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IL RUOLO DELLA VITAMINA D NEL PAZIENTE CON MALATTIE RENALI

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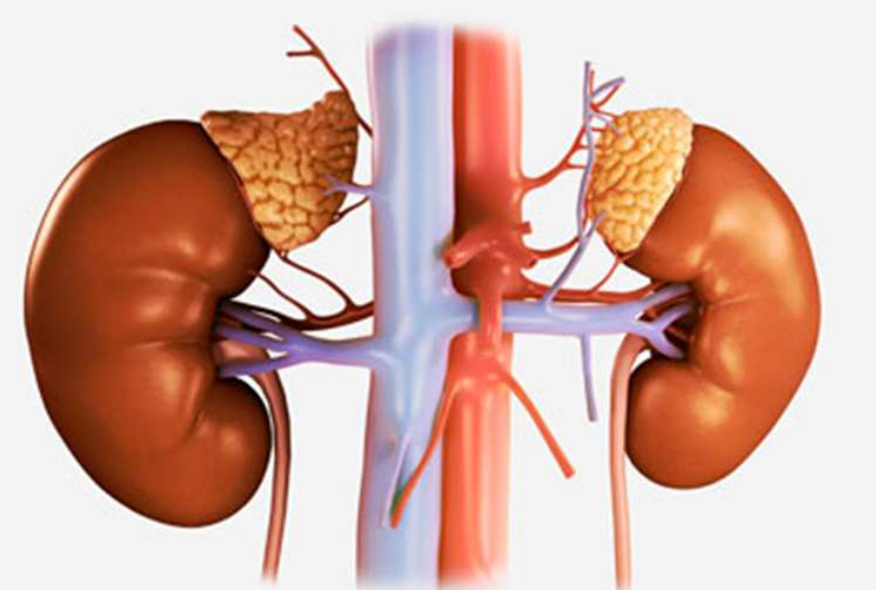
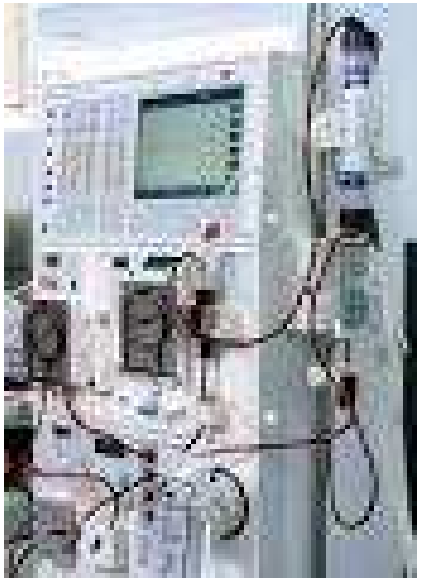
MD, PhD
UOC di Nefrologia e Dialisi

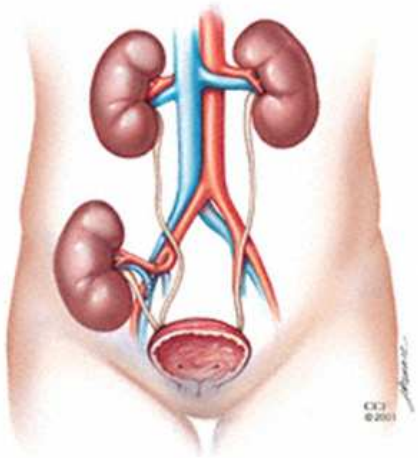
Role of Vitamin D



Chronic Kidney Disease



Dialysis



Kidney Transplant Recipients

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Review Article

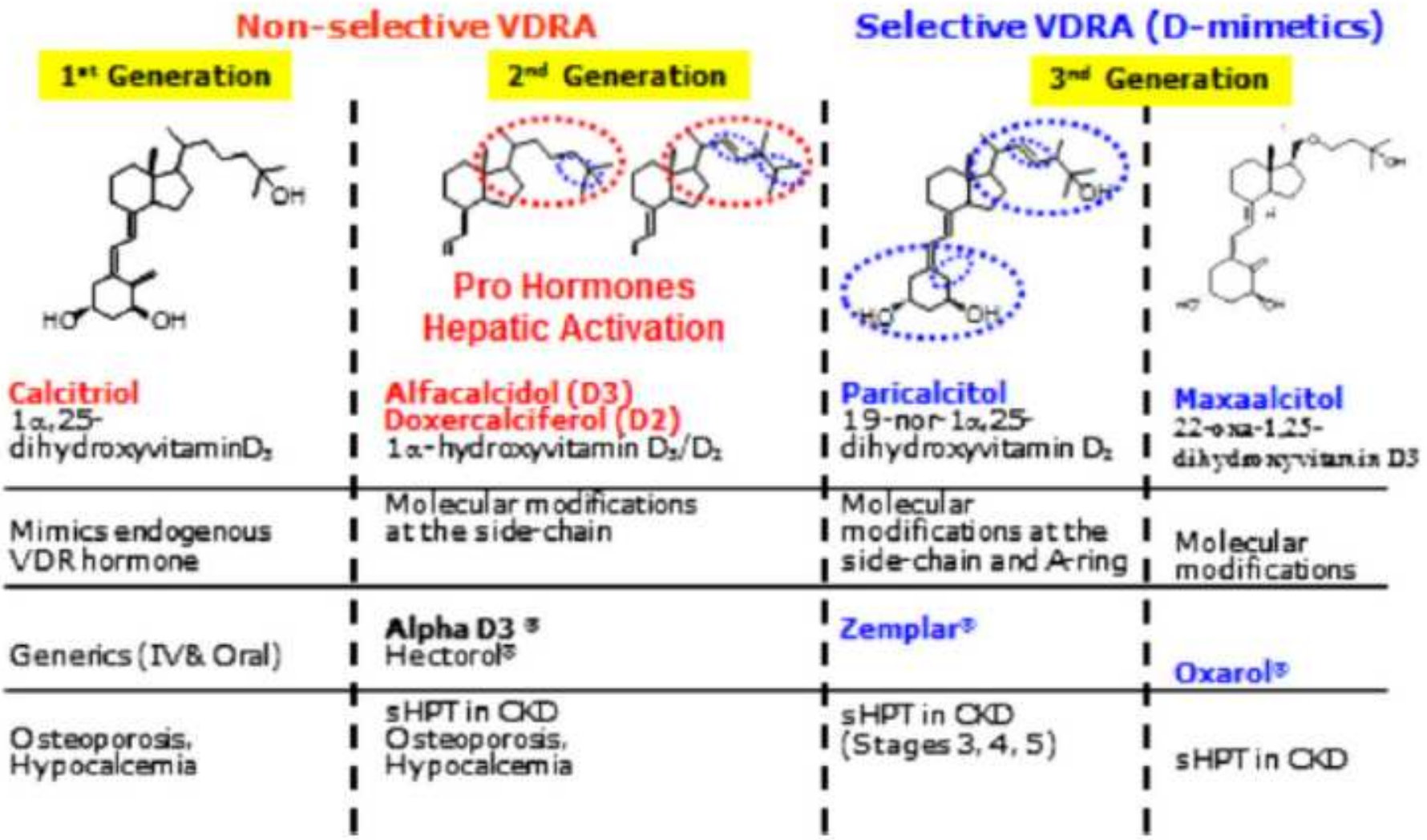
Prevalence and Prognostic Implications of Vitamin D Deficiency in Chronic Kidney Disease

	Nutritional vitamin D		VDRA	
		Hydroxylation required to activate VDR		Hydroxylation required to activate VDR
Vitamin D2 and its analogs	Ergocalciferol	25-hydroxylation and 1-hydroxylation	Paricalcitol 19-nor1,25$(OH)_2D_3$	—
			Doxercalciferol 1a$(OH)D_2$	25-hydroxylation
Vitamin D3 and its analogs	Cholecalciferol	25-hydroxylation and 1-hydroxylation	Calcitriol 1,25$(OH)_2D_3$	—
			Alfacalcidol 1a$(OH)D_3$	25-hydroxylation
	Calcifediol	1-hydroxylation	Oxacalcitriol 22oxa1,25$(OH)_2D_2$	—

	Affinity to vitamin D receptor	Serum total concentration	Half-life	Risk of hypercalcemia
25(OH)D	(1)*	9.0–34.0 ng/mL (500)*	480 hrs	Low
1,25$(OH)_2$D	(100–200)*	20–60 pg/mL (1)*	15 hrs	High

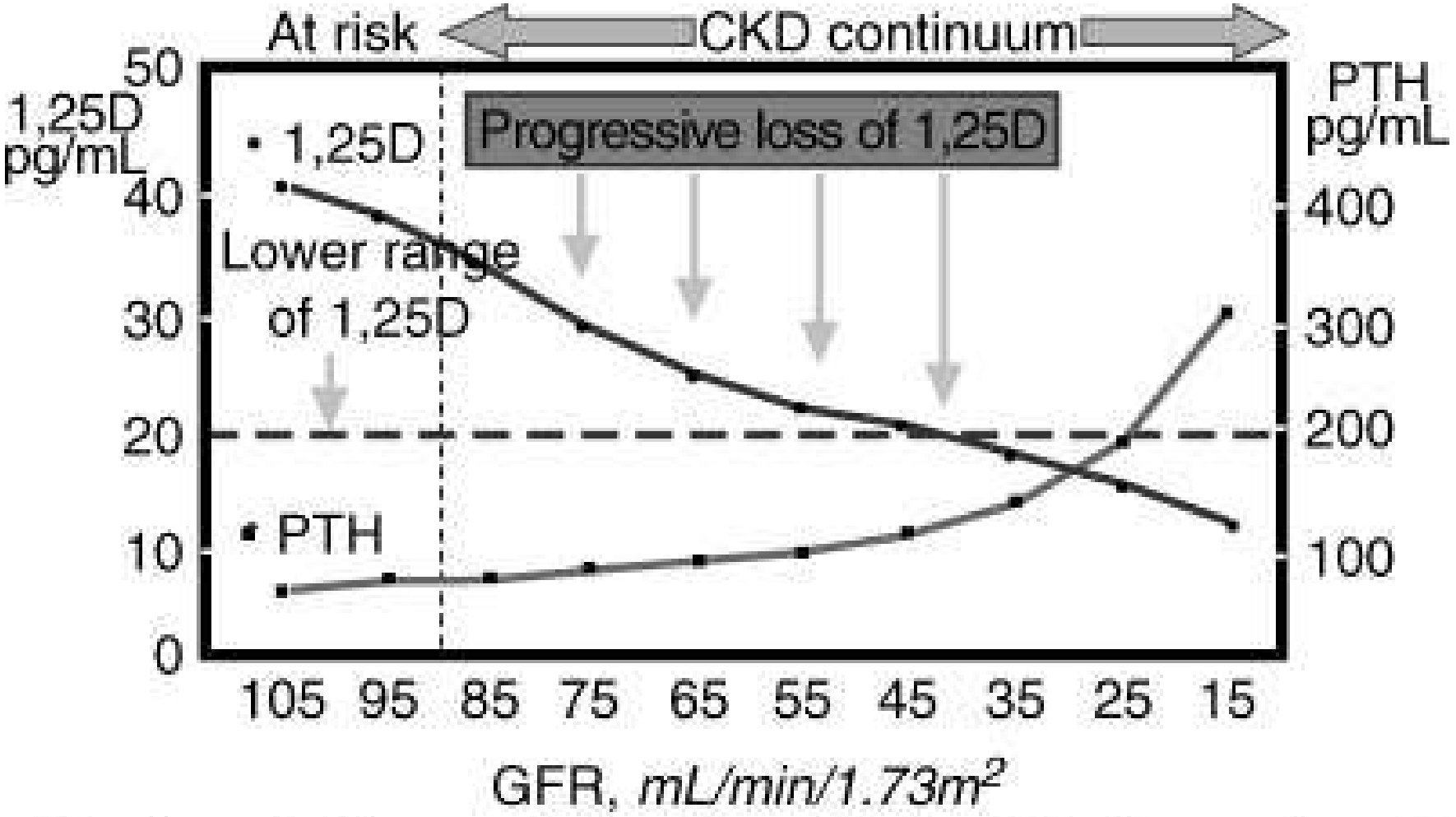
Yoshitsugu Obi et al. 2015

Calcitriol V.S. Paricalcitol



Goldsmith et al. Sem. in Nephr, 2014

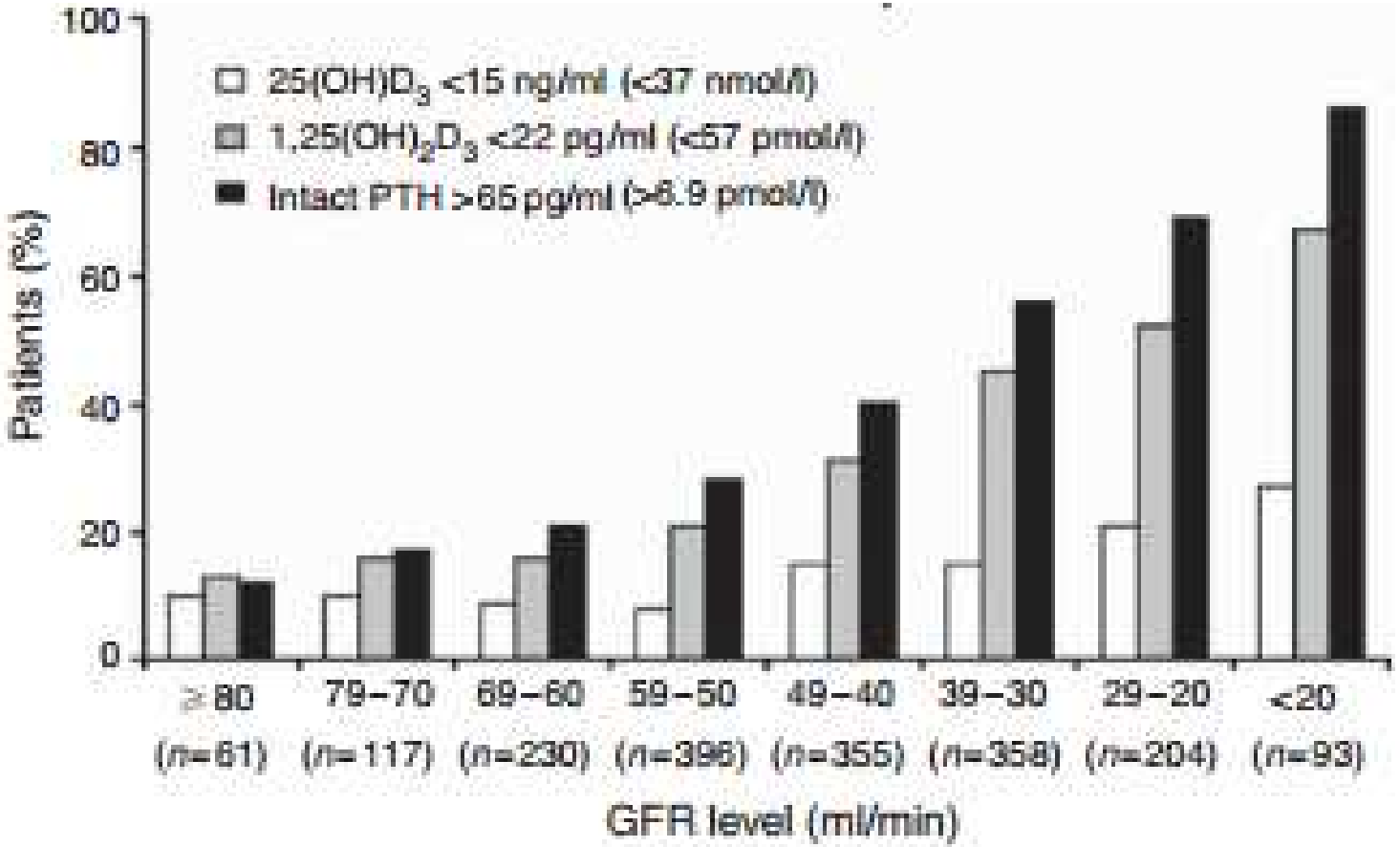
Vitamin D Physiology in CKD



Emilio Gonzalez-Parra et al. NDT 2012

Chapter 3: Management of progression and complications of CKD

Kidney International Supplements (2013) **3**, 73–90; doi:10.1038/kisup.2012.66

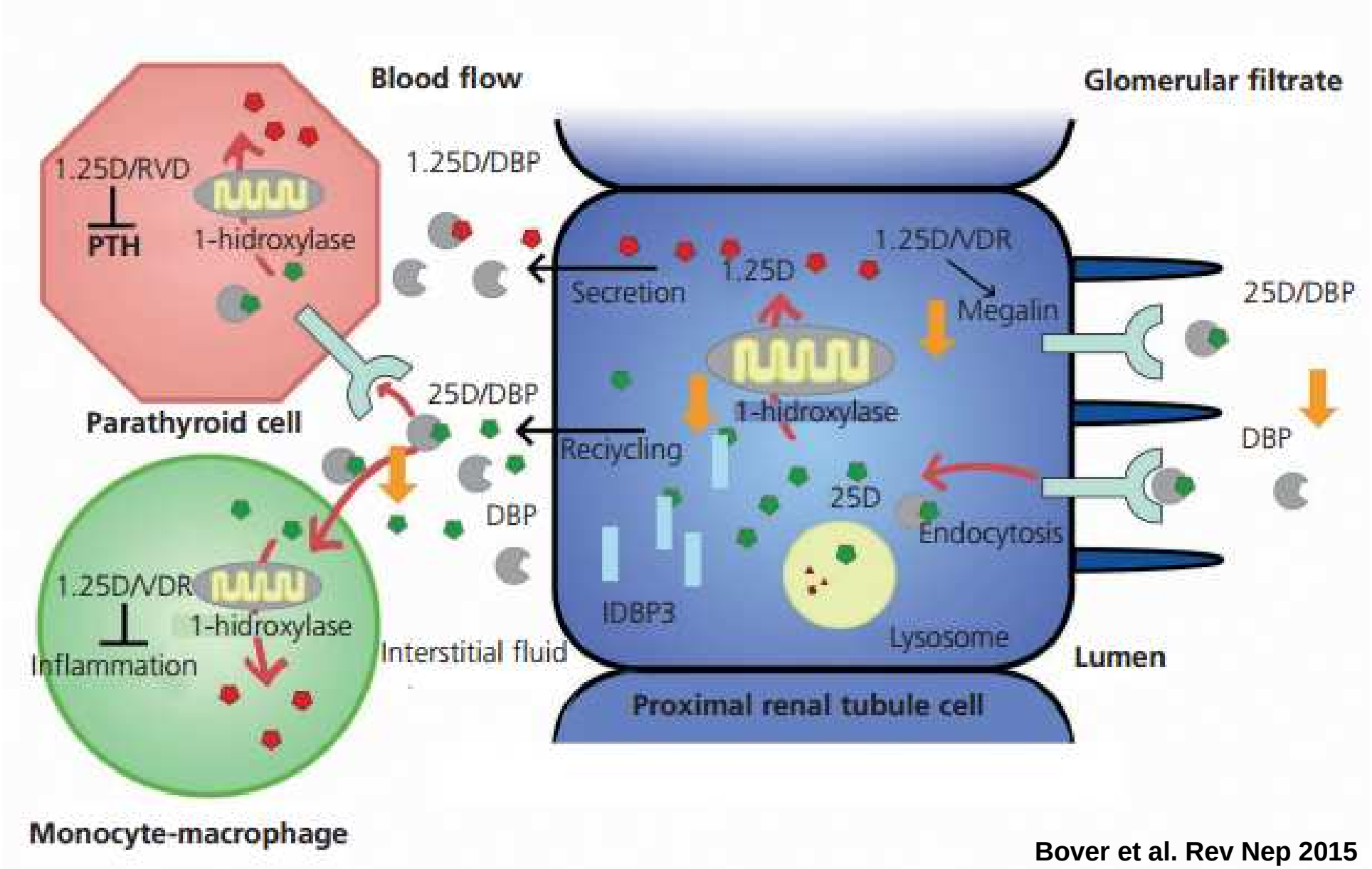


VITAMIN D STATUS IN KIDNEY TRASPLANT RECIPIENTS : AN ITALIAN COHORT REPORT

25-hydroxyvitamin D levels, ng/ml	< 10	≥ 10 - 20	≥ 20 - 30	≥30
Patient, % (n)	34.1 (45)	36.4 (48)	19.7 (26)	9.8 (13)
Age, y.	56±10	50±12	56±11	63±11 ●●
Male, %	68.2	64.6	76.9	71.4
Smokers, %	9.1	6.3	23.1	7.1
BMI kg/m2	24±3	24±3	24±3	22±4
Outdoor Workers	65.9	66.7	84.6	78.6
Dialysis Months before TX*	31±24	24±22	34±43	23±24
TX* Months	121±127	105±92	123±98	125±107
eGFR ml/min	49±27	55±17	54±17	57±20
Serum Calcium mmol/l	2.2±0.3	2.3±0.1	2.3 ±1.6	2.3±0.1
Serum Phosphorus mg/dl	3.2±0.8	3.1±0.7	3.3±0.5	3.4±0.6
Calcidiol ng/mL	6.7±1.9	14.3±3.0	24.5±2.6	32±2.3
PTH pg/ml	113±64	121±94	76±27	63±21 ●●
Urinary Calcium mmol/die	2.3±2.3	3.2±2.6	3.0±2.6	3.3±3.3
Urinary Phosphorus g/die	0.6±0.2	0.74±0.29	0.77±0.32	0.95±1.6 ●

Battaglia et al. Abstract ERA-EDTA 2016

Renal mechanism of VDR activation



Bover et al. Rev Nep 2015

Abnormal Vitamin D Physiology in CKD

Calcidiol deficiency

Reduced sun exposure, reduced skin synthesis, reduced ingestion of foods rich in vitamin D

Loss of DBP with proteinuria

Calcitriol deficiency

Reduced calcidiol availability, reduced renal 1-ahydroxylase availability, down-regulation of renal 1-α hydroxylase from hyperphosphatemia and FGF-23, reduced endocytotic uptake by megalin

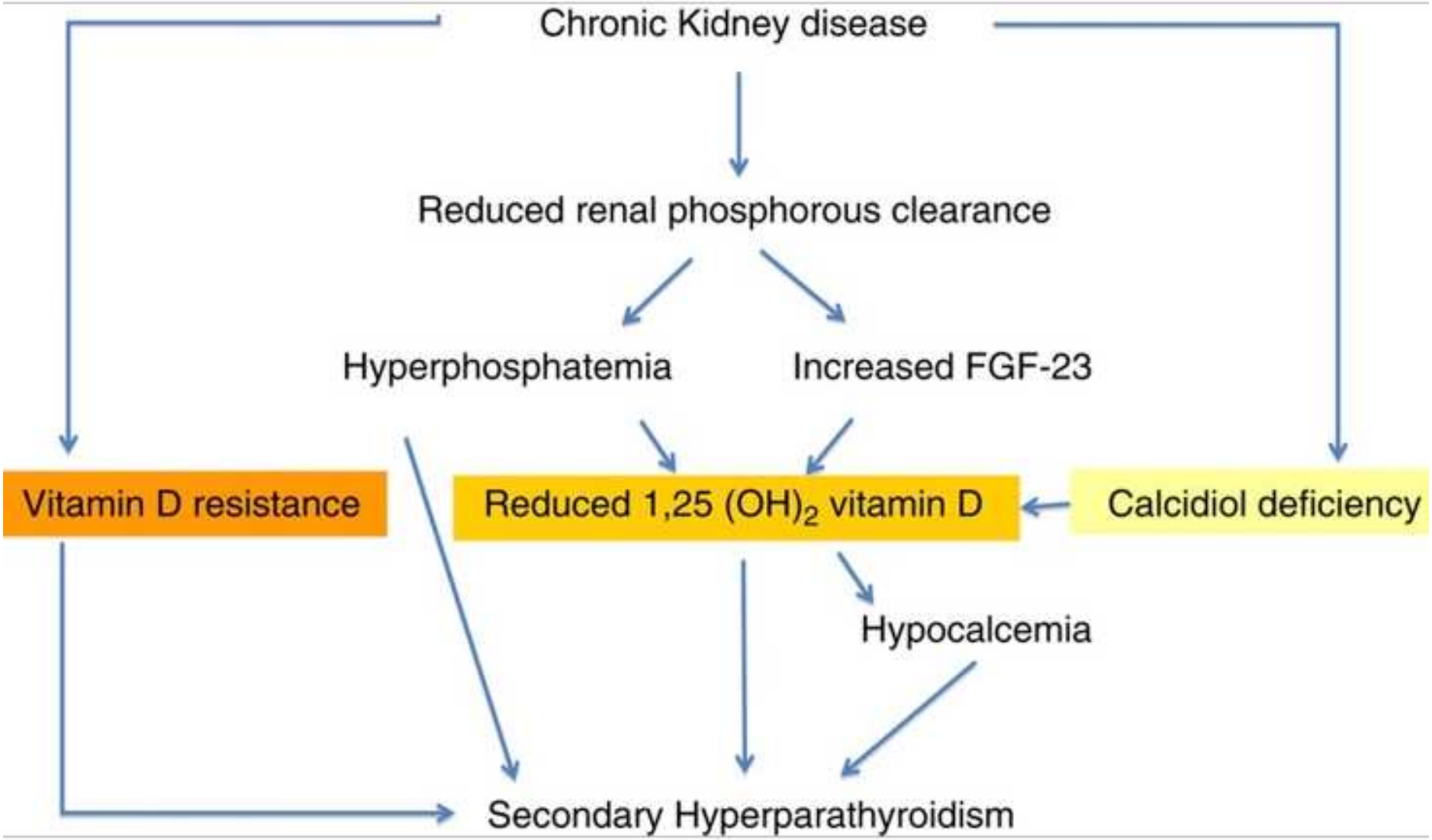
Increased degradation of calcitriol by PTH and FGF-23

Calcitriol resistance

Loss of VDR in parathyroid glands, impaired binding of active vitamin D to VDR and impaired binding of vitamin D–VDR complex to the VDR element

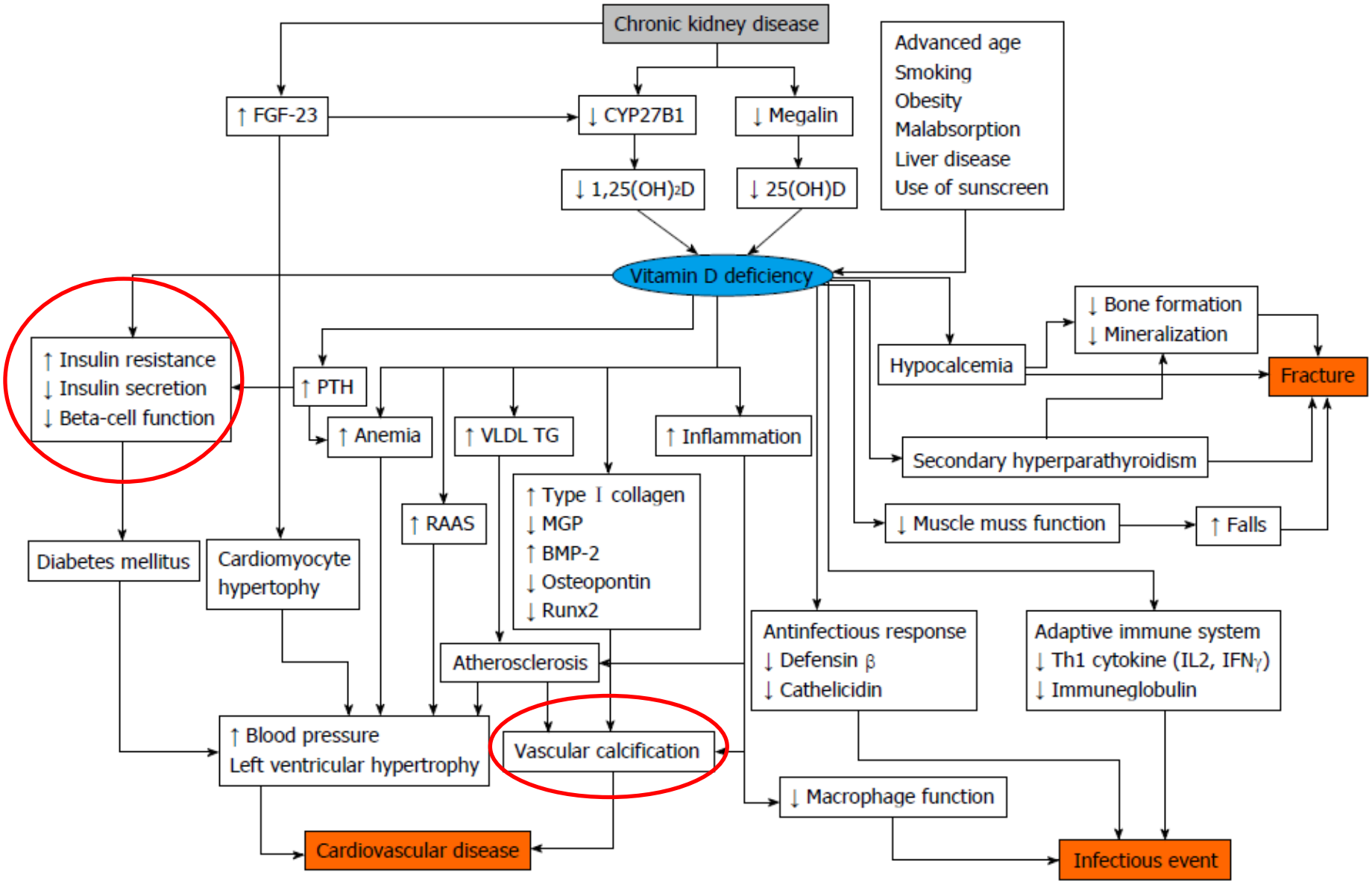
Goldsmith et al. Sem. in Nephr, 2014

“Classic” Role of Vitamin D



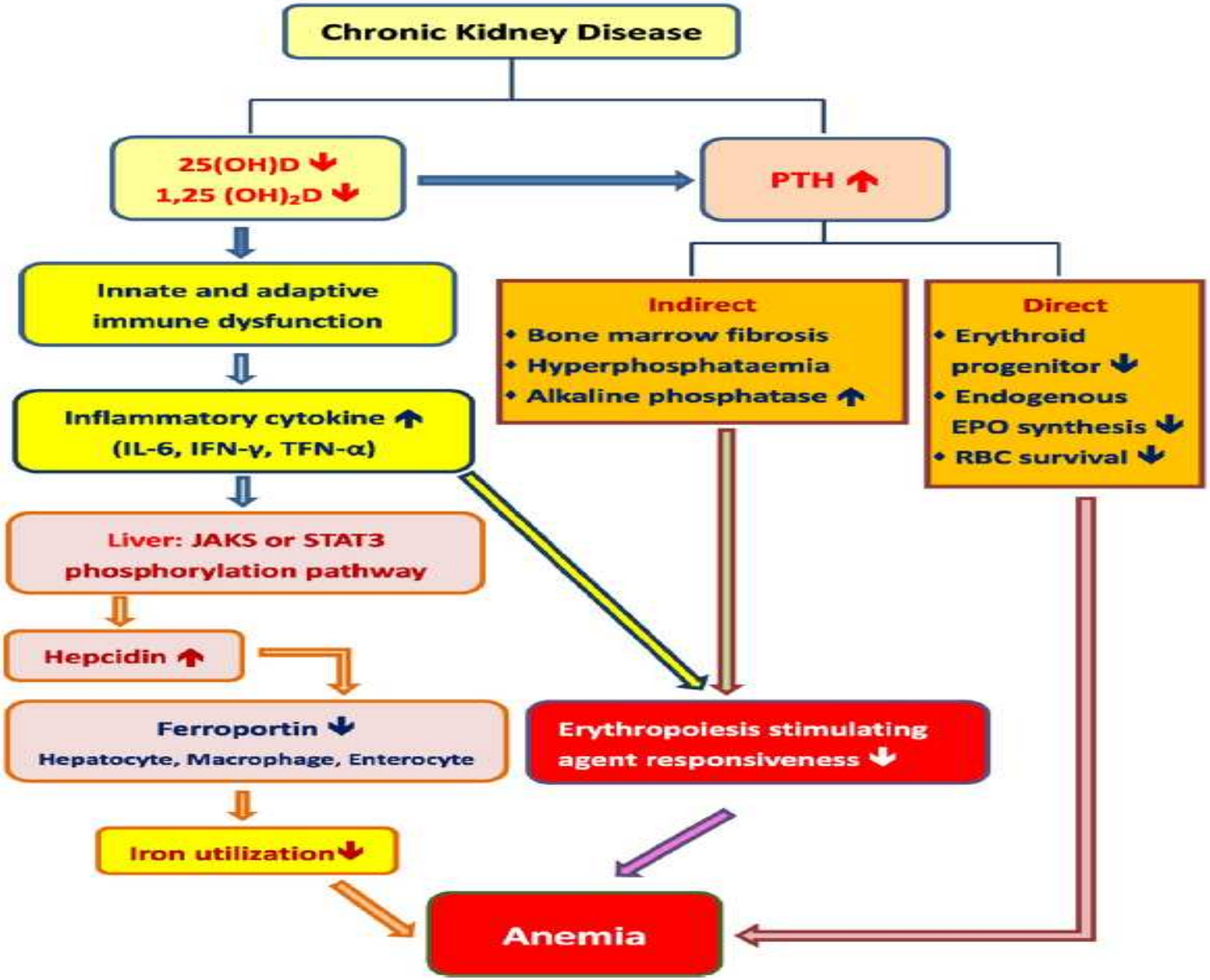
Nigwekar SU et al., Bonekey Rep. 2014

“Pleiotropic” Role of Vitamin D



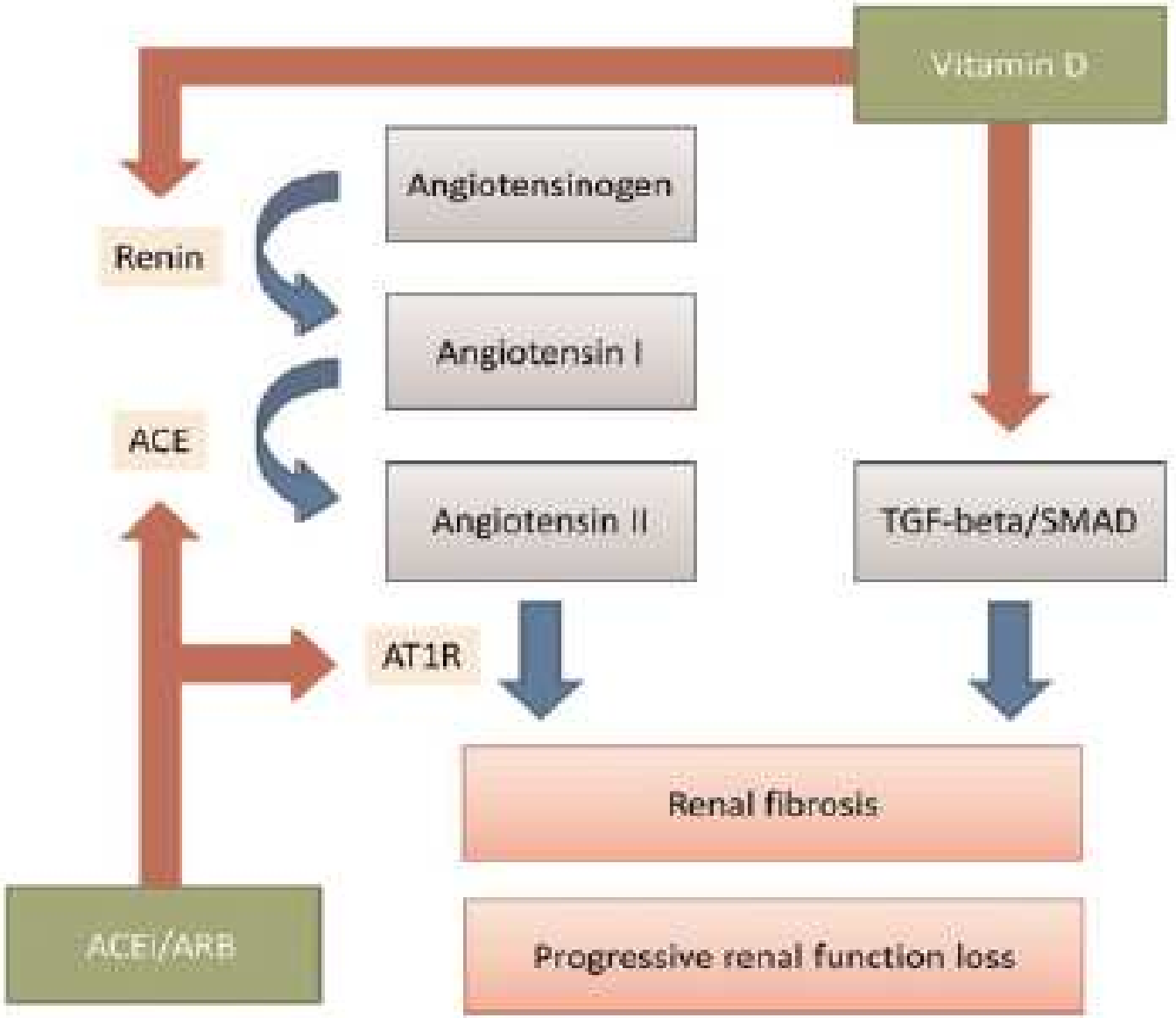
Akio Nakashima et al. WJD 2016

Vitamin D and Anemia in CKD



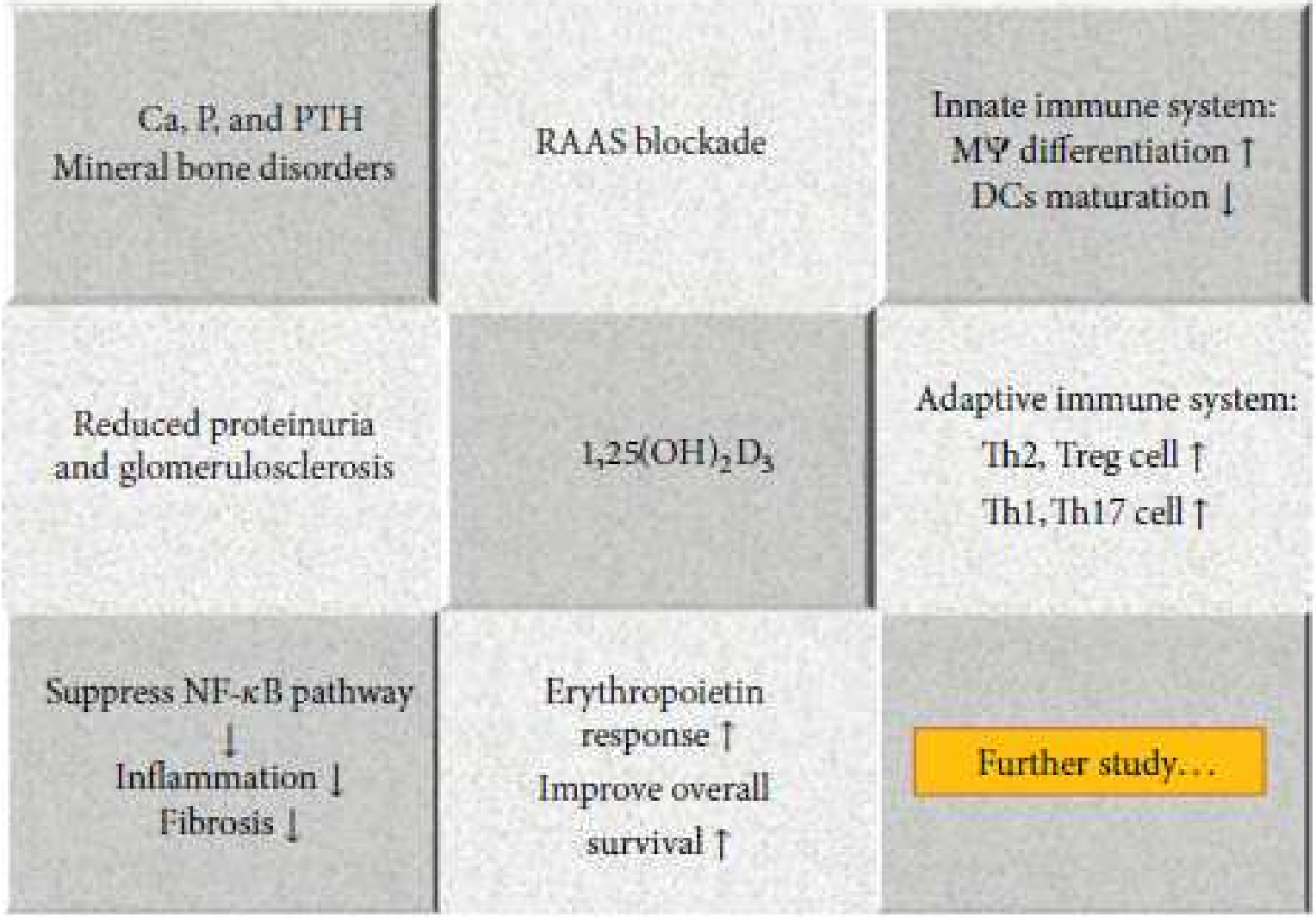
Wc Liu et al. Clinica Acta 2016

Renoprotective Role of Vitamin D



Humalda et All. NDT 2015

Vitamin D and CKD: What else??



Cheng-Lin Lang Endocrinology 2014

REVIEW Mater Sociomed. 2015 Apr; 27(2): 122-124

Vitamin D in the Patients with Chronic Kidney Disease: When, to Whom and in Which Form

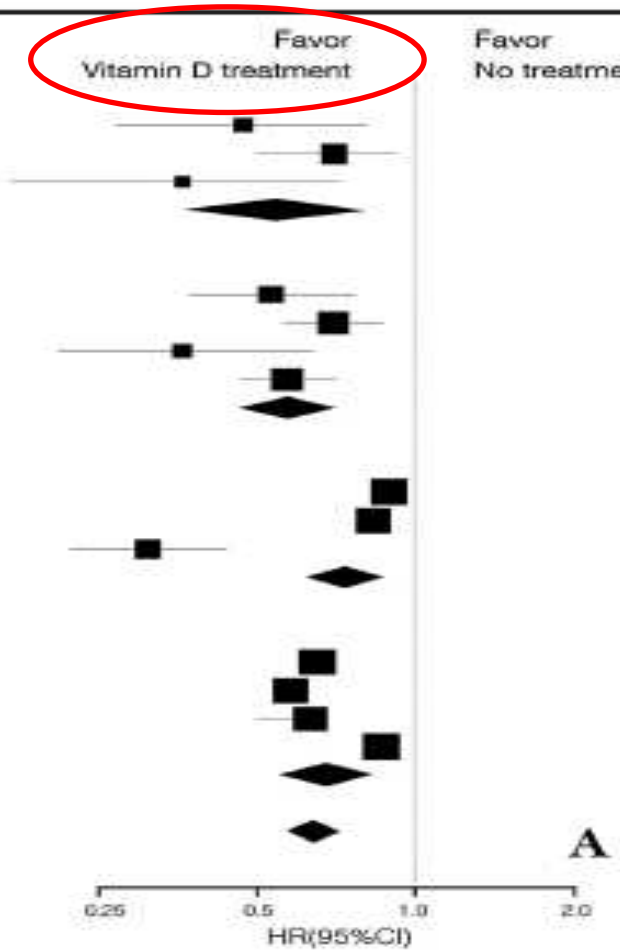
Drasko Pavlovic, Dajana Katicic, Tonko Gulin, Josipa Josipovic

RESEARCH ARTICLE Open Access

Vitamin D supplementation and mortality risk in chronic kidney disease: a meta-analysis of 20 observational studies

Zhenfeng Zheng[1], Huilan Shi[2], Junya Jia[1], Dong Li[1] and Shan Lin[1*]

Investigator	Patients (No.)	Weight (%)	Hazard Ratio (95%CI)
alfacalcidol vs no treatment			
Sugiura et al. 2010	665	3.01	0.47 (0.27-0.81)
Jean et al. 2011	648	5.96	0.70 (0.50-0.92)
Ogawa et al. 2012	190	1.98	0.36 (0.17-0.72)
Subtotal	1503	10.96	0.54 (0.37-0.80)
Heterogeity: I^2=45.4%, P=0.16			
calcitrol vs no treatment			
Kovesdy et al. 2008	520	4.99	0.53 (0.37-0.77)
Shoben et al. 2008	1418	7.53	0.70 (0.56-0.87)
Chang et al. 2009	702	2.95	0.36 (0.21-0.64)
Brancaccio et al. 2011	1889	7.60	0.57 (0.46-0.71)
Subtotal	4529	23.07	0.57 (0.46-0.70)
Heterogeity: I^2=47.8%, P=0.13			
paricalcitol vs no treatment			
Kalantar-Zadeh et al. 2006	11965	10.39	0.89 (0.85-0.93)
Shinaberger et al. 2008	16857	10.42	0.83 (0.80-0.87)
Brancaccio et al. 2011	1230	5.29	0.31 (0.22-0.44)
Subtotal	32052	26.10	0.73 (0.62-0.87)
Heterogeity: I^2=94.7%, P=0.00			
any vitamin D vs no treatment			
Tentori et al. 2006	14967	10.17	0.65 (0.61-0.70)
Naves-Diaz et al. 2008	16004	10.07	0.58 (0.54-0.63)
Wolf et al. 2008	5110	9.25	0.63 (0.50-0.65)
Tentori et al. 2009	38066	10.38	0.86 (0.82-0.90)
Subtotal	74147	39.87	0.67 (0.55-0.83)
Heterogeity: I^2=96.9%, P=0.00			
Total	112231	100.00	0.64 (0.57-0.72)
Heterogeity: I^2=93.7%; P=0.00			



Nutritional Vitamin D in CKD: Guidelines

Guidelines	25(OH)D assessment	25(OH)D targets	Replenishment	Therapeutic indication
KDOQI 2003 [K/DOQI 2003 Am J Kidney Dis]	In the presence of PTH above the recommended range	≥30 ng/ml	6 months course of ergocalciferol at escalating doses according to basal levels 25(OH)D <5 ng/ml: 50,000 IU/week orally for 12 weeks then monthly or 500,000 IU as single IM dose 25(OH)D 5–15 ng/ml: 50,000 IU/week orally for 4 weeks then monthly 25(OH)D 15–50 ng/ml 50,000 IU/month orally	First line therapy against SHPT
KDIGO 2009 [KDIGO (2009) Kidney Int suppls]	At baseline and during further treatment in CKD 3–5D	As suggested for general population	–	First line therapy against SHPT
KDIGO 2012 [KDIGO CKD (2012). Kidney Int Suppl]	Do not assess 25(OH)D routinely in the absence of suspected deficiency	–	–	Not to be prescribed in the absence of deficiency to suppress PTH
ERBP 2010 [Goldsmith DJA (2010). Nephrol Dial Transplant]	At least once in CKD 3–4	25(OH)D levels >30 ng/ml as normal; replenish if 25(OH)D <12.5 ng/ml	–	Treat SHPT and offer potential Vitamin D pleiotropic effects
NICE 2014 [NICE	In all patients with CKD 4–5	≥20 ng/ml	–	Treat 25(OH)D deficiency and SHPT

Active Vitamin D in CKD: Guidelines

Guidelines	CKD stage	PTH target	Indication to start VDRA
KDOQI 2003	3	35–70 pg/ml	Start calcitriol, or alfacalcidol, or doxercalciferol in the presence of 25(OH)D levels <30 ng/ml and PTH levels above the suggested range
[K/DOQI 2003 Am J Kidney Dis]	4	70–110 pg/ml	
	5 d	150–130 pg/ml	
KDIGO 2009	3–5	Unknown	Start calcitriol or Vitamin D analogs to raise PTH levels above the normal range despite the correction of low 25(OH)D deficiency, hypocalcemia and hyperphosphatemia
[KDIGO (2009) Kidney Int suppls]		Maintaining PTH within the normal laboratory range is suggested	
KDIGO 2012	G3b–G5	Unknown	Start VDRA in the presence of PTH levels raising above the upper normal laboratory range only after ascertained absence of suspected or documented 25(OH)D deficiency, hyperphosphatemia and hypocalcemia
[KDIGO CKD (2012). Kidney Int Suppl]		Maintaining PTH within the normal laboratory range is suggested	
ERBP 2010	–	–	–
[Goldsmith DJA (2010). Nephrol Dial Transplant]			
NICE 2014	4–5	–	Start active vitamin D (alfacalcitol or calcitriol) in patients suffering from symptomatic CKD-MBD and GFR <30 ml/min despite an achieved 25(OH)D adequacy
[NICE guidance. nice.org.uk/cg182]			

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Review Article

Which Vitamin D in CKD-MBD? The Time of Burning Questions

VDRA	Nutritional vitamin D
(i) Are VDRA superior to placebo in terms of cardiovascular events and survival?	(i) Which are the optimal thresholds independently linked to SHPT and survival?
(ii) Do vitamin D analogs provide a better achievement of patient centered outcomes compared to calcitriol?	(ii) Which is the best nutritional vitamin D regimen in terms of type and doses to replenish deficiency and treat SHPT?
(iii) Is any VDRA superior to the others in achieving KDIGO targets and improving albuminuria, LVH, VC, bone health, hospitalizations, and survival?	(iii) Will the replenishment be a cost-effective prevention against SHPT and CKD-MBD?
(iv) Will paricalcitol ameliorate CKD progression and cardiovascular events through the benefits on albuminuria and LVH?	(iv) Will the replenishment improve CKD progression, diabetes, infections, and survival?
(v) Should VDRA be suspended in those patients reaching PTH levels ≤ 150 pg/mL?	(v) Will the coadministration of native and active vitamin D be additive against CKD-MBD, infections, diabetes, and mortality?

Galassi et al. 2014

Vitamin D in patients with chronic kidney disease: a position statement of the Working Group "Trace Elements and Mineral Metabolism" of the Italian Society of Nephrology

- Optimal 25(OH)D levels are still not defined: 25(OH)D levels 30 ng/ml
- The best therapeutic strategy to replenish 25(OH)D status is unknown
- Treatment should be discontinued with 25(OH)D levels 100 ng/ml
- Assessing 25(OH)D levels twice a year,at the end of winter and of summer
- Active vitamin D therapy should be started in patients in CKD stages 3–5 with PTH above the normal range and normal levels of circulating 25(OH)D in the absence of hypercalcemia and/or hyperphosphatemia.
- The potential additive effect of VDRA warrants confirmation in further RCTs on the long run.

Morrone et al. JN 2016

Grazie per l’attenzione