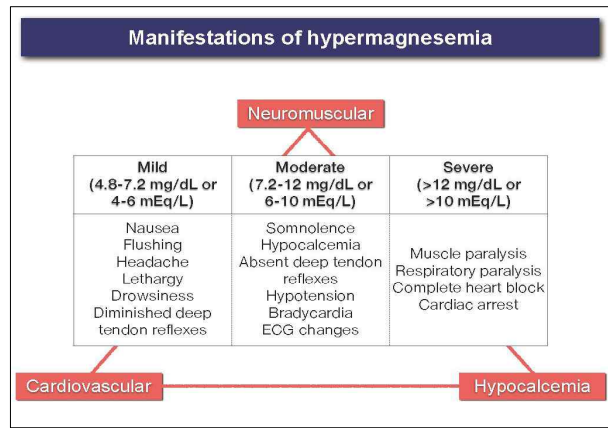
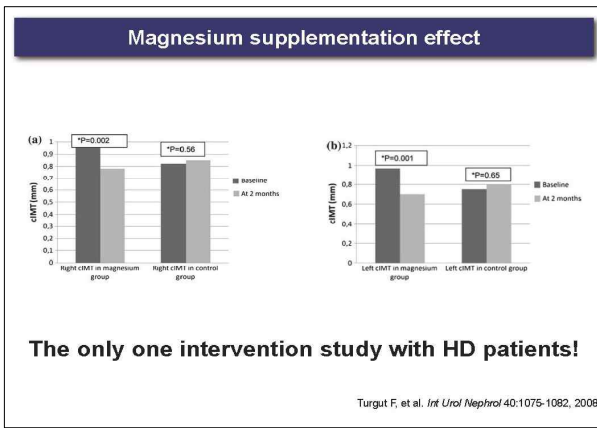
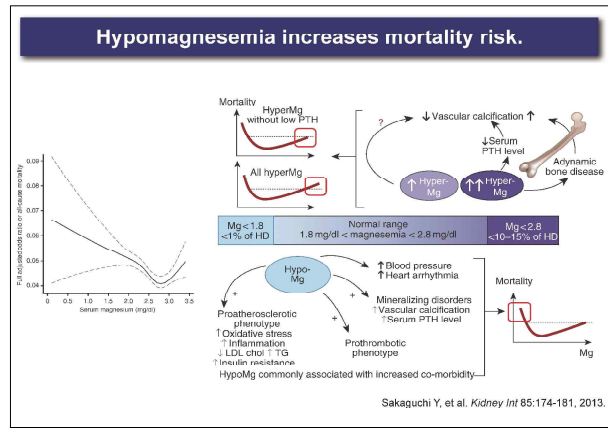
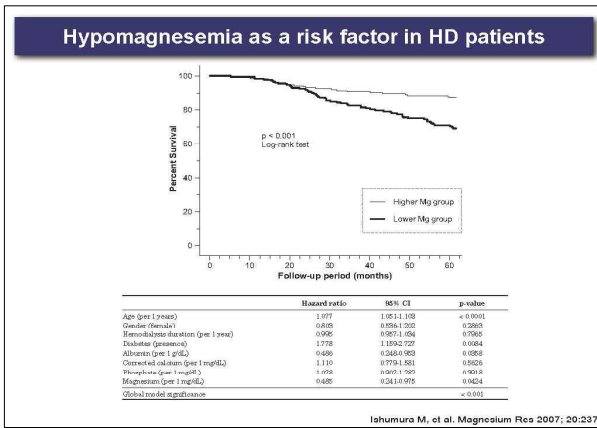


Problem Areas – Cardiovascular Disorder

Is Mg Supplementation Beneficial in HD Patients?

이화여자대학교 신장내과

류 동 열



Conclusions

Hypomagnesemia may be significantly associated with an increased risk of mortality in HD patients.

Interventional studies are needed to clarify whether magnesium supplementation is beneficial for improving patient prognosis.

마그네슘 기반의 인결합제

이화여자대학교 의학전문대학원 내과학교실

류동열

각종 초기 지표들이 사망위험도에 미치는 영향

Inorganic phosphate is a true uremic toxin !!!

Block GA, et al. *J Am Soc Nephrol* 16(9):2209-2219, 2001.

CKD-Mineral & Bone Disorder (MBD)

★ Definition: A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolites
- Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
- Vascular or other soft tissue calcification

CHRONIC KIDNEY DISEASE—MINERAL AND BONE DISORDER

CKD-MBD

Moe S, et al. *Kidney Int* 69: 1945, 2006

Analysis from DOPPS

Phosphorus, mg/dL

Yeung EW, et al. *Kidney Int* 67:1179-1187, 2005
Kimata N, et al. *Hemodial Int* 11:340-348, 2007.

고인산혈증은 사망율을 증가시킨다

Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) for Mortality
Alkaline mortality	3	4681	1.20 (1.01-1.41)
Refine adjustment	10	87694	1.15 (1.05-1.23)
All studies combined	13	92545	1.15 (1.01-1.33)
Cardiovascular mortality	1	17326	Not estimable
Refine adjustment	2	5881	1.14 (1.05-1.24)
All studies combined	3	22567	1.10 (1.04-1.17)

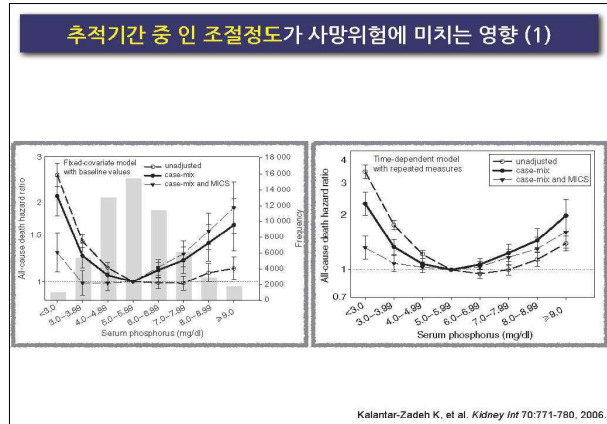
Phosphorus	No. of Cohorts	No. of Participants	Relative Risk (95% CI) for Mortality
Alkaline mortality	1	17326	Not estimable
Refine adjustment	3	87732	1.01 (0.90-1.03)
All studies combined	4	101958	1.01 (0.90-1.03)
Cardiovascular mortality	1	17326	Not estimable
Refine adjustment	1	5041	Not estimable
All studies combined	2	22567	1.00 (0.91-1.11)

Calcium	No. of Cohorts	No. of Participants	Relative Risk (95% CI) for Mortality
Alkaline mortality	2	20367	1.07 (0.91-1.24)
Refine adjustment	6	32759	1.00 (0.90-1.03)
All studies combined	8	190166	1.00 (0.90-1.06)
Cardiovascular mortality	1	17326	Not estimable
Refine adjustment	1	2041	Not estimable
All studies combined	2	22567	1.15 (1.08-1.23)

Palmer SC, et al. *JAMA* 2011; 305:1119

CKD-MBD의 치료 권고안 별 목표치

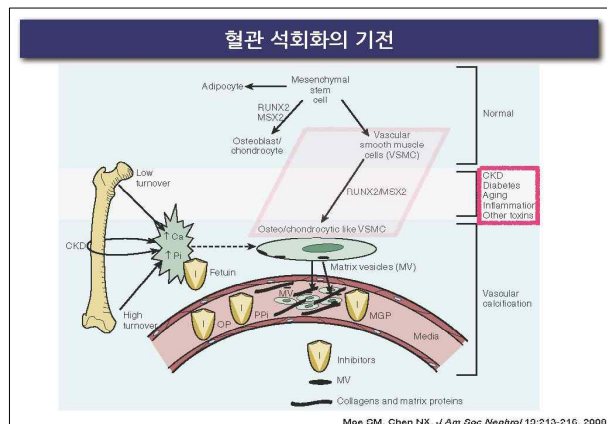
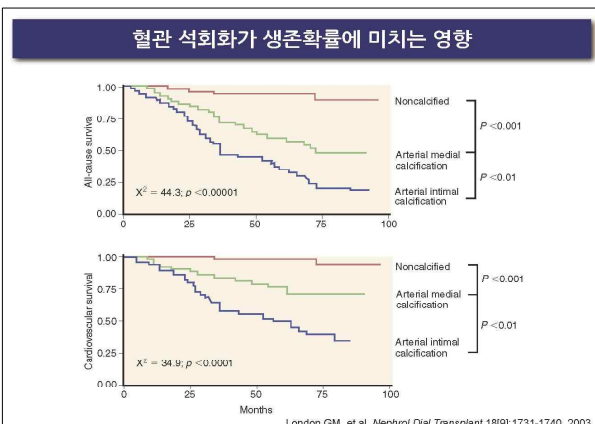
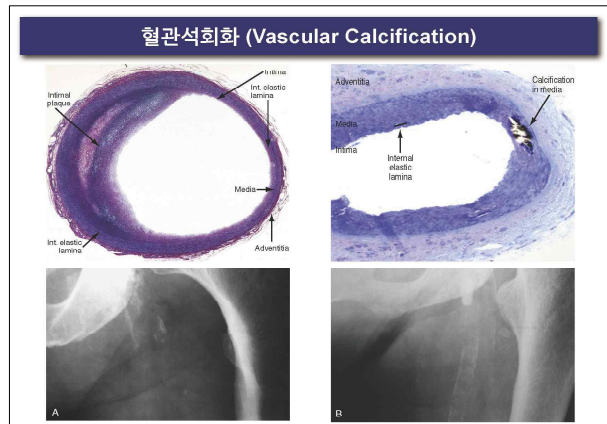
CKD STAGE	GFR (mL/min/1.73 m)	Guideline	Phosphorus (mg/dL)	Corrected Ca (mg/dL)	Ca X P	Intact PTH (pg/mL)
3	30-59	K/DOQI	2.7-4.6	8.4-10.2		35-70
		KDIGO	Same range as general population			
4	15-29	K/DOQI	2.7-4.6	8.4-10.2		70-110
		KDIGO	Same range as general population			
5	< 15, dialysis	K/DOQI	3.5-5.5	8.4-9.5	< 55	150-300
		KDIGO	Normal range. Avoid hyperphosphatemia	Normal range. Avoid hypercalcemia	Use not endorsed	Avoid PTH <2 or >9 times the upper normal limit

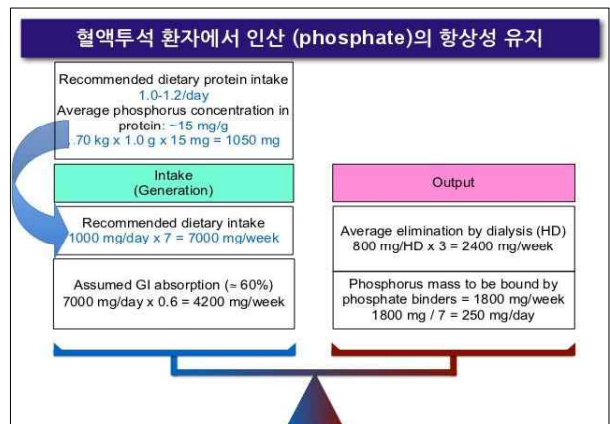
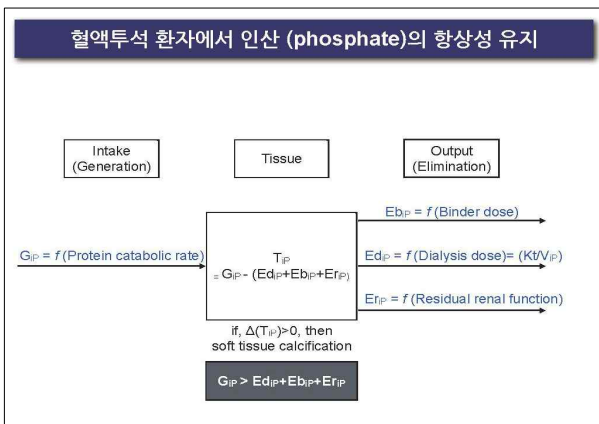
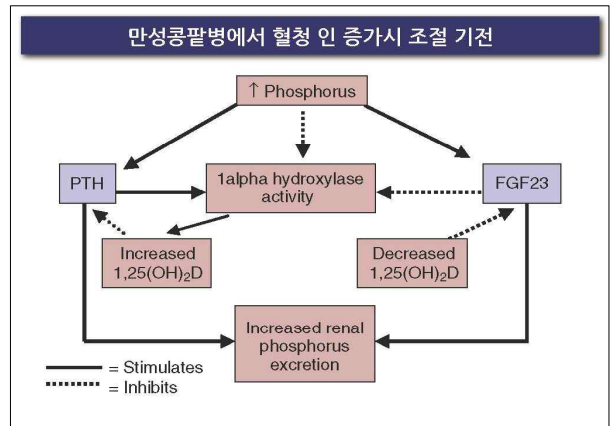
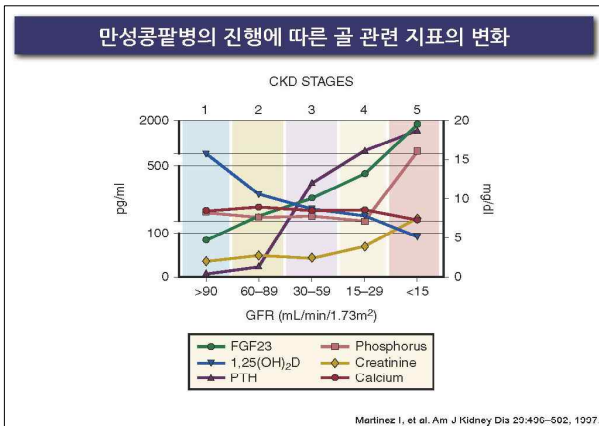
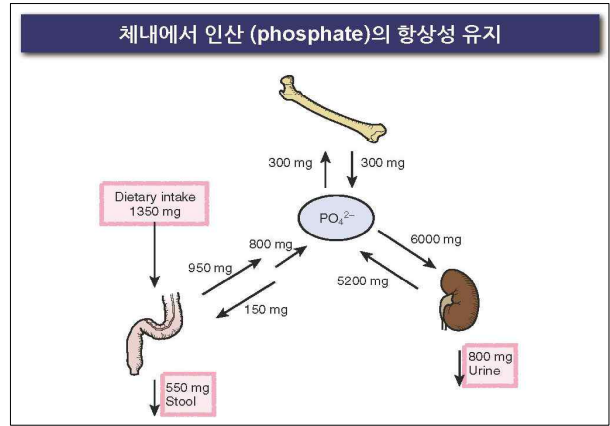
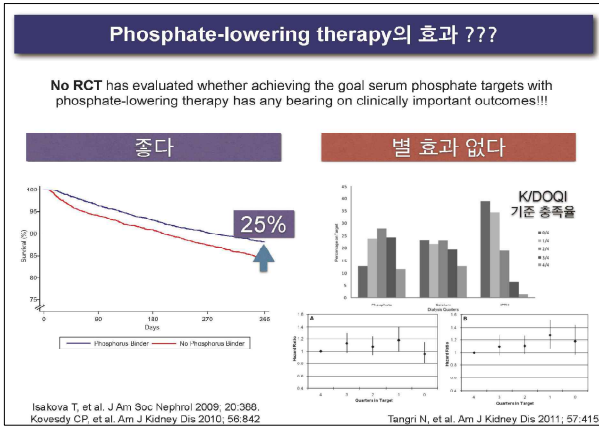


추적기간 중 인 조절정도가 사망위험에 미치는 영향 (2)

	Baseline values as predictors (n=552)	Time-dependent predictors with 6-month lag (n=578)	Time-dependent predictors (n=592)
Serum calcium (mg/dL) quartile level			
< 8.97	0.92 (0.60-1.39)	0.91 (0.58-1.43)	1.31 (0.83-2.05)
8.97-9.33	1.0 (reference)	1.0 (reference)	1.0 (reference)
9.33-9.73	1.13 (0.79-1.64)	1.17 (0.76-1.80)	1.33 (0.85-2.07)
> 9.73	1.05 (0.69-1.62)	1.37 (0.93-2.02)	1.52 (1.02-2.26)*
Serum phosphate (mg/dL) quartile level			
< 4.3	1.04 (0.79-1.53)	1.36 (0.89-2.06)	1.10 (0.74-1.64)
4.3-5.1	1.0 (reference)	1.0 (reference)	1.0 (reference)
5.1-6.0	1.01 (0.69-1.47)	1.83 (1.20-2.72)**	1.08 (0.70-1.67)
> 6.0	1.54 (1.01-2.35)*	1.41 (0.93-2.13)	1.57 (1.01-2.35)*
Serum CaP (mg ² /dL ²) quartile level			
< 40.2	0.94 (0.64-1.39)	1.11 (0.73-1.68)	1.30 (0.85-1.98)
40.2-42.7	1.0 (reference)	1.0 (reference)	1.0 (reference)
42.7-46.4	1.03 (0.71-1.49)	1.37 (0.90-2.07)	1.50 (0.98-2.31)
> 46.4	1.35 (0.89-2.05)	1.28 (0.86-1.89)	1.87 (1.25-2.82)**
Serum PTH (pg/mL) quartile level			
< 76	0.77 (0.51-1.19)	0.65 (0.44-0.98)*	0.86 (0.55-1.33)
76-160	1.03 (0.68-1.55)	0.67 (0.43-1.04)	1.01 (0.64-1.59)
160-308	1.0 (reference)	1.0 (reference)	1.2 (reference)
> 308	0.84 (0.55-1.28)	1.23 (0.76-1.98)	1.68 (1.21-2.28)*
No vitamin D medication use	1.0 (reference)	1.0 (reference)	1.0 (reference)
Vitamin D medication use	0.62 (0.44-0.86)*	0.73 (0.54-0.98)*	0.74 (0.56-1.03)*

Malamat MI, et al. *Kidney Int* 77:351-357, 2006





혈액투석 환자에서 혈중 인산 농도 저하 방법

- 1 Removal
- 2 Restriction
- 3 Inhibition
- 4 Preservation

혈액투석을 통한 인산 제거의 특성

혈액투석을 통해 인산 제거를 증가시키는 방법

$\frac{Kt}{V_{iP}}$

Kuhlmann MK. *Hemodial Int* 10:338-345, 2006.

인 섭취량을 줄이기 위해 알아야 할 것들 (1)

3 major sources

- Natural phosphorus contained to raw or unprocessed food as cellular and protein constituents
 - Milk and milk products: 20-30%
 - Meat, poultry, and fish: 20-30%
 - Grain products: 20-30%
- Phosphorus added to foods during processing (4/0 mg/day in 1990 and can be increased by as much as 1 g/day)
 - Restructured meats (chicken nuggets & hot dogs)
 - Processed & spreadable cheeses
 - "Instant" products (puddings & sauces)
 - Refrigerator bakery products
 - Beverages
- Phosphorus contained to dietary supplements
 - Multivitamins (< 150 mg/pill)

Uribarri J et al. *Semin Dial* 16:186-188, 2003.

인 섭취량을 줄이기 위해 알아야 할 것들 (2)

Bioavailability

- Natural phosphorus contained to raw or unprocessed food as cellular and protein constituents
 - Milk and milk products
 - Meat, poultry, and fish
 - Grain products

~60%
- Phosphorus added to foods during processing (470 mg/day in 1990 and can be increased by as much as 1 g/day)
 - Restructured meats (chicken nuggets & hot dogs)
 - Processed & spreadable cheeses
 - "Instant" products (puddings & sauces)
 - Refrigerator bakery products
 - Beverages

~100%
- Phosphorus contained to dietary supplements
 - Multivitamins (< 150 mg/pill)

Uribarri J et al. *Semin Dial* 16:186-188, 2003.

인 섭취량을 줄이기 위해 알아야 할 것들 (3)

Source	Type	Examples	GI absorption	Phosphorus-to-Protein ratio	Advantage
Plant protein	Organic	Nuts Beans Chocolate	20-40%	5-15 mg/g	Protein gain
Animal protein	Organic	Fish Meat Chicken	40-60%	10-20	High value protein & amino acid
Additives Preservatives Enhanced foods Processed foods Fast food	Inorganic	Soft drink Fast food	~100%	> 50	No gain

인 섭취량을 줄이기 위해 알아야 할 것들 (4)

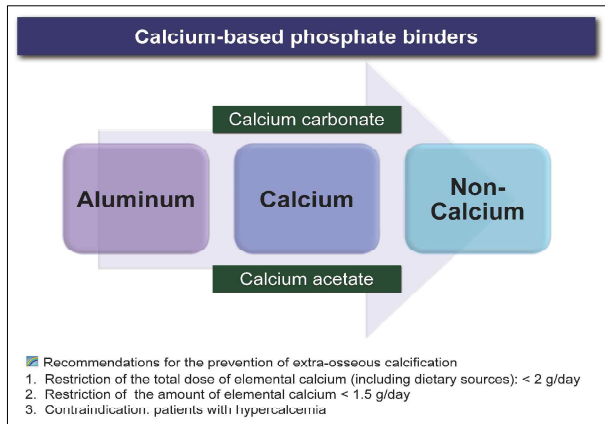
식품	인 함유량 (100g 기준)	음료	인 함유량 (340 mL 기준)
코카콜라 클래식	17	인 < 10 mg	
우유 (지방 3.3%)	93	환타 (오렌지맛 이외)	< 10
바닐라 아이스크림	105	미닛메이드	< 10
캠데기 계거한 닭고기	147	마운틴듀	< 10
닭 간	175	네스티 (레몬향)	< 10
슬라이스 빵	247	펄시 (펄시 내추럴)	< 10
냉지크기 우유살	252	스프라이드	< 10
달걀	376	인 > 10 mg	
체다 치즈	512	코카콜라	62
		다이아트 콜라	27
		환타 (오렌지맛)	11
		게토레이	36
		립톤아이스티	98-114
		네스티 (레몬향 이외)	47-71
		펄시 (펄시 내추럴 이외)	54

인 결합제

- ★ The principal rationale
 - Hyperphosphatemia is associated with increased mortality in ESRD
 - Phosphate is the principal factor leading to calcification of extracellular matrix.
- ★ Adequate evidence with regard to mortality does not exist at present to favor non-calcium- over calcium- based phosphate binders.
- ★ Some data suggest that vascular calcification is attenuated with sevelamer compared with calcium containing binders; however, there is no evidence that this translates into clinically important outcomes.
- ★ Effects on bone histology are largely similar between non-calcium- and calcium-based phosphate binders. However, calcium containing phosphate binders are associated with increased calcium levels and decreased serum PTH levels compared with non-calcium containing phosphate binders.
- ★ The optimal choice of phosphate binder depends upon the serum calcium level and PTH level, presence of adynamic bone disease on bone biopsy and/or vascular calcification, and side effects.

CKD-MBD의 치료제

AGENTS	TARGET	PTH	FGF23	Ca	P	COST	RISK
Calcium-based binders							
Calcium carbonate	Intestinal Phosphate Absorption	↓	I	↑	↓	Lowest	Hypercalcemia
Calcium acetate		↓	I	↑	↓	Low	Vascular calcifications
Calcium-free binders							
Sevelamer HCl	Intestinal Phosphate Absorption	↔	I	↔	↓	High	Acidosis, GI tolerance
Sevelamer carbonate		↔	I	↔	↓	High	GI tolerance
Lanthanum carbonate		↔	I	↔	↓	High	Lanthanum retention
Aluminum hydroxide		↔	I	↔	↓	Low	Aluminum retention
Magnesium							
Vitamin D sterols	VDR	↓	↑	↑	↑	High	Hypercalcemia
Cinacalcet HCl	CaSR	↓	↓	↓	I	Highest	Hypocalcemia Nausea/Vomiting



Sevelamer (vs. Calcium-based binders)

좋다

별 차이 없다

Mortality

Block GA, et al. *Kidney Int* 2005; 68:1815.
 Di Iorio B, et al. *Clin J Am Soc Nephrol* 2012; 7:487.
 Di Iorio B, et al. *Am J Kidney Dis* 2013; 62:771.

Suki WN, et al. *Kidney Int* 2007; 72:1130.
 Tonelli M, et al. *Nephrol Dial Transplant* 2007; 22:2856.
 St Peter WL, et al. *Am J Kidney Dis* 2008; 51:445.

Calcification

Chertow GM, et al. *Kidney Int* 2002; 62:245.
 Block GA, et al. *Kidney Int* 2005; 68:1815.
 Block GA, et al. *Kidney Int* 2007; 71:438.
 Chertow GM, et al. *Nephrol Dial Transplant* 2004; 19:1489.

Qunibi W, et al. *Am J Kidney Dis* 2008; 51:952.

Bone histology

Ferreira A, et al. *J Am Soc Nephrol* 2008; 19:405.
 Barreto DV, et al. *Nephron Clin Pract* 2008; 110:c273.
 Salusky IB, et al. *J Am Soc Nephrol* 2005; 16:2501.

Sevelamer (vs. Calcium-based binders)

좋다

안 좋다

Lower Ca, Higher P & PTH

Serologic parameters

Chertow GM, et al. *Kidney Int* 2002; 62:245.
 Block GA, et al. *Kidney Int* 2005; 68:1815.
 Block GA, et al. *Kidney Int* 2007; 71:438.
 Chertow GM, et al. *Nephrol Dial Transplant* 2004; 19:1489.
 Qunibi W, et al. *Am J Kidney Dis* 2008; 51:952.
 Kestenbaum B, *Am J Kidney Dis* 2008; 51:877.

Metabolic acidosis

Sevelamer hydrochloride (Renagel) >
 Sevelamer carbonate (Renvela)

Delmez J, et al. *Clin Nephrol* 2007; 68:386.

Economic impact

Manns B, et al. *Kidney Int* 2004; 66:1239.
 Manns B, et al. *Nephrol Dial Transplant* 2007; 22:2867.

Lanthanum

좋다

별 차이 없다

Mortality

Wilson R, et al. Curr Med Res Opin 2009; 25:3021.

Bone histology

Malluche HH, et al. Clin Nephrol 2008; 70:284.
D'Haese PC, et al. Kidney Int Suppl 2003; 157:3.
Freemont T, et al. Clin Nephrol 2005; 63:138.
Spasovski GB, et al. Nephrol Dial Transplant 2006; 21:2217.

Lower Ca & PTH

Serologic parameters

Joy MS, et al. Am J Kidney Dis 2003; 42:96.
Hutchison AJ, et al. Nephrol Dial Transplant 2004; 19:1902.
Finn WF, et al. Clin Nephrol 2004; 62:193.
Hutchison AJ, et al. Nephron Clin Pract 2005; 100:c8.
Freemont T, et al. Clin Nephrol 2005; 63:138.
Altmann P, et al. Kidney Int 2007; 71:252.

Lanthanum

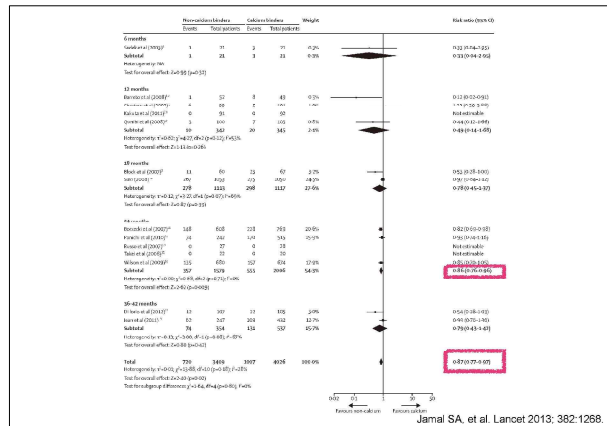
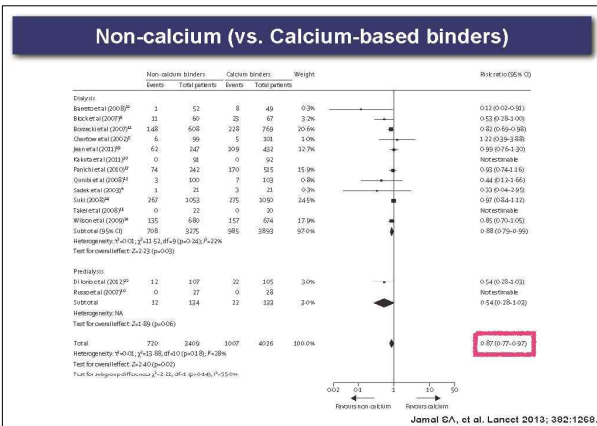
차이 없다

아직 잘 모른다

Side effect

Joy MS, et al. Am J Kidney Dis 2003; 42:96.
Hutchison AJ, et al. Nephrol Dial Transplant 2004; 19:1902.
Finn WF, et al. Clin Nephrol 2004; 62:193.
Hutchison AJ, et al. Nephron Clin Pract 2005; 100:c8.
Freemont T, et al. Clin Nephrol 2005; 63:138.
Altmann P, et al. Kidney Int 2007; 71:252.

Slatopolsky E, et al. Kidney Int 2005; 68:2809.
Aime S, et al. Kidney Int 2007; 72:1162.



Others - Magnesium

Int J Nephrol (2008) 40:397-401
DOI: 10.1007/s12325-007-9360-0

ORIGINAL ARTICLE

Magnesium carbonate for phosphate control in patients on hemodialysis. A randomized controlled trial

Ioannidis P, Tzannaki A, Antonia N, Papaioakim M, Mitsios W, Stella Kaglia V, Vassilios V, Spafidaki S, Nikolaidis E, Kallivretaki S, Dimitrios G. Oreopoulos

Journal of Renal Nutrition, Vol 17, No 6 (November), 2007; pp 416-422

Magnesium Carbonate Is an Effective Phosphate Binder for Chronic Hemodialysis Patients: A Pilot Study

David M. Spiegel, MD,* Beverly Farmer, RN,* Gerard Smits, PhD,† and Michel Chouhrouh, MD*

Magnesium-containing antacids (such as magnesium hydroxide) have also generally been avoided in patients with kidney dysfunction. This is because of the risk of hypermagnesemia and the frequent development of diarrhea.

Others - Magnesium

Nephrol Dial Transplant (2010) 25: 3707-3717

Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability

Angel L.M. de Francisco¹, Michael Leung², Adrian C.ovic³, Markus Keitel⁴, Ewa Bendyk-Loranc⁵, Gabriel M. Mircescu⁶, Caecilia Scholz⁷, Pedro Ponce⁸, and Jutta Prusick-Duesten⁹

Amberio (Amg) Pharmaceuticals, L.P. Inc. doi: 10.1093/ndt/gfp323 Copyright © 2010, International Society for Nephrology

MgCaCO₃ VERSUS CaCO₃ IN PERITONEAL DIALYSIS PATIENTS - A CROSS-OVER PILOT TRIAL

Baigalmaa Evsanaa,¹ Irene Liu,² Babak Alizadeh,³ Sara Mahdavi,⁴ Gursan Bajra,⁵ Jerry Gula,⁶ Michelle Tam,⁷ Elena Sze,⁸ Janet M. Roscoe,⁹ Paul Y. Tam,⁹ and Tabo Sikaneta⁹

Newer agents (1) - Nicotinamide

Clin J Am Soc Nephrol 2: 1249-1254, 2007.

Niacin Lowers Serum Phosphate and Increases HDL Cholesterol in Dialysis Patients

Daniela Müller, Heidrun Mehling, Björn Otto, Regine Bergmann-Lips, Friedrich Luft, Jens Jordan, and Ralph Kettritz

Clin J Am Soc Nephrol 3: 1131-1138, 2008.

A Randomized, Double-Blind, Placebo-Controlled Trial of Niacinamide for Reduction of Phosphorus in Hemodialysis Patients

Steven C. Cheng, Daniel O. Young, Yihung Huang, James A. Delmez, and Daniel W. Coyne

Newer agents (2) - PA21

Clin J Am Soc Nephrol 8: 280-289, 2013.

Randomized Clinical Trial of the Iron-Based Phosphate Binder PA21 in Hemodialysis Patients

Rudolf P. Wüthrich, Michel Chonchol, Adrian Covic, Sylvain Cailliant, Edward Chong, and James A. Tuntin

Agent	Change in serum phosphorus (mg/dL)
PA21 1.25g/day	-0.19
PA21 5.0g/day	-1.26
PA21 7.5g/day	-1.47
PA21 10.0g/day	-1.28
PA21 12.5g/day	-1.28
Sevelamer HCl 4.8g/day	-1.26

Legend: Efficacy population (n=150), Per protocol population (n=120)

Preservation of residual renal function

Clin J Am Soc Nephrol 10: 1160-1205, 2012.

Association of Circulating Fibroblast Growth Factor-23 with Renal Phosphate Excretion among Hemodialysis Patients with Residual Renal Function

Mengying Wang, Li Yu, Hanming Li, Yong Lin, Zhibo Zhang, Chuanming Hao, and Jing Chen

Kidney Int Clin Pract 33 (2014) 58-64

Significance of residual renal function for phosphate control in chronic hemodialysis patients

Harin Rhee^{1,2}, Ji Young Yang², Woo Jin Jung¹, Min Ji Shin^{1,2}, Byung Yoon Yang^{1,2}, Sang Heon Song^{1,2}, Ilm Seon Kwak^{1,2}, Eun Young Seong^{1,2*}

- Avoiding nephrotoxic drugs
- Use of ultrapure dialysate & biocompatible membranes
- Decreasing dialysis frequency
- Avoidance of aggressive water removal

CKD-MBD의 예방/치료 알고리즘 (1)

예방

치료

- Calcitriol analogue treatment paradigm
- Calcimimetic and fixed calcitriol analogue treatment paradigm

CKD-MBD의 예방/치료 알고리즘 (2)

Calcitriol analogue treatment paradigm

Titrate dose active vit D
 Paricalcitol 2 to 18 mcg IV 3x/week
 Doxercalciferol 1 to 18 mcg IV 3x/week
 Calcitriol 0.5 to 8 mcg IV 3x/week

CKD-MBD의 예방/치료 알고리즘 (3)

Calcimimetic and fixed calcitriol analogue treatment paradigm

Cinacalcet HCl
 30 mg PO q day
 Titrate at 2 week intervals to next highest dose (up to 180 mg/day)

Fixed low dose active vit D
 Paricalcitol 2 mcg IV 3x/week
 Doxercalciferol 1 mcg IV 3x/week
 Calcitriol 0.5 mcg IV 3x/week

Summary

- Target serum phosphate levels: 3.5 ~ 5.5 mg/dL
- Restriction of dietary phosphate: 900 mg/day
- The patient should be encouraged to avoid unnecessary dietary phosphate (as in phosphorus-containing food additives, dairy products, certain vegetables, many processed foods, and colas), while maintaining the intake of high biologic value sources of protein.
- Optimization of dialysis therapy (ex. nocturnal HD)
- Administration of phosphate-binding agents, which would be based upon calcium levels and the presence of comorbid conditions