KSCCM
제 39 차 정기학술대회

Vitamin therapy in critically ill patients

허진원
울산의대 서울아산병원

서울아산병원

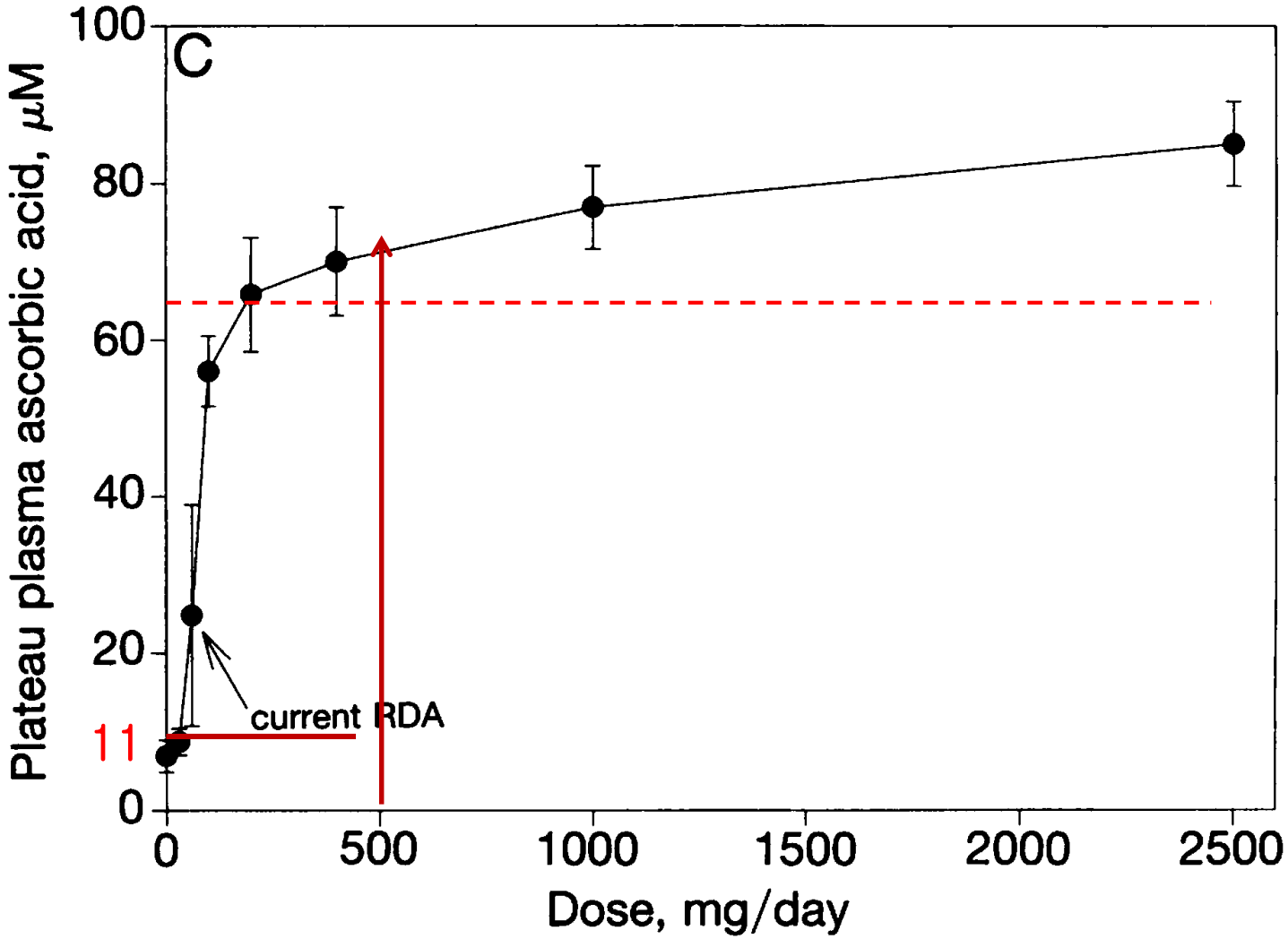
Old concept

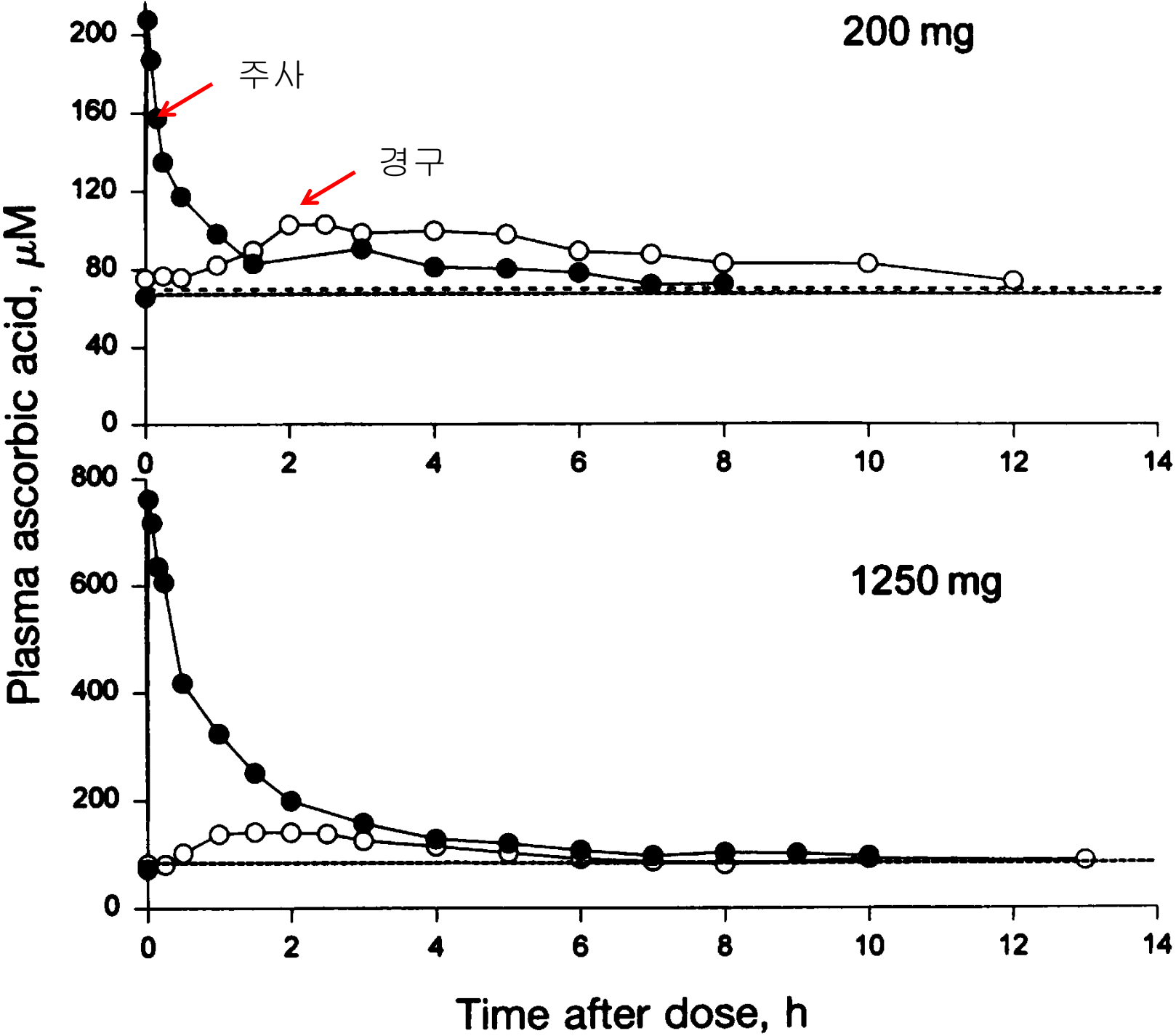
Vitamin therapy

New interest

Metabolic Resuscitation

Healthy volunteer



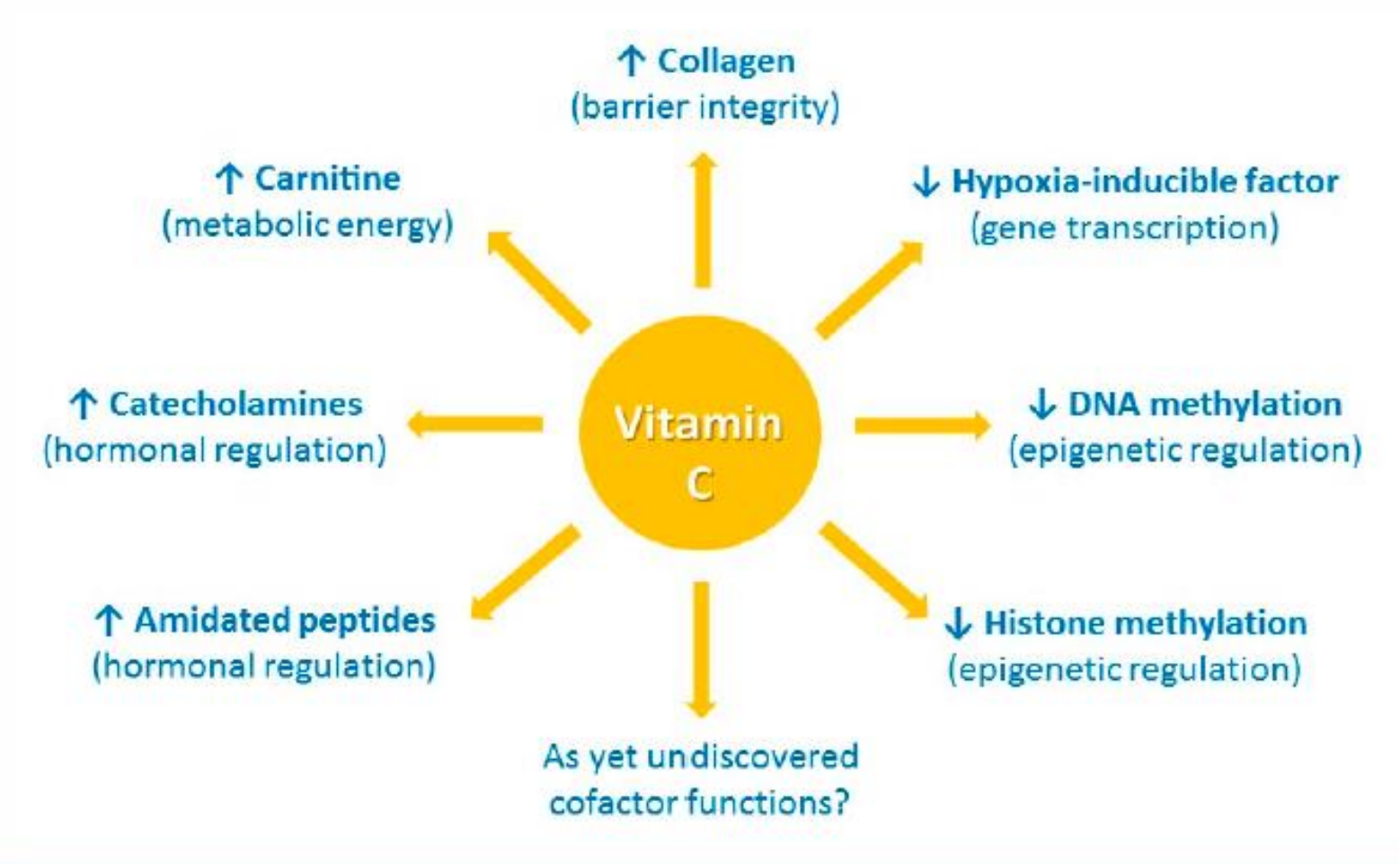

200 mg
주사
경구
1250 mg
Plasma ascorbic acid, μM
Time after dose, h
0
40
80
120
160
200
400
600
800
2
4
6
8
10
12
14

Vitamin C..

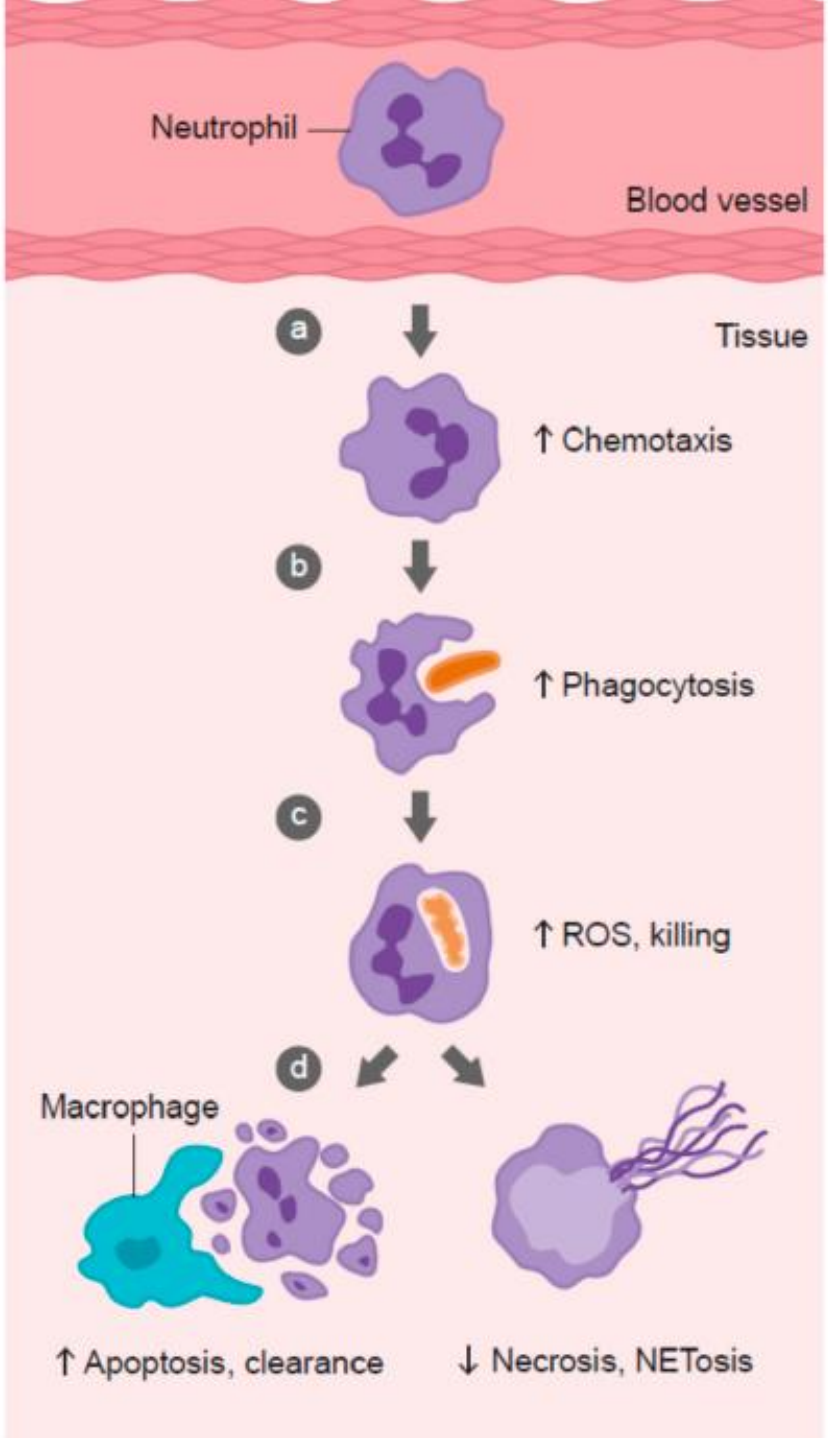
- Alfred Hess (1920) summarized a series of autopsy findings as follows:

"*pneumonia, lobular or lobar, is one of the most frequent complications (of scurvy) and causes of death*" and "*secondary pneumonias, usually broncho-pneumonic in type, are of common occurrence and in many (scurvy) epidemics constitute the prevailing cause of death*"

- ✓ cofactor for a family of biosynthetic and gene regulatory monooxygenase and dioxygenase enzymes



- ✓ phagocyte function



Author Journal Year	Population Nr of patients	Vitamin C supplementation	Plasma ascorbic acid level d 1 (μmol/L)	Plasma ascorbic acid level, d 3-7 (μmol/L)
Schorah CJ Am J Clin Nutr, 1996	Critically ill patients N=62	PN containing AA in some patients	11.0 (8-22)	
Long CL. J Surg Research, 2003	Critically ill trauma/sepsis N=12	d 1-2: 300 mg/d iv d 3: 100mg/d iv	6.3±17.1	16.0 ± 2.9
Beale RJ. Intensive Care Med,2008	Sepsis N=27 N=28	 1500 mg, ent. 250 mg, ent.	 10.6 (1.9-159.4) 17.0 (2.8-78.5)	 58.6 (5.4-189.9) 14.3 (2.4-179.6)
Nogueira CR. Hops Nutr, 2013	ICU patients requiring EN N=23 N=11	 Standard EN 600 mg vit C ent.	 68.4±102.6 28.5±22.8	 34.2 ±22.8 75.8±102.6
Fowler AA. J Transl Med,2014	Septic shock, N=24 (all) N=8 N=8 N=8	 Placebo Vit C 50 mg/kg iv, 4D Vit C 200 mg/kg iv, 4D	 20.2 (11-45) 16.7 (14-28) 17 (11-50)	 15.6 (7-27) 331 (110-806) 3082 (1592-5722)
De Grooth HJ. Intensive Care Med 2014	Critically ill ,N=51 Sepsis/SIRS (n=28) Cardiac arrest (n=23)	Standard EN	Deficiency 14% 20 (13-32) 28 (18-38)	Deficiency 16% 28 (18-38) 19 (17-23)
Van Zanten A.R.H. JAMA, 2014	Sepsis N=152 N=149	 ± 690 mg/d ent. ± 195 mg/d ent.	 7.5 (0.0-72.0) 8.4 (0.0-140.0)	 14.0 (0.0-70.6) 6.8 (0.0-38.0)
Carr A.C. Crit Care, 2017	Sepsis N=24 Non-sepsis N=17	EN(64%):102 ± 54 mg/d PN(27%): 206±106 mg/d Combination(10%) : 195 ± 144 mg/day	14.6±8.7 Deficiency 40% 19.7±9.3 Deficiency 25%	No significant change between day 1-4

Increased needs

Intervention

Author Journal Year	Design Population	No of patients	Intervention	Outcomes
Nathens AB. Ann Surg 2002	RCT Single-center Trauma and MOF	301 294	- Vit C iv 1-g tid. Vit-E ent 1000 IU tid. - with PN: Vit C 100 mg, Vit-E 10 IU/D with EN: Vit C 340 mg/L, Vit E 60 IU/L *During ICU admission or 28-days*	Pulmonary morbidity ↓ (RR 0.81) New MOF ↓ (RR 0.43) LOS ventilation ↓ LOS ICU ↓
Crimi E. Anesth Analg 2004	RCT Critically ill trauma,cardiogenic shock	105 111	- Vit C 500 mg/d in EN Vit E 400 IU/d in EN - saline solution *For 10-d*	Ventilator-free days ↓ (15.7 vs. 11.2, p=0.01) 28-d mortality ↓ (43.7% vs.67.8%,p<0.05)
Collier BR JPEN 2008	Prospective vs. retrospective 1-yr cohort Single-center Trauma	2272 2022	• Vit C 1 g iv or orally tid + Vit E orally 1000 IU tid. + selenium 200 μg iv For 7-days or until hospital discharge	LOS ICU ↓ (3 d vs 2 d, p = .001) LOS hospital ↓ (4 d vs 3 d, p<.001) Mortality ↓ (6.1% vs 8.5%, p = .001)

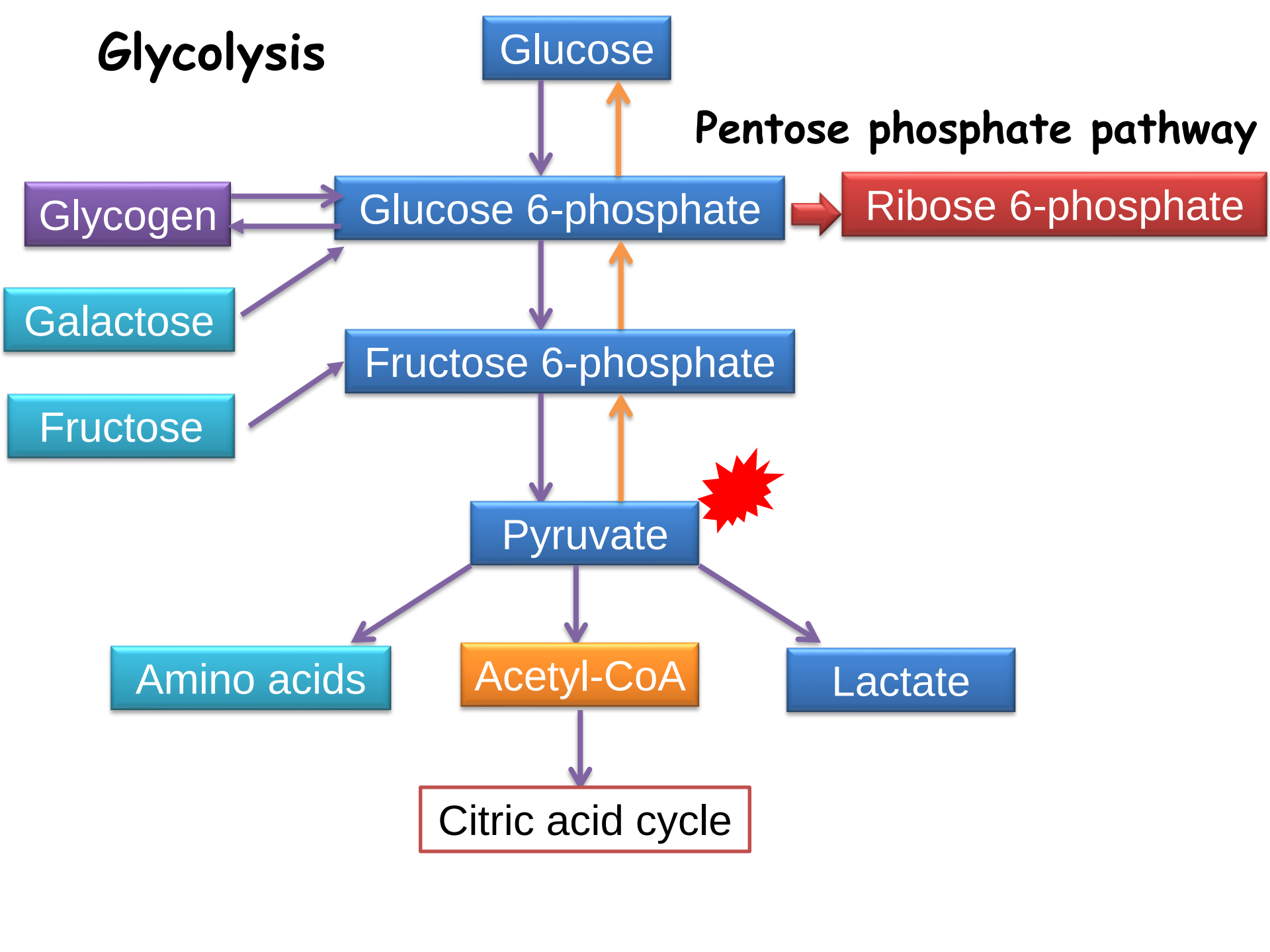
Author Journal Year	Design Population	N of patients	Intervention	Outcomes
Heyland D New Engl J Med 2013	RCT, Multi-center 2-by-2 Critically ill adults with MOF	307 300	• Se 500 μg iv → Se 300 μg, Zn 20 mg, β-carotene 10 mg, Vit E 500 mg, Vit C 1.5 g • Placebo During ICU admission/28 D	No difference in 28-d mortality or length of stay.
Zabet MH J Res Pharm Pract 2016	RCT Single-center Surgical septic shock	14 14	• Vit C iv 25 mg/kg 4x d for 72 hours • placebo For 72-hours	Dose and duration of norepinephrine ↓ 28-day mortality 14% vs. 64% (p=0.009)
Marik PE Chest 2017	Retrospective before/after Single-center Severe sepsis / septic shock & PCT ≥ 2 mg/L	47 47	• Vit C iv 1.5 g iv every 6-h for 4-d + hydrocortisone 50 mg every 6-h + thiamine iv 200 mg every 12-h For 4-d or ICU discharge • hydrocortisone 50 mg every 6-h at discretion of the attending physician	Hospital mortality 8.5% vs. 40.4% Duration vasopressors 18.3 vs. 54.9 h Vit C: ΔSOFA ↑, RRT ↓, Procalcitonin clearance ↑

Vitamin C

- Deficiency : common
- Optimal dose : 0.5-3 g /day intravenously (최근 6g 이상)
- Optimal duration : ?

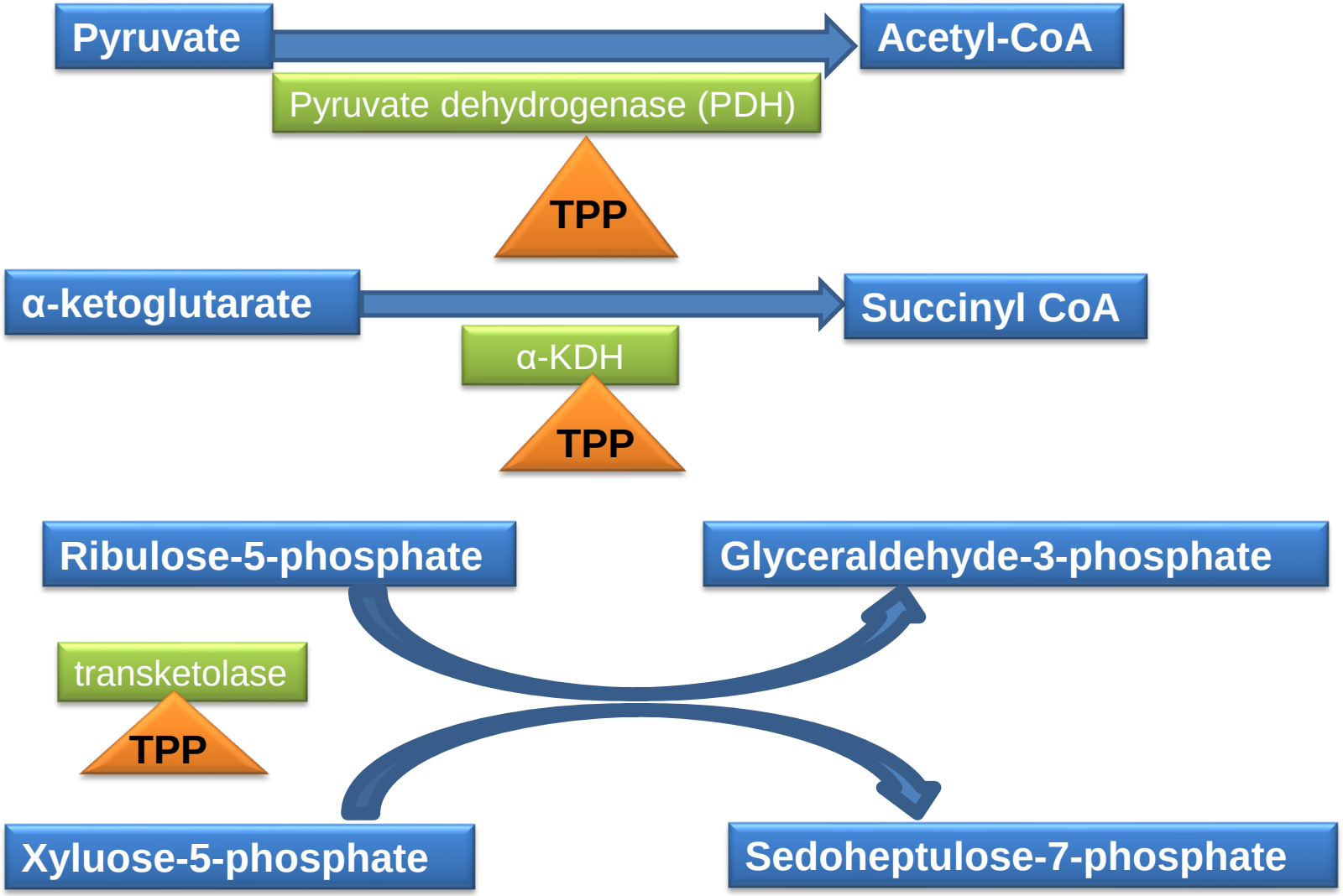
  oxidative stress 가 최대인 상황에서 사용—

  단기간 사용 가능
- Outcome : Inflammatory marker (CRP), duration of vasopressor, ICU stay, Hospital stay, Mortality
- Combination with other antioxident ?
- Safety concern : urinary oxalate crystallisation and pro-oxidant effect


Glycolysis
Glucose
Pentose phosphate pathway
Glycogen
Glucose 6-phosphate
Ribose 6-phosphate
Galactose
Fructose 6-phosphate
Fructose
Pyruvate
Amino acids
Acetyl-CoA
Lactate
Citric acid cycle

Thiamine...

Precursor of thiamine pyrophosphate (TPP)



Thiamine supplementation

- recommended daily intakes (RDI): 1.3 mg/day
- enteral nutrition: 2.2 -2.9 mg per 1500 kcal daily feed
- standard intravenous complement :3 to 4 mg/day
- doses recommended for Wernicke's encephalopathy

  alcoholic abuse : 200 - 500 mg i.v. three times daily

  nonalcoholic abuse : 100- 200 mg/day

  → 500 mg I.V 3 times per day for 2-3 days, to be reduced to 50-100 mg/day after stabilization.
- for refeeding syndrome

  Day 1, 200 - 300 mg i.v., 30 min before starting feeding

  → 200 - 300 mg daily i.v. or orally until 3 day

  → 100mg during nutrition

Intervention

Author Journal Year	Design	Population N of patients	Intervention	Outcomes
Donnino M W et al Crit Care Med 2016	RCT Double blind	Septic shock with lactate (>3 mmol/l) n=43 n= 45	for 7 days or until hospital discharge • 200 mg, IV, bid • placebo	In the thiamine deficient patients (≤ 7 nmol/L); lactate levels decreased more and mortality was lower
Marik PE Chest 2017		47 47	• Vit C iv 1.5 g iv every 6-h for 4d + hydrocortisone 50 mg every 6h + thiamine iv 200 mg every 12-h • hydrocortisone 50 mg every 6h at discretion of the attending physician	Hospital mortality 8.5% vs. 40.4% Duration vasopressors 18.3 vs. 54.9 h Vit C: ΔSOFA ↑, RRT ↓, Procalcitonin clearance ↑

Vitamin B

- Deficiency : common
- Optimal dose : 300 mg I.V daily at risk patients
- Optimal duration : first 72 hr ?
- Outcome : lactate, mortality
- Combination with ?
- Safety concern : unknown

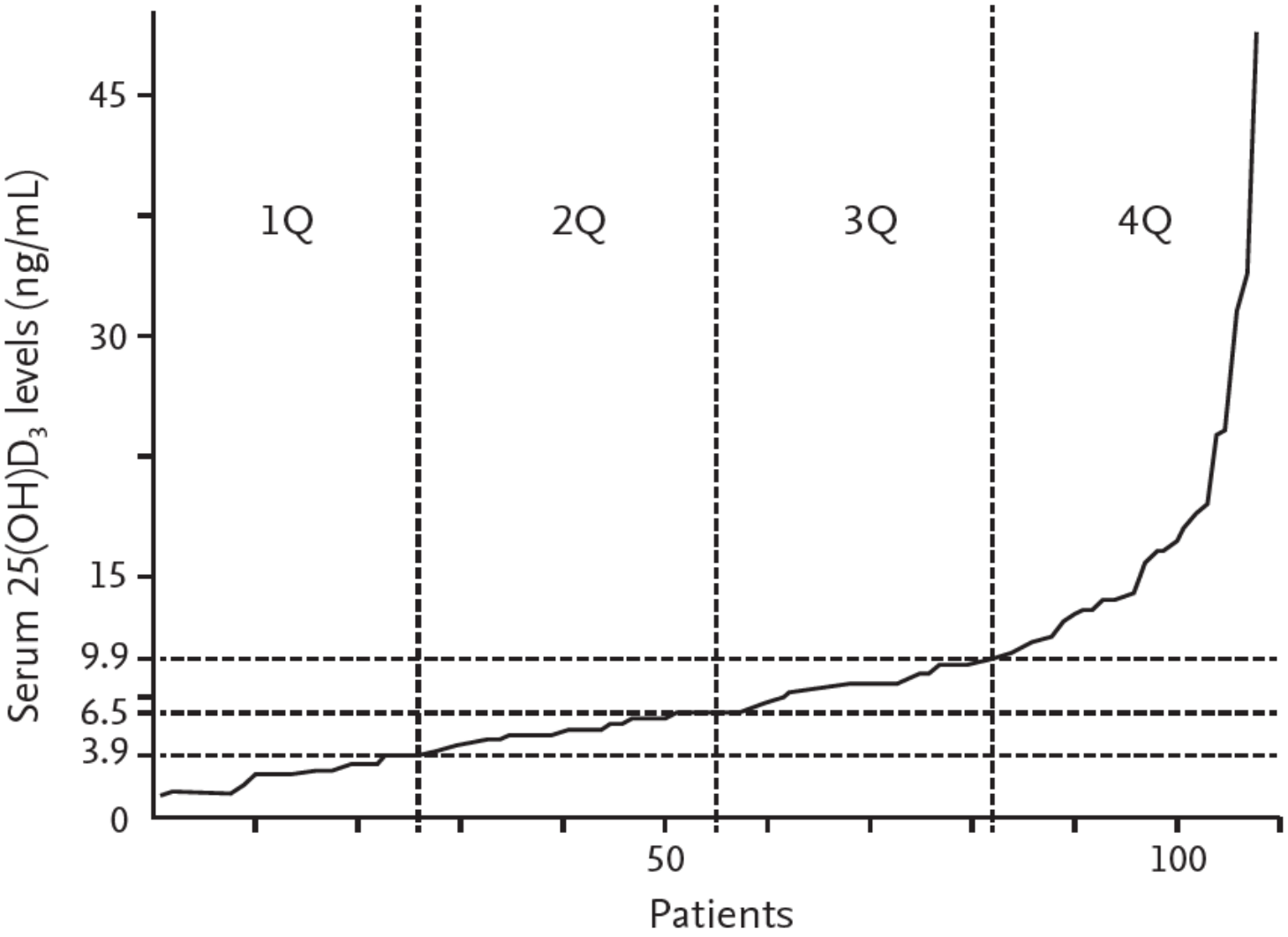
Prevalence of vitamin D deficiency in Korea: Results from KNHANES 2010 to 2011

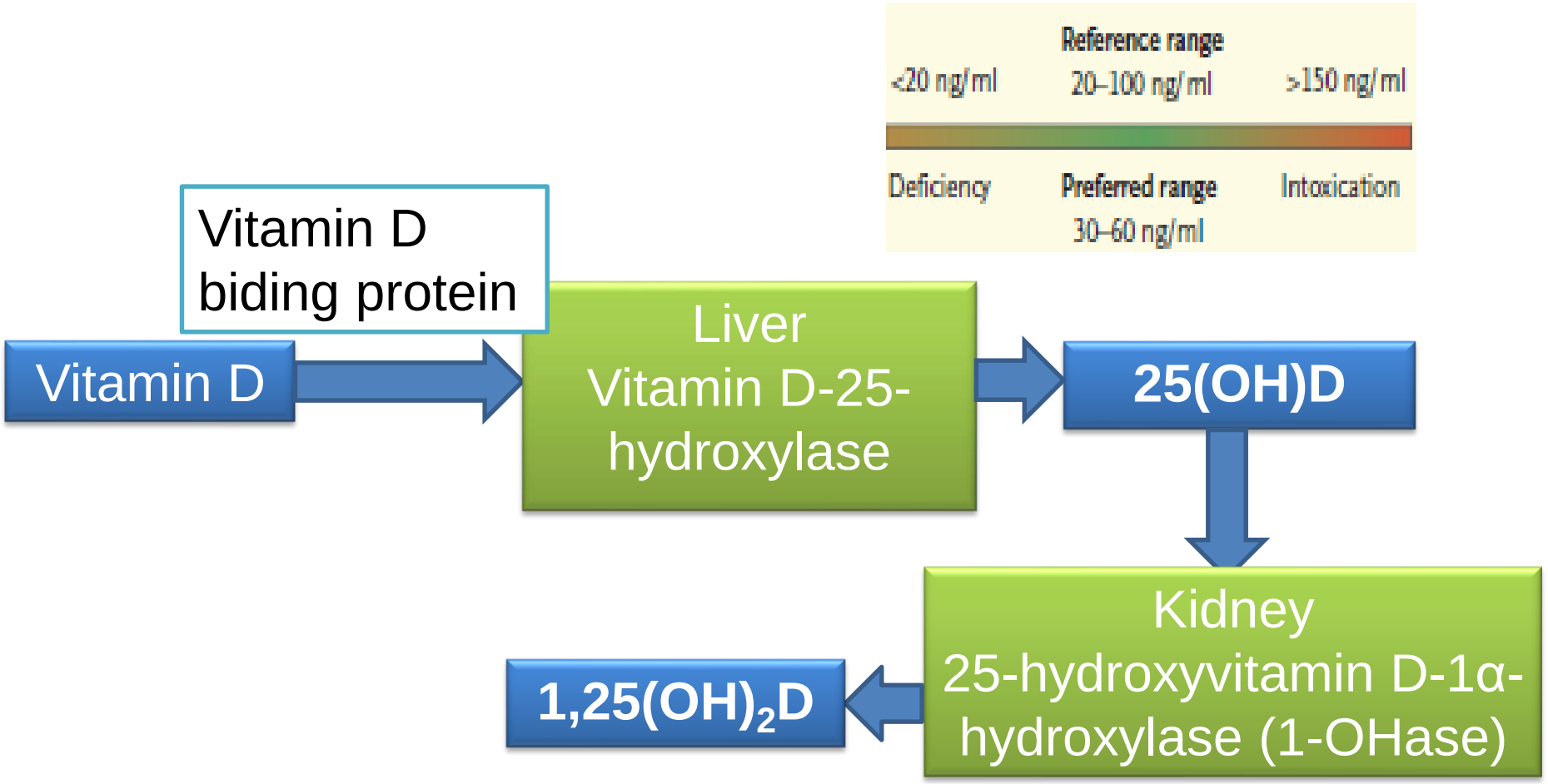
Parameter		Total		Male		Female	
		Estimated %	Unweighted frequency	Estimated %	Unweighted frequency	Estimated %	Unweighted frequency
25(OH)D, ng/mL	Deficient (<10)	7.3%	973	5.1%	268	9.7%	705
	Insufficient (10 to <20)	64.4%	8,553	60.8%	3,537	68.0%	5,016
	Optimal (20 ≤)	28.3%	3,993	34.2%	2,216	22.4%	1,777
	25(OH)D-total	100.0%	13,519	100.0%	6,021	100.0%	7,498

8.4 ng/mL

Parameter	Subgroups	25(OH)D, ng/mL				25(OH)D status, EF (Std. E.)%			χ^2	p
		Estimated mean	Std. E.	95% CI		Deficient	Insufficient	Sufficient		
				Lower	Upper					
Age	10–19	16.95	.257	16.44	17.45	6.8 (1.2)	68.5 (2.0)	24.7 (1.9)	263.587	p< .001
	20–29	16.68	.297	16.10	17.27	5.2 (1.1)	73.6 (2.2)	21.2 (2.2)		
	30–39	17.65	.279	17.10	18.20	5.6 (0.9)	65.6 (2.0)	28.9 (2.1)		
	40–49	18.68	.290	18.11	19.25	4.6 (0.8)	56.7 (2.2)	38.7 (2.3)		
	50–59	19.81	.312	19.20	20.42	4.3 (0.8)	51.3 (2.2)	44.4 (2.2)		
	60–69	20.20	.342	19.53	20.88	2.8 (0.7)	50.7 (2.4)	46.5 (2.4)		
	70–79	20.51	.443	19.64	21.38	5.6 (1.4)	45.3 (2.6)	49.1 (2.8)		
	80 ≤	20.13	.987	18.19	22.07	5.5 (1.4)	36.4 (5.6)	58.1 (6.1)		

- ✓ serum level of 25-hydroxy vitamin D3 at the time of diagnosis of ARDS between April 2005 and March 2016




Reference range
<20 ng/ml
20–100 ng/ml
>150 ng/ml
Deficiency
Preferred range
30–60 ng/ml
Intoxication
Vitamin D biding protein
Vitamin D
Liver
Vitamin D-25-hydroxylase
25(OH)D
Kidney
25-hydroxyvitamin D-1α-hydroxylase (1-OHase)
1,25(OH)2D

Vit D supplementation

- recommended daily intakes (RDI): 600-800 IU daily
  - ↑ 1500 to 2000 IU /day at risk
- High loading dose for restoring 25-hydroxyvitamin D level
- parenteral multivitamin: 200 or 220 IU of native vitamin D
- Up to 10000 IU daily : safe

Intervention

Author, Journal, Year	Design Population	N of patients	Intervention	Outcomes
Amrein K. Crit Care 2011	RCT MICU 25OHD <20 ng/ml	25	1x 540,000 IU D_3 enteral vs. placebo	Normalization of vitamin D levels in most patients, no adverse events; no difference in 28-d mortality or length of stay.
Amrein K. JAMA 2014	RCT Mixed ICU, 25OHD <20 ng/ml	475	1x 540,000 IU D_3, enteral, then 5x 90,000 IU D_3/M vs. placebo	- No difference in hospital length of stay, overall no significant mortality benefit - significant mortality benefit in the predefined subgroup with severe vitamin D deficiency (25OHD) < 12
Han JE J of Clin & transl. end ocrinology 2016	RCT ICU, mechanically ventilated	30	5dx50,000 IU D_3, enteral or 5dx100,000 IU D_3, enteral vs. placebo	Shorter hospital stay, dose dependent increase of vitamin D levels increased hCAP18 mRNA-expression compared to the placebo group

Vitamin D

- Deficiency : common
- Optimal dose : loading dose 필요

  up to 10,000 IU/day
- Optimal duration :

  Native vitamin D3 or D2 : half –life 2-3 weeks
- Outcome : ICU stay, ventilator day, mortality
- Combination with ?
- Safety concern : Hypercalcemia, Acute renal failure, Nephroclacinosis

Conclusion

- 결핍이 흔하다
- Vit D 외에는 임상에서 측정이 어렵다
- 결핍이 심한 군에서 효과적이다
- 중환자에서 고농도를 추천한다
- 특별한 부작용은 없다
- 치료기간에 대한 근거가 부족하다