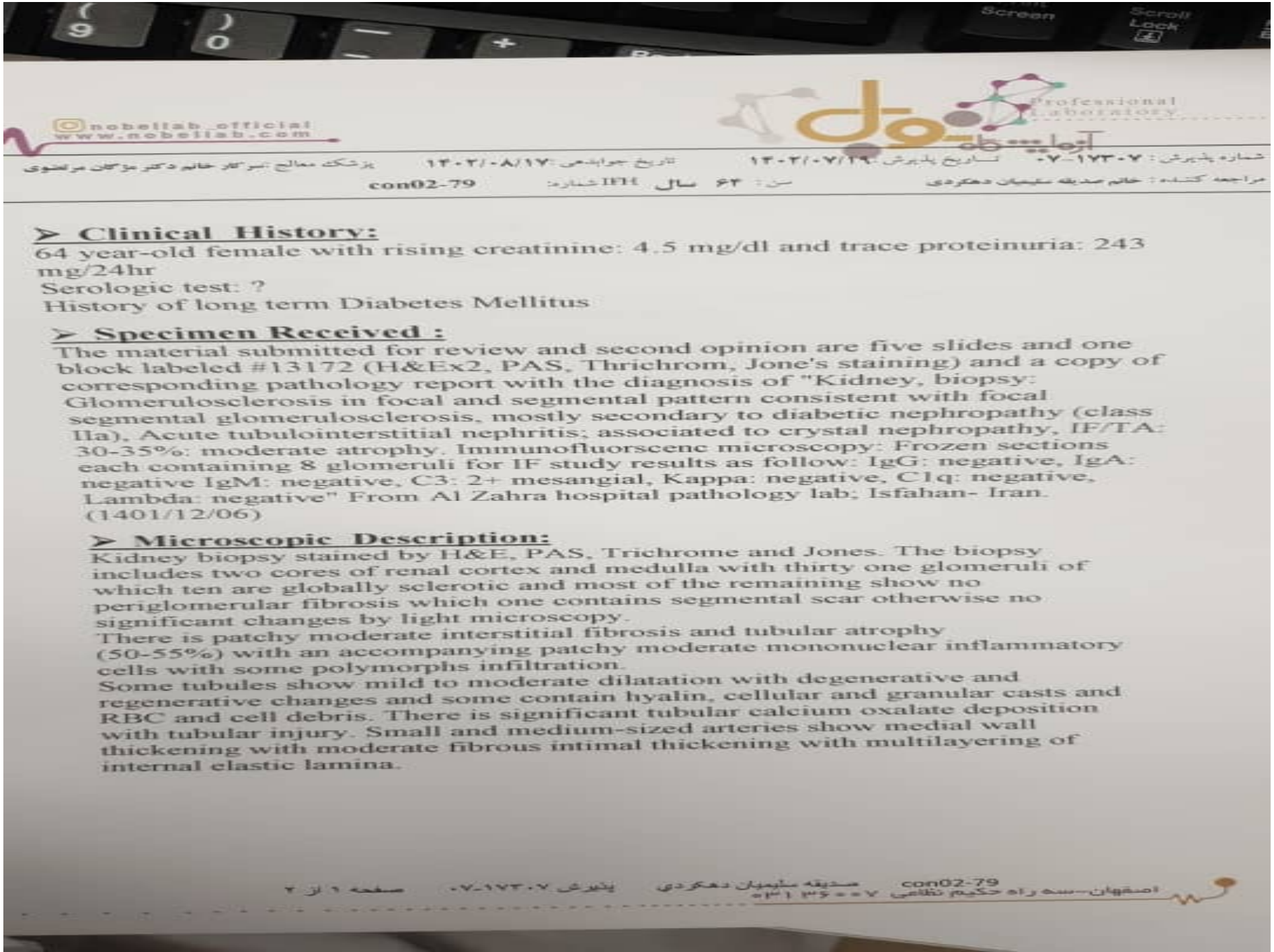
Signa



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شماره پذیرش: ۰۷-۱۷۳۰۷ تاریخ پذیرش: ۱۴۰۲/۰۷/۱۹ تاریخ جوابدهی: ۱۴۰۲/۰۸/۱۷ پزشک معالج: سرکار خانم دکتر مؤمنان مرتضوی

مراجعه کننده: خانم صدیقه سلیمیان دهکردی سن: ۶۴ سال IHH شماره: con02-79

➢ Clinical History:

64 year-old female with rising creatinine: 4.5 mg/dl and trace proteinuria: 243 mg/24hr
Serologic test: ?
History of long term Diabetes Mellitus

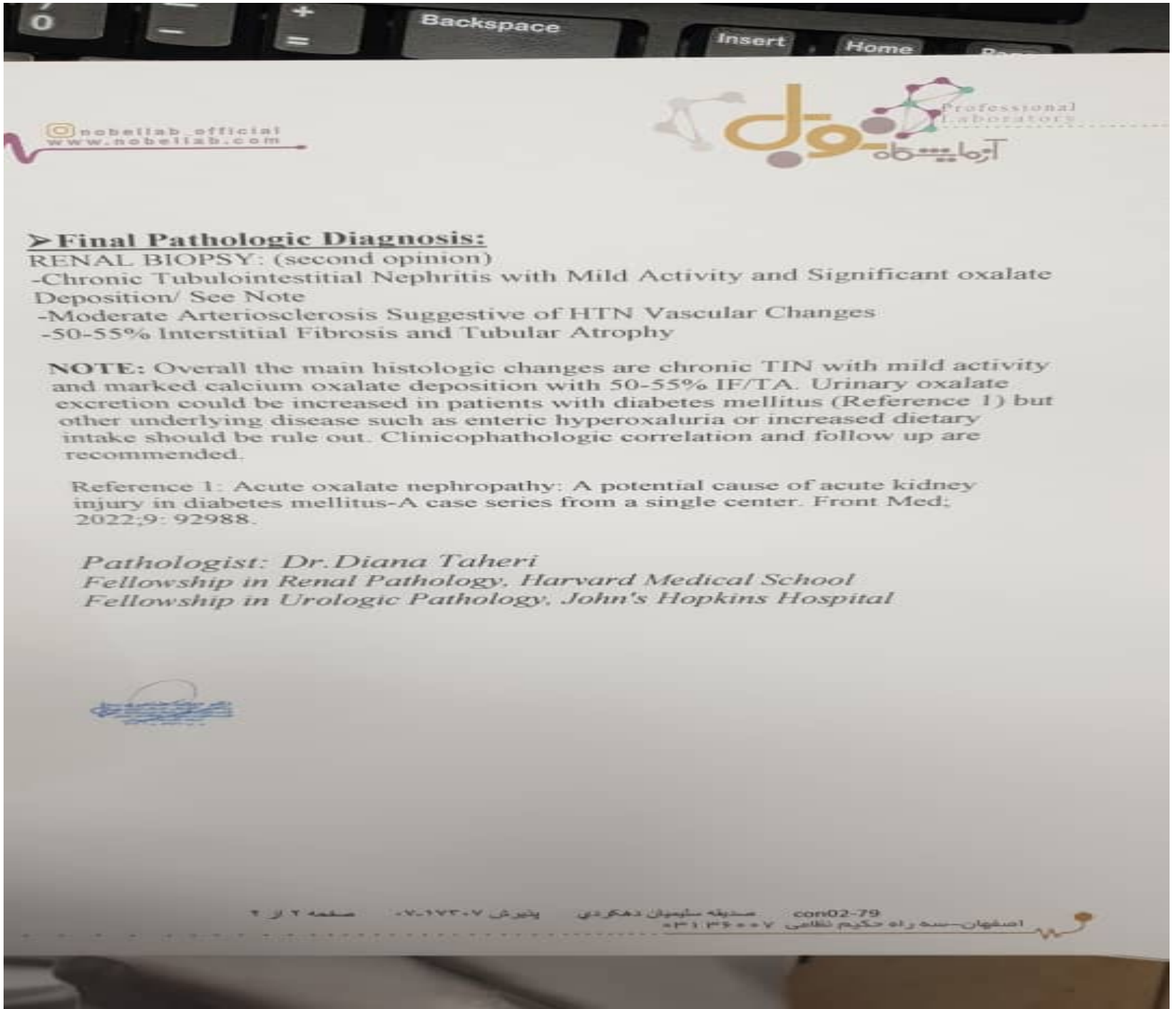
➢ Specimen Received :

The material submitted for review and second opinion are five slides and one block labeled #13172 (H&Ex2, PAS, Thrichrom, Jone's staining) and a copy of corresponding pathology report with the diagnosis of "Kidney, biopsy: Glomerulosclerosis in focal and segmental pattern consistent with focal segmental glomerulosclerosis, mostly secondary to diabetic nephropathy (class IIa), Acute tubulointerstitial nephritis; associated to crystal nephropathy, IF/TA: 30-35%: moderate atrophy. Immunofluorscenc microscopy: Frozen sections each containing 8 glomeruli for IF study results as follow: IgG: negative, IgA: negative IgM: negative, C3: 2+ mesangial, Kappa: negative, C1q: negative, Lambda: negative" From Al Zahra hospital pathology lab; Isfahan- Iran. (1401/12/06)

➢ Microscopic Description:

Kidney biopsy stained by H&E, PAS, Trichrome and Jones. The biopsy includes two cores of renal cortex and medulla with thirty one glomeruli of which ten are globally sclerotic and most of the remaining show no periglomerular fibrosis which one contains segmental scar otherwise no significant changes by light microscopy.
There is patchy moderate interstitial fibrosis and tubular atrophy (50-55%) with an accompanying patchy moderate mononuclear inflammatory cells with some polymorphs infiltration.
Some tubules show mild to moderate dilatation with degenerative and regenerative changes and some contain hyalin, cellular and granular casts and RBC and cell debris. There is significant tubular calcium oxalate deposition with tubular injury. Small and medium-sized arteries show medial wall thickening with moderate fibrous intimal thickening with multilayering of internal elastic lamina.

اصفهان- سه راه حکیم نظامی ۰۳۱ ۳۶ ۰ ۰ ۷



➢Final Pathologic Diagnosis:

RENAL BIOPSY: (second opinion)

-Chronic Tubulointestitial Nephritis with Mild Activity and Significant oxalate Deposition/ See Note

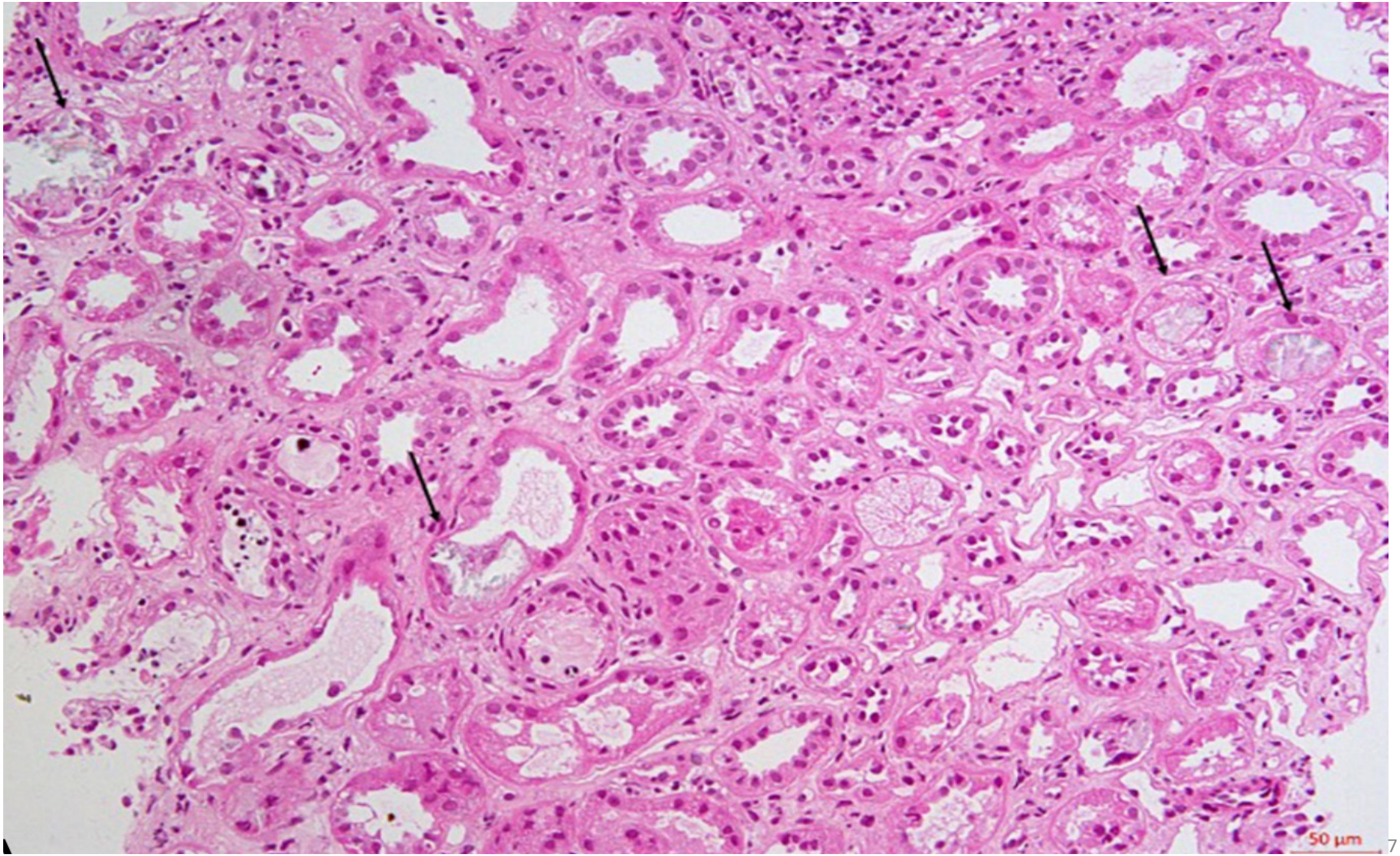
-Moderate Arteriosclerosis Suggestive of HTN Vascular Changes

-50-55% Interstitial Fibrosis and Tubular Atrophy

NOTE: Overall the main histologic changes are chronic TIN with mild activity and marked calcium oxalate deposition with 50-55% IF/TA. Urinary oxalate excretion could be increased in patients with diabetes mellitus (Reference 1) but other underlying disease such as enteric hyperoxaluria or increased dietary intake should be rule out. Clinicophathologic correlation and follow up are recommended.

Reference 1: Acute oxalate nephropathy: A potential cause of acute kidney injury in diabetes mellitus-A case series from a single center. Front Med; 2022;9: 92988.

Pathologist: Dr.Diana Taheri
Fellowship in Renal Pathology, Harvard Medical School
Fellowship in Urologic Pathology, John's Hopkins Hospital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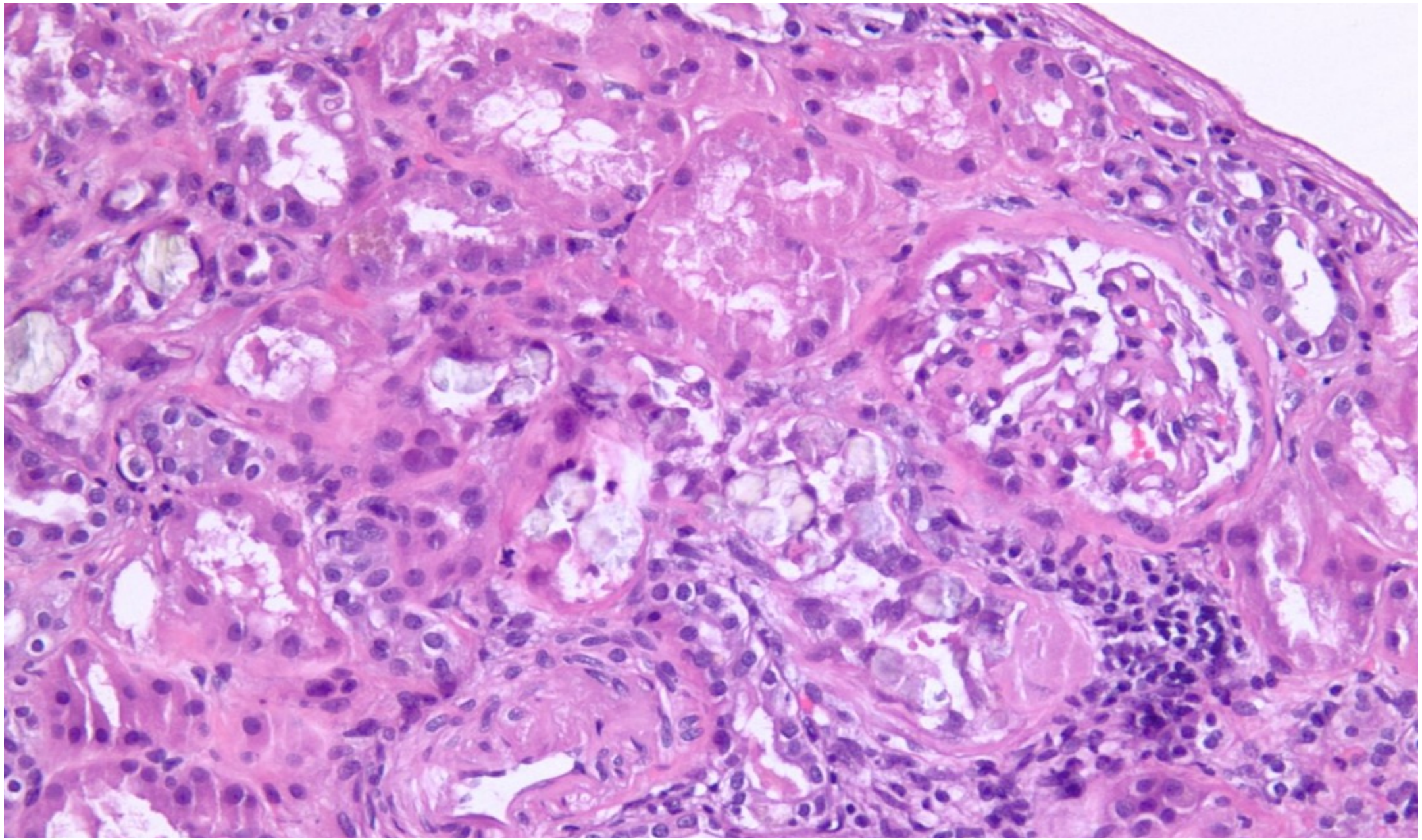
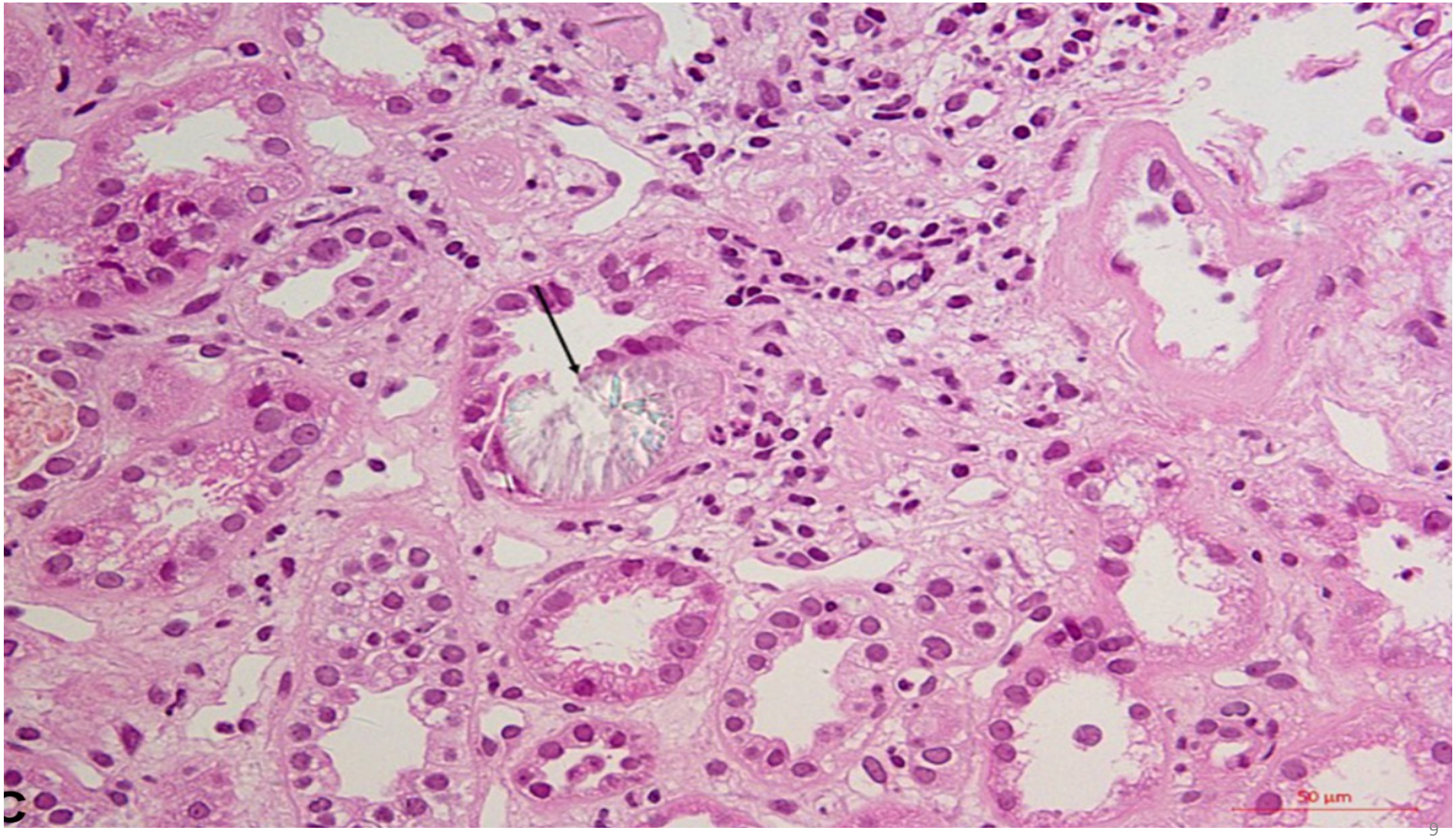
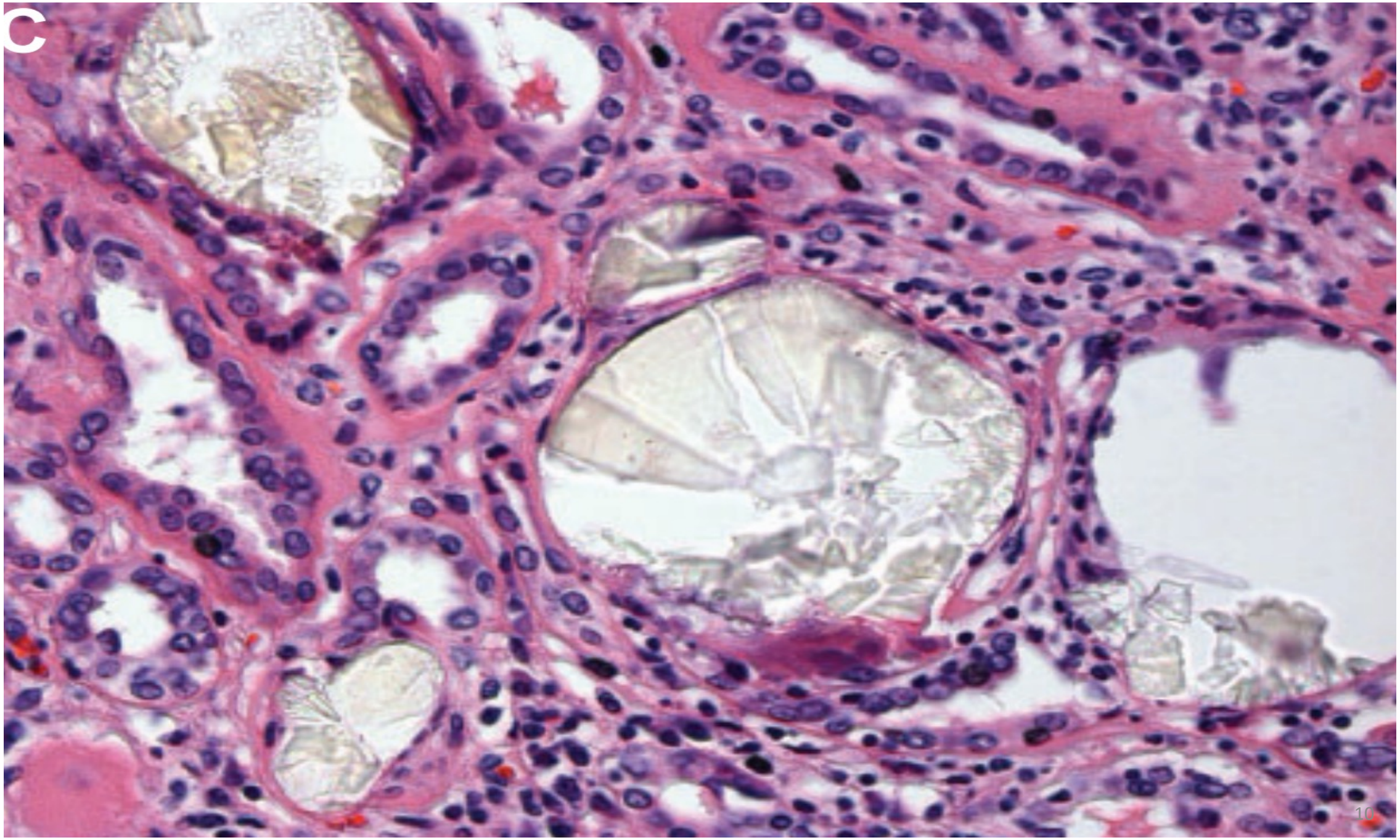



50 µm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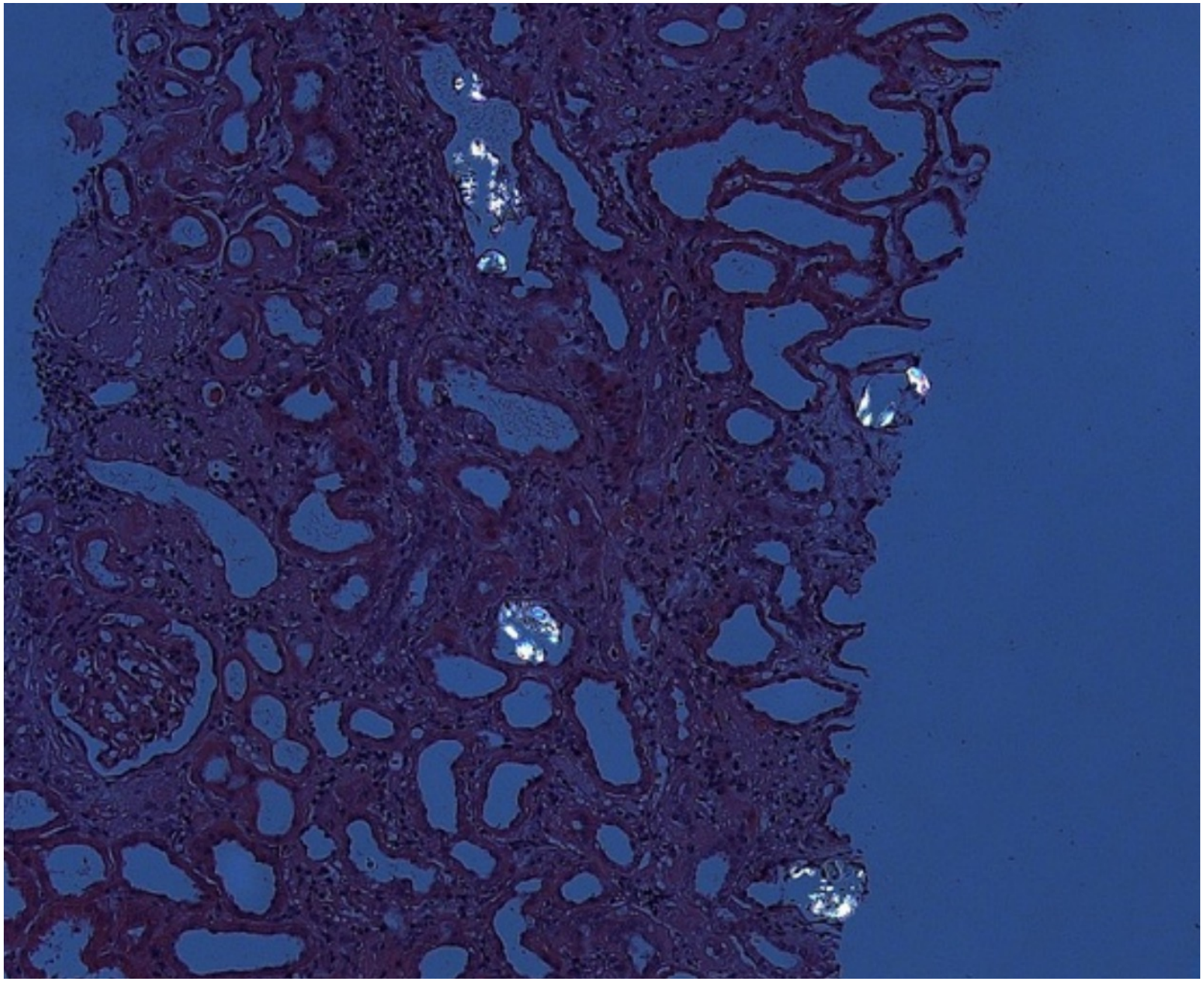

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 August 2022
DOI 10.3389/fmed.2022.929880

OPEN ACCESS

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Acute oxalate nephropathy: A potential cause of acute kidney injury in diabetes mellitus—A case series from a single center

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Introduction

- Patients with diabetes mellitus (DM) may develop diabetic kidney disease (DKD), which develops progressively with a gradual decline in kidney function.
- Therefore, causes other than DKD should be differentiated when acute kidney injury (AKI) occurs in patients with DM.
- Acute oxalate nephropathy (AON) is diagnosed by the characteristic finding of widespread deposition of oxalate crystals in the kidney, which is a relatively uncommon cause of AKI in clinical practice
- The kidney serves as the main excretory organ of circulating oxalate.
- Patients with DM have been found to have increased urinary oxalate excretion.

Causes of hyperoxaluria

- The causes of hyperoxaluria can be either primary or secondary .
- Primary hyperoxaluria refers to a group of autosomal recessive disorders with enzymatic defects in the glyoxylate pathway, which results in overproduction of oxalate and subsequent hyperoxaluria .
- Recurrent urolithiasis is the common clinical presentation of primary hyperoxaluria, which generally progresses to end-stage kidney disease (ESKD).

Secondary hyperoxaluria

- Secondary hyperoxaluria is more common than primary hyperoxaluria.
- Oxalate may be derived exogenously from increased dietary oxalate intake and/or net availability of oxalate in the intestine .
- However, some patients have no evidence of exogenous oxalate derivatives, indicating the potential role of endogenous synthesis in the development of secondary hyperoxaluria.
- Interestingly, some oxalate precursors have been found with increased circulating levels in patients with DM, which are also identified as potential metabolite markers of DM in recent studies .

- Six male patients with biopsy-proven AON out of a total of 5,883 native kidney biopsies were identified, aged 58.3 ± 9.1 years at the time of kidney biopsy.
- Only one patient who had received Roux-en-Y gastric bypass surgery took oxalate-rich food before the onset of the disease.
- None of them had clinical features of enteric malabsorption.
- Three patients were currently on renin-angiotensin system inhibitor treatment for hypertension, and 5 of them received non-steroidal anti-inflammatory drugs

Demographic, clinical features and potential hyperoxaluria enabling factors of 6 patients with acute oxalate nephropathy.

Patients	1	2	3	4	5	6
Age at onset	50	74	53	57	51	64
Sex	Male	Male	Male	Male	Male	Male
BMI (kg/m^2)	23.5	24.2	28.3	18.9	25.7	19
Blood pressure (mmHg)	120/80	165/83	190/94	135/74	132/80	129/79
HbA1c	8.70%	6.40%	NA	6.70%	5.70%	5.90%
Medical history						
Diabetes mellitus	Yes	Yes	Yes	Yes	Yes	Yes
Duration (years)	13	Unknown	10	10	4	10
Treatment (OAD/Insulin)	Insulin	OAD	OAD	Insulin	OAD	OAD
Hypertension	Yes	Yes	Yes	Yes	No	Yes
Duration (years)	13	50	0.5	NA	/	10
Treatment	RASI + β-Blocker	CCB	RASI + β-Blocker	CCB	/	RASI
Chronic kidney disease	No	No	No	No	No	No

Hyperoxaluria-enabling factors						
Increased intake of oxalate precursors	No	No	No	No	No	Spinach
Increased oxalate availability in the colon due to fat malabsorption						
Chronic pancreatitis/pancreatic insufficiency	No	No	No	No	No	No
Roux-en-Y bypass surgery	No	No	No	No	No	Yes
Decreased intestinal oxalate degradation						
Recent antibiotic use	No	No	No	No	No	No

NA, not available; OAD, oral antidiabetic drugs; NSAIDs, non-steroid anti-inflammatory drugs.

Regarding pathological findings, acute tubular epithelial injury with extensive oxalate deposition was the most prominent finding. The tubular cells presented with vacuolar and granular degeneration and effacement of the brush margin, with occasional atrophy found. The interstitium was edematous with the focal distribution of fibrosis. Focal infiltration of

- Three patients presented with oliguria and 4 patients needed dialysis at the beginning with none requiring dialysis at discharge.

- Four patients received a course of corticosteroid treatment empirically.

- Among them, two patients had estimated glomerular filtration rate (eGFR) recovered to over 60 ml/min/1.73 m^2, while the other two patients remained with kidney dysfunction at the last follow-up.

Discussion

- Kidney excretion accounts for the majority of daily oxalate excretion from the body.
- Circulating oxalate is freely filtered at the glomerulus, reabsorbed, and secreted by the proximal tubule.
- Multiple studies have shown that the 24-h urine excretion of oxalate was higher in individuals with DM than in those patients without DM

Discussion…

- Nephrolithiasis is a common comorbidity of DM, with calcium oxalate as the most common composition of stones.
- In a retrospective analysis of 462 patients with nephrolithiasis, patients with DM excreted greater urinary oxalate than those patients without DM.
- In a recent report from the Chronic Renal Insufficiency Cohort (CRIC) Study with 3,123 established CKD, individuals with DM had 11% higher 24-h urinary oxalate excretion than those patients without diabetes.
- These results indicate that patients with DM are at risk for hyperoxaluria-enabling conditions.

Discussion….

- Most reported AON cases in the literature have attributed the cause to either high intakes of oxalate-containing foods or oxalate precursors (12–15) or malabsorption induced by short-bowel syndrome , including:

-celiac disease ,

- gastric surgery (Roux-en-Y gastric bypass) ,

-inflammatory bowel disease ,

-chronic pancreatitis or pancreatic insufficiency, *etc*.

Discussion….

- **Glyoxylate** is an immediate precursor of oxalate.
- In recent years, glyoxylate has been identified as a potential metabolite marker of type 2 DM .
- A retrospective study showed that the plasma level of glyoxylate was elevated in diabetic subjects, even up to 3 years before diabetes diagnosis .

Discussion….

Glyoxal, another important precursor involved in endogenous oxalate synthesis in humans, has also been found to have higher plasma levels in diabetic patients than in controls, as well as increased urinary oxalate excretion .

- Therefore, the potential contribution of these metabolic components of diabetes to the development of hyperoxaluria in DM needs to be studied more.

Discussion….

- In the present study, all of our patients presented with AKI with the finding of universal oxalate crystal deposition in tubules and/or the interstitia in kidney biopsy.
- The deposition of oxalate in the kidney is subjected to several factors, including supersaturation, precipitation, crystal aggregation, and adhesion .
- Decreased urine output with severe supersaturation may cause massive crystal deposition, renal epithelial cell damage, inflammation, and necrosis, resulting in AKI .
- The formation of highly concentrated urine in the dehydrated state is an essential prerequisite for crystal precipitation and deposition
- Notably, RASIs and/or NSAIDs were concurrently used in most of our patients at the onset of the disease.
- These drugs might enhance renal hypoperfusion at the glomerular level under the condition of volume depletion, contributing further to the urine concentration.

Discussion….

- Furthermore, *in vitro* studies showed that prostaglandins may decrease the adhesion ability of calcium oxalate to renal epithelial cells .
- As NSAIDs downregulate prostaglandin production , it is feasible to speculate that NSAID use is predisposed to a greater likelihood of adhesion of oxalate crystals to the tubular epithelium.
- In this regard, we hypothesize that factors, which either decrease urinary flow in renal tubules or increase the adhesion ability of oxalate crystals to the epithelium, contribute convergently to the development of acute oxalate nephropathy when superimposed on hyperoxaluria in DM.

Outcomes of AON

- Some patients experienced complete recovery of kidney function, while the other patients had residual kidney dysfunction with some remaining dialysis dependent.
- The recommended treatments include hydration, oral calcium supplements, alkalization, and correction of hyperoxaluria-enabling conditions

- Previous studies have reported inconsistent impacts on the recovery of kidney function by oral citrate supplements and intravenous fluids containing sodium bicarbonate .
- Many nephrologists also empirically use steroids for the management of AON, without confirming the effectiveness of steroids to date

Discussion….

- The **inflammasome** has been identified to play a critical role in the process of oxalate-induced epithelial injury in recent studies.
- Interleukin-1β (IL-1β) is released upon activation of the NLRP3 inflammasome .
- Administration of an IL-1 receptor antagonist (IL-1ra) has been demonstrated to attenuate oxalate-induced AKI in an animal model.
- Whether IL-1ra treatment is effective in the treatment of AON in clinical practice needs to be studied further.

REVIEW ARTICLES | JULY 27 2023

Oxalate Nephropathy and the Mechanism of Oxalate-Induced Kidney Injury

Subject Area: Nephrology

Daorina Bao; Yu Wang; Ming-hui Zhao

Kidney Dis 1–10.
https://doi.org/10.1159/000533295 Article history

ARTICLE CONTENTS

Abstract

Background: Hyperoxaluria is a major cause of oxalate nephropathy, which can lead to impaired renal function presenting as acute kidney injury, acute on chronic kidney disease, or chronic kidney disease. The Chronic Renal Insufficiency Cohort study showed that higher urinary oxalate

Cause of acute oxalate nephropathy in diabetic patients

- A possible explanation for this is that undetectable pancreatic exocrine insufficiency may exist in those diabetic patients .
- In addition, increased generation of endogenous oxalate precursors, such as glyoxylate and glyoxal, in diabetes has been hypothesized .
- Furthermore, in a mouse model of diabetes (C57BLKS/JLepr$^{-/-}$), glyoxylate levels were six-fold higher in diabetic mice than in control mice , supporting the above hypothesis.

Clinical Kidney Journal, 2022, vol. 15, no. 2, 194–204

doi: 10.1093/ckj/sfab145
Advance Access Publication Date: 12 August 2021
CKJ Review

CKJ REVIEW

Oxalate nephropathy: a review

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Cause of acute oxalate nephropathy in diabetic patients

- Diabetes has also been associated with increased oxalate excretion, perhaps via an increase in oxalate precursors such as glyoxylate and glyoxal that has been observed in diabetes .
- Furthermore, diabetes is associated with dysfunction of the gastrointestinal tract, including gastroparesis and diabetes-related enteropathy , which would make these patients prone to volume depletion and an increase in urine supersaturation of calcium oxalate.
- Not all patients with hyperoxaluria develop ON and a concomitant insult such as volume depletion is likely one key factor in precipitating it.


Treatment

Treatments discussed in this review

rt By: Search Rank Page Order Found in 1 section < > Do

	supersaturation	take with urinary alkalinization may slow progression [82]	
Pyridoxine	Increase function of AGT	Useful in some PH1 [9]	–
Citrate	Inhibit calcium oxalate crystallization	May stabilize or improve renal function in some cases [69]	–
Liver transplant	Restore oxalate metabolism primarily in PH1 [9]	PH2 may not necessarily respond and no data in PH3 [9]	–
Lumasiran	RNAi of glycolate oxidase enzyme [70]	FDA approved—no long-term data on outcomes.	Single-arm study in advanced kidney disease ongoing—NCT04152200
Nedosiran	RNAi of LDH enzyme [72]	Trial ongoing in PH1 and PH2	NCT03847909
Secondary hyperoxalurias			–
High fluid intake	Lowers urinary calcium oxalate supersaturation [10]		–
EH			–
Increased calcium and low fat intake	Use calcium to bind oxalate in gut	Generally can lower urine oxalate in short term studies [10, 12]	–
Lower oxalate intake	decrease gut oxalate	Variable results [10, 12]	–
Citrate	Inhibit calcium oxalate crystallization	Only data is in stone patients with low urine citrate [10, 12]	–
Sevelamer	Fatty acid binding	Non-significant decrease in urine oxalate in single trial [76]	–
Cholestyramine	Decrease bile acids	Conflicting results [10, 12]	–
Microbiome manipulation	Increase oxalate degradation in gut	Have generally not been effective [64]	–
Reversal of bariatric surgery	Reverse malabsorption	Single case report with Roux-en-Y [79]	
Reloxilase (ALLN-177)	Recombinant oxalate decarboxylase	Limited data—clinical trial ongoing [77]	NCT03847090
Cytokine/inflammasome inhibition	Block downstream inflammation leading to fibrosis	Animal studies only so far [80, 81] Potentially also could be useful in PH and ingestions	–
Ingestions			–
Identify and remove offending agent from diet			–
EG			–
Ethanol	Competitively inhibits metabo-	Reduces formation of toxic	–

Urinary oxalate as a potential mediator of kidney disease in diabetes mellitus and obesity

Orhan Efe,[1] Ashish Verma,[2] and Sushrut S. Waikar[2]
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The publisher's final edited version of this article is available at Curr Opin Nephrol Hypertens

Go to:

Abstract

Purpose of review:

Hyperoxaluria can cause kidney disease through multiple mechanisms, including tubular

Cause of acute oxalate nephropathy in diabetic patients

- Individuals with diabetes have increased levels of plasma glyoxal (a protein glycation product) and glyoxylate, both of which are precursors for oxalate.
- Increased gut absorption of oxalate in obesity may be due to obesity-associated inflammation.
- A recent study in individuals with chronic kidney disease found that higher 24h urinary oxalate excretion was independently associated with increased risk of kidney disease progression, especially in individuals with diabetes and obesity

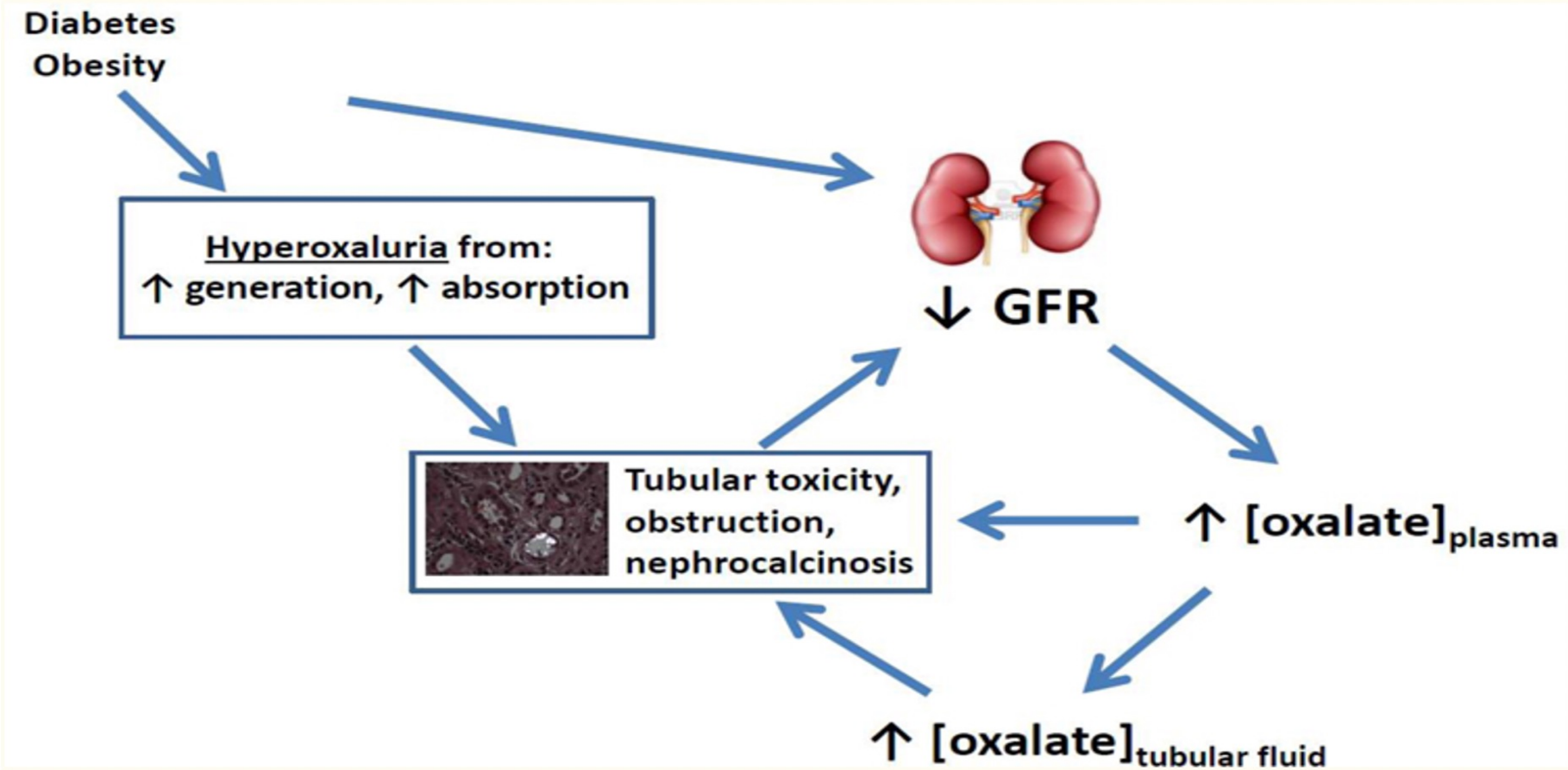

Figure 1

A schematic depicting how higher levels of oxalate absorption or generation in diabetes or obesity could contribute to the development or progression of chronic kidney disease.

Go to:

Hyperoxaluria

- In human studies that have examined predictors of 24h urinary oxalate excretion in stone formers, clinical variables that have been linked to higher urinary oxalate excretion include age, higher BMI, diabetes, and higher fructose and oxalate intake

Glyoxylate

- A retrospective analysis of long-term blood donors found that elevated serum glyoxylate levels predicted the diagnosis of diabetes mellitus by up to 3 years, in analyses performed with matching for age, gender, and BMI.

Glyoxal

- Another potential precursor of oxalate is glyoxal, an alpha-oxoaldehyde which can be generated from the glycation of proteins or from lipid peroxidation from hyperglycemia in diabetes.
- Glyoxal has been hypothesized to be an important source of endogenous oxalate synthesis in humans and a source of oxidative stress.
- In a small study, glyoxal was found to correlate with HBA1C, fasting glucose, and microalbuminuria.
-

Alpha-oxoaldehyde, methylglyoxal

- Another related alpha-oxoaldehyde, methylglyoxal, was also found to be associated with incident cardiovascular disease and mortality in prospective studies of 1,003 type 2 and 159 type 1 diabetic patients.
- Baseline and six-year longitudinal methylglyoxal levels were inversely correlated eGFR in 1481 screen-detected type 2 diabetic patients.
- In a prospective three-year observational study of 150 individuals with CKD stages 3–5, higher methylglyoxal levels (tertiles 2 and 3 compared with tertile 1) were associated with a >2-fold and > 6-fold increased risk for progression to ESRD, respectively.

Potential for future therapeutics

- If the association between hyperoxaluria and CKD in the setting of diabetes and/or obesity is indeed causal, then therapeutic strategies aimed at lowering urinary oxalate excretion may prove fruitful to prevent CKD or slow its progression.
- Reducing oxalate absorption from the gastrointestinal tract may be accomplished by dietary modifications (e.g., avoiding high oxalate-containing foods; supplemental calcium), medications to bind oxalate in the gut (e.g., calcium or non-calcium-containing phosphorous binders), or medications to enzymatically degrade in the gastrointestinal tract.
- Reducing oxalate generation by the liver is being explored for the treatment of primary hyperoxaluria using gene-targeting technologies to inhibit enzymes involved in oxalate metabolism.,

an puli. IV, intravenous.

Table 2. Foods with high oxalate content and estimated amounts

Substance	Oxalate content in mg/100 g
Purslane	910–1679
Spinach varieties	320–1260
Garden orach	300–1500
Rhubarb	260–1235
Sorrel	270–730
Cocoa	170–623
Beet leaves	121–920
Beet root	76–675
Almonds	431–490
Cashews	231–262
Hazelnuts	167–223
Peanuts	96–705
Carambola/star fruit	80–730
Buckwheat	269–271
Soy	179–187
Coffee	50–150
Black tea (100 mL brewed)[a]	48–92

[a]Tea 100 g fresh weight content estimated much higher (300–2000), green tea (6–26) and herbal tea (0–8) much lower estimates/100 mL.
Sources: Noonan [59] Massey *et al.* [60], Tsai *et al.* [61] and Chai *et al.* [62].

database, comprising 1% of native biopsies. Twenty-one of the cases had adequate clinical data. Fifty-seven percent were diabetic and 76% were hypertensive. Sixty-two percent had underlying CKD with a mean eGFR of 36 mL/min/1.73 m^2 prior to

Potential for future therapeutics

- Recently, Le Dudal et al. showed promising results with **stiripentol**, an antiepileptic drug that inhibits lactate dehydrogenase 5 isoenzyme (the last step of hepatic oxalate production).

- Stiripentol reduced oxalate generation *in vitro* and in rat models protected kidneys from oxalate-induced injury from ethylene glycol intoxication and chronic calcium oxalate nephropathy.

Conclusion

- Acute oxalate nephropathy is a rare but potentially devastating trigger of AKI in patients with DM.
- Physicians should be more alert about this condition, especially in the setting of oxalate precipitation/attachment-enabling conditions, and perform the renal biopsy in time to establish the diagnosis.
- How to properly treat patients to alleviate oxalate-induced injury needs to be studied further.

Thanks for attention