MINERAL METABOLISM DISTURBANCES IN KIDNEY DISEASE

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KIDNEY RESEARCH INSTITUTE

MINERAL METABOLISM DISTURBANCES IN KIDNEY DISEASE

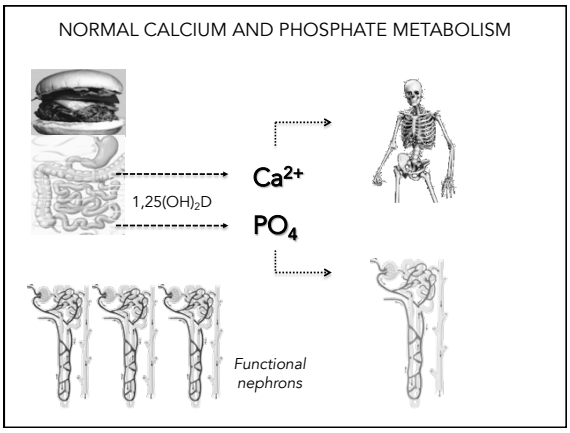
Pathogenesis of mineral metabolism disorders in kidney disease

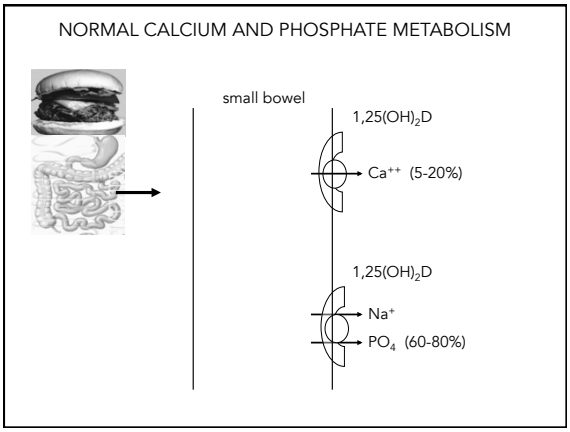
Suspected clinical consequences of mineral metabolism disorders

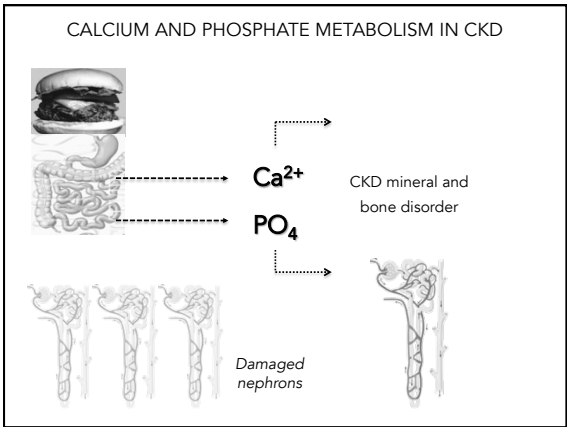
Evidence for treatment of mineral metabolism disorders

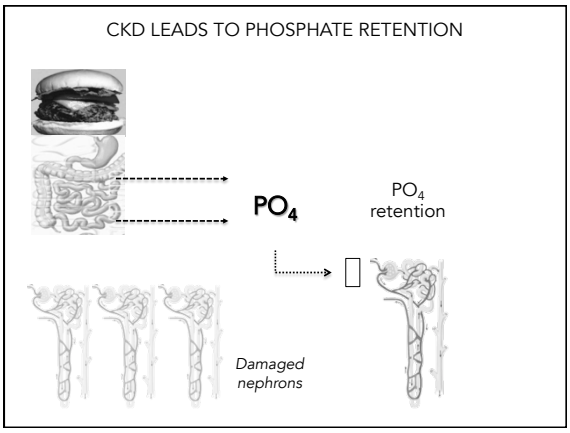
MINERAL METABOLISM DISTURBANCES IN KIDNEY DISEASE

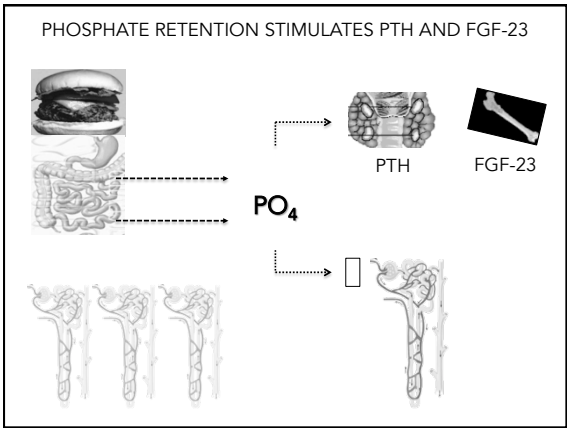
PATHOGENESIS

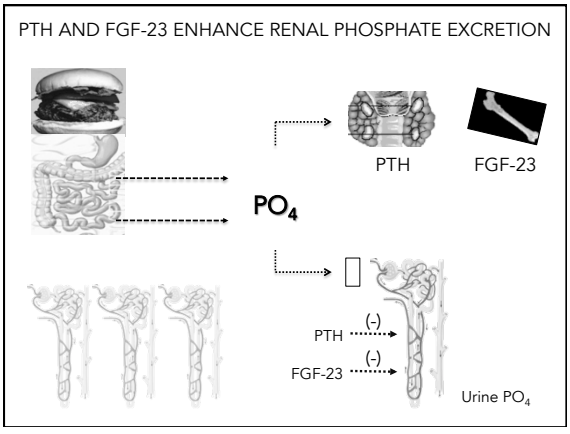

NORMAL CALCIUM AND PHOSPHATE METABOLISM
Ca^{2+}
$1,25(OH)_2D$
PO_4
Functional nephrons


NORMAL CALCIUM AND PHOSPHATE METABOLISM
small bowel
$1,25(OH)_2D$
Ca^{++} (5-20%)
$1,25(OH)_2D$
Na^+
PO_4 (60-80%)

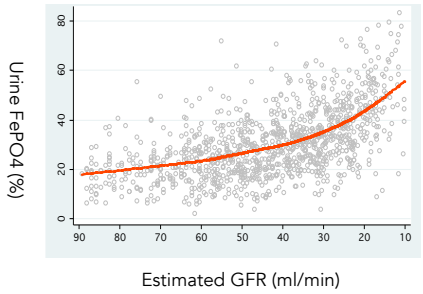

CALCIUM AND PHOSPHATE METABOLISM IN CKD
Ca^{2+}
PO_4
CKD mineral and bone disorder
Damaged nephrons


CKD LEADS TO PHOSPHATE RETENTION
PO4
PO4 retention
Damaged nephrons


PHOSPHATE RETENTION STIMULATES PTH AND FGF-23
PTH
FGF-23
PO4


PTH AND FGF-23 ENHANCE RENAL PHOSPHATE EXCRETION
PTH
FGF-23
PO4
PTH
(-)
FGF-23
(-)
Urine PO4

FRACTIONAL PHOSPHATE EXCRETION INCREASES IN CKD



Seattle Kidney Study N=353

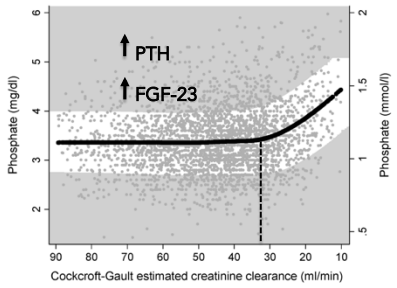
PHOSPHATE RETENTION THEORY OF CKD-MBD

Chronic nephron loss leads to phosphate retention

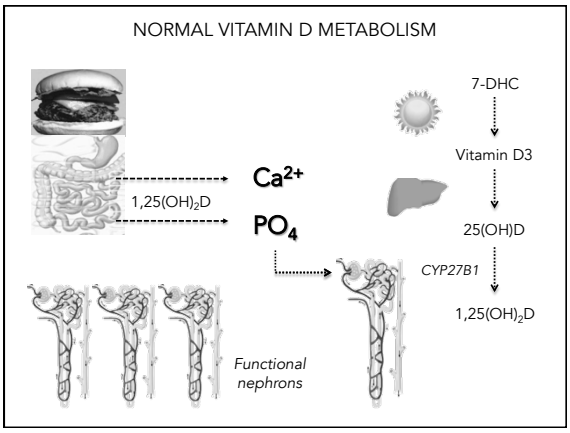
PO_4 retention stimulates phosphaturic hormones PTH and FGF-23

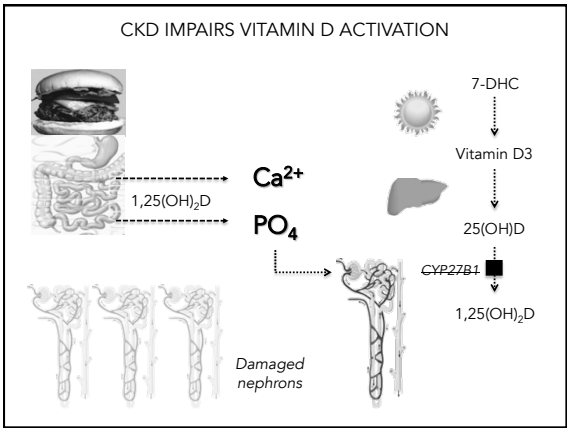
PTH and FGF-23 enhance renal PO_4 excretion by proximal tubules

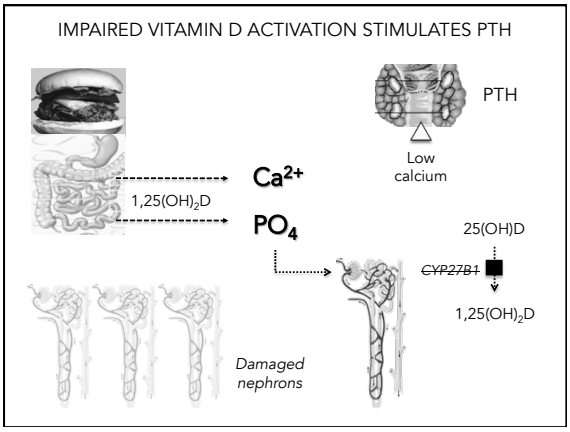
PHOSPHATE RETENTION THEORY OF CKD-MBD



Kestenbaum et al JASN 2005


NORMAL VITAMIN D METABOLISM
7-DHC
Vitamin D3
25(OH)D
CYP27B1
1,25(OH)2D
Ca2+
PO4
1,25(OH)2D
Functional nephrons


CKD IMPAIRS VITAMIN D ACTIVATION
7-DHC
Vitamin D3
25(OH)D
CYP27B1
1,25(OH)2D
Ca2+
PO4
1,25(OH)2D
Damaged nephrons


IMPAIRED VITAMIN D ACTIVATION STIMULATES PTH
PTH
Low calcium
25(OH)D
CYP27B1
1,25(OH)2D
Ca2+
PO4
1,25(OH)2D
Damaged nephrons

VITAMIN D THEORY OF CKD-MBD

Chronic nephron loss impairs $1,25(OH)_2D$ synthesis by kidneys

Inadequate $1,25(OH)_2D$ reduces intestinal Ca^{2+} and PO_4 absorption

Lower serum calcium concentrations stimulate PTH

CKD-MBD IS COMPLEX CONSTELLATION OF FINDINGS

Chronic kidney disease mineral bone disorder (CKD-MBD)

- Imbalances in mineral levels and reflexive hormones
- Serum phosphate, PTH, FGF-23 concentrations elevated
- Serum calcium and 1,25(OH)2D concentrations reduced
- Potential consequences for bone and cardiovascular health

MINERAL METABOLISM DISTURBANCES IN CKD

CLINICAL CONSEQUENCES

MINERAL METABOLISM DISTURBANCES IN CKD

Consequences

- High phosphate
- High PTH
- High FGF-23
- Low $1,25(OH)_2D$

Suspected links with disease

Associations with outcomes

PO_4 STIMULATES CALCIFICTION IN EXPERIMENTAL MODELS

Smooth muscle cells

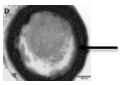
Exogenous phosphate

Runx2
Alkaline phosphatase

Jono, Circ Res 2000

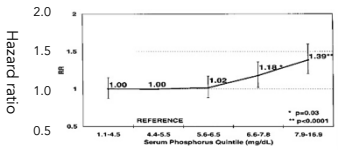
Chronic kidney disease

Dietary phosphate



El-Abbadi, KI 2009

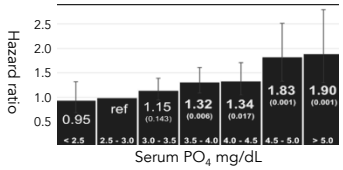
HIGHER SERUM PO_4 LEVELS ASSOCIATED WITH MORTALITY



Serum PO_4 mg/dL

Hemodialysis patients

Block AJKD 1998



Serum PO_4 mg/dL

CKD patients

Kestenbaum JASN 2005

IMPROVED OUTCOMES AFTER PARATHYROIDECTOMY

4,558 dialysis patients undergoing parathyroidectomy 1990-1999

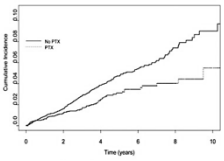
4,558 control dialysis patients not undergoing parathyroidectomy

Matched by age, race, sex, cause of ESRD, dialysis duration and modality

All-cause mortality

Time from PTX	Deaths per 1000 person-years: PTX group (N=4,558)	Control group (N=4,558)	Adjusted hazard ratio	P-value
0-30 days	385.8	148.0	2.72	<0.001
31-90 days	257.7	179.5	1.45	<0.001
91 days–1 year	159.5	184.3	0.90	0.031
1 year–3 years	145.8	177.5	0.85	<0.001
> 3 years	147.8	174.0	0.85	0.014

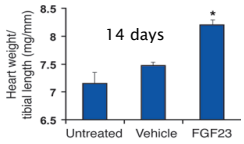
Hip fracture

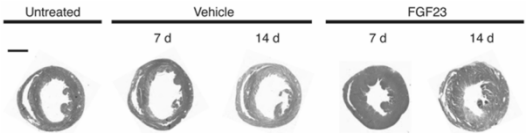


Rudser KI 2004

FGF-23 STIMULATES CARDIOMYOCYTE GROWTH

Intra-myocardial injection with rFGF-23 in mice



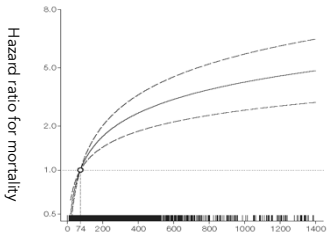


Faul JCI 2011

FGF-23 ASSOCIATED WITH MORTALITY

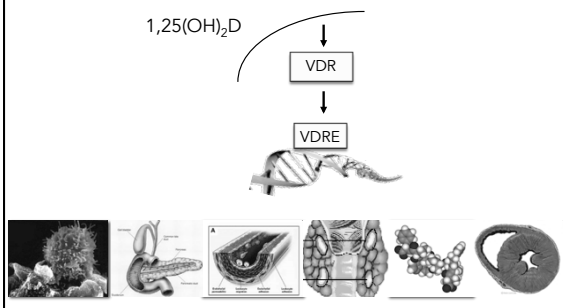
Chronic Renal Insufficiency Cohort Study (CRIC)

3,879 CKD patients

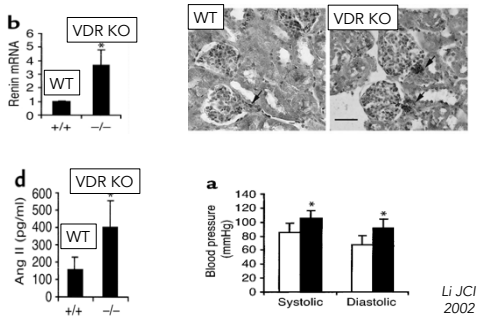


Isakova JAMA 2011

CALCITRIOL MODULATES *MANY* GENETIC PATHWAYS



CALCITRIOL DECREASES RENIN EXPRESSION



Li JCI 2002

MINERAL METABOLISM DISTURBANCES IN CKD

TREATMENT

TREATMENT OF MINERAL METABOLISM DISTURBANCES

Why treat?

- Experimental evidence for toxicity
- Associations with clinical outcomes
- Condition will progress if not treated

Should motivate careful evaluation of the risks and benefits of treatments for mineral metabolism disorders on patient outcomes

TREATMENT OF MINERAL METABOLISM DISTURBANCES

Why treat anemia in CKD?

- Experimental evidence for toxicity
- Associations with clinical outcomes
- Condition will progress if not treated

EPO raises hemoglobin levels

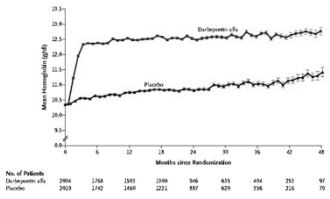
Test or treat?

TREATMENT OF MINERAL METABOLISM DISTURBANCES

Randomized trial of 4,038 diabetic CKD patients with Hg <11 g/dL

Received Aranesp or identical appearing placebo every two weeks

Careful titration of EPO dosing



Pfeffer et al NEJM 2009

TREATMENT OF MINERAL METABOLISM DISTURBANCES

Table 2. Composite and Component End Points.*

End Point	Darbepoetin Alfa (N=2012)	Placebo (N=2026)	Hazard Ratio (95% CI)	P Value†
	number (percent)			
Primary end points				
Cardiovascular composite end point‡	632 (31.4)	602 (29.7)	1.05 (0.94–1.17)	0.41
Death from any cause	412 (20.5)	395 (19.5)	1.05 (0.92–1.21)	0.48
Myocardial infarction§	124 (6.2)	129 (6.4)	0.96 (0.75–1.22)	0.73
Stroke§	101 (5.0)	53 (2.6)	1.92 (1.38–2.68)	<0.001
Heart failure§	205 (10.2)	229 (11.3)	0.89 (0.74–1.08)	0.24
Myocardial ischemia	41 (2.0)	49 (2.4)	0.84 (0.55–1.27)	0.40
Renal composite end point (ESRD or death)	652 (32.4)	618 (30.5)	1.06 (0.95–1.19)	0.29
ESRD	338 (16.8)	330 (16.3)	1.02 (0.87–1.18)	0.83

TREATMENT OF MINERAL METABOLISM DISTURBANCES

Intervention

Serum phosphate
5.5 mg/dL

Metabolism
Genetics
Diet

Serum phosphate
4.0 mg/dL

Metabolism
Genetics
Diet

TREATING HIGH PHOSPHATE LEVELS IN CKD

Kidney disease
Elevated serum PO_4

ASSIGN

PO_4 binder
Dietary restriction

Clinical events
Side effects
Patient outcomes

Placebo
No treatment

TREATING HIGH PHOSPHATE LEVELS IN CKD

Kidney disease
Elevated serum PO_4

ASSIGN

PO_4 binder
Dietary restriction

Placebo
No treatment

Clinical events
Side effects
Patient outcomes

NO trials of PO_4 binders *versus* placebo on clinical events

PHOSPHATE BINDERS LOWER SERUM PO_4 IN DIALYSIS

Poly[allylamine Hydrochloride] (RenaGel): A Noncalcemic Phosphate Binder for the Treatment of Hyperphosphatemia in Chronic Renal Failure

Glenn M. Chertow, MD, MPH, Steven K. Burke, MD, J. Michael Lazarus, MD, Kurt H. Stenzel, MD, Duane Wombolt, MD, Dennis Goldberg, PhD, Joseph V. Bonventre, MD, PhD, and Eduardo Slatopolsky, MD

Table 2. Selected Laboratory Data by Study Phase: Intent-to-Treat Analysis

Parameter	Baseline	Washout	Treatment	Probability Value*
Phosphorus (mg/dL)				0.037
Placebo	4.5 ± 1.8	7.0 ± 2.1	7.2 ± 2.4	
RenaGel	4.9 ± 1.7	6.6 ± 2.1	5.4 ± 1.7	
Calcium (mg/dL)				NS
Placebo	10.0 ± 0.8	9.6 ± 0.5	9.4 ± 0.6	
RenaGel	9.7 ± 1.1	9.3 ± 0.9	9.3 ± 0.6	
Bicarbonate (mEq)				NS
Placebo	22.8 ± 4.6	21.6 ± 1.6	20.9 ± 2.1	
RenaGel	21.6 ± 4.4	20.7 ± 4.1	20.4 ± 4.1	
Cholesterol (mg/dL)				0.013
Placebo	173 ± 37	171 ± 39	177 ± 35	
RenaGel	173 ± 37	165 ± 37	149 ± 32	
HDL (mg/dL)				NS
Placebo	47 ± 10	44 ± 10	48 ± 11	
RenaGel	43 ± 10	44 ± 12	45 ± 16	

NOTE. Duration of each phase = 14 ± 3 days.

DIETARY INTERVENTION LOWERS SERUM PO_4 IN DIALYSIS

279 hemodialysis patients in Northeastern Ohio

Randomly assigned to education or regular care

- 30 mins counseling on phosphate content of foods and additives
- Magnifier to read food labels
- Handouts for phosphate content at local fast food restaurants

	Baseline PO_4	**Final PO_4**	**Difference**	**P-value**
Intervention	7.2 ±1.2	6.2 ±1.7	-1.0	<0.001
Control	7.1 ±1.0	6.7 ±1.9	-0.4	0.02

Sullivan et al, JAMA 2009

PHOSPHATE BINDERS IN CKD

Phosphate Normalization Trial

eGFR 20-45 ml/min

Serum PO_4 3.5–6.0 mg/dL

PTH <500 pg/mL

- Calcium acetate (n=30)
- Lanthanum (n=30)
- Sevelamer (n=30)
- Placebo (n=58)

9 months

Drug titration to 3-4 units tid

Cholecalciferol 1000 IU/day

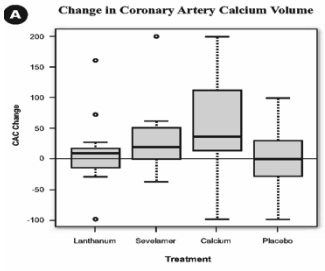
Block et al, JASN 2012

PHOSPHATE BINDERS IN CKD

	PO_4 binders (n=65)	Placebo (n=41)
24-hour urine PO_4	-22%	+1%
Serum PO_4	-0.3 mg/dL	0 mg/dL
Serum PTH	+0%	+21%
Serum FGF-23	-5%	+2% (NS)
Bone mineral density	+4%	+1%

P-values <0.05 for all differences unless otherwise noted

PHOSPHATE BINDERS IN CKD



PHOSPHATE BINDERS IN CKD

Chue, JASN 2013

109 Stage III CKD patients

Sevelamer *versus* placebo

9 months

NO changes in

- Serum PO_4
- LV mass
- LV diastolic function

Seifert, Am J Nep 2013

38 Stage III CKD patients

Lanthanum *versus* placebo

12 months

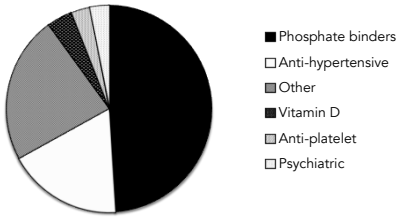
NO changes in

- Serum PO_4
- Pulse wave velocity
- Coronary calcification

PHOSPHATE BINDERS ARE A MAJOR PILL BURDEN

Prevalent U.S. dialysis patients

Daily pill burden median = 19 (IQR 14, 26)



Chiu et al, CJASN 2009

ASSOCIATION OF DIETARY PO_4 WITH OUTCOMES IN CKD

MDRD sub-study

795 CKD patients with mean GFR of 33 ml/min

Dietary PO_4 intake estimated from 24-hour urine collection

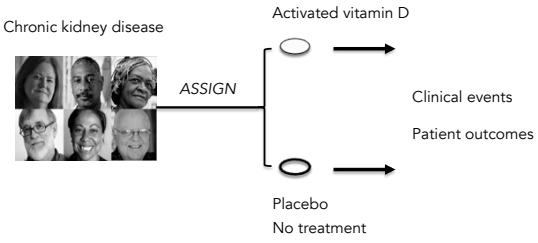
589 ESRD events and 191 CV deaths over 16 years follow-up

Selamet et al KI 2016

ASSOCIATION OF DIETARY PO_4 WITH OUTCOMES IN CKD

	Dietary PO_4 (mg/day)	ESRD Hazard ratio (95% CI)	CV mortality Hazard ratio (95% CI)
Q1	100 - 608	*reference*	*reference*
Q2	609 - 788	0.98 (0.77, 1.24)	1.12 (0.73, 1.72)
Q3	789 - 1008	1.03 (0.79, 1.33)	1.08 (0.69, 1.70)
Q4	1009 - 2211	1.10 (0.82, 1.46)	0.93 (0.56, 1.56)
	p-value	p = 0.48	p = 0.97
Fully adjusted models for demographics, co-morbidities, meds, GFR			

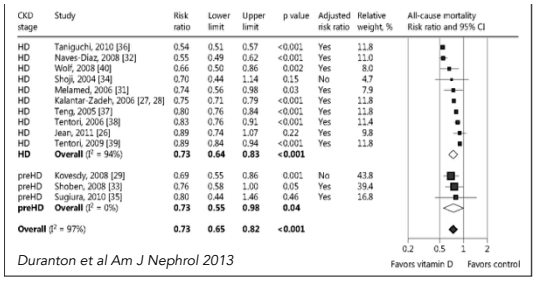
TREATING LOW VITAMIN D LEVELS IN CKD



NO trials of vitamin D *versus* placebo on clinical events

ACTIVATED VITAMIN D ASSOCIATED WITH SURVIVAL

Comparing activated vitamin D treatment *versus* no treatment

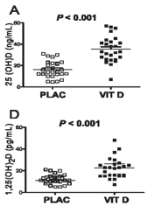


Duranton et al Am J Nephrol 2013

SUBSTRATE VITAMIN D RAISES 1,25(OH)$_2$D LEVELS IN ESRD

61 chronic hemodialysis patients with serum 25(OH)D <30 ng/dL

Cholecalciferol 25,000 IU weekly X 13 weeks *versus* placebo



	Treatment	Placebo
Serum 25(OH)D	+18.1 ng/dL	-2.0 ng/dL
Serum 1,25(OH)$_2$D	+9.5 pg/mL	-3.0 pg/mL

However, no effect on PTH

Massart AJKD 2014

MINERAL METABOLISM DISTURBANCES IN KIDNEY DISEASE

PO_4 retention and impaired 1,25(OH)$_2$D synthesis play important roles in the development of CKD-MBD

Experimental evidence suggests that CKD-MBD contributes to vascular calcification and premature cardiovascular disease

No clinical trials of treatments for CKD-MBD on clinical outcomes

Clinical care remains PO_4 binders, dietary PO_4 restriction, activated vitamin D products, and cinacalcet