Université Claude Bernard Lyon 1

Phosphate and nutrition in the dialysis patient

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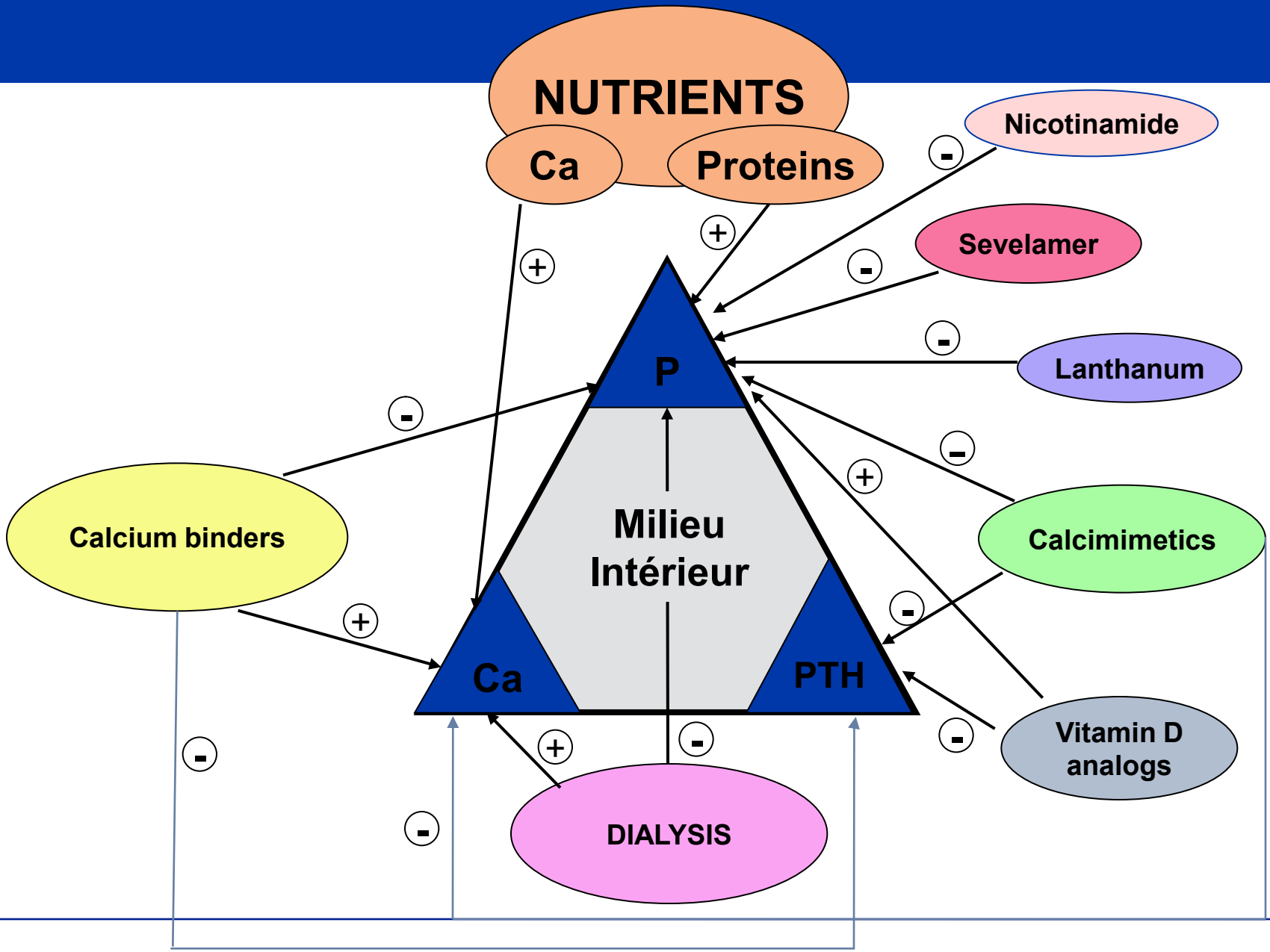
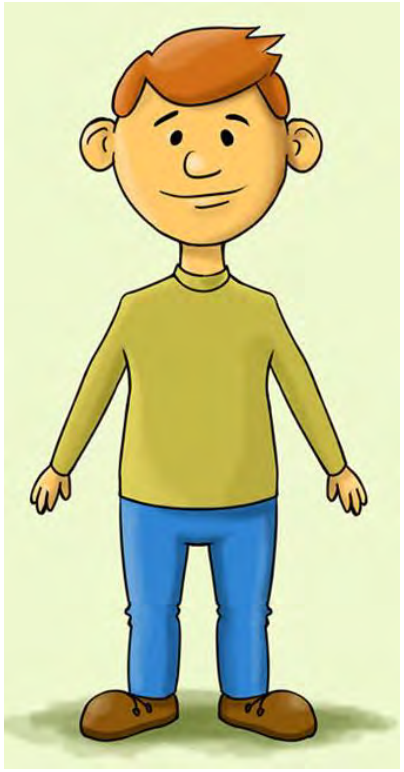

NUTRIENTS
Ca
Proteins
Nicotinamide
Sevelamer
Lanthanum
Calcium binders
Calcimimetics
Vitamin D analogs
DIALYSIS
P
Milieu Intérieur
Ca
PTH
+
-

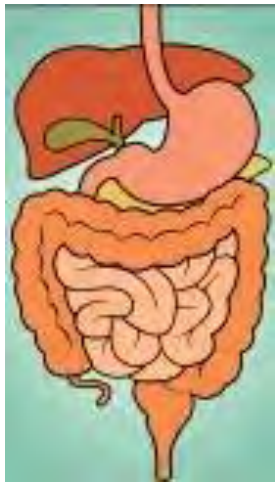
This leaves a 70 kg anuric patient consuming 1.1 g/kg/day of protein with about **12 mmol/day** of excess phosphate

70 kg anuric patient

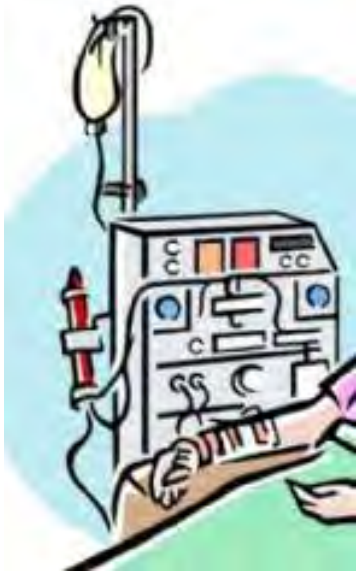


77 g/day protein intake

60-80% intestinal absorption



HD removes about 2400-3000 mg phosphorus/week

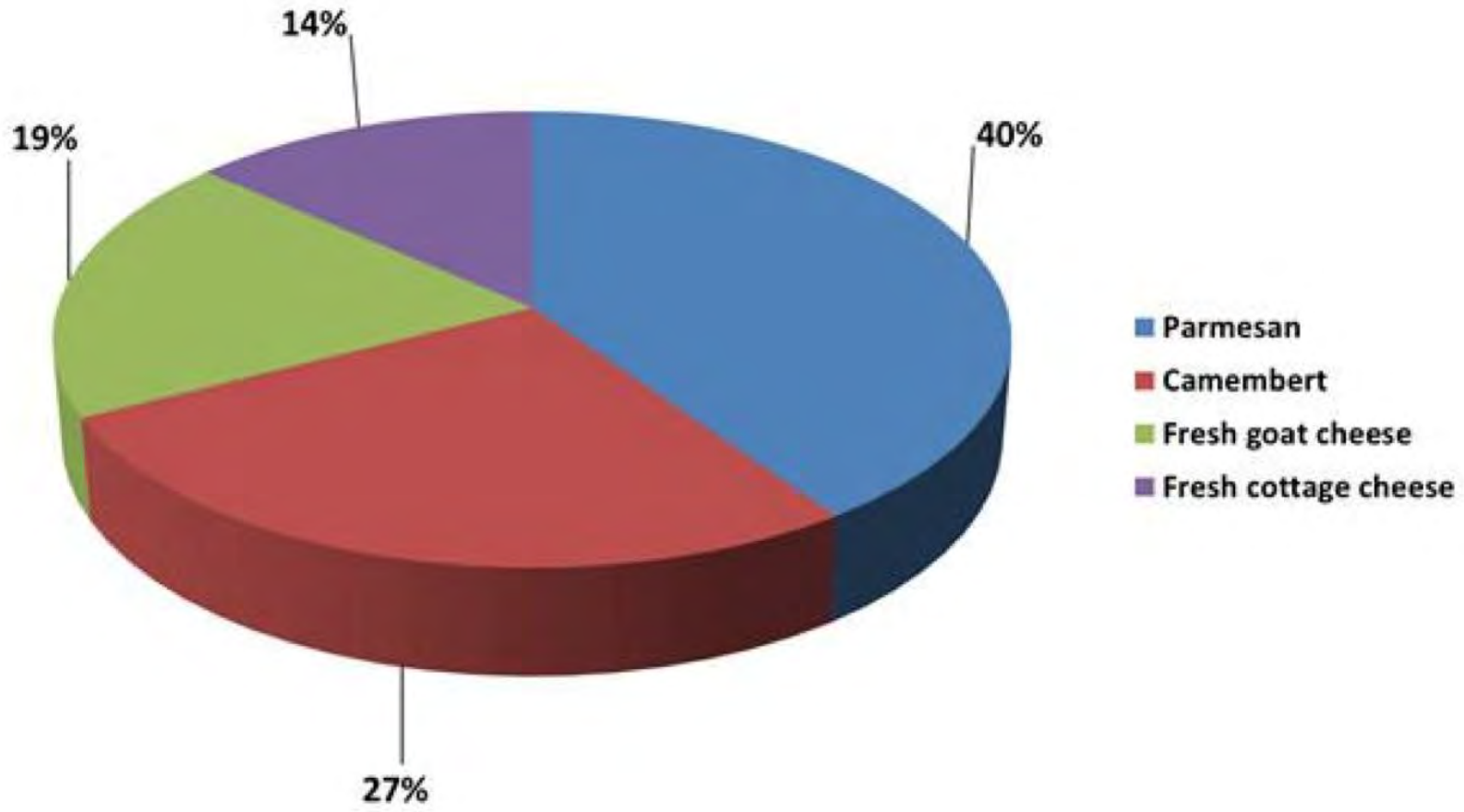


1 g 'PBED' binds about 45 mg P

Approximately **8g of calcium carbonate or 'phosphate binder equivalent dose'** are required to bind **12 mmol/day** phosphate

courtesy E.Lindley

Which cheese brings most phosphorus ? (NDT Educational 2013)



Cheese phosphate content (100 g)

	Kcal	g prot	mg phosphorus	mg calcium	mg sodium	mg phos/g prot
Melted cheese	***284***	***12,4***	***757***	***303***	***650***	***61,0***
beaufort	398	26,6	728	995	628	27,4
emmental	381	28,4	666	1055	244	23,5
comté	407	28,4	664	909	412	23,4
gruyère	428	29,8	606	1036	328	20,3
morbier	347	23,6	520	760	990	22,0
pyrénnée (goat)	393	23,8	499	721	740	21,0
cantal	365	23,9	494	798	875	20,7
tomme	362	22,6	480	626	807	21,2
St marcellin	291	12,7	442	138	1009	34,8
roquefort	363	18,7	430	608	1600	23,0
cancaillotte	122	14,5	425	144	502	29,3
reblochon	325	20,8	339	514	555	16,3
bleu de bresse	354	17,5	320	450	602	18,3
maroilles	376	28,5	320	350	937	11,2
camembert	277	22,5	307	456	595	13,6
St nectaire	331	20,9	304	539	477	14,5
bleu d'auvergne	347	19,9	301	563	1136	15,1
crottin chèvre	354	20,8	266	144	410	12,8
munster	328	19,8	265	370	682	13,4
brie	330	18,4	220	313	647	12,0
petit suisse 20%	96	9,6	125	117	34	13,0

cheese fondue (one serving)	1200 mg

- **Phosphorus toxicity**
- **Serum phosphorus and protein intake**
- **Phosphorus and nutrients**
- **Dietary interventions: are they efficient?**
- **Artificially added phosphorus**
- **Phosphorus and binders**

Serum phosphorus and longevity

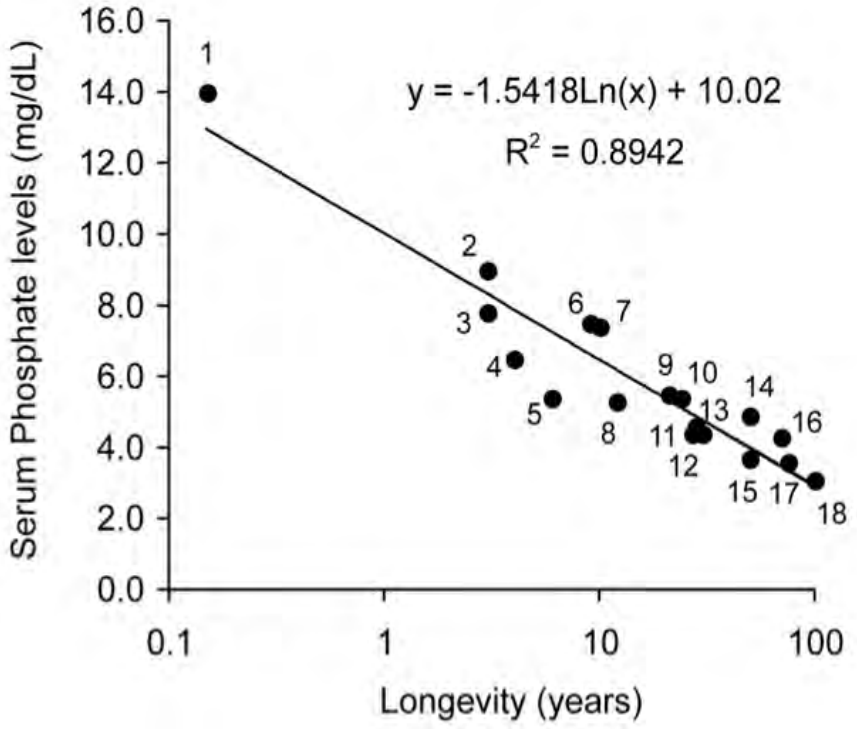
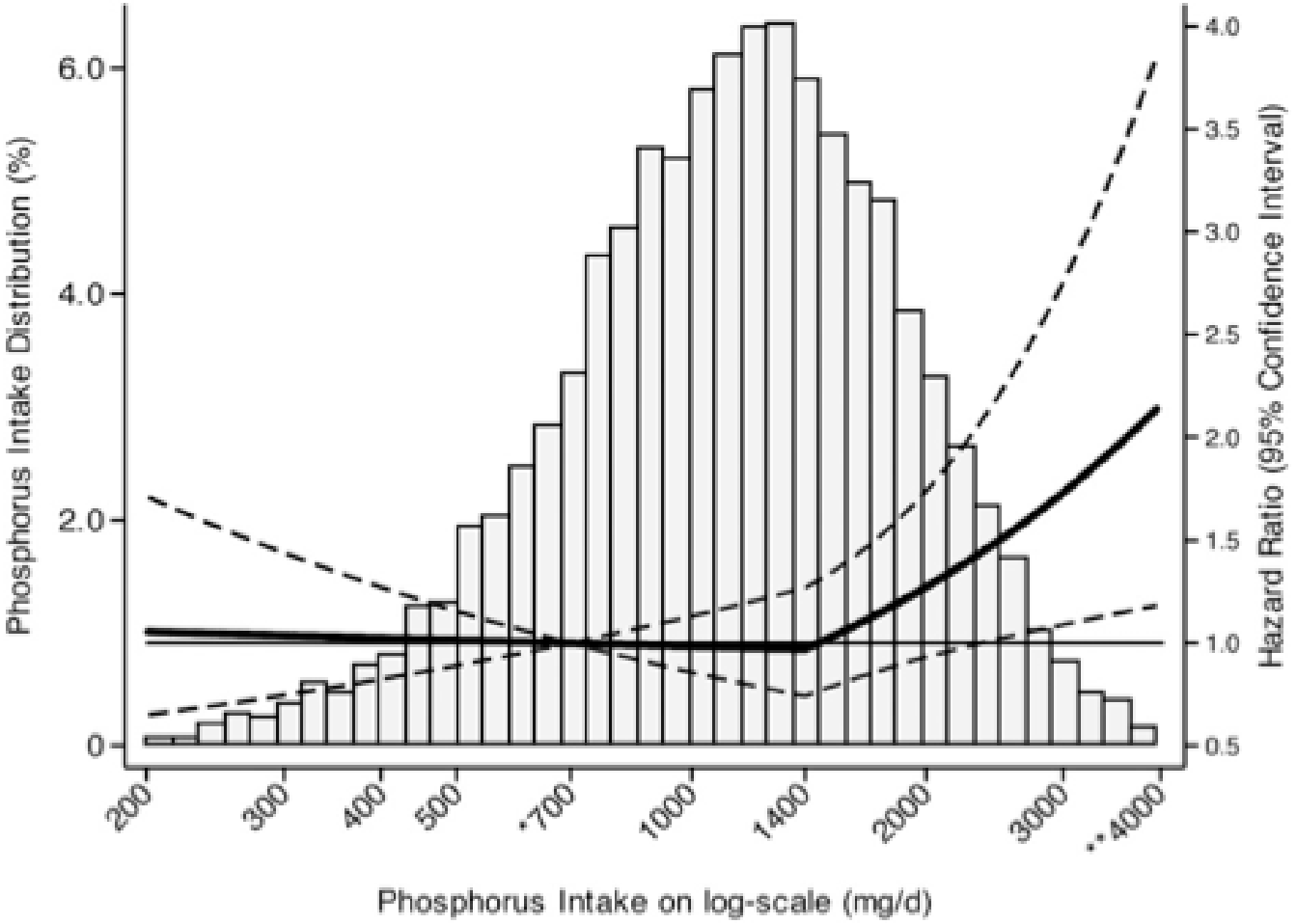


Figure 2.
Relation between longevity and serum phosphate in mammals. 1: *Klotho*$^{-/-}$ mouse, 2: Mouse, 3: Rat, 4: Hamster, 5: Gerbil, 6: Nutria, 7: Rabbit, 8: Guinea pig, 9: Sheep, 10: Squirrel, 11: Porcupine, 12: Naked mole rat, 13: Flying fox, 14: Bear, 15: Rhinoceros, 16: Elephant, 17: Human, 18: Human (centenarian). Serum phosphate leves are average or median values, whichever available in literatures (Asadi et al., 2007; Feldhamer et al., 2003; Field et al., 1998; Gorbunova et al., 2008; Heard et al., 2006; Holliday, 1995; Kuro-o et al., 1997; Moreau et al., 2003; Munson et al., 1998; Passeri et al., 2008; Pugh, 2002; Ramsay, 2003; Segawa et al., 2007; Thrall et al., 2004; Tuntasuvan et al., 2002; Yahav et al., 1993).

Kuro-O M, Mech Ageing Devel 2010

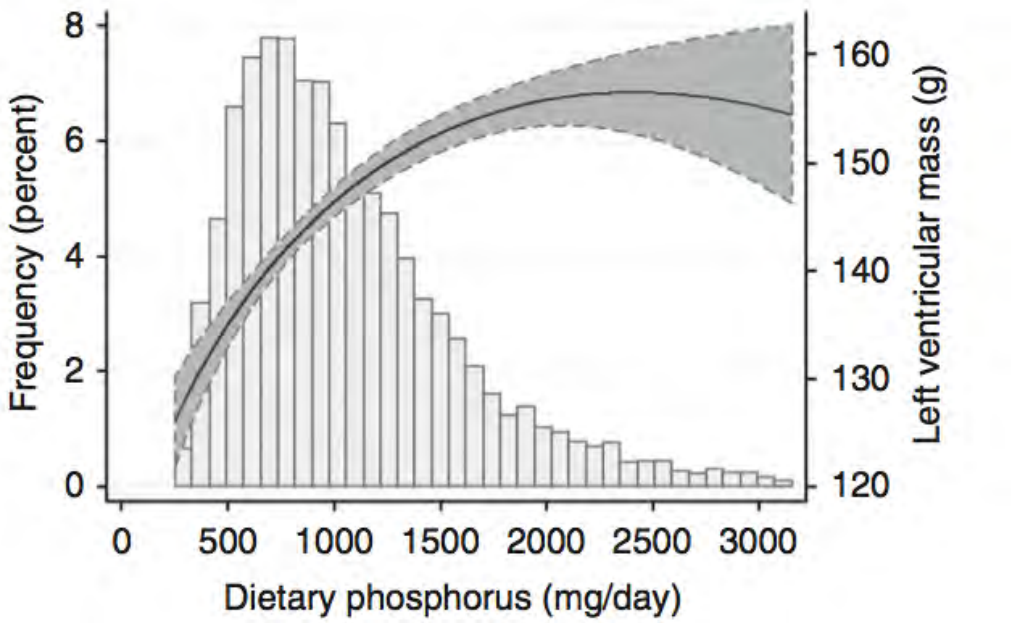
NHANES cohort 9600 adults



Chang et al. Am J Clin Nutr 2014;99:320

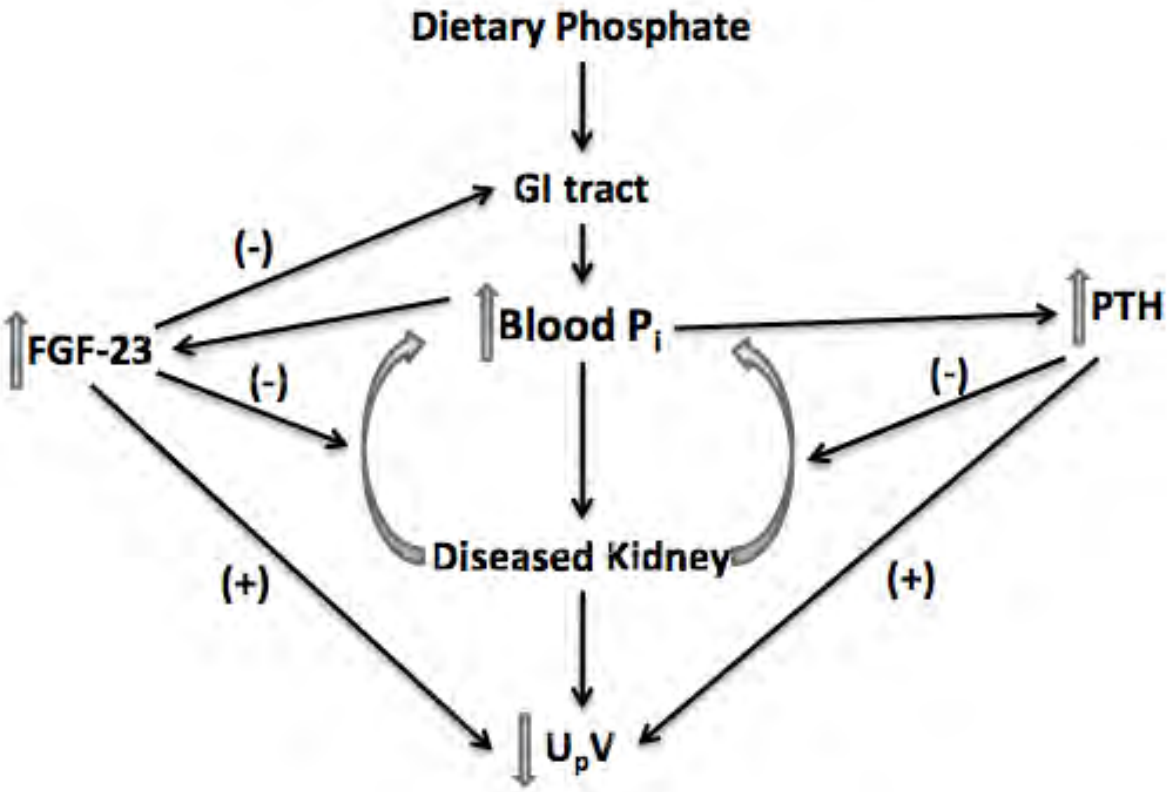
Dietary phosphorus is associated with greater left ventricular mass

Kalani T. Yamamoto[1], Cassianne Robinson-Cohen[2], Marcia C. de Oliveira[3], Alina Kostina[1], Jennifer A. Nettleton[3], Joachim H. Ix[4,5], Ha Nguyen[6], John Eng[7], Joao A.C. Lima[8], David S. Siscovick[9], Noel S. Weiss[2] and Bryan Kestenbaum[1,2]



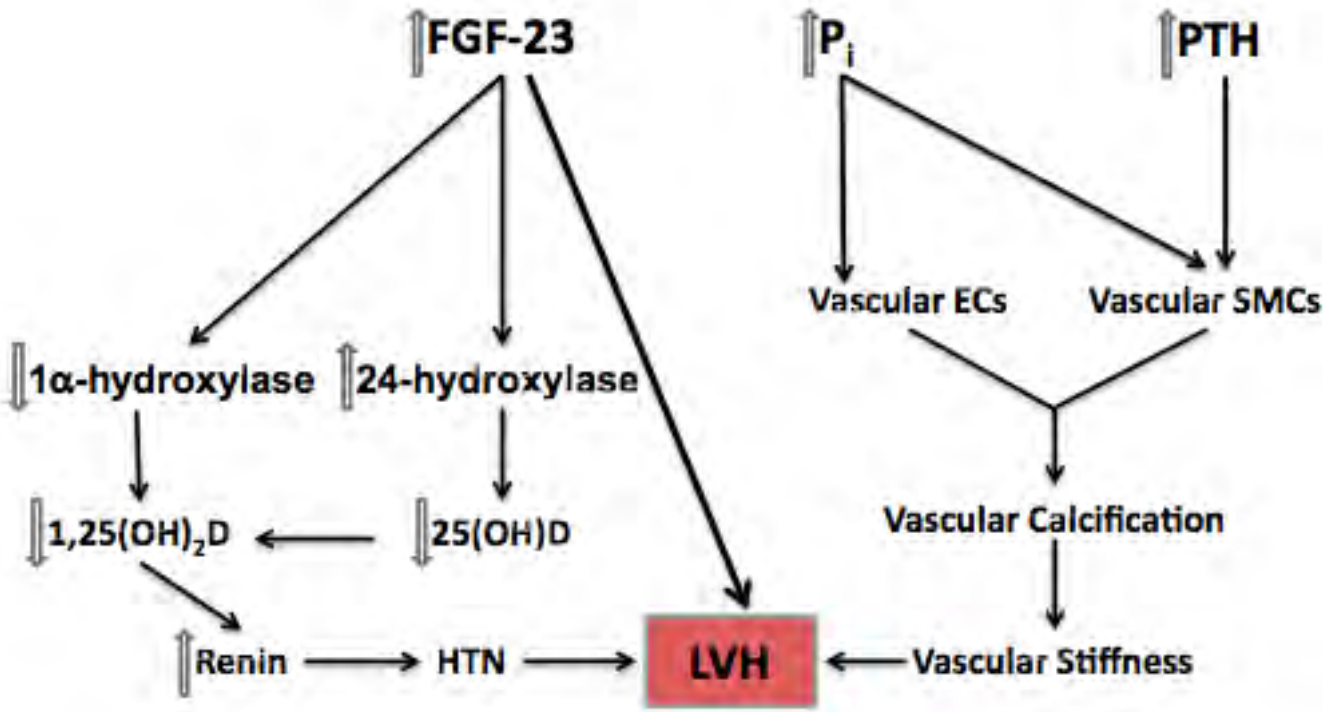
Yamamoto et al, Kidney Int 2013

CKD-Mineral bone disease physiopathology



Weinman et al. Am J Kidney Dis 2013;62:1006

CKD-MBD and related cardiovascular disease



Weinman et al. Am J Kidney Dis 2013;62:1006

- **Phosphorus toxicity**
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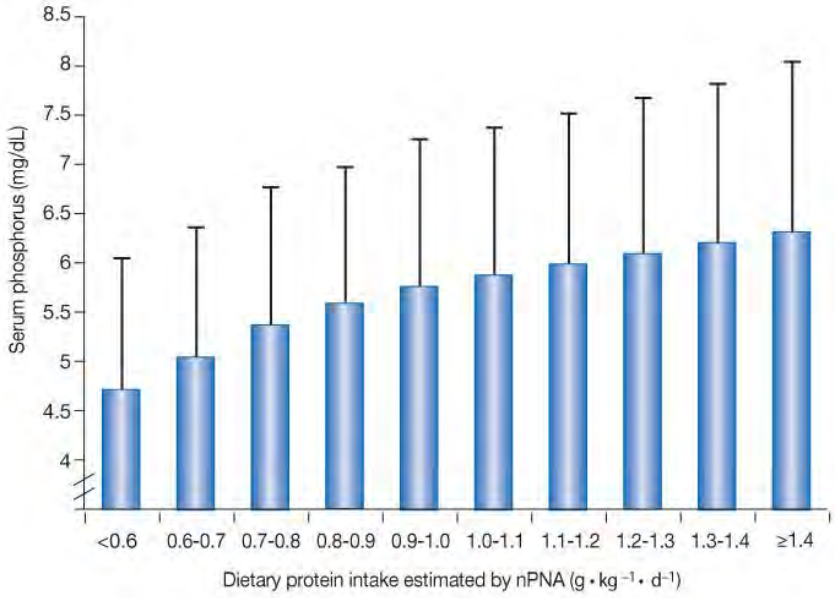
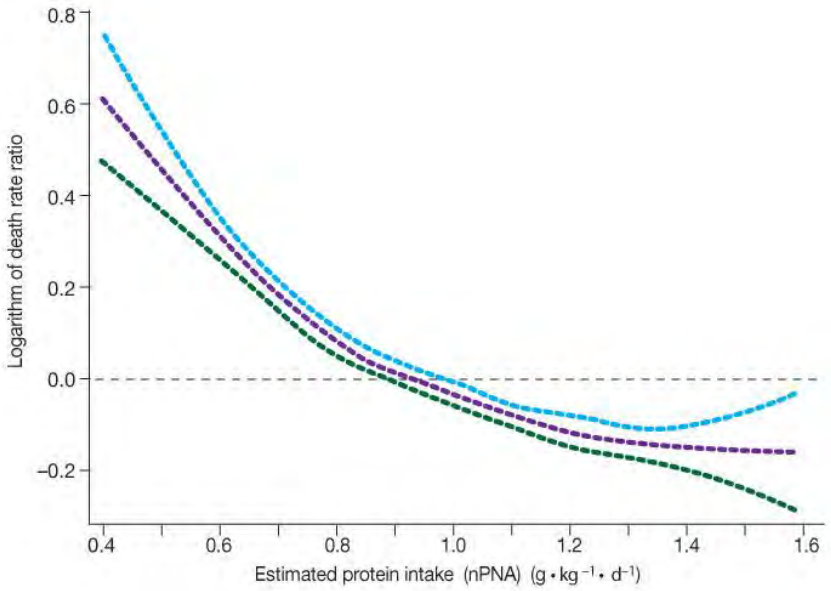
- **Phosphorus and binders**

Association between dietary protein intake, serum phosphorus and mortality

- Low protein intake: increase in mortality





Study design: Cohort study to evaluate if a decline in serum phosphorus and a concomitant decline in protein intake was associated with increased risk of death

Patients: 30,075 maintenance HD patients

Shinaberger et al. Am J Clin Nutr 2008

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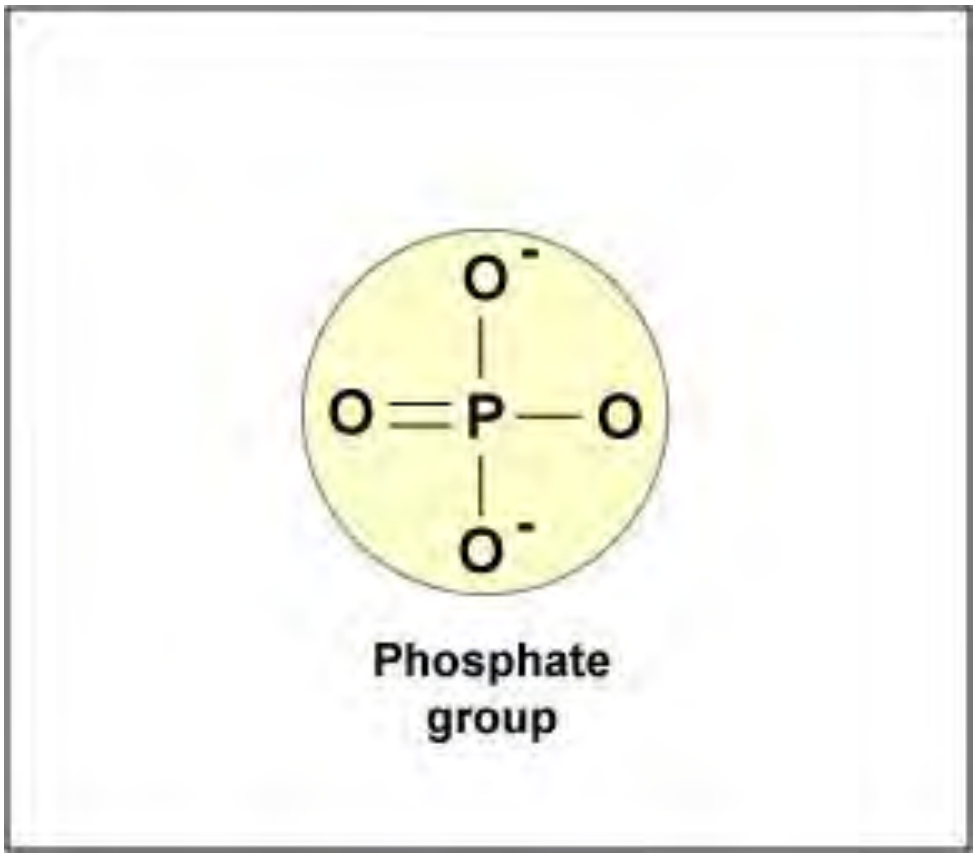
Phosphorus Absorption



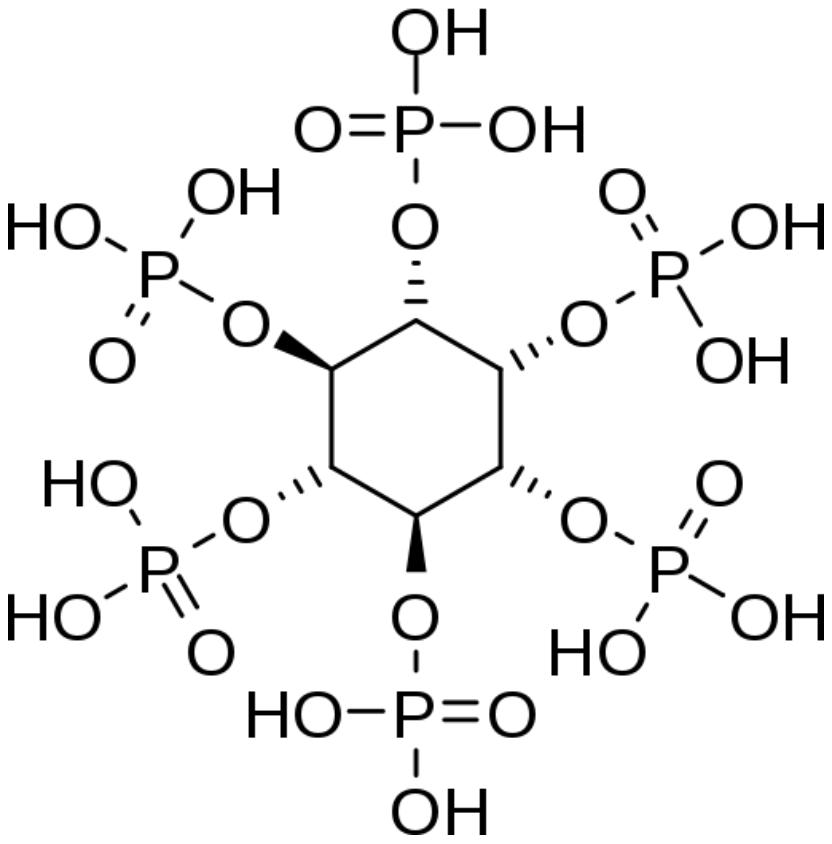
- Passive paracellular and via NaPi cotransporters in luminal brush border

- Absorb inorganic phosphate

- Alkaline phosphatase hydrolyzes organic phosphates into inorganic phosphate for absorption

Courtesy J. Scialla

Bioavailability of Phosphorus in Plant Foods



Phytic acid

Accounts for 60-90% of phosphorus in cereals, legumes, seeds, and nuts

Dense storage form of phosphorus and antioxidant

Poorly absorbed in humans due to deficient phytase

Courtesy J. Scialla

Protein Source & Metabolic Effects in CKD

Unadjusted mean values (± standard deviation) of metabolic parameters by quintiles of percent plant protein

	1 <24% (n=587)	2 24–29% (n=588)	3 30–35% (n=588)	4 36–44% (n=587)	5 >44% (n=588)	p-trend
Serum phosphate (mg/dL)	3.67 ± 0.66	3.73 ± 0.64	3.69 ± 0.65	3.69 ± 0.61	3.69 ± 0.66	0.69
FGF23 (RU/mL)[†]	138 (92, 239)	144 (95, 247)	143 (94, 224)	139 (95, 232)	134 (88, 215)	0.60
24 urinary phosphate (mg)	849 ± 369.96	812 ± 363.71	768 ± 347.17	752 ± 318.22	697 ± 331.06	<0.001
iPTH (pg/mL)[†]	53 (34, 87)	54 (33, 90)	51 (33, 83)	53 (34, 84)	52 (35, 84)	0.83
Serum bicarbonate (mEq/L)	24.47 ± 3.17	24.50 ± 3.05	24.50 ± 3.07	24.85 ± 3.22	24.82 ± 3.19	0.07

[†]Median (interquartile range)

FGF23 = fibroblast growth factor 23; iPTH = intact parathyroid hormone

CRIC study, 3000 CKD pts, GFR 45 ml/min

Scialla et al. J Renal Nutr, 2012; 22: 379-388.

Phosphate and FGF 23: modulation by nutrients

Phosphate intake, 800 mg/d, either from meat or vegetarian (randomized cross over)

	Before Meat (casein) Diet	After Meat (casein) Diet	Before Vegetarian (grain) Diet	After Vegetarian (grain) Diet	*P* (paired *t* test)[a]
Average daily phosphorus intake (mg/day)		810 ± 27		795 ± 51	NS
Plasma phosphorus (mg/dl)	3.5 ± 0.6	3.7 ± 0.6	3.5 ± 0.6	3.2 ± 0.5	0.02
Plasma intact PTH (pg/ml)	58 ± 31	46 ± 29	58 ± 39	56 ± 30	0.002
Plasma FGF23 (pg/ml)	72 ± 39	101 ± 83	84 ± 65	61 ± 35	0.008
Plasma calcium (mg/dl)	9.2 ± 0.4	9.4 ± 0.7	9.3 ± 0.4	9.1 ± 0.3	NS
Creatinine clearance (ml/min)	47 ± 16	47 ± 16	43 ± 11	44 ± 16	NS
Urine 24-hour calcium excretion (mg/24 h)	66 ± 69	77 ± 48	60 ± 59	71 ± 43	NS
Urine 24-hour phosphorus excretion (mg/24 h)	836 ± 187	583 ± 216	778 ± 190	416 ± 233	0.07

Moe et al. C JASN 2011;6:257

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Salami di Cinghiale
Schinkenknacker
Schinkenkrakauer
Cocktail - Knacker
Bockwurst natur

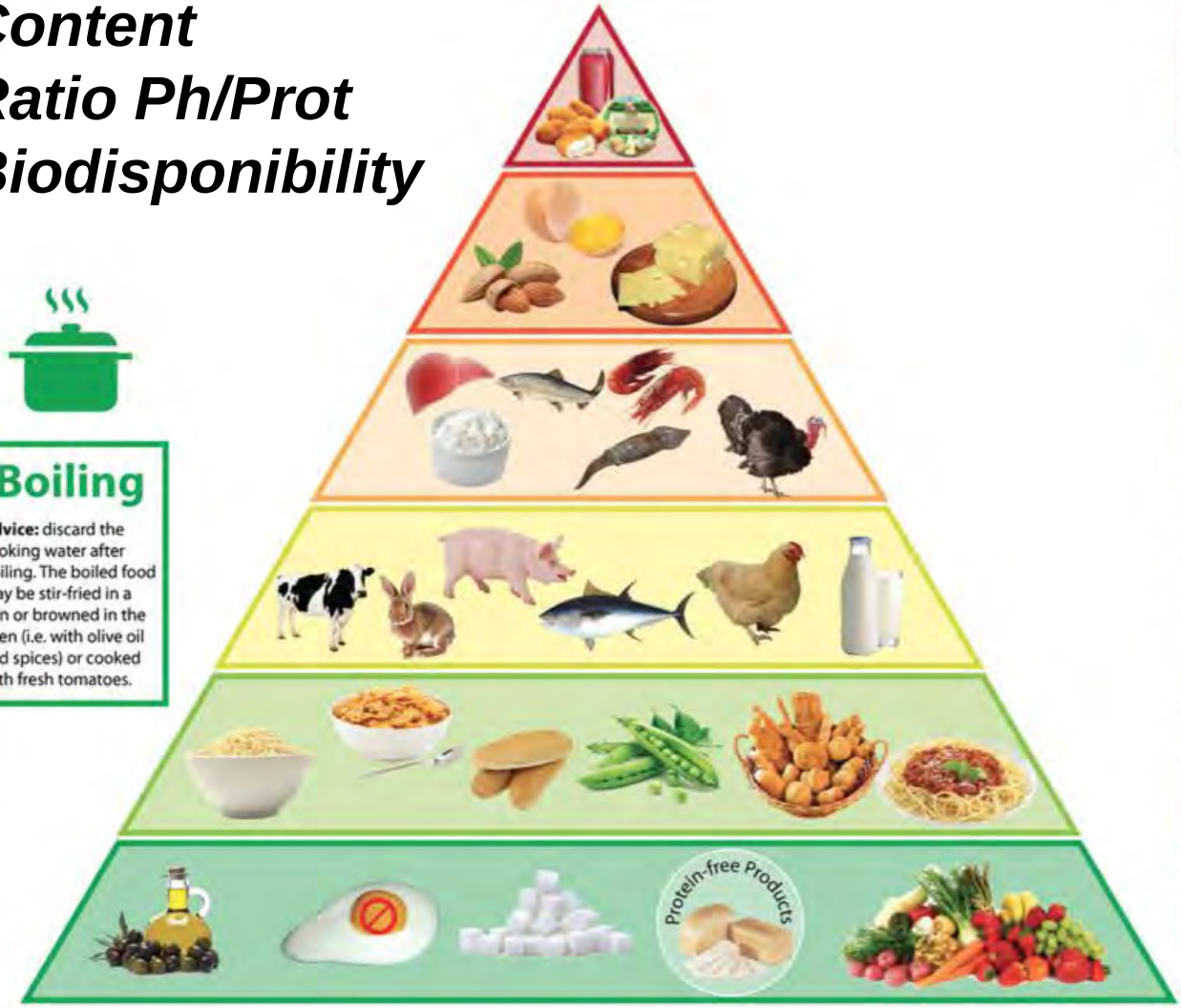
Sausages and phosphorus

aliment	apports par portion	%apports par portion
Salami de dinde cuit (portion : 55g)	146mg	21%
Saucisson de foie (portion : 55g)	127mg	18%
Jambon de dinde (portion : 55g)	126mg	18%
Saucisse de dinde (portion : 55g)	111mg	16%
Pâté de foie (portion : 55g)	110mg	16%
Chipolata (portion : 55g)	101mg	14%
Roulé de dinde (portion : 55g)	101mg	14%
Saucisse fumée (portion : 55g)	94mg	13%
Pain de viande au poivre (portion : 55g)	94mg	13%
Boeuf froid tranché (fin) (portion : 55g)	92mg	13%
Braunschweiger (portion : 55g)	92mg	13%
Saucisse fumée (porc) (portion : 55g)	89mg	13%
Saucisse fumée (boeuf) (portion : 55g)	88mg	13%
Blanc de dinde rôtie (portion : 55g)	87mg	12%
Jambon haché (portion : 55g)	86mg	12%
Jambon tranché (portion : 55g)	84mg	12%
Chorizo (portion : 55g)	83mg	12%
Saucisse de veau (portion : 55g)	83mg	12%
Saucisse bratwurst (portion : 55g)	82mg	12%
Saucisse de boeuf (portion : 55g)	78mg	11%
Saucisson de bologne (portion : 55g)	76mg	11%
Saucisson de bière (porc et boeuf) (portion : 55g)	74mg	11%
Saucisson de bologne (dinde) (portion : 55g)	72mg	10%
Salami sec (portion : 30g)	69mg	10%
Saucisse fumée (porc et boeuf) (portion : 55g)	67mg	10%
Roulé de poulet (portion : 55g)	67mg	10%
Salami de boeuf cuit (portion : 55g)	62mg	9%
Cervelas (portion : 55g)	61mg	9%
Saucisse porc et boeuf (portion : 55g)	59mg	8%
Saucisse fumée (poulet) (portion : 55g)	59mg	8%
Saucisson de bière (portion : 55g)	57mg	8%
Saucisse knackwurst (portion : 55g)	54mg	8%
Saucisse de bière (boeuf) (portion : 55g)	53mg	8%
Mortadelle (portion : 55g)	53mg	8%
Saucisse de bologne (boeuf) (portion : 55g)	48mg	7%
Rôti de viande froid (portion : 55g)	47mg	7%
Salami de boeuf sec (portion : 30g)	43mg	6%
Fromage de tête (portion : 55g)	32mg	5%
Boudin (portion : 55g)	12mg	2%

12 to 146 mg per portion of 55g

Phosphate food pyramid and CKD

Content
Ratio Ph/Prot
Biodisponibility



Boiling

Advice: discard the cooking water after boiling. The boiled food may be stir-fried in a pan or browned in the oven (i.e. with olive oil and spices) or cooked with fresh tomatoes.

Beverages and Foods with phosphate-additives (E338-343 E450-458 E540-545):
soft drinks (cola in particular), dehydrated milk, processed cheese, processed meat (i.e. chicken nuggets), dessert, instant cappuccino…

Hard cheeses: parmesan, cheddar, emmentaler, pecorino…
Nuts
Yolk

Meat (a): sausages, offal (liver, brain)…
Poultry (a): turkey…
Fish (a): shrimp, squid, salmon…
Soft cheeses: cottage, cream, mozzarella cheese…

Meat (b): rabbit, lamb, ham with no preservatives, pork, veal…
Poultry (b): chicken…
Fish (b): trout, tuna fish, cod, hake, sole…
Milk , yogurt…

Cereals: bread, pasta, rice, cous cous, maize flour, cornflakes…
Legumes: peas, broad beans, beans, chickpeas, lentils, soy…

Egg white
Fruits and vegetables (c)
Olive oil and vegetables fats (d) (i.e. vegetable margarine, corn oil, peanut oil…)
Butter (d)
Sugar (e)
Protein-free products (f)

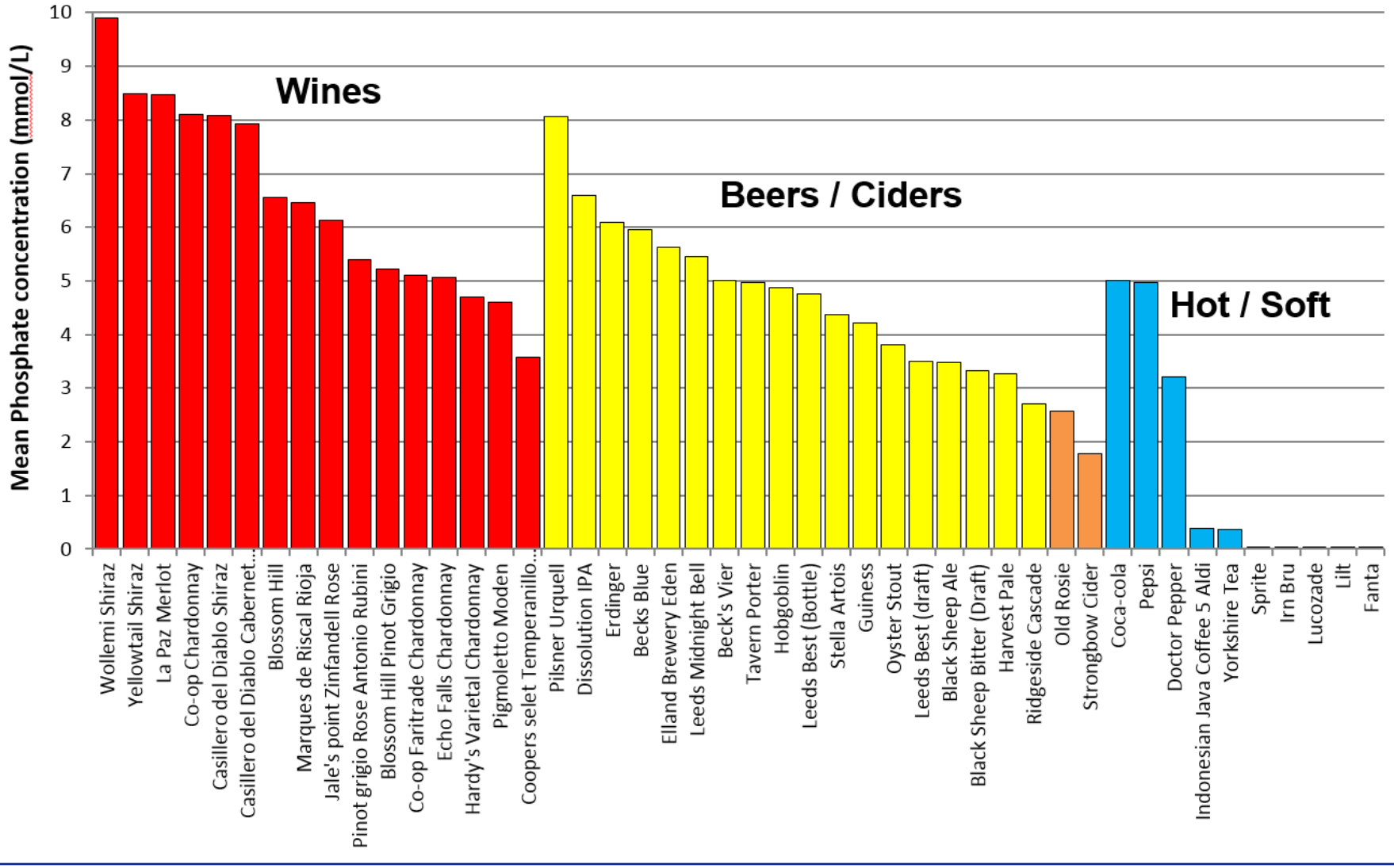
D'Alessandro et al, BMC Nephrol 2015:16:9

Phosphate in beverages

- The phosphate in beverages is readily absorbed.
- Beverages are often consumed between meals, without a phosphate binder.
- Additives may be listed on food labels but the quantity of phosphate per serving is not.
- The phosphate present in beer and wine is not mentioned on the label as it is not usually from additives.
  - Home-made beer and wine may have di-ammonium phosphate added as a nutrient for the yeast
  - Professional brewers (in Yorkshire) disapprove of additives!

Lindley et al, JREN 2014;24:353-56

Drinks vary widely in PO4



Lindley et al, JREN 2014;24:353-56

500mL

500mL

500mL

500mL

500mL

Added phosphate in processed foods and drinks

- Sodas, colas, fanta,…

- Coca-Cola: +30% phosphoric acid in 2005
- Coca-Cola 170 mg/L
- Coca-Cola light 70 mg/L

- Chocolate bars (Mars, Nuts,…)
- Nutella
- Melted cheese
- Rice which does not stick

Why do industrials add phosphate ?

- Increase in conservation time and shelf duration
- Increase in water content (increase meat weight by 10-15%...)
- Keeps food a nice color
- a 300 mg « processed meat » contains 300 mg instead of 50 mg phosphate

Triphosphates	
N°	Descriptif
E 451 I	Triphosphate pentasodique
E 451 II	Triphosphate pentapotassique
E 452 I	Polyphosphates sodiques
E 452 II	Polyphosphates potassiques
E 452 III	Polyphosphates calco-sodiques
E 452 IV	Polyphosphates calciques
E 459	Béta-cyclodextrine

Additives with phosphate (limited list – Europe)

List A - Additives with phosphate components - Europe and Australasia

On European food labels the number will be prefixed by the letter 'E'

101	Riboflavin-5'-phosphate sodium
240	Potassium phosphate monobasic
338	Orthophosphoric acid Phosphoric Acid
339	Disodium hydrogen orthophosphate Sodium dihydrogen orthophosphate Sodium phosphate monobasic Sodium phosphate dibasic Sodium phosphate tribasic
341	Acid calcium phosphate Calcium hydrogen orthophosphate Calcium phosphate monobasic Calcium phosphate dibasic Calcium phosphate tribasic Monocalcium orthophosphate Tricalcium orthophosphate
343	Magnesium hydrogen phosphate Magnesium hydrogen dibasic Magnesium hydrogen tribasic
442	Ammonium phosphatides Ammonium salts of phosphatic acid
450	Acid sodium pyrophosphate Disodium dihydrogen diphosphate Disodium dihydrogen pyrophosphate Pentasodium triphosphate Polyphosphates, potassium and sodium Potassium polyphosphates Potassium tripolyphosphate Sodium acid pyrophosphate Sodium polyphosphates Sodium pyrophosphate Sodium tripolyphosphate Tetrapotassium diphosphate Tetrasodium diphosphate Trisodium diphosphate Trisodium orthophosphate
450(a)	Ammonium phosphate dibasic
450(a)	Ammonium phosphate monobasic
540	Dicalcium diphosphate
541	Sodium aluminium phosphate, acidic Sodium aluminium phosphate, basic
542	Bone phosphate, edible Edible bone phosphate
544	Calcium polyphosphates Polyphosphates, calcium
545	Ammonium polyphosphates Polyphosphates, ammonium
627	Guanosine 5' - (disodium phosphate)
631	Inosine 5' - (disodium phosphate)
1410	Monostarch phosphate
1412	Distarch phosphate
1413	Phosphated distarch phosphate
1414	Acetylated distarch phosphate
1442	Hydroxypropyl distarch phosphate

ORIGINAL RESEARCH

Results of a Pilot Program to Improve Phosphorus Outcomes in Hemodialysis Patients

Tracy J. Mayne, PhD, Debbie Benner, MA, RD, CSR,* Kathy Ricketts, MS, RD, LDN,† Mary Burgess, MS, RD,* Steve Wilson, PhD,* Lynne Poole, MSc,‡ Michael Smyth, MRCGP, FRCS,‡ Carey Colson, MS,* and Mahesh Krishnan, MD, MBA, MPH**

Mayne et al, J Renal Nutr 2012;22:472

Dietary intervention and phosphate control

Table 2. Biometric Measures Before and After Program Implementation

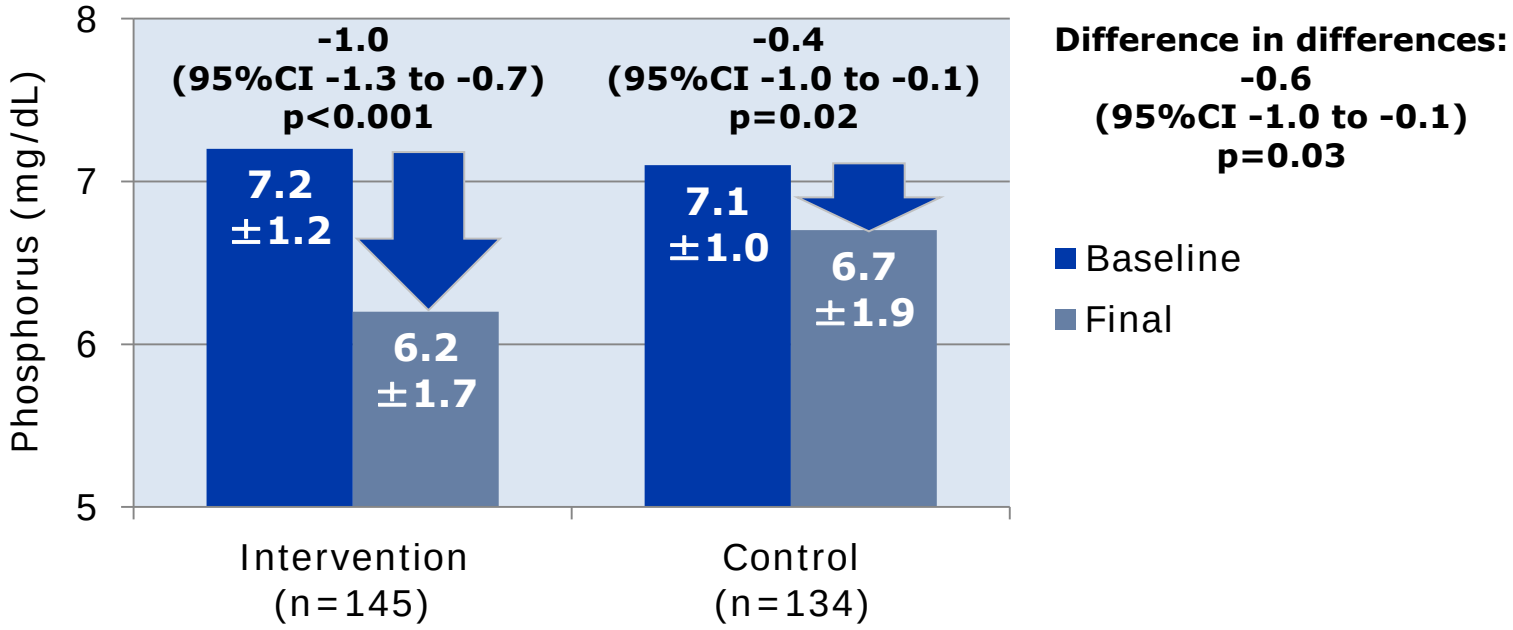
Biomarker	Baseline		Month 6		Change*		Change *P* Value	
	Mean ± SD	% in Range†	Mean ± SD	% in Range	Mean ± SD	% in Range	Mean	% in Range
Phosphorus (mg/dL)	5.3 ± 0.2	61.6% ± 5.2%	5.1 ± 0.3	71.3% ± 9.0%	−0.2 ± 0.2	9.6% ± 5.9%	0.01	≤.01
cCalcium (mg/dL)	8.9 ± 0.1	86.2% ± 4.2%	8.9 ± 0.09	90.3% ± 3.3%	0.01 ± 0.14	4.1% ± 6.4%	0.92	.12
PTH (pg/mL)	377.1 ± 52.9	39.1% ± 2.4%	368.8 ± 65.7	44.5% ± 7.0%	−8.3 ± 70.9	5.5% ± 6.1%	0.75	.04
Albumin (g/dL)	3.8 ± 0.04	N/A	3.8 ± 0.06	N/A	0.01 ± 0.07	N/A	0.58	N/A
nPCR (g/kg/day)	0.98 ± 0.07	N/A	0.97 ± 0.07	N/A	−0.01 ± 0.03	N/A	0.35	N/A

*Change may not add exactly due to rounding.
†Ranges for calcium, <9.6 mg/dL; PTH, 150–300 pg/mL; phosphorus, <5.5 mg/dL.

Mayne et al, J Renal Nutr 2012;22:472

Effect of dietary phosphorus additives on phosphorus control

Educating ESRD patients to avoid phosphorus-containing food additives resulted in modest improvements in hyperphosphataemia.



Study design: Cluster randomised controlled trial (Intervention: education on avoiding foods with phosphorus additives; Control: usual care)

Patients: 279 patients with elevated baseline serum phosphorus levels (>5.5 mg/dL)

Sullivan et al. JAMA. 2009;301(6):629-35

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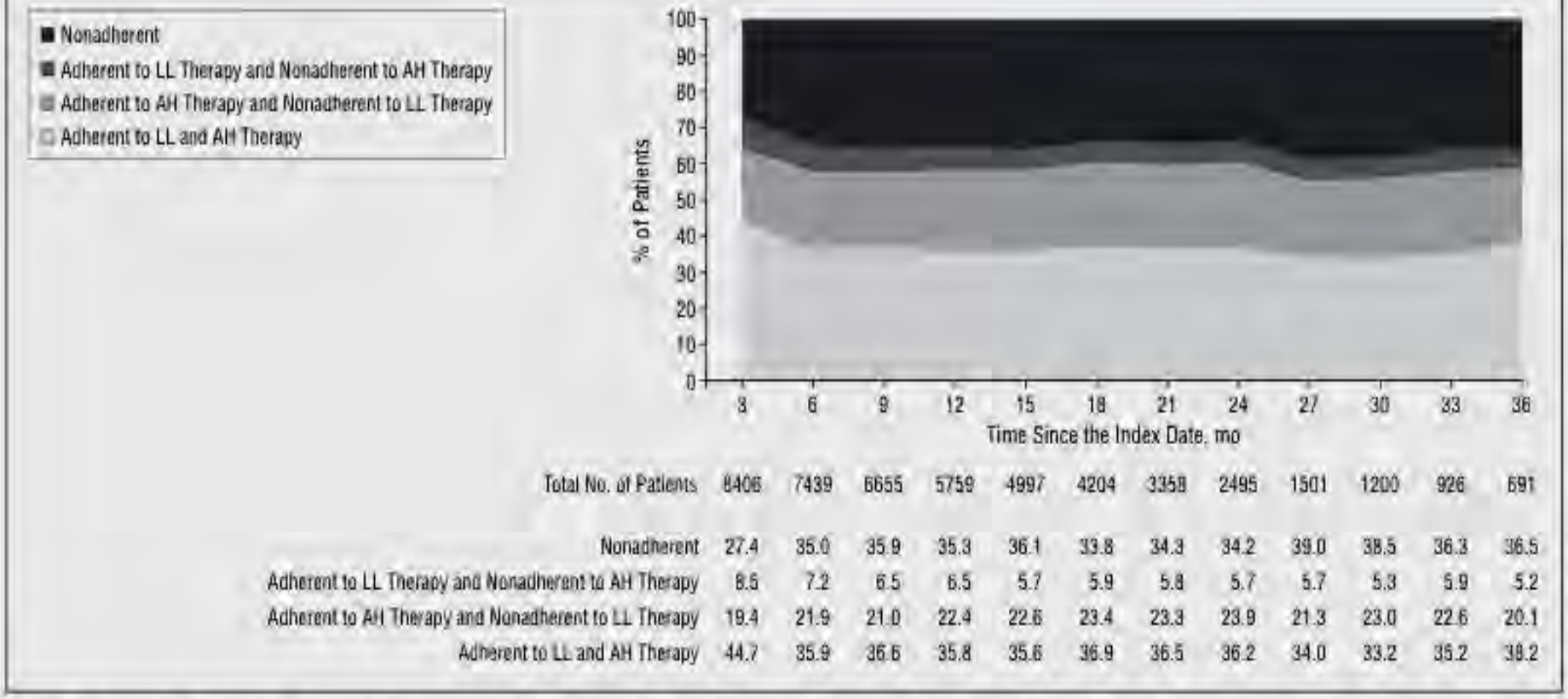
Compliance to drugs (lipid lowering + antiHTN)



	3	6	9	12	15	18	21	24	27	30	33	36
Total No. of Patients	8406	7439	6655	5759	4997	4204	3358	2495	1501	1200	926	691
Nonadherent	27.4	35.0	35.9	35.3	36.1	33.8	34.3	34.2	39.0	38.5	36.3	36.5
Adherent to LL Therapy and Nonadherent to AH Therapy	8.5	7.2	6.5	6.5	5.7	5.9	5.8	5.7	5.7	5.3	5.9	5.2
Adherent to AH Therapy and Nonadherent to LL Therapy	19.4	21.9	21.0	22.4	22.6	23.4	23.3	23.9	21.3	23.0	22.6	20.1
Adherent to LL and AH Therapy	44.7	35.9	36.6	35.8	35.6	36.9	36.5	36.2	34.0	33.2	35.2	38.2

Figure. Patterns of patient adherence to concomitant therapy over 3 years. The index date was defined as the date concomitant therapy (ie, second drug) was initiated. Percentages at each date may not total 100 because of rounding. AH indicates antihypertensive; LL, lipid-lowering.

Chapman et al, Arch Int Med 2005

Phosphate binders binding properties

Phosphate binder	Binding capacity, mg/g (mg/tablet)	Daily dose, mg/day	Tablets/day, *n*
Calcium acetate 667 mg/tablet	50 (33)	6000	9
Calcium carbonate 400 mg/tablet[b]	19[a] (8)	6315	16
Sevelamer carbonate 800 mg/tablet	33 (26)	9090	12
Lanthanum carbonate 1000 mg/tablet	115 (115)	2610	3

Fouque et al, Am J Kidney Dis 2014

Is nutritional phosphorus a risk factor in CKD?

NO	YES
When it comes from protein	When it comes from additives
From vegetal protein +++	For taste, conservation, colour
	For water content and weight increases (+15%)
800 mg (CKD) to 1200 mg(MD)	+ 500 to 1000 mg/day
40-60% absorbed	100% absorbed
Net balance = 0 mg/day (Kt/V, time, HDF, diet and phosphate binders)	**Net balance + 500 to 1000 mg/day**

Phosphorus control at population level

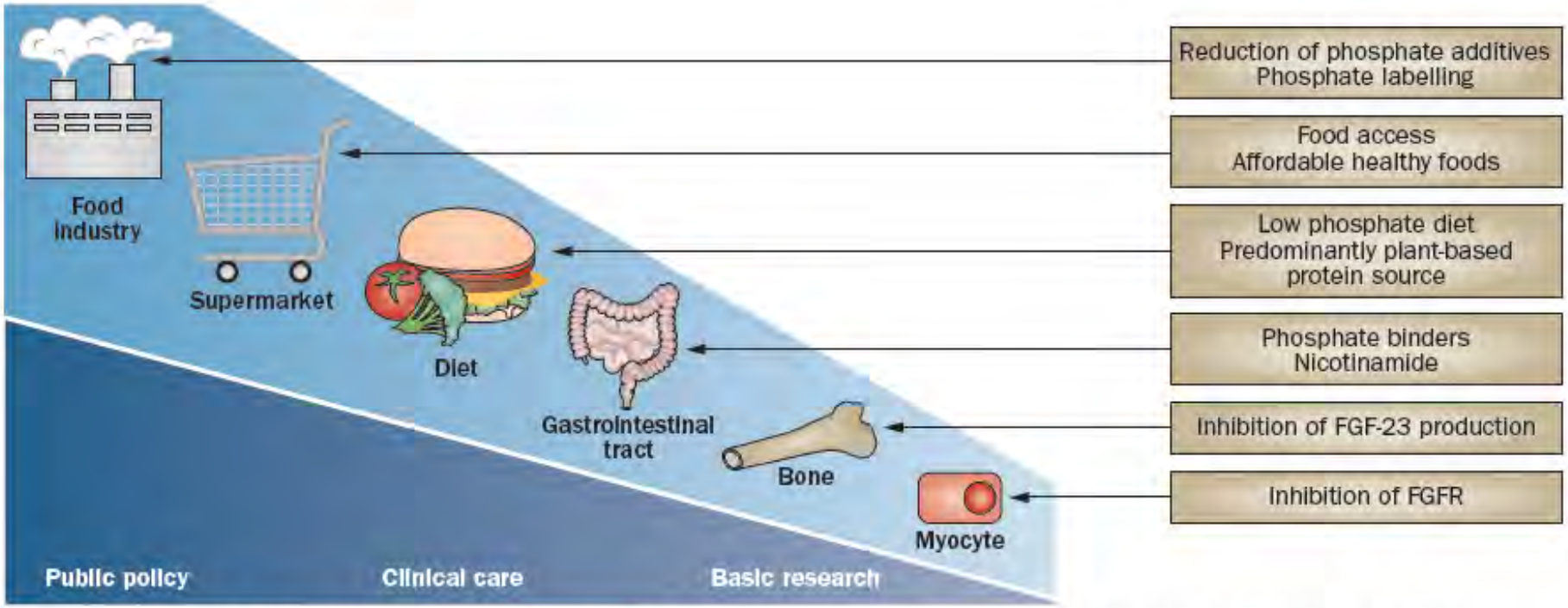


Figure 4 | Potential interventions to target phosphate homeostasis at the population, patient and molecular levels. Approaches to reduce phosphate and FGF-23 levels could engage health policy (regulation of the food industry, subsidies for healthy food), public health (public education, informative food labelling) and clinical medicine (patient education, pharmaceutical development). Abbreviations: FGF-23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor.

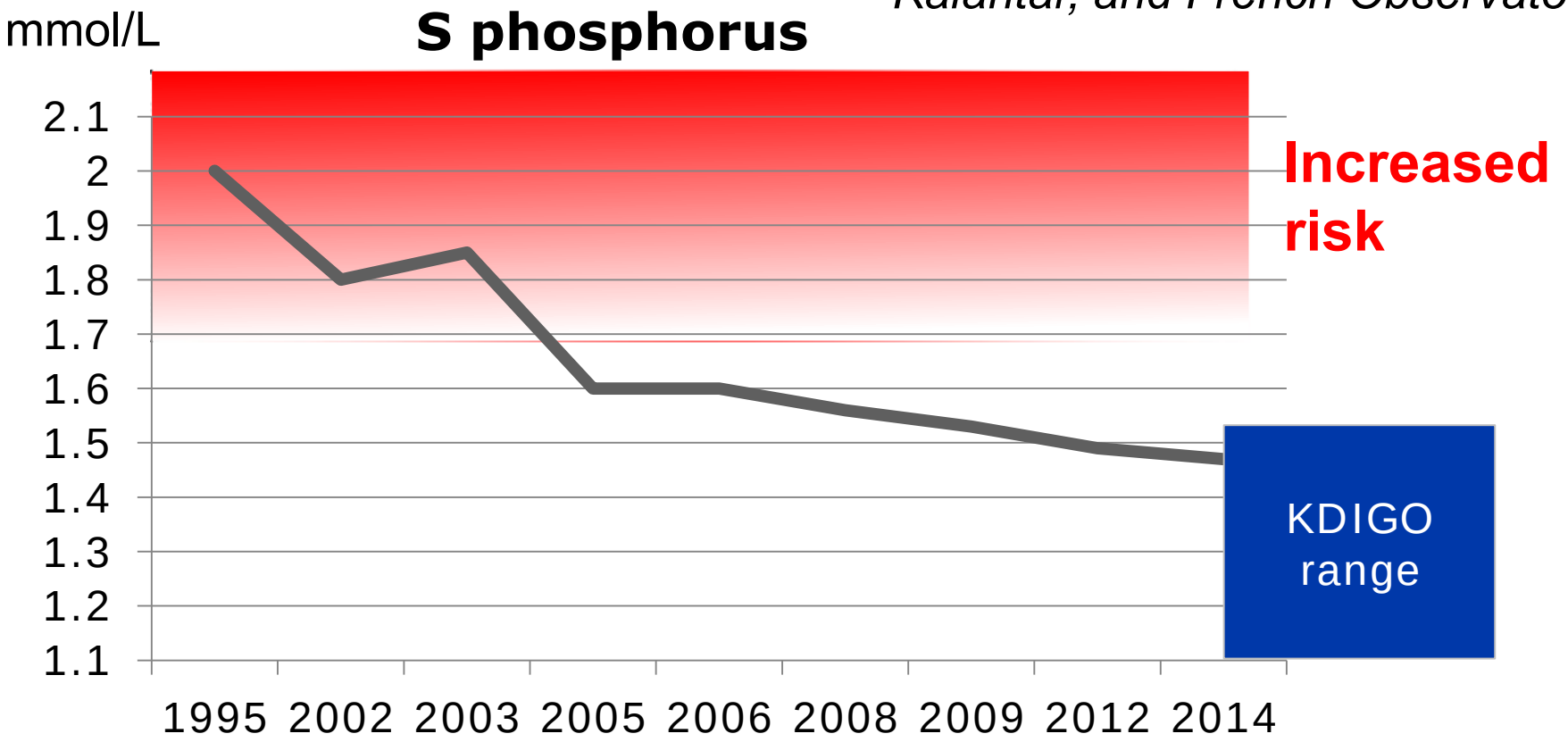
Scialla et al, Nat Rev Nephrol 2014; 10:268

Take home messages

- There is a contradiction between optimal protein intake and phosphorus intake limitation
- Reduced protein intake is associated with increased mortality in patients on maintenance dialysis; therefore, restricting dietary protein may not be the best method of controlling phosphorus intake in these patients
- Dietary phosphorus absorption is reduced by vegetable fibers
- Hidden inorganic phosphorus added in processed food is readily absorbed and can be as high as 1000 mg per day
- Phosphate binders have varying equivalent doses and differ in their calcium content, and potential effects on PTH and FGF23
- Adherence to binders is a cornerstone to the correction of phosphorus abnormalities and ways to improve adherence should be encouraged

Serum phosphate control over time in dialysis

Data compiled from Block, Dopps, Kalantar, and French Observatory



A success story !

Pelletier et al, Nephrol Dial Transplant 2011


Thank you for your attention !