CKD-MBD

Role of the Calciprotein particles (CPPs)

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Disclosure

Disclosure of Financial Relationships

The author declares no conflicting interest

Hideki Kawanishi

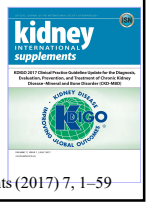
CKD-MBD

Terminology

ROD (Renal osteodystrophy): Bone fracture

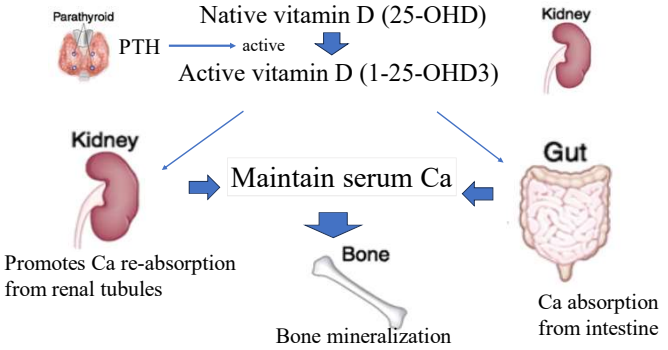
CKD-MBD (mineral and bone disorder)
: Vascular Calcification

Need for the balance of Bone vs calcification

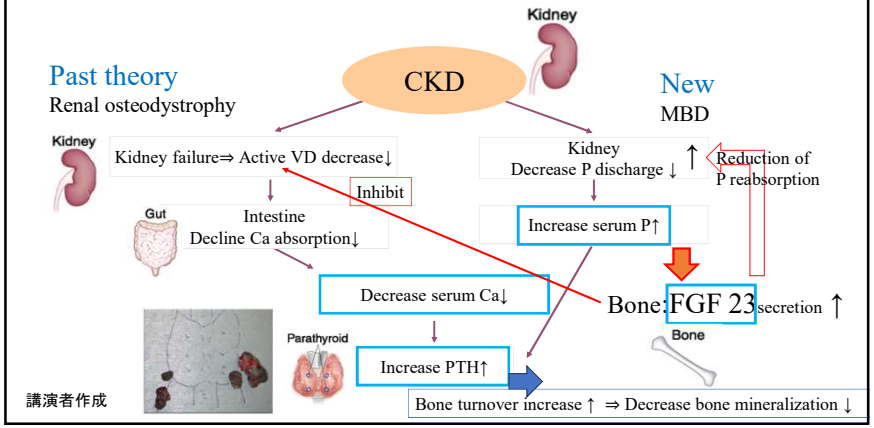


Kidney International Supplements (2017) 7, 1–59

Normal Ca metabolize



Renal osteodystrophy (ROD) to mineral and bone disorder (MBD)



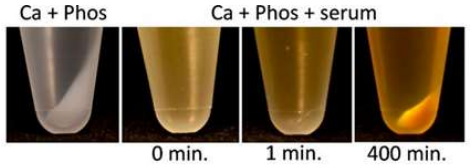
講演者作成

Vascular calcification

Calciprotein particles (CPPs)

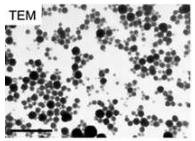
Pasch A et al. JASN 2012;23:1744-1752

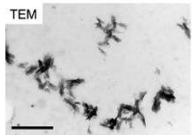
- Ca + P ⇒ crystalline hydroxyapatite [Ca10(PO4)6(OH)2]
- Ca + P + Serum ⇒ soluble colloidal particles
  - Primary CPPs (radius 75 nm)
  - Secondary CPPs (radius 120 nm)



Crystal in water

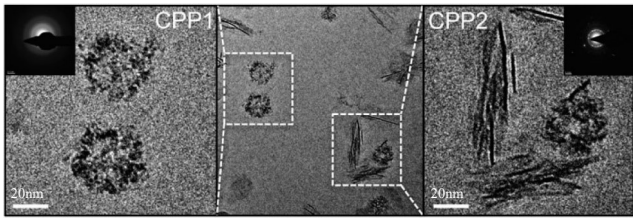
CPPs formation in serum





CPP: primary & secondary

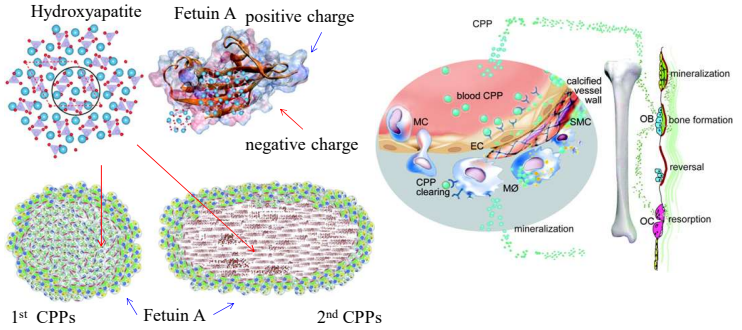
Holt SG, Smith ER NDT 2016; 31:1583-1587



Cryo-TEM analysis

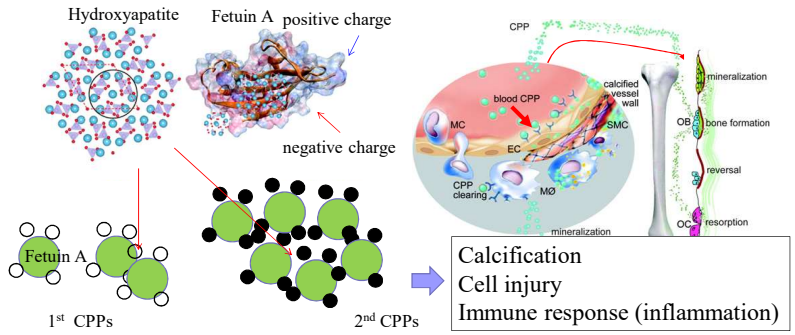
Fetuin A-CPPs

Jahnen-Dechent W et al. Circulation Research 2011;108:1494-1509



Fetuin A-CPPs

Jahnen-Dechent W et al. Circulation Research 2011;108:1494-1509

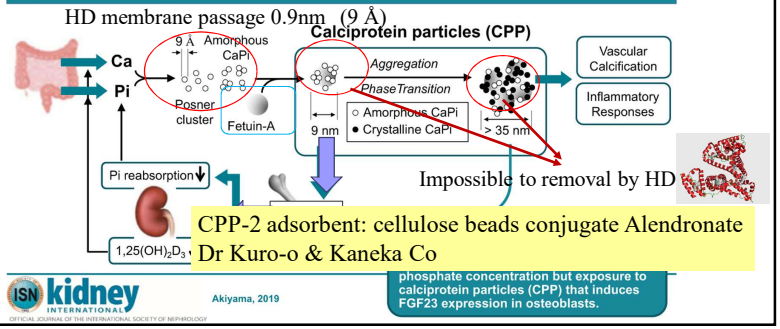


Calcification
Cell injury
Immune response (inflammation)

CPP-1 regulate FGF23

Akiyama K…..Kuro-o M, KI 2020;97:702-712

Regulation of fibroblast growth factor-23 expression in osteoblasts by calciprotein particles



CPP-2 adsorbent: cellulose beads conjugate Alendronate
Dr Kuro-o & Kaneka Co

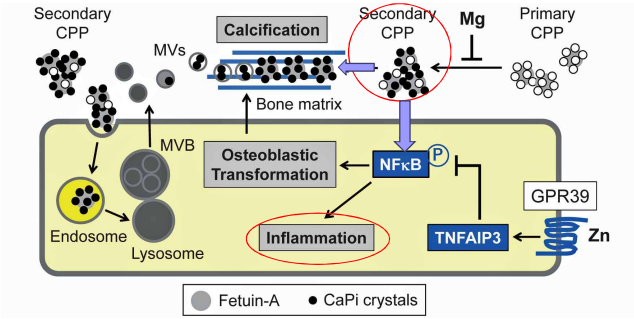
ISN kidney INTERNATIONAL

Akiyama, 2019

phosphate concentration but exposure to calciprotein particles (CPP) that induces FGF23 expression in osteoblasts.

CPP-1 regulate FGF23

Kuro-o M, J Atheroscler Thromb 2021;28:203-213

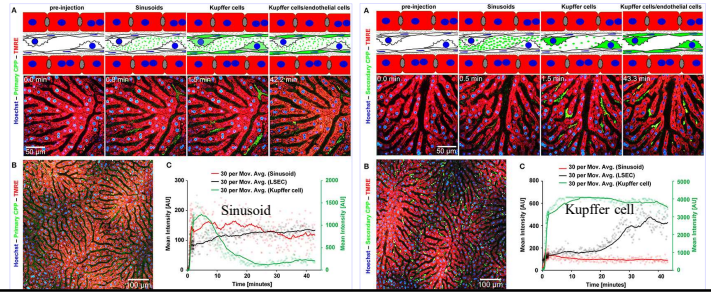


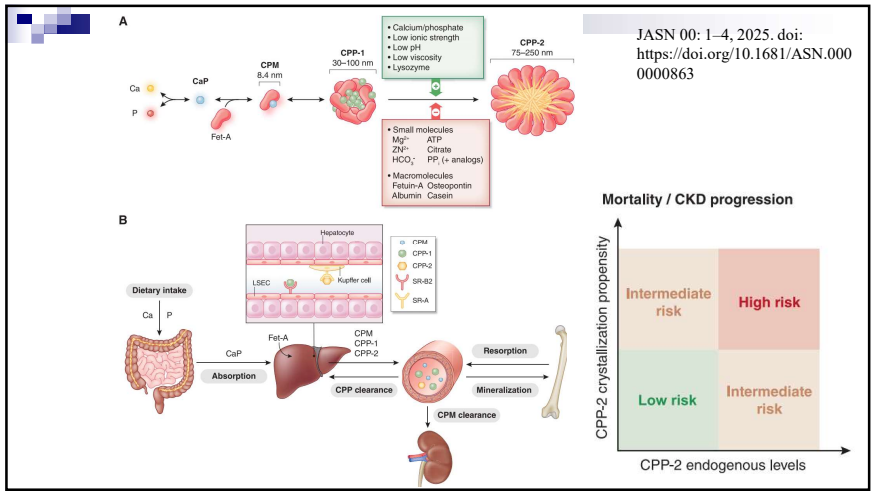
CPP clearance

Köppert S, et al., Front Immunol. 2018 Sep 4;9:1991. doi: 10.3389/fimmu.2018.01991. eCollection 2018.

- Mice, injected CPP, two-photon microscopy
- Liver clearance

CPP-1 CPP-2

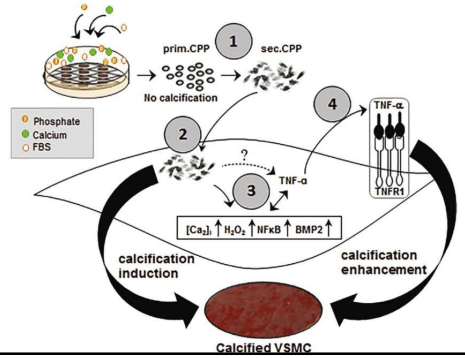




JASN 00: 1–4, 2025. doi: https://doi.org/10.1681/ASN.0000000863

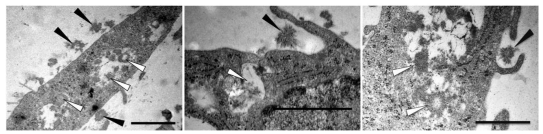
Calcification of VSM cell is induced Secondary CPP & enhanced by TNF-α

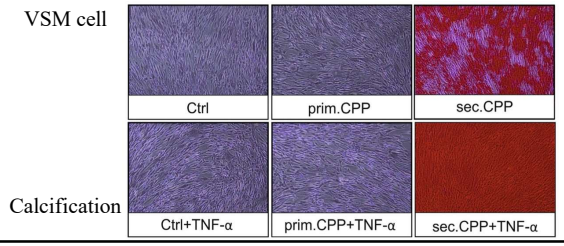
Aghagolzadeh P, Pasch A et al., Atherosclerosis 2016; 251:404-414



Calcification of VSM cell is induced Secondary CPP & enhanced by TNF-α

Aghagolzac





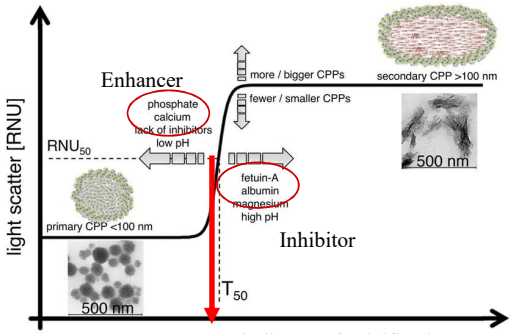
Vascular calcification

Calciprotein particles (CPPs)

Pasch A et al. JASN 2012;23:1744-1752

T50

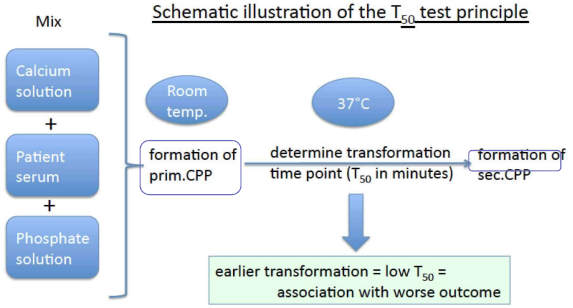
Marker of VC



T50: indicator of calcification

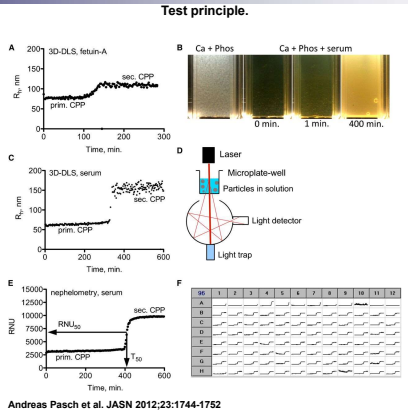
T50 *Pasch A et al. JASN 2012;23:1744-1752*

Schematic illustration of the T_{50} test principle



CPPs T_{50}

Pasch A et al. JASN 2012;23:1744-1752



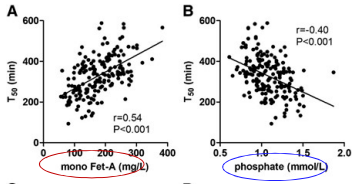
Calciprotein particles (CPPs)

Smith ER et al. JASN 2014;25:339-348

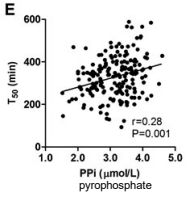
Correlation to T50

- CKD III

Marker of VC



Progress calcification



Inhibit Calcification

HD/HDF-T50

CPP-T50 improve by HD

Dekker M, Pasch A, Canaud B et al., PLoS ONE 2016;e0151508

- HF-HD(n30),
- On-line HDF(post 21.7L)(n34),
- pre/post HD

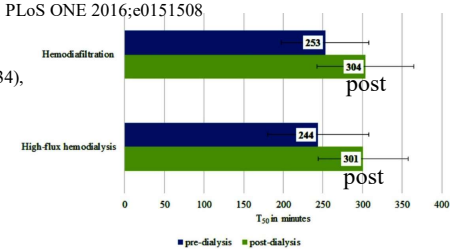


Table 8. Bivariate correlation pooled analyses of high-volume hemodiafiltration patients.

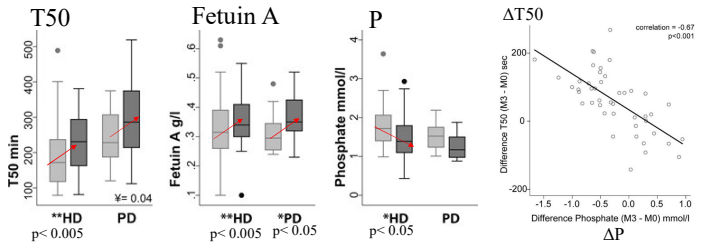
	Pre-dialysis		Post-dialysis		Delta	
	r	P	*r*	P	*r*	P
T_{50} (min) and phosphate (mmol/L)	-0.035	0.73	**-0.227**	**0.03**	**-0.396**	**<0.0001**
T_{50} (min) and magnesium (mmol/L)	**0.261**	**0.01**	0.080	0.44	-0.041	0.25
T_{50} (min) and calcium (mmol/L)*	-0.089	0.39	-0.186	0.07	0.011	0.92
T_{50} (min) and albumin (g/L)	**0.416**	**<0.001**	**0.493**	**<0.001**	0.084	0.42
T_{50} (min) and fetuin-A (g/L)	**0.671**	**<0.001**	**0.764**	**<0.001**	0.144	0.16
T_{50} (min) and bicarbonate (mmol/L)	0.238	0.18				
ΔT_{50} (min) and dialysate bicarbonate (mmol/L)	**0.377**	**0.03**				

Dialysis intiation -T50

Dialysis initiation improves calcification propensity

Belen Ponte B et al., NDT 2020;35:495–502,

- HD 46, PD 12, initiation / 3 months



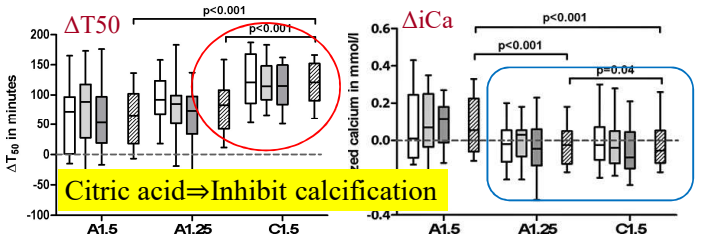
Citric-acid dialysate -T50

Citric-acid dialysate improves the calcification propensity

Ter Meulen KJ et al,. PLoS One. 2019 Dec 5;14(12):e0225824.

Multicenter Prospective Randomized Cross-Over Trial, N: 20

- A 1.5: Ca 3.0mEq/L, acetate 3.0, Mg 0.5mmol/l,
- A 1.25: Ca 2.5mEq/L acetate 3.0, Mg 0.5mmol/l
- C 1.5: Ca 3.0mEq/L. citric acid 1.0, Mg 0.5mmol/l
- Cross-Over: A1.5→A1.25/C1.5 →C1.5/A1,25



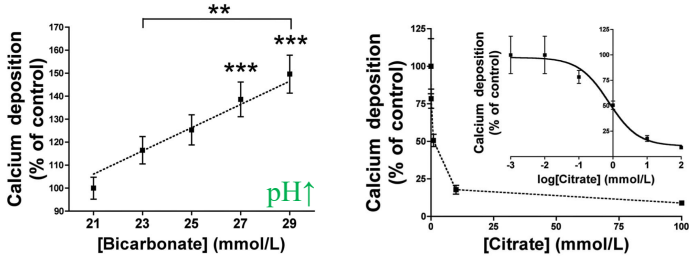
Citric acid⇒Inhibit calcification

Citric acid dialysate-calcification

Citric acid dialysate: Inhibit calcification

Villa-Bellosta R et al., Scientific Reports | (2019) 9:11374

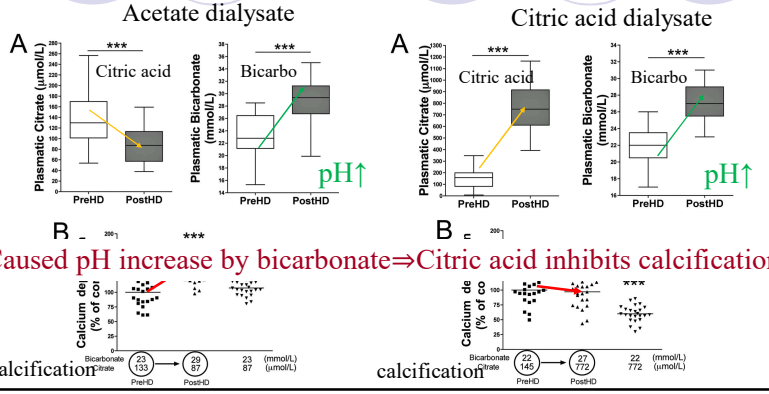
- Citric acid: citrate 1 mmol/L without acetate, bicarbonate 35 mmol/l
- Acetate: acetate 3–4 mmol/L, bicarbonate 35 mmol/l
- Culture rats aortic rings +Serum(^{45}Ca radiotracer) = Calcification



Citric acid dialysate-calcification

Citric acid dialysate: Inhibit calcification

Villa-Bellosta R et al., Scientific Reports | (2019) 9:11374



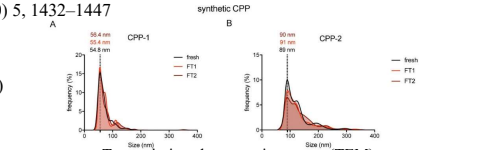
Caused pH increase by bicarbonate⇒Citric acid inhibits calcification:

CPP analysis : Radius,

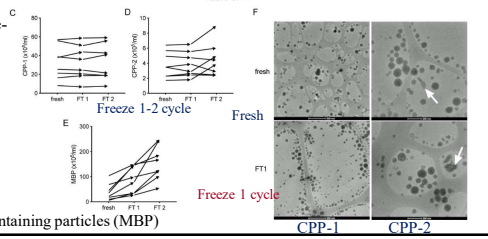
Direct measure: Calciprotein Particles in HD

Smith ER et al., Kidney Int Rep (2020) 5, 1432–1447

- Freeze-thaw (FT) cycles (25ºC-> -80ºC -> 25ºC x2)
- CPP-1 and CPP-2 are stable to a single freeze thaw,
- MBP counts increase markedly following freeze-thaw cycling.



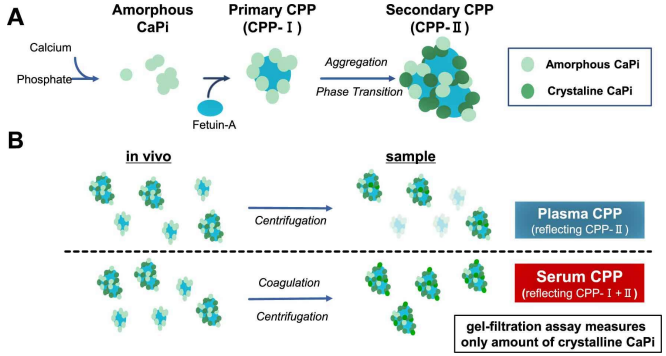
Transmission electron microscopy (TEM)



Membrane bound mineral-containing particles (MBP)

Direct analysis of CPP

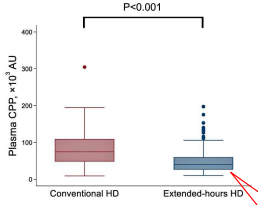
Nishibori N….Kuro-o M….Maruyama S et al., Clinical Kidney Journal , 2024, vol. 17, no. 6, sfae121



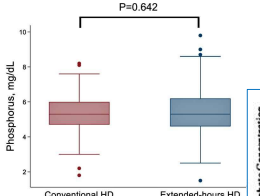
CPP & extended-hours HD

Nishibori N….Kuro-o M….Maruyama S et al., Clinical Kidney Journal , 2024, vol. 17, no. 6, sfae121

CPP-II Plasma

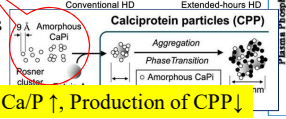


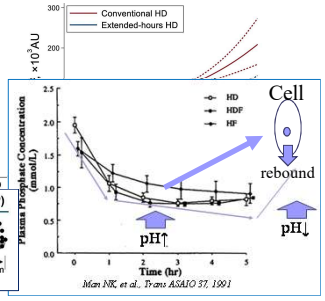
Serum P



3–5 hours n = 197

> 6 hours n = 185



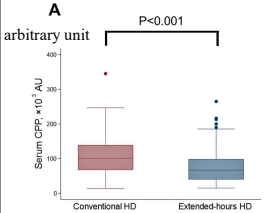


Removal volume of Ca/P ↑, Production of CPP↓

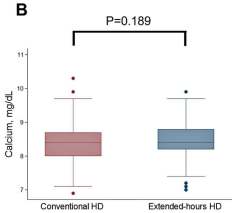
CPP & extended-hours HD

Nishibori N….Kuro-o M….Maruyama S et al., Clinical Kidney Journal , 2024, vol. 17, no. 6, sfae121

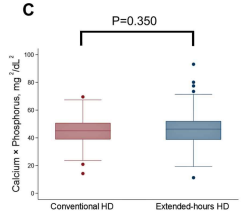
CPP-I+II Serum



P



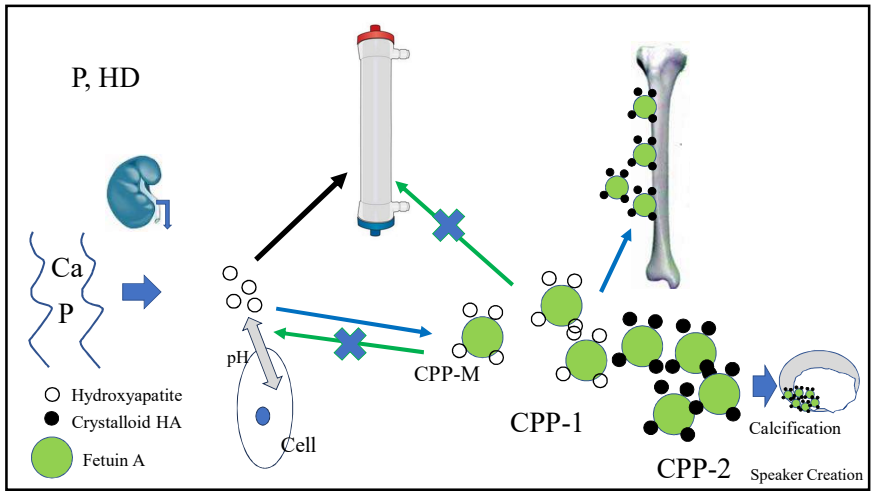
CaxP



3–5 hours n = 197

> 6 hours n = 185

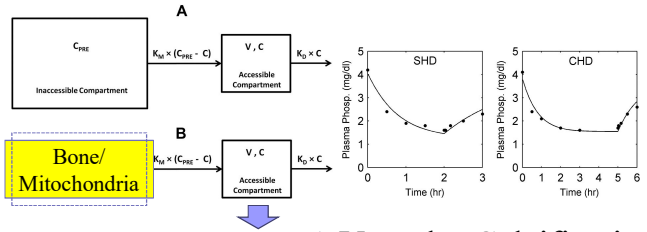
P rebounds during long-term HD



Kinetic Model of Phosphorus Mobilization during and after Short and Conventional Hemodialysis

Agar BU, Leypoldt JK et al., CJASN2011; 6: 2854-2860

- Pseudo-one-compartment model



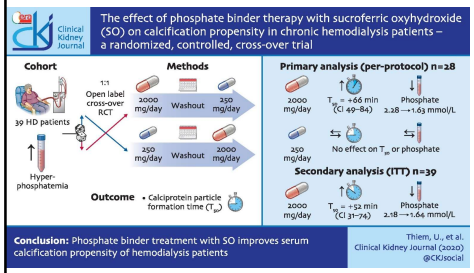
CPP ⇨ Vascular Calcification

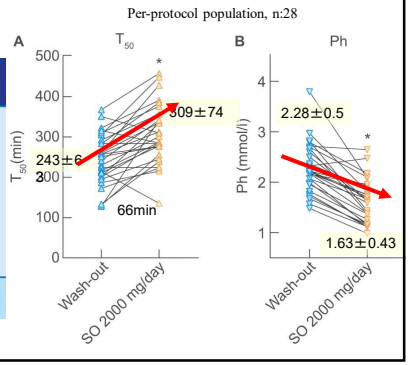
CPP/HD

CPP; Sucroferric oxyhydroxide

Thiem U et al., Clinical Kidney Journal, 2021;14:631–638

- HD-pts, n:39, RCT, crossover
- Sucroferric oxyhydroxide 2000mgday vs 250mg/day



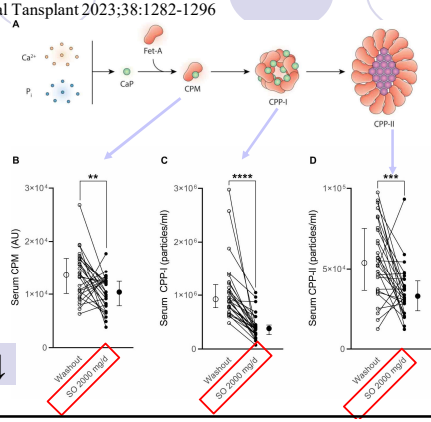


CPP/Sucroferric oxyhydroxide

CPP; Sucroferric oxyhydroxide

Thiem U et al. Nephrol Dial Tansplant 2023;38:1282-1296

- Novel fluorescent probe–based flow cytometric assay



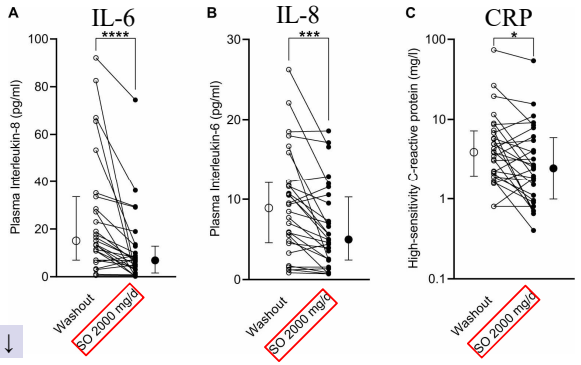
SO→CPP ↓

CPP/Sucroferric oxyhydroxide

CPP; Sucroferric oxyhydroxide

Thiem U et al., Nephrol Dial Tansplant 2023;38:1282-1296

- Novel fluorescent probe–based flow cytometric assay



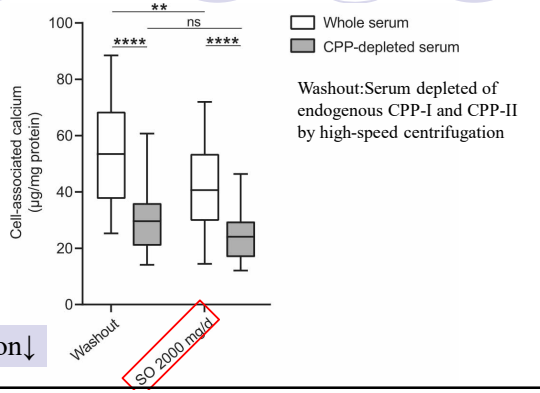
SO→CPP↓ → Cytokine ↓

CPP/Sucroferric oxyhydroxide

CPP; Sucroferric oxyhydroxide

Thiem U et al., Nephrol Dial Tansplant 2023;38:1282-1296

- Novel fluorescent probe–based flow cytometric assay
- Culture VSMC+CPP
- Calcification



Washout:Serum depleted of endogenous CPP-I and CPP-II by high-speed centrifugation

SO→VSMC calcification↓

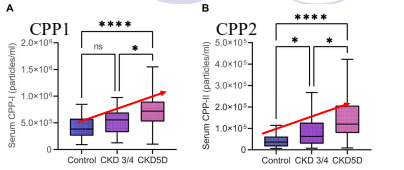
CPP/Sucroferric oxyhydroxide

CPP; Sucroferric oxyhydroxide

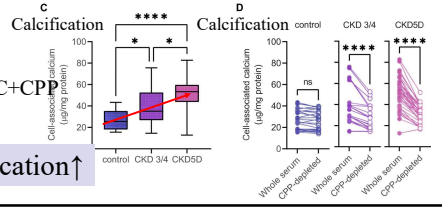
Thiem U et al., Nephrol Dial Tansplant 2023;38:1282-1296

- Novel fluorescent probe–based flow cytometric assay
- CKD stage
- FLELSI cohort serum

CPP level



Culture VSMC+CPP
Calcification

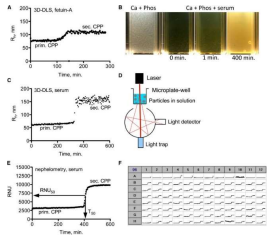


Eliminates endogenous CPPs

CKD : CPP level /calcification↑

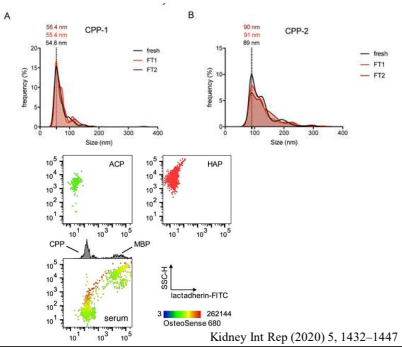
T50 & Radius

- T50 = Measure the risk of CPP formation (P, Ca, Fetuin A, alb…)
  ⇒ Predictor of prognosis



Andreas Pasch et al. JASN 2012;23:1744-1752

- Radius = Actual measurement of CPP⇒ Risk of calcification



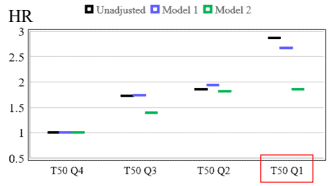
Kidney Int Rep (2020) 5, 1432–1447

T50/CKD

CKD, T50 and CAC

Bundy JD et al., AJKD 2019;76:806-814

- CRIC study: eGFR 20-70mL/min
- CAC (Coronary Artery Calcification) score
- T50



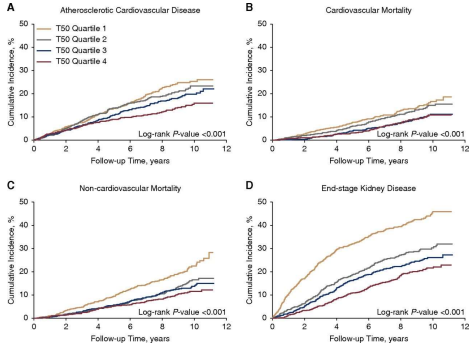
	Continuous: Per 1-SD[a] ↓ T_{50}	Categorical T_{50} Q4 (≥367 min)	T_{50} Q3 (322-366 min)	T_{50} Q2 (271-321 min)	T_{50} Q1 (≤270 min)	*P* for Linear Trend
Participants With Baseline CAC > 0 (n = 460): Increase ≥ 100 Agatston U/y, RR (95% CI)						
n/N[b]		12/113	20/114	23/118	34/115	
Unadjusted	1.48 (1.25-1.74)	1.00 (reference)	1.72 (0.88-3.37)	1.86 (0.97-3.57)	2.86 (1.55-5.25)	<0.001
Model 1[c]	1.46 (1.24-1.73)	1.00 (reference)	1.73 (0.92-3.26)	1.94 (1.11-3.39)	2.66 (1.53-4.62)	<0.001
Model 2[d]	1.28 (1.07-1.53)	1.00 (reference)	1.39 (0.72-2.69)	1.81 (1.05-3.12)	1.86 (1.05-3.32)	0.02
Participants With Baseline CAC > 0 (n = 460): Increase ≥ 200 Agatston U/y, RR (95% CI)						
n/N[b]		4/113	4/114	12/118	17/115	
Unadjusted	1.98 (1.48-2.65)	1.00 (reference)	1.03 (0.27-4.03)	2.91 (0.97-8.74)	4.29 (1.49-12.35)	<0.001
Model 1[c]	1.92 (1.39-2.66)	1.00 (reference)	1.03 (0.31-3.35)	3.15 (1.34-7.38)	3.08 (1.27-7.47)	0.003
Model 2[d]	1.81 (1.36-2.41)	1.00 (reference)	1.19 (0.33-4.32)	3.30 (1.53-7.13)	2.95 (1.25-6.97)	0.005

T50/CKD

CKD, T50 and CVD, Event

Bundy JD et al., CJASN 2019, 14 1562-1571

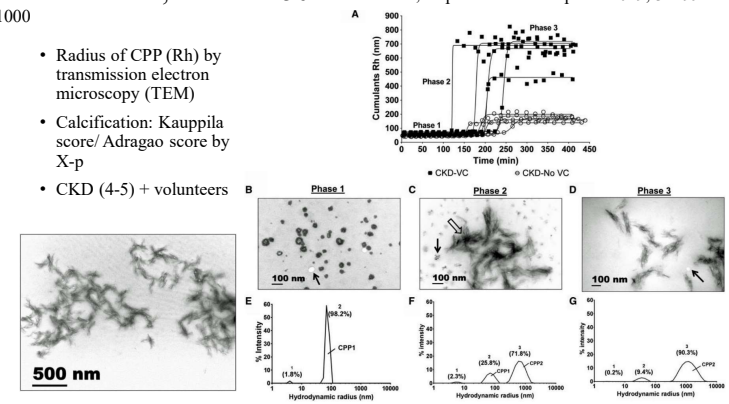
- CRIC study: eGFR 20-70mL/min
- Event CVD
- T50



CPP/CKD: Radius

Radius of CPP, but not T50 Chen W et al., Nephrol Dial Transplant: 2019; 34: 992–1000

- Radius of CPP (Rh) by transmission electron microscopy (TEM)
- Calcification: Kauppila score/ Adragao score by X-p
- CKD (4-5) + volunteers



CPP/CKD: Radius

Radius of CPP, but not T50 Chen W et al., Nephrol Dial Transplant: 2019; 34: 992–1000

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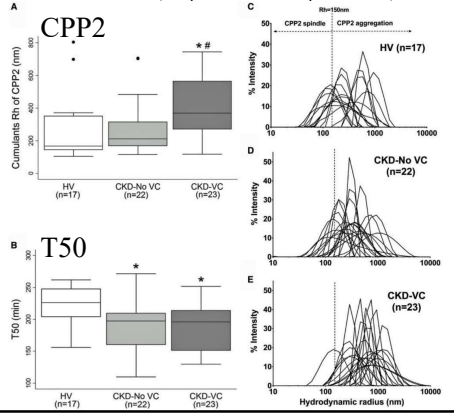


Serum CPP Size and T50 with Arterial Calcification, Arterial Stiffness, and Mortality in Incident Hemodialysis Patients

Chen W et al., Am J Kidney Dis. doi: 10.1053/j.ajkd.2020.05.031

CPP/CKD: mortality

- Incident HD patients (n = 402 CPP2/ n = 388 T50)
- Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study

Exploratory Analysis of CPP2 Size and T_{50} With All-Cause Mortality

	CPP2 Size (per 100 nm)				T_{50} (per 100 min)			
	Participants	Deaths	HR (95% CI)	*P*	Participants	Deaths	HR (95% CI)	*P*
Unadjusted	402	188	1.14 (1.04-1.24)	0.01	388	182	0.94 (0.83-1.06)	0.3
Model 1	372	169	1.17 (1.05-1.31)	0.004	358	163	0.93 (0.82-1.07)	0.3
Model 2	367	167	1.14 (1.01-1.28)	0.03	353	161	0.98 (0.85-1.13)	0.8
Model 3	367	167	1.21 (1.07-1.38)	0.003	353	161	0.97 (0.84-1.13)	0.7
Model 4	351	158	1.14 (1.02-1.28)	0.02	337	152	0.94 (0.81-1.08)	0.4
Model 5	370	168	1.17 (1.05-1.31)	0.005	356	162	0.94 (0.82-1.07)	0.4

Note: Cox proportional hazard models were used. A total of 195 individuals died after a median follow-up of
race), comorbid conditions (diabetes and coronary artery disease). Model 2 adjusted for demographics, co
(calcium, phosphoros, and fibroblast growth factor 23). Model 3 adjusted for demographics, comorbid condit
for demographics, comorbid conditions, and dp-MGP and osteoprotegerin levels. Model 5 adjusted for dem
Abbreviations: CI, confidence interval; CPP2, secondary calciprotein particle; HR, hazard ratio; T_{50}, half-m

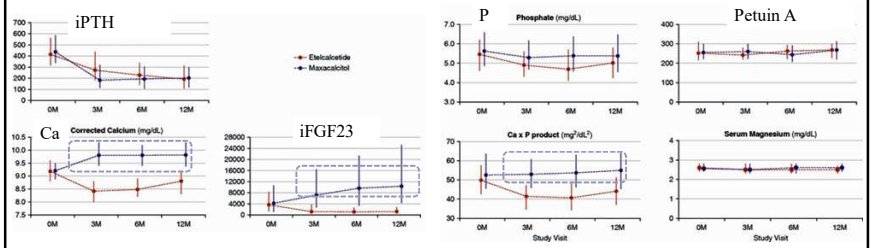
Model 1: age, sex, race, DM, coronary artery
Model 2: + Ca, P, FGF-23
Model 3: + albumin, fetuin-A
Model 4: + dp-MGP, osteoprotegerin
Model 5: +CRP

Comparative Effects of Etelcalcetide and Maxacalcitol on Serum Calcification Propensity in Secondary Hyperparathyroidism

Shoji T et al., Clin J Am Soc Nephrol 2021;16:599-612

T50:Calcimimetics vs VD

- Calcimimetics (Etelcalcetide 167) vs VDR (Maxacalcitol 159), T50
- RCT, multicenter, open-label, blinded end point trial
- IV etelcalcetide 5 mg thrice weekly or IV maxacalcitol 5 or 10 μg thrice weekly



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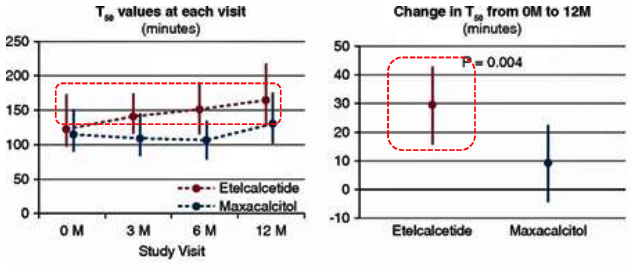
Shoji T et al., Clin J Am Soc Nephrol 2021;16:599-612

T50:Calcimimetics vs VD

- Calcimimetics (Etelcalcetide 167) vs VDR (Maxacalcitol 159), T50

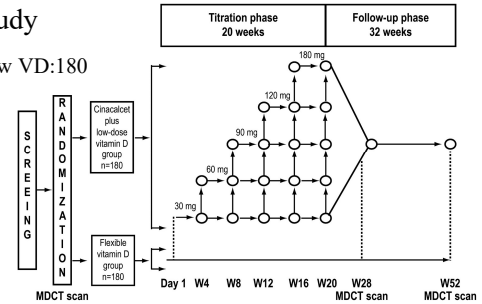


Cinacalcet-HCL : vascular calcification

Raggi P et al., NDT 2011; 26:1327-1339

- ADVANCE study

Cinacalcet+Low VD:180

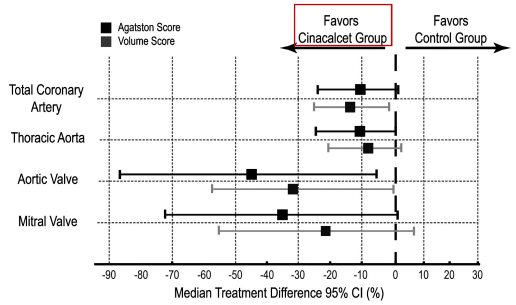


Conventional dose VD:180

Cinacalcet-HCL: vascular calcification

Raggi P et al., NDT 2011; 26:1327-1339

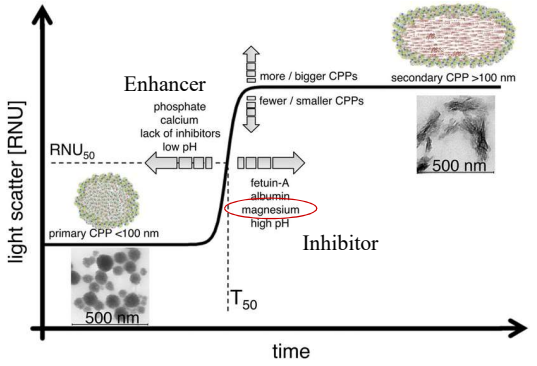
- ADVANCE study



Vascular calcification

Calciprotein particles (CPPs)

Pasch A et al. JASN 2012;23:1744-1752

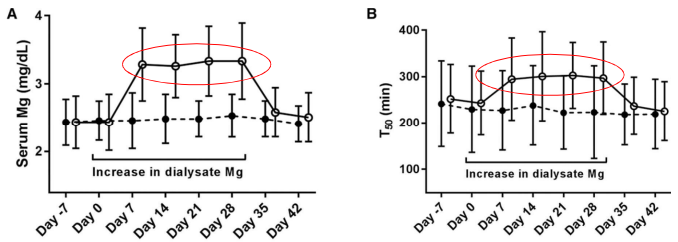


Mg / calcification

Dialysate Magnesium on CPPs, RCT

Bressendorff I, Pasch A et al., Clin J Am Soc Nephrol 13, 2018. doi: https://doi.org/10.2215

- Dialysate Mg 1.0mEq/L vs 2.0, RCT n 29: 30



Mg / calcification

Dialysate Magnesium on CPPs, RCT

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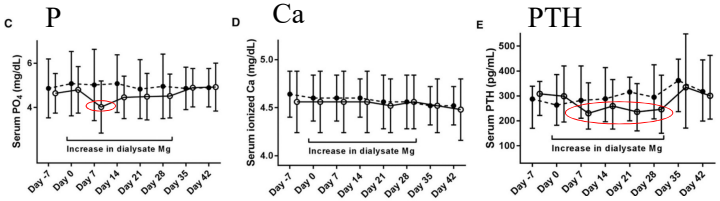
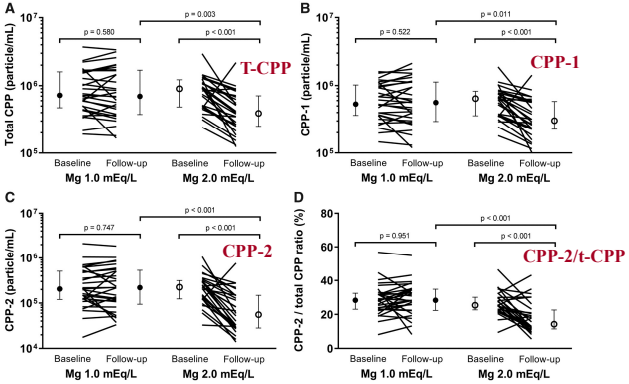


Mg / CPP

Dialysate Magnesium on CPPs, RCT, *post hoc analysis*

Bressendorff I, Pasch A et al., Nephrol Dial Transplant (2021) 36: 713–721

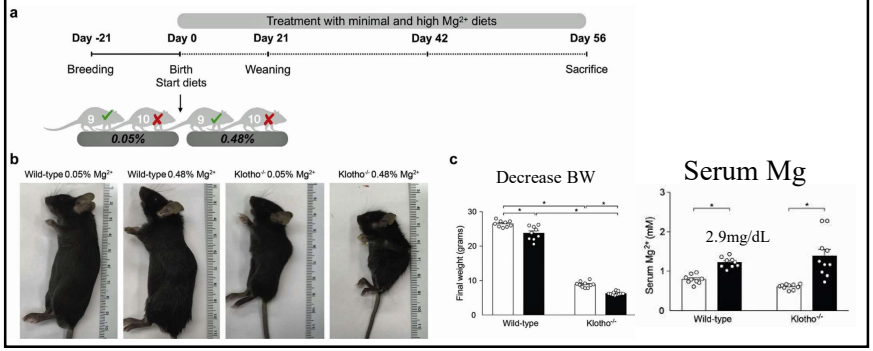


Mg / calcification

Magnesium prevents vascular calcification

Anique D. ter Braake et al., Kidney Intern (2020) 97, 487–501

- Klotho knock-out mice + high Mg diet

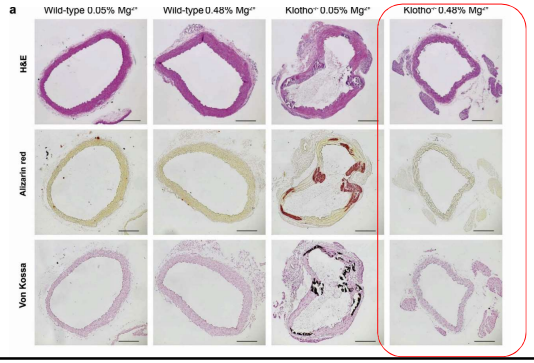


Mg / calcification

Magnesium prevents vascular calcification

Anique D. ter Braake et al., Kidney Intern (2020) 97, 487–501

- Klotho knock-out mice + high Mg diet → Suppression of calcification

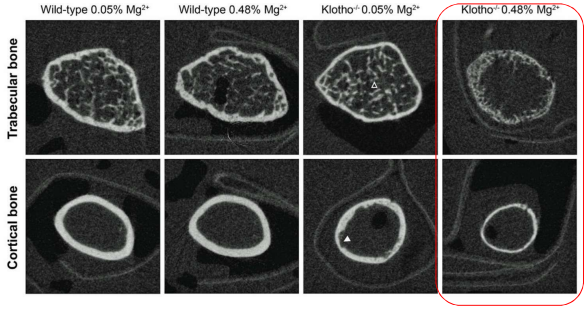


Mg / bone formation

Magnesium prevents vascular calcification

Anique D. ter Braake et al., Kidney Intern (2020) 97, 487–501

- Klotho knock-out mice + high Mg diet → Decrease Mineralization

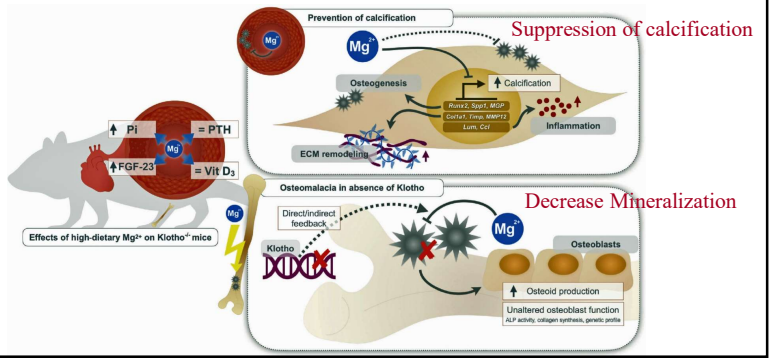


Mg / Double-sided action

Magnesium prevents vascular calcification

Anique D. ter Braake et al., Kidney Intern (2020) 97, 487–501

- Klotho knock-out mice + high Mg diet

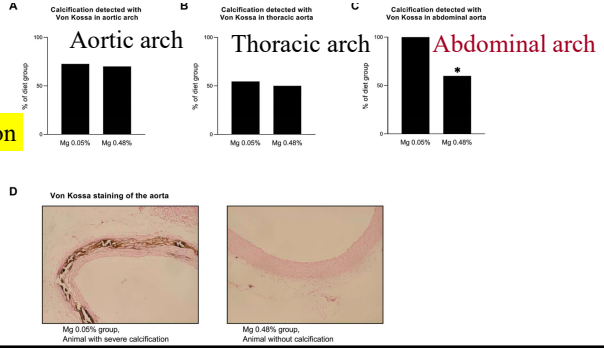


Dietary magnesium, vascular calcification in animal model of CKD

Leenders NHJ et al. NDT 2022; 37:1049-1058

- Rat Partial nephrectomy: diet P1.2% + Mg 0.05% vs 0.48%

Calcification



Dietary magnesium, vascular calcification in animal model of CKD

Leenders NHJ et al. NDT 2022; 37:1049-1058

Table S2. Micro-computed tomography analysis of femoral bone in partially nephrectomized rats fed either a high or normal magnesium diet.

Bone mineralization

	0.05% Mg diet n=6	0.48% Mg diet n=7	p-value
Femur length (mm)	38 ± 5	42 ± 4	0.08
Trabecular bone			
Bone mineral density, BMD (g/cm²)	0.58 ± 0.06	0.38 ± 0.14	0.01
Bone volume fraction, BV/TV (%)	57 ± 6	35 ± 17	0.02
Trabecular separation, Tb.Sp (mm)	0.11 ± 0.01	0.21 ± 0.18	0.22
Trabecular thickness, Tb.Th (mm)	0.10 ± 0.01	0.07 ± 0.01	<0.01
Trabecular number, Tb.N (1/mm)	8.1 ± 0.7	6.8 ± 3.7	0.47
Cortical bone			
Tissue mineral density, TMD (g/cm²)	1.09 ± 0.04	1.07 ± 0.10	0.74
Total area inside periostial envelope, Tt.Ar (mm²)	16 ± 3	20 ± 9	0.34
Cortical bone area, Ct.Ar (mm²)	12 ± 2	16 ± 11	0.43
Cortical area fraction, Ct.Ar/Tt.Ar (%)	76 ± 6	72 ± 20	0.66
Cortical thickness including pores, Ct.Th.iPo (mm)	1.05 ± 0.15	1.11 ± 0.51	0.80
Cortical thickness bone only, Ct.Th.ePo (mm)	0.15 ± 0.03	0.28 ± 0.21	0.19
Porosity fraction, Po.V/Ct.V (%)	26 ± 7	22 ± 22	0.72

Micro-CT showed abnormal high cortical porosity or cortical trabecularization and dense trabecular bone with an abnormal appearance in femurs from rats of both diet groups。

A normal morphological appearance of femurs was observed in some of the animals in the high dietary magneium group (43%) but not in the normal magnesium group

Dietary magnesium, vascular calcification in animal model of CKD

Leenders NHJ et al. NDT 2022; 37:1049-1058

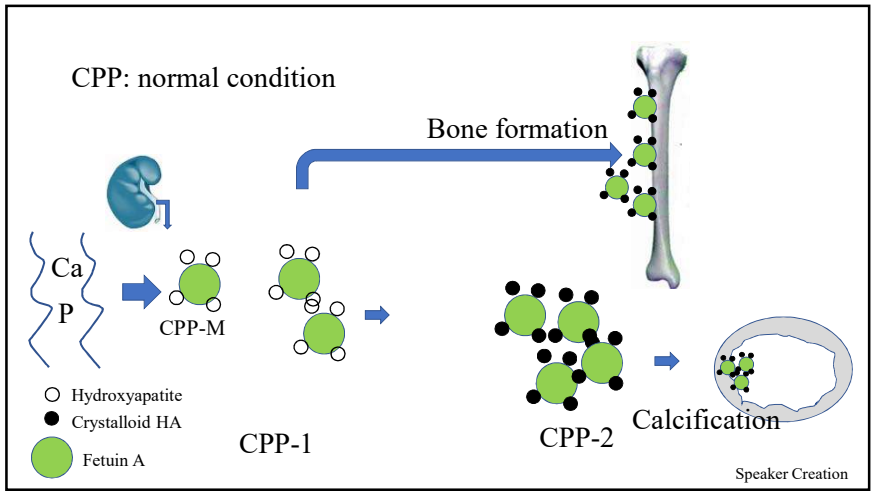
- Rat Partial nephrectomy: diet P1.2% + Mg 0.05% vs 0.48%

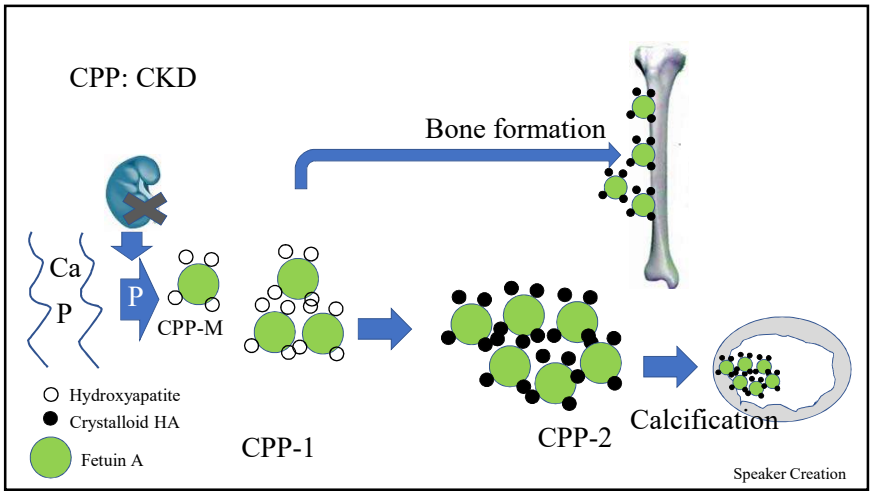
Table 3. Electrolytes 8 weeks after nephrectomy

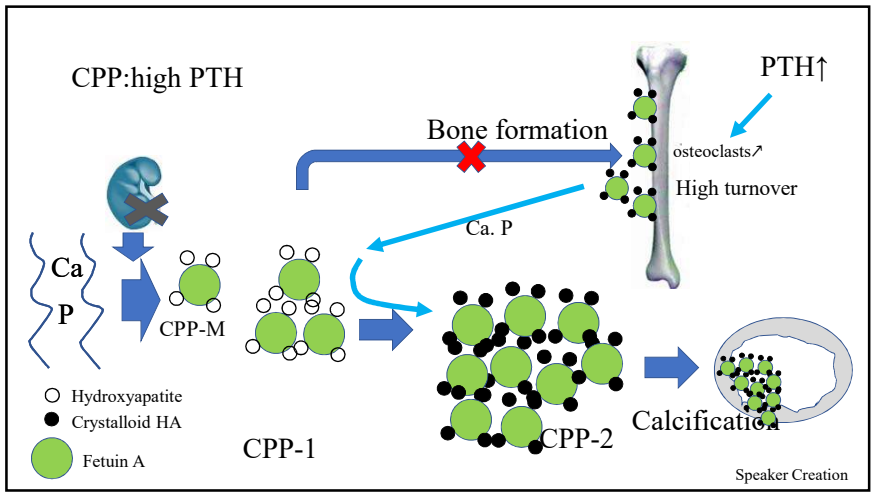
Electrolytes	0.05% w/w Mg diet	0.48% w/w Mg diet	P-value
Week 8 ($n = 21$)			
Plasma concentrations			
Magnesium (mmol/L)	0.67 ± 0.13	1.27 ± 0.34	<0.01
Calcium (mmol/L)	2.34 ± 0.35	2.33 ± 0.39	0.94
Albumin (mmol/L)	13 ± 4	15 ± 3	0.23
Phosphate (mmol/L)	5.1 ± 1.5	4.3 ± 1.5	0.23
Week 8—only animals that were housed in metabolic cages ($n = 10$)			
Plasma concentrations			
Magnesium (mmol/L)	0.68 ± 0.17	1.25 ± 0.34	0.01
Calcium (mmol/L)	2.17 ± 0.43	2.39 ± 0.21	0.33
Albumin (mmol/L)	12 ± 5	15 ± 2	0.25
Phosphate (mmol/L)	5.7 ± 1.8	4.4 ± 1.0	0.18
Urine excretion			
Magnesium (mmol/24 h)	0.11 ± 0.03	0.58 ± 0.07	<0.01
Calcium (mmol/24 h)	0.04 ± 0.02	0.02 ± 0.01	0.18
Phosphate (mmol/24 h)	5.4 ± 2.2	6.4 ± 1.8	0.48

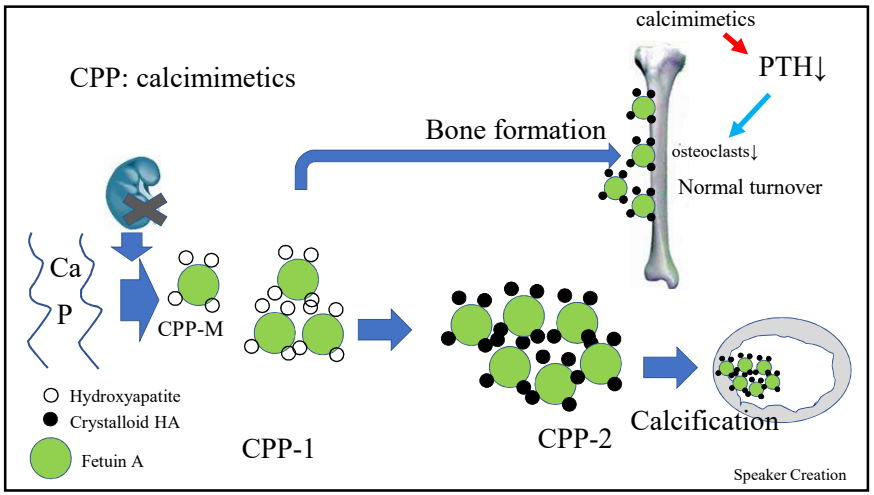
Values are expressed as mean ± SD.

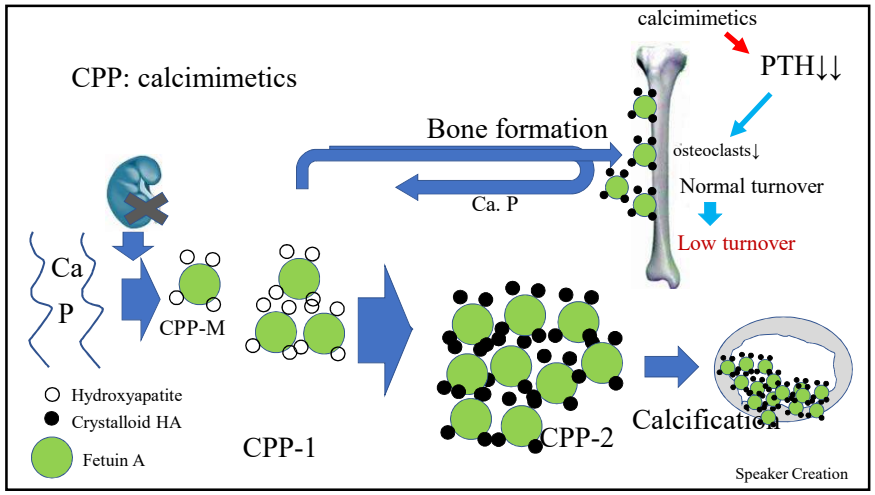
1.62 vs 3.08mg/dl

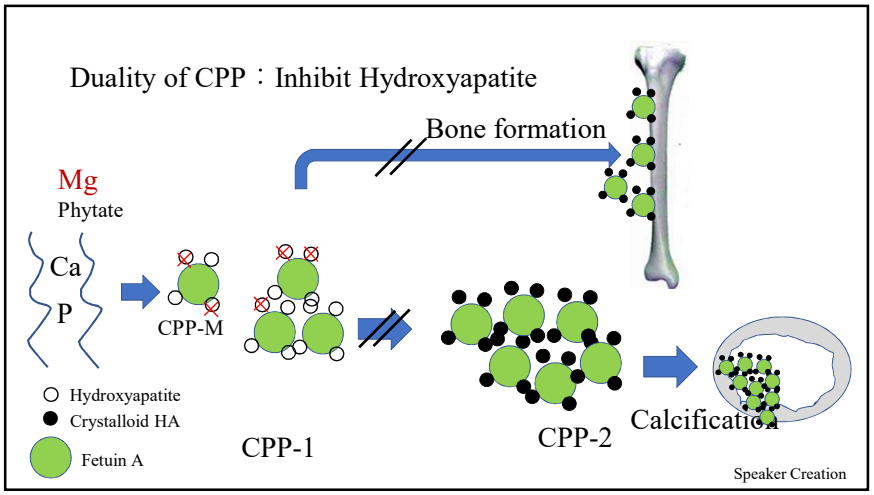

CPP: normal condition
Bone formation
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation

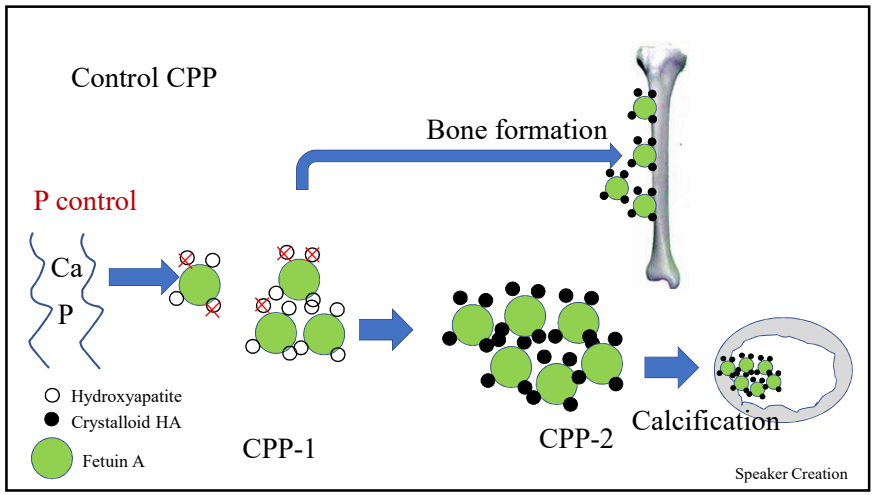

CPP: CKD
Bone formation
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation

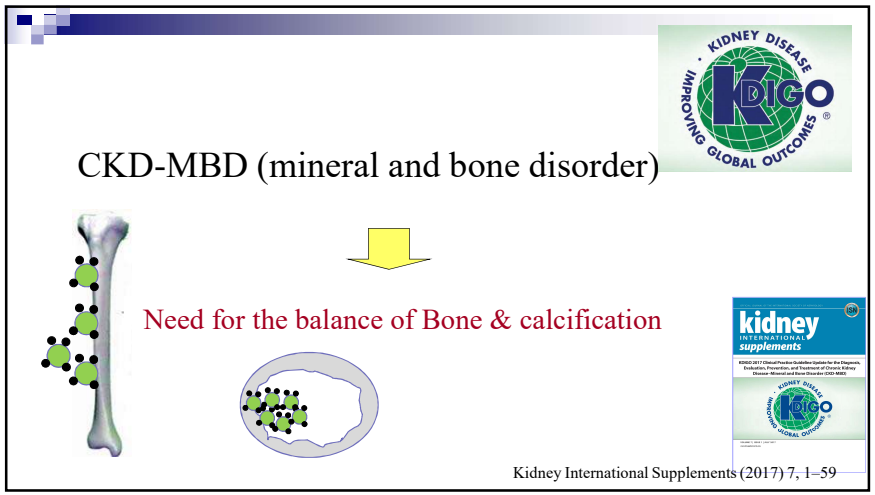

CPP:high PTH
PTH↑
Bone formation
osteoclasts↗
High turnover
Ca. P
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation


calcimimetics
CPP: calcimimetics
PTH↓
Bone formation
osteoclasts↓
Normal turnover
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation

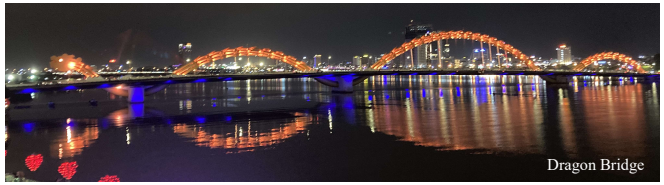

CPP: calcimimetics
calcimimetics
PTH↓↓
Bone formation
osteoclasts↓
Normal turnover
Ca. P
Low turnover
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation


Duality of CPP：Inhibit Hydroxyapatite
Bone formation
Mg
Phytate
Ca
P
CPP-M
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation


Control CPP
Bone formation
P control
Ca
P
Hydroxyapatite
Crystalloid HA
Fetuin A
CPP-1
CPP-2
Calcification
Speaker Creation


CKD-MBD (mineral and bone disorder)
Need for the balance of Bone & calcification
kidney
Kidney International Supplements (2017) 7, 1–59

Thank you for your attention


Dragon Bridge

If you have any questions, e-mail to

h-kawanishi@tsuchiya-hp.jp


Miyajima/ Hiroshima