



**Optimizing the management
of your patients' vitamin D deficiency**
The value of vitamin D testing



Vitamin D deficiency

Vitamin D deficiency is highly prevalent, particularly in the elderly and people with osteoporosis.^{1,2}

Epidemiology

A high prevalence of vitamin D deficiency has been documented in many studies worldwide irrespective of age, health status or latitude.¹ However, vitamin D deficiency is particularly common in elderly populations, where osteoporosis is a frequent comorbidity (Table 1, Figure 1).^{1,2} Clinical consequences of vitamin D deficiency in this population include an increased risk of falls³ and fractures.^{4,5} Clinical risk factors for vitamin D deficiency include decreased intake, principally due to limited sunlight exposure, and abnormalities in gastrointestinal, kidney and liver function.² Sufficient sunlight exposure is essential for maintaining adequate vitamin D levels, thus, features of 'modern living,' such as clothing habits, reduced time spent outdoors and the use of sunscreen, predispose individuals to vitamin D deficiency.² Factors influencing vitamin D status are shown in Table 2.⁶

Patient population

Nursing home or housebound residents, mean age 81 years

Elderly ambulatory women, aged > 80 years

Women with osteoporosis, aged 70–79 years

Patients with hip fractures, mean age 77 years

African American women, aged 15–49 years

Adult hospitalized patients, mean age 62 years

Vitamin D deficiency (% patients)

25–50%

44%

30%

23%

42%

57%

Table 1: Prevalence of vitamin D deficiency in commonly encountered clinical patient populations in the USA.²

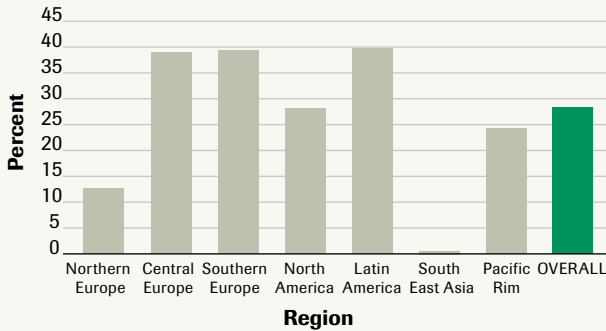


Figure 1: Prevalence of 25(OH) vitamin D < 20 ng/mL among 7,564 postmenopausal women with osteoporosis aged 31–80 years, by region.¹

A number of biological and environmental factors combine to influence vitamin D status.⁶

Table 2: Factors influencing vitamin D status.⁶

Factors influencing vitamin D status

Synthesis of vitamin D from sunlight

Exposure to ultraviolet radiation

- Latitude
- Season
- Use of sunscreen
- Clothing

Skin

- Pigmentation
 - Temperature
 - Scarring e.g. burns
 - Age
-

Bioavailability of vitamin D

Gastrointestinal malabsorption of vitamin D

- Celiac disease
- Biliary obstruction
- Chronic pancreatitis
- Liver failure
- Cystic fibrosis
- Crohn's disease
- Gastric bypass
- Bile acid-binding medication (e.g. colestyramine, colestipol)

Obesity

Enzyme activity

- 1- α -hydroxylase: Serum phosphorus, Parathyroid hormone, Genetic mutations
 - 25-hydroxylase: Concentration of 25(OH) vitamin D
 - Cytochrome P450 enzymes (CYP24, CYP3A4): Medications (phenobarbital, phenytoin, carbamazepine, rifampicin, antiretrovirals)
-

Other factors

Kidney disease

- Chronic kidney disease
- Nephrotic syndrome

Liver disease

- Cholestatic liver disease
- Parenchymal liver disease
- Hepatic failure

Granulomatous disorders and malignancies

- Sarcoidosis, tuberculosis, fungal granulomas, berylliosis
 - Certain tumors (tumor-induced osteomalacia)
-

Vitamin D plays a crucial role in calcium and bone metabolism.⁶

Biological role of vitamin D

Vitamin D has been recognized as a vital component in bone metabolism and bone health since it was discovered almost a century ago. 1,25 (OH)₂ vitamin D, the only active form of vitamin D, plays a crucial role in calcium and bone metabolism by increasing bone turnover, increasing intestinal calcium absorption and decreasing parathyroid hormone (PTH) secretion (Figure 2).^{4,6} In addition, vitamin D plays an important role in skeletal muscle function.^{4,5,7} It is now thought that a combination of bone and muscle effects contribute to increased risk of falls and fractures associated with vitamin D deficiency.^{5,8}

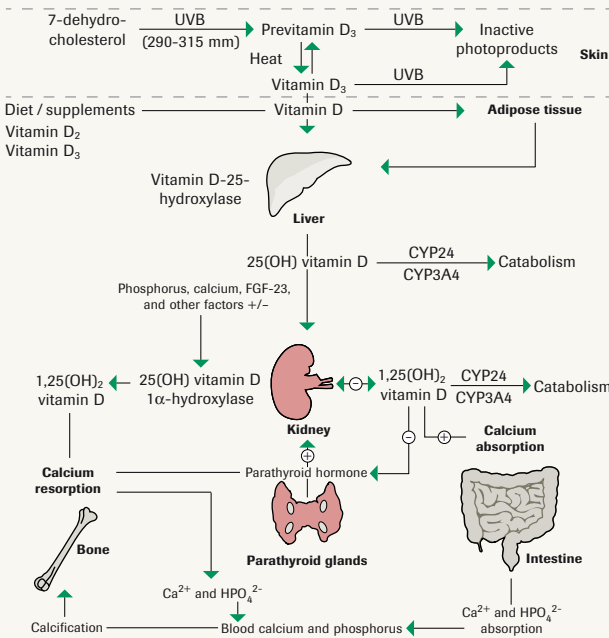


Figure 2: Vitamin D metabolism and effects.⁴ Ca²⁺: calcium; FGF-23: fibroblast growth factor 23; HPO₄²⁻: phosphorus; UVB: ultraviolet B.

Clinical benefits of vitamin D supplementation

Vitamin D supplementation improves muscle strength, balance and mobility in the elderly.⁹⁻¹²

Supplementation with high-dose vitamin D has been shown to improve muscle strength, balance and mobility in elderly people with impaired muscle function.⁹⁻¹¹ The effect of vitamin D supplementation on muscle strength and mobility in elderly women (aged 70–90 years) was assessed in a 1-year, population-based, double-blind, randomized, controlled trial (RCT).⁹ A total of 302 community-dwelling women with vitamin D deficiency were randomized to receive either vitamin D₂ (1,000 IU/day) plus calcium citrate (1 g/day) or calcium citrate (1 g/day) plus placebo. In those with baseline values in the lowest tertile of strength, vitamin D improved muscle strength (hip extensors 22.6%, hip adductors 13.5% [Table 3]). Mobility (timed up and go test) was significantly improved in those with impaired mobility at baseline (17.5%, $p < 0.05$ [Fig. 3]).⁹

In addition, a meta-analysis of data from RCTs in elderly men and women aged ≥ 60 years demonstrated that vitamin D supplementation (800–1,000 IU/day) reduced postural sway ($p = 0.04$), improved mobility (TUAG, $p = 0.03$) and increased lower extremity strength ($p = 0.04$).¹⁰ In a 16-week, double-blind, placebo controlled trial in elderly men and women (aged ≥ 70 years) with vitamin D deficiency, vitamin D supplementation (8,400 IU/week) significantly ($p = 0.047$) improved balance in a subgroup of patients who had a high level of mediolateral body sway at baseline.¹¹

Tertile of strength (kg)	Mean (Standard Error) % difference in change (vitamin D vs placebo)
Hip extensor	
Lowest	22.6% (9.5%)*
Middle	-3.8% (5.9%)
Highest	-1.1% (5.1%)
Hip adductor	
Lowest	13.5% (6.7%)*
Middle	-6.8% (4.5%)
Highest	-0.2% (4.2%)

Values are mean (standard error), * $p < 0.05$.
 Extensor: low = ≤ 11 kg, medium = 12-15 kg, high = ≥ 16 kg
 Adductor: low = ≤ 12 kg, medium = 13-16 kg, high = ≥ 17 kg

Table 3: Supplementation with high-dose vitamin D (1,000 IU/day) improves muscle strength in elderly women with vitamin D deficiency and impaired muscle strength.⁹

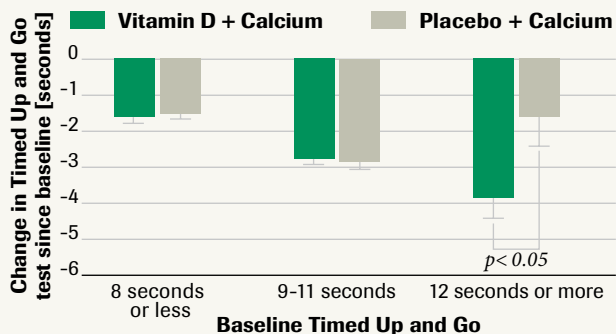


Figure 3: Supplementation with high-dose vitamin D (1,000 IU/day) improves mobility in elderly women with vitamin D deficiency and impaired mobility.⁹

High-dose vitamin D supplementation, in combination with calcium, significantly reduces the risk of falls in the elderly.¹²⁻¹⁶

Prevention of falls

High-dose vitamin D supplementation (≥ 700 IU/day), in combination with calcium, effectively reduces the risk of falling in elderly people (> 63 years).¹²⁻¹⁵ Supplementation with high-dose vitamin D reduces the number of fall incidents,¹²⁻¹⁵ the number of people who fall,^{12,13} the number of people with multiple falls^{14,16} and the number of falls that require medical attention.¹⁶ The reductions in the risk of falling have been demonstrated in community-dwelling elderly people^{12,15} and in inhabitants of nursing homes.^{13,14,15} A key factor in management of vitamin D deficiency is long-term maintenance dosing once the patient's 25(OH)D level is in the optimal range.² Adherence to a daily dose of at least 800 to 2,000 IU is required to avoid recurrence of vitamin D deficiency.²

In a study of 242 men and women (aged ≥ 70 years) with serum 25(OH) vitamin D levels below 31 ng/mL, supplementation with vitamin D (800 IU/day) and calcium (1,000 mg/day) reduced the number of people with first falls after 20 months by 39% compared with calcium alone ($p < 0.01$) (Figure 4).¹²

In a meta-analysis of seven RCTs in men and women over 65 years of age, vitamin D supplementation (≥ 700 IU/day, $n = 1,921$) reduced the number of falls by 19%.¹⁵ Furthermore, the analysis demonstrated that the higher the achieved level of 25(OH) vitamin D, the more pronounced the reduction in fall incidents. With 25(OH) vitamin D levels > 24 ng/mL there was a significant reduction (23%) in falls whereas no significant effect was observed with 25(OH) vitamin D levels < 24 ng/mL.¹⁵

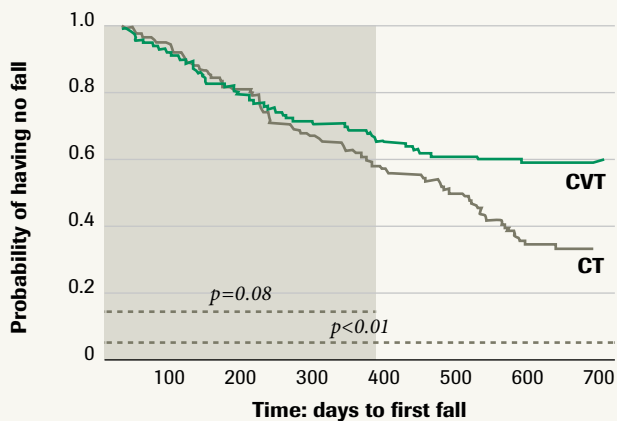


Figure 4: The probability of having a fall is significantly lower with calcium (1,000 mg/day) + vitamin D (800 IU/day) [CVT] compared with calcium alone (1,000 mg/day) [CT] in men and women aged ≥ 70 years.¹²

High-dose vitamin D supplementation significantly reduces the risk of non-vertebral and hip fractures in the elderly and in postmenopausal women.^{17,18}

Prevention of fractures

A meta-analysis of double-blind RCTs demonstrated that high-dose vitamin D supplementation (482-770 IU/day) significantly reduced the risk of hip and nonvertebral fractures in elderly men and women (≥ 65 years) by approximately 20%.¹⁷ The relative risk (RR) [95% confidence interval, CI] was 0.80 [0.72–0.89] ($n = 33,265$ individuals from 9 trials) for nonvertebral fractures and 0.82 [0.69–0.97] ($n = 31,872$ individuals from 5 trials) for hip fractures (Figure 5). High-dose vitamin D supplementation reduced the risk of nonvertebral fractures in community-dwelling and institutionalized older individuals by 29% and 15% respectively, and the effects were independent of additional calcium supplementation. Hip fracture reduction was significant among community-dwelling individuals (21%) and among institutionalized individuals receiving cholecalciferol (28%).

In addition, the analysis found that the reduction in fracture risk increased with the 25(OH) vitamin D level achieved (Figure 6).¹⁷

In another meta-analysis of RCTs, high-dose vitamin D supplementation (> 700 IU/day), in combination with calcium, significantly reduced the risk of nonvertebral

and hip fractures in postmenopausal women by 17.0% and 29.1% respectively.¹⁸ RR [95% CI] was 0.77 [0.63–0.93, 4 studies] for nonvertebral fractures and 0.70 [0.53–0.90, 5 studies] for hip fractures.¹⁸

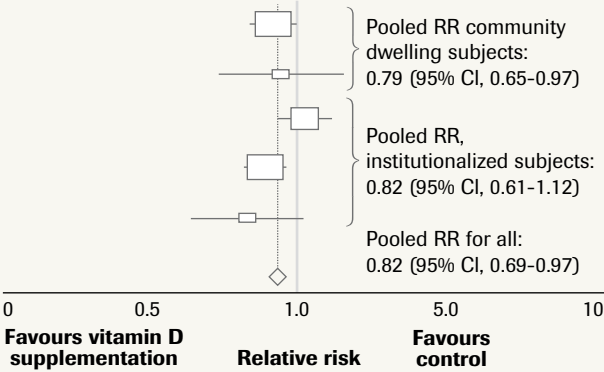


Figure 5: A meta-analysis of double-blind RCTs demonstrated that high-dose vitamin D supplementation (600–800 IU/day) reduces the risk of hip fractures in elderly men and women (≥ 65 years).¹⁷

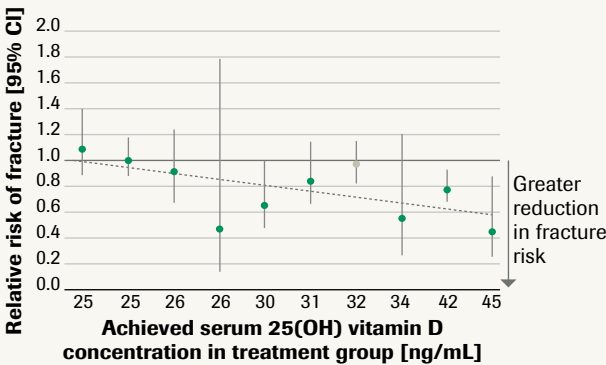


Figure 6: The reduction in non-vertebral fracture risk following high-dose vitamin D supplementation (482–770 IU/day) increases with the level of 25(OH) vitamin D achieved.¹⁷ Each data point along the X-axis represents an individual trial.

● trials with cholecalciferol (D₃) ● trial with ergocalciferol (D₂)
 ----- trend line through the point estimates of all trials.¹⁷

Vitamin D measurement

Due to large interindividual variability, measurement of 25(OH) vitamin D is necessary, both before and during supplementation, to ensure optimal levels are reached.^{19–23}

Clinical rationale

Measurement of 25(OH) vitamin D, before and during supplementation, is necessary for effective patient management.^{19–23} Indeed, standard supplementation, in the absence of 25(OH) vitamin D measurement, can result in unnecessary polypharmacy for some elderly patients¹⁹ as well as to the under-treatment of severe deficiencies.²⁰

The need for accurate measurement of vitamin D levels during follow-up is related to the substantial interindividual variation in 25(OH) vitamin D serum levels post-supplementation (Figure 7).^{21–23} Potential factors influencing vitamin D levels are listed in Table 4. However, interindividual variation has also been shown to remain after correction for body weight and baseline vitamin D levels.²¹ Moreover, in a RCT in 60 community-dwelling women aged ≥ 65 years, 37% of the participants receiving vitamin D supplementation remained deficient in vitamin D after 6 months (Table 5).²¹ These data highlight that one post-supplementation measurement may not be sufficient; further testing may enable the physician to adjust dosage and also ascertain patient compliance.

Given the large variations in vitamin D metabolism^{21–23} and response,²¹ alongside the documented dose-dependent

effect both of received and achieved dose,¹⁷ effective measurement and monitoring of vitamin D has the potential to improve dose individualization and encourage compliance with therapy.

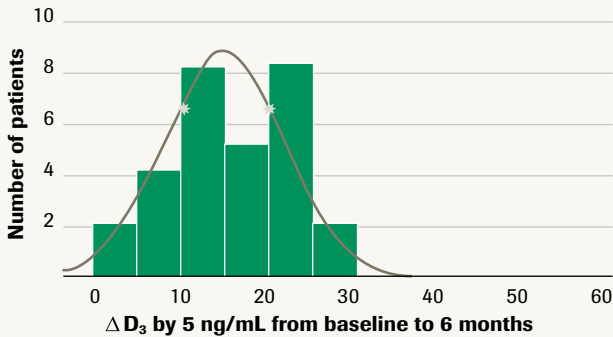


Figure 7: Substantial interindividual variation in serum levels of 25(OH) vitamin D following supplementation with vitamin D (1,000 IU/day).²¹

Factors that may influence post-supplementation serum level of 25(OH) vitamin D

- Absorption rate
- Adherence
- Assay used
- Body mass index
- Dose/dosing frequency of supplementation
- Endogenous vitamin D status (see table 2)
- Pregnancy and lactation
- Vitamin D baseline level
- Vitamin D supplement type
- Other medications

Table 4: Factors that may influence serum levels of 25(OH) vitamin D following supplementation.
2,8,21,23,24,26,27

25(OH) vitamin D at 6 months, ng/mL	Patients % (n)
< 20	37% (10)
20-29.9	43% (13)
≥ 30	20% (6)

Table 5: Vitamin D deficiency persists in a high percentage of elderly women (≥ 65 years) despite high-dose vitamin D supplementation (1,000 IU/day).²¹

Expert opinion-based recommendations support the testing of high-risk groups in clinical practice at baseline and at 3 month intervals.^{2,8,24}

Target groups – Expert recommendations

A number of recently published guidelines provide practical guidance on vitamin D measurement.^{2,8,24,25,26}

There is general consensus of expert opinion regarding the high-risk groups that would benefit from vitamin D testing (Table 6). Expert opinion is also generally similar for the recommended frequency of testing (baseline and at 3 months until a desirable level is achieved), although the precise target levels for serum 25(OH) vitamin D are a matter of debate (Figure 8).^{2,8,24,25,26,28}

Furthermore, whilst serum 1,25(OH)₂D testing can provide useful information in selected patients (e.g. with acquired/inherited disorders of vitamin D and phosphate metabolism), the Endocrine Society Task Force guidelines recommend performing serum 25(OH) D testing in patients at risk of vitamin D deficiency.²⁶

Recommended populations for vitamin D testing

Patients likely to have (or be at risk of) bone loss due to:

- Osteoporosis or risk of osteoporosis^{8,24,26,29}
- Osteomalacia or rickets^{8,26,29}
- Fractures^{2,26}
- Older age and a recent fall^{8,26,29}
- Hyperparathyroidism^{26,29}

Patients with decreased endogenous production of 25(OH)D, such as:

- Institutionalized or homebound patients^{8,24}
- Individuals with decreased sunlight exposure or dark skin^{2,24}

Patients with non-standard metabolism/catabolism of 25(OH)D due to:

- Obesity in children and adults (BMI >30kg/m²)^{8,26}
- Pregnancy and lactation in women^{8,26}
- Corticosteroid treatment^{8,26}
- Malabsorption syndromes^{2,24,26,29}
- Hepatic failure^{2,26}
- Granulomatomas^{26,29}
- Chronic kidney disease and transplant recipients^{2,8,26,29}

Table 6: Consensus of expert recommendations for target populations for vitamin D testing.^{2,8,24,26,29}

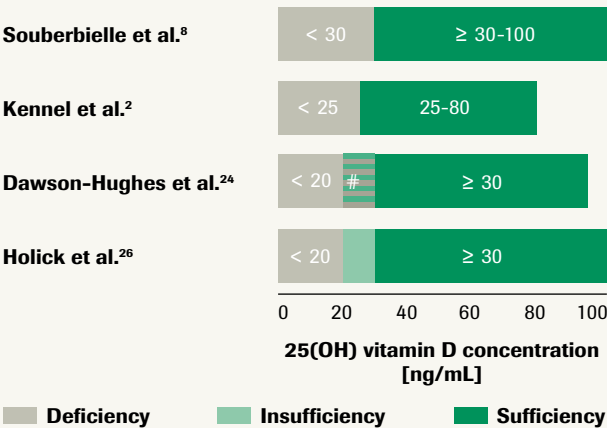


Figure 8: Expert recommendations for target levels of serum 25(OH) vitamin D. In this figure adaptation, vitamin D concentrations are expressed in ng/mL, where 1 ng/mL is equal to 2.496 nmol/L.^{2,8,25,26}

#8 out of 10 of IOF Working Group agreed 30 ng/mL, remaining 2 felt target is 20-30 ng/mL

References

1. Reginster, J.Y. (2005). The high prevalence of inadequate serum vitamin D levels and implications for bone health. *Curr Med Res Opin* 21(4), 579-586.
2. Kennel, K.A., Drake, M.T., Hurley, D.L. (2010). Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc* 85(8), 752-757.
3. Snijder, M.B., van Schoor, N.M., Pluijm, S.M., et al. (2006). Vitamin D status in relation to one-year risk of recurrent falling in older men and women. *J Clin Endocrinol Metab* 91(8), 2980-2985.
4. Holick, M.F. (2007). Vitamin D deficiency. *N Engl J Med* 357(3), 266-281.
5. van den Bergh, J.P., Bours, S.P., van Geel, T.A., Geusens, P.P. (2011). Optimal use of vitamin D when treating osteoporosis. *Curr Osteoporosis Rep* 9(1), 36-42.
6. Tsiaras, W.G., & Weinstock, M.A. (2011). Factors influencing vitamin D status. *Acta Derm Venereol* 91(2), 115-124.
7. Wicherts, I.S., van Schoor, N.M., Boeke, A.J., et al. (2007). Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 92(6), 2058-2065.
8. Souberbielle, J.C., Body, J.J., Lappe, J.M., et al. (2010). Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* 9(11), 709-715.
9. Zhu, K., Austin, N., Devine, A., Bruce, D., Prince, R.L. (2010). A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *J Am Geriatr Soc* 58(11), 2063-2068.
10. Muir, S.W., & Montero-Odasso, M. (2011). Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 59(12), 2291-2300.
11. Lips, P., Binkley, N., Pfeifer, M., et al. (2010). Once-weekly dose of 8400 IU vitamin D3 compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. *Am J Clin Nutr* 91(4), 985-991.
12. Pfeifer, M., Begerow, B., Minne, H.W., et al. (2009). Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int* 20(2), 315-322.
13. Flicker, L., MacInnis, R.J., Stein, M.S., et al. (2005). Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *J Am Geriatr Soc* 53(11), 1881-1888.
14. Bischoff, H.A., Stähelin, H.B., Dick, W., et al. (2003). Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res* 18(2), 343-351.
15. Bischoff-Ferrari, H.A., Dawson-Hughes, B., Staehelin, H.B., et al. (2009). Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 339, b3692.
16. Kärkkäinen, M.K., Tuppurainen, M., Salovaara, K., et al. (2010). Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). *Maturitas* 65(4), 359-365.
17. Bischoff-Ferrari, H.A., Willett, W.C., Wong, J.B., et al. (2009). Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med* 169(6):551-561.
18. Bergman, G.J., Fan, T., McFetridge, J.T., Sen, S.S. (2010). Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. *Curr Med Res Opin* 26(5), 1193-1201.
19. Dutch Association Clinical Geriatricians, Comprehensive Geriatric Assessment.
20. CBO-guideline Osteoporosis and Fracture Prevention.
21. Giusti, A., Barone, A., Pioli, G., et al. (2010). Heterogeneity in serum 25-hydroxy-vitamin D response to cholecalciferol in elderly women with secondary hyperparathyroidism and vitamin D deficiency. *J Am Geriatr Soc* 58(8), 1489-1495.
22. van Schoor, N.M., Visser, M., Pluijm, S.M., et al. (2008). *Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone* 42(2), 260-266.
23. van Groningen, L., Opdenoordt, S., van Sorge, A., et al. (2010). Cholecalciferol loading dose guideline for vitamin D-deficient adults. *Eur J Endocrinol* 162(4), 805-811.
24. Dawson-Hughes, B., Mithal, A., Bonjour, J.P., et al. (2010). IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int* 21(7), 1151-1154.
25. Dawson-Hughes, B. (2012). What is the optimal Dietary intake of vitamin D for reducing fracture risk? *Calcif Tissue Int*. May 17 [epub ahead of print].
26. Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., et al. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96(7), 1911-1930.
27. Autier, P., Gandini, S., Mullie, P. (2012). A systematic review: influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. *J Clin Endocrinol Metab* Jun 14, Epub ahead of print.
28. Holick, M.F., Binkley N.C., Bischoff-Ferrari H.A., et al. (2012). Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. *J Clin Endocrinol Metab* 97(4), 1153-1158.
29. Souberbielle, J.C., Courbebaisse, M., Cormier, C., et al. (2012). When should we measure vitamin D concentration in clinical practice? *Scand J Clin Lab Invest Suppl.* 243:129-35.

COBAS and LIFE NEEDS ANSWERS
are trademarks of Roche.

©2012 Roche

Roche Diagnostics International Ltd
CH-6343 Rotkreuz
Switzerland
www.cobas.com