A QUANTUM OF SUNLIGHT:
NEW PERSPECTIVES ON VITAMIN D

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FT. WALTON BEACH, PANAMA CITY

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A QUANTUM OF SUNLIGHT:
NEW PERSPECTIVES ON VITAMIN D

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BILOXI, MS

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DISCLOSURES

In accordance with ACCME standards for commercial support, I have no disclosures to report at this time, and no off-label products will be included as part of our presentation or discussion. Neither my spouse nor I have any affiliations or financial interests which should be disclosed.

Laura Cable, PharmD
Presenter

Stephen Farrow, MD
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1. Thanks to our current national practice of taking a vitamin daily, the United States has avoided the Vitamin D insufficiency epidemic that has swept most first-world countries?

2. Milk has one of the most naturally-abundant concentrations of dietary vitamin D?

3. Megalin binds Vitamin D hormone to the nuclear receptor Vitamin D response element?

4. Dihydrotachysterol (DHT) is recommended as one of the most economical forms for routine daily Vitamin D supplementation?

5. Unfortunately, calcipotriene has proven ineffective in the topical treatment of psoriasis, and was recently taken off the market?

6. Due to the risk of hypercalcaemia, most healthy people should have their Vitamin D blood levels tested before beginning daily Vitamin D supplementation?
U.S. Is Facing Vitamin D Deficiency Epidemic

BY MITCHEL L. ZOLER

A vitamin D deficiency epidemic has hit the United States, and current recommendations for vitamin D supplements are inadequate to counter it.


Comparing serum vitamin D levels from these two periods showed the prevalence of vitamin D insufficiency, defined as a serum level of less than 10 ng/mL, jumped threefold, from 2% in 1988-94 to 6% in 2001-2004, Dr. Adit A. Ginde from the University of Colorado in Denver and his associates reported in the Archives of Internal Medicine (2009;169:626-32).

Increased intake of vitamin D, to 1,000 IU/day or more, particularly during the winter in higher latitudes when cutaneous production is minimal, and judicious sun exposure would likely improve overall U.S. health, the report said.

Large controlled trials of such a higher supplement level are needed to assess their impact on general health and mortality, the researchers added.

"Current recommendations for vitamin D supplementation [200-600 IU/day] are inadequate to achieve optimal serum D levels in most of the U.S. population," the researchers wrote.

That’s a function not only of the declining average level of serum vitamin D among Americans, but also a higher target for the optimal serum level. "Increasing evidence suggests that [a serum level of] 30 ng/mL or even 40 ng/mL may be required for optimum health." In contrast, the 2001-2004 NHANES samples showed an average serum level of 24 ng/mL for all age groups surveyed, ranging from age 12 years to older than 60 years.

The analysis included serum specimens from 18,883 people aged 12 or older surveyed in 1988-1994, and 13,369 specimens collected during 2001-2004. During 1988-1994, the average vitamin D level ranged from 28 ng/mL for people 60 or older to 32 ng/mL among those aged 12-19.

"The prevalence of vitamin D deficiency depends on the cutoff used. When a cutoff of less than 20 ng/mL was applied, the deficiency prevalence was 22% during the earlier period and 36% more recently.

Deficiency prevalence also varied by race and ethnicity. For example, the prevalence of serum levels less than 10 ng/mL among African Americans spiked from 9% during 1988-1994 to 29% during 2001-2004.

But variations in vitamin D levels by age and gender during 1988-1994 were essentially eliminated in the 2001-2004 survey.

Another way to assess the findings was to look at the prevalence of serum levels vitamin D of 30 ng/mL or higher, the minimum level required for general health benefits by current standards. In 1988-1994, 45% of the people sampled met this criterion; by the 2001-2004 survey it was met in only 23% of the sample.

Among African Americans the prevalence of 30 ng/mL or greater dropped from 12% during the earlier survey to 3% in the more recent NHANES study.

Several factors probably contributed to the rise in vitamin D deficiency, the authors suggested. A prime culprit was probably increased use of sunscreen with a higher sun-protection factor (see sidebar).

Sunscreen with a sun-protection factor of 15 cuts vitamin D synthesis by 99%. Decreased outdoor activity and obesity are also probable contributing factors.
VITAMIN

An organic compound – technically containing an amine group – that an organism must consume in minute amounts to support its metabolism
THE FAT-SOLUBLE “VITAMINS”

VITAMIN A  RETINOL
VITAMIN K  PHYTONADANTONE
VITAMIN D  CALCITRIOL
VITAMIN E  TOCOPHEROL
DISCOVERY OF VITAMIN D

- Ancient Egypt (night blindness Rx by liver → vitamin A deficiency)
- 1644 Daniel Whistler – Rickets
- 1749 James Lind – Scurvy (vitamin C in 1931)
- 1865 Armand Trousseau – Rickets (cod liver oil, sun)
- 1929 Adoph Windaus – D1, 2, 3
- 1968 Vitamin D hepatic and renal active metabolites
NATIVE VITAMIN D SYNTHESIS

7-dehydrocholesterol to cholecalciferol – UV and Heat

- **UV-A**
  - Penetrates ozone, clouds, glass
  - ?Nonmelanoma skin cancer
- **UV-B, ~295-300nm**
  - Strata spinosum and basale
  - melanocytes and MSH
  - ?melanoma
- **UV-C**
  - Filtered by ozone filtration
  - Severe burns
NATIVE VITAMIN D SYNTHESIS

7-dehydrocholesterol to cholecalciferol – Influences:

• Atmospheric opacity
• Incident sunlight angle
• Clothing and shelter
• Complexion
• Sun screen
LATITUDE AND VITAMIN D PRODUCTION

• 0° latitude (Bahamas) – 100 nmol/L (~250ug (10,000IU)/d)
• 30° north latitude (VAGCVHCS) – adequate
• 40° north latitude (Detroit, Boston) – 4 months adequate UV-B
  • (~24% vitamin D deficient)
• 45° north latitude – chronic vitamin D deficit
**NUTRITIONAL OPTIONS FOR VITAMIN D REPLETION**

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Vitamin D Content (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herring</td>
<td>3 oz</td>
<td>1383</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>1 tbsp</td>
<td>1360</td>
</tr>
<tr>
<td>Salmon, cooked</td>
<td>3.5 oz</td>
<td>360</td>
</tr>
<tr>
<td>Mackerel, cooked</td>
<td>3.5 oz</td>
<td>345</td>
</tr>
<tr>
<td>Sardines, canned</td>
<td>1.75 oz</td>
<td>250</td>
</tr>
<tr>
<td>Tuna, canned</td>
<td>3 oz</td>
<td>200</td>
</tr>
<tr>
<td>Soy Milk (fortified)</td>
<td>8 oz</td>
<td>100</td>
</tr>
<tr>
<td>Milk, skim (fortified)</td>
<td>8 oz</td>
<td>100</td>
</tr>
<tr>
<td>Egg, whole</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>
ABSORPTIVE, INTRACELLULAR, AND CIRCULATING PROTEINS IN VITAMIN D BINDING AND 1α–HYDROXYLATION
TRADITIONAL VITAMIN D SYNTHESIS AND ACTIVITY

- 7-dehydrocholesterol
- Cholecalciferol (Vitamin D3)
- Ergocalciferol (Vitamin D2)
- UV light skin
- Liver
  - Calcidiol (25-hydroxy Vitamin D)
- Kidney
  - Calcitriol (1,25-dihydroxy Vitamin D)
  - 24,25-dihydroxyvitamin D

- Increased intestinal absorption of calcium
- Bone resorption
- Decreased renal calcium and phosphate excretion
<table>
<thead>
<tr>
<th>CALCITRIOL RECEPTORS</th>
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<tbody>
<tr>
<td>Adipose</td>
</tr>
<tr>
<td>Osteoblast</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Muscle (cardiac)</td>
</tr>
<tr>
<td>Bone Marrow</td>
</tr>
<tr>
<td>Parathyroid</td>
</tr>
<tr>
<td>Pituitary</td>
</tr>
<tr>
<td>Colon</td>
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<tr>
<td>Hair Follicle</td>
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<tr>
<td>Dental</td>
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</tbody>
</table>
RENAL AND EXTRARENAL 1,25(OH)D3 SERVES ENDOCRINE, AUTOCRINE, AND PARACRINE FUNCTIONS
VITAMIN D ANALOGS

DOXERCALCIFEROL

MAXITOL

CALCITRIOL

PARICALCITOL
PARICALCITOL IN FLAT AND THREE-DIMENSIONAL PROJECTIONS
CALCITRIOL BOUND TO NUCLEAR RECEPTOR
VITAMIN D:

MEDICATION FORMS AND USES
MEDICATION FORMS OF VITAMIN D

• Vitamin D3---Cholecalciferol
  • Normally made in the skin from sunlight
  • The natural form found in the human body
• Vitamin D2---Ergocalciferol (Calciferol, Drisdol)
  • Found in plants
• 25-hydroxyvitamin D---Calcidiol (calcifediol)
  • Product from vitamin D hydroxylation in the liver
  • Major circulating form of vitamin D
  • Blood levels are the best indicator of vitamin D sufficiency
  • Not available in USA as a drug product
• 1,25-dihydroxyvitamin D---Calcitriol
  • Product from calcidiol hydroxylation in the kidney
  • Most active form of vitamin D
  • Levels should not be used to determine Vitamin D deficiency
VITAMIN D METABOLITES

- Calcitriol (Calcijex, Rocaltrol, Vectical)
  - active form of vitamin D$_3$
- Alfacalcidol
  - Alfacalcidol (1-alpha-hydroxycholecalciferol)
  - Synthetic; 1a-hydroxylated; Hepatic 25-hydroxylation to 1,25-dihydroxycholecalciferol (Calcitriol)
  - No apparent therapeutic advantage over calcitriol
- Calcifediol (Calderol)
  - 25-hydroxylated form of cholecalciferol (vitamin D$_3$)
  - No longer available in the USA
- Dihydrotachysterol (DHT; Intensol)
  - Synthetic reduction tachysterol (close isomer of vitamin D)
- Falecalcitriol
  - Active form of vitamin D$_3$
  - Availability?
- Maxacalcitol
  - Availability?
VITAMIN D ANALOGUES

- Doxercalciferol (Hectorol)
  - synthetic analogue of vitamin D2
- Paricalcitol (Zemplar)
  - synthetic analogue of calcitriol
<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>INDICATIONS FOR USE²⁰</th>
<th>HOW SUPPLIED²⁰</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3</td>
<td>Vitamin D deficiency and prophylaxis Falls; Prophylaxis (Bischoff-Ferrari 2004 &amp; 2006, Sato 2005, Broe 2007, Flicker 2005) At risk of coronary heart disease Hypoparathyroidism Osteodystrophy Osteoporosis Rickets</td>
<td>Oral Tablet: 400 IU, 1000 IU, 2000 IU Available in multivitamins and in Calcium supplements in 400 IU or 800 IU **All above available OTC</td>
</tr>
<tr>
<td>MEDICATION</td>
<td>INDICATIONS FOR USE(^{20})</td>
<td>HOW SUPPLIED(^{20})</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Vitamin D2 (Ergocalciferol)</td>
<td><strong>Familial, x-linked, vitamin D - refractory hypophosphatemic rickets</strong>&lt;br&gt;<strong>Hypoparathyroidism</strong>&lt;br&gt;<strong>Renal osteodystrophy</strong>&lt;br&gt;<strong>Vitamin D deficiency and prophylaxis</strong>&lt;br&gt;<strong>Anticonvulsant drug-induced osteomalacia</strong>&lt;br&gt;<strong>Falls; Prophylaxis</strong> <em>(Prince 2008)</em>&lt;br&gt;<strong>Osteomalacia</strong>&lt;br&gt;<strong>Osteoporosis</strong>&lt;br&gt;<strong>Pseudohypoparathyroidism</strong>&lt;br&gt;<strong>Renal osteodystrophy</strong></td>
<td>Oral Capsule: 25,000 IU, 50,000 IU (usually not dosed more than 3x/week)&lt;br&gt;Oral Tablet: 400 IU&lt;br&gt;Oral Liquid: 8,000 IU/ML&lt;br&gt;Available in some multivitamins usually as 400 IU&lt;br&gt;<strong>higher doses are Rx only</strong></td>
</tr>
<tr>
<td>MEDICATION</td>
<td>INDICATIONS FOR USE(^{20})</td>
<td>HOW SUPPLIED(^{20})</td>
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<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Doxercalciferol</td>
<td><strong>Hyperparathyroidism due to renal insufficiency, in patients with stage 3 or 4 chronic kidney disease</strong>&lt;br&gt;<strong>Hyperparathyroidism due to renal insufficiency - Renal dialysis</strong></td>
<td>Intravenous Solution: 2 MCG/ML&lt;br&gt;Oral Capsule: 0.5 MCG, 2.5 MCG</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td><strong>Renal impairment, chronic / 2ndary Hyperparathyroidism (treatment and prophylaxis)</strong></td>
<td>Intravenous Solution: 0.002 MG/ML, 0.005 MG/ML&lt;br&gt;Oral Capsule, Liquid Filled: 1 MCG, 2 MCG, 4 MCG</td>
</tr>
<tr>
<td>MEDICATION</td>
<td>INDICATIONS FOR USE&lt;sup&gt;20&lt;/sup&gt;</td>
<td>HOW SUPPLIED&lt;sup&gt;20&lt;/sup&gt;</td>
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<tr>
<td>----------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dihydrotachysterol</td>
<td>Hypoparathyroidism, Tetany, Renal osteodystrophy, Rickets</td>
<td>Capsule: 0.125 mg Solution, oral concentrate: 0.2 mg/mL (30 mL) [contains alcohol 20%]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tablet : 0.125 mg, 0.2 mg, 0.4 mg</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>Same as calcitriol</td>
<td>Available as oral and IV formulations</td>
</tr>
<tr>
<td>MEDICATION</td>
<td>INDICATIONS FOR USE&lt;sup&gt;20&lt;/sup&gt;</td>
<td>HOW SUPPLIED&lt;sup&gt;20&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Calcitriol</td>
<td>Hypocalcemia (Hypoparathyroidism, Postsurgical, Idiopathic)</td>
<td>Intravenous Solution: 1 MCG/ML</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia (Pseudohypoparathyroidism)</td>
<td>Oral Capsule, Liquid Filled: 0.25 MCG, 0.5 MCG</td>
</tr>
<tr>
<td></td>
<td>Hypocalcemia (Renal dialysis)</td>
<td>Oral Solution: 1 MCG/ML</td>
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<tr>
<td></td>
<td>Secondary hyperparathyroidism</td>
<td></td>
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<tr>
<td></td>
<td>Familial, x-linked, vitamin D-refractory, hypophosphatemic rickets</td>
<td></td>
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<tr>
<td></td>
<td>Hypoalbuminemia</td>
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<tr>
<td></td>
<td>Osteoporosis</td>
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TOPICALS

• Calcitriol and Calcipotriene
  • Used for psoriasis

• Vitamin D also found in some anti-aging topicals (OTC)
OTHER REPORTED USES OF VITAMIN D

  - Observational studies have shown a decreased cancer risk with high Vitamin D blood levels
  - Randomized trials using vitamin D supplements have had mixed results however some may not be using an adequate supplement dose.

• **Cardiovascular Disease** (Martins 2007, Dohnig 2008)
  - Showed a correlation between low vitamin D levels and having HTN, diabetes, high triglycerides or obesity.
  - Low vitamin D levels linked to cardiovascular mortality
  - Hypertension: (Pfeifer, 2001, Rostand 1997)
    - BP increases with decreased sun exposure. Vitamin D supplementation shown to decrease BP in elderly women.
OTHER REPORTED USES OF VITAMIN D

  - Studies suggest that vitamin D supplementation can decrease the risk of developing type I or type II diabetes
  - Suggested that patients who are deficient in Vitamin D are at higher risk of having insulin resistance and the metabolic syndrome.

- **Multiple Sclerosis** (Munger 2004 & 2006, Hayes 1997)
  - High blood levels of vitamin D have been associated with lower risk of MS.
ADDITIONAL VITAMIN D USES

• Congestive heart failure
• Crohn's disease
• Epilepsy (during anticonvulsant therapy)
• Fanconi syndrome
• Hearing loss
• Hepatic osteodystrophy
• Immune response
• Multiple sclerosis (protective effect)
• Muscle weakness
• Myelodysplastic syndrome

• Nutritional status (breast-feeding women and infants)
• Osteogenesis imperfecta
• Physical performance
• Proximal myopathy
• Rheumatoid arthritis
• Scleroderma
• Seasonal affective disorder (SAD)
• Senile warts
• Tooth retention
• Weight loss (combination therapy)
SCREEN FOR 25(OH)_3 DEFICIENCY

• Non-high risk?
  • No screen, but 1.2g elemental Ca and 800 IU Vitamin D daily

• House-bound, Malabsorption, Osteoporosis, Northern climate, Elderly

• Before instituting bisphosphonate therapy

• Evaluate potential Vitamin D-specific disease states and seek Endocrinology consultation as appropriate
EVALUATION AND REPLETION

VITAMIN D REPLETION STRATEGIES

- Insufficiency
  - Less than 30 ng/mL (75nmol/L)
    - D3, 800-1000 units daily \(\rightarrow\) achieve sufficiency over 3 months’ time

- Deficiency
  - Less than 20 ng/mL (50nmol/L)
    - D2 or D3, 50,000 units once per week for 6-8 weeks, then 800-1000 units D3 daily
    - Alternatively, D3, 300,000 (three hundred-thousand) units in one or two doses per year

- Malabsorption – Patient-Specific
  - Vitamin D, 10,000 to 50,000 units daily for gastrectomy or malabsorption
  - May require hydroxylated vitamin D metabolites, or sun/sunlamp therapy
  - Alternatively, D3, 300,000 (three hundred thousand) units in one or two doses per year
  - Monitor (unexpected calcium imbalance could occur any time)
    - Check D3 levels in \(~3\) months, adjust dose as needed
EVALUATION AND PREPLETION

- IN COMMON USAGE, VITAMIN D IN REGARDS TO REPLETION REFERS TO EITHER D2 (ERGOCALCIFEROL) OR D3 (CHOLECALCIFEROL)

- VITAMIN D RECEPTORS ARE UBIQUITOUS IN THE BODY. THIS DISTRIBUTION HELPS EXPLAIN VITAMIN D’S APPARENT DIVERSE PHYSIOLOGY- MODULATING EFFECTS

- VITAMIN D LIKELY EXECUTES MANY OF ITS DIVERSE EFFECTS IN CONCERT WITH MANY OTHER PLAYERS, SUCH AS VITAMINS A AND K IN BONE METABOLISM

- WATCH FOR FUTURE CHANGES IN VITAMIN D REPLACEMENT PHILOSOPHY AND GUIDELINES AS THEY CONTINUE TO EVOLVE
1. According to nuclear receptor theory, which of the fat-soluble vitamins acts with vitamin D to modulate gene product expression?

2. If necessary, vitamin D can be replaced by a single intramuscular injection given twice annually.

3. Are cholecalciferol and ergocalciferol therapeutically equivalent according to current theory?

4. Fish produce vitamin D through direct action of ultraviolet light B?

5. In lieu of screening, what are the current recommended daily doses of Vitamin D and Calcium supplementation?

6. If necessary, individuals at latitudes of up to 45o can fulfill their annual vitamin D requirements by daily outdoor sun exposure?
1. According to nuclear receptor theory, which of the fat-soluble vitamins acts with vitamin D to modulate gene product expression? **Vitamin A (Retinoic Acid)**

2. If necessary, vitamin D can be replaced by a single intramuscular injection given twice annually. **True (300,000 (three hundred thousand) units in one or two doses per year is an option)**

3. Are cholecalciferol and ergocalciferol therapeutically equivalent according to current theory? **Yes (According to current theory, yes, though the debate continues)**

4. Fish produce vitamin D though direct action of ultraviolet light B? **No (UV-B does not adequately penetrate water. Fish concentrate vitamin D by eating zooplankton)**

5. In lieu of screening, what are the current recommended daily doses of Vitamin D and Calcium supplementation? **1.2g elemental Ca and 800 IU Vitamin D daily**

6. If necessary, individuals at latitudes of 40° can fulfill their annual vitamin D requirements by daily outdoor sun exposure? **False (People at these latitudes have a 24% chance of deficiency)**
PRE-TEST ANSWERS

1. Thanks to our current national practice of taking a vitamin daily, the United States has avoided the Vitamin D insufficiency epidemic that has swept most first-world countries?
   Answer False. NHANES (National Health and Nutrition Examination Survey) documented a three-fold increase in Vitamin D insufficiency, from 2% to 6% between 1994 and 2004.

2. Milk has one of the most naturally-abundant concentrations of dietary vitamin D?
   Answer False. Answer False. Tuna, mackerel, fish live, beef liver, cheese, egg yolks, and mushrooms contain varying amounts of vitamin D. Unfortified milk is not considered a significant dietary source of Vitamin D.
3. Megalin binds Vitamin D hormone to the nuclear receptor Vitamin D response element?
   Answer  False  Megalin, also known as Low density lipoprotein-Related Protein 2 (LRP2), is an endocytic receptor on the apical membranes of proximal tubule cells (PTC) in the kidney and other cells. In the kidney, Megalin facilitates reabsorption and metabolism serum transport proteins such as Vitamin D Binding Protein as a step in the 1a hydroxylation of D-Binding Protein (DBP)-bound 25(OH)D3.

4. Dihydrotachysterol (DHT) is recommended as one of the most economical forms for routine daily Vitamin D supplementation?
   Answer  False. Dihydrotachysterol is primarily indicated as treatment for hypoparathyroidism and tetany.
5. Unfortunately, calcipotriene has proven ineffective in the topical treatment of psoriasis, and was recently taken off the market?
   Answer False. Calcipotriene, in combination with betamethasone dipropionate, is one topical agent which is FDA-approved for the treatment of psoriasis.

6. Due to the risk of hypercalcaemia, most healthy people should have their Vitamin D blood levels tested before beginning daily Vitamin D supplementation?
   Answer False. Daily supplementation of healthy individuals with 1.2g elemental Ca and 800 IU Vitamin D daily, without prior Vitamin D level determination, can be safe and effective.