Extension of Multi-Scale Systems Pharmacology Model (MSPM) to Evaluate Effect of Vitamin D3 (D3) Pharmacokinetics (PK) on Bone Health

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Overview

1. Vitamin D is important in maintaining calcium balance and bone health. Its natural form is Vitamin D3.
2. D3 dosing affects relevant bone health markers (e.g., serum calcium, 25OHD3 and PTH) and endpoints (lumbar spine bone-mineral density (BMDLS)).
3. Vitamin D3 PK model [2] integrated with an existing MSPM that described calcium homeostasis and bone remodeling [3] to explore the effect of Vitamin D3 dosing recommendations on relevant bone-health endpoints.

Objectives

1. To explore the effect of combined D3 plus calcium supplementation (D3CA) on bone-health endpoints (i.e., serum PTH, BMDLS))
2. To evaluate D3 dose and 25OHD3 threshold recommendations for reaching target BMDLS or PTH levels and compare to Institute of Medicine (IOM) recommendations (400-600 IU/d D3; 40-50 nmol/L 25OHD3)

Background

1. Vitamin D3 and its metabolites maintain bone health by facilitating the absorption of calcium (Ca) from the gut and kidneys (calcitriol = 1,25$(OH)_2$D) (Fig. 1)

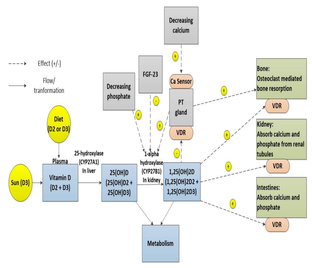


Fig. 1: Metabolism of Vitamin D and its role in Ca homeostasis

Methods

Meta-analysis data search strategy

- *Data*: Public source calcitriol (pmol/L), bone-marker and BMDLS (g/cm2) data in healthy or osteoporotic populations were collected from literature (all mean-level data)
- Data collected following Vitamin D3, with (D3CA) or without calcium (D3), supplementation
- *Bone-marker data*: serum PTH (pg/mL), serum-corrected calcium (mmol/L), serum CTX (pg/mL), serum BSAP (ug/L), serum P1NP (ug/L)

Vitamin D3-MSPM Integration

- Integration described conversion of 25OHD3 to calcitriol using ordinary differential equations
- Fit gamma-related parameter to calcitriol and BMDLS data (independently) following D3 or D3CA supplementation
  - Potential structures for 25OHD3-calcitriol conversion: power model, EMAX, EMAX with inhibition on Michaelis-Menten parameter
  - *Nelder-Mead* optimization method in the stats R package [4]
- External predictive check used for model evaluation of final integrated model using model-naive PTH and serum Ca data

References

[1] K.T. Baron, A.C. Hindmarsh, L.R. Petzold, B. Gillespie, C. Margossian, and Metrum Research Group LLC (). mrgsolve: Simulation from ode-based population pk/pd and systems pharmacology models., 2016.

[2] A.S. Ocampo-Pelland, M.R. Gastonguay, J.F. French, and M.M. Riggs. Model-based meta-analysis for development of a populationpharmacokinetic (ppk) model for vitamin d3 and its 25ohd3 metabolite using both individual and arm-level data. *Journal of Pharmacokinetics and Pharmacodynamics*, 43(2):191–206, 2016.

[3] M. Peterson and M. Riggs. A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. *Bone*, 46:49–63, 2010.

[4] R Development Core Team, Vienna, Austria. *R: A Language and Environment for Statistical Computing*, 2008.

Methods (2)

Population-Level Simulations

- Serum calcitriol, serum PTH, and BMDLS responses to 1 year of D3 (800, 1000, 2000 IU/d) with or without calcium (0, 300, 1000 mg/d)
- Serum calcitriol response to 1 year of D3 supplementation (400, 800, 2000 IU/d) over a range of calcitriol baselines (50-110 pmol/L)
- Explore D3 dose and 25OHD3 threshold recommendations for reaching BMDLS and PTH targets after 1 year of D3 with or without 1000 mg/d calcium supplementation (25OHD3 BL = 30 nmol/L)
  - Synthesized information from D3-25OHD3 dose-exposure simulation [2] and 25OHD3-BMDLS/PTH relationship simulation
- Software: R, mrgsolve [1]

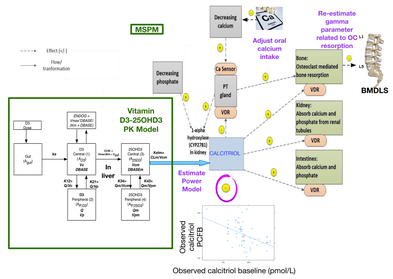
Results: Meta-Analysis Data Search & Integrated Model Structure

Table 1: Summary of bone-marker and BMD studies used to fit (F) or validate (V) the integrated Vitamin D3-MSPM

Treatment	Endpoint	Doses	RT/REG	Arms	Total Subjects	Studies	Use
D3 only	serum calcitriol	357-50000 IU/d	PO/MD	33	839	13	F
D3 only	serum PTH	29-100000 IU/d	PO/MD, SD	64	1879	31	V
D3 only	serum calcium	29-200000 IU/d	PO/MD	49	1492	25	V
D3 only	serum P1NP	400, 1000 IU/d	PO/MD	2	159	1	V
D3 only	serum BSAP	400-2000 IU/d	PO/MD	8	148	4	V
D3 only	BMDLS	400-3571 I/d	PO/MD	5	403	3	F
D3 + calcium	serum calcitriol	400-2000 IU/d; 600-1300 mg/d	PO/MD	6	3092	5	F
D3 + calcium	serum PTH	400-300000 IU/d; 320-1500 mg/d	PO/MD, SD	24	3092	18	V
D3 + calcium	serum calcium	400-5000 IU/d; 320-1350 mg/d	PO/MD	13	2821	13	V
D3 + calcium	serum P1NP	400 IU/d; 800 mg/d	PO/MD	1	32	1	V
D3 + calcium	serum BSAP	400-1000 IU/d; 500-1500 mg/d	PO/MD	5	532	4	V
D3 + calcium	BMDLS	400-5000 IU/d; 250-1350 mg/d	PO/MD	8	646	6	F
Totals	calcitriol			39		18	F
	BMDLS			13		9	F
	validation			107		58	V

Vitamin D3-MSPM Integrated Model Structure

Fig. 2: Final integrated Vitamin D3 model with MSPM (PCFB = percent change from baseline)[a]



Modifying calcitriol ODE & AOH0 taken from Peterson & Riggs [3]

- Power model chosen due to mathematical parameter non-identifiability with more complex models (θ_1 = optimized parameter)
- Calcitriol self-inhibition implemented by parameterizing γ as an inverse function of $A_{\text{calcitriol}}$
- A gamma parameter, relevant to osteoclast resorption, was re-estimated to describe BMDLS response to Vitamin D3 with or without calcium supplementation

$$AOH0 = \frac{A0_{\text{calcitriol}} * 9}{C_{\text{calcitriol,OBS}}} \quad (1)$$

$$\gamma = \frac{\theta_1}{A_{\text{calcitriol}}} \quad (2)$$

$$C25D3scale = \frac{C0_{25D3}}{(\frac{T69 * A0_{\text{calcitriol}}}{AOH0})^{\frac{1}{\gamma}}} \quad (3)$$

$$\frac{d(A_{\text{calcitriol}})}{dt} = (\frac{C_{25D3}}{C25D3scale})^{\gamma} * AOH - T69 * A_{\text{calcitriol}} \quad (4)$$

$A_{\text{calcitriol}}$ = calcitriol ($A0_{\text{calcitriol}}$ = initial) amount (pmol)
$C_{calcitriol,obs}$ = observed calcitriol concentration (pmol/L)
C_{25D3} = 25OHD3 concentration (nmol/L)
AOH = 1-alpha-hydroxylase (AOH0=initial) enzyme production rate (mmol/h)

[a] Vc/Vcm=D3/25OHD3 central volume of distribution (L); Q/Qm=inter-compartmental clearance (L/h); Vp/Vpm=peripheral volume of distribution (L); DBASE/DBASEm=baseline concentrations (nmol/L); ENDOG = endogenous rate of D3 production (nmol/h); VMAX=enzyme rate of production (nmol/h); Km=D3 Michaelis-Menten parameter (nmol/L); A_{D3}/A_{25OHD3}=amounts in central compartments (nmol); A_{gut} = D3 amount in gut (nmol); $A_{P,D3}/A_{P,25OHD3}$=amounts in peripheral compartments (nmol)

Results: Diagnostics & Simulation

Fig. 3: Calcitriol (left) and BMDLS (right) goodness of fit (black = total dataset, green = D3, red = D3CA)

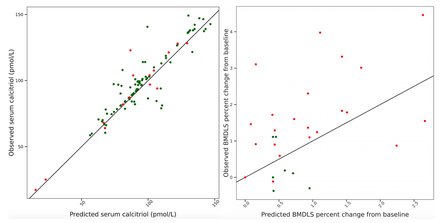


Fig. 4: External predictive checks into observed serum calcium concentrations (D3: CaTrt = 0, D3CA: CaTrt =1); peach horizontal strips indicate D3 dose (IU/d), Ca dose (mg/d), ID, respectively

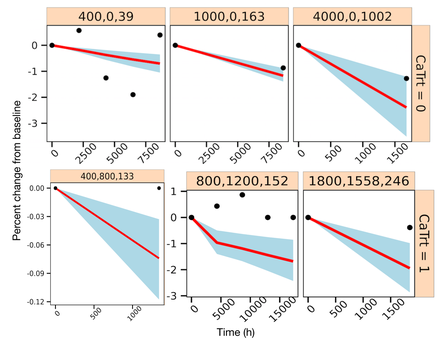


Fig. 5: External predictive checks into observed serum PTH concentrations (D3: CaTrt = 0, D3CA: CaTrt =1); peach horizontal strips indicate D3 dose (IU/d), Ca dose (mg/d), ID, respectively

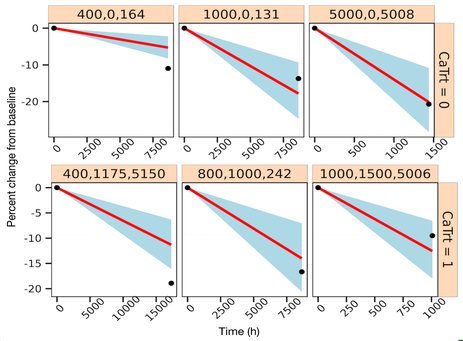


Fig. 6: Simulated physiologic response to Vitamin D3 supplementation with or without calcium (left); calcitriol response to Vitamin D3 dosing across baselines (right); peach horizontal strips indicate D3 dose (IU/d)

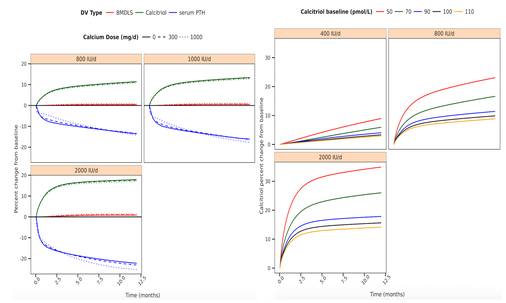
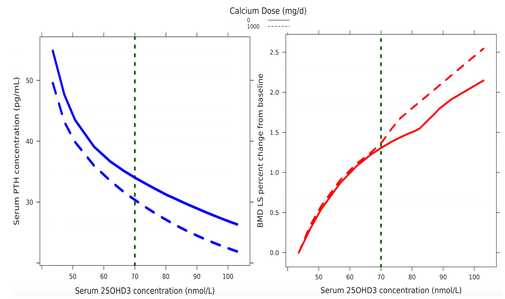


Fig. 7: Simulated relationship between serum 25OHD3 levels and serum PTH concentration (left) and BMDLS (right)



Tables 2-3: Model-predicted D3 doses and 25OHD3 levels with (D3CA) or without 1000 mg/d calcium for reaching target BMDLS percent increases (top) or PTH levels (bottom) after 1 year (25OHD3 BL = 30 nmol/L, PTH BL 50-60 pg/mL)

Target BMD % Increase	D3 Dose (IU/d)	D3CA (IU/d)	25OHD3 after D3 (nmol/L)	25OHD3 after D3CA (nmol/L)	PTH after D3 (pg/mL)	PTH after D3CA (pg/mL)
0.5	300	300	50	50	46	42
1	400	400	61	60	38	35
1.5	1000	700	80	73	32	30
2	3100	2000	97	87	28	26
2.5	> 5000	5000	> 100	100	< 27	23

Target PTH (pg/mL)	D3 Dose (IU/d)	D3CA (IU/d)	25OHD3 after D3 (nmol/L)	25OHD3 after D3CA (nmol/L)	BMD % after D3	BMD % after D3CA
>=50	200	200	44	44	0	0
40	300-400	300	57	51	0.7	0.6
30	1500	700	85	70	1.7	1.6
25	> 5000	2000	> 102	88	> 2.1	2

Conclusions

- A power model as a function of 25OHD3 concentration described the conversion of 25OHD3 to calcitriol and its apparent self-inhibition
- External predictive checks indicated adequate model performance for predicting bone health marker responses to Vitamin D3 with or without calcium
- Vitamin D3 with calcium administration is more effective than Vitamin D3 alone at raising BMDLS and decreasing PTH levels
  - Calcium administration is more potent at increasing/decreasing BMDLS/PTH for 25OHD3 >70 nmol/L because of the non-linear D3 clearance
- Model simulations (25OHD3 BL = 30 nmol/L) indicated necessary 25OHD3 levels somewhat higher than those recommended by the IOM (40-50 nmol/L) for raising BMDLS >1%
  - BMDLS 1.5-2%: 25OHD3 80-100 nmol/L without 1000 mg/d calcium; 1000-3100 IU/d D3
- Vitamin D3 dose and 25OHD3 threshold recommendations with 1000 mg/d calcium decreased relative to Vitamin D3 supplementation alone for BMDLS increases >1%

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