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# **Understanding Peripheral Neuropathy Associated *with* Kidney Disease**

Wednesday, April 10, 2024

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***Presenter:***  
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# Peripheral Neuropathy in Chronic Kidney Disease

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Icahn School  
of Medicine at  
**Mount  
Sinai**

# Objectives

- Basic Understanding of Chronic Kidney Disease (CKD)
- Symptoms and signs of neuropathy in CKD
- Management of PN in CKD
- Pain medications in CKD

## Patient case # 1

A 64-year-old man with a 15-year history of poorly controlled type 2 diabetes and a 10-year history of hypertension had developed multiple diabetes-related complications within the last 5 years. He experienced a fairly rapid decrease in kidney function noted 2 years ago. Four years ago, he noted symptoms of peripheral neuropathy manifested as shooting pain and numbness with loss of light touch, thermal, and vibratory sensation in a stocking distribution. Last year, he developed a nonhealing ulcer on the plantar aspect of his left foot that was complicated by gangrene and resulted in a below-the-knee amputation of the left leg 1 year ago. He now reports new onset of weakness, lightheadedness, and dizziness on standing that affects his daily activities. He reports lancinating pain in his right lower extremity, worse in the evening.

Medications include Insulin, metoprolol, lisinopril, atorvastatin and aspirin.

Blood pressure is 127/69 mm Hg. Strength is normal, but with complete loss of all sensory modalities to the knee in his remaining limb and up to the wrists in both upper extremities.

Today's laboratory evaluations show a serum creatinine level of 3.8 mg/dL, estimated glomerular filtration rate of 24 mL/min/1.73 m<sup>2</sup>, hemoglobin A1c level of 7.9%, and urine protein excretion of 2.1 g/1 g of creatinine.

## Patient case # 2

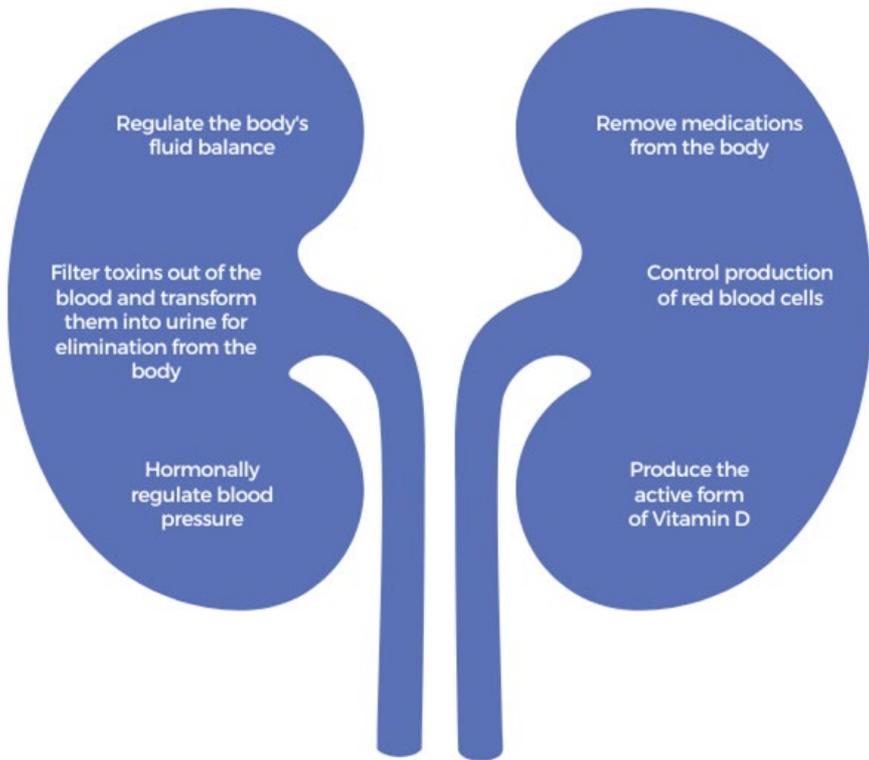
A 48 year old man with ESKD presented with severe decreased sensation in his bilateral feet, originated from bottom of his feet, and gradually advanced to above the ankle level over the course of 2–3 years.

He reported the sensation of “walking on cushions”, as well as progressive difficulty with ambulation. Additionally, he complained of ongoing pain in bilateral legs, as well as dysaesthesia in bilateral hands. He had been diagnosed with ESKD at age 37, secondary to poorly controlled hypertension and has been on dialysis for the last 11 years.



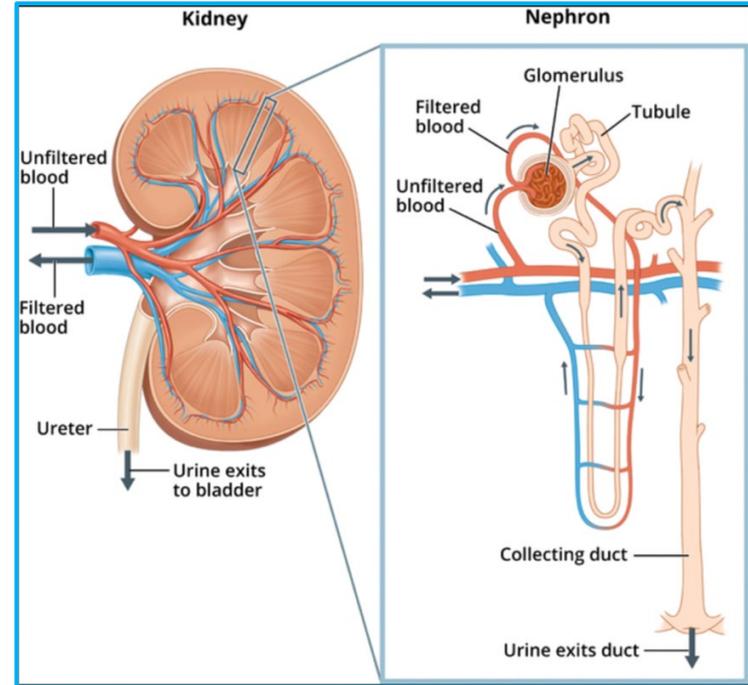
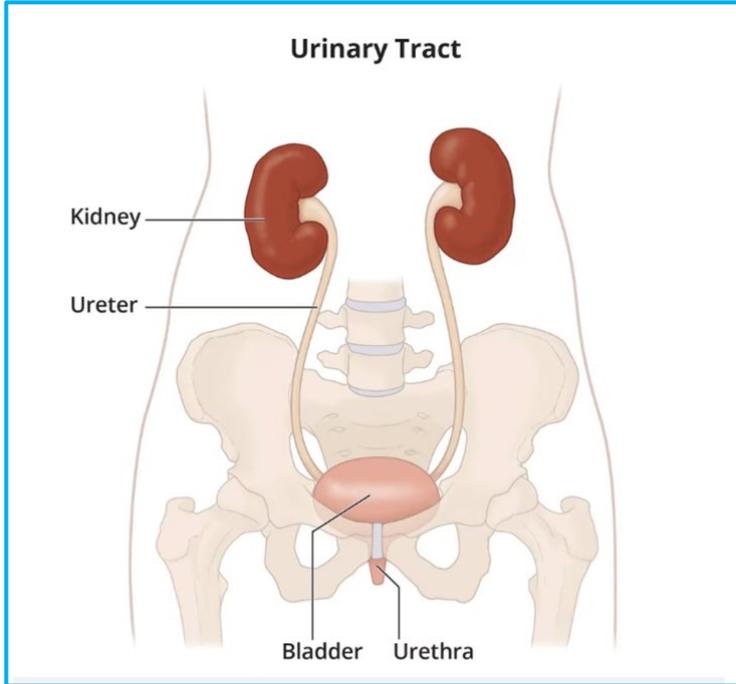
# What do the kidneys do??

## Filtration and clearance of toxins from the body



**Fun Fact: Your kidneys filter about 200 liters of blood every day. During this process, your kidneys remove waste, which leaves your body as urine (pee). Most people pee about 1-2L per day.**

# Basics of Kidneys and the Urinary System



**Functional unit of kidney is called Nephron which is made up of Glomerulus and Tubules**

## How do we measure kidney function

- ▶ Kidney function capacity is measured as GFR ( Glomerular Filtration Rate)
- ▶ Complicated Equation based on measurement of serum creatinine and variables - age and sex. Race is no longer a variable.
- ▶ Urine tests are used to measure protein leaking from the kidney.
- ▶ Kidney ultrasound is done to see if any anatomic defects exist.

### eGFR

*Estimated  
Glomerular  
Filtration Rate*



### Blood test

Shows how well  
your kidneys filter  
(clean) your blood



### uACR

*Urine Albumin to  
Creatinine Ratio*



### Urine test

Shows if your kidneys  
are leaking protein  
(albumin) into your  
urine, which may mean  
kidney damage

# CKD-EPI Creatinine Equation (2021)

Expressed as a single equation:

$$eGFR_{Cr} = 142 \times \min(S_{Cr}/\kappa, 1)^\alpha \times \max(S_{Cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

where:

$S_{Cr}$  = standardized serum creatinine in mg/dL

$\kappa$  = 0.7 (females) or 0.9 (males)

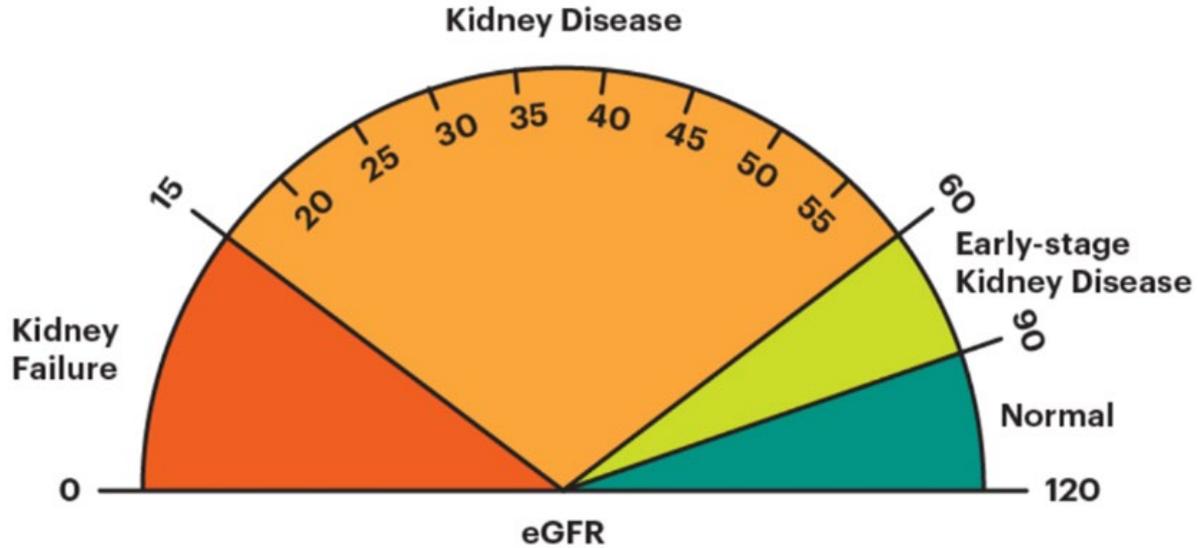
$\alpha$  = -0.241 (female) or -0.302 (male)

$\min(S_{Cr}/\kappa, 1)$  is the minimum of  $S_{Cr}/\kappa$  or 1.0

$\max(S_{Cr}/\kappa, 1)$  is the maximum of  $S_{Cr}/\kappa$  or 1.0

Age (years)

- eGFR of 90 or higher is in the normal range
- eGFR of 60 -89 may mean early-stage kidney disease
- eGFR of 15 -59 may mean kidney disease
- eGFR below 15 may mean kidney failure



CKD is classified on the basis of:

- Cause (C)
- GFR (G)
- Albuminuria (A)

				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+



More than **1** in **7**

15% of US adults are estimated to have chronic kidney disease—that is about 37 million people.



*“37 million people in the US have CKD*

*There are 10,000 nephrologists in the US*

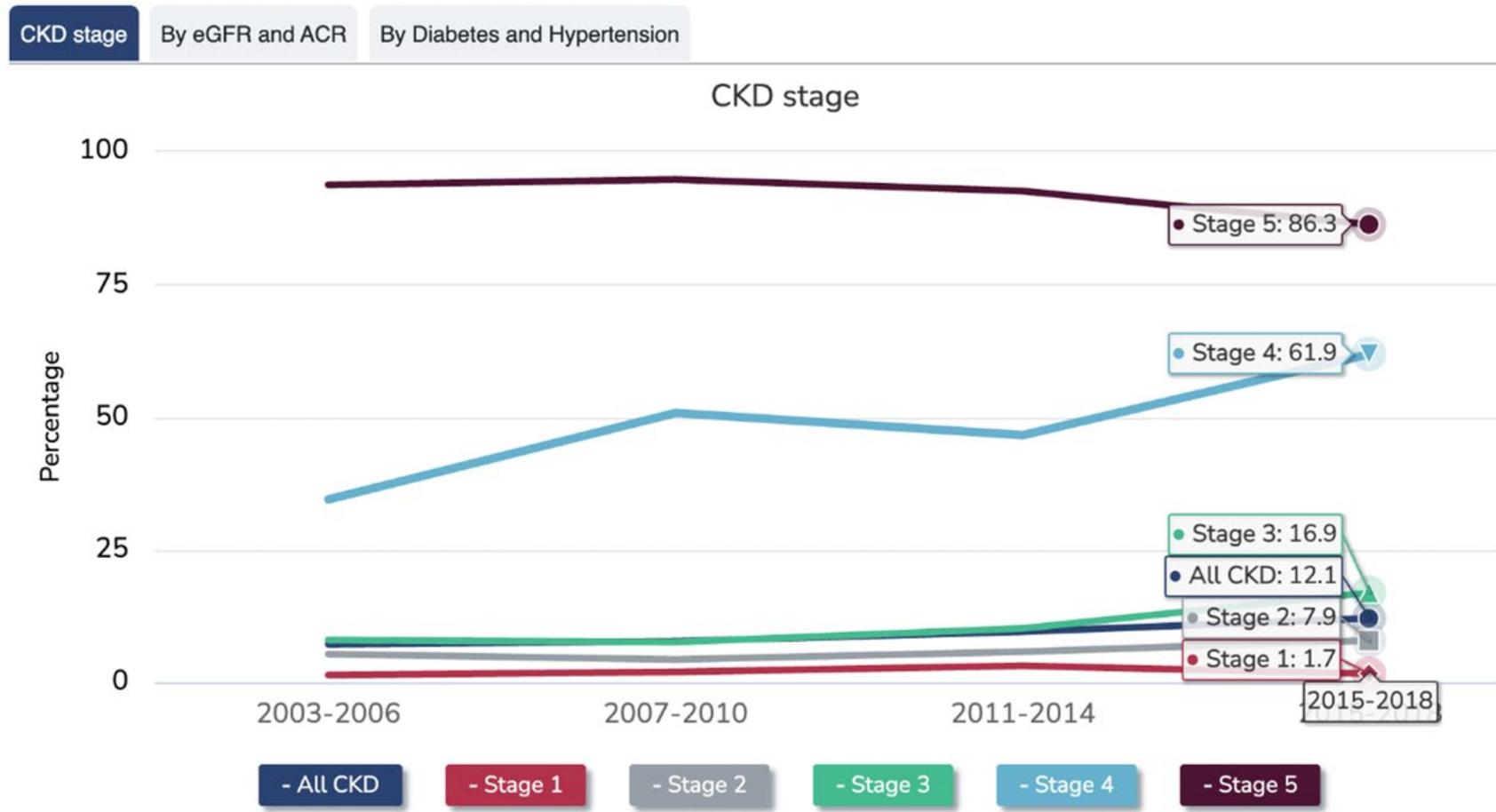
*So that works out to 3,700 CKD patients per nephrologist.”*

It takes a village to care for the CKD community

Figure 2.1 Prevalence of CKD (%), overall and by CKD stage among Medicare beneficiaries aged  $\geq 66$  years, 1999-2018



Figure 1.11 Percentage of U.S. adults with CKD aware of their kidney disease, 2003-2018



## Symptoms of Kidney Disease

Many people living with CKD do not have any symptoms until the more advanced stages and/or complications develop. If symptoms do happen, they may include:

- ▶ Foamy urine
- ▶ Urinating (peeing) more often or less often than usual
- ▶ Itchy and/or dry skin
- ▶ Feeling tired
- ▶ Nausea
- ▶ Loss of appetite
- ▶ Weight loss without trying to lose weight

People who have more advanced stages of CKD may also notice:

- ▶ Trouble concentrating
- ▶ Numbness or swelling in your arms, legs, ankles, or feet
- ▶ Achy muscles or cramping
- ▶ Shortness of breath
- ▶ Vomiting
- ▶ Trouble sleeping
- ▶ Breath smells like ammonia (also described as urine-like or “fishy”)

# Etiology of Kidney Disease:

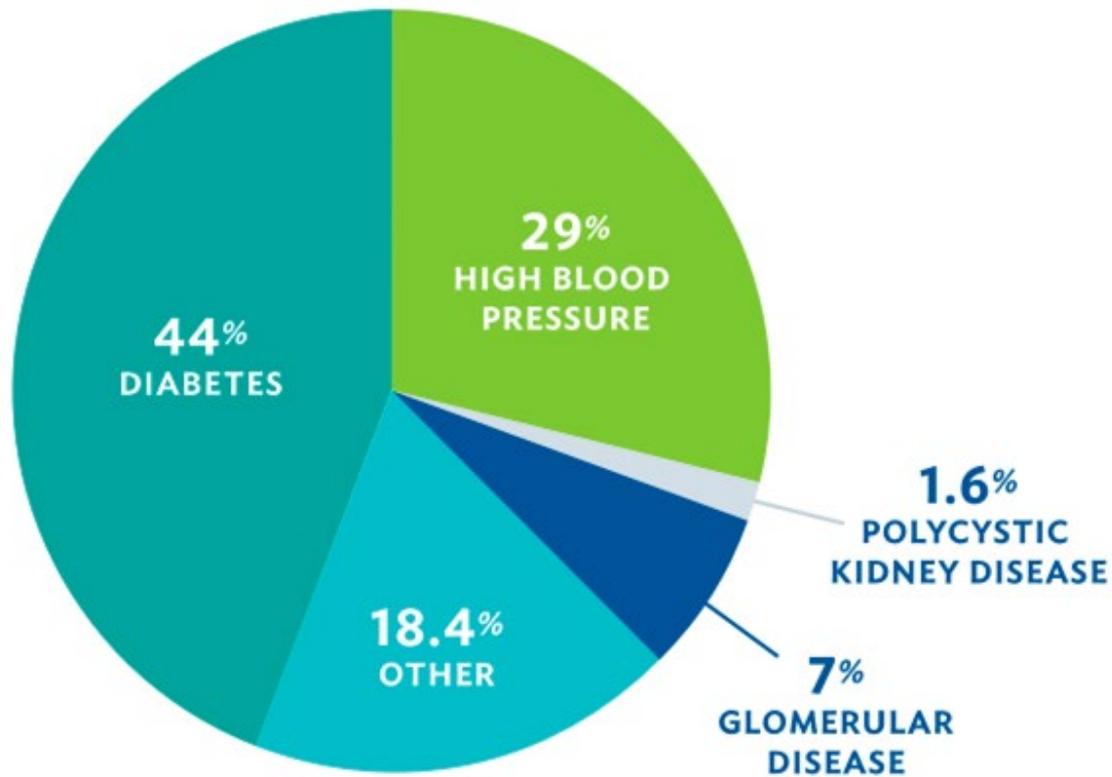
## Common Causes:

- Diabetes
- High blood pressure (hypertension)
- Heart disease and/or heart failure
- Obesity
- Over the age of 60
- Smoking and/or use of tobacco products

## Uncommon Causes

- Glomerular diseases: glomerulonephritis, IgA nephropathy (IgAN), and HIV nephropathy
- Inherited conditions: polycystic kidney disease
- Autoimmune conditions: lupus (lupus nephritis)
- Severe infections: sepsis and hemolytic uremic syndrome (HUS)

## Understanding the Causes of Chronic Kidney Disease



## Who Needs Screening?

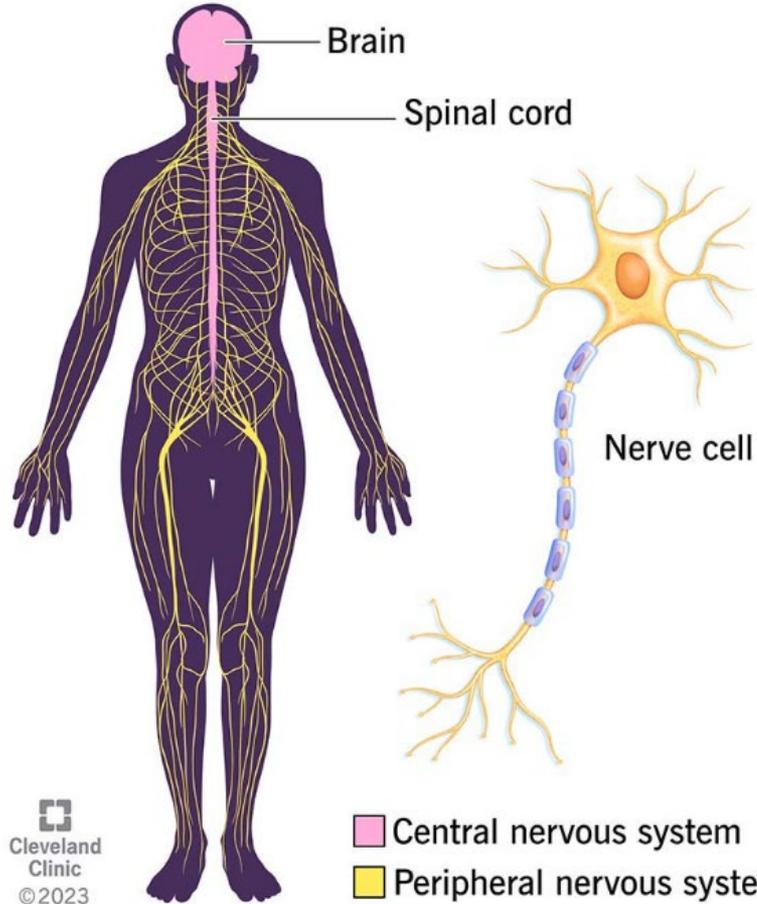
Insufficient evidence to support general population-based testing for chronic kidney disease

Targeted testing for chronic kidney disease among high-risk populations

- ▶ Diabetes
- ▶ Hypertension
- ▶ Obesity
- ▶ Age > 60
- ▶ Family history
- ▶ APOL1 gene



# Nervous system





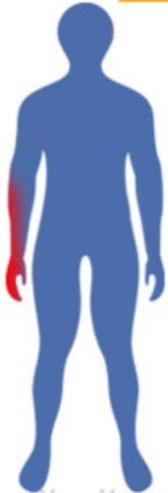
## What is Peripheral Neuropathy?

Affects 30 million people in the US.

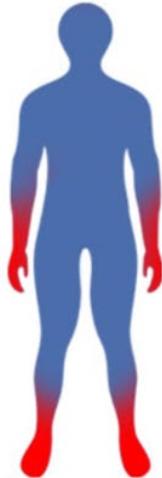
It is not one single disease.

It can affect one nerve (mononeuropathy) or many nerves (polyneuropathy)

### Types of Peripheral Neuropathy



Mononeuropathy



Polyneuropathy



Mononeuropathy Multiplex

## Common Causes of Peripheral Neuropathy

- ▶ Diabetes
- ▶ Alcohol
- ▶ Chemotherapy drugs
- ▶ Autoimmune diseases
- ▶ Infections: COVID-19, HIV, Herpes Zoster
- ▶ Vitamin Deficiency: Vitamin B12, thiamine, folic acid
- ▶ Toxins

# Neurological complications of CKD

## Central Nervous System

Dialysis  
dysequilibrium

Acute  
encephalopathy  
Eg. Uremic  
Hypercalcemic  
Aluminium



PRES  
Eg. HTN  
Drugs

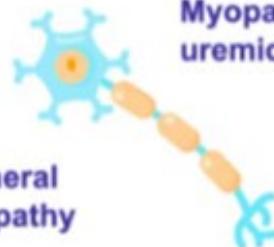
Stroke

Dementia

## MECHANISMS

Uremic toxins  
Electrolyte imbalances  
Nutritional deficiency  
Inflammation  
Drugs  
Therapies  
Co-morbidities

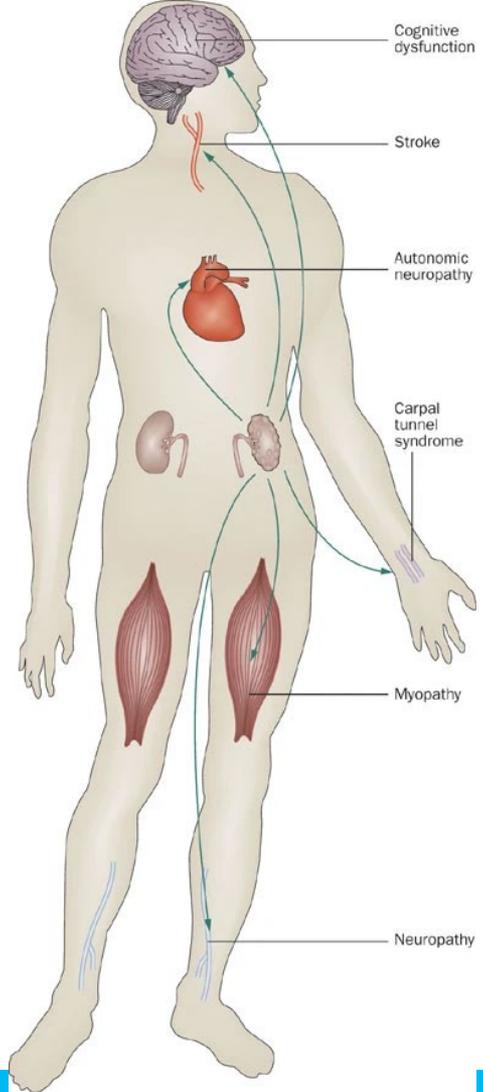
## Peripheral Nervous System



Myopathy-  
uremic

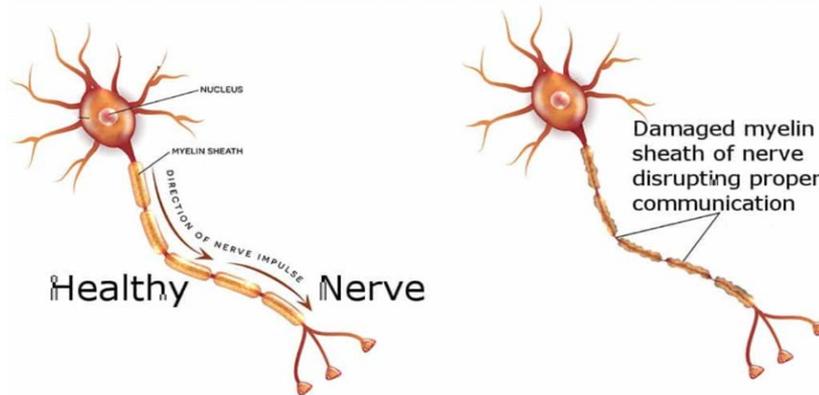
Peripheral  
neuropathy

Autonomic neuropathy



# Uremic Neuropathy

- ▶ Distal, symmetric, mixed sensorimotor polyneuropathy
- ▶ Demyelination and axonal degeneration: Axonal degeneration is the primary abnormality
- ▶ Most severe distally and longer axons are affected first
- ▶ Relative sparing of small afferent neurons
- ▶ Typically involves lower extremities more than the upper extremities
- ▶ Sensory Symptoms precede motor symptoms
- ▶ Progress to stocking neuropathy and wasting of distal leg muscles



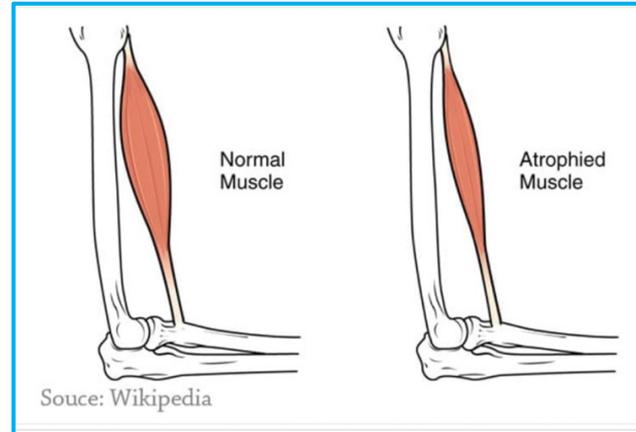
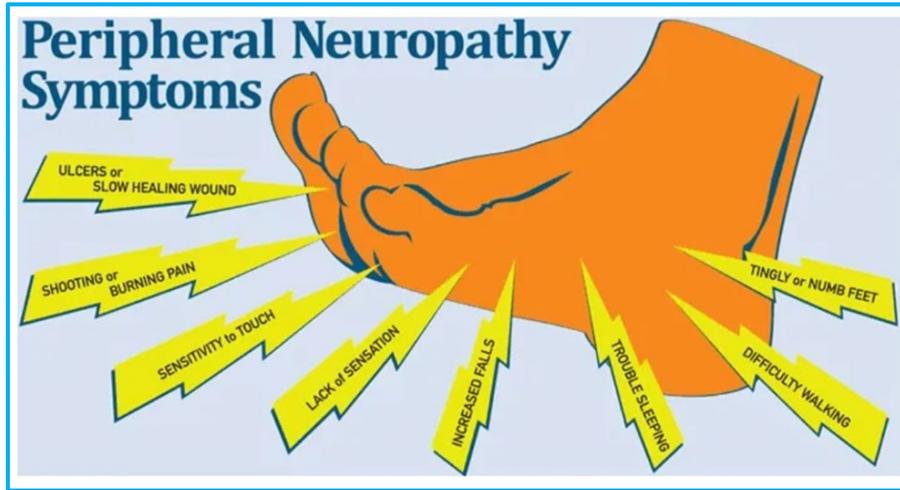
## Incidence of Uremic Neuropathy

- ▶ Among patients on dialysis, 60 to 100 percent of patients have electrophysiologic signs of impaired nerve function, although a lower percentage of patients are symptomatic
- ▶ According to one cross-sectional study conducted on 100 adult patients of chronic kidney disease between 18 and 75 years of age with serum creatinine greater than 2 mg/dL. Based on Neurological Symptom Score and Nerve Conduction studies.

Stage	Clinical features	Percentage
0	No neuropathy (T-NSS <2 with normal NCS)	30
1	Asymptomatic neuropathy (T-NSS = 0 with $\geq 2$ abnormalities on NCS/neurological examination)	6
2	Symptomatic neuropathy (T-NSS $\geq 2$ with normal NCS or T-NSS $\geq 1$ with abnormal NCS; neuropathic symptoms non-disabling)	51
3	Disabling neuropathy (T-NSS $\geq 2$ with normal NCS or T-NSS $\geq 1$ with abnormal NCS; neuropathic symptoms reported to be disabling)	13

Aggarwal, H. K., Sood, S., Jain, D., Kaverappa, V., & Yadav, S. (2013). Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. *Renal Failure*, 35(10), 1323–1329.

# Signs and Symptoms



## Symptoms of Uremic Neuropathy

- ▶ Cramps, muscle twitches, or increased pain sensation in the feet and legs
- ▶ Pain, numbness, and tingling in the feet and legs
- ▶ Feeling of “pins and needles”
- ▶ Paradoxical heat sensation
- ▶ Restless leg syndrome
- ▶ Imbalance
- ▶ Muscle weakness or reduced sensation may occur

## What Causes Uremic Neuropathy

- ▶ Exact cause is not known
- ▶ Possible etiologies:
  - ▶ Middle molecules: phenols, myo inositol, beta2-microglobulin
  - ▶ Deficiencies of Thiamine, Zinc and Biotin
  - ▶ Decreased Transketolase Activity
  - ▶ Hyperparathyroidism and hyperphosphatemia
  - ▶ Hyperkalemia : Alterations in membrane excitability

## Diagnosis of Peripheral Neuropathy



**Physical Examination**



**Blood Tests**



**MRI**



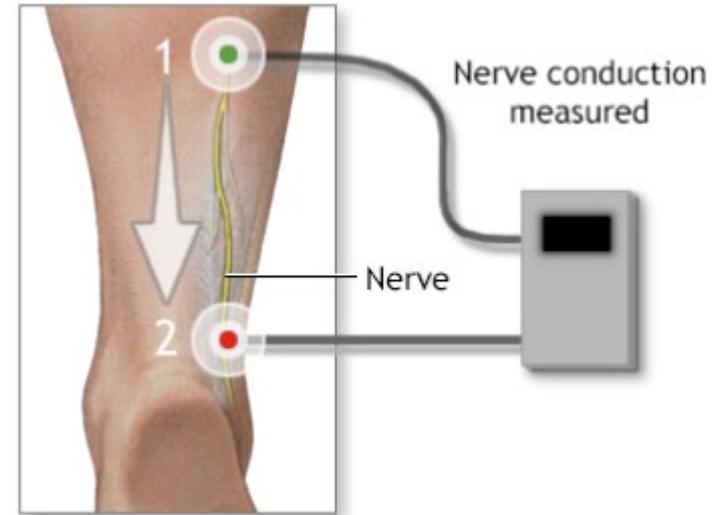
**Skin Biopsy**



**Electromyography**

## Diagnosis of Uremic Neuropathy

- ▶ Diagnosis of Exclusion
- ▶ Complete Examination of the nervous system
- ▶ Imaging tests: CT scan and MRI of brain, if indicated
- ▶ Labs
  - Vitamin B12 and folate levels
  - Thyroid, liver and kidney function
  - Vasculitis evaluation
  - Oral glucose tolerance test
  - Antibodies to nerve components
  - Lyme disease
  - HIV
- ▶ Nerve conduction studies remain the gold standard in diagnosis of uremic neuropathy.
- ▶ NCS demonstrates generalized neuropathy of the axonal type, reductions in sensory amplitudes > motor amplitudes
- ▶ Sural nerve sensory amplitude is the most sensitive indicator of uremic neuropathy
- ▶ Peroneal nerve most commonly used



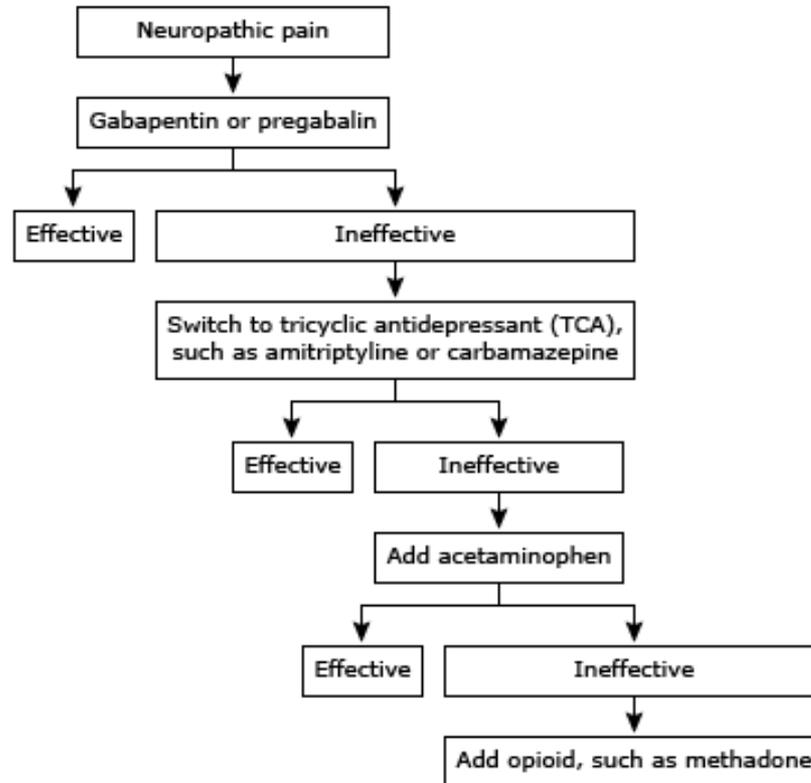
## Treatment of Uremic Neuropathy

- Uremic polyneuropathy is an indication for kidney replacement therapy, including either dialysis or transplantation.
- Among patients who are on dialysis, symptoms of uremic neuropathy are an indication to determine if the dialysis prescription is adequate and usually to increase the amount of delivered dialysis, even if the minimum target Kt/V is being achieved with the current prescription.
- Reversibility is questionable. The degree to which polyneuropathy improves with dialysis is directly related to the severity of clinical symptoms prior to initiation. Complete resolution may occur among patients who have only mild sensory symptoms although subclinical abnormalities may still be detectable by electrophysiologic testing.
- Among patients with more severe symptoms, they may persist even after many years of dialysis.
- For suitable transplantation candidates, transplantation may reverse the symptoms of neuropathy, even when dialysis has failed to do so (based on case reports)
- According to current opinion, serial measurements of nerve conduction velocity do not offer a reliable index for the adequacy of regular hemodialysis because clinical manifestations are more closely related to loss of axons than to demyelination

# Management of Uremic Neuropathy

- ▶ Topical anesthetics
- ▶ Vitamin and other mineral deficiencies need to be corrected
- ▶ Non-medication treatments:
  - Relaxation techniques
  - Yoga and meditation
- ▶ Physical therapy: Nerve dysfunction can lead to muscle weakness and balance problems, which may be helped by physical therapy.
- ▶ Transcutaneous electrical nerve stimulation (TENS): Electrodes reduce pain by delivering a mild electrical current into painful areas.
- ▶ Acupuncture: Thin needles inserted into the body may affect nerve function, combat neuroinflammation, or stimulate natural healing and pain-killing functions of the nervous system.

# Management of Neuropathic Pain in advanced CKD



Renal adaptation of the WHO 3-Step analgesic ladder		
	Recommended drugs	Not recommended drugs
Step 1 Mild pain (1 – 3)	Acetaminophen (paracetamol)	NSAIDs COX-2 inhibitors
Step 2 Moderate pain (4 – 6)	Tramadol Hydrocodone Oxycodone (plus acetaminophen)	Codeine
Step 3 Severe pain (7 – 10)	Fentanyl Methadone Hydromorphone Oxycodone (plus acetaminophen)	Morphine

Table 2. Modification of the WHO three-step analgesic ladder for ESRD according to Barakzoy and Moss, 2006 [5].



# Pain Management in CKD

General principle	Specific consideration in CKD
"By mouth"	<p>Hemodialysis patients have easy IV access. However, this is to be avoided as the route of administration for analgesics for chronic pain management.</p> <p>Oral or transdermal routes are preferred.</p>
"By the clock"	<p>Some patients with mild pain may achieve adequate pain relief with analgesic dosing post-hemodialysis only. An example would be mild neuropathic pain dosed with gabapentin postdialysis.</p>
"By the ladder"	<p>Careful selection of analgesics for each step of the ladder, taking into account degree of kidney failure, is critical.</p> <p>Sustained-release preparations are generally not recommended in patients with advanced CKD*.</p>
"For the individual"	<p>Chronic pain is often experienced in the context of numerous other physical, psychosocial, and spiritual concerns, including end-of-life issues. Close attention to these other issues must not be forgotten as part of the pain management strategy.</p>
"Attention to detail"	<p>There are no studies on the long-term use of analgesics in patients with CKD. Careful attention must be paid to efficacy and safety.</p> <p>The impact on overall symptom burden, physical function, emotional state, cognition, and QOL should be assessed routinely.</p>

Medication	Percent excreted in the urine	T one-half normal (hours)	T one-half dialysis (ESKD) (hours)	Hemodialysis	Peritoneal dialysis	Comments and recommendations on use in advanced CKD*
Acetaminophen (paracetamol) <sup>[1-4]</sup>	<5	1 to 4	Unchanged	Dialyzed	Not dialyzed	Accumulation of inactive metabolites. Analgesic of choice for mild-moderate pain. No dose reduction required.
Codeine <sup>[5-7]</sup>	0 to 16	2.5 to 4	13 to 18.9	Not dialyzed	Unlikely to be dialyzed	Metabolized to morphine derivatives and known to cause profound hypotension and CNS and respiratory depression. Not recommended in advanced CKD.
Tramadol <sup>[8-10]</sup>	90 (30 unchanged; 60 as metabolites)	6	11	Dialyzed	Unknown	Unpredictable risk of serious overdosing or underdosing after administration of standard doses. Not recommended in advanced CKD.
Morphine	10	2 to 3	Unchanged	Parent and active metabolites dialyzed	Not dialyzed	Rapid accumulation of active metabolites in advanced CKD resulting in clinically significant opioid toxicity including sedation, confusion, myoclonus, and respiratory depression. Not recommended in advanced CKD.
Hydromorphone <sup>[11,12]</sup>	6	2 to 5	3.2 on dialysis; 5.9 nondialysis days	Active metabolite (H3G) dialyzed	Unknown	Much better tolerated in advanced CKD than morphine with less toxic metabolites. Pharmacodynamic data have shown less neuroexcitation compared with morphine and a greater than 65% reduction in pain over dosing intervals with no clinically significant opioid toxicity when given in low doses and monitored carefully.
Fentanyl <sup>[13]</sup>	<7	2 to 7	Possibly increased	Not dialyzed	Not dialyzed	Inactive metabolites. Most pharmacokinetic studies in advanced CKD use parenteral rather than transdermal fentanyl. Generally considered safe for use in advanced CKD if monitored carefully.
Gabapentin <sup>[25-27]</sup>	Approximately 100	5 to 7	52 to 132	Dialyzed	Possibly dialyzed	Freely crosses the blood-brain barrier. Dose postdialysis. The following are maximum doses: <ul style="list-style-type: none"> <li>▪ eGFR 50 to 79 mL/min/1.73 m<sup>2</sup>: 600 mg three times per day</li> <li>▪ eGFR 30 to 49 mL/min/1.73 m<sup>2</sup>: 300 mg three times per day</li> <li>▪ eGFR 15 to 29 mL/min/1.73 m<sup>2</sup>: 300 mg twice per day</li> <li>▪ eGFR &lt;15 mL/min/1.73 m<sup>2</sup>: 300 mg once per day</li> </ul>

## Why do we need to pay attention to Uremic Neuropathy?

- ▶ Poor exercise tolerance
- ▶ Reduced functional capacity
- ▶ Falls and fractures
- ▶ One study has reported an association between PN and walking speed with quality of life in patients with CKD.
- ▶ Overall increased morbidity and mortality

## Patient # 1 Follow up

- ▶ Managing Diabetes is Critical - change in Insulin regimen to achieve target A1C=7
- ▶ He should be started on gabapentin therapy with slow titration of dosage up to 700 mg twice daily.
- ▶ Next step: duloxetine could be added beginning at 20 mg/d, slowly titrating up to 60 mg/d.
- ▶ Next step: addition of opioid.
- ▶ Non-pharmacological therapies

## Patient # 2 Follow up

- ▶ Increase dialysis frequency and time
- ▶ Transplant evaluation
- ▶ Medications for symptom control
- ▶ Foot care will be critical

## Take Home Messages

- ▶ Peripheral neuropathy is very common in advanced CKD and dialysis patients.
- ▶ Diagnosis of exclusion, nerve conduction studies may be needed.
- ▶ Exact etiology is unclear but likely due to accumulation of uremic toxins .
- ▶ Treatment is increasing dialysis dose or kidney transplantation; along with medications for pain control and non-pharmacological treatments
- ▶ Caution with pain medication selection and dose in CKD patients.
- ▶ Renal transplant is the best possible way to treat and possibly reverse uremic neuropathy



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# Questions?

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