Uraemic Pruritus, Restless Legs & Fatigue

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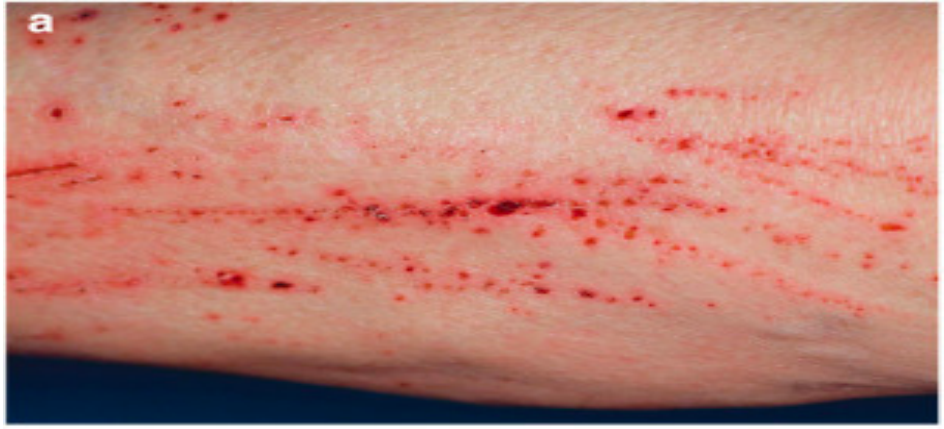
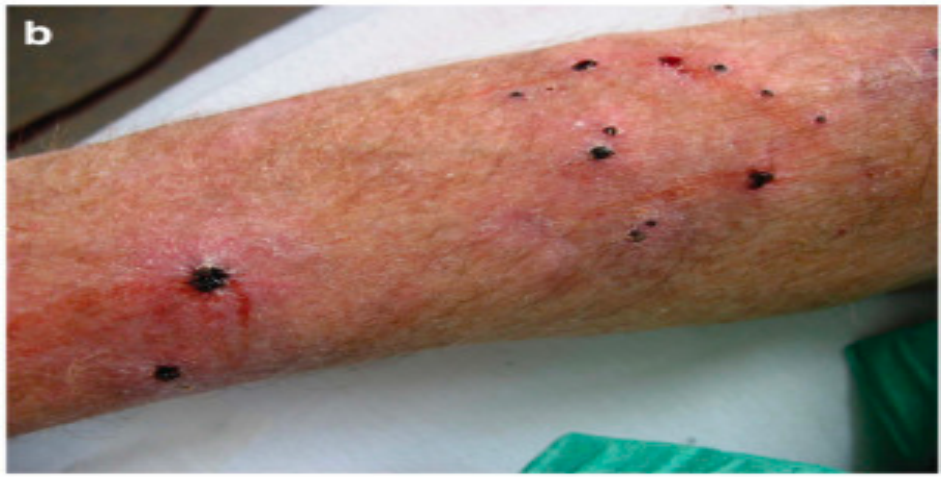
Uraemic pruritus

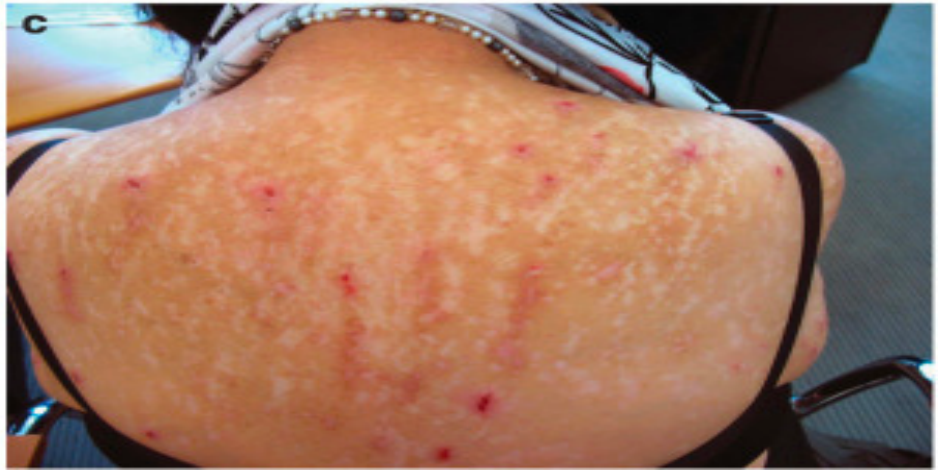
- Common
- Distressing, significantly affects quality of life
- More intense itch ↔ worse survival
- CKD-aP may also be more likely to suffer restless leg syndrome

History and Physical

- Clinical presentation – variable
- Itching generally worse at night
- Commonly affected areas = back and arms
  - Other areas of the body are also bothersome.
- Affected area – may remain constant or migrate with time







Thomas Mettang, Andreas E. Kremer,
Uremic pruritus,KI,2015,

Uraemic pruritus

- A clinical diagnosis
- Most people attribute itching to uraemic pruritus without an alternate diagnosis
- Essential to rule out other causes of pruritus
  - drugs, liver disease, thyroid disease, and dermatologic diseases

Pathophysiology – Pruritogens

- Pruritogens activate histamine-dependent and independent neurons to send itch signals to the CNS

- Small cohort of C fibres are dedicated to the transmission of itch
  - 10% are histamine dependent and 90% are histamine independent

- Proposed pruritogenic toxins include aluminium, calcium, phosphate, and parathyroid hormone

Pathophysiology – Xerosis

- Characterised by rough and scaly skin

- A large number of patients with CKD have dry skin
  - But not all patients with severely dry skin suffer from itching

Pathophysiology – Inflammation

- An imbalance between the cutaneous immune system and the nervous system contributes to inflammation and itch sensation

- Increased number of mast cells & mast cell activity in the dermis is found in patients with CKD

Pathophysiology – Nerves

- CKD patients may have primary alterations in nociceptive sensory pathways in the peripheral and/or central nervous system
- Peripheral neuropathy resulting from diseased sensory neurons and interneurons – also postulated to contribute to itch
- The degree of paraesthesia with respect to pain correlates with the severity of itch

Pathophysiology – Opioid pathway

- This hypothesis is based on the observation that pruritus can be triggered by opioid agonists
- Imbalance between mu and kappa opioid receptors (mu overstimulation and kappa antagonism) → itching
- KOR system suppresses itch

Treatment

- Non-pharmacological first
  - emollients
  - avoid hot showers
  - avoid soap
  - cut fingernails

- Topical treatments
  - Capsaicin, lignocaine, menthol combinations through compounding pharmacy

Gabapentinoids

- First line treatment after non-pharmacological management for pruritis

- Mechanism of action of gabapentin in uremic pruritus – still unclear.
  - May act on the voltage-dependent calcium-ion channels, inhibiting neuronal calcium influx and nerve impulses across synapses → interrupting the series of events that lead to uremic pruritus

- Side effects include dizziness, somnolence, confusion, ataxia

International Journal of Dermatology

Review

Gabapentin for uremic pruritus: a systematic review of randomized controlled trials

Kathleen May V. Eusebio-Alpapara MD, Rochelle L. Castillo MD, Belen L. Dofitas MD

First published: 28 November 2019 | https://doi.org/10.1111/ijd.14708 | Citations: 32

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Cochrane Database of Systematic Reviews | Review - Intervention

Interventions for itch in people with advanced chronic kidney disease

Daniel Hercz, Simon H Jiang, Angela C Webster Authors' declarations of interest

Version published: 07 December 2020 Version history

https://doi.org/10.1002/14651858.CD011393.pub2

Collapse all Expand all

Dosage

- Start low and adjust dose based on eGFR

- For eGFR 15 or patients on RRT:
  - gabapentin 100mg nocte second nightly or nocte after haemodialysis
  - pregabalin 25mg nocte second night or nocte after haemodialysis

- Both gabapentin and pregabalin are dialysable
  - about 50-60%

Other options

- Evening primrose oil (over-the-counter) 1-2 capsules bd
  - No known side effects (affects gamma linoleic acid)

- Sertraline (second line) 50mg daily

- Doxepin (second line): commence at 10mg nocte, up-titration to 10mg bd

Other options – UV therapy

- UV-B modulates immune response by altering cytokine production

- Side effects reported include sunburn and tanning

Other options – Opioid receptor modulation

- Difelikefalin = selective kappa-opioid receptor agonist
  - indicated for treating CKD-aP in adult hemodialysis patients
  - anti-pruritic and anti-inflammatory effects are attributed to its KOR activation on peripheral sensory neurons and immune cells

- Does not cross the BBB → does not cause the severe characteristic CNS adverse effects linked with opioids

Safety and efficacy of difelikefalin for the treatment of CKD-associated pruritus in patients on hemodialysis

Kidney Medicine

Phase 3 RCTs
KALM-1 & KALM-2
12 weeks (N = 851)

Open label supportive studies
CLIN 3101 & CLIN 3105
54 weeks (N = 1,306)

Adults on hemodialysis with **moderate-to-severe CKD-associated pruritus** (CKD-aP)

Clinically meaningful improvements in:

	Itch intensity	Itch-related QOL	
	≥ 3-point ↓ of WI-NRS* at 12 weeks	≥ 15-point ↓ of Skindex-10 at 12 weeks	≥ 5-point ↓ of 5-D Itch at 12 weeks**
Difelikefalin 0.5 mcg/kg IV x3/week	**51%**	**55%**	**52%**
1:1	P < 0.001	P < 0.001	P = 0.01
Placebo	**35%**	**40%**	**42%**

*WI-NRS - Worst Itching Intensity Numerical Rating Scale; **Effect maintained > 64 weeks

Adverse events

Placebo-controlled cohort, AEs mostly mild-to-moderate

	Placebo	Difelikefalin
Diarrhea	5.7%	**9.0%**
Dizziness	3.8%	**6.8%**
Nausea	4.5%	**6.6%**
Gait disturbance	5.4%	**6.6%**
Hyperkalemia	3.5%	**4.7%**
Headache	2.6%	**4.5%**

Conclusion: Results from the pooled KALM studies show rapid and sustained efficacy of difelikefalin for the treatment of CKD-aP in patients treated by hemodialysis. Difelikefalin demonstrated an acceptable safety profile and was well tolerated with long-term use.

References: (1) Topf J, Wooldridge T, McCafferty K, et al. Efficacy of difelikefalin for the treatment of moderate-to-severe pruritus in hemodialysis patients: pooled analysis of KALM-1 and KALM-2 phase 3 studies. **(2)** Fishbane S, Wen W, Munera C, et al. Safety and tolerability of difelikefalin for the treatment of moderate-to-severe pruritus in hemodialysis patients: pooled analysis from the phase 3 clinical trial program. *Kidney Medicine*, 2022.

VA by @CTeodosiu

Previously trialed treatments

- Topical tacrolimus
- Increasing dialysis
  - In several large epidemiological studies, dialysis adequacy (as measured by Kt/V) did not consistently correlate with the frequency of CKD-aP
- Controlling secondary hyperparathyroidism
  - Associations between CKD-aP with the levels of serum PTH, serum calcium, and phosphate are inconsistent between different studies

Restless Legs

Restless legs

- Spontaneous movement of the limbs (mainly legs) associated with unpleasant, sometimes painful sensation which is relieved by moving the affected limb

- Prevalence between 15-30%
  - notably higher than general population (5-10%)

- More patients with CKD-A-RLS demonstrated increased mortality, increased incidence of cardiovascular accident, depression, insomnia and impaired quality of life

- Brain iron deficiency, dopaminergic neurotransmission abnormalities and increased glutamate levels – thought to play a role

- Kidney-related RLS – correlated with lower hemoglobin level, transferrin saturation < 20%, and poor response to epoetin alfa

- Goals of therapy =
  - reduce or eliminate symptoms of RLS &
  - improve daytime function, sleep, and quality of life

- Iron therapy should not be prescribed empirically for RLS → may result in iron overload

Non-pharmacological treatment

- Exercise

- A few small studies have shown that aerobic exercise during dialysis sessions can decrease the severity of RLS

Drugs that can worsen symptoms of restless legs syndrome (RLS)

Alcohol, caffeine
Antidepressants (except bupropion)
Antipsychotics
Dopamine-blocking antiemetics (eg, metoclopramide)
Centrally-acting antihistamines (eg, diphenhydramine)

Gabapentinoids

- Usually preferred – can also manage co-existing symptoms such as itch, neuropathic pain

› J Pain Symptom Manage. 2015 Apr;49(4):782-9. doi: 10.1016/j.jpainsymman.2014.08.010. Epub 2014 Sep 8.

Efficacy and safety of gabapentin for uremic pruritus and restless legs syndrome in conservatively managed patients with chronic kidney disease

Hicham I Cheikh Hassan [1], Frank Brennan [2], Gemma Collett [3], Elizabeth A Josland [3], Mark A Brown [3]

Dopamine receptor agonists

- Ropinirole rather than pramiprexole – less renally excreted
- Onset of action: 90-120 minutes
- Main adverse effects: nausea, lightheadedness, and fatigue
  - Reversible with drug discontinuation
- Long-term use carries a risk for augmentation of symptoms

Opioids

- Have shown promising results in the treatment of refractory idiopathic RLS, but there have been no studies in CLD/dialysis patients

- The trials used oxycodone which is renally excreted

Quick case

61yo with ESRF on home hemodialysis (previously failed PD)

BG

- ALL diagnosed 2003 with a relapse in 2006
  - Whole body radiation, AlloHCT
  - Treatment complicated by neurological illness with residual cognitive impairment and dilated cardiomyopathy
- Post transplant limbic encephalitis and temporal lobe seizures post tx of ALL
- Multiple DVTs on anticoagulation
- Depression and anxiety
- Primary hypogonadism on testosterone
- Hypothyroidism
- Osteoporosis with minimal trauma fractures
- High cholesterol

Medications

Calcitriol 0.25mcg M/W/F
Calcium carbonate 600mg TDS
Carbamazepine 100mg BD
Coloxyl and senna
Rosuvastatin 10mg daily
Thyroxine 125mcg daily
Frusemide 80mg BD
Irbesartan 150mg daily
Labetalol 200mgBD
Pregabalin 25mg nocte every second day
Magmin 1 BD
Mirtazapine 30mg daily
Paraceramol 1g BD
Warfarin
Reandron IM every 4 months

Previously intolerant of gabapentin (drowsy)

Issues

- Poor cognition – history difficult to obtain
- Burning pain mainly in the lower limbs – worse at night & on dialysis
  - To alleviate pain
    - Puts his feet in hot water overnight
    - Multiple showers during the day
    - Some relief when he gets up and moves

What we did…

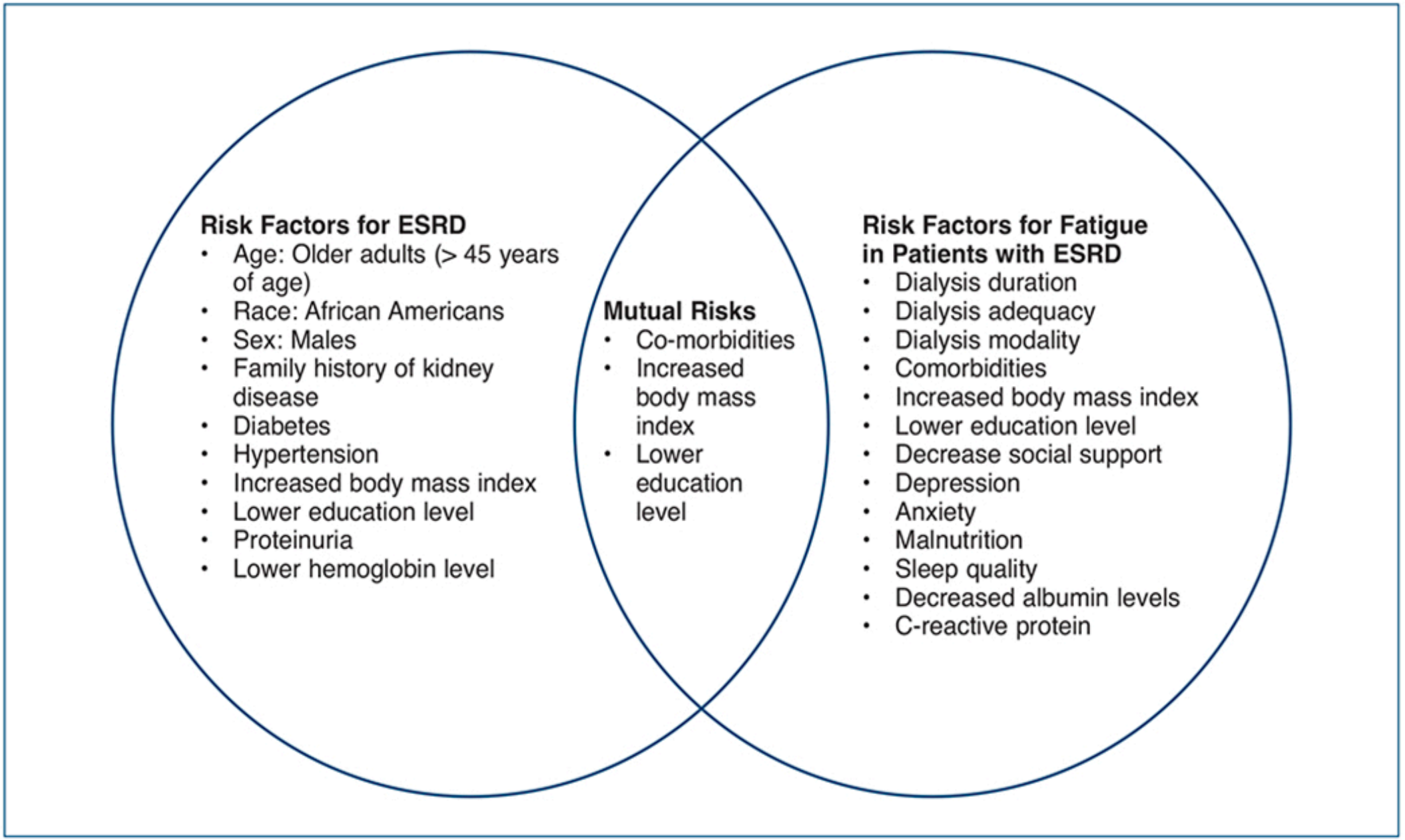
Fatigue in CKD

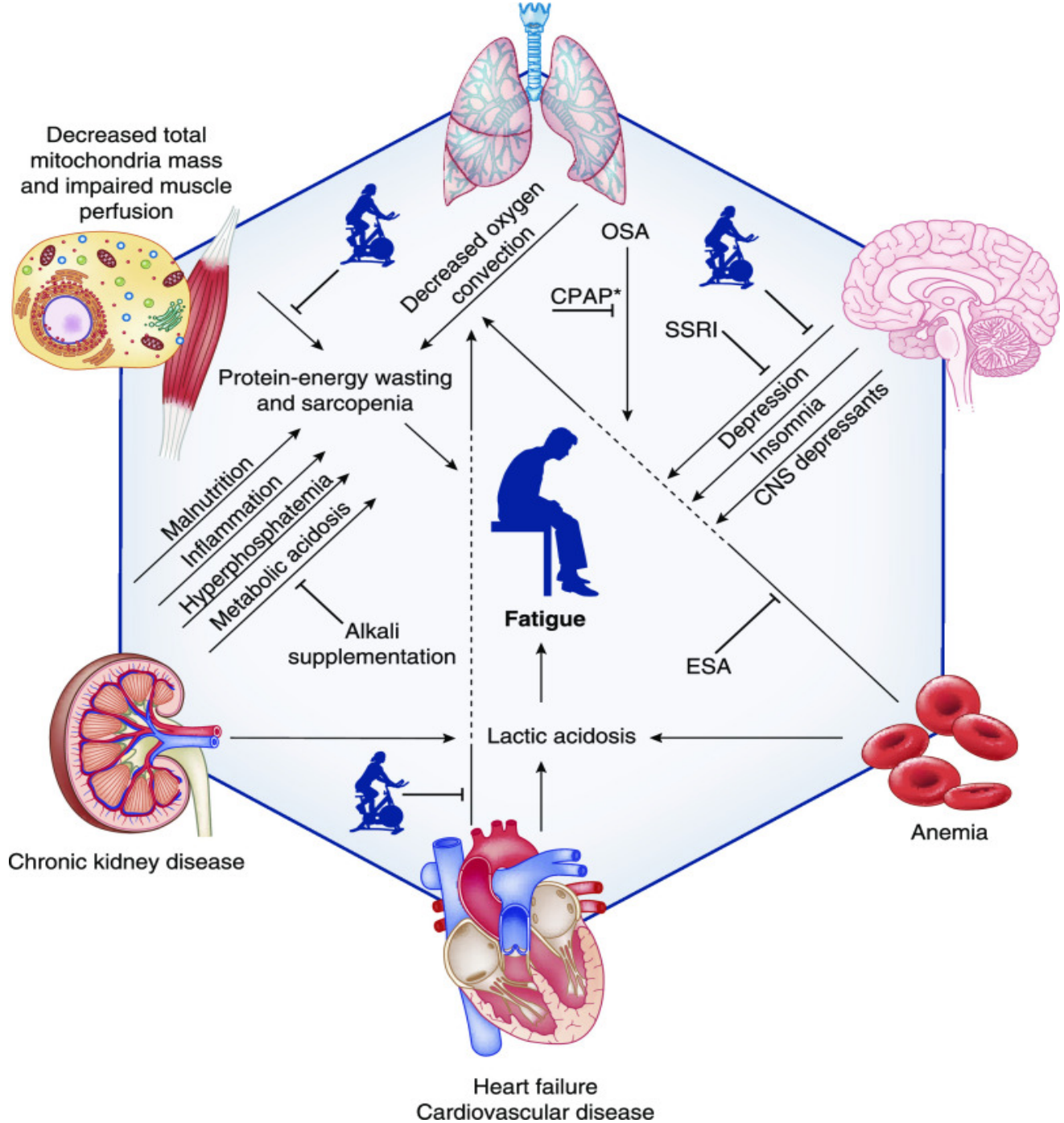
Fatigue in CKD

- Complex, multidimensional, subjective experience that encompasses both physical and psychologic symptoms

- Extreme and persistent tiredness, weakness, exhaustion, or lack of energy that is out of proportion to their degree of exertion, and may interfere with physical functioning

- Fatigue affects 60-97% of individuals with ESRD undergoing hemodialysis
- One of the most common symptoms in patients on NFD pathway
- Associated with increased risk for cardiovascular events and contributing to higher mortality rates


Risk Factors for ESRD
• Age: Older adults (> 45 years of age)
• Race: African Americans
• Sex: Males
• Family history of kidney disease
• Diabetes
• Hypertension
• Increased body mass index
• Lower education level
• Proteinuria
• Lower hemoglobin level
Mutual Risks
• Co-morbidities
• Increased body mass index
• Lower education level
Risk Factors for Fatigue in Patients with ESRD
• Dialysis duration
• Dialysis adequacy
• Dialysis modality
• Comorbidities
• Increased body mass index
• Lower education level
• Decrease social support
• Depression
• Anxiety
• Malnutrition
• Sleep quality
• Decreased albumin levels
• C-reactive protein


Decreased total mitochondria mass and impaired muscle perfusion
Decreased oxygen convection
OSA
CPAP*
SSRI
Protein-energy wasting and sarcopenia
Depression
Insomnia
CNS depressants
Malnutrition
Inflammation
Hyperphosphatemia
Metabolic acidosis
Alkali supplementation
Fatigue
ESA
Lactic acidosis
Chronic kidney disease
Anemia
Heart failure
Cardiovascular disease

Non-pharmacological interventions

- Prioritising activities, planning ahead
  - spreading out tasks throughout the day/week, pacing
- Making things easily accessible
  - living on one floor, keeping things you use often close by
- Home modifications with OT input – shower chair/bottle/rails
- Good sleep hygiene
  - waking up at the same time, limiting naps and caffeine, going to bed when tired
- Exercise

Pharmacological interventions

- Treatment of anaemia – ESA
- Correction of acidosis – sodium bicarbonate treatment
- Treatment of underlying conditions
  - E.g., restless legs/itch/pain which may impact sleep
- Recognise and manage depression

Thank you!

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