Muscle Metabolism and Function and the Importance of Vitamin in CKD

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Potential Conflicts of Interest: Pinta Biotherapeutics, Nephroceuticals, Fresenius Kabi

Topics to be Discussed

1. High prevalence of 25(OH)D and 1,25(OH)D3 deficiency in CKD.
2. Asssociation of Vit D Deficiency with sarcopenia and decreased muscle function.
3. Increased falls with Vit D deficiency.
4. Vitamin D reduces falls in CKD patients.
5. Need for Vit D for normal muscle mitochondrial oxidative function.

Vitamin D in Chronic Kidney Disease

An increased prevalence of deficiency of both

25-hydroxycholecalciferol (25(OH)D3)

and

1,25-dihydroxycholecalciferol (1,25(OH)2D3, Calcitriol)

are reported in CKD and ESKD patients who do not receive supplements.

Prevalence of 25(OH)Vitamin D Deficiency in NonDialyzed CKD (1)

1. 3011 people studied from 3rd NHANES.
2. GFR determined from serum creatinine and MDRD Equation.

Stage	% of Cohort
1	44%
2	27%
3	27%
4	1%

Mehrotra et al. Kidney International 2009;76:977-983

Prevalence of 25(OH)Vitamin D Deficiency in NonDialyzed CKD (2)

Serum 25(OH)D ng/ml	Category	% of Cohort
<15	Deficient	12%
15-30	Insufficient	52%
>30	Sufficient	36%

Mehrotra et al. Kidney International 2009;76:977-983

Prevalence of 25(OH)D Deficiency and Response to Cholecalciferol in CKD (1)

1. **210 nondialyzed CKD Pts Stages 3, 4, 5**
2. **Vitamin D deficiency (serum 25(OH)D <30 ng/mL) in CKD patients:**

   Stage 3 40.7%

   Stage 4 61.5%

   Stage 5 85.7%
3. **Vitamin D deficiency was more common in pts with diabetes mellitus, lower eGFR & proteinuria: urine protein, 1.0 vs 0.31 g/day**

Kim et al. J Renal Nutrition December, 2013

Prevalence of 25(OH)D Deficiency and Response to Cholecalciferol in CKD (2)

4. Treatment of vitamin D deficient patients with cholecalciferol 1000 IU/day resulted in:

Serum 25(OH)D ≥30 ng/mL

in 76.5% at 3 months

in 89.7% at 6 months

Lower response rates were observed in patients with lower baseline serum 25(OH)D and with greater proteinuria

Kim et al. J Renal Nutrition December 2013

Retrospective study of ergocalciferol, 50,000 IU, given orally at weekly intervals to 183 Veterans. Average number of doses: 10.9±6.0; mean duration of vitamin D2 treatment: 9.5 months

TABLE 3. Predictors of an inadequate response to vitamin D supplementation defined by low ratio of change in serum 25(OH)D level/1000 IU ergocalciferol in univariate and multivariable analyses

	Univariate			Multivariable[a]		
Predictor variables	**OR**	**95% CI**	***P***	**OR[b]**	**95% CI**	***P***
Race (1 = white, 0 = black)	0.63	0.35–1.12	0.12			
Age (yr)	1.00	0.98–1.02	0.98			
Sex (1 = male, 0 = female)	0.42	0.17–1.05	0.06			
BMI (kg/m^2)	1.01	0.97–1.06	0.56			
HTN (1 = presence, 0 = absence)	1.18	0.60–2.34	0.63			
DM (1 = presence, 0 = absence)	1.82	1.01–3.27	0.05	2.18	1.09–4.33	0.027
Season (1 = winter, 0 = summer)	0.91	0.50–1.65	0.75			
Baseline serum albumin (gm/dL)	1.44	0.69–3.03	0.33			
Baseline serum calcium (mg/dL)	0.99	0.63–1.58	0.98			
Baseline serum 25(OH)D (ng/mL)	1.13	1.08–1.19	<0.0001	1.14	1.08–1.21	<0.0001
Baseline eGFR (mL/min/1.73m^2)	0.97	0.96–0.99	<0.0001	0.97	0.96–0.99	<0.0001

[a] Hosmer-Lemeshow goodness-of-fit statistics $\chi^2(8)$ of 5.32 and P value 0.72 suggesting that the model fits our data well. Variance inflation factor: 1.04 for eGFR, 1.04 for DM and 1.04 for 25(OH)D.

[b] Variable excluded ($P > 0.10$) during stepwise logistic regression modeling.

Alshayeb et al. Am J Med Sci 2013;345:314-320

Factors Impairing $1,25(OH)_2D$ Synthesis and Activity in CKD (1)

Decreased $1,25(OH)_2D$ Synthesis:

1. Reduced 25(OH)D concentrations
2. Decreased delivery of 25(OH)D to renal tubules due to low renal blood flow and GFR
3. Decreased number of nephrons
4. Inhibition of 1-α-hydroxylase by FGF23 or acidemia
5. Impaired response of 1-α-hydroxylase to PTH

Adverse Effects of 25(OH)D or 1,25(OH)D Deficiency on Skeletal Muscle

1. Decreased skeletal muscle (SKM) size
2. Decreased SKM strength (H. Glerup Calcified Tissues Int, 2000;66:419)
3. Reduced insulin secretion and increased insulin resistance

In 135 MHD patients (69 Male/66Female) Upper Leg Force is Associated with Serum 25OHD Levels and is Usually Decreased with Low Serum 25-OHD, Usually Normal with Normal 25-OHD, and More Often Low with Excess or Toxic 25-OHD levels

Table 1. Result of lower extremity force in relation to 25-OHD.

	Leg force			*P*-value
	<5 kg	5–10 kg	>10 kg	
25-OHD				
<30 ng/mL	72.9%	24.7%	2.4%	0.02
30–70 ng/mL	43.9%	53.7%	2.4%	
>70 ng/mL	57.1%	42.9%	0%	

Zahed et al. Saudi J Kidney Dis Transpl 2014;25:998-1003

CKD, MHD and Hip Fractures (1)

1. Hip fractures occur in up to 5% of stage 3-4 CKD patients vs ~1.3% and ~0.7% in normal women and men.

2. In MHD patients ≥66y/o, incidence of hip fractures was increased and rose from 11.9/1000 pt-yrs in 1993 to 21.6/1000 pt-yrs in 2004 and then declined to 16.6/1000 pt-yrs by 2010.

Marks Int J Gen Med 2010;3:1; Arenson et al AJKD 2013;62:747
Delgado & Frassetto AJKD 2013;62:653-655

CKD and Hip Fractures (2)

3. In contrast, peak hip fracture in Medicare patients >66y/o was lower and peaked at only 10.6/1000 pt-yrs.

4. Suggested causes for increased hip fractures in MHD patients include aging, CKD-Bone Mineral Disease with hyperparathyroidism and vitamin D deficiency.

5.Causes for the downward trend in hip fractures since 2004 probably include more frequent use of 1,25(OH)2D3 and its analogues and cinacalcet.

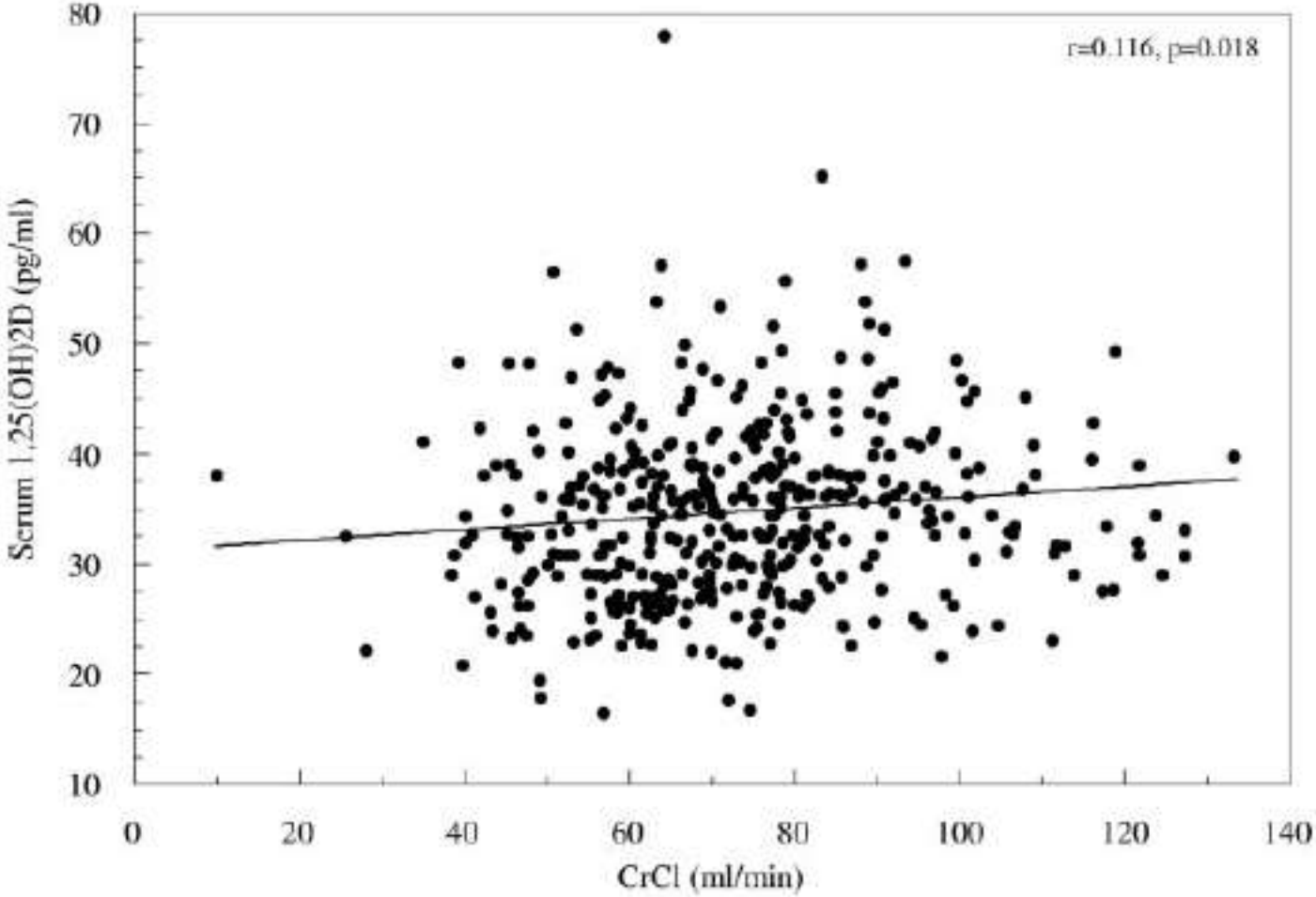


FIG. 1. Correlation graph between measured CrCl and serum $1,25(OH)_2D_3$.

Gallagher et al JCEM 2007;92:51-58

Low Serum 1,25(OH)2D3, Reduced GFR, and Falls in Elderly Women

1. In 489 elderly women, age 65-77 years, those with CrCl <60mL/min (mean±SE, 50.3 ±0.69) had more falls per person(p=.007) over 36 months but not more fallers.

2. Women with this lower GFR had reduced intestinal Ca absorption, decreased serum 1,25(OH)2D and normal serum 25(OH)D.

3. Those randomized to 1,25(OH)D, 0.25mcg bid, had significantly less falls (by 53% in those with CrCl <60mL/min and by 30% in those with CrCl ≥60mL/min.

Gallagher et al JCEM 2007;92:51-58; J Steroid Biochem Mol Biol 2007;103:610-613

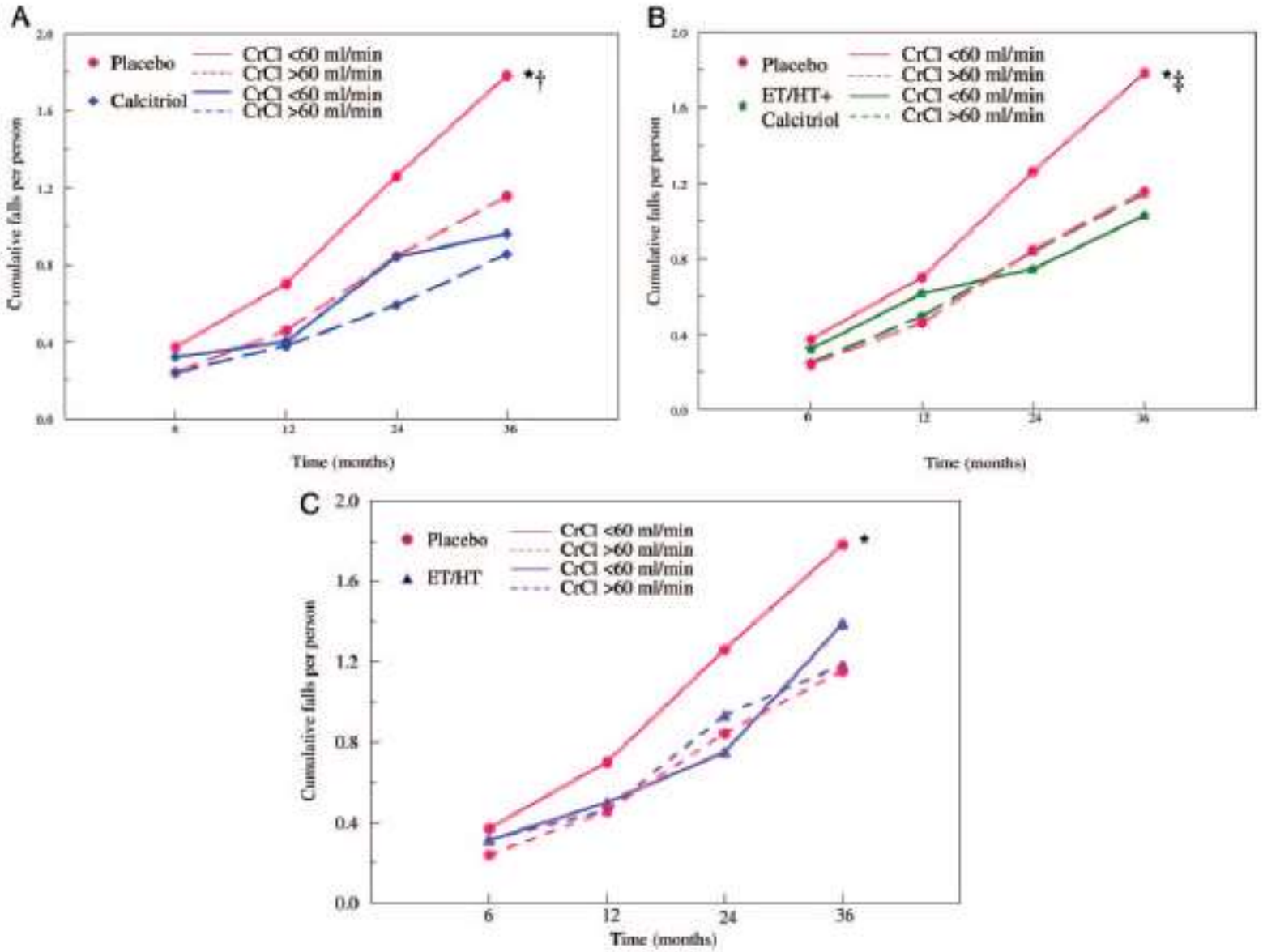


FIG. 2. Cumulative number of falls per person in the placebo and calcitriol groups (A); placebo and ET/HT + calcitriol groups (B); and placebo and ET/ HT groups (C) over the treatment period in women with CrCl less than 60 and more than 60 ml/min. The data were adjusted for significant covariates: number of comorbid conditions, smoking status, and PASE score. *, $P < 0.05$, compared with placebo CrCl greater than 60 ml/min; †, $P < 0.05$, compared with calcitriol CrCl less than 60 ml/min; ‡, $P < 0.05$, compared with calcitriol + ET/HT CrCl less than 60 ml/min.

Gallagher et al JCEM 2007;92:51=58

76 MHD Patients Observed for 1 Year with 2 year Followup. Outcomes of Single Fallers vs Recurrent Fallers.

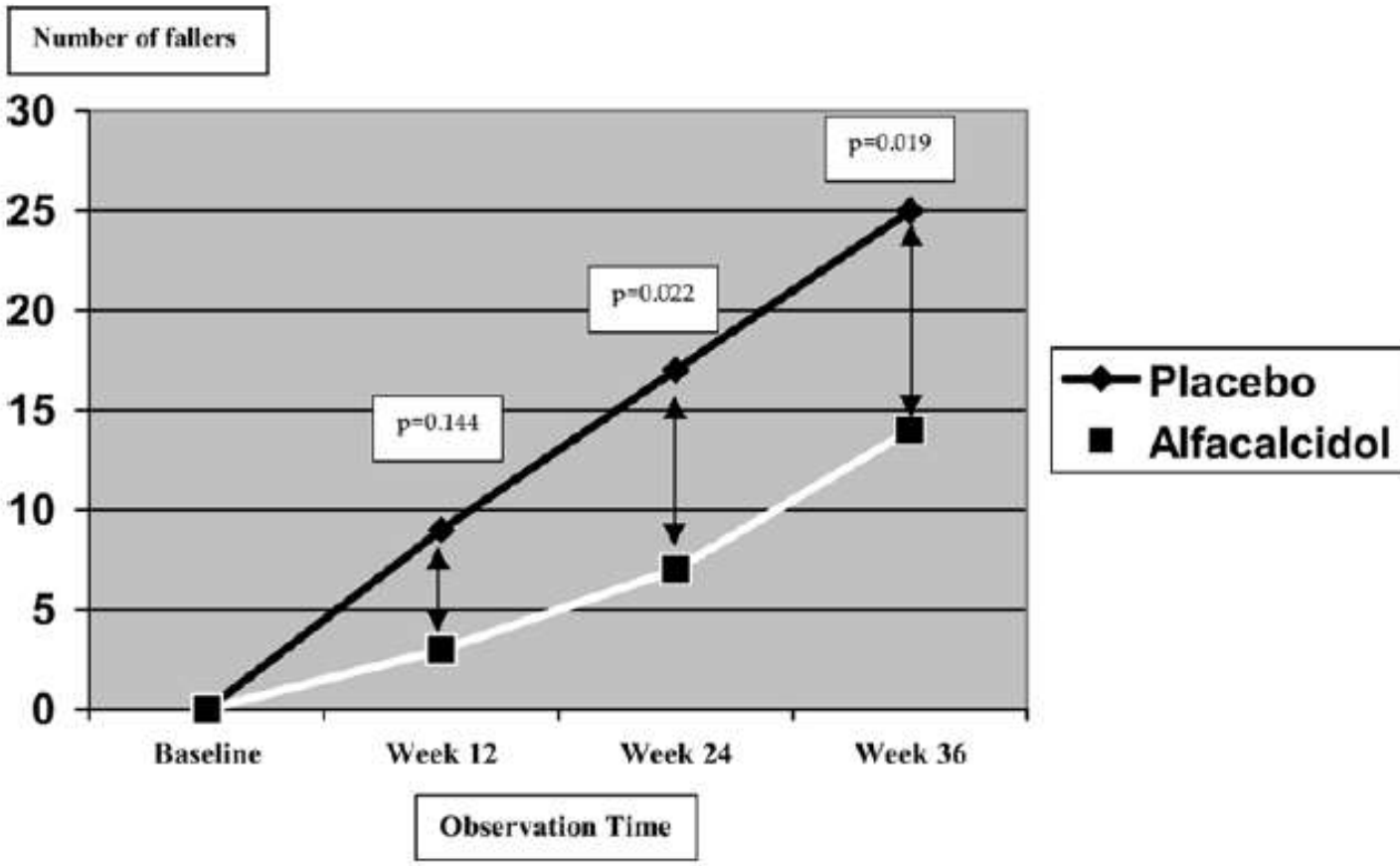
Outcome	Single fallers (14) vs. non-fallers (56)		Recurrent fallers (6) vs. non-fallers (56)	
	adjusted risk ratio	p value	adjusted risk ratio	p value
All-cause death	1.67	0.37	3.52	0.11
Nursing home admission, %	1.88	0.331	5.88	0.017
Number of all hospitalizations	2.01	0.007	2.43	0.021
Hospital stay, days	1.10	0.79	3.99	<0.001

[1] Risk ratios were adjusted for the significant risk factors in the regression models.

Abdel-Rahman et al Nephron Clin Pract 2011;118:c278-c284

From Swiss Aims Study. Randomized, Double-Blind Prospective Trial of Elderly (≥70 y/o) 378 Men and Women given Placebo or 1 ug/day of Alfacalcidol (1α-dihydroxycholecalciferol) for 36 weeks. No. of Fallers Was Significantly Lower in People Given Alfacalcidol.

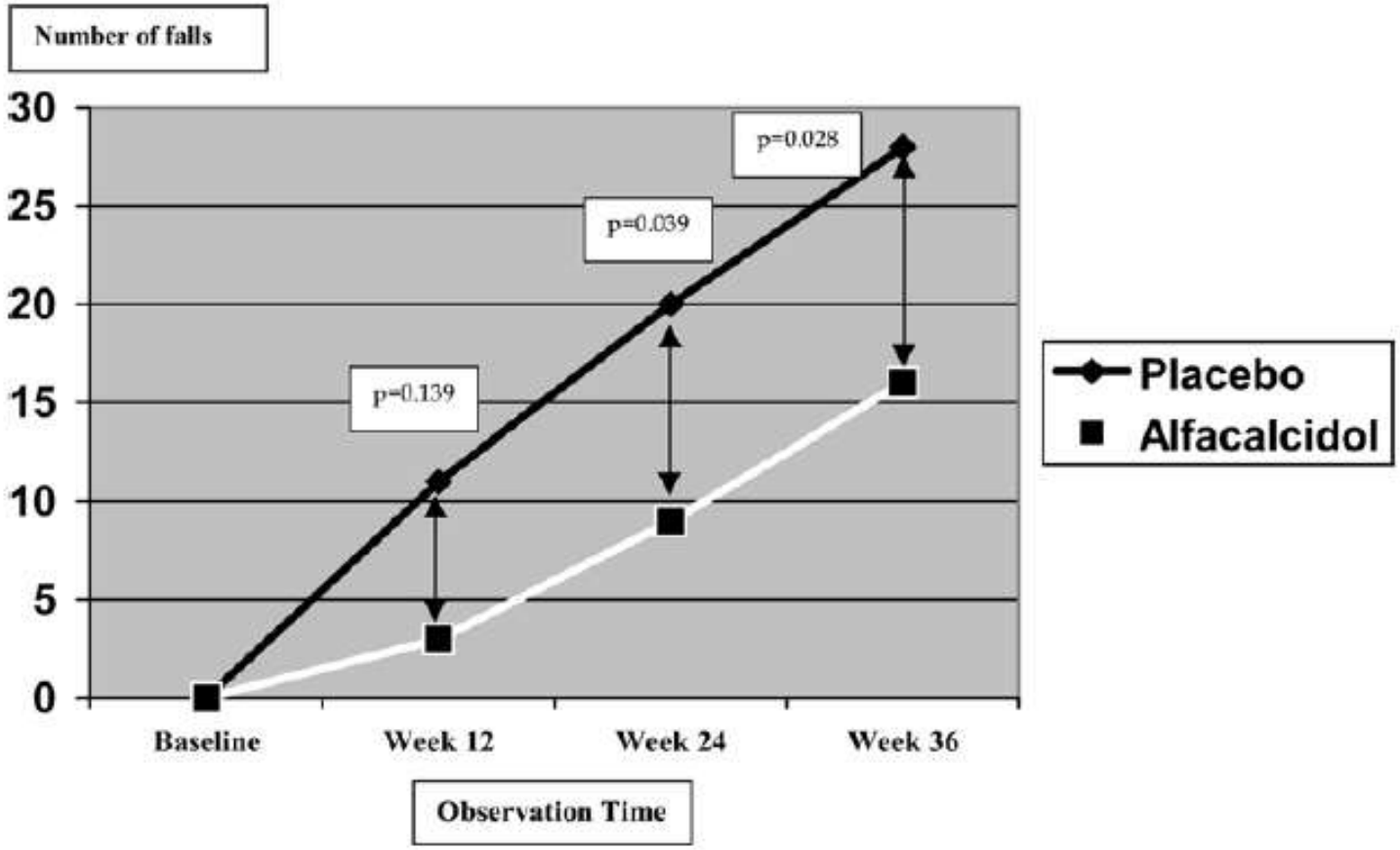
Fig. 1 Number of fallers over time according to treatment groups



Dukas et al. Osteoporosis Int 2005;16:198-203

From Swiss Aims Study. Randomized, Double-Blind Prospective Trial of Elderly (≥70 y/o) 378 Men and Women given Placebo or 1 ug/day of Alfacalcidol (1α-dihydroxycholecalciferol) for 36 weeks. No. of Falls Was Significantly Lower in People Given Alfacalcidol.

Fig. 2 Number of falls over time according to treatment groups



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From Swiss Aims Study. Randomized, Double-Blind Prospective Trial of Elderly (≥70 y/o) 378 Men and Women given Placebo or 1 ug/day of Alfacalcidol (1α-dihydroxycholecalciferol) for 36 weeks. No. of Falls and No. of Fallers Were Significantly Lower in People Given Alfacalcidol who had CrCl <65 mL/min (n=142), but Not in Those with CrCl ≥65 mL/min.

Table 2 Effect of alfacalcidol in elderly men and women on number of fallers and falls according to creatinine clearance: cut-off < 65 ml/min/≥65 ml/min

Creatinine clearance	Parameter	Multivariate Adjusted OR (95% CI)	Number of fallers/falls Alfacalcidol vs Placebo	*P*-value
<65 ml/min	Fallers	0.26 (0.08–0.80)	14/25	0.019[a]
	Falls	0.29 (0.09–0.88)	16/28	0.028[a]
≥65 ml/min	Fallers	0.92 (0.34–2.52)	26/21	0.875[a]
	Falls	0.93 (0.34–2.54)	32/23	0.885[a]

[a]Controlled for age, gender, BMI, previous falls, use of diuretics, albumin serum levels, calcidiol, D-hormone and iPTH serum levels at baseline and during follow-up, total daily calcium intake and coffee consumption, use of diuretics, marcoumar, aspirin, estrogens and multivitamins, number of co-morbidities and physical activity

Dukas et al. Osteoporosis Int 2005;16:198-203

Muscle Strength and Function in 25 Vitamin D Deficient CKD Patients Before and After 1-2 Courses of po Cholecalciferol 50,000 iu/week for 4-8 Weeks

Table 1. Pretreatment and posttreatment clinical characteristics and scores of objective physical performance tests, muscle strength tests and balance tests of Stage 3 – 4 CKD patients.

Stage 3 – 4 CKD patients			
	Pretreatment	Posttreatment	
	Mean ± SD	Mean ± SD	
25 (OH)D (ng/ml) (nmol/l)	6.9 ± 3.5 (17.2 ± 8.7)	52.0 ± 40.9 (129.7 ± 102.2)	p < 0.05
PTH(pg/ml)	127.2 ± 91.2	160.5 ± 118.1	NS
Calcium (mg/dl)	9.3 ± 0. 6	9.4 ± 0.7	NS
Phosphorus (mg/dl)	3.9 ± 0.8	4.7 ± 0.9	p < 0.05
Albumin (mg/dl)	4.5 ± 0.6	4.5 ± 0.4	NS
Hemoglobin (g/dl)	12.1 ± 1.9	11.7 ± 1.7	NS
Balance tests			
TUG test (s)	7.8 ± 1.4	7.2 ± 1.5	p < 0.05
Static balance (functional reach test)	20.6 ± 5.8	23.7 ± 6.3	p < 0.05
Overall stability index	4.5 ± 1.2	3.4 ± 0.9	p < 0.05
Ant-post stability index (eye open)	3.4 ± 1.0	2.6 ± 0.7	p < 0.05
Med-lat stability index (eye open)	3.1 ± 0.9	2.3 ± 0.7	p < 0.05
Physical performance tests			
Gait velocity test (s)	26.9 ± 2.3	25.7 ± 1.9	p < 0.05
Timed chair stand test (s)	10.7 ± 2.2	9.3 ± 1.9	p < 0.05
Stair climb test (s)	9.6 ± 4.1	8.6 ± 3.7	p < 0.05
Isometric strength			
(Hand grip test)	26.0 ± 9.2	27.7 ± 9.2	p < 0.05
Isokinetic strength			
Knee extension peak torque at 60°/sec N.m	95. 8 ± 27.2	99.2 ± 27	NS
Knee flexion peak torque at 60°/sec N.m	44.8 ± 16.9	50.6 ± 16.6	NS
Knee extension peak torque at 120°/sec N.m	66.7 ± 17.2	73.9 ± 17.6	p < 0.05
Knee flexion peak torque at 120°/sec N.m	34.5 ± 13.7	36.4 ± 12.2	NS

Taskapan et al Clinical Nephrology 2011;76:110-116

Muscle Strength and Function in 47 Vitamin D Deficient CPD Patients Before and After 1-2 Courses of po Cholecalciferol 50,000 iu/week for 4-8 Weeks

Table 2. Pretreatment and posttreatment clinical characteristics and scores of objective physical performance tests, muscle strength tests and balance tests of PD patients.

Stage 5 CKD patients on PD			
	Pretreatment	Posttreatment	
	Mean ± SD	Mean ± SD	
25 (OH)D (ng/ml) (nmol/l)	5.7 ± 3.3 (14.2 ± 8.2)	41.9 ± 21.1 (104.5 ± 52.6)	$p < 0.05$
PTH (pg/ml)	518.4 ± 361.1	473.2 ± 403.7	NS
Calcium (mg/dl)	9.4 ± 1.1	9.5 ± 0.9	NS
Phosphorus (mg/dl)	4.6 ± 1.3	4.9 ± 1.1	NS
Albumin (mg/dl)	4.1 ± 0.3	4.2 ± 0.4	NS
Hemoglobin (g/dl)	10.6 ± 1.8	10.7 ± 1.7	NS
Balance tests			
TUG test (s)	8.6 ± 2.0	7.6 ± 1.9	$p < 0.05$
Static balance, (functional reach test)	21.1 ± 6.5	23.9 ± 6.7	$p < 0.05$
Overall stability index	4.5 ± 1.51	3.6 ± 1.1	$p < 0.05$
Ant-post stability index, (eye open)	3.4 ± 1.1	2.7 ± 0.8	$p < 0.05$
Med-lat stability index, (eye open)	3.1 ± 1.1	2.4 ± 0.8	$p < 0.05$
Physical performance tests			
Gait velocity test (s)	27.7 ± 3.2	25.8 ± 2.9	$p < 0.05$
Timed chair stand test (s)	10.9 ± 3.6	9.5 ± 3.0	$p < 0.05$
Stair climb test (s)	10.7 ± 5.1	9.5 ± 4.7	$p < 0.05$
Isometric strength			
(Hand grip test)	22.6 ± 8.8	25.3 ± 9.9	$p < 0.05$
Isokinetic strength			
Knee extension, peak torque at 60°/sec N.m	81.3 ± 32.1	85.9 ± 34	$p < 0.05$
Knee flexion, peak torque at 60°/sec N.m	35.6 ± 18.6	41.4 ± 23.8	$p < 0.05$
Knee extension, peak torque at 120°/sec N.m	59.2 ± 19.7	65.4 ± 25.2	NS
Knee flexion, peak torque at 120°/sec N.m	29.1 ± 16.3	31.7 ± 15.6	$p < 0.05$

Taskapan et al Clinical Nephrology 2011;76:110-116

Effect of Vitamin D on Skeletal Muscle Mass and Strength in CKD Patients

Relation Between Serum 1,25(OH)2D &Physical Performance (PP) & Thigh Muscle Area in Stage 3 and 4 CKD

1. 26 CKD patients- 13 stage 3 and 13 stage 4.
2. 61±Sd 13 years; 92% men.
3. 73% were vitamin D deficient (n=10) or insufficient (n=9)
4. Many PP measures correlated more closely with 1,25(OH)2D than with 25(OH)D.

Gordon et al. J Renal Nutrition 2012;22:423-433

Relation Between Serum 1,25(OH)2D &Physical Performance (PP) & Thigh Muscle Area in Stage 3 and 4 CKD

5. Variance in mid-thigh cross-sectional area by MRI was most closely approximated by serum 1,25(OH)2D, plasma Ca and daily physical activity.
6. These data suggest that 1,25(OH2)D is a determinant of PP and thigh muscle size.

Gordon et al. J Renal Nutrition 2012;22:423-433

Table 3. Associations Between Levels of 25-Hydroxyvitamin D (25(OH)D) and 1,25-Dihydroxyvitamin D ($1,25(OH)_2D$) and Physical Performance Measures

	Usual Gait Speed (cm/second)	Fast Gait Speed (cm/second)	6-Minute Walk	Static Balance (1 Leg)	Sit-to-Stand Time (5 Repetitions)	Isokinetic Strength (90°/second)	Isokinetic Strength (180°/second)	Isometric MVC
Serum 25(OH)D	$r = 0.41$	$r = 0.14$	$r = 0.20$	$r = 0.07$	$r = -0.32$	$r = 0.01$	$r = 0.04$	$r = 0.02$
	$P \pm .04$	$P = .51$	$P = .33$	$P = .75$	$P = .13$	$P = .95$	$P = .86$	$P = .78$
Serum $1,25(OH)_2D$	$r = 0.46$	$r = 0.36$	$r = 0.38$	$r = 0.42$	$r = -0.42$	$r = 0.35$	$r = 0.48$	$r = 0.35$
	$P \pm .02$	$P = .08$	$P = .06$	$P \pm .03$	$P \pm .04$	$P = .08$	$P \pm .02$	$P = .08$

MVC, maximal voluntary contraction.

Gordon et al. J Renal Nutrition 2012;22:423-433

Table 4. Results of Multivariable Regression Analyses on Physical Performance Measures

n = 26	Usual Gait Speed (cm/second)		Fast Gait Speed (cm/second)		6-Minute Walk (feet)		Sit-to-Stand Time (10 repetitions) (seconds)	
Predictor Variable	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value	Coefficient	*P* Value
$1,25(OH)_2D$ serum level, pg/mL	0.74	.002	1.19	.02	8.93	.02	−0.25	.02
BMI, kg/m^2	−2.25	<.001	−5.40	<.001	−36.06	<.001	0.704	.006
Intercept	172.42	–	307.67	–	2293.67	–	11.09	–
r	Overall $r = 0.76$		Overall $r = 0.75$		Overall $r = 0.73$		Overall $r = 0.64$	
	$r^2 = 0.57$		$r^2 = 0.55$		$r^2 = 0.54$		$r^2 = 0.40$	
Significance of the model	$P < .001$		$P < .001$		$P < .001$		$P = .003$	

$1,25(OH)_2$, 1,25-dihydroxyvitamin D; BMI, body mass index.

Gordon et al. J Renal Nutrition 2012;22:423-433

Table 5. Results of Multivariable Regression Analysis on the Quadriceps Muscle Area

n = 24	Cross-sectional Area of Quadriceps (cm^2)	
Predictor Variable	Coefficient	*P* Value
$1,25(OH)_2D$ serum level, pg/mL	0.370	.02
Plasma calcium, mg/dL	−13.981	.02
Physical activity, per 1,000 arbitrary units*	0.07756	.04
Intercept	170.68	–
r	Overall $r = 0.73$	
	$r^2 = 0.54$	
Significance of the model	$P = .005$	

$1,25(OH)_2$, 1,25-dihydroxyvitamin.
*By 3-dimensional accelerometry.

Gordon et al. J Renal Nutrition 2012;22:423-433

Potential Mechanisms by which Vitamin D may Increase Skeletal Muscle Function Mass and Function

Figure 4. Western blot of homogenates of human skeletal muscle obtained by muscle biopsy. The VDR is seen at a M_r of 48,000. Dots - Mr 47K.

Figure 5. Western blot of human skeletal muscle mitochondria obtained by muscle biopsy. The VDR is seen at a M_r of 48,000.

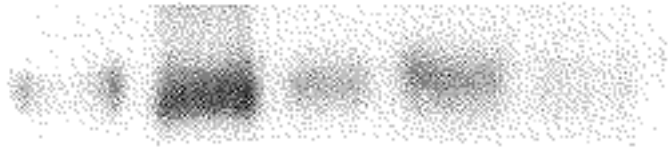

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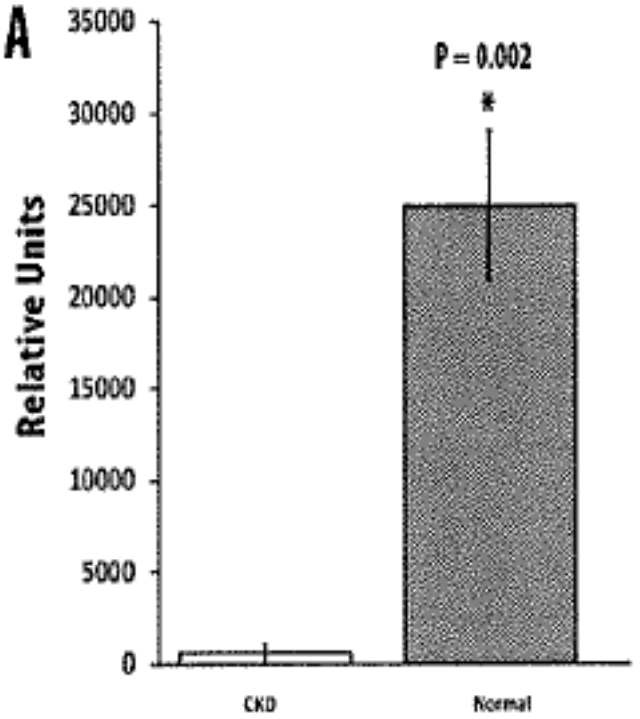
Figure 13. VDR concentrations are reduced in skeletal muscle from CKD patients.



Vitamin D Actions on Mitochondria

Mitochondrial Oxidative Function Pre-Post Exercise in Gastroc-Soleus Muscles of 12 Vit. D Deficient Adults Before & After Cholecalciferol Rx & in 15 Healthy Adults

Table 1. Biochemistry, ^{31}P-MRS Measurements Undertaken on Skeletal Muscle and Questionnaires in Vitamin D-Deficient Subjects Before and After Cholecalciferol Therapy and in Healthy Controls

Mean ± SD	Baseline (Vitamin D Deficient)	Follow-Up (After Vitamin D Supplementation)	*P* Value	Healthy Controls
Biochemistry				
Serum 25OHD, nmol/L	8.83 ± 4.28	113.8 ± 51.5	<.001	44.2 ± 29.4
Serum calcium, mmol/L	2.29 ± 0.1	2.35 ± 0.1	.24	NA
Serum phosphate, mmol/L	0.99 ± 0.1	1.12 ± 0.2	.19	NA
Alkaline phosphatase, U/L	86.7 ± 15.5	78.5 ± 9.5	.16	NA
Rest				
Pi, mM	2.63 ± 0.48	2.78 ± 0.47	.38	2.94 ± 0.59
PCr, mM	31.77 ± 3.20	32.09 ± 4.19	.77	32.39 ± 1.28
Pi/PCr	0.083 ± 0.02	0.087 ± 0.02	.35	0.090 ± 0.02
pH, U	7.04 ± 0.03	7.05 ± 0.03	.28	7.04 ± 0.03
End of exercise				
PCr drop, fractional	0.25 ± 0.14	0.24 ± 0.10	.81	0.21 ± 0.08
Nadir pH, U	6.99 ± 0.08	7.00 ± 0.05	.34	6.91 ± 0.28
Maximum proton efflux, mM/min	3.63 ± 4.37	3.70 ± 1.83	.95	2.59 ± 1.69
Recovery				
$\tau_{1/2}$PCr, sec	34.44 ± 8.18	27.84 ± 9.54	<.001	35.66 ± 14.62
$\tau_{1/2}$ADP, sec	26.84 ± 6.58	21.93 ± 6.81	.003	27.49 ± 9.12

Abbreviation: NA, not available. Data are expressed as mean ± SD. Paired *t* tests were undertaken for comparisons before and after cholecalciferol therapy.

Sinha et al J Clin Endocrinol Metab 2013;98:E509-E513

Mitochondrial Oxidative Function Pre-Post Exercise in Gastrocnemius-Soleus Muscles of 12 Severely Vitamin D Deficient Adults Before and After Cholecalciferol Rx and in 15 Healthy Adults

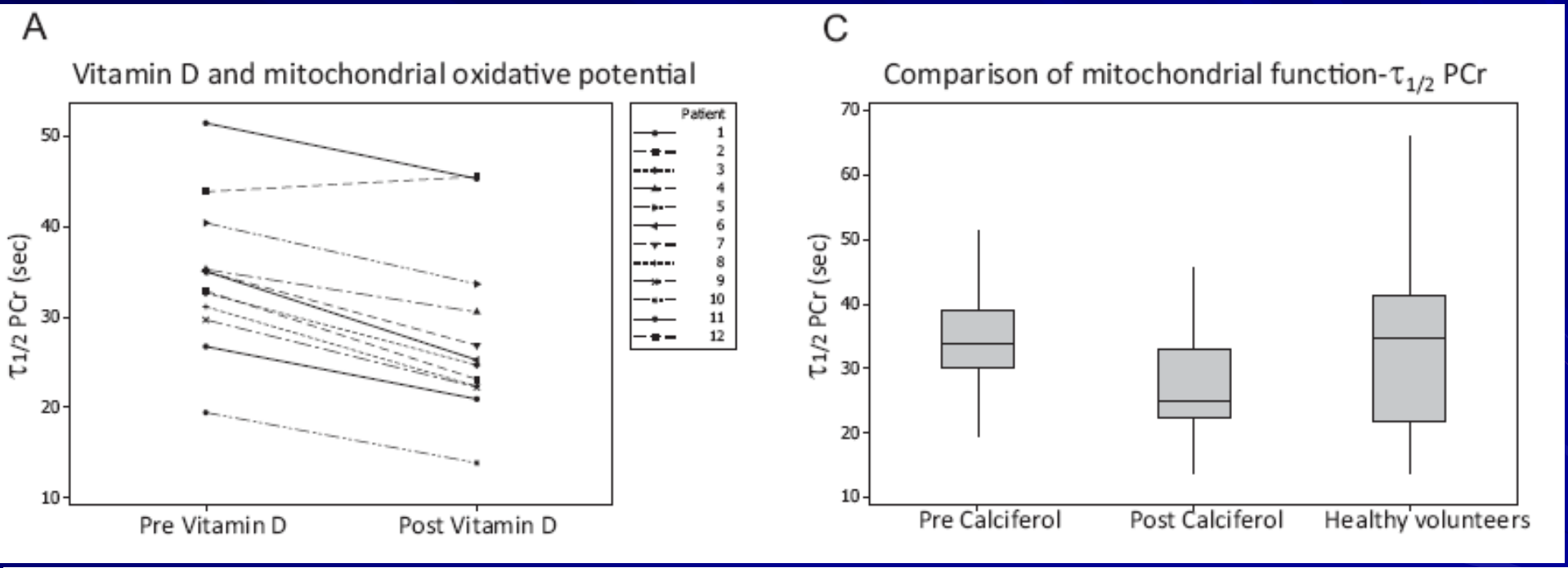


Figure 1. A–D, Comparison of $\tau_{1/2}$PCr kinetics before and after cholecalciferol therapy (A); serum 25OHD levels at presentation with vitamin D deficiency and then after cholecalciferol therapy (B); comparison of mitochondrial function ($\tau_{1/2}$PCr) before and after vitamin D therapy and in healthy volunteers (C); a linear regression model examining the relationship between serum 25OHD and $\tau_{1/2}$PCr. This model includes data from both before and after vitamin D treatment subjects and healthy controls ($r = -0.41$, r^2 adjusted = 14.67%, $P = .009$) (D).

Sinha et al J Clin Endocrinol Metab 2013;98:E509-E513

Mitochondrial Oxidative Function Pre-Post Exercise in Gastrocnemius-Soleus Muscles of 12 Severely Vitamin D Deficient Adults Before and After Cholecalciferol Rx and in 15 Healthy Adults

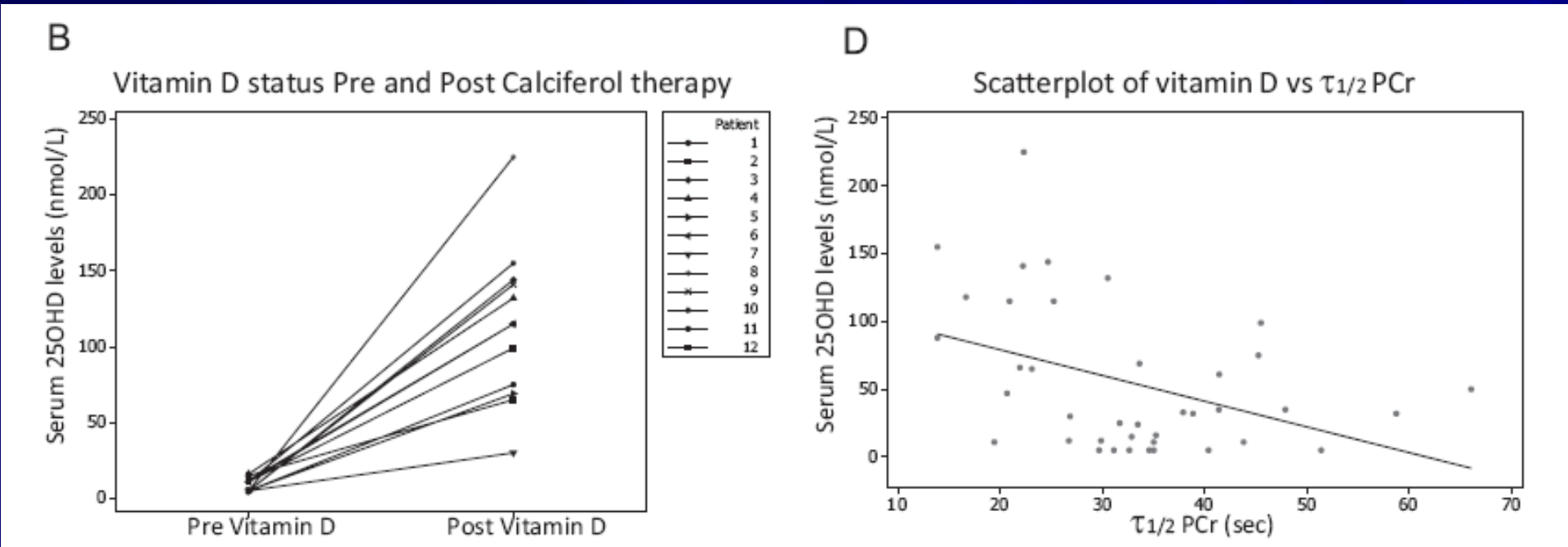


Figure 1. A–D, Comparison of $\tau_{1/2}$PCr kinetics before and after cholecalciferol therapy (A); serum 25OHD levels at presentation with vitamin D deficiency and then after cholecalciferol therapy (B); comparison of mitochondrial function ($\tau_{1/2}$PCr) before and after vitamin D therapy and in healthy volunteers (C); a linear regression model examining the relationship between serum 25OHD and $\tau_{1/2}$PCr. This model includes data from both before and after vitamin D treatment subjects and healthy controls ($r = -0.41$, r^2 adjusted = 14.67%, $P = .009$) (D).

Sinha et al J Clin Endocrinol Metab 2013;98:E509-E513

Limitations of Data in this Field

1. Few randomized, prospective controlled trials.
2. Most studies had small sample sizes.
3. Not all studies indicate that vitamin D reduces number of number of fallers or number of falls per patient .

END

25-HydroxyVitamin D Insufficiency and Deficiency and Mortality in CKD Patients

Meta-Analysis of 20 Studies of Effects of Vitamin D Therapy on Mortality in Non-Dialyzed CKD and ESKD Patients

Zhang et al. BMC Nephrology 2013;13:199

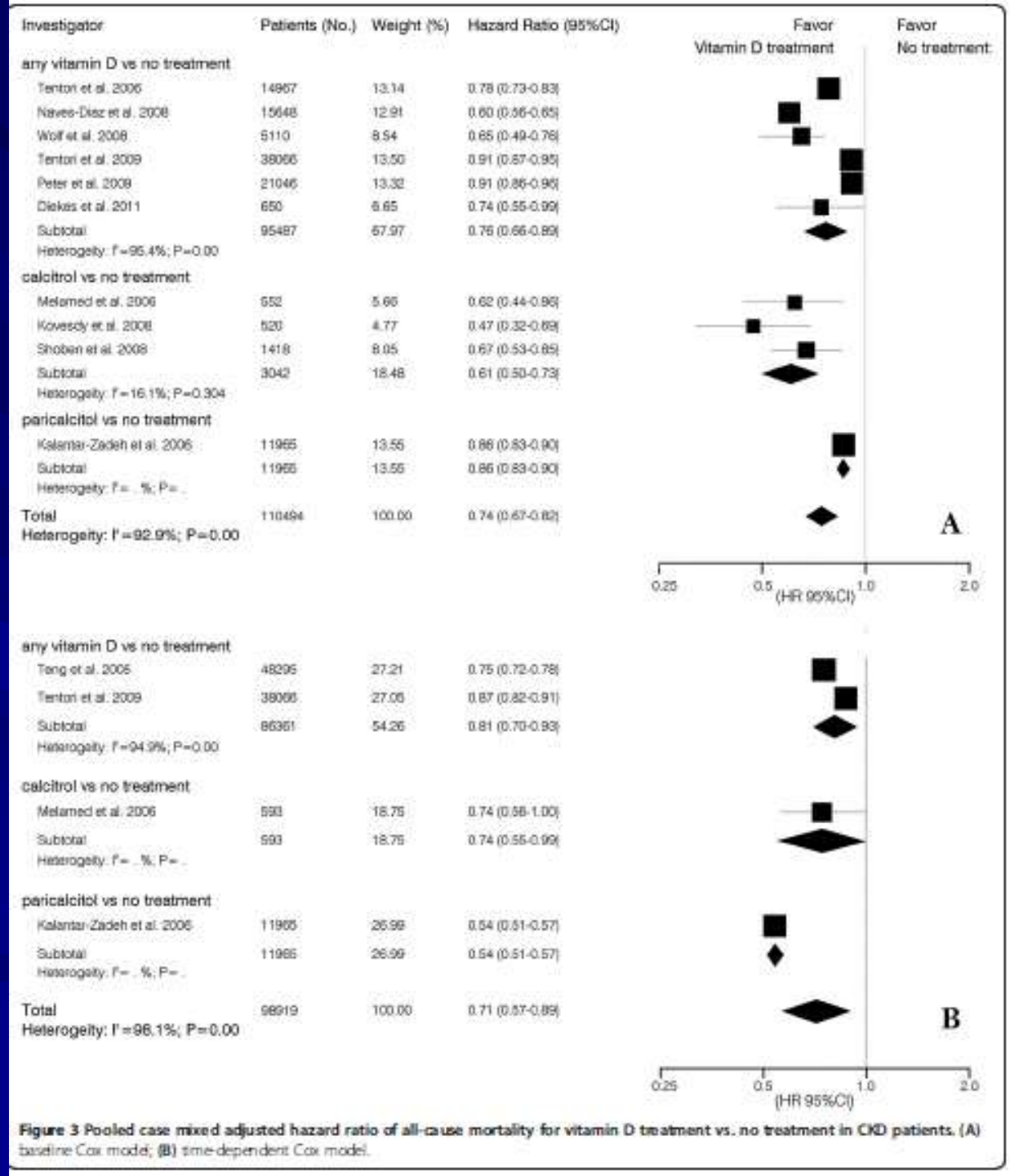


Figure 3 Pooled case mixed adjusted hazard ratio of all-cause mortality for vitamin D treatment vs. no treatment in CKD patients. (A) baseline Cox model; (B) time-dependent Cox model.

Proposed Doses of Vitamin D in CKD (Stages 3-5) and ESKD (1)

1. CKD Stages 3-5 or Nephrotic Proteinuria:

i. **Cholecalciferol, ~800-1200 IU/day**

ii. **With deficiency of 25(OH)D, give up to 2000 IU/day ?**

iii. **1.25-Dihydroxycholecalciferol, 0.25-0.5 ug/day, paricalcitol,~1-2 ug/day, doxercalciferol, 1- 3.5 ug/day**

Proposed Doses of Vitamin D in CKD (Stages 3-5) and ESKD (2)

2. Maintenance Hemodialysis and Chronic Peritoneal Dialysis:

i. **Cholecalciferol, ~800-1200 IU/day**

ii. **With deficiency of 25(OH)D, give up to 2000 IU/day ?**

iii. **1.25-dihydroxycholecalciferol 0.25-0.5 ug/day, Paricalcitol ~1- 4 ug3x/week, doxercalciferol 10-20 ug 3x/week**

Some Adverse Effects of 25(OH)D or 1,25(OH)D Deficiency

1. Impaired Immune Function
2. Inflammatory State and Oxidative Stress
   Increased serum IL-6, soluble vascular cell adhesion factor, malondialdehyde, myeloperoxidase
3. Insulin Resistance
4. Impaired Pancreatic Secretion of Insulin?

25-HydroxyVitamin D Insufficiency and Deficiency is Associated with an Increased Incidence of albuminuria and CKD and More Rapid Progression of Renal Failure and Cardiovascular Disease in CKD Patients

Possible Mechanisms by which Vitamin D Deficiency May Promote Progression of CKD and Increase Cardiovascular Disease (1)

<u>25(OH)cholecalciferol Suppresses</u>

i. Parathyroid hormone secretion.

ii. The Renin –Angiotensin system (RAS) which may increase renin & angiotensin II (A-II) production.

iii. Causes inflammation at least partly through NF-κB which promotes inflammation & fibrosis.

Possible Mechanisms by which Vitamin D Deficiency May Promote Progression of CKD and Increase Cardiovascular Disease (2)

<u>25(OH)cholecalciferol deficiency</u>

iv. May lead to markedly increased intrarenal interstitial A-II

v. Increases blood pressure (via RAS activation?)

vi. Increases albuminuria (via RAS activation?)

Possible Mechanisms by which Vitamin D Deficiency may Promote Progression of CKD and Increase Cardiovascular Disease (3)

25(OH)cholecalciferol deficiency

vii. Increases vascular smooth muscle proliferation

viii. Engenders vascular calcification

ix. Leads to insulin resistance

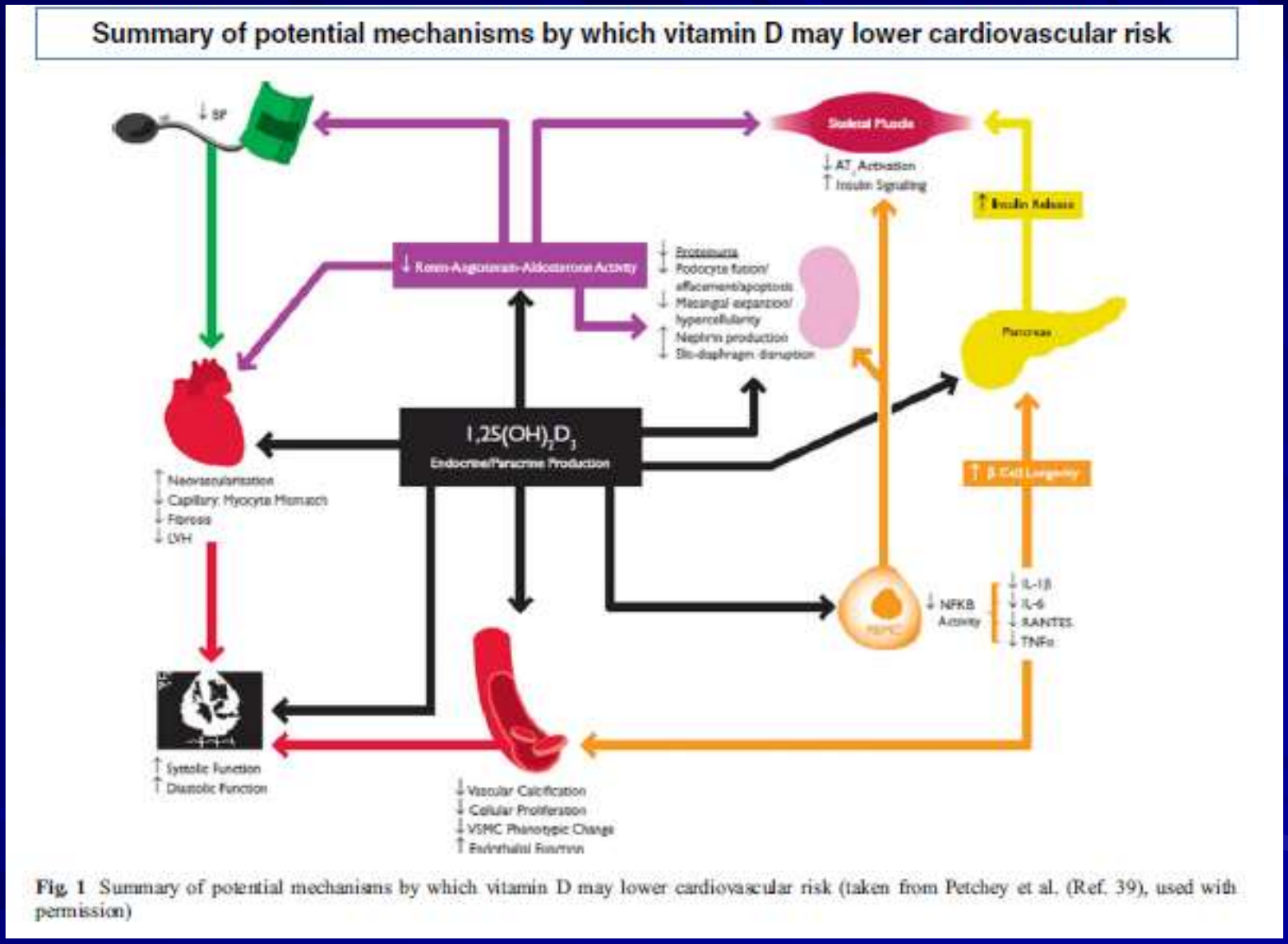


Fig. 1 Summary of potential mechanisms by which vitamin D may lower cardiovascular risk (taken from Petchey et al. (Ref. 39), used with permission)

Querfeld, U. Pediatric Nephrology 2013;78:605-610

Possible Mechanisms by which Vitamin D Deficiency may Promote Progression of CKD and Increase Cardiovascular Disease (3)

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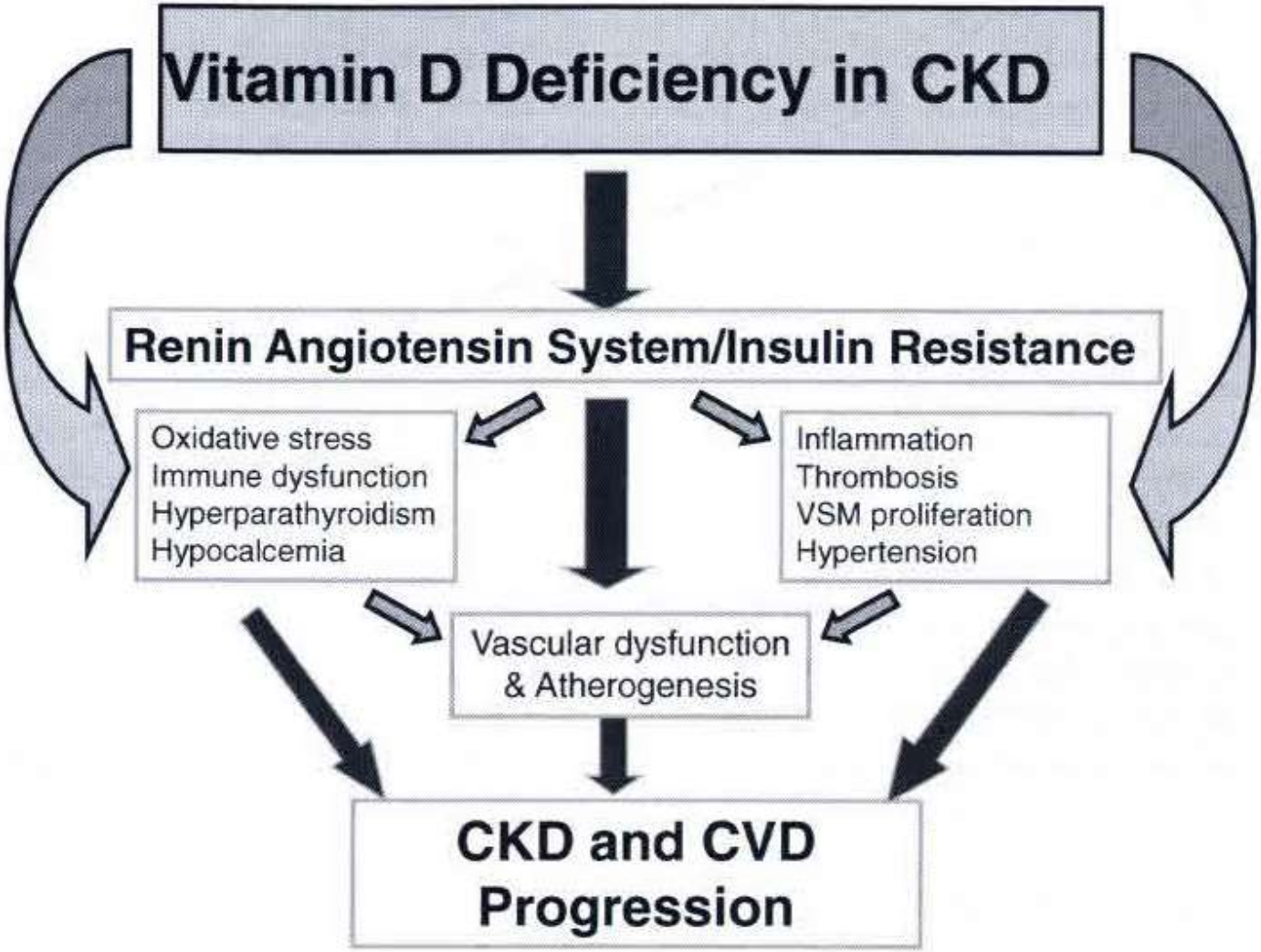


Fig 1. Conceptual model of major pathways through which vitamin D deficiency in patients with chronic kidney disease (CKD) may lead to CKD progression and complications such as premature cardiovascular disease (CVD). VSM – vascular smooth muscle. Adapted from ref 17.

Williams et al, Ethnicity & Disease 2009;19:S5-8

Exercise Training: Effects on Exercise Capacity Summary

Type of Exercise	No. Signific. Improved	Type of Improvement
Endurance	1	Cardiopulmonary
Strength	5	Strength & Physical Perform
End & Strength	6	Strength & Cardiopulmonary
No Exercise	0	----------

EFFECT OF RESISTANCE TRAINING ON SYSTEMIC INFLAMMATION IN CKD PATIENTS (1)

Dependent Variables	Low-Protein Diet + Resistance Training (n = 14)	Low-Protein Diet Alone (control) (n = 12)	P* Group Effect
CRP (mg/L)			
Week 0	7.8 (6.0)	6.2 (6.0)	
Week 12	6.1 (6.0)	7.7 (6.0)	
Change	-1.7 (0.0)	1.5 (0.0)	
			0.049
Serum IL-6 (pg/mL)			
Week 0	11.3 (10.5)	7.7 (6.9)	
Week 12	6.9 (6.5)	10.0 (9.8)	
Change	-4.2 (-3.6)	2.3 (3.0)	0.012

NOTE: Data expressed as mean ± SD and geometric mean (median). Castaneda et al; AJKD 43:607, 2004

EFFECT OF RESISTANCE TRAINING ON SYSTEMIC INFLAMMATION IN CKD PATIENTS (2)

Dependent Variables (n = 12)	Low-Protein Diet + Resistance Training (n = 14)	Low-Protein Diet Alone (control)	*P** Group Effect
Serum transferrin mg/dL)			
Week 0	178 ± 32	175 ± 34	
Week 12	258 ± 52	177 ± 37	
Change	80 ± 25	2 ± 34	0.042
Serum albumin (g/dL)			
Week 0	3.7 ± 0.3	3.8 ± 0.4	
Week 12	3.8 ± 0.2	3.6 ± 0.4	
Change	0.1 ± 0.2	-0.2 ± 0.2	0.091

NOTE: Data expressed as mean ± SD and geometric mean (median). Castaneda et al; AJKD 43:607, 2004

EFFECT OF NANDROLONE DECANOATE (ND) AND EXERCISE TRAINING (ExTx) ON SKELETAL MUSCLE

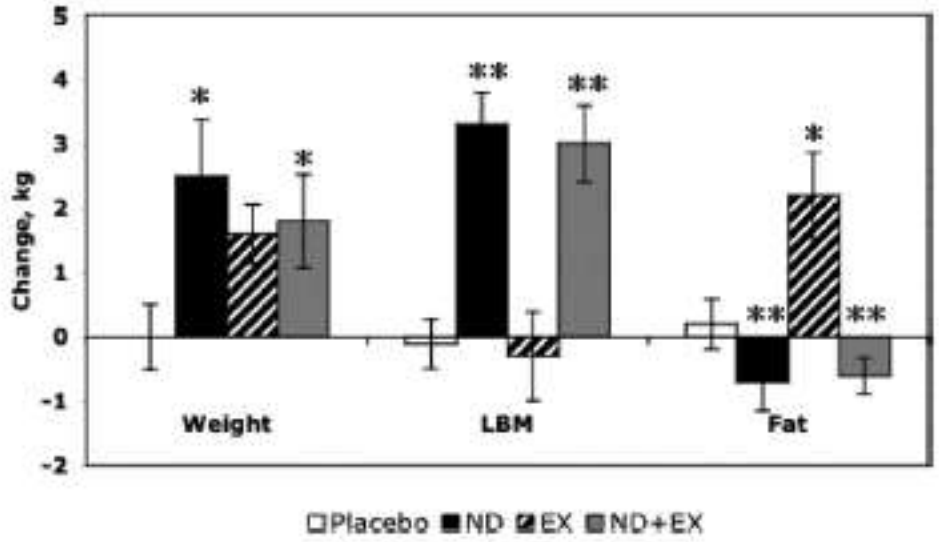


Figure 2. Changes in body composition. Changes in body composition from baseline to 12 wk as measured by dual-energy x-ray absorptiometry (DEXA) are shown. □, placebo group; ■, nandrolone (ND) group; ▨, exercise (EX) group; ▤, nandrolone plus exercise (ND+EX) group. Error bars show SEM. $*P < 0.05$; $**P < 0.001$.

Johansen et al JASN 2006;17:2307-2314

EFFECT OF NANDROLONE DECANOATE (ND) & EXERCISE TRAINING (ExTx) ON SKELETAL MUSCLE

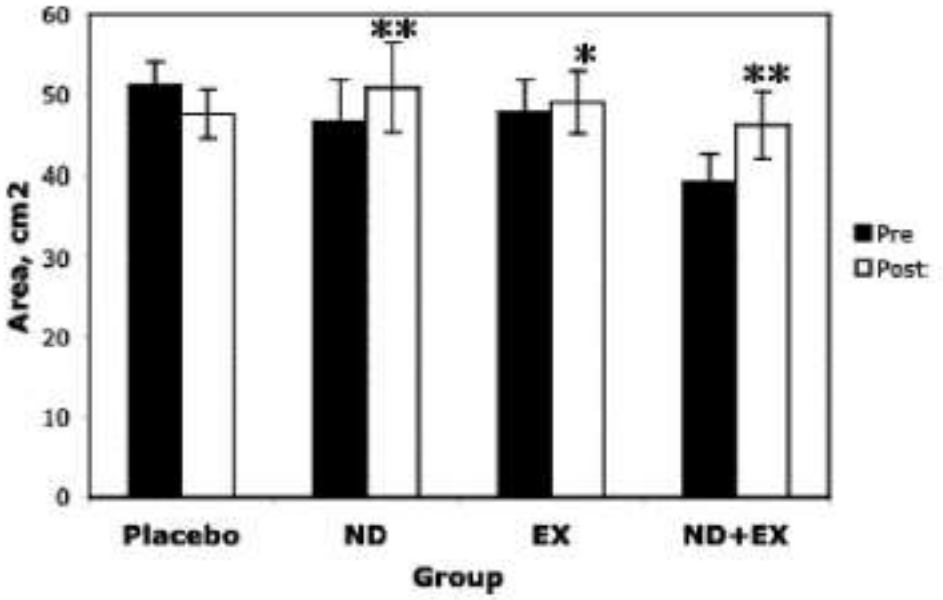


Figure 3. Changes in quadriceps muscle size. ■, baseline quadriceps contractile muscle cross-sectional area, measured using magnetic resonance imaging; □, postintervention quadriceps muscle cross-sectional area. Error bars show SEM. $^{*}P < 0.05$; $^{**}P < 0.001$. Groups are as follows: Placebo, weekly placebo injections; ND, weekly nandrolone decanoate injections; EX, lower extremity resistance exercise training during dialysis sessions plus weekly placebo injections; ND+EX, weekly nandrolone decanoate injections plus lower extremity resistance exercise training during hemodialysis sessions.

Johansen et al JASN 2006; 17:2307-2314

	No Rx	ND	ExTx	ND+ExTx
Muscle strength				
knee extension 3RM (lb)				
baseline	19.2 ± 8.7	13.0 ± 7.1	14.0 ± 8.4	16.7 ± 8.7
3 mo	20.0 ± 9.1	14.4 ± 7.3	22.6 ± 11.6	24.9 ± 8.4
change	0.8 ± 2.0	1.4 ± 2.1	8.6 ± 6.9	8.2 ± 6.2
hip abduction 3RM (lb)				
baseline	11.8 ± 4.3	9.1 ± 6.0	8.5 ± 5.2	10.3 ± 4.6
3 mo	11.8 ± 5.9	9.2 ± 6.3	15.4 ± 6.9	18.1 ± 6.0
change	−0.1 ± 2.5	0.1 ± 2.2	6.9 ± 5.0	7.8 ± 4.6
hip flexion 3RM (lb)				
baseline	10.9 ± 4.5	6.4 ± 6.1	7.6 ± 5.3	9.7 ± 4.7
3 mo	11.4 ± 6.3	7.4 ± 6.6	13.7 ± 6.8	16.9 ± 8.3
change	0.5 ± 2.7	1.0 ± 2.5	6.1 ± 4.3	7.2 ± 5.5
isokinetic knee extension at 90 degrees/s (Nm)				
baseline	41.7 ± 19.4	30.7 ± 22.4	39.2 ± 25.1	43.6 ± 26.9
3 mo	43.3 ± 22.8	41.3 ± 26.3	46.8 ± 28.9	49.9 ± 27.8
change	1.6 ± 9.3	10.6 ± 23.9	7.6 ± 12.3	6.3 ± 11.0
isokinetic knee extension at 120 degrees/s (Nm)				
baseline	38.4 ± 22.5	33.3 ± 27.5	35.1 ± 23.9	35.5 ± 23.2
3 mo	40.2 ± 21.1	39.5 ± 30.6	43.9 ± 26.1	45.6 ± 26.2
change	1.8 ± 10.2	6.2 ± 14.1	8.8 ± 12.4	10.2 ± 9.7

EFFECT OF NANDROLONE DECANOATE (ND) & EXERCISE TRAINING (ExTx) ON SKM

Johansen et al JASN 2006;17:2307

Exercise Training and SKM mRNA Summary (1)

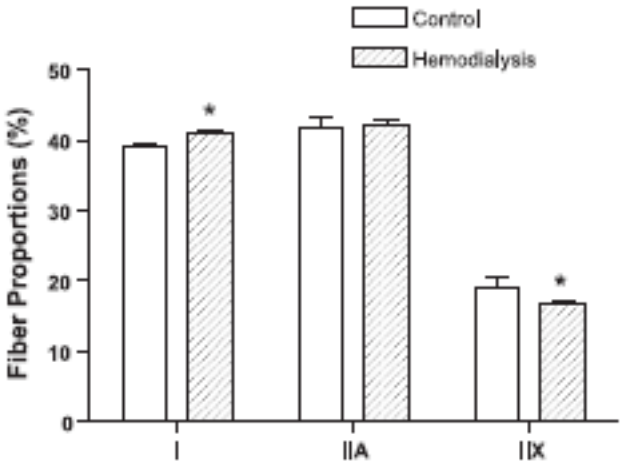
- In vastus lateralis of sedentary MHD patients as compared to sedentary normals:
- mRNA levels tend to be decreased for IGF-IEa, IGF-II, IGF-IR, and IGFBP-2.

EFFECTS OF DECONDITIONING ON SKELETAL MUSCLE (1)

1. Fiber atrophy and decreased muscle mass.
2. Decreased enzymes involved in aerobic energy production and mitochondrial density.
3. Decreased capillary density (increased diffusion distance for oxygen transport).
4. Type IIa fibers transform into IIx/IIb fibers – decreasing aerobic capacity.
5. Decreased cardiac reserve.

EFFECTS OF DECONDITIONING ON SKELETAL MUSCLE (2)

6. Increased percent body fat.
7. Decreased levels of anabolic hormones.
8. End result includes decrease in VO_{2max} and lactic acid threshold.
9. Many maintenance dialysis patients have a very sedentary lifestyle.



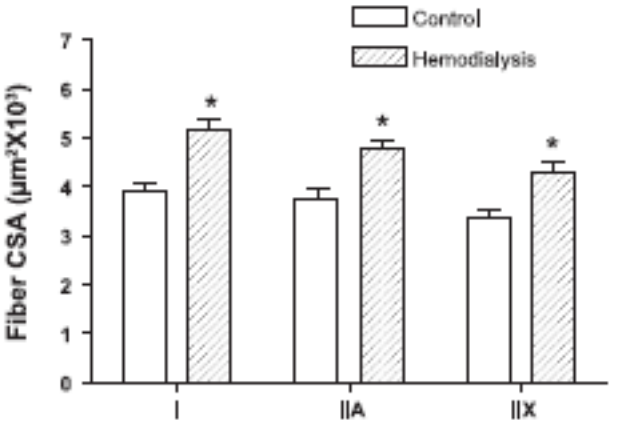


Fig. 1. Proportions of types I, IIA, and IIX muscle fibers (*top*) in the vastus lateralis of control subjects (open bars) and maintenance hemodialysis (MHD) patients (hatched bars). There was a small (2%), but significantly greater, proportion of type I fibers and lower proportion of type IIX fibers in MHD patients ($P < 0.05$). Mean cross-sectional areas (CSA) from individual type I, IIA, and IIX muscle fibers (*bottom*) were significantly larger by 33% ($P < 0.001$), 26% ($P < 0.01$), and 28% ($P < 0.05$), respectively, in MHD patients. Values are means ± SE. *Significantly different from control group.

Lewis et al. J Appl Physiol 2012;112:72-78

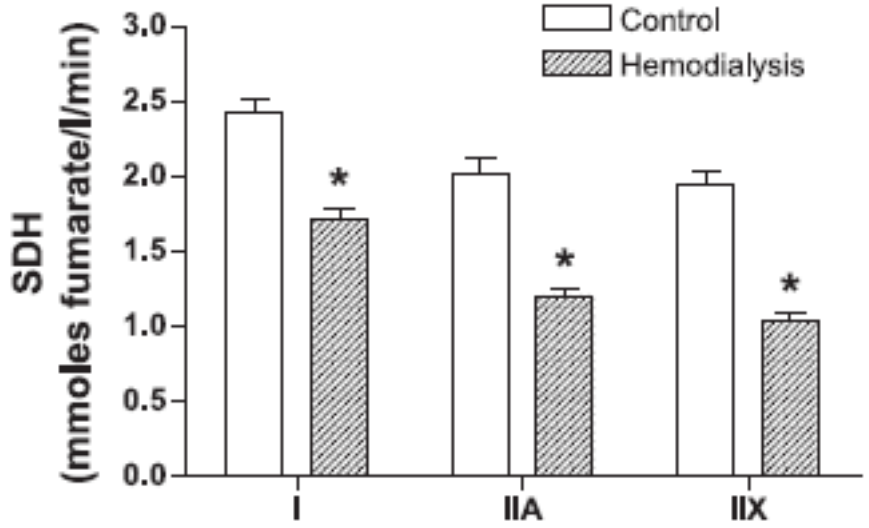


Fig. 2. Mean succinate dehydrogenase (SDH) activity from individual type I, IIA, and IIX muscle fibers in the vastus lateralis of MHD patients (hatched bars) were lower by 29% ($P < 0.0001$), 40% ($P < 0.0001$), and 47% ($P < 0.0001$), respectively, compared with control subjects (open bars). Values are means ± SE. *Significantly different from control group.

Lewis et al. J Appl Physiol 2012;112:72-78

Table 3. *Indexes of capillarity in control and chronic hemodialysis patients*

	Capillaries per Fiber	Capillary-to-Fiber Ratio	Capillary Density, number/mm^2
Control	4.22 ± 0.45	1.66 ± 0.16	544 ± 162
Hemodialysis	4.74 ± 0.11*	1.84 ± 0.08§	362 ± 113§

Values are means ± SE. *$P < 0.001$, significantly different from control. §$P < 0.0001$, significantly different from control.

Lewis et al. J Appl Physiol 2012;112:72-78

Lewis et al. J Appl Physiol 2012;112:72-78

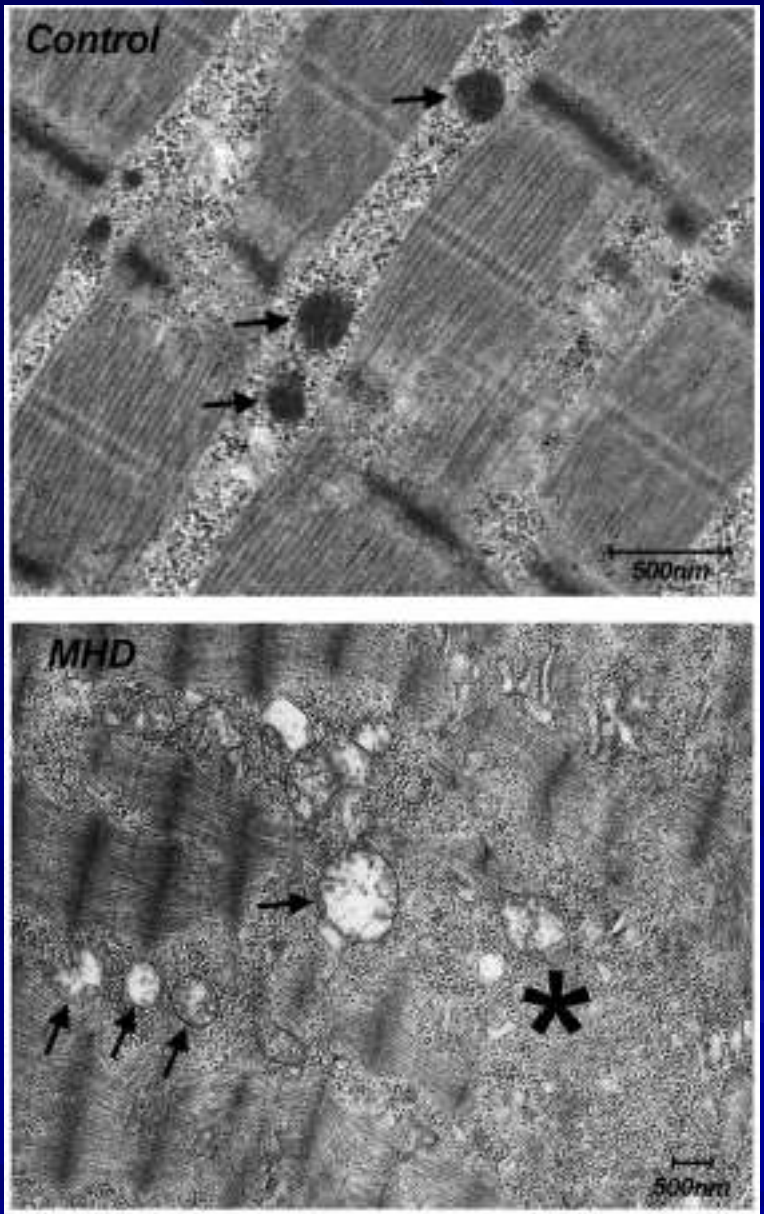


Fig. 4. Representative ultrastructure of the vastus lateralis muscle from a healthy control subject (*top*) and from a MHD patient (*bottom*). Note a cluster of swollen mitochondria (arrows) and an area of Z-band disruption (*) with hemodialysis. Note difference in scale bars between control and MHD. Mitochondria (arrows) in controls are clearly seen at ×3 the magnification of MHD, and their average size is still smaller than or comparable with MHD.

Higher Muscle Quality (i.e., Hand Grip Strength Divided by Arm Lean Mass) is Associated with Survival in 272 MHD Patients Independent of Age, Diabetes Mellitus or Serum Albumin

Yoda et al.
Biomedicine Phamcotherapy 2012;66:266-270

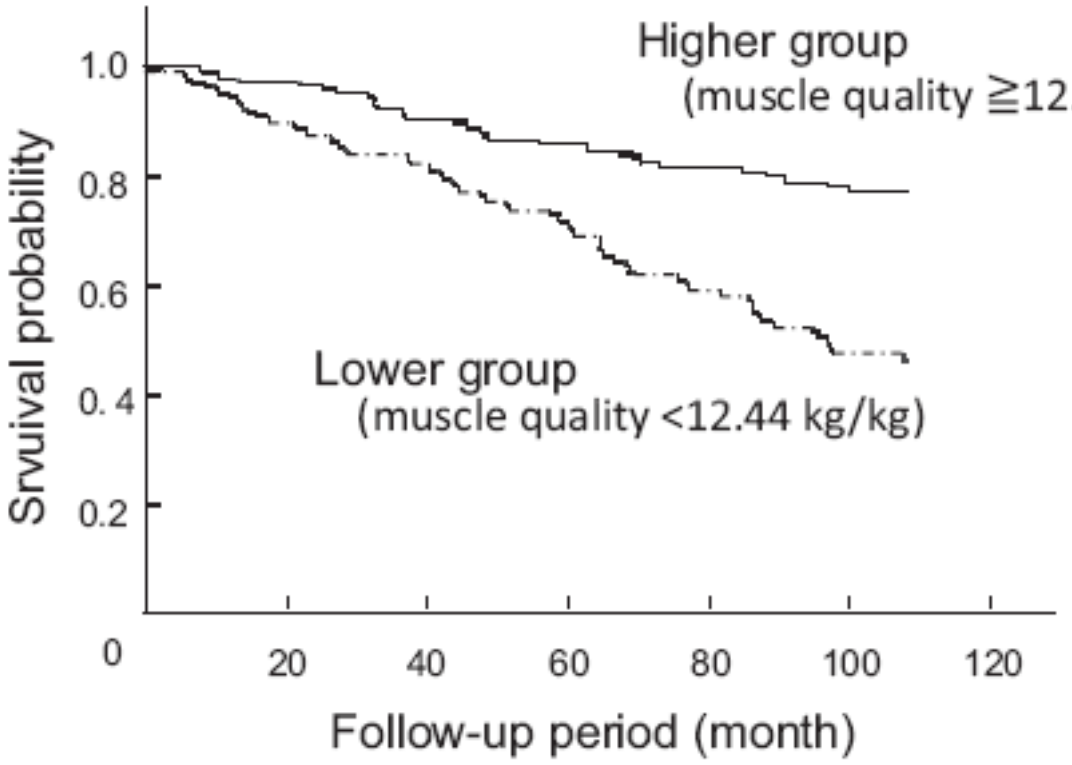


Fig. 1. Kaplan-Meier analyses are performed to examine the association between muscle quality and all-cause mortality. Patients with higher ($\geq$ 12.44 kg/kg) muscle quality elucidated significantly lower rate of all-cause death than those with lower ($<$ 12.44 kg/kg) muscle quality ($P < 0.0001$ by log-rank test).