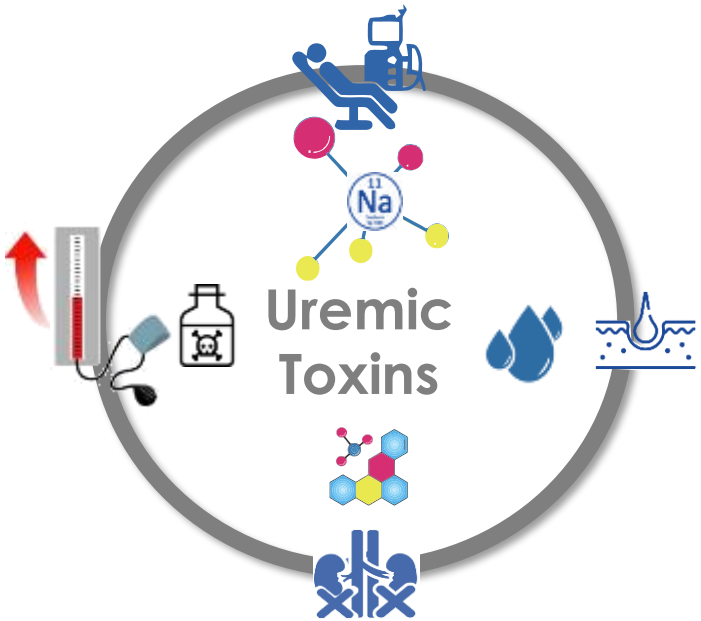


ACTUALITÉS
NÉPHROLOGIQUES
Jean Hamburger
HÔPITAL NECKER
NECKER SEMINARS IN NEPHROLOGY

Les mardi 13 et mercredi 14 mai 2025

Is Sodium a Uremic Toxin?

Prof. Bernard Canaud
Montpellier University, School of Medicine, Montpellier-F
& MTX Consulting Int. Montpellier-F

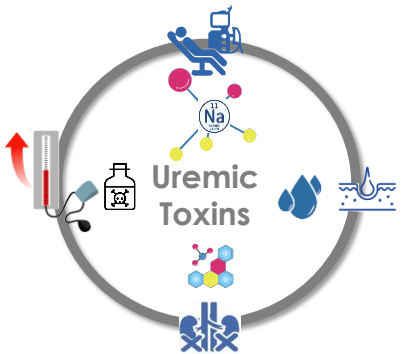
Disclosures

Bernard Canaud, MD, PhD

- Emeritus Professor of Medicine, Montpellier University, Montpellier, France
- Emeritus Medical Officer, Fresenius Medical Care, Bad Homburg, Germany
- Owner and CEO of MTX Consult Int. Montpellier, France
- Engaged in interactions and contracts with medical device and pharmaceutical companies, including Fresenius Medical Care, INVIZIUS, UBIPLUG, THERADIAL, MEDCOMP, WITHINGS and PHYSIDIA
- Member of Scientific Committee of CONVINCE

Outline

Is Sodium a Uremic Toxin?



1 What is a Uremic Toxin?

2 How are Uremic Toxins Current Classified?

3 How Does Sodium Fit?
What is the Evidence?

4 How to Manage Sodium?
What are the Tools?

5 Summary & Key Takeaways

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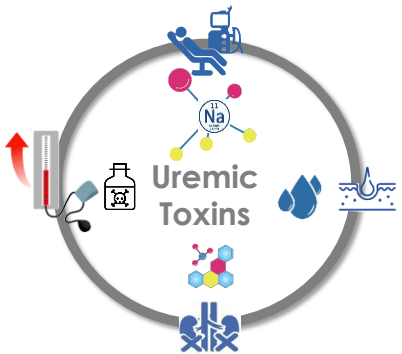

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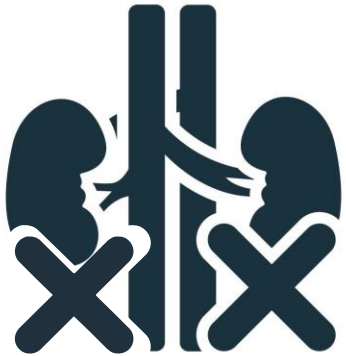
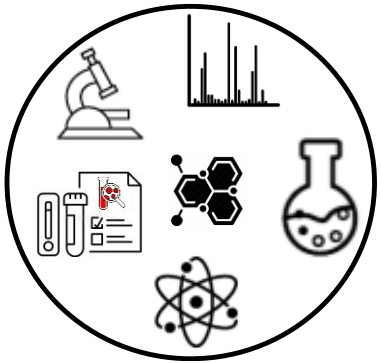
Understanding Uremia and Uremic Syndrome

End Stage
Kidney Disease

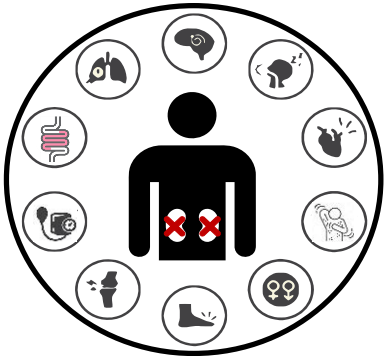


Biochemical
& Hematological, Endocrine Disorders



Retention of Uremic Solutes
Alteration of Uremic Milieu

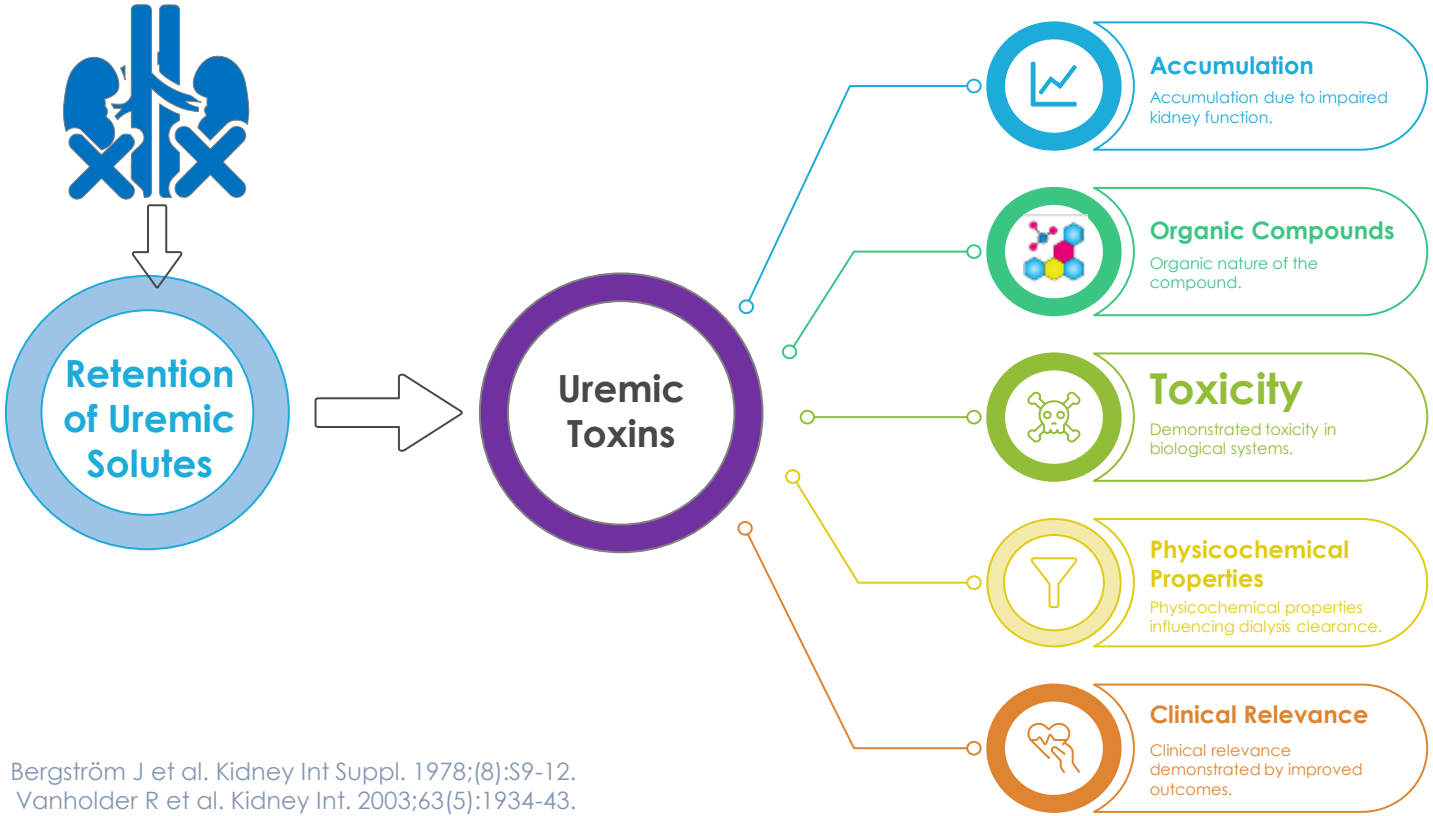
Uremic
Syndrome



Constellation of Systemic
Signs and Symptoms

UREMIA

Bergström's Criteria for Defining Uremic Toxins



Bergström J et al. Kidney Int Suppl. 1978;(8):S9-12.
Vanholder R et al. Kidney Int. 2003;63(5):1934-43.
Bowry SK, et al. Clin Kidney J. 2021; 14(Suppl 4):i17-i31.
Rosner MH, et al. Clin J Am Soc Nephrol. 2021; 16(12):19181928.

Outline

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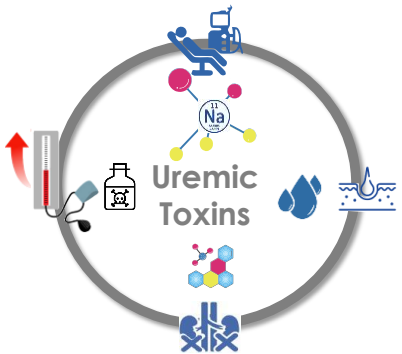

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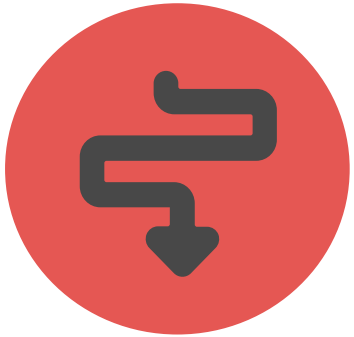
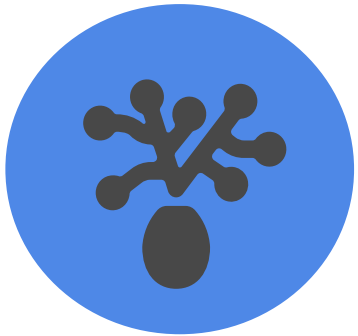
Understand Uremic Toxins and Toxicity?





Traditional

Focuses on toxin accumulation,
molecular weight,
pharmacokinetics,
and associated harmful effects

Modern

Emphasizes the complexity of the uremic milieu, its biological effects, interactions, and the role of KRT and treatment schedules in toxin removal

EUTox Group Classification of Uremic Toxins by Molecular Weight and Pharmacokinetics

Endogenous & Exogenous Metabolism

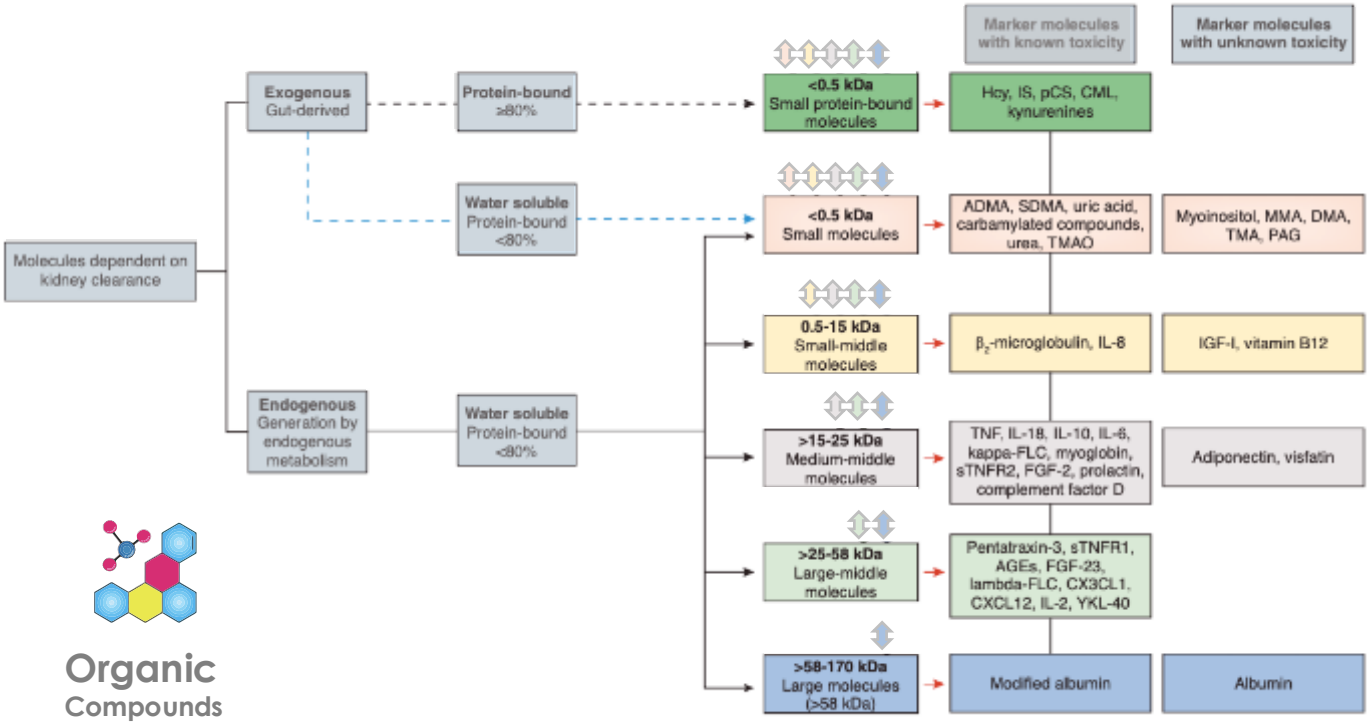
Organic Compounds

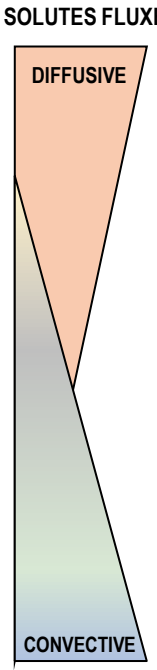
Small MW Water-Soluble Solutes MW < 500 Daltons n = 45)	**Protein-Bound Solutes** MW 500–22,000 Daltons (n = 25)	**Middle–Large Molecules** MW 500–12,000 Daltons (n = 22) of which >12,000 Daltons (n = 12)
Asymmetric Dimethylarginine	3-deoxyglucosone	Adrenomedullin
Benzylalcohol	Carboxy-Methyl-Propyl-Furanpropionic Acid (CMPF)	Atrial Natriuretic Peptide
ß-Guanidinopropionic Acid	Fructoselysine	ß2-Microglobulin
ß-Lipotropin	Glyoxal	ß-endorphin
Creatinine	Hippuric Acid	Cholecystokinin
Cytidine	Homocysteine	Clara Cell Protein
Guanidine	Hydroquinone	Complement Factor D
Guanidinoacetic Acid	Indole-3-acetic Acid	Cystatin C
Guanidinosuccinic Acid	Indoxyl Sulfate	Degranulation Inhibiting Protein I
Hypoxanthine	Kinurenine	Delta-sleep-inducing Peptide
Malondialdehyde	Kynurenic Acid	Endothelin
Methylguanidine	Methylglyoxal	Hyaluronic Acid
Myoinositol	N-carboxymethyllysine	Interleukin 1ß
Orotic Acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig Light Chain
Oxalate	Phenol	Lambda-Ig Light Chain
Pseudouridine	P-ohhippuric Acid	Leptin
Symmetric Dimethylarginine	Quinolinic Acid	Methionine-Enkepahlin
Urea	Spermidine	Neuropeptide Y
Uric Acid	Spermine	Parathyroid Hormone
Xanthine		Retinol Binding Protein
		Tumor Necrosis Factor Alpha

EUTox
European Uremic Toxin Work Group of the ESAO

Vanholder R. et al *Kidney Int*, 2003, 63; 84: S6–S10

Revised MW-Based Classification of Uremic Toxins and their Removal by Kidney Replacement Therapy





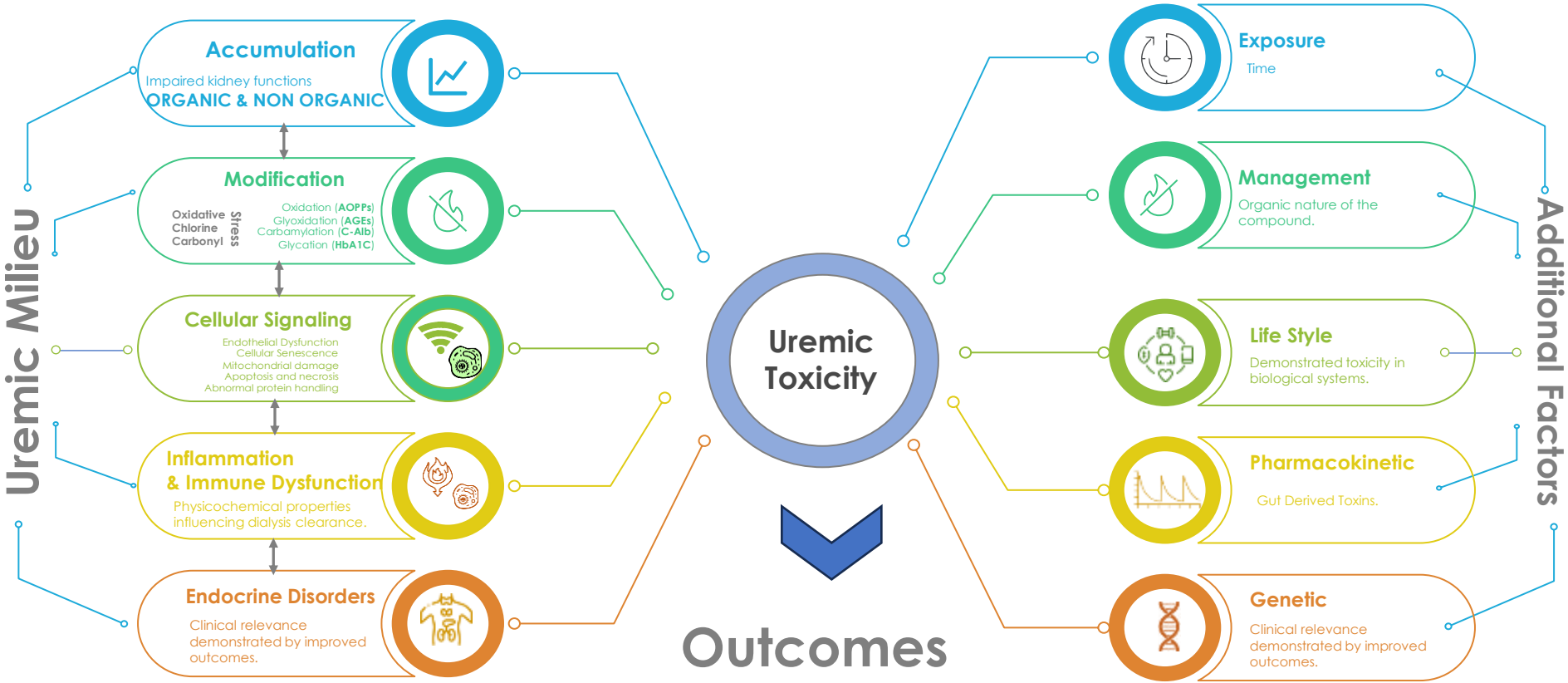
Renal Replacement Therapy Options

removed by:

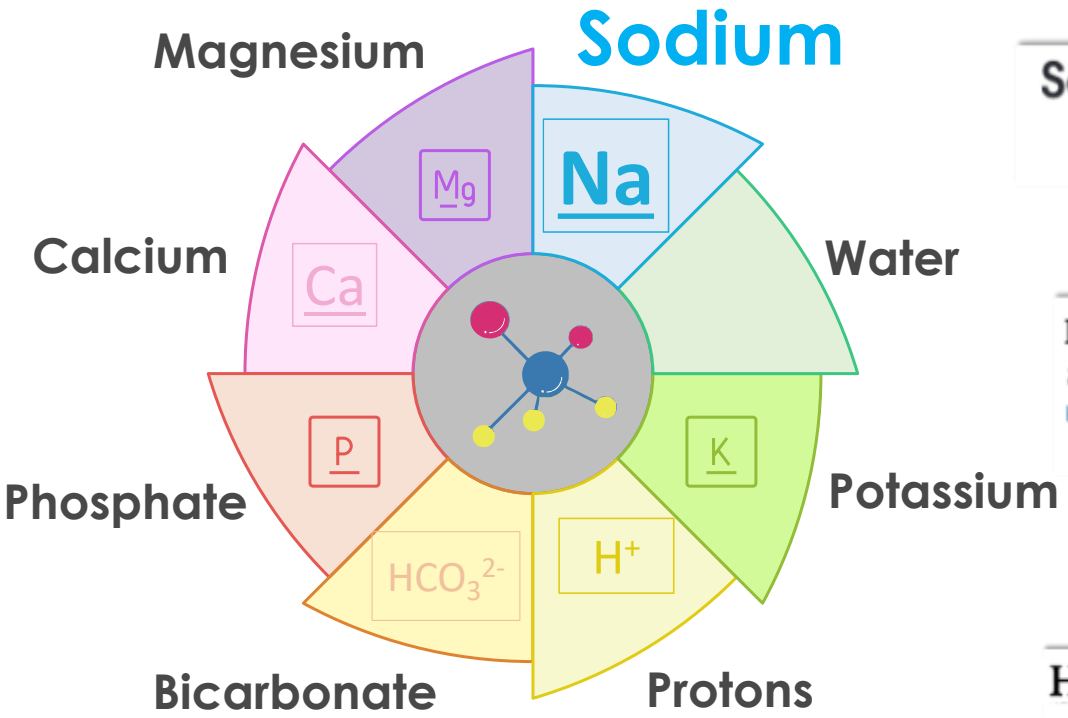
- low-flux HD
- high-flux HD
- HDF
- MCO HDx
- HCO HD

Rosner MH et al, *Clin J Am Soc Nephrol.* 2021;16(12):1918–28.

Modern Concepts of Uremic Toxins and Toxicity



Overlooked Non-Organic Compounds Potentially Acting as Uremic Toxins



Salt, the Neglected Silent Killer
Stanley Shaldon* and Joerg Vienken†
Sem Dialysis 2009; 22(3):264-26

Hyperphosphataemia : a silent killer of patients with renal failure?
Kerstin Amann ✉, Marie-Luise Gross, Gérard M. London, Eberhard Ritz
Nephrol Dial Transplant 1999;14(9):2085-2087

Hyperkalemia: A Potential Silent Killer
I. DAVID WEINER and CHARLES S. WINGO
J Am Soc Nephrol 9: 1535–1543, 1998

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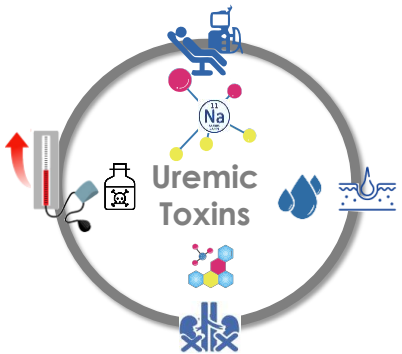

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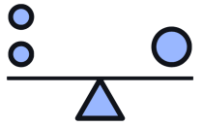
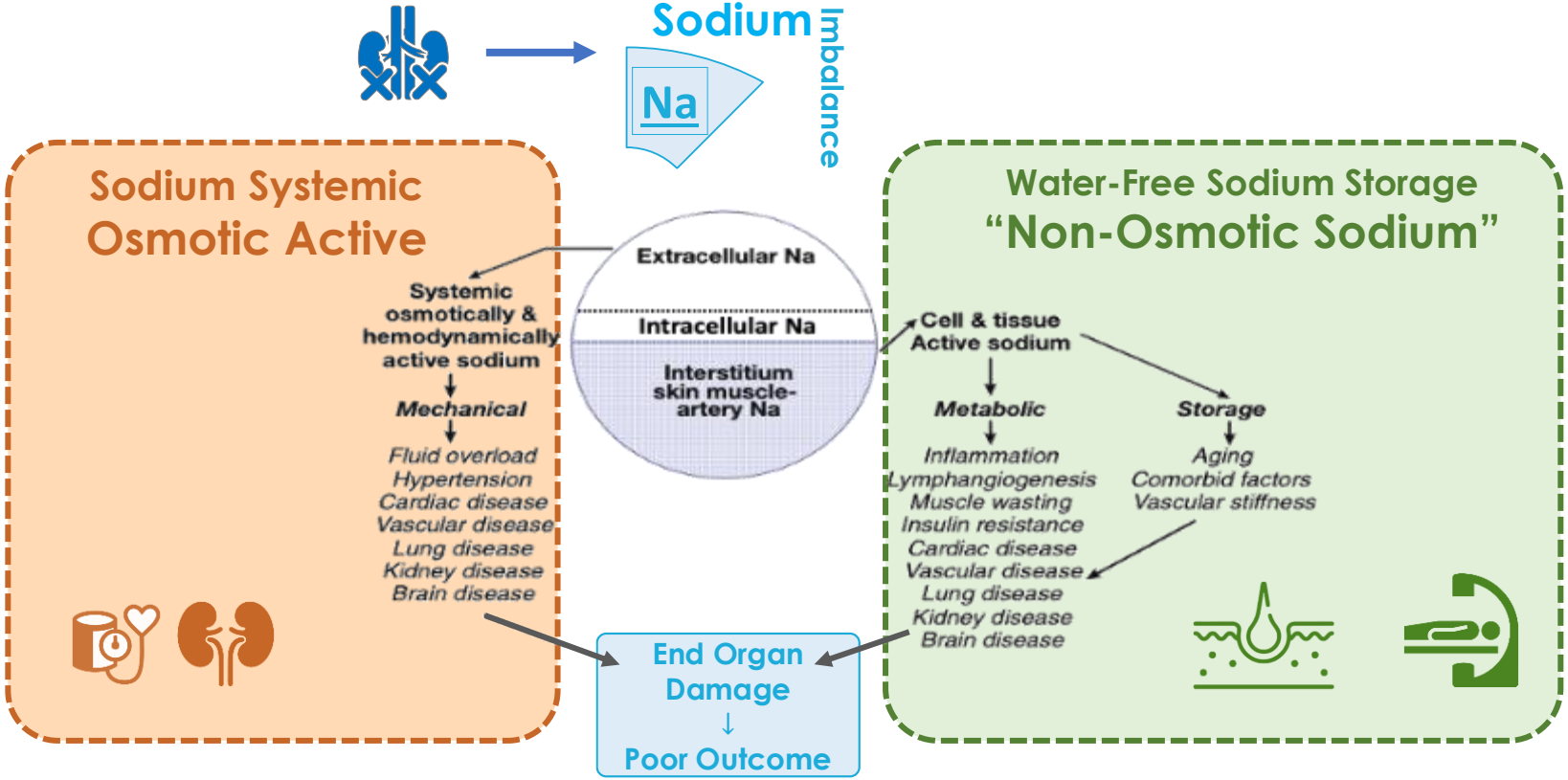
Evolving Insights into Sodium Physiology

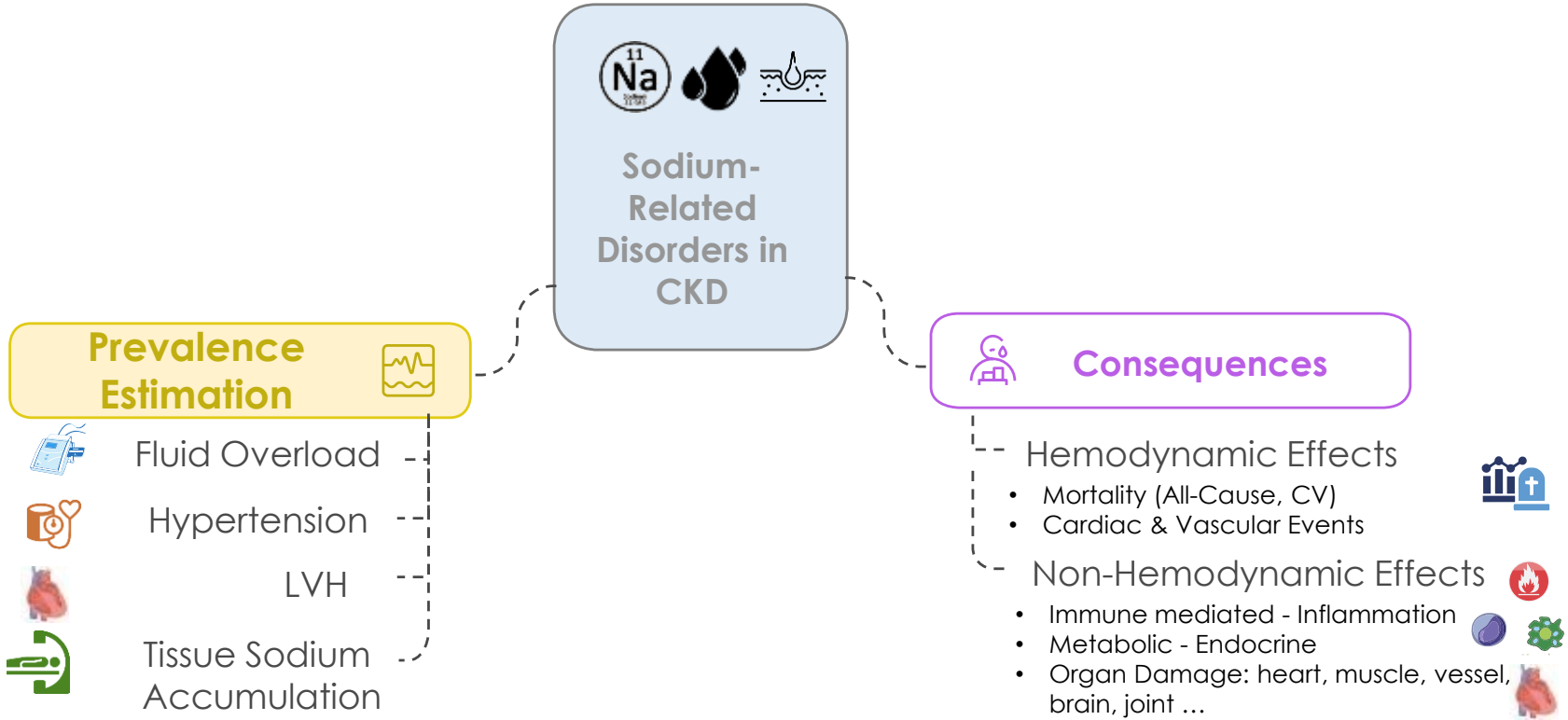
Era	Searcher	Key Concept	Sodium Insight	
19th Century	*Claude Bernard*	***'Milieu intérieur'***	Internal constancy includes sodium balance	
20th Century	*Arthur Guyton*	***Renal-body fluid feedback system***	Kidneys regulate sodium & Blood Pressure	
21st Century	*Jens Titze*	***Non-osmotic sodium storage & immune links***	Sodium is stored in tissues, not just fluids	

Tissue Sodium: A New Player in Uremic and Cardiovascular Pathophysiology That Must Be Considered



Canaud B et al. *Kidney Int.* 2019;95:296–309

Sodium-Related Disorders in Chronic Kidney Disease



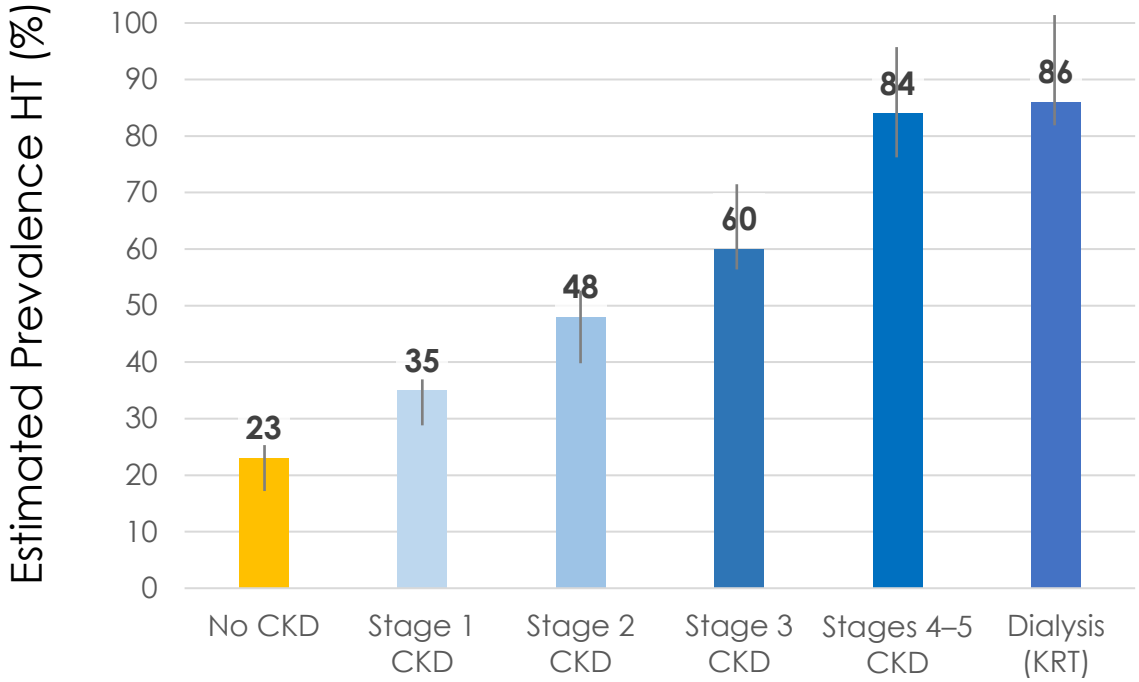
Estimated Prevalence of Hypertension Across CKD Stages

Office Blood Pressure

CKD Stage	Hypertension Prevalence (%)	Notes / Source Highlights
No CKD	~23%	Baseline prevalence in adults without CKD
Stage 1 CKD	~35–37%	Increasing trend in hypertensive population with stage 1 CKD from ~4.9% to 7.0% prevalence (age-standardized)
Stage 2 CKD	~48%	Prevalence rises with CKD severity
Stage 3 CKD	~60%	Includes stages 3a and 3b; stage 3b prevalence decreased slightly from 2.9% to 2.1% (age-standardized) over time
Stages 4–5 CKD	~84%	High prevalence in advanced CKD; stages 3 to 5 CKD prevalence in hypertensive adults decreased from 10.9% to 8.9%
Dialysis (KRT)	~86%	Very high prevalence in patients on hemodialysis, with poor BP control in many

Prevalence of Hypertension Increases With CKD Stage

Office Blood Pressure

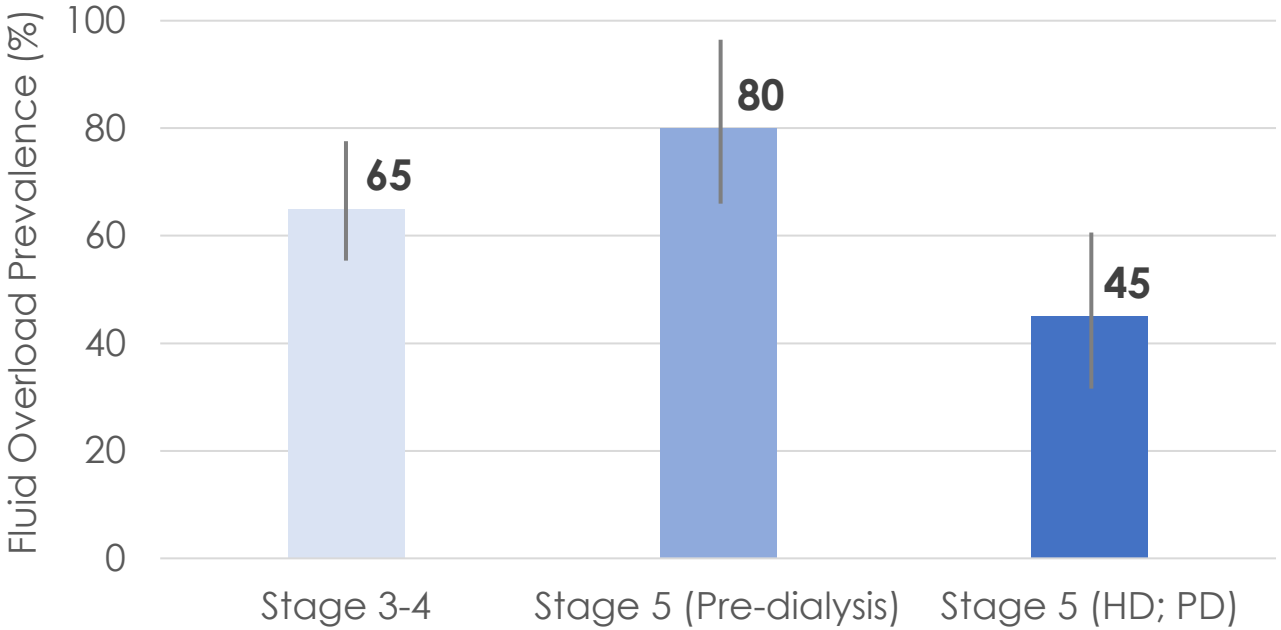


Tedla FM et al, Int J Hypertens. 2011;2011:132405.- Tsuchida-Nishiwaki M et al, Sci Rep. 2021;11(1):14990. - Burnier M et al, Circ Res. 2023;132(8):1050-1063. - Law JP et al, J Hum Hypertens. 2023;37(1):1-19. Zeng X et al, Hypertension. 2023;80(10):2149-2158.

Prevalence of Fluid Overload Assessed by Multifrequency Bioimpedance Using Objective Thresholds in Dialysis

Study / Source	Number of Patients	Dialysis Modality	Definition of Fluid Overload	Fluid Overload (%)
Dekker et al. MONDO consortium (KI 2017)	8,883	Hemodialysis	OH > +1.1 L (severe FO > +2.5 L)	**66.2**
Zoccali et al. EuCLID (JASN 2017)	39,566	Hemodialysis	OH/ECW index > 15% (men), >13% (women)	**46.4**
Ronco et al. IPOD-PD Study (NDT 2015)	1,092	Peritoneal Dialysis	OH > +1.1 L	**56.4**
Van Biesen et al. EuroBCM study (PlosOne 2011)	639	Peritoneal Dialysis	OH > +2.5 L	**25.0**
Pinter et al. EuCLID (CJASN 2024)	68,196	Hemodialysis	Relative FO >7% (any), severe FO >13–15%	**61.0**

Prevalence of Fluid Overload Across CKD Stages Assessed by Multifrequency Bioimpedance



Dekker..; Zoccali…; Ronco…; Van Biesen…; Pinter…)

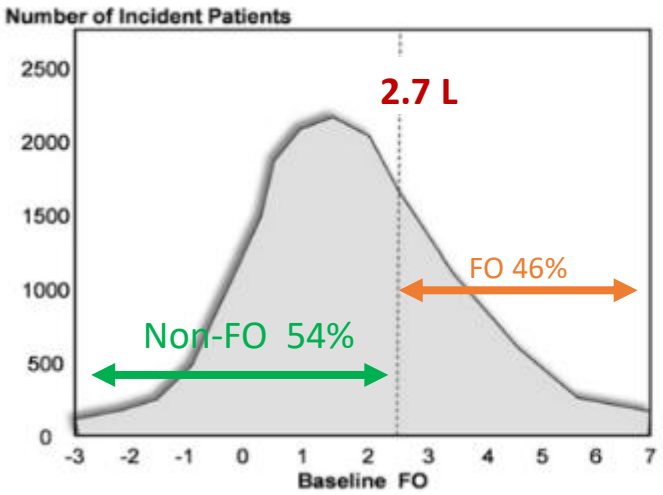
Severe Fluid Overload and Hypertension Are Present in Approximately Half of Incident Hemodialysis Patients

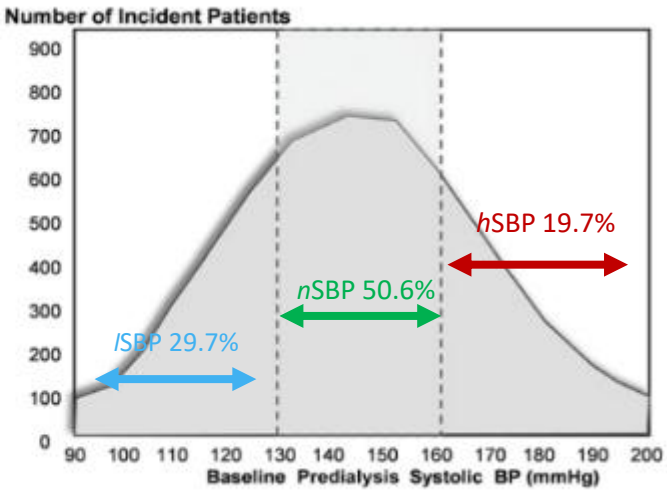
Observational Cohort Study
European NephroCare Network
EuCLID

39,566 incident HD Patients
- Advanced analytics
- Statistical Modeling

Outcomes:
I^{ary} Outcomes
- Fluid Status (MF-BIA)
- Blood Pressure

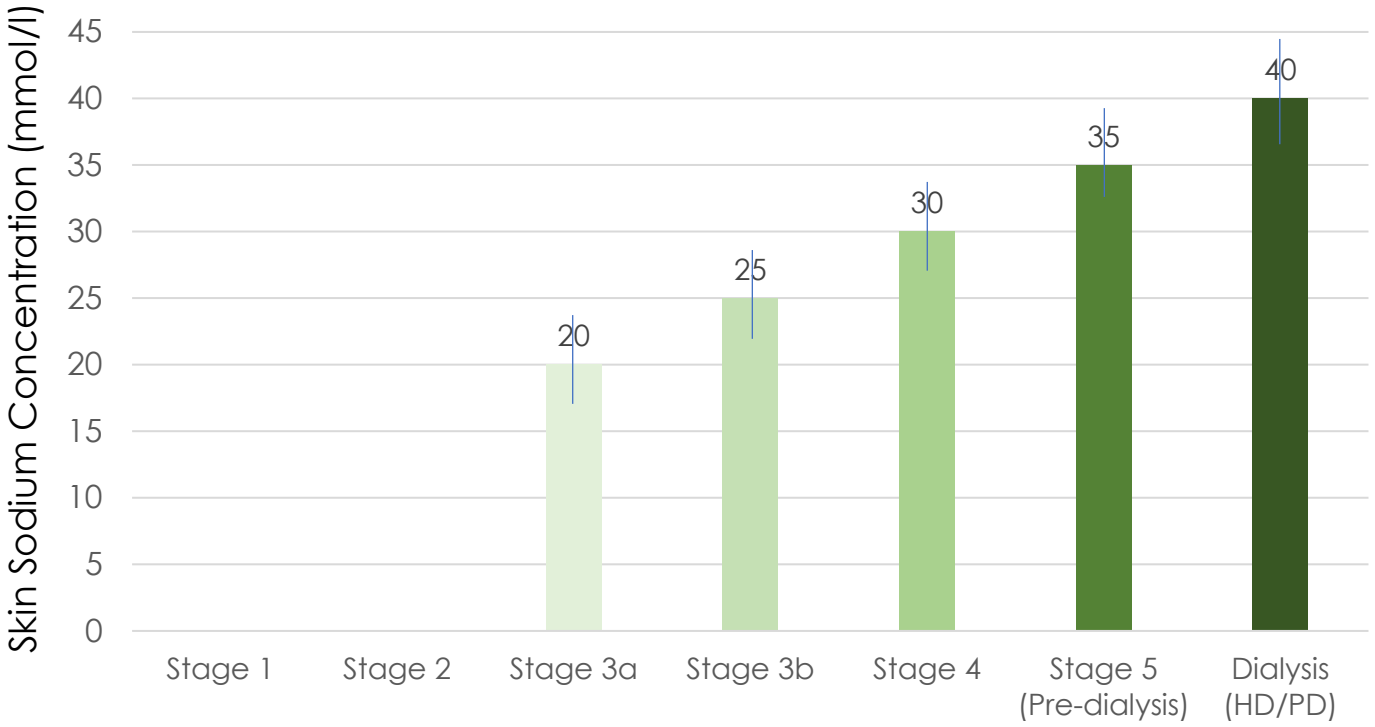
II^{ary} Outcomes
- Survival (all-cause)





Zoccali C et al, *J Am Soc Nephrol.* 2017;28(8):2491-2497.

Skin Sodium Content Increases With CKD Stage



Sahinoz M et al, Nephrol Dial Transplant. 2020;36(7):1307–17 - Qirjazi E et al, Nephrol Dial Transplant. 2020:gfaa036 - Rossitto G et al, Nat Commun. 2020;11(1):4222 - Schneider MP et al, J Am Soc Nephrol. 2017;28(6):1867-1876. - Dahlmann A et al, Kidney Int. 2015;87(2):434-41. - Lemoine S et al, Am J Kidney Dis. 2021;78(1):156-159 - Kopp C et al, Kidney Int Rep. 2024;9(5):1310-1320.

Estimated Prevalence of Left Ventricular Hypertrophy Across CKD Stages

CKD Stage	Estimated Prevalence of LVH	Key Associated Factors
Early CKD (Stages 1-2)	**16 – 31%**	Hypertension, anemia, reduced GFR
Advanced CKD (Stages 3-4)	**60 – 75%**	Volume overload, systolic/diastolic hypertension
ESRD (Stage 5, non-dialysis)	**62.8 – 94.3%**	Duration of hypertension, anemia, uremic toxins
HD patients	**54.7 – 94.4%**	Dialysis duration, fluid overload, anemia

Charytan D. Curr Opin Nephrol Hypertens. 2014;23(6):578-85. - Di Lullo L et a, Cardiorenal Med. 2015;5(4):254-66.
Zoccali C et al, Cardiovasc Res. 2023;119(11):2017-2032. - Imaizumi T et al. Kidney Int. 2023;103(5):949-961. - Goulas I et al, J Hypertens. 2023;41(5):699-707.

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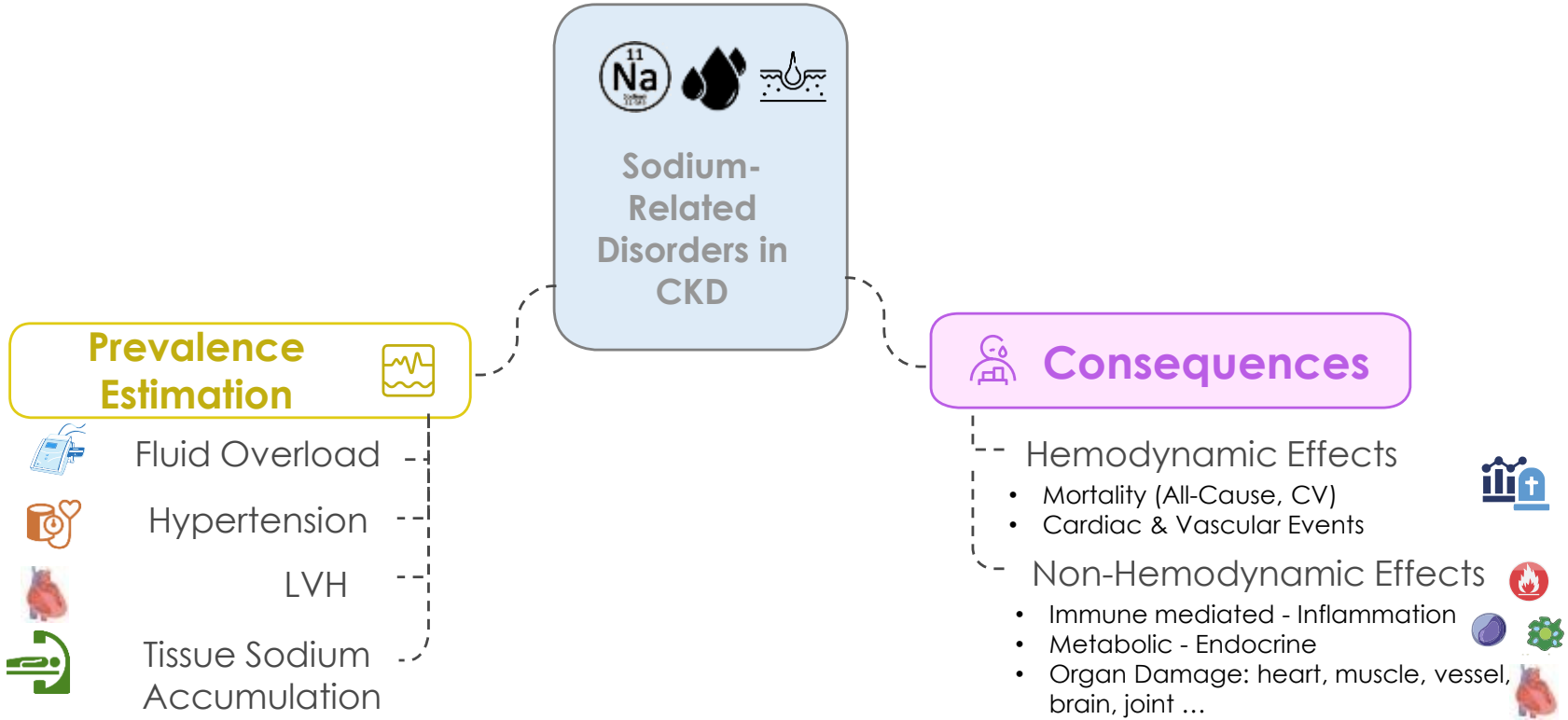


High Systolic (≥130 mmHg) and Diastolic (≥90 mmHg) BP Significantly Increase Renal Risk and Worsen Outcomes

Post Hoc Analysis of a Prospective, Cluster-RCT

Aim

Association between BP levels and renal outcomes in patients with CKD

Population

- 2100 CKD patients aged 40–74 years;
- stages 1–5 CKD; Subgroup analysis based on proteinuria and eGFR levels.

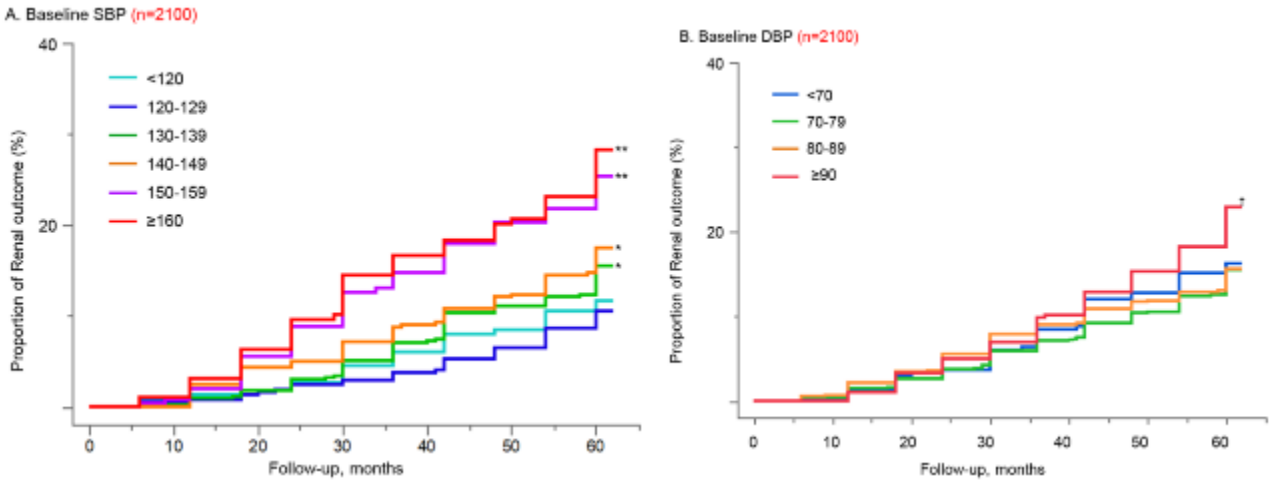
Methods

- Blood pressure categorized at baseline and 1 year.
- Primary renal outcome: ≥40% reduction in eGFR or progression to ESRD.
- Stratification by systolic BP (SBP) and diastolic BP (DBP) groups.
- Cox proportional hazards modeling adjusted for key confounders.

Outcomes

- **Primary**: Association between BP levels and risk of renal outcome.
- **Secondary**: Impact of BP control after 1 year and effect of lifestyle intervention group.

✓ Best renal outcomes SBP 120–129 & DBP < 80 mmHg



FROM-J Study

Frontier of Renal Outcome Modifications in Japan

Tsuchida-Nishiwaki M et al, Sci Rep. 2021;11(1):14990.

CV Mortality Risk is Elevated in Hypertensive CKD Stage 4-5 and HD Patients, With a Stronger at SBP > 160 mmHg in HD

Prospective Observational Cohort Study (US)

Aim

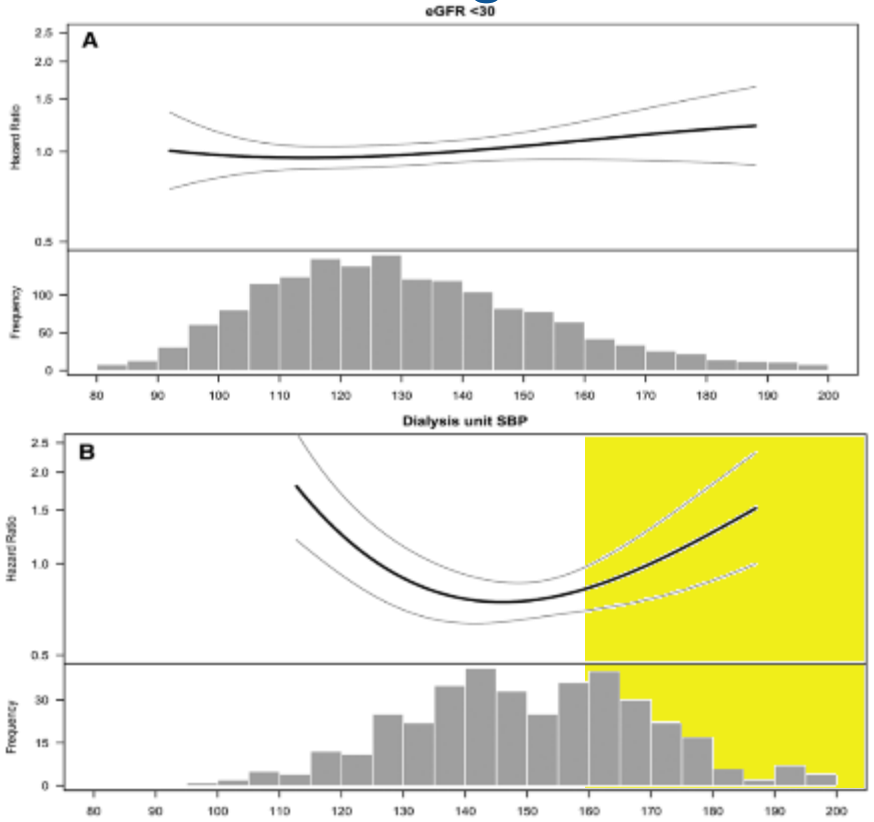
Association SBP) and mortality in CKD patients
Before and afeer initiation of HD

Method

- CKD eGFR <30 mL/min/1.73 m² (n= 1 705) → HD
- After HD initiation, SBP in HD unit (n=403) and outside (n=326).
- Cox proportional-hazards models adjusted for confounders

Outcomes

- SBP and all-cause mortality
- Before and after HD initiation



CRIC
Chronic Renal Insufficiency Cohort Study

Bansal N et al, Hypertension. 2015;65(1):93-100.

Increasing Severity Levels of Fluid Overload is Associated with Decreased Survival in Hemodialysis

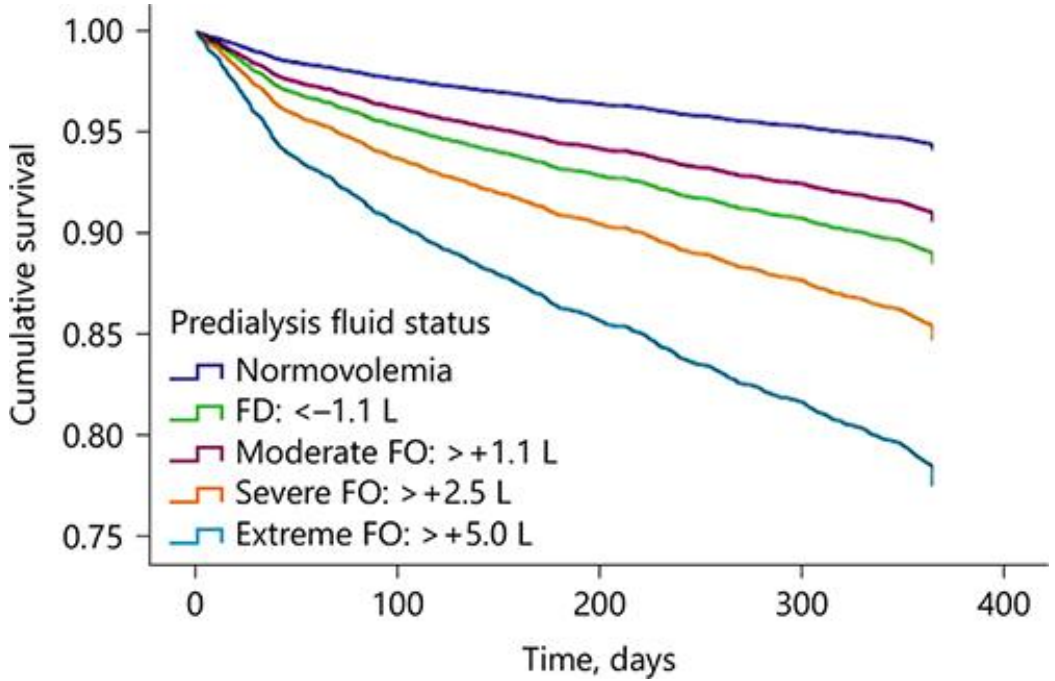
Observational Multicenter Cohort Study (European MOND Initiative)

8863 prevalent HD Patients
- Advanced analytics
- Statistical Modeling

Outcomes:

I^{ary} Outcomes
- Fluid Status (MF-BIA pre/postHD)
- Blood Pressure

II^{ary} Outcomes
- Survival (all-cause)



Dekker MJ et al, Kidney Int. 2017;91(5):1214-1223
Vander Sande F et al, Blood Purif. 2019;49(1-2):178-184.

Fluid Overload Is an Independent Risk Factor Regardless of Predialysis Systolic Blood Pressure

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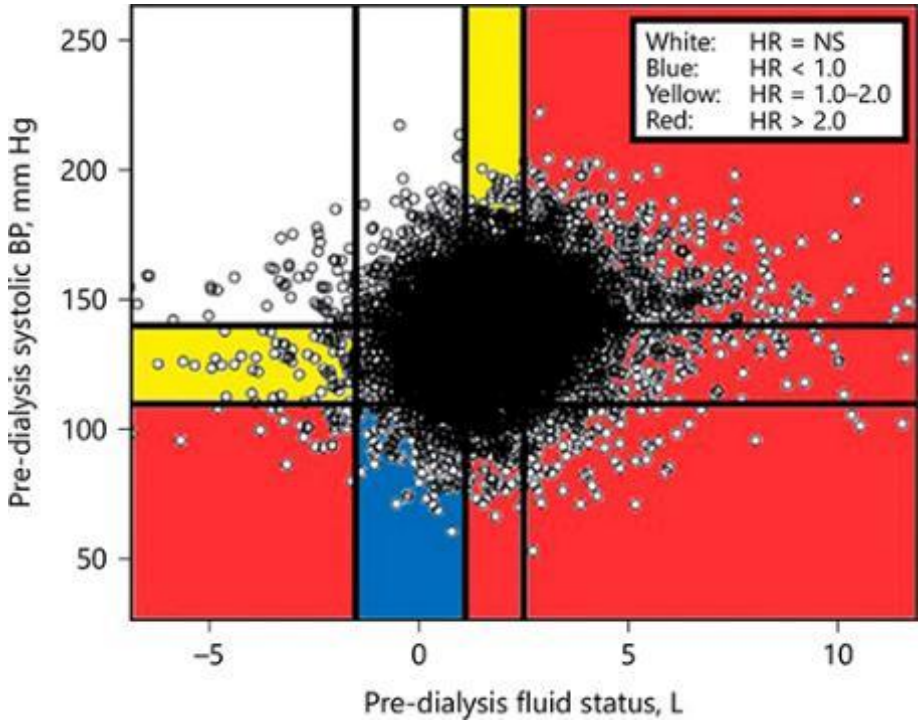

Dekker MJ et al, Kidney Int. 2017;91(5):1214-1223
Vander Sande F et al, Blood Purif. 2019;49(1-2):178-184.

Chronic Fluid Overload Is an Independent and Additive Risk Factor for All-Cause Mortality in HD Patients

Observational Cohort Study

European NephroCare Network

EuCLID

39,566 incident HD Patients

- Advanced analytics
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Outcomes:

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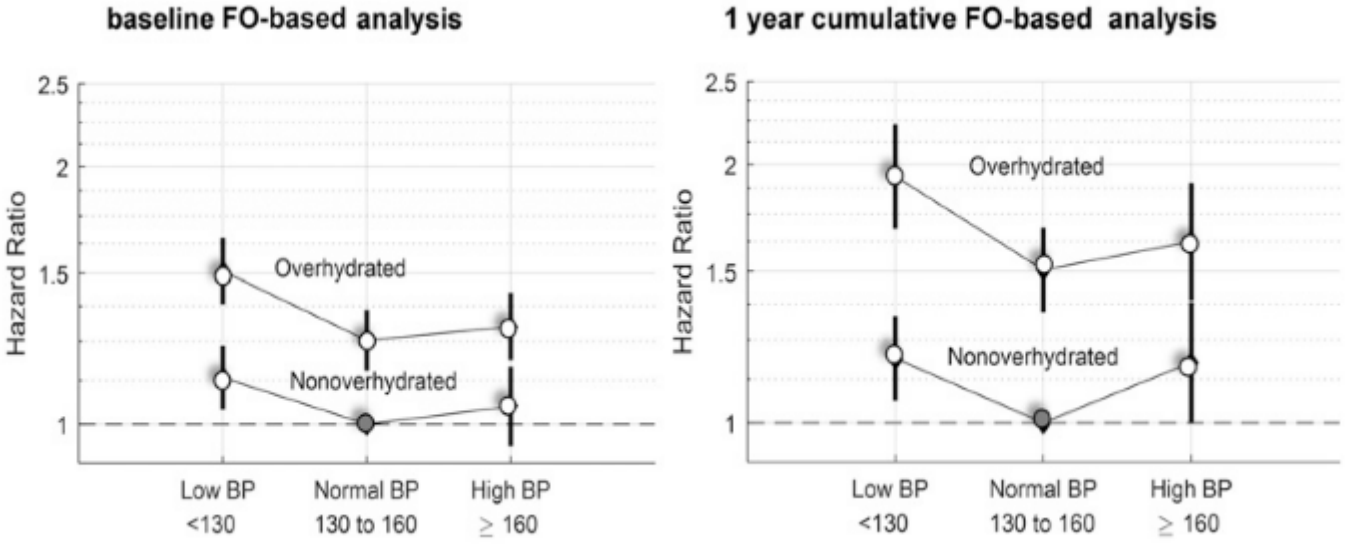


Zoccali C et al, *J Am Soc Nephrol.* 2017;28(8):2491-2497.

The Adjusted Relative Risk of Death Increases as Serum Sodium Levels Decrease

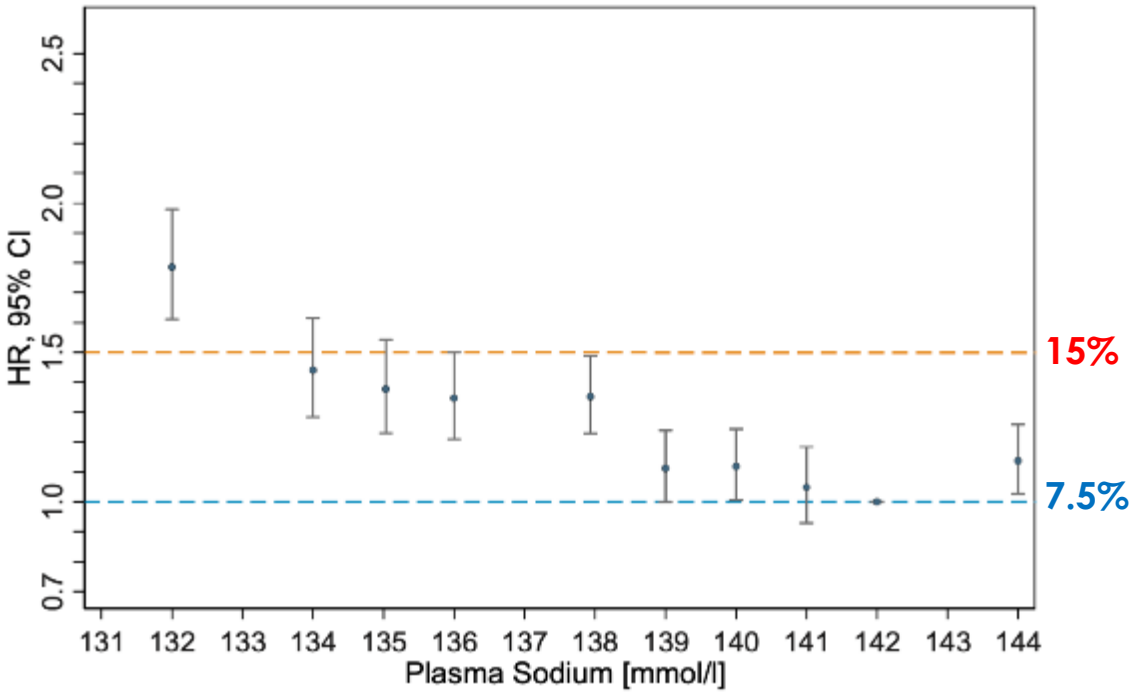
Methods

International, multi-centre
European Clinical Database 5,
Fresenius Medical Care Network

72,163 incident HD patients
10-year follow-up 25 countries

Monthly lab testing p[Na^+]
Bioimpedance fluid status
Advanced statistical modelling

Patient outcomes



Pinter J et al, Nephrol Dial Transplant. 2023;38(10):2248-2256.

The Adjusted Relative Risk of Death Increases Exponentially With the Degree of Fluid Overload

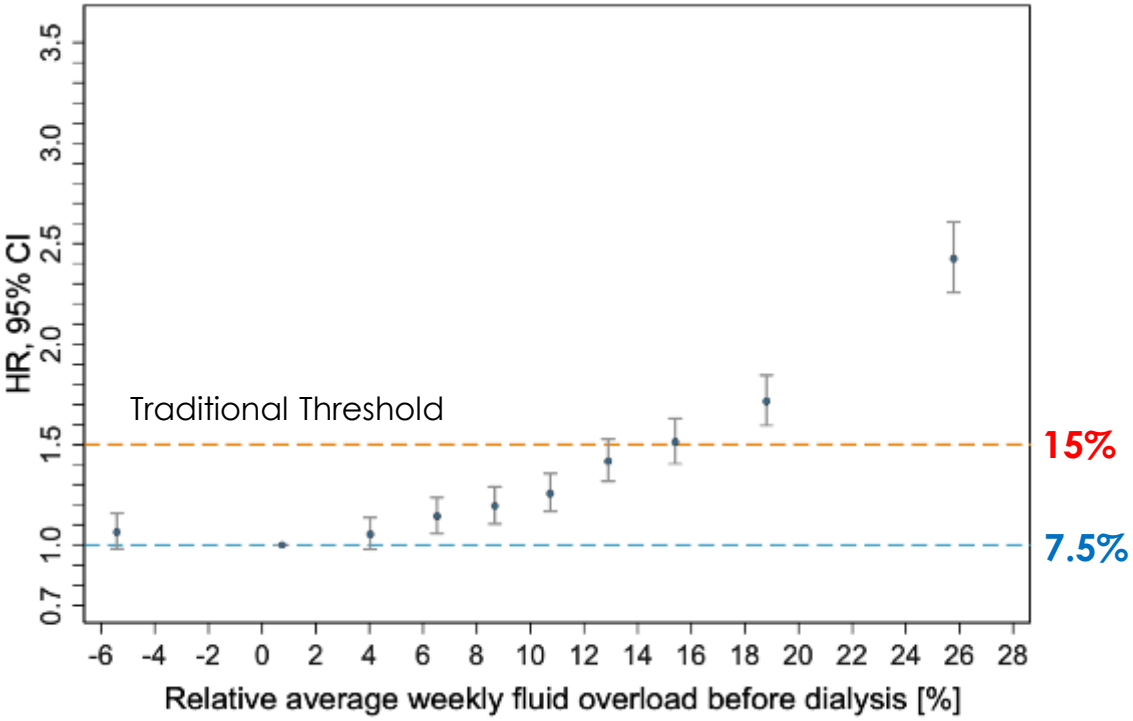
Methods

International, multi-centre
European Clinical Database 5,
Fresenius Medical Care Network

72,163 incident HD patients
10-year follow-up 25 countries

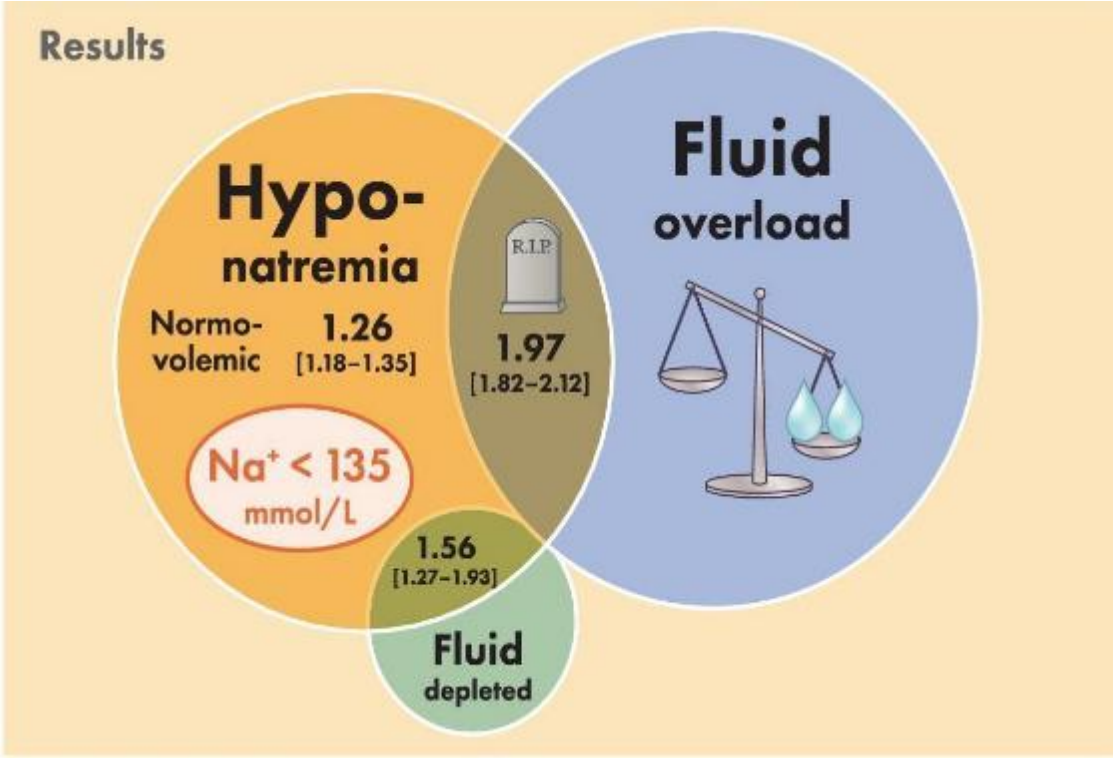
Monthly lab testing p[Na^+]
Bioimpedance fluid status
Advanced statistical modelling

Patient outcomes



Pinter J et al, Nephrol Dial Transplant. 2023;38(10):2248-2256.

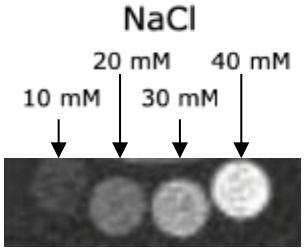
The Relative Risk of Death Is Significantly Increased When Fluid Overload and Hyponatremia Coexist

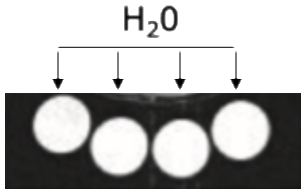


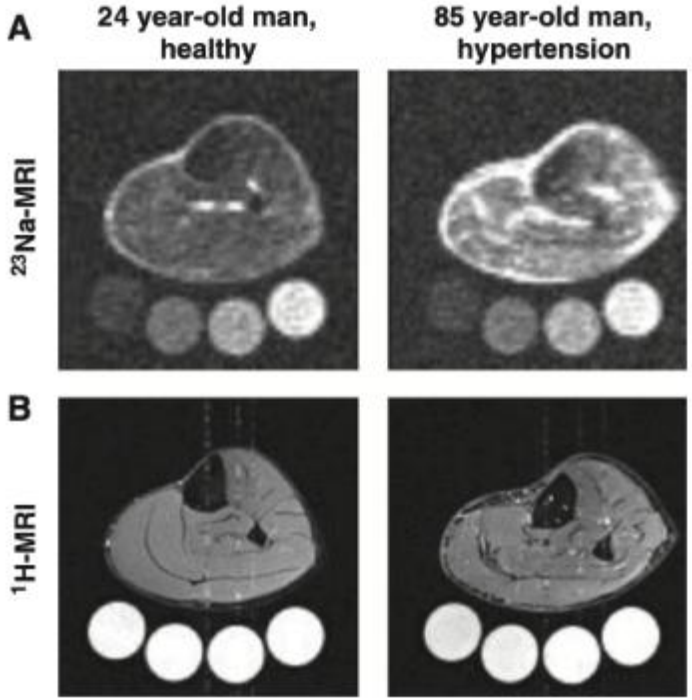
The relative risk of death is greatly increased by volume overload or hyponatremia, and further worsened when both conditions are combined

Pinter J et al, Nephrol Dial Transplant. 2023;38(10):2248-2256.

Assessment of Tissue Sodium Content Relies on Sodium-23 Magnetic Resonance Imaging (^{23}Na MRI)







Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Skin Sodium Content Increases With Age, Male Sex, and Hypertension

Cross-Sectional Observational Study

Aims

- Investigate tissue sodium (Na+) accumulation in muscle and skin.
- Assess relationship with age, sex, hypertension, and treatment effects.

Population

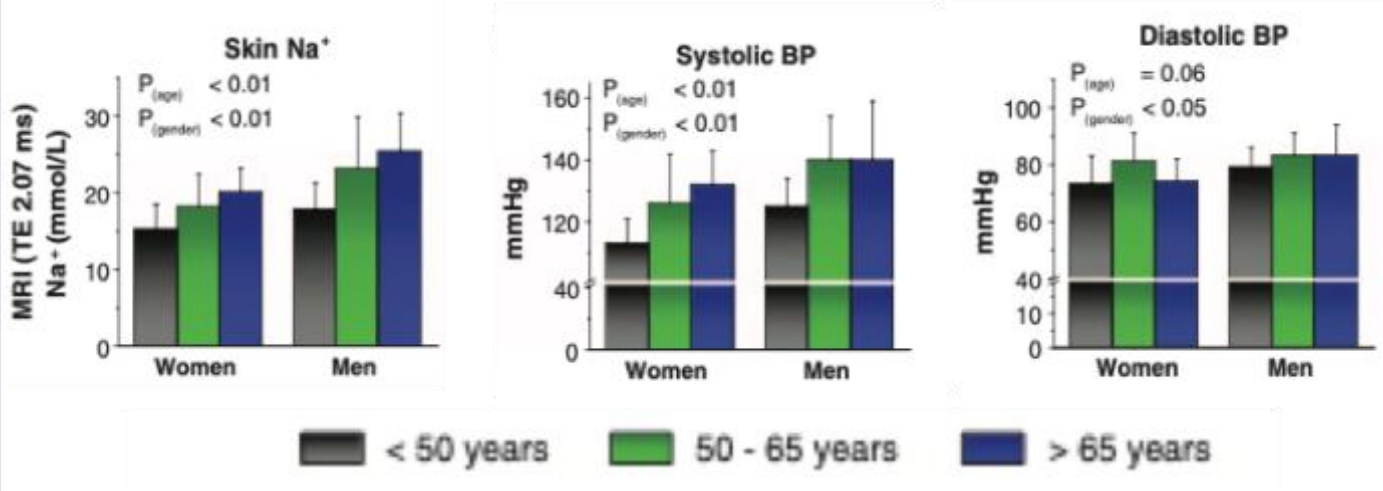
113 adults: 56 healthy controls, 57 patients with essential hypertension.
Age : 22–90 years; 44 women, 69 men.

Methods

- 23Na-MRI for sodium content (skin and muscle).
- 1H-MRI for water content.
- BP measurement and clinical assessment

Outcomes

- Differences in tissue sodium content between healthy and hypertensive subjects
- Effect of age and sex on tissue sodium accumulation.
- Association of sodium storage with blood pressure.
- Effect of spironolactone treatment on tissue sodium. Water-free sodium storage in muscle.



Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Skin and Muscle Sodium Increase With Aging and Hypertension, With a Slower Rise In Females

Cross-Sectional Observational Study

Aims

- Investigate tissue sodium (Na+) accumulation in muscle and skin.
- Assess relationship with age, sex, hypertension, and treatment effects.

Population

113 adults: 56 healthy controls, 57 patients with essential hypertension.
Age : 22–90 years; 44 women, 69 men.

Methods

- 23Na-MRI for sodium content (skin and muscle).
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- BP measurement and clinical assessment

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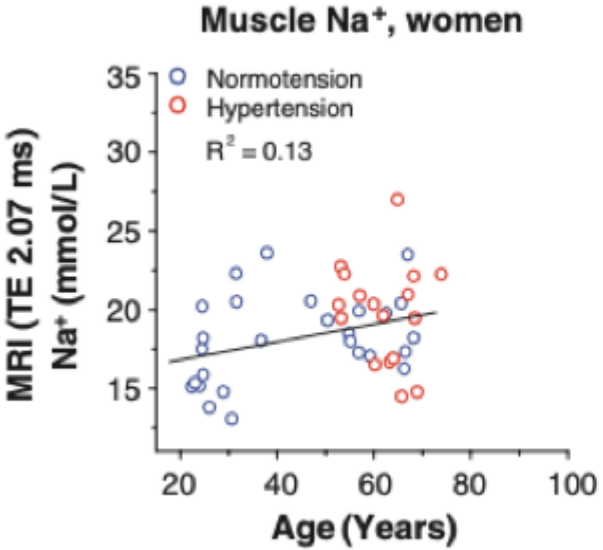

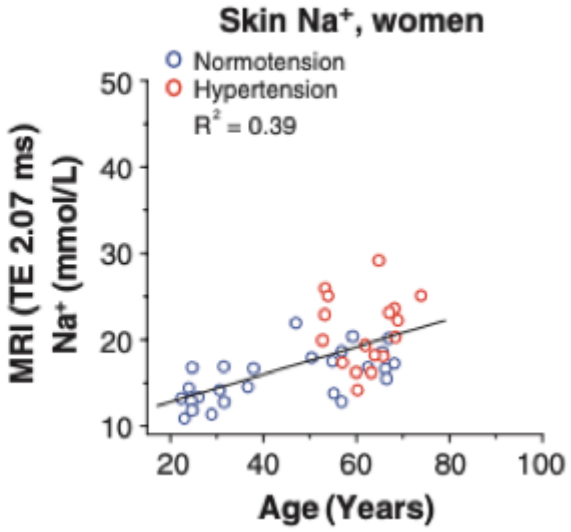

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Skin and Muscle Sodium Increase With Aging and Hypertension, With a Steeper Rise in Males

Cross-Sectional Observational Study

Aims

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Methods

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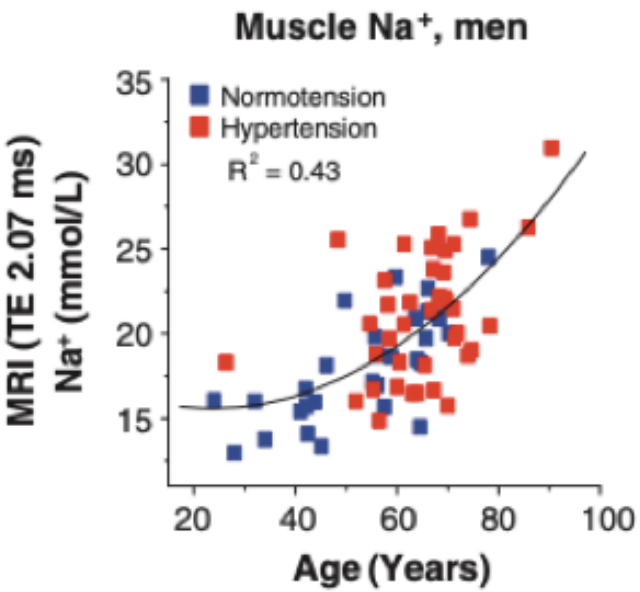

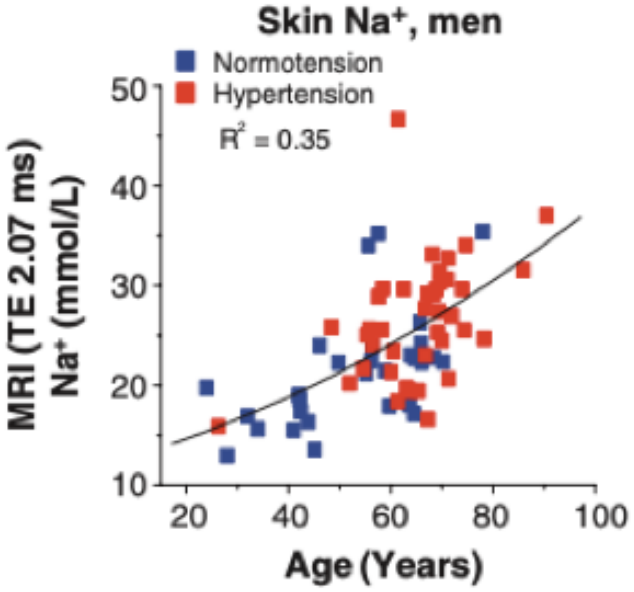

Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Skin Water, But Not Muscle Water, Increases With Hypertension, Male Sex, and Aging

Cross-Sectional Observational Study

Aims

- Investigate tissue sodium (Na+) accumulation in muscle and skin.
- Assess relationship with age, sex, hypertension, and treatment effects.

Population

113 adults: 56 healthy controls, 57 patients with essential hypertension.
Age : 22–90 years; 44 women, 69 men.

Methods

- 23Na-MRI for sodium content (skin and muscle).
- 1H-MRI for water content.
- BP measurement and clinical assessment

Outcomes

- Differences in tissue sodium content between healthy and hypertensive subjects
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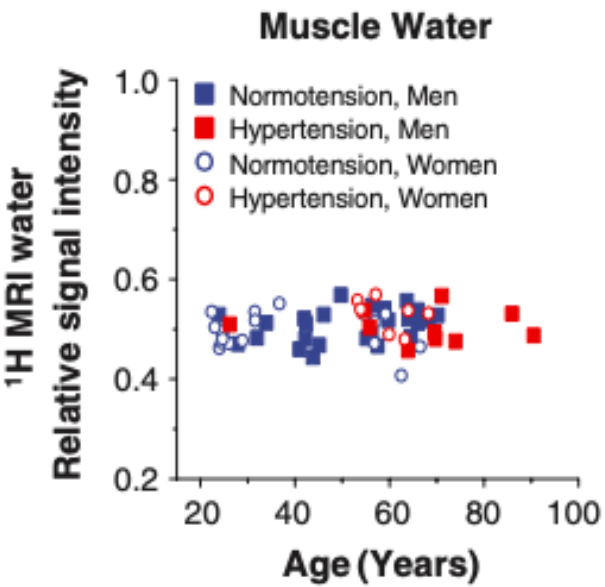
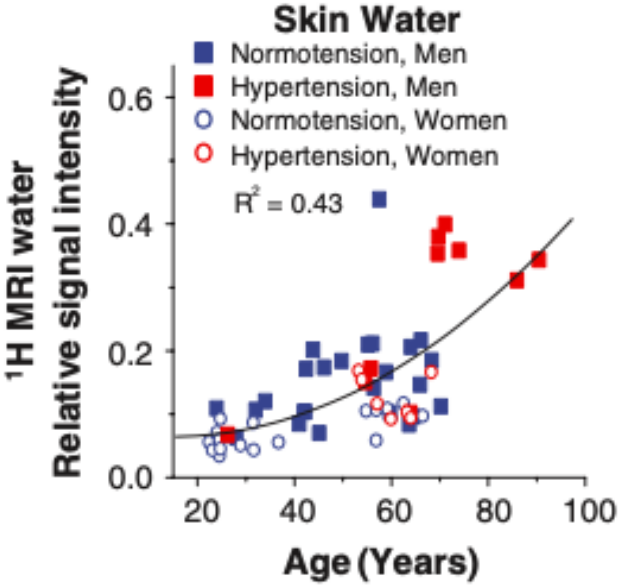
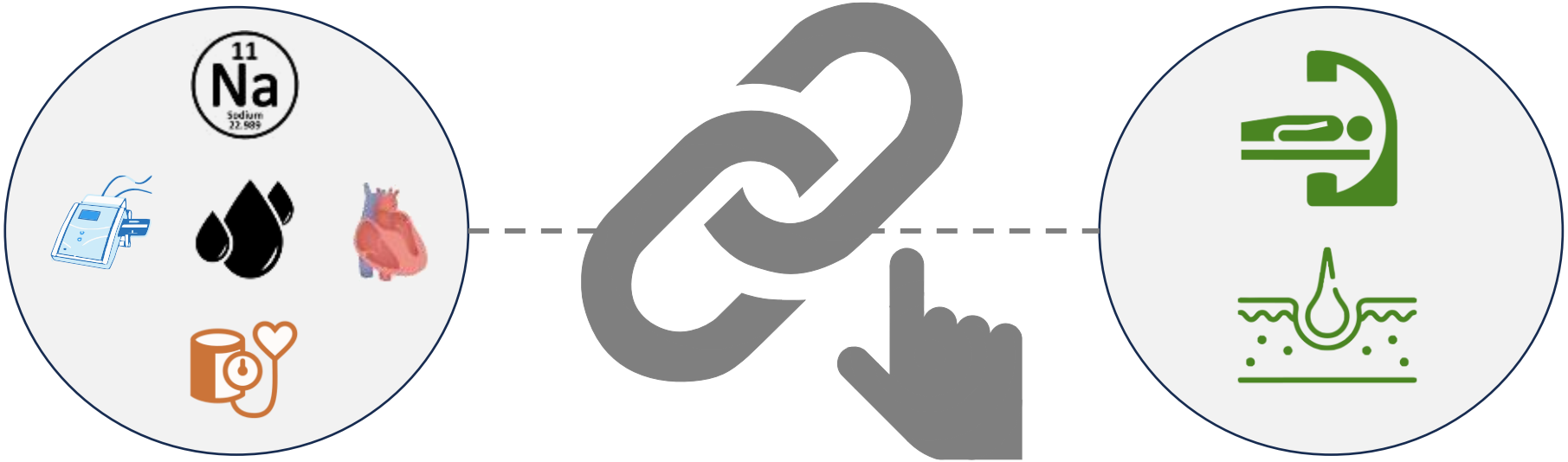




Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Is There a Link Between Sodium Imbalance, Fluid Overload, Hypertension, and Skin Sodium Content?



Tissue Sodium Content (Muscle and Skin) Is Higher In HD Patients With Type 2 Diabetes Mellitus Compared To Matched HD Patients Without Diabetes

Observational Case-Control Study

Aims

Investigate tissue sodium in T2DM-HD compared to non-diabetic HD patients.

Population

- 40 HD patients: 10 with T2DM,
- 30 matched non-diabetic controls
- (matched by age and sex).

Methods

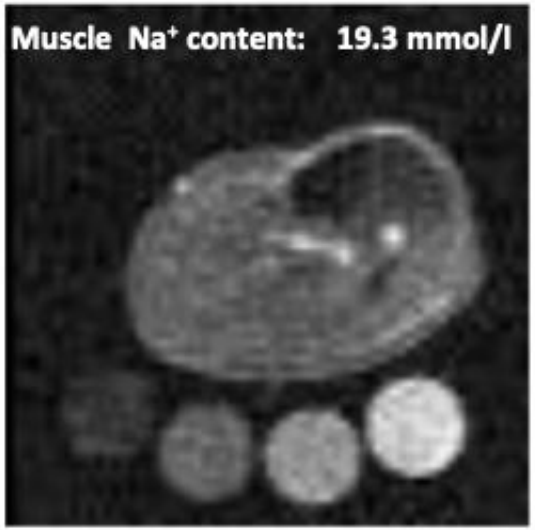
- 23Na-MRI for muscle and skin sodium content;
- 1H-MRI for muscle fat; Body Composition Monitor for fluid distribution; pre- and post-HD measurements.

Outcomes

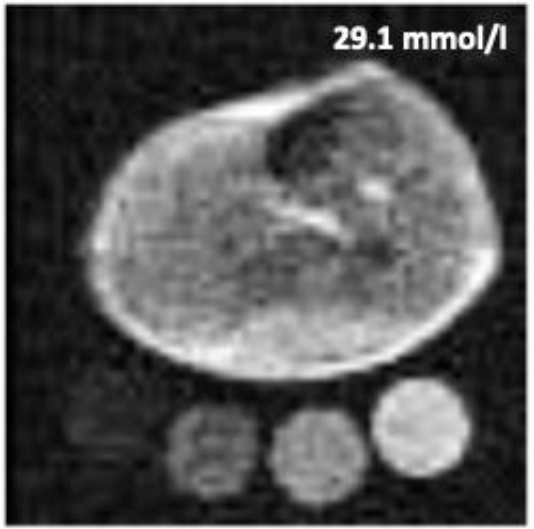
- Primary: Tissue sodium content comparison Be tween groups.
- Secondary: Relationship between HbA1c, extracellular water (ECW) excess, and sodium mobilization during HD.

^{23}Na -MR images

Male 60 y/o patient,
Control HD



Male 58 y/o patient,
T2DM-HD



Kopp C et al, *Kidney Int*. 2018;93(5):1191–1197.

Fluid Overload Increases with CKD Stage and Shows Weak Association with Hypertension

Cross-sectional observational substudy (CARVIDA) of **GCKD.**

Aims

Relationship with skin sodium content, fluid status with LVH in CK 3b-5 patients

Methods

- 23Na-MRI used to measure skin sodium;
- bioimpedance spectroscopy;
- cardiac MRI for left ventricular mass.

Patients

- 99 CKD patients
- eGFR median 51 ml/min/1.73m² (range 13-127).

Parameter	OH			*P* Value
	<−0.8 L, *n*=29	−0.8 to +0.1 L, *n*=34	>0.1 L, *n*=35	
Age, yr, median (range)	63 (39–76)	61 (25–78)	69 (23–75)	0.26
Sex, men/women	16/13	15/19	26/9	0.04
Weight, kg, mean (95% CI)	86 (81 to 92)	82 (75 to 89)	88 (82 to 93)	0.34
Height, cm, mean (95% CI)	170 (166 to 175)	170 (167 to 174)	174 (172 to 176)	0.15
Body mass index, kg/m^2, median (range)	28 (24–41)	28 (18–39)	28 (20–39)	0.30
Office SBP, mmHg, mean (95% CI)	133 (127 to 140)	131 (126 to 135)	135 (130 to 140)	0.58
Office DBP, mmHg, mean (95% CI)	82 (78 to 86)	80 (77 to 83)	80 (76 to 83)	0.60
24-h SBP, mmHg, mean (95% CI)	124 (120 to 129)	123 (120 to 127)	129 (124 to 133)	0.12
24-h DBP, mmHg, mean (95% CI)	76 (72 to 79)	76 (74 to 79)	78 (75 to 81)	0.51
Hypertension, %	90	94	91	0.81
Treatment resistant hypertension, %	10	15	17	0.74
Number of BP medications, median (range)	2 (0–4)	3 (0–5)	2 (0–6)	0.24

CARVIDA Study

[GCKD]

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Skin Sodium Content Increases With CKD Stage and Tends to Rise With Hypertension

Cross-sectional observational substudy (CARVIDA) of **GCKD.**

Aims

Relationship with skin sodium content, fluid status with LVH in CK 3b-5 patients

Methods

- 23Na-MRI used to measure skin sodium;
- bioimpedance spectroscopy;
- cardiac MRI for left ventricular mass.

Patients

- 99 CKD patients
- eGFR median 51 ml/min/1.73m² (range 13-127).

Parameter	Skin Sodium <16.8 mmol/L, *n*=30	16.8–22.2 mmol/L, *n*=31	>22.2 mmol/L, *n*=32	*P* Value
Age, yr, median (range)	54 (23–76)	67 (46–75)	70 (47–78)	<0.001
Sex, men/women	9/21	19/12	24/7	0.001
Weight, kg, mean (95% CI)	79 (73 to 86)	85 (80 to 91)	93 (87 to 99)	0.005
Height, cm, mean (95% CI)	170 (167 to 173)	172 (168 to 176)	173 (170 to 176)	0.40
Body mass index, kg/m^2, median (range)	27 (18–37)	28 (23–41)	30 (23–39)	0.02
Office SBP, mmHg, mean (95% CI)	129(123 to 135)	133 (127 to 139)	135 (131 to 140)	0.22
Office DBP, mmHg, mean (95% CI)	81 (77 to 85)	82 (79 to 86)	78 (73 to 82)	0.18
24 h-SBP, mmHg, mean (95% CI)	122 (118 to 126)	124 (121 to 127)	132 (127 to 137)	0.002
24 h-DBP, mmHg, mean (95% CI)	78 (75 to 81)	76 (74 to 79)	77 (72 to 81)	0.64
Hypertension, %	83	90	100	0.07
Treatment resistant hypertension, %	10	10	23	0.25
Number of BP medications, median (range)	1 (0–4)	1 (0–5)	3 (0–6)	<0.001

CARVIDA Study

[GCKD]

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Skin Sodium Is a Stronger Predictor of LVH Than BP or Fluid Overload, Suggesting Sodium-Driven Cardiac Hypertrophy

Cross-sectional observational substudy (CARVIDA) of **GCKD.**

Aims

Relationship with skin sodium content, fluid status with LVH in CK 3b-5 patients

Methods

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- bioimpedance spectroscopy;
- cardiac MRI for left ventricular mass.

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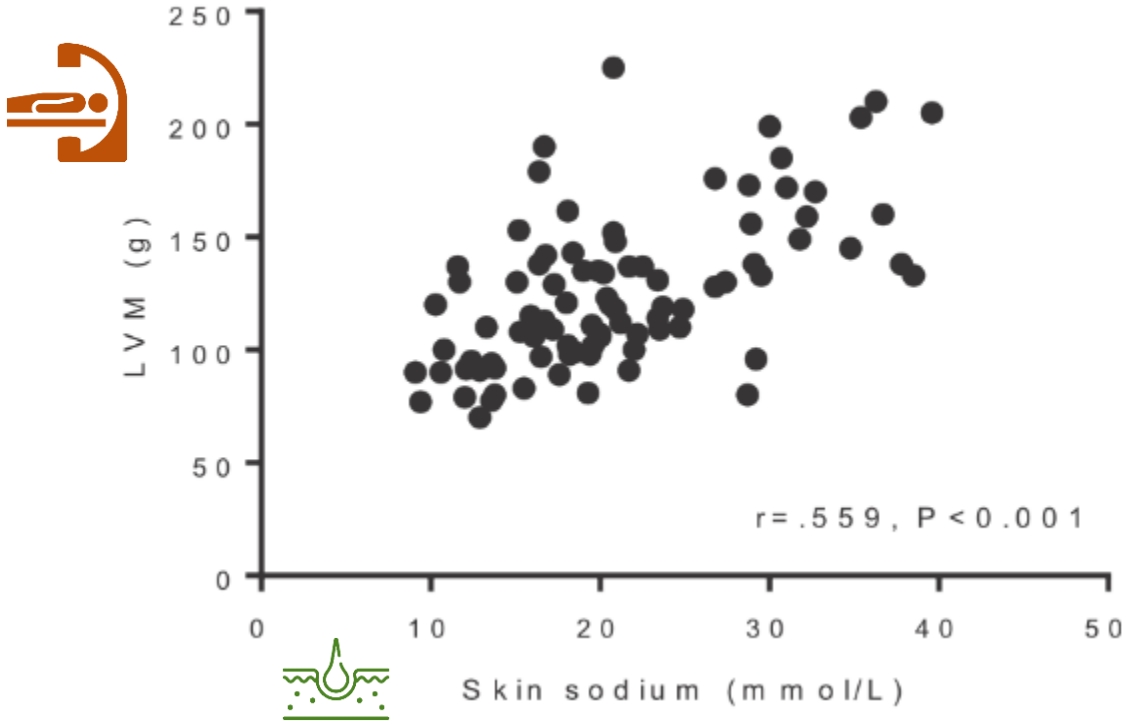


CARVIDA Study

[GCKD]

Schneider MP et al, *J Am Soc Nephrol 2017;* 28: 1867–1876

Tissue Na Content (Muscle-Skin) is Higher in T2 Diabetes Mellitus HD Patients than in Age-Gender Matched HD Patients

Observational Case-Control Study

Aims

Investigate tissue sodium in T2DM-HD compared to non-diabetic HD patients.

Population

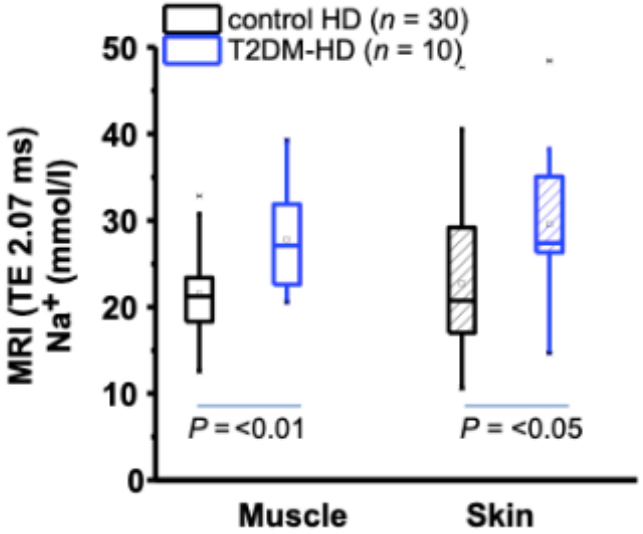
- 40 HD patients: 10 with T2DM,
- 30 matched non-diabetic controls
- (matched by age and sex).

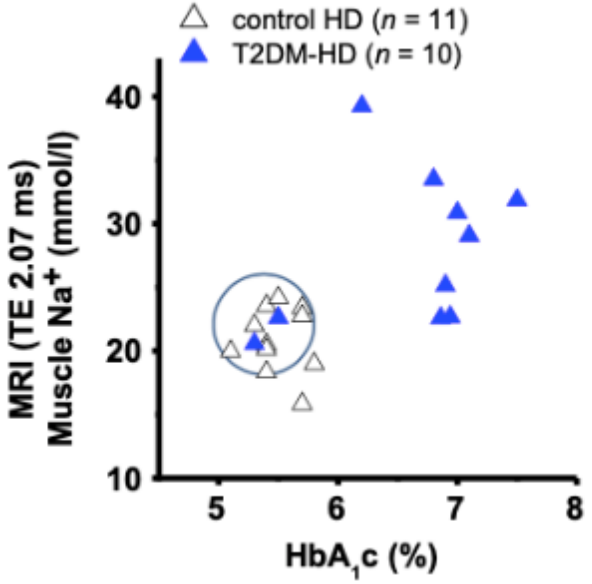
Methods

- 23Na-MRI for muscle and skin sodium content;
- 1H-MRI for muscle fat; Body Composition Monitor for fluid distribution; pre- and post-HD measurements.

Outcomes

- Primary: Tissue sodium content comparison Be tween groups.
- Secondary: Relationship between HbA1c, extracellular water (ECW) excess, and sodium mobilization during HD.





Kopp C et al, *Kidney Int*. 2018;93(5):1191–1197.

Tissue Sodium Accumulation Predominates in Muscle In CKD5 Hemodialysis Patients

Cross-sectional Pilot Study

Aim

To investigate the association between tissue sodium accumulation and peripheral insulin sensitivity in HD patients.

Population

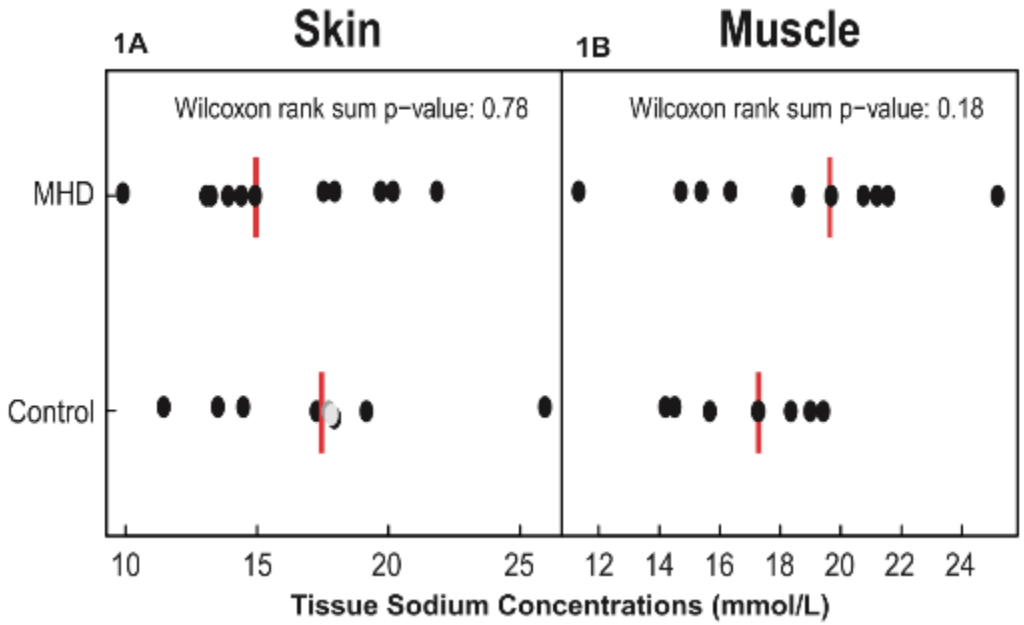
11 HD patients
8 healthy controls.

Methods

- Hyperinsulinemic-euglycemic-euaminoacidemic clamp to assess glucose (GDR) and leucine disposal rates (LDR)
- 23Na MRI to measure tissue sodium concentrations in muscle and skin
- Body composition by DEXA
- Statistical analysis with linear regression adjusted for potential confounders

Outcomes

- **Primary:** Association between tissue sodium (muscle and skin) and insulin sensitivity (GDR and LDR)
- **Secondary:** Comparison of tissue sodium content between MHD patients and controls



Deger SM et al. *J Cachexia Sarcopenia Muscle*. 2017;8(3):500–507.

Tissue Sodium Accumulation in Skin is Associated with Peripheral Insulin Sensitivity In Hemodialysis Patients

Cross-sectional Pilot Study

Aim

To investigate the association between tissue sodium accumulation and peripheral insulin sensitivity in HD patients.

Population

11 HD patients
8 healthy controls.

Methods

- Hyperinsulinemic-euglycemic-euaminoacidemic clamp to assess glucose (GDR) and leucine disposal rates (LDR)
- 23Na MRI to measure tissue sodium concentrations in muscle and skin
- Body composition by DEXA
- Statistical analysis with linear regression adjusted for potential confounders

Outcomes

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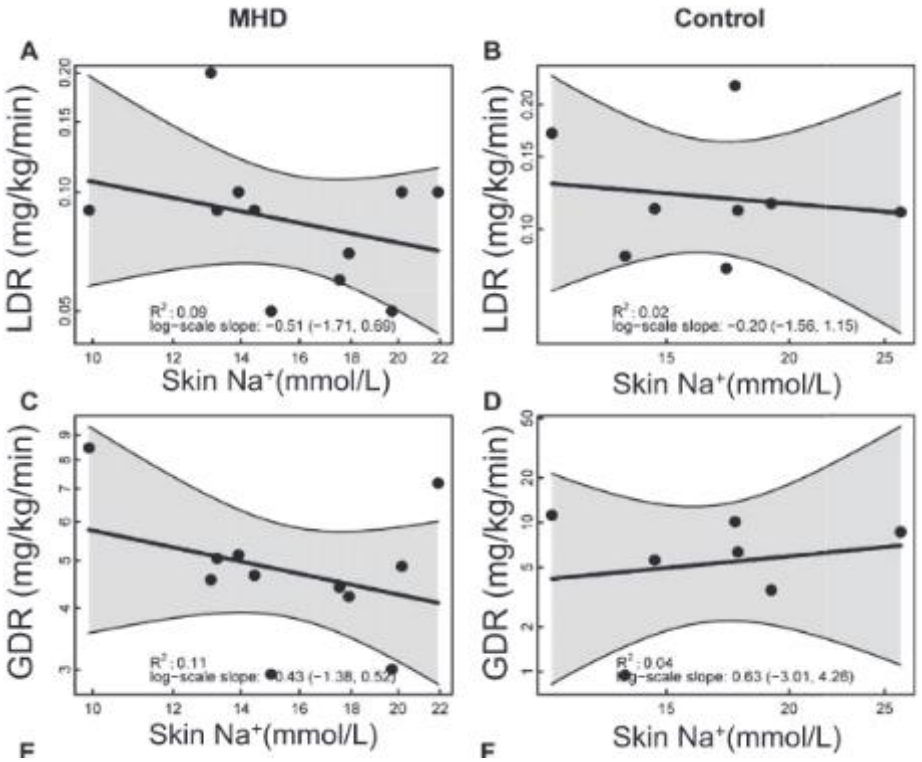

Deger SM et al. *J Cachexia Sarcopenia Muscle*. 2017;8(3):500–507.

While Muscle Sodium Accumulation Is Inversely Associated With Insulin Sensitivity in HD Patients

Cross-sectional Pilot Study

Aim

To investigate the association between tissue sodium accumulation and peripheral insulin sensitivity in HD patients.

Population

11 HD patients
8 healthy controls.

Methods

- Hyperinsulinemic-euglycemic-euaminoacidemic clamp to assess glucose (GDR) and leucine disposal rates (LDR)
- 23Na MRI to measure tissue sodium concentrations in muscle and skin
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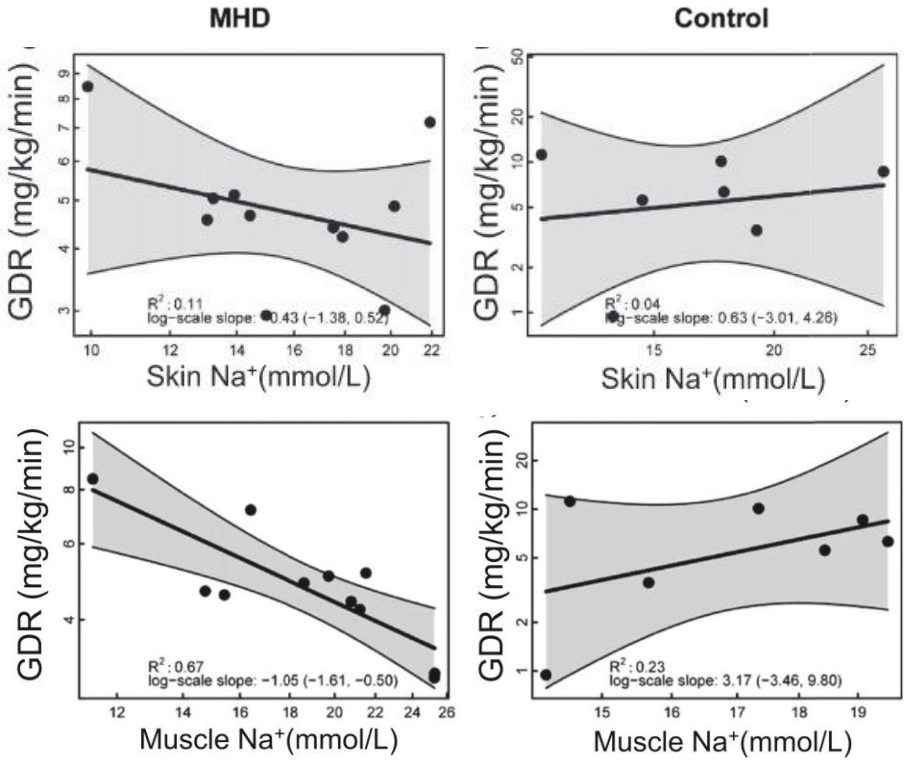


Deger SM et al. *J Cachexia Sarcopenia Muscle*. 2017;8(3):500–507.

High Salt Intake Reprograms Muscle Metabolism Toward Ketogenesis, Fat Oxidation, Amino Acid Release, and Glucocorticoid-Driven Catabolism to Conserve Body Water

Prospective Intervention Trials In Mice and Ultra-long-Term Salt Balance Study In Humans.

Aim

- To investigate how high salt intake affects:
- Body water conservation, energy metabolism, and induces muscle catabolism through urea osmolyte generation.

Population

Mice: C57BL/6J male mice on low-salt or high-salt diets.
Humans: 10 healthy men undergoing 6g/d and 12g/d salt intake interventions.

Methods

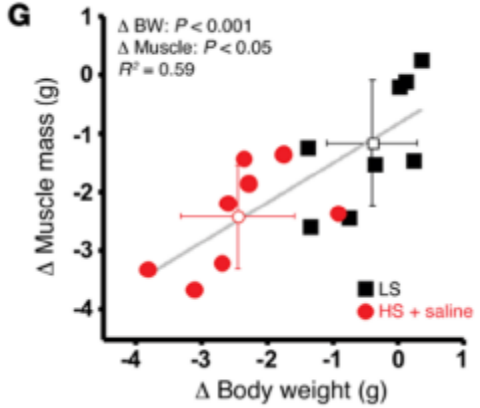
- Dietary salt interventions with controlled water access. Measurements of urinary electrolytes, osmolality, urea.
- Tissue arginase activity, metabolomics (LC-MS/MS).
- Muscle protein catabolism (Western blot, NMR spectroscopy).
- Cardiovascular telemetry (heart rate, blood pressure).

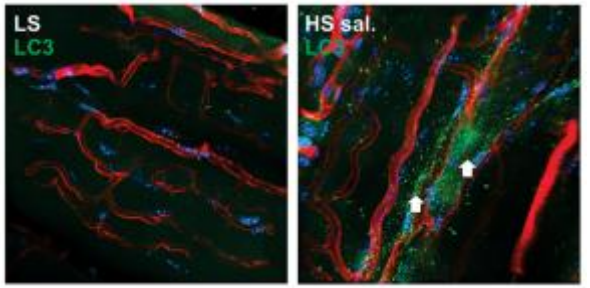
Outcomes

- Changes in renal urea recycling, tissue and plasma urea.
- Muscle catabolism, autophagy markers.
- Body composition changes (lean mass loss).
- Cardiovascular energy expenditure.
- Glucocorticoid hormone levels.

Low Na
(6 g NaCl)

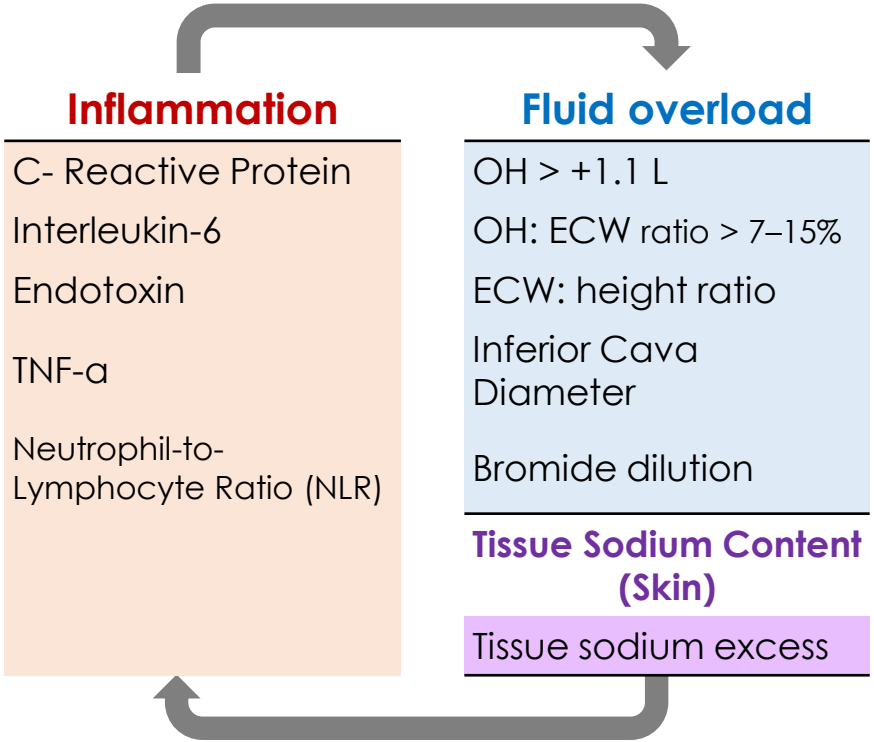
High Na
(12 g NaCl)





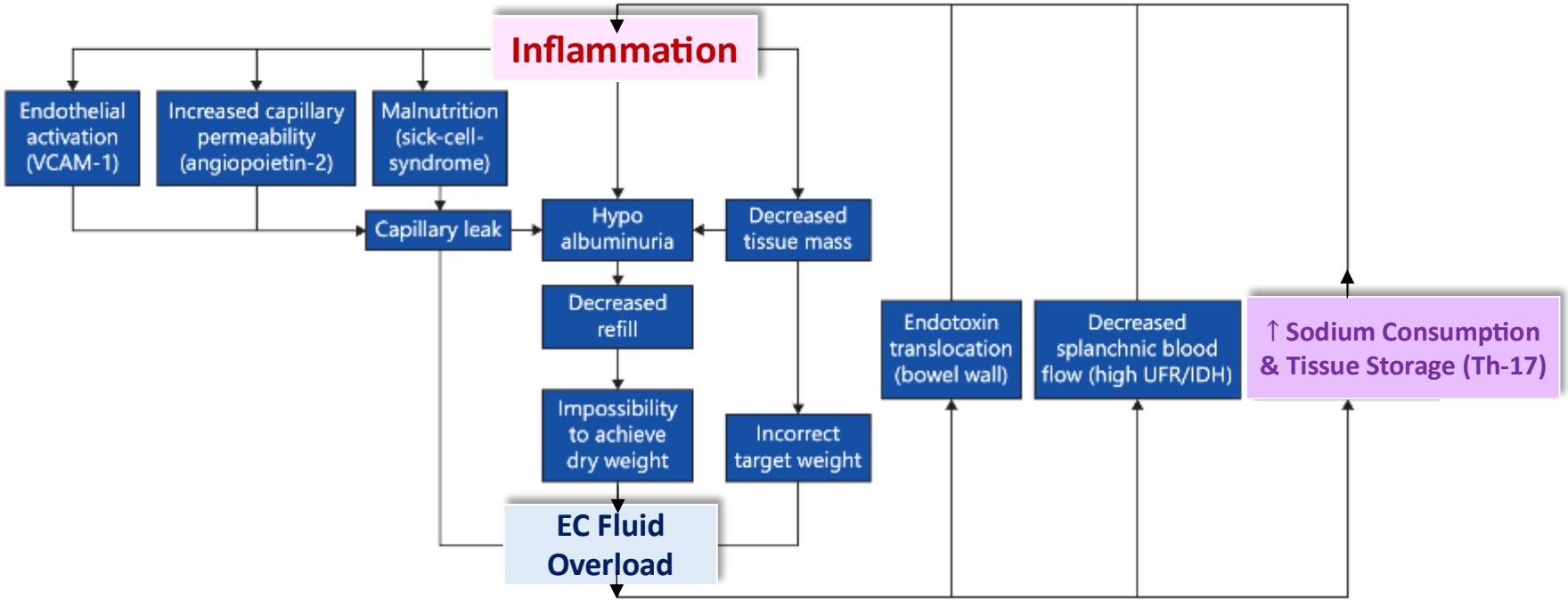
Kitada K et al, *J Clin Invest*. 2017;127(5):1944-1959.

Fluid Overload, Tissue Sodium Excess and Inflammation Axis



Adapted from Dekker MJE et al, *Blood Purif*. 2018;45(1-3):159-165.

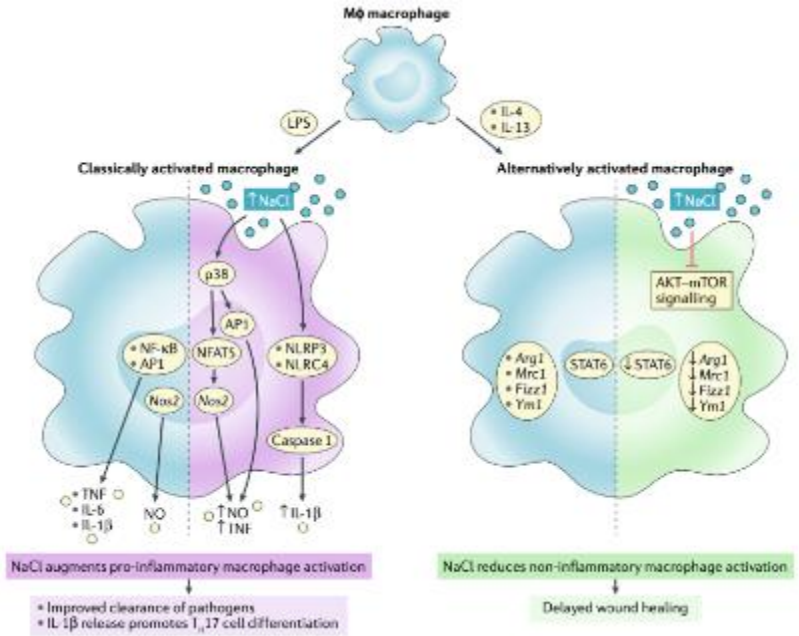
Sodium Imbalance Interplay with Inflammation and Immune compromized condition



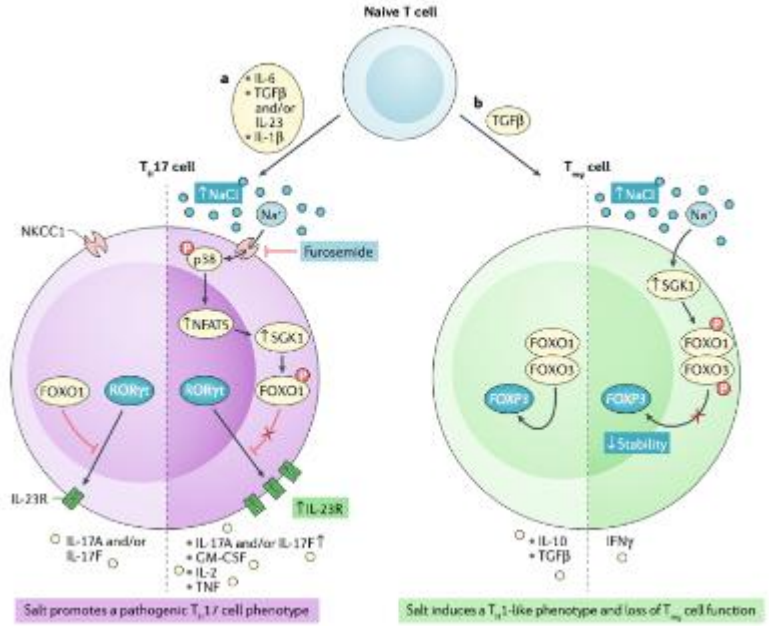
Dekker MJE et al, *Blood Purif*. 2018;45(1-3):159-165.

Ambivalent Role of Tissue Sodium In Modulating Immune Cell Function: Inflammatory Signaling

Inflammatory Signaling

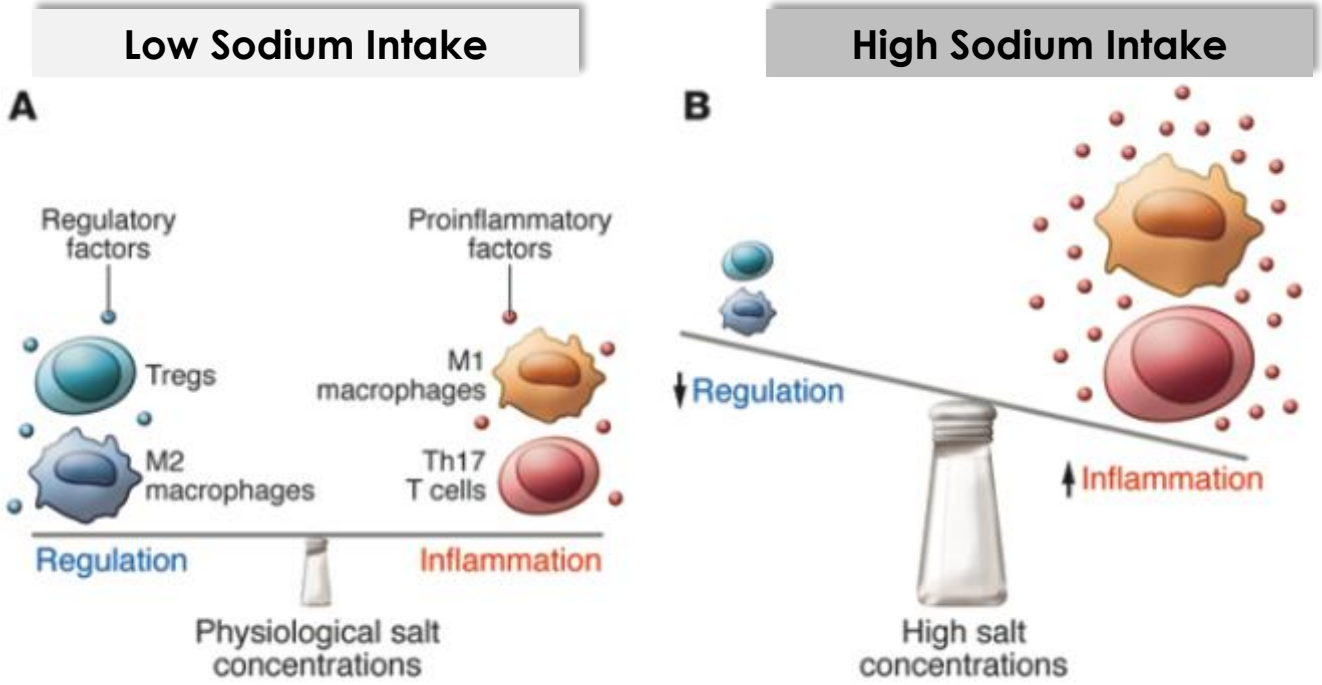


T Cell Regulation



Wilck N et al. *Nat Rev Nephrol.* 2019;15(9):546–558.

Over-Salting Ruins the Balance of the Immune Menu



Min B et al. *J Clin Invest.* 2015;125(11):4002–4004.

Isotonic Tissue Sodium Accumulation Reflects Extracellular Fluid Expansion, Driven by Local Biomechanical Tonic Stress

Aim:
Assess tissue sodium (Na+) accumulation in HT and aging

Design: Multi-phase Translational design

SHRSP hypertensive

WKY Normotensive

76 Hypertensive pts
(skin punch biopsies, 23Na-MRI)

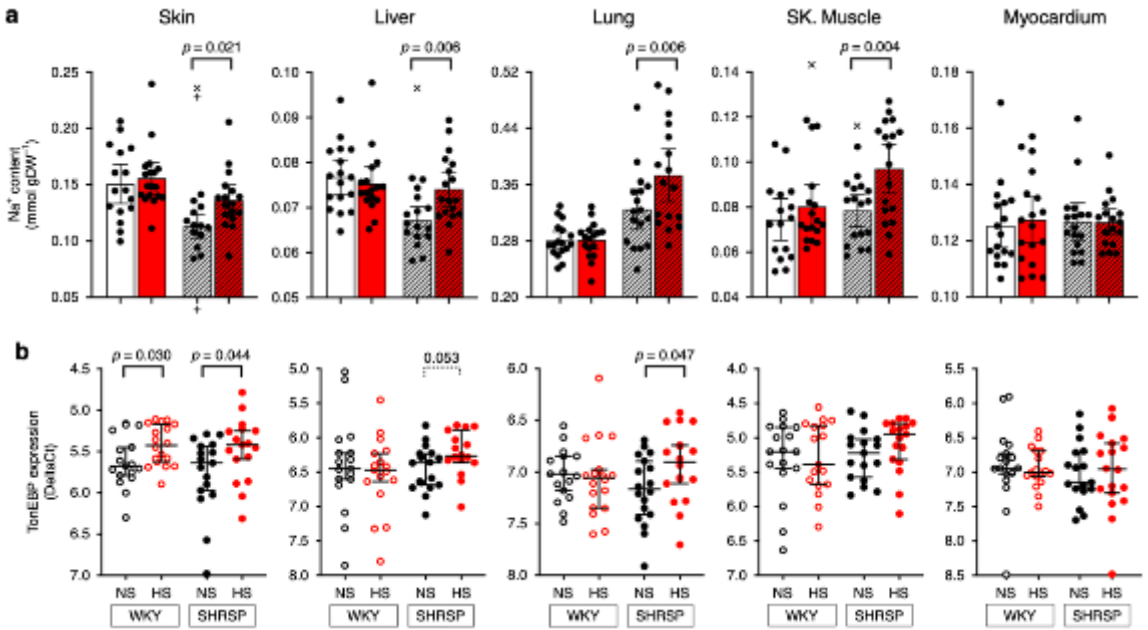
Method:

Rats:
- 3-wk salt-loading (1% NaCl)
- vs. control; measure Na+
- & K+ via flame photometry.

Histology:
- tissue water content,
- TonEBP/NFAT5 gene expression analysis

Humans:
- 23Na-MRI,
- histochemical skin biopsy analysis (Na+, K+, water content).

Clinical correlation
- BP, age, NT-proBNP, and TEWL

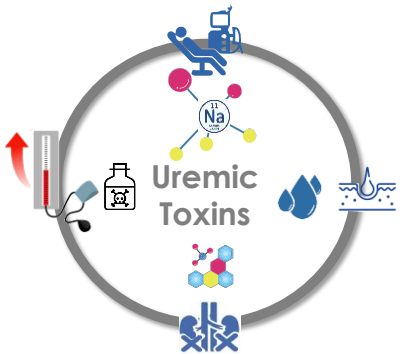


TonEBP (Tonicity-Responsive Enhancer-binding Protein)/NFAT5: pleiotropic stress-responsive protein

Rossitto G et al, *Nat Commun.* 2020;11(1):4222.

Outline

Is Sodium a Uremic Toxin?



1 What is a Uremic Toxin?

2 How are Uremic Toxins Current Classified?

3 How Does Sodium Fit?
What is the Evidence?

4 **How to Manage Sodium?**
What are the Tools?

5 Summary & Key Takeaways

Spironolactone Lowers Tissue Sodium in Refractory Hypertension

Cross-Sectional Observational Study

Aims

- Investigate tissue sodium (Na+) accumulation in muscle and skin.
- Assess relationship with age, sex, hypertension, and treatment effects.

Population

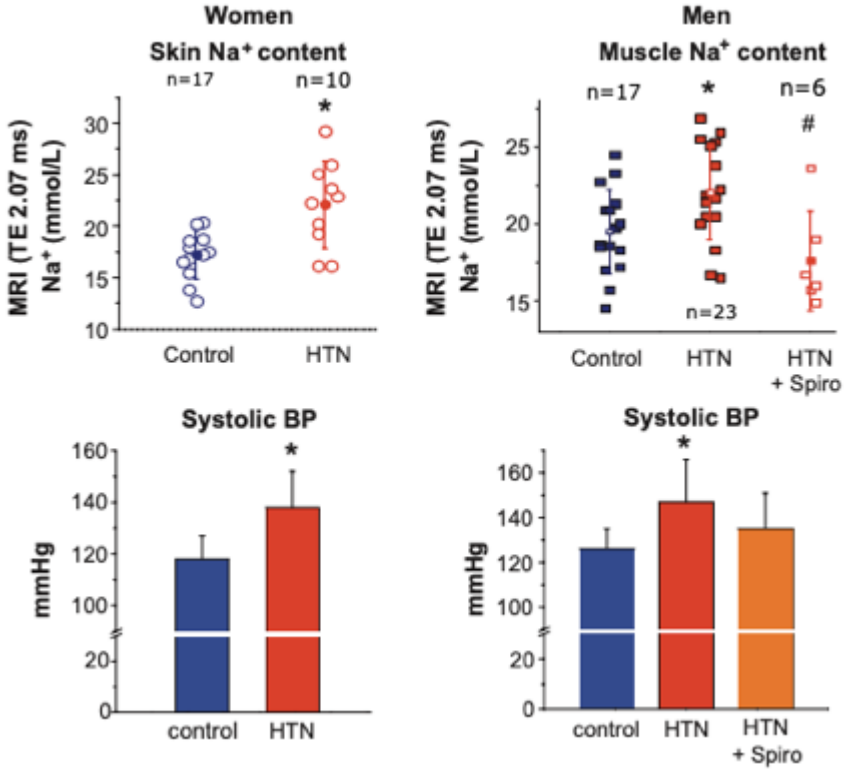
113 adults: 56 healthy controls, 57 patients with essential hypertension.
Age : 22–90 years; 44 women, 69 men.

Methods

- 23Na-MRI for sodium content (skin and muscle).
- 1H-MRI for water content.
- BP measurement and clinical assessment

Outcomes

- Differences in tissue sodium content between healthy and hypertensive subjects
- Effect of age and sex on tissue sodium accumulation.
- Association of sodium storage with blood pressure.
- Effect of spironolactone treatment on tissue sodium. Water-free sodium storage in muscle.



Kopp C et al, *Hypertension*. 2013;61(3):635–640.

Dapagliflozin: Superior to Placebo in Glucose and Blood Pressure Control and Weight Loss in T2D

Prospective, Randomized Placebo-Controlled Cross-Over Trial.

Aim

To assess whether SGLT-2 inhibition (dapagliflozin) reduces tissue sodium content in patients with T2DM

Population

59 patients with T2DM
(mean age 60.3 years)

Methods

- Dapagliflozin 10 mg daily

vs placebo for 6 weeks each,

- 23Na-MRI to measure skin and muscle sodium.
- Metabolic, blood pressure, and body composition measurements.
- 24-h urinary sodium excretion.
- Ambulatory blood pressure monitoring.

Outcomes

- **Primary**: Change in tissue sodium content (skin and muscle) by 23Na-MRI.
- **Secondary**: Changes in fasting and postprandial glucose, body weight, blood pressure, urinary sodium excretion.

	Placebo Mean ± SD (change from baseline)	p-value vs. baseline	Dapagliflozin Mean ± SD (change from baseline)	p-value vs. baseline
BMI (kg/m²)	29.9 ± 4.2 (+ 0.1)	0.846	29.5 ± 4.1 (−0.3)	< 0.001
HbA1c (%)	6.79 ± 0.8 (+ 0.12)	0.064	6.62 ± 0.7 (− 0.05)	0.224
Glucose				
Fasting (mg/dl)	135 ± 32 (+ 2.0)	0.325	114 ± 19 (−18)	< 0.001
Postprandial[1] (mg/dl)	180 ± 67 (+ 1.0)	0.766	154 ± 46 (− 24)	< 0.001
Office blood pressure				
Systolic (mmHg)	129 ± 13 (− 0.1)	0.340	126 ± 12 (− 4.0)	0.015
Diastolic (mmHg)	79 ± 8.7 (− 1.0)	0.827	78 ± 8.8 (− 2.0)	0.058
Heart rate (bpm)	67.8 ± 9.6 (− 1.3)	0.123	68.2 ± 10.6 (− 0.9)	0.332
24-h ambulatory blood pressure				
Systolic (mmHg)	129 ± 10.8 (− 0.5)	0.172	126 ± 10.8 (−3.0)	0.010
Diastolic (mmHg)	77.1 ± 7.3 (0.0)	0.765	75.4 ± 7.7 (−2.0)	0.024
Heart rate (bpm)	75.7 ± 9.5 (+ 1.4)	0.997	74.1 ± 7.6 (− 0.8)	0.849
Haematocrit (%)	40.3 ± 3.1 (+ 0.2)	0.389	41.1 ± 2.9 (+ 1.0)	< 0.001
Serum sodium conc. (mmol/l)	138.1 ± 1.6 (− 0.5)	0.034	138.3 ± 1.6 (− 0.3)	0.308
Urinary sodium excretion over 24 h (mmol/day)	222.5 ± 103.6 (− 6.0)	0.660	210.1 ± 71.2 (+ 6.5)	0.586

Karg MV et al. *Cardiovasc Diabetol* 2018:17:5

But Also, Dapagliflozin Selectively Reduces Skin Sodium, Not Muscle Sodium, After 6 Weeks

Prospective, Randomized Placebo-Controlled Cross-Over Trial.

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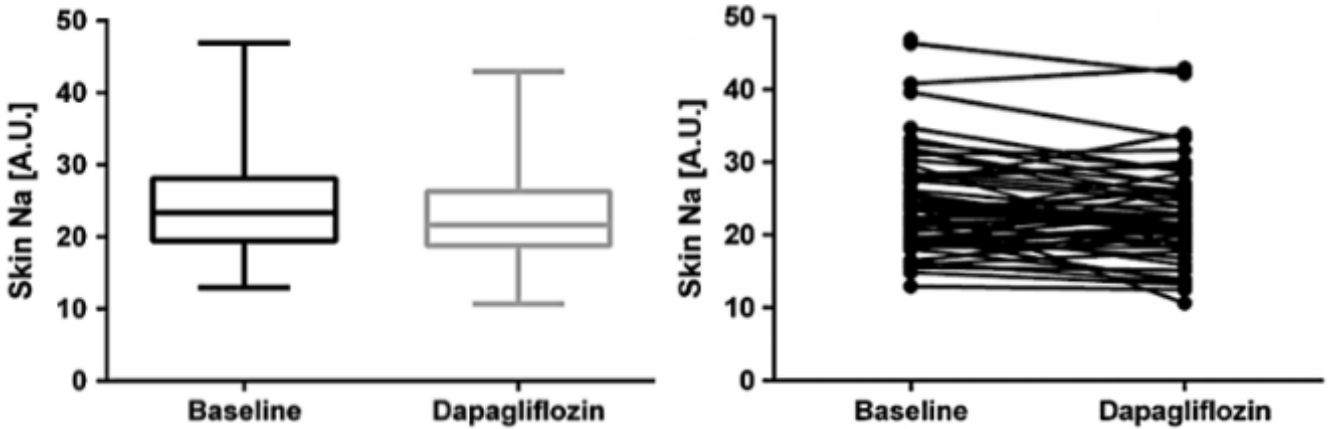
Outcomes

- **Primary**: Change in tissue sodium content (skin and muscle) by 23Na-MRI.
- **Secondary**: Changes in fasting and postprandial glucose, body weight, blood pressure, urinary sodium excretion.

Skin Na [A.U.]: 24.1±6.5 to **22.7±6.4**, *p=0.013*



A.U. : Arbitrary Units

Karg MV et al. *Cardiovasc Diabetol* 2018:17:5

Dapagliflozin Lowers Ambulatory Blood Pressure More Than Office BP vs. Placebo

Prospective, Randomized Placebo-Controlled Cross-Over Trial.

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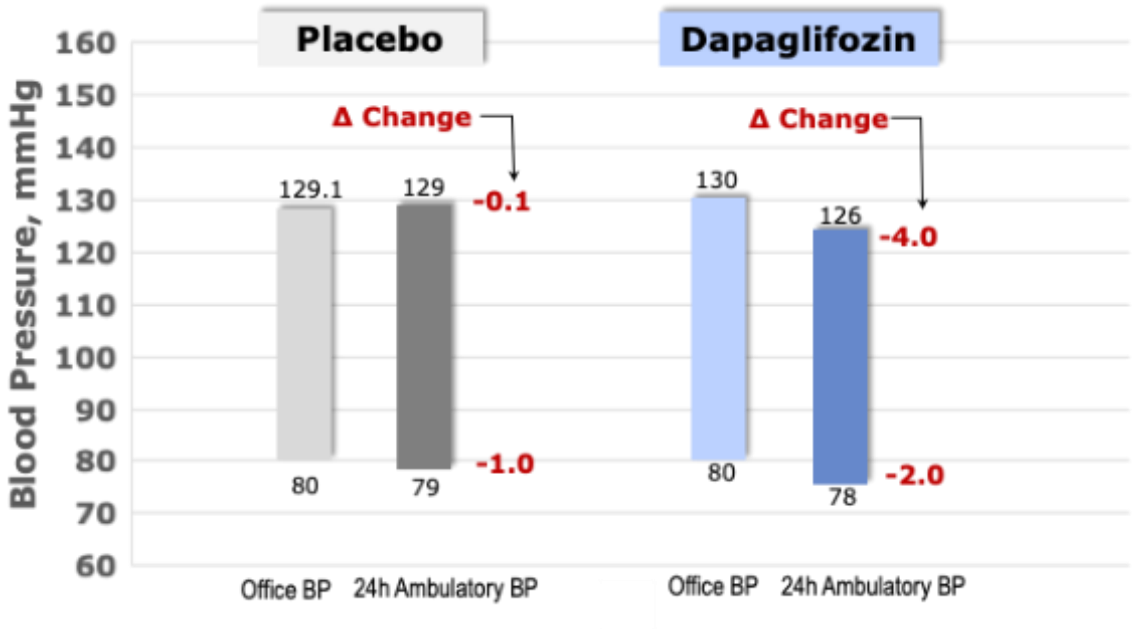


Karg MV et al. *Cardiovasc Diabetol* 2018:17:5

Fluid Volume Reduction by Additional Ultrafiltration Is Effective and Tolerable for BP Control in HD Patients

Randomized Controlled Trial

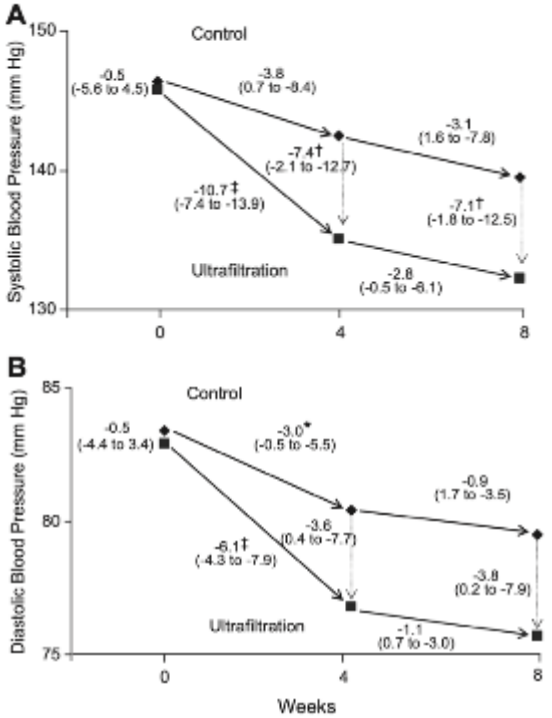
Aim
Effect of fluid volume reduction on blood pressure in hypertensive HD patients

Population
150 hypertensive HD patients
(100 in UF group vs. 50 in control group).

Methods
- UF probing to reduce dry weight
- 44-hour post-dialysis ABPM).
- KDQOL assessment.
- No change in anti-HT medications and tHD.

Outcomes
- **Primary:** Change in systolic interdialytic ambulatory BP at 8 weeks.
- **Secondary:** Changes in diastolic BP, dry weight, KDQOL scores, and hypovolemia symptoms.

- Additional ultrafiltration reduced postdialysis weight by ~1 kg.
- Systolic BP reduced by ~6.6 mm Hg and diastolic BP by ~3.3 mm Hg at 8 weeks.
- >50% had a ≥10 mm Hg reduction in systolic BP.

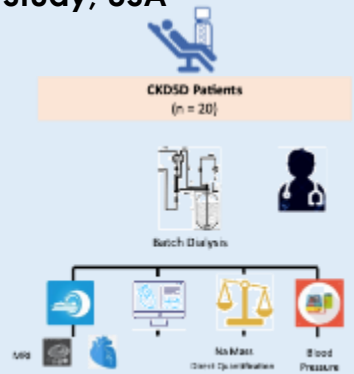


DRIP Study
Dry Weight Reduction in HT HD Patients

Agarwal R et al, *Hypertension*. 2009;53(3):500-7.

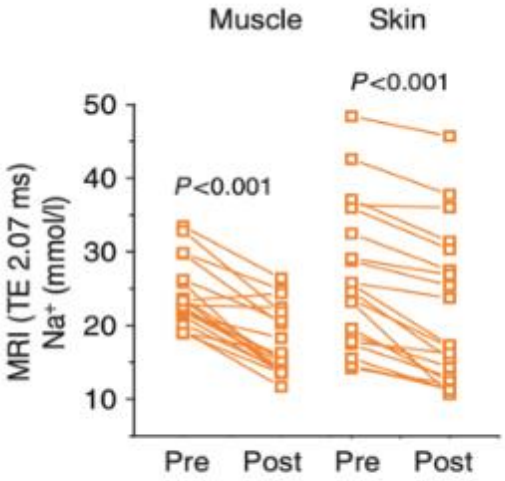
HD Effectively Removes Tissue Sodium (Skin, Muscle) and May Help Control Tissue Sodium Levels if the Dialysate Sodium is Appropriately Prescribed

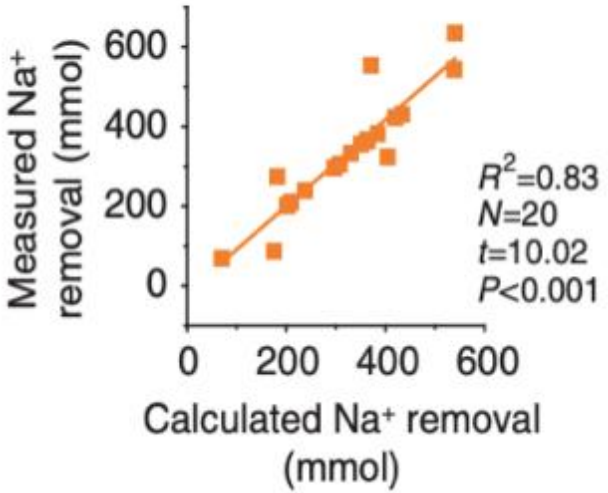
Prospective Direct Dialysis Quantification Study, USA



I^{ary} Outcomes

- Sodium mass transfer
- Skin Na content
- Hemodynamic

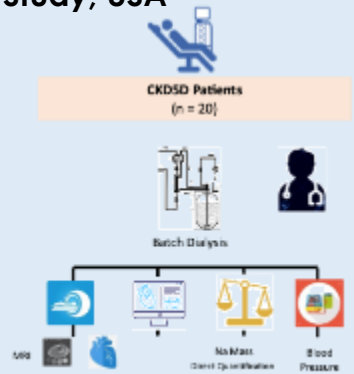




Dahlmann A et al, *Kidney Int*. 2015;87, 434–441

Visualization of Tissue Sodium (Skin, Muscle) Elimination through Dialysis using 23Na MRI Scan

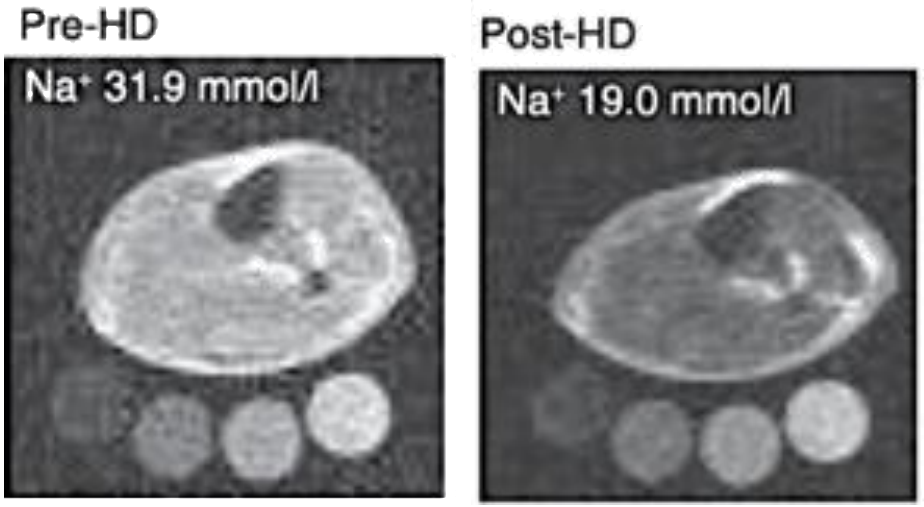
Prospective Direct Dialysis Quantification Study, USA



I^{ary} Outcomes

- Sodium mass transfer
- Skin Na content
- Hemodynamic

Man, 75 year,
High Na^+ removal
UF rate: 2.7 l



Dahlmann A et al, *Kidney Int.* 2015;87, 434–441

Long-Term Effects of Dialysate Sodium Concentration on Hemodynamics and Tissue Sodium Content

Cross sectional Study

Canada Ontario - 2 HD facilities

Investigator centers of RESOLVE study

dNa 137

dNa 140

>3 months exposure

Patient Phenotype

UF Volume
Blood Pressure
Interdialytic Weight Gain
Natremia

Sodium Tissue Content

^{23}Na MRI (skin/muscle)

	Whole Population (N = 36)	$[Na^+]_D$ Prescription	
		137 mmol/L (n = 18)	140 mmol/L (n = 18)
Age, y	65 (40-82)	66 (47-79)	65 (40-82)
Male sex	22 (61%)	10 (55%)	12 (66%)
Systolic BP, mm Hg	132 (95-181)	128 (97-181)	133 (95-171)
Diastolic BP, mm Hg	77 (56-100)	73 (61-90)	79 (43-99)
Hypertension	31 (86%)	15 (83%)	16 (88%)
Ultrafiltration volume, mL	2.3 (0-4)	2 (0.4-4)	2.5 (0-4)
Intradialytic weight, kg	2 (1.3-5)	1.65 (0-3.2)	2.3 (0.1-5)
Pre-HD Serum Na^+, mmol/L	137 (129-144)	136 (129-143)	138[a] (133-141)

Lemoine S et al, *Am J Kidney Dis* 2021;78(1): 156-159

Tissue Sodium Content Is Significantly Higher in Patients Receiving a Dialysate Sodium Concentration of 140 mmol/L

Cross sectional Study

Canada Ontario- 2 HD facilities

Investigator centers of RESOLVE study

dNa 137

dNa 140

>3 months exposure

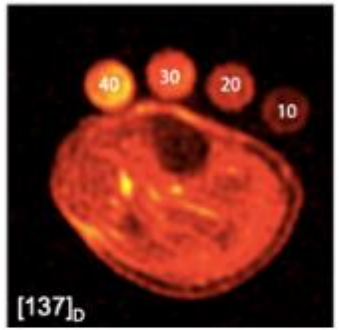
Patient Phenotype

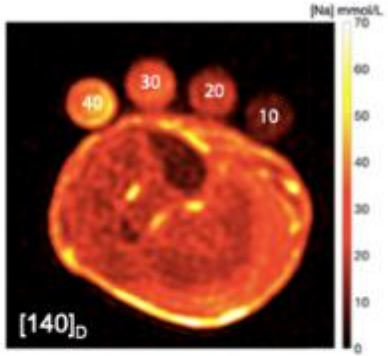
UF Volume
Blood Pressure
Interdialytic Weight Gain

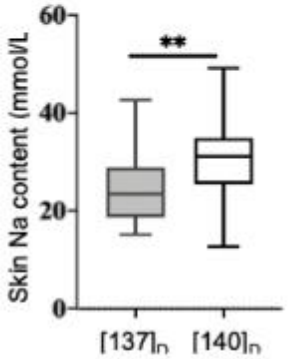
Natremia

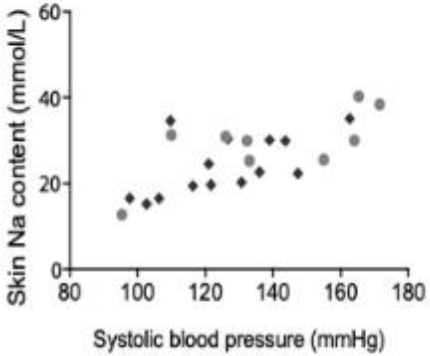
Sodium Tissue Content

^{23}Na MRI (skin/muscle)





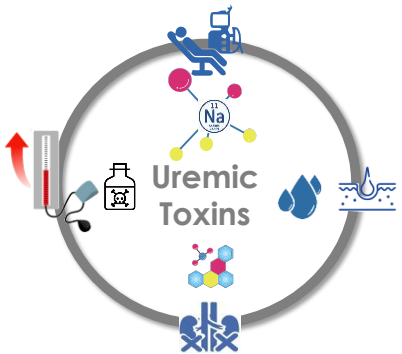




Lemoine S et al, *Am J Kidney Dis* 2021;78(1): 156-159

Outline

Is Sodium a Uremic Toxin?



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What is the Evidence?

4 How to Manage Sodium?
What are the Tools?

5 **Summary & Key Takeaways**

Summary

- ✓**Sodium** displays key characteristics of a **uremic toxin**, both functionally and mechanistically.
- ✓**Sodium excess** and related fluid disorders exert **toxic effects** via **hemodynamic** and **biomechanical** mechanisms, especially in CKD, hypertension, diabetes, and the elderly.
- ✓**Tissue sodium storage** (e.g., in skin) represents a **paradigm shift** in understanding sodium-related toxicity and warrants clinical attention.

Key Takeaways

- ✓**Sodium accumulation** and **imbalance** in CKD remain **underestimated drivers of cardiovascular risk** and burden.
- ✓**Sodium acts** as both a **risk factor** and a **risk modifier** in CKD and dialysis patients and **should be actively managed**.
- ✓**Sodium control** must be re-evaluated as a **core component of uremic toxicity management**, especially in dialysis.
- ✓**Improved sodium management** using **new therapies** and **tools** may reduce cardiovascular mortality in CKD and dialysis populations.