EU Risk management plan (RMP)
for generic medicinal product

Active substance(s) (INN or common name):	cholecalciferol (vitamin D3)
Pharmaco-therapeutic group (ATC Code):	Vitamin D and analogues, cholecalciferol. ATC code: A11CC05D
Name of Marketing Authorisation Holder or Applicant:	S.A.L.F. S.p.A. Laboratorio Farmacologico
Number of medicinal products to which this RMP refers:	2
Product(s) concerned (brand name(s)):	Vitamin D3 S.A.L.F. 100,000 I.U./ml solution for injection Vitamin D3 S.A.L.F. 300,000 I.U./ml solution for injection

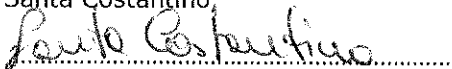| Data lock point for this RMP	July 14th, 2017	Version number	01
Date of final sign off	<September 22th, 2017>		

Part I: Product(s) Overview

Administrative information on the RMP

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
Part II Safety Specification	SV Post authorisation experience Only required for updates to the RMP	Not Applicable	Not Applicable
	SVIII Summary of the safety concerns	July 14th, 2017	01
Part III Pharmacovigilance Plan	Only needed if reference product has additional PhV activities	Not Applicable	Not Applicable
Part IV Plan for post-authorisation efficacy studies	Only needed if reference product has imposed post-authorisation efficacy studies	Not Applicable	Not Applicable
Part V Risk Minimisation Measures		July 14th, 2017	01
Part VI Summary of RMP		July 14th, 2017	01
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	July 14th, 2017	01
	ANNEX 3 Worldwide marketing status by country	July 14th, 2017	01
	ANNEX 4 Synopsis of clinical trial programme	Not Applicable	Not Applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme	Not Applicable	Not Applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III	Not Applicable	Not Applicable
	ANNEX 7 Specific adverse event follow-up forms	Not Applicable	Not Applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	ANNEX 8 Protocols for studies in Part IV	Not Applicable	Not Applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV	Not Applicable	Not Applicable
	ANNEX 10 Details of proposed additional risk minimisation activities	Not Applicable	Not Applicable
	ANNEX 11 Mock up examples	Not Applicable	Not Applicable
	ANNEX 12 Other supporting data	July 14th, 2017	01

* A new RMP version number should be assigned each time any Parts/modules are updated

QPPV name

QPPV signature

Santa Costantino

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number of contact person   +39 335 1318126

Overview of versions:

Version number of last agreed RMP:

Version number	Not Applicable
Agreed within	Not Applicable

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
Initial version.	Not Applicable	Not Applicable

For each product in the RMP

Invented name(s) in the European Economic Area (EEA)	Vitamin D3 S.A.L.F. 100,000 I.U./ml solution for injection Vitamin D3 S.A.L.F. 300,000 I.U./ml solution for injection
Authorisation procedure	National procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Vitamin D3, also known as cholecalciferol; is chemically described as (1S,3Z)-3-[(2E)-2-[(1R,3ar,7as)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidene-cyclohexan-1-ol. Molecular weight is 384.648 g/mol and chemical formula is $C_{27}H_{44}O$. Vitamin D3 corrects a chronic condition of the same and increases intestinal calcium absorption.
Indication(s) in the EEA Current (if applicable)	Not Applicable .
Proposed (if applicable)	Prevention and treatment of Vitamin D deficiency.
Posology and route of administration in the EEA Current (if applicable)	Not Applicable
Proposed (if applicable)	VITAMIN D3 S.A.L.F. can be administered daily, weekly, monthly or yearly (see section 5.2). In case of oral therapy, it is recommended to administer VITAMIN D3 S.A.L.F. during meals. Intramuscular therapy is indicated only in case of malabsorption syndromes. Prevention of Vitamin D deficiency: preventive administration of VITAMIN D3 S.A.L.F. is recommended in all conditions characterized by a greater risk of deficiency or increased need. It is generally accepted that prevention of vitamin D deficiency is needed: – systematically in newborns (especially in premature newborns), in infants, in the pregnant woman (last quarter) and in the woman who is breastfeeding at the end of winter and spring, in the elderly, or even in the child and the adolescent if solar exposure is insufficient; – under the following conditions: o lack of sun exposure or intense skin pigmentation, unbalanced diet (low-calcium diet, vegetarian diet, etc.),

	extensive dermatological diseases or granulomatous diseases (tuberculosis, leprosy, etc.); o patients treated with anti-convulsants (barbiturates, phenytoin, primidone); o patients treated with long-term corticosteroid therapies; o digestive disorders (intestinal malabsorption, mucoviscidosis or cystic fibrosis); o liver failure. Treatment of Vitamin D deficiency: the lack of vitamin D should be ascertained clinically and/or by means of appropriate laboratory tests. Treatment is aimed at restoring the deposits of vitamin D and will be followed by a maintenance therapy if the risk of deficiency persists, with a vitamin D dose suitable for prevention (see "Prevention of Vitamin D deficiency"). In most cases patient should not exceed a cumulative dose of 600,000 IU yearly, unless otherwise suggested by the doctor.
Pharmaceutical form(s) and strengths Current (if applicable)	Not Applicable, unauthorised
Proposed (if applicable)	Solution for injection, 100,000 I.U./ml Solution for injection, 300,000 I.U./ml

Country and date of first authorisation worldwide

Not Applicable, unauthorised

Country and date of first launch worldwide

Not Applicable, unauthorised

Country and date of first authorisation in the EEA

Not Applicable, unauthorised

Is the product subject to additional monitoring in the EU?   Yes ☐   No ☒

Part II: Safety Specification

Part II: Module SV - Post-authorisation experience
(Only required for updates to the RMP)

Not Applicable

Part II: Module SVIII - Summary of the safety concerns

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypercalcaemia • Hypercalciuria • Hypersensitivity
Important potential risks	• Teratogenicity
Missing information	• None

Part III: Pharmacovigilance Plan

No additional PhV activities have been identified on the reference product DIBASE. Therefore, no additional PhV activities has been proposed.

Part IV: Plans for post-authorisation efficacy studies

No additional post-authorisation efficacy studies have been identified on the reference product DIBASE. Therefore, no post-authorisation efficacy studies have been proposed.

Part V: Risk minimisation measures

V.1   Risk minimisation measures by safety concern

Important identified risks

Hypercalcaemia	
Objective(s) of the risk minimisation measures	Inform to healthcare professionals about this risk
Routine risk minimisation measures	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalcaemia. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis. • Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Warning in section 4.5 that the concomitant use of anticonvulsants or barbiturates may reduce the effect of vitamin D3 by metabolic inactivation. In the case of treatment with thiazide diuretics, which reduce urinary calcium elimination, serum calcium concentration checks are recommended. In case of treatment with medicines containing digitalis, oral calcium administration combined

Hypercalcaemia	
	with vitamin D increases the risk of digitalis toxicity (arrhythmia). Therefore, a close medical supervision and, if necessary, electrocardiographic monitoring and serum calcium concentration checks are required. • Listed in section 4.8: hypercalcaemia. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage. • Provision of information in section 5.3 that, in repeated dose toxicity studies, the most commonly observed effects were: increased calcium, decreased phosphaturia and proteinuria. At high doses, hypercalcaemia was observed. In a prolonged state of hypercalcemia, the most common histological (calcification) abnormalities were in the kidneys, heart, aorta, testis, thymus and intestinal mucosa.
	Comment Not Applicable
	Other routine risk minimisation measures Not proposed
Additional risk minimisation measure(s)	Objective and justification of why needed Not proposed
	Proposed actions/components and rationale Not Applicable

Hypercalciuria	
Objective(s) of the risk minimisation measures	Inform to healthcare professionals about this risk
Routine risk minimisation measures	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalciuria. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis. • Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Listed in section 4.8: hypercalciuria. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage.
	Comment Not Applicable

Hypercalciuria	
	Other routine risk minimisation measures Not proposed
Additional risk minimisation measure(s)	Objective and justification of why needed Not proposed
	Proposed actions/components and rationale Not Applicable

Hypersensitivity	
Objective(s) of the risk minimisation measures	Inform to healthcare professionals about this risk
Routine risk minimisation measures	Proposed text in the SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypersensitivity to cholecalciferol or to any of the excipients. • Listed in section 4.8: hypersensitivity reactions.
	Comment Not Applicable
	Other routine risk minimisation measures Not proposed
Additional risk minimisation measure(s)	Objective and justification of why needed Not proposed
	Proposed actions/components and rationale Not Applicable

Important potential risks

Teratogenicity	
Objective(s) of the risk minimisation measures	Inform to healthcare professionals about this risk
Routine risk minimisation measures	Proposed text in SmPC:

Teratogenicity	
	• Warining in section 4.6 that in first 6 months of pregnancy, vitamin D should be taken with caution, due to the risk of teratogenic effects. • Provision of information in section 5.3 that reproductive toxicity studies have shown that cholecalciferol has no adverse effects on fertility and reproduction. At doses equivalent to therapeutic ones, cholecalciferol has no teratogenic activity.
	Comment Not Applicable
	Other routine risk minimisation measures Not proposed
Additional risk minimisation measure(s)	Objective and justification of why needed Not proposed
	Proposed actions/components and rationale Not Applicable

Missing information

No missing information was identified.

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	The Marketing Authorisation Holder will evaluate the effectiveness of risk minimisation measures on ongoing basis within continuous risk-benefit evaluation.
Criteria for judging the success of the proposed risk minimisation measures	No increase in frequency of spontaneous reports of these identified and potential risks. No safety action of competent authorities related to these risks.
Planned dates for assessment	This RMP needs to be updated with the issues raised as question within the assessment report as well as periodically updated as defined by the GVP module V rev 1.
Results of effectiveness measurement	Not applicable, this is the initial version of this RMP.

Effectiveness of risk minimisation measures	
Impact of risk minimisation	Broad impact is expected in the target population.
Comment	Not applicable.

V.2   Risk minimisation measure failure

Not Applicable.

V.3   Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisatio n measures
Hypercalcaemia	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalcaemia. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis. • Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Warning in section 4.5 that the concomitant use of anticonvulsants or barbiturates may reduce the effect of vitamin D3 by metabolic inactivation. In the case of treatment with thiazide diuretics, which reduce urinary calcium elimination, serum calcium concentration checks are recommended. In case of treatment with medicines containing digitalis, oral calcium administration combined with vitamin D increases the risk of digitalis toxicity (arrhythmia). Therefore, a close medical supervision and, if necessary, electrocardiographic monitoring and serum calcium concentration checks are required.	Not proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Listed in section 4.8: hypercalcaemia. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage. • Provision of information in section 5.3 that, in repeated dose toxicity studies, the most commonly observed effects were: increased calcium, decreased phosphaturia and proteinuria. At high doses, hypercalcaemia was observed. In a prolonged state of hypercalcemia, the most common histological (calcification) abnormalities were in the kidneys, heart, aorta, testis, thymus and intestinal mucosa.	
Hypercalciuria	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalciuria. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis.	Not proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Listed in section 4.8: hypercalciuria. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage.	
Hypersensitivity	Proposed text in the SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypersensitivity to cholecalciferol or to any of the excipients. • Listed in section 4.8: hypersensitivity reactions.	Not proposed
Teratogenicity	Proposed text in SmPC: • Warining in section 4.6 that in first 6 months of pregnancy, vitamin D should be taken with caution, due to the risk of teratogenic effects. • Provision of information in section 5.3 that reproductive toxicity studies have shown that cholecalciferol has no adverse effects on fertility and reproduction. At doses equivalent to therapeutic ones, cholecalciferol has no teratogenic activity.	Not proposed

Part VI: Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hypercalcaemia • Hypercalciuria • Hypersensitivity
Important potential risks	• Teratogenicity
Missing information	• None

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable, no additional PhV studies/activities proposed.

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not applicable, no additional post-authorisation efficacy studies proposed/ongoing.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypercalcaemia	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalcaemia. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its	Not proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisatio n measures
	active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis. • Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Warning in section 4.5 that the concomitant use of anticonvulsants or barbiturates may reduce the effect of vitamin D3 by metabolic inactivation. In the case of treatment with thiazide diuretics, which reduce urinary calcium elimination, serum calcium concentration checks are recommended. In case of treatment with medicines containing digitalis, oral calcium administration combined with vitamin D increases the risk of digitalis toxicity (arrhythmia). Therefore, a close medical supervision and, if necessary, electrocardiographic monitoring and serum calcium concentration checks are required. • Listed in section 4.8: hypercalcaemia. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage. • Provision of information in section 5.3 that, in repeated dose toxicity studies, the most commonly observed effects were: increased calcium, decreased phosphaturia and proteinuria.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	At high doses, hypercalcaemia was observed. In a prolonged state of hypercalcemia, the most common histological (calcification) abnormalities were in the kidneys, heart, aorta, testis, thymus and intestinal mucosa.	
Hypercalciuria	Proposed text in SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypercalciuria. • Warning in section 4.4 that in elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium. The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D; therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis. • Warning in section 4.4 that in case of hypercalcemia it is necessary to reduce the dose or discontinue treatment. • Listed in section 4.8: hypercalciuria. • Warning/provision of information in section 4.9 that tratment with VITAMIN D3 S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children. Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration. Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia. Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy. Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures. Discontinuation of the treatment with VITAMIN D3 S.A.L.F. and rehydratation of the patient are necessary in case of overdosage.	Not proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypersensitivity	Proposed text in the SmPC: • Warning in section 4.3 that the product is contraindicated in case of hypersensitivity to cholecalciferol or to any of the excipients. • Listed in section 4.8: hypersensitivity reactions.	Not proposed
Teratogenicity	Proposed text in SmPC: • Warining in section 4.6 that in first 6 months of pregnancy, vitamin D should be taken with caution, due to the risk of teratogenic effects. • Provision of information in section 5.3 that reproductive toxicity studies have shown that cholecalciferol has no adverse effects on fertility and reproduction. At doses equivalent to therapeutic ones, cholecalciferol has no teratogenic activity.	Not proposed

VI.2   Elements for a public summary

VI.2.1   Overview of disease epidemiology

Vitamin D deficiency appears to be a widespread global problem prevalent in all age groups. Estimates suggest that up to 1 billion people around the world may have vitamin D deficiency or insufficiency. [1]

Vitamin D deficiency causes rickets (condition in which bones become soft and weak, which can lead to bone deformities) in children and will precipitate and exacerbate osteopenia (weak bones), osteoporosis (low bone density), and fractures in adults.[2]

The National Health and Nutrition Examination Survey 2005 to 2006 data analyzed for vitamin D levels in adult participants shows that overall occurrence rate of vitamin D deficiency was 41.6%, with the highest rate seen in B lacks (82.1%), followed by Hispanics (69.2%). Vitamin D deficiency was significantly more common among those who had no college education, were obese (over-weight), with a poor health status, hypertension, low high -density lipoprotein cholesterol level, or not consuming milk daily.[3]

VI.2.2   Summary of treatment benefits

Vitamin D is an endogenous substance, synthesised in the skin when exposed to UV light, it can also be supplied via food or as a drug. Poor intake of vitamin D, together with lack of sunlight exposure, disorders that decrease the absorption of vitamin D or the conversion of vitamin D into its active forms, can cause vitamin D deficiency.

Vitamin D deficiency results in a decrease in the efficiency of intestinal calcium uptake, which may lead to osteopenia, osteoporosis and increased risk of fracture. Vitamin D deficiency and secondary hyperparathyroidism may also result in a mineralization defect of the skeleton, that can cause bone softening diseases like rickets in children and osteomalacia in adults.

Cholecalciferol (vitamin D3) is a well-known substance that has been on the market for decades.

Use of cholecalciferol to prevent and treat vitamin D deficiency, in order to maintain or reach physiological serum levels of its active form and avoid the consequences of vitamin D deficiency is supported by the published data.

VI.2.3   Unknowns relating to treatment benefits

No unknowns relating to treatment benefits have been identified.

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[1] Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-281

[2] Holick MF. The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health Public Health Reviews. 2010;32(1): 267-283.

[3] Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011;31(1):48-54.

VI.2.4   Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
too high levels of calcium in the blood (hypercalcaemia)	This effect originates from the underlying mechanism of action of the active substance. Taking vitamin D can lead a high calcium level in the blood (hypercalcaemia). You may feel or be sick, lose your appetite, have constipation, stomachache, feel very thirsty, have muscle weakness, drowsiness or confusion. Hypercalcaemia may also occur when colecalciferol is taken together with certain other drugs, e.g. medicines for epilepsy such as barbiturates, other vitamin D containing medicines, medicines to control the rate of heart beat, diuretics (water tablets), calcium supplements, medicines to treat tuberculosis, medicines leading to poor absorption of fat (e.g. orlistat, colestyramine, liquid paraffin), medicines to treat fungal infections (i.e. ketoconazole, itraconazole), actinomycin, glucocorticoids (steroid hormones such as hydrocortisone or prednisolone).	This effect is hardly preventable. The dose of colecalciferol can be reduced, when these side effects occur or when too high level of calcium is detected in blood during regular check. Concomitant use of other medicines, which may lead to hypercalcaemia, should always be consulted with a physician in charge.
too high levels of calcium in the urine (hypercalciuria)	Too high levels of calcium in the urine have been seen after intake of products containing vitamin D3. As a consequence of hypercalcaemia, too much calcium in your urine may appear.	Follow the recommendations provided in the product information which states you should not take colecalciferol if you have too high levels of calcium in the urine, and you should tell your doctor if you have had kidney problems. At high doses of vitamin D 3, the calcium levels may be monitored and particular caution is recommended in patients with a history of kidney stones.
Allergic (hypersensitivity) reactions	Allergic (hypersensitivity) reactions such as itching, rash or hives have been seen after intake of products containing vitamin D3	Follow the recommendations provided in the product information which states that you should not take this medicine if you are allergic (hypersensitive) to vitamin D3 or any of the other ingredients of this product.

Important potential risks

Risk	What is known
Teratogenicity	Studies in animals have shown reproductive toxicity of high doses of vitamin D. At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. There are no indications that vitamin D at therapeutic doses is teratogenic in human.

Important missing Effects on fertility information

No missing information was identified.

VI.2.5   *Summary of risk minimisation measures by safety concern*

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6   *Planned post authorisation development plan (if applicable)*

No post authorisation development plan was proposed.

VI.2.7   *Summary of changes to the risk management plan over time*

Not applicable. This is the initial version of this RMP.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 - SmPC & Package Leaflet (EN Translation)

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT Vitamin D₃ S.A.L.F. 100,000 I.U./ml solution for injection Vitamin D₃ S.A.L.F. 300,000 I.U./ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION *Vitamin D₃ S.A.L.F. 100,000 I.U./ml solution for injection* Each ampoule contains: cholecalciferol (vitamin D₃) 2.5 mg equal to 100,000 I.U. *Vitamin D₃ S.A.L.F. 300,000 I.U./ml solution for injection* Each ampoule contains: cholecalciferol (vitamin D₃) 7.5 mg equal to 300,000 I.U. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM Solution for injection.

4. CLINICAL INFORMATION

4.1 Therapeutic indications
Prevention and treatment of Vitamin D deficiency.

4.2 Dosage and method of administration

VITAMIN D₃ S.A.L.F. can be administered daily, weekly, monthly or yearly (see section 5.2). In case of oral therapy, it is recommended to administer VITAMIN D₃ S.A.L.F. during meals (see section 5.2). Intramuscular therapy is indicated only in case of malabsorption syndromes.
Prevention of Vitamin D deficiency: preventive administration of VITAMIN D₃ S.A.L.F. is recommended in all conditions characterized by a greater risk of deficiency or increased need. It is generally accepted that prevention of vitamin D deficiency is needed:
o   systematically in newborns (especially in premature newborns), in infants, in the pregnant woman (last quarter) and in the woman who is breastfeeding at the end of winter and spring, in the elderly, or even in the child and the adolescent if solar exposure is insufficient;
o   under the following conditions:
■   lack of sun exposure or intense skin pigmentation, unbalanced diet (low-calcium diet, vegetarian diet, etc.), extensive dermatological diseases or granulomatous diseases (tuberculosis, leprosy, etc.);
■   patients treated with anti-convulsants (barbiturates, phenytoin, primidone);
■   patients treated with long-term corticosteroid therapies;
■   digestive disorders (intestinal malabsorption, mucoviscidosis or cystic fibrosis);
■   liver failure.

Treatment of Vitamin D deficiency: the lack of vitamin D should be ascertained clinically and/or by means of appropriate laboratory tests. Treatment is aimed at restoring the deposits of vitamin D and will be followed by a maintenance therapy if the risk of deficiency persists, with a vitamin D dose suitable for prevention (see "Prevention of Vitamin D deficiency"). In most cases you should not exceed a cumulative dose of 600,000 IU yearly, unless otherwise suggested by your doctor.

The following dosage chart is given as an indication and should be adapted to the doctor's judgment based on the nature and seriousness of the deficiency (see also section 4.4).
VITAMIN D₃ S.A.L.F. 100,000 I.U./ml solution for injection
Infants up to 24 months of age

Treatment: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) once a month for 4-6 months.

Children and adolescents (2-18 years of age)

Prevention: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 4-8 months.

Treatment: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) once a month for 4-6 months.

Pregnant women

The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) at the beginning of the last quarter.

Adults and Elderly

Prevention: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 4 months. In the event of a high risk of deficiency, the doctor will assess whether the dose should be increased to 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 2 months.

Treatment: The recommended dose is 2 ampoules (200,000 IU of Vitamin D₃) once a month for 3 months.

VITAMIN D₃ S.A.L.F. 300,000 I.U./ml solution for injection **Children and adolescents (2-18 years of age)**

Prevention: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) once a year.

Treatment: The recommended dose is 1 ampoule (300,000 IU of vitamin D₃) to be repeated after 3 months.

Adults and Elderly

Prevention: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) once a year. In the event of a high risk of deficiency, the doctor will assess whether the dose should be increased to 1 ampoule (equivalent to 300,000 IU vitamin D₃) every 6 months.

Treatment: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) to be repeated after 6 weeks.

Instructions for Use The doses can be administered orally or intramuscularly. **4.3 Contraindications**
Hypersensitivity to cholecalciferol or to any of the excipients (see section 6.1). Hypercalcemia, hypercalciuria. Kidney stones (nephrolithiasis, nephrocalcinosis). Renal impairment (see section 4.4). **4.4 Special warnings and precautions for use**

In case of a prolonged administration with high doses, it is recommended to monitor the serum 25-hydroxychalcalcopherol level. Stop treatment with VITAMIN D₃ S.A.L.F. when the serum 25-hydroxycholecalciferol level exceeds 100 ng/ml (equal to 250 nmol/l).

In elderly patients being already treated with cardiac or diuretic glycosides, it is important to monitor serum and urinary calcium.

In case of hypercalcemia or kidney failure, reduce the dose or discontinue treatment.

To avoid an overdose, consider the cumulative dose of vitamin D in case of combination with treatments containing vitamin D, vitamin D-enriched food, or in case of use of vitamin D-enriched milk.

Increases in dosage may be required in the following cases:

- patients treated with anticonvulsants or barbiturates (see section 4.5),
- patients treated with corticosteroid therapy (see section 4.5);
- patients treated with hypolipidemic drugs such as cholestipol, cholestyramine and orlistat (see section 4.5)
- patients treated with aluminum-containing antacids (see section 4.5)
- obese patients (see section 5.2)
- digestive disorders (intestinal malabsorption, mucoviscidosis or cystic fibrosis);
- liver failure.

The product should be prescribed with caution to patients suffering from sarcoidosis, due to the possible increase in vitamin D metabolism in its active form. In such patients the level of serum and urinary calcium should be monitored. Patients with impaired renal function have an altered metabolism of vitamin D;

therefore, if they are to be treated with cholecalciferol, it is necessary to monitor the effects of calcium and phosphate on homeostasis.

4.5 Interaction with other medicinal products and other forms of interaction
The concomitant use of anticonvulsants or barbiturates may reduce the effect of vitamin D3 by metabolic inactivation. In the case of treatment with thiazide diuretics, which reduce urinary calcium elimination, serum calcium concentration checks are recommended.
Concomitant use of glucocorticosteroids may reduce the effect of vitamin D3.
In case of treatment with medicines containing digitalis, oral calcium administration combined with vitamin D increases the risk of digitalis toxicity (arrhythmia). Therefore, a close medical supervision and, if necessary, electrocardiographic monitoring and serum calcium concentration checks are required.
Concomitant use of aluminum-containing antacids may interfere with the medicine efficacy, reducing vitamin D absorption, while preparations containing magnesium may cause the risk of hypermagnetism.
Animal studies have suggested a possible enhancement of warfarin action when administered with calciferol. Although there is no such evidence with the use of cholecalciferol, caution should be used when the two medicines are used simultaneously. Cholestyramine, colestipol and orlistat reduce the vitamin D absorption, while chronic alcoholism decreases the Vitamin D level in the liver.

4.6 Fertility, pregnancy and breastfeeding
Pregnancy
In first 6 months of pregnancy, vitamin D should be taken with caution, due to the risk of teratogenic effects (see section 4.9).
Breastfeeding
When necessary, vitamin D may be prescribed during breastfeeding. This supplementation does not replace the administration of vitamin D in the infant.

4.7 Effects on ability to drive and use machines
No data are available on the effects of the product on the ability to drive. However, an effect on such capacity is unlikely.

4.8 Undesirable effects
If dosage is in accordance with the individual needs, VITAMIN D3 S.A.L.F. is well tolerated thanks to the body's ability to accumulate cholecalciferol in adipose and muscular tissue (see section 5.2).
Side effects reported after using vitamin D are as follows:
Immune system disorders:
hypersensitivity reactions.
Metabolism and nutrition disorders:
weakness, anorexia, thirst.
Psychiatric disorders:
somnolence, confusional state.
Nervous system disorders:
headache.
Gastrointestinal disorders:
constipation, flatulence, abdominal pain, nausea, vomiting, diarrhea, metallic taste, dry mouth.
Skin and subcutaneous tissue disorders:
rash, itching.
Renal and urinary disorders:
nephrocalcinosis, polyuria, polydipsia, renal failure.
Diagnostic tests:
hypercalciuria, hypercalcemia.
Reporting suspected adverse reactions

Reporting suspected adverse reactions occurring after the authorization of the medicine is important, as it allows continuous monitoring of the benefit/risk ratio of the medicine. Healthcare professionals are required to report any suspected adverse reaction via the national reporting system on the web site www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose
Tratment with VITAMIN D₃ S.A.L.F. should be discontinued if serum calcium exceeds 10.6 mg/dl (2.65 mmol/l) or if urinary calcium exceeds 300 mg/24 h in adults or 4-6 mg/kg/day in children.
Overdose is manifested as hypercalciuria and hypercalcemia, with the following symptoms: nausea, vomiting, thirst, polydipsia, polyuria, constipation and dehydration.
Chronic overdoses may lead to vascular and organ calcification, as a result of hypercalcemia.
Overdose during the first 6 months of pregnancy may have toxic effects on the fetus: there is a correlation between overdose or extreme maternal sensitivity to vitamin D during pregnancy and delay in child's physical and mental development, supravalvular aortic stenosis and retinopathy.
Maternal hypercalcemia may also lead to the suppression of parathyroid function in infants resulting in hypocalcemia, tetanus and seizures.
Treatment in case of overdose
Discontinue the treatment with VITAMIN D3 S.A.L.F. and rehydrate patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Vitamin D and analogues, cholecalciferol.
ATC code: A11CC05D
Vitamin D corrects a chronic condition of the same and increases intestinal calcium absorption.

5.2 Pharmacokinetic properties
As with other liposoluble vitamins, the absorption of cholecalciferol in the intestinal tract is favored by concomitant intake of fatty foods. Cholecalciferol is present in the bloodstream in association with specific α-globulins that carry it to the liver, where it is hydroxylated to 25-hydroxy-cholecalciferol. A second hydroxylation takes place in the kidneys, where 25-hydroxy-colecalciferol is converted to 1,25-dihydroxy-cholecalciferol, which represents the active metabolite of vitamin D responsible for the effects on phosphocalcal metabolism.
Non-metabolised cholecalciferol is accumulated in adipose and muscular tissue to be made available according to the body's needs: for that reason VITAMIN D₃ SALF can also be administered weekly, monthly or yearly. Obesity reduces the bioavailability of vitamin D due to the excess of adipose tissue.
Vitamin D is eliminated through feces and urine.

5.3 Preclinical safety data
Preclinical studies conducted in various animal species show that toxic effects occur in animals at doses substantially higher than those for therapeutic use in humans. In repeated dose toxicity studies, the most commonly observed effects were: increased calcium, decreased phosphaturia and proteinuria.
At high doses, hypercalcaemia was observed. In a prolonged state of hypercalcemia, the most common histological (calcification) abnormalities were in the kidneys, heart, aorta, testis, thymus and intestinal mucosa. Reproductive toxicity studies have shown that cholecalciferol has no adverse effects on fertility and reproduction.
At doses equivalent to therapeutic ones, cholecalciferol has no teratogenic activity.
Cholecalciferol has no potential mutagenic and carcinogenic activity.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients
Refined olive oil for injectable preparations.

6.2 Incompatibilities
No incompatibilities with other medicinal products are known.

6.3 Shelf-life
2 years.

6.4 Special precautions for storage
Do not store at a temperature above 30° C. Store in the original package in order to protect from the light. Do not freeze.

6.5 Nature and contents of container
Amber glass ampoule. Each pack contains 5 ampoules.

6.6 Special precautions for disposal and other handling
Any unused product and waste resulting from this medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
S.A.L.F. S.p.A. Laboratorio Farmacologico - Via Marconi, 2 - Cenate Sotto (BG) - Italy - Tel. +39 (035) 940097

8. MARKETING AUTHORISATION NUMBER(S)
VITAMIN D₃S.A.L.F. 100,000 I.U./ml solution for injection - 5 x 1 ml ampoules xxxxxxxxx
VITAMIN D₃S.A.L.F. 300,000 I.U./ml solution for injection - 5 x 1 ml ampoules xxxxxxxxx

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION
AIFA Determination

10. DATE OF REVISION OF THE TEXT

Package leaflet: Information for the user

Vitamin D₃ S.A.L.F. 100,000 I.U./ml solution for injection Vitamin D₃ S.A.L.F. 300,000 I.U./ml solution for injection (CHOLECALCIFEROL)

Read all of this leaflet carefully, before you start using this medicine, because it contains important information for you.
- Keep this leaflet, you may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet:
1. What Vitamin D₃ S.A.L.F. is and what it is used for
2. What you need to know before using Vitamin D₃ S.A.L.F.
3. How to use Vitamin D₃ S.A.L.F.
4. Possible side effects
5. How to store Vitamin D₃ S.A.L.F.
6. Contents of the pack and other information

1. What Vitamin D₃ S.A.L.F. is and what it is used for
Vitamin D₃ S.A.L.F. contains cholecalciferol and is indicated for the prevention and treatment of vitamin D deficiency.

2. What you need to know before using Vitamin D₃ S.A.L.F.
Do not use Vitamin D₃ S.A.L.F.:
- if you are allergic to cholecalciferol (Vitamin D₃) or to any of the other ingredients of this medicine (listed in section 6);
- if you have high levels of calcium in the blood (hypercalcemia) or in the urine (hypercalciuria);
- if you suffer from kidney stones (nephrolithiasis) or calcium deposits in the kidneys (nephrocalcinosis);
- if you suffer from kidney disease (kidney failure) (see section "Warnings and precautions").

Warnings and precautions
Ask your doctor or pharmacist before using Vitamin D₃ S.A.L.F. Your doctor may recommend the use of Vitamin D₃ S.A.L.F. to prevent vitamin D deficiency:
- in newborns (especially if premature) and infants,
- during the last trimester of pregnancy,
- in women who are breastfeeding at the end of winter and spring,
- in the elderly,
- in case of insufficient solar exposure, especially in the child and adolescent,
- in case of an unbalanced diet (eg a low calcium diet or a vegetarian diet),
- in case of extensive skin diseases, infectious diseases (such as tuberculosis, leprosy), digestive diseases or liver diseases (hepatic failure),
- in patients receiving treatment for epilepsy or long-term therapy with certain anti-inflammatory drugs.

Your doctor may require periodic medical tests to check the levels of vitamin D or calcium in the blood and urine in the following cases:
- if you are to be treated with Vitamin D₃ S.A.L.F. for a long time and with high doses;
- if you are elderly and are already being treated with medicines used to cure certain heart disease (cardiac glycosides) or medicines that reduce blood pressure by increasing urine production (diuretics);
- if you suffer from sarcoidosis, an inflammatory disease that may involve the whole organism and lead to the formation of nodules;
- if you have high vitamin D or calcium levels, your doctor will reduce the dose or stop treatment with Vitamin D₃ S.A.L.F..
Generally, you should not take Vitamin D₃ S.A.L.F. if you suffer from kidney failure (see section "Do not use Vitamin D₃ S.A.L.F."); but if your doctor believes that a treatment with Vitamin D₃ S.A.L.F. is absolutely necessary, you will have to carry out periodic medical tests to check the levels of calcium and phosphate in the blood. In case of high calcium and phosphate levels, your doctor will reduce the dose or stop treatment with Vitamin D₃ S.A.L.F..
Inform your doctor in the following cases, as it may be necessary to increase the dosages compared to those listed in section 3 "How to use Vitamin D₃ S.A.L.F.":
- if you are taking medicines used to treat epilepsy (anticonvulsants or barbiturates) (see section "Other Medicines and Vitamin D₃ S.A.L.F.");
- if you are taking cortisone, medicine to treat inflammation (see section "Other Medicines and Vitamin D₃ S.A.L.F.");
- if you are taking medicines to reduce fat in your blood such as colestipol, cholestyramine and orlistat (see section "Other Medicines and Vitamin D₃ S.A.L.F.");
- if you are taking aluminum-containing antacids, medicines to treat excessive presence of acid in the stomach, that may also flow back into the esophagus (see section "Other Medicines and Vitamin D₃ S.A.L.F.");
- if you are obese;
- if you suffer from digestive disorders (intestinal malabsorption, mucoviscidosis or cystic fibrosis);
- if you suffer from a liver disease (liver failure).

Other medicines and Vitamin D₃ S.A.L.F.
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.
In particular, tell your doctor if you are taking the following medicines, as they may reduce the effect of Vitamin D₃ S.A.L.F.:
- medicines used to treat epilepsy (anticonvulsants or barbiturates);
- medicines used to reduce fat in the blood such as colestipol, cholestyramine and orlistat;
- aluminum-containing antacids, medicines to treat excessive presence of acid in the stomach, that may also flow back into the esophagus;
- cortisone, medicines to treat inflammations.
If you are taking the following medicines, tell your doctor, who will carefully monitor you and consider whether further medical tests are needed:
- thiazide diuretics, medicines to treat high blood pressure, by increasing urine production;
- medicines to treat certain heart disorders;
- magnesium-containing preparations;
- warfarin, a medicine to make the blood more fluid.

Vitamin D₃ S.A.L.F. with food, drink and alcohol
Tell your doctor if you are taking other products that already contain vitamin D, vitamin D-enriched food, or if you use vitamin D-enriched milk, so that he/she can consider the cumulative dose of vitamin D that you are taking and avoid excessive doses (see section "Warnings and Precautions"). Taking high amounts of alcohol for a long time (chronic alcoholism) decreases the vitamin D level in the liver.

Pregnancy, breastfeeding and fertility
If you are pregnant, think you may be pregnant, are planning to become pregnant or are breastfeeding, you should ask your doctor or pharmacist for advice before using this medicine.
Pregnancy
During the first 6 months of pregnancy, your doctor will prescribe this medicine only if clearly needed, due to the risk of harmful effects on the fetus.
Breastfeeding
If necessary, your doctor will prescribe this medicine during breastfeeding. This does not replace the administration of vitamin D in the newborn.

Driving and using machines
Vitamin D₃ S.A.L.F. is unlikely to affect your driving ability.

3. How to use Vitamin D₃ S.A.L.F.
Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist, if you have any doubt.
Dosage and duration of treatment will be assessed by your doctor based on your health status.
Do not exceed the doses indicated by your doctor.
The doses may be taken orally or by intramuscular injection.
In case of oral administration, you should take Vitamin D₃ S.A.L.F. during meals.
Intramuscular therapy is indicated only in case of malabsorption syndromes.

Vitamin D₃ S.A.L.F. 100,000 IU/ml solution for injection
Infants up to 24 months of age
Treatment: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) once a month for 4-6 months.
Children and adolescents (2-18 years of age)
Prevention: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 4-8 months.
Treatment: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) once a month for 4-6 months.
Pregnant women
The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) at the beginning of the last quarter.
Adults and Elderly
Prevention: The recommended dose is 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 4 months. In the event of a high risk of deficiency, the doctor will assess whether the dose should be increased to 1 ampoule (equivalent to 100,000 IU of Vitamin D₃) every 2 months.
Treatment: The recommended dose is 2 ampoules (200,000 IU of Vitamin D₃) once a month for 3 months.

Vitamin D₃ S.A.L.F. 300,000 IU/ml solution for injection
Children and adolescents (2-18 years of age)
Prevention: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) once a year.
Treatment: The recommended dose is 1 ampoule (300,000 IU of vitamin D₃) to be repeated after 3 months.
Adults and Elderly
Prevention: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) once a year. In the event of a high risk of deficiency, the doctor will assess whether the dose should be increased to 1 ampoule (equivalent to 300,000 IU of vitamin D₃) every 6 months.
Treatment: The recommended dose is 1 ampoule (equivalent to 300,000 IU of vitamin D₃) to be repeated after 6 weeks.

If you use more Vitamin D₃ S.A.L.F. than you should
If accidentally swallowed or in case of an accidental overdose of Vitamin D₃ S.A.L.F. S.A.L.F., tell your doctor immediately or go to the nearest hospital.
In case of overdose, serum and urinary calcium levels may increase. Symptoms are as follows: nausea, vomiting, thirst, severe thirst (polydipsia), increased amount of excreted urine (polyuria), constipation and dehydration.
Chronic excessive doses can lead to calcium deposits in blood vessels and organs.
An excessive use of vitamin D in the first 6 months of pregnancy may cause serious damage to the fetus and the baby.

If you forget to take Vitamin D₃ S.A.L.F.
Do not use a double dose to make up for a missed dose.
If you have any doubts about the use of this medicine, talk to your doctor or pharmacist.

4. Possible side effects Like all medicines, this medicine can cause side effects, although not everybody gets them.
The side effects you may experience by using Vitamin D are as follows:
- allergic reactions;
- weakness, loss of appetite (anorexia), thirst;
- dyspnoea, confusional state;
- headache, gas disorder (flatulence), belly pain, nausea, vomiting, diarrhea, metallic taste, dry mouth, itching;
- excessive calcium deposits in the kidneys (nephrocalcinosis), increased amount of excreted urine (polyuria), intense thirst (polydipsia), kidney disorders (kidney failure);
- increased levels of calcium in the blood (hypercalcemia) and in the urine (hypercalciuria).

Reporting of side effects
If you experience any side effects, including those not listed in this information leaflet, please talk to your doctor or pharmacist. You can also report side effects directly via the national reporting system on the website:
http://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vitamin D₃ S.A.L.F.
Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date stated on the package after "EXP.". The expiration date refers to the last day of that month.
Do not store above 30°C. Store in the original package to protect from light. Do not freeze.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. This will help protect the environment.

6. Contents of the pack and other information
What Vitamin D₃ S.A.L.F. contains
Vitamin D₃ S.A.L.F. 100,000 IU/ml solution for injection
- The active substance is cholecalciferol (vitamin D₃) (each ampoule contains 2.5 mg equivalent to 100,000 IU)
- The other ingredient is refined olive oil for injection.
Vitamin D₃ S.A.L.F. 300,000 IU/ml solution for injection
- The active substance is cholecalciferol (vitamin D₃) (each ampoule contains 7.5 mg equal to 300,000 IU)
- The other ingredient is refined olive oil for injection.
What Vitamin D₃ S.A.L.F. looks like and contents of pack

Vitamin D3 S.A.L.F. is a solution contained in amber glass ampoules:
Vitamin D3 S.A.L.F. 100,000 IU/ml solution for injection
It is available in packs of 5 ampoule of 100,000 IU/ml.
Vitamin D3 S.A.L.F. 300,000 IU/ml solution for injection
It is available in packs of 5 ampoules of 300,000 IU/ml.

Marketing Authorisation Holder and Manufacturer S.A.L.F. S.p.A. Laboratorio Farmacologico - Via Marconi, 2 - Cenate Sotto (BG) - Italy- Tel: +39 035 94 00 97

This leaflet was last revised in ....

Annex 3 - Worldwide marketing authorisation by country (including EEA)

Not applicable.

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable.

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable.

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Not applicable.

Annex 7 - Specific adverse event follow-up forms

Not applicable.

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 9 - Newly available study reports for RMP parts III & IV

Not applicable.

Annex 10 – Details of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 11 – Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable.

Annex 12 – Other supporting data (including referenced material)

Index of included material

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-281
2. Holick MF. The Vitamin D Defi ciency Pandemic: a Forgotten Hormone Important for Health Public Health Reviews. 2010; Vol. 32, No 1, 267-283.
3. Forrest KY1, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011 Jan;31(1):48-54.

Copies of references are attached after this page (not included in the RMP document) in the order given in the index of included material.

MEDICAL PROGRESS

Vitamin D Deficiency

Michael F. Holick, M.D., Ph.D.

From the Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, the Vitamin D, Skin, and Bone Research Laboratory, Boston University Medical Center, Boston. Address reprint requests to Dr. Holick at Boston University School of Medicine, 715 Albany St., M-1013, Boston, MA 02118, or at mfholick@bu.edu.

ONCE FOODS WERE FORTIFIED WITH VITAMIN D AND RICKETS APPEARED to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D–deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. In this review I consider the nature of vitamin D deficiency, discuss its role in skeletal and nonskeletal health, and suggest strategies for its prevention and treatment.

SOURCES AND METABOLISM OF VITAMIN D

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements.[1-4] A diet high in oily fish prevents vitamin D deficiency.[3] Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D_3, which is rapidly converted to vitamin D_3 (Fig. 1).[1] Because any excess previtamin D_3 or vitamin D_3 is destroyed by sunlight (Fig. 1), excessive exposure to sunlight does not cause vitamin D_3 intoxication.[2]

Few foods naturally contain or are fortified with vitamin D. The "D" represents D_2 or D_3 (Fig. 1). Vitamin D_2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D_3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in over-the-counter vitamin D supplements, but the form available by prescription in the United States is vitamin D_2.

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (Fig. 1), which is used to determine a patient's vitamin D status[1-4]; 25-hydroxyvitamin D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D.[1-4] The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels.[1-4] Fibroblast growth factor 23, secreted from the bone, causes the sodium–phosphate cotransporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25-dihydroxyvitamin D synthesis.[5] The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25-dihy-

droxyvitamin D (Fig. 1).[2,3,6] It also induces the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D into biologically inactive, water-soluble calcitroic acid.[2-4]

DEFINITION AND PREVALENCE OF VITAMIN D DEFICIENCY

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).[7-10] 25-Hydroxyvitamin D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng per milliliter (75 to 100 nmol per liter), at which point parathyroid hormone levels begin to level off (at their nadir).[10-12] Furthermore, intestinal calcium transport increased by 45 to 65% in women when 25-hydroxyvitamin D levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter).[13] Given such data, a level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter (52 to 72 nmol per liter) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter or greater can be considered to indicate sufficient vitamin D.[14] Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter).

With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[7-12,15-22] According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.[7-12,15-22] More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D — below 30 ng per milliliter (75 nmol per liter).[12,22]

Children and young adults are also potentially at high risk for vitamin D deficiency. For example, 52% of Hispanic and black adolescents in a study in Boston[23] and 48% of white preadolescent girls in a study in Maine[24] had 25-hydroxyvitamin D levels below 20 ng per milliliter. In other studies, at the end of the winter, 42% of 15- to 49-year-old black girls and women throughout the United States had 25-hydroxyvitamin D levels below 20 ng per milliliter,[25] and 32% of healthy students, phy-

sicians, and residents at a Boston hospital were found to be vitamin D–deficient, despite drinking a glass of milk and taking a multivitamin daily and eating salmon at least once a week.[26]

In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.[1,7,11,16-22] People living near the equator who are exposed to sunlight without sun protection have robust levels of 25-hydroxyvitamin D — above 30 ng per milliliter.[27,28] However, even in the sunniest areas, vitamin D deficiency is common when most of the skin is shielded from the sun. In studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng per milliliter.[29-32] Also at risk were pregnant and lactating women who were thought to be immune to vitamin D deficiency since they took a daily prenatal multivitamin containing 400 IU of vitamin D (70% took a prenatal vitamin, 90% ate fish, and 93% drank approximately 2.3 glasses of milk per day)[33-35]; 73% of the women and 80% of their infants were vitamin D–deficient (25-hydroxyvitamin D level, <20 ng per milliliter) at the time of birth.[34]

CALCIUM, PHOSPHORUS, AND BONE METABOLISM

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed.[2-4] The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80% (Fig. 1).[2-4,13]

In one study, serum levels of 25-hydroxyvitamin D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more.[8] When the level was 30 ng per milliliter or less, there was a significant decrease in intestinal calcium absorption[13] that was associated with increased parathyroid hormone.[10-12] Parathyroid hormone enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D.[2-4,6] Parathyroid hormone also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts (Fig. 1).[1-3] Osteoclasts dissolve the mineralized collagen matrix in bone, causing os-

teopenia and osteoporosis and increasing the risk of fracture.[7,8,11,16-21]

Deficiencies of calcium and vitamin D in utero and in childhood may prevent the maximum deposition of calcium in the skeleton.[36] As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing secondary hyperparathyroidism.[7,9-12] Hypomagnesemia blunts this response, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin D levels fall below 20 ng per milliliter.[37] Parathyroid hormone increases the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which further exacerbates the vitamin D deficiency. Parathyroid hormone also causes phosphaturia, resulting in a low-normal or low serum phosphorus level. Without an adequate calcium–phosphorus product (the value for calcium times the value for serum phosphorus), mineralization of the collagen matrix is diminished, leading to classic signs of rickets in children[1,28] and osteomalacia in adults.[7,38]

Whereas osteoporosis is unassociated with bone pain, osteomalacia has been associated with isolated or generalized bone pain.[39,40] The cause is thought to be hydration of the demineralized gelatin matrix beneath the periosteum; the hydrated matrix pushes outward on the periosteum, causing throbbing, aching pain.[7] Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain.[7,40] One study showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D.[41]

OSTEOPOROSIS AND FRACTURE

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis.[16,20] It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime. Chapuy et al.[21] reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D_3 daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%. A 58%

Figure 1 (facing page). Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism.

During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D_3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter "D" represents D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D–binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng per milliliter [50 to 250 nmol per liter], the preferred range is 30 to 60 ng per milliliter [75 to 150 nmol per liter].) This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to the biologically active form — 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (−) the renal production of 1,25(OH)$_2$D. 1,25(OH)$_2$D decreases its own synthesis through negative feedback and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. 1,25(OH)$_2$D increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)$_2$D to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. 1,25(OH)$_2$D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25(OH)$_2$D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-κB ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate calcium (Ca^{2+}) and phosphorus (HPO$_4{}^{2-}$) levels promote the mineralization of the skeleton.

reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D_3 and 500 mg of calcium per day.[42]

A meta-analysis of seven randomized clinical
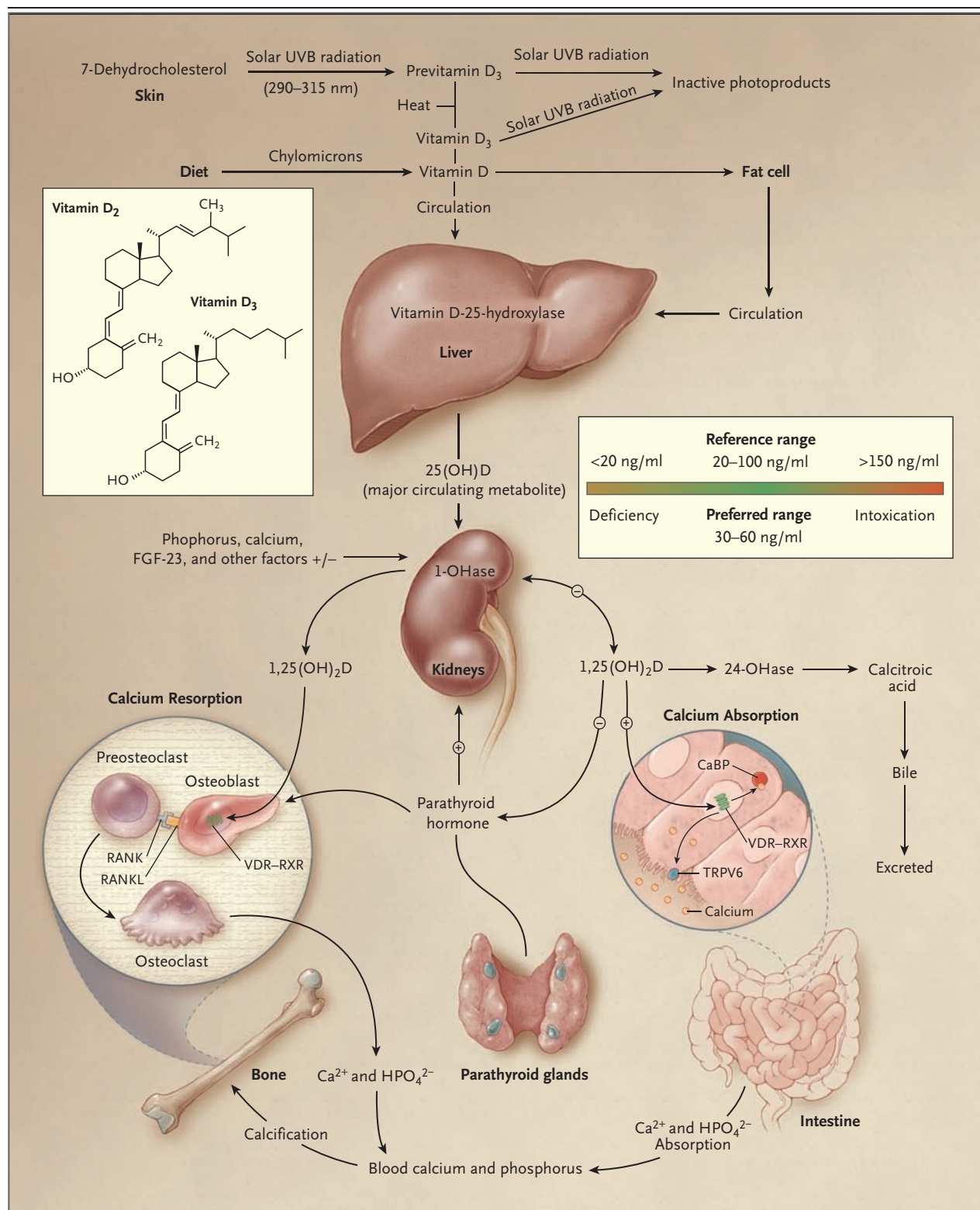
Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D$_2$ and D$_3$.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D$_3$
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D$_3$ or D$_2$
Canned (3.5 oz)	About 300–600 IU of vitamin D$_3$
Sardines, canned (3.5 oz)	About 300 IU of vitamin D$_3$
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D$_3$
Tuna, canned (3.6 oz)	About 230 IU of vitamin D$_3$
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D$_3$
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D$_2$
Sun-dried (3.5 oz)	About 1600 IU of vitamin D$_2$
Egg yolk	About 20 IU of vitamin D$_3$ or D$_2$
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D$_3$
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D$_3$
Fortified orange juice	About 100 IU/8 oz vitamin D$_3$
Infant formulas	About 100 IU/8 oz vitamin D$_3$
Fortified yogurts	About 100 IU/8 oz, usually vitamin D$_3$
Fortified butter	About 50 IU/3.5 oz, usually vitamin D$_3$
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D$_3$
Fortified cheeses	About 100 IU/3 oz, usually vitamin D$_3$
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D$_3$
Supplements	
Prescription	
Vitamin D$_2$ (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D$_2$) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D$_2$, or D$_3$‡
Vitamin D$_3$	400, 800, 1000, and 2000 IU

* IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.
† About 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.
‡ When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D$_2$; cholecalciferol or vitamin D$_3$ indicates that the product contains vitamin D$_3$.

trials that evaluated the risk of fracture in older persons given 400 IU of vitamin D$_3$ per day revealed little benefit with respect to the risk of either nonvertebral or hip fractures (pooled relative risk of hip fracture, 1.15; 95% confidence interval [CI], 0.88 to 1.50; pooled relative risk of nonvertebral fracture, 1.03; 95% CI, 0.86 to 1.24). In studies using doses of 700 to 800 IU of vitamin D$_3$ per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D$_3$ as compared with calcium or placebo.[8] A Women's Health Initiative study that compared the effects of 400 IU of vitamin D$_3$ plus 1000 mg of calcium per day with placebo in more than 36,000 postmenopausal women confirmed these results, reporting an increased risk of kidney stones but no benefit with respect to the risk of hip fracture.

The Women's Health Initiative study also showed that serum levels of 25-hydroxyvitamin D had little effect on the risk of fracture when levels were 26 ng per milliliter (65 nmol per liter) or less. However, women who were most consistent in taking calcium and vitamin D$_3$ had a 29% reduction in hip fracture.[43] Optimal prevention of both nonvertebral and hip fracture occurred only in trials providing 700 to 800 IU of vitamin D$_3$ per day in patients whose baseline concentration of 25-hydroxyvitamin D was less than 17 ng per milliliter (42 nmol per liter) and whose mean concentration of 25-hydroxyvitamin D then rose to approximately 40 ng per milliliter.[8]

Evaluation of the exclusive use of calcium or vitamin D$_3$ (RECORD trial) showed no antifracture efficacy for patients receiving 800 IU of vitamin D$_3$ per day.[44] However, the mean concentration of 25-hydroxyvitamin D increased from 15.2 ng per milliliter to just 24.8 ng per milliliter (37.9 to 61.9 nmol per liter), which was below the threshold thought to provide antifracture efficacy.[8] Porthouse and colleagues,[45] who evaluated the effect of 800 IU of vitamin D$_3$ per day on fracture prevention, did not report concentrations of 25-hydroxyvitamin D. Their study had an open design in which participants could have been ingesting an adequate amount of calcium and vitamin D separate from the intervention. This called into question the conclusion that vitamin D supplementation had no antifracture benefit.[8]

MUSCLE STRENGTH AND FALLS

Vitamin D deficiency causes muscle weakness.[1,7,8,28] Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.[1,8]

Performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels increased from 4 to 16 ng per milliliter (10 to 40 nmol per liter) and continued to improve as the levels increased to more than 40 ng per milliliter (100 nmol per liter).[8] A meta-analysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.[8] The same meta-analysis examined the frequency of falls and suggested that 400 IU of vitamin D_3 per day was not effective in preventing falls, whereas 800 IU of vitamin D_3 per day plus calcium reduced the risk of falls (corrected pooled odds ratio, 0.65; 95% CI, 0.4 to 1.0).[8] In a randomized controlled trial conducted over a 5-month period, nursing home residents receiving 800 IU of vitamin D_2 per day plus calcium had a 72% reduction in the risk of falls as compared with the placebo group (adjusted rate ratio, 0.28%; 95% CI, 0.11 to 0.75).[46]

NONSKELETAL ACTIONS OF VITAMIN D

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D.[1-4,6] In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase.[1-3,6]

Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.[1,2,47] It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.[1-3,6,47] One practical application is the use of 1,25-dihydroxyvitamin D_3 and its active analogues for the treatment of psoriasis.[48,49]

1,25-Dihydroxyvitamin D is also a potent immunomodulator.[2-4,6,50] Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the vitamin D receptor gene and the 25-hydroxyvitamin D-1α-hydroxylase gene. Increased production of 1,25-dihydroxyvitamin D_3 result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25-hydroxyvitamin D fall below 20 ng per milliliter (50 nmol per liter), the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D–deficient, are more prone to contracting tuberculosis than are whites, and tend to have a more aggressive form of the disease.[51] 1,25-dihydroxyvitamin D_3 inhibits renin synthesis,[52] increases insulin production,[53] and increases myocardial contractility (Fig. 2).[54]

LATITUDE, VITAMIN D DEFICIENCY, AND CHRONIC DISEASES

CANCER

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.[55-65] Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.[56,59-61,64] An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25-hydroxyvitamin D (the odds ratio at 16.2 ng per milliliter [40.4 nmol per liter] was 1.0, and the odds ratio at 39.9 ng per milliliter [99.6 nmol per liter] was 0.53; P≤0.01). Serum 1,25-dihydroxyvitamin D levels were not associated with colorectal cancer.[61] A prospective study of vitamin D intake and the risk of colorectal cancer in 1954 men showed a direct relationship (with a relative risk of 1.0 when vitamin D intake was 6 to 94 IU per day and a relative risk of 0.53 when the intake was 233 to 652 IU per day, P<0.05).[56] Participants in the Women's Health Initiative who at baseline had a 25-hydroxyvitamin D concentration of less than 12 ng per milliliter (30 nmol per liter) had a 253% increase in the risk of colorectal cancer over a follow-up period of 8 years.[62] In a study
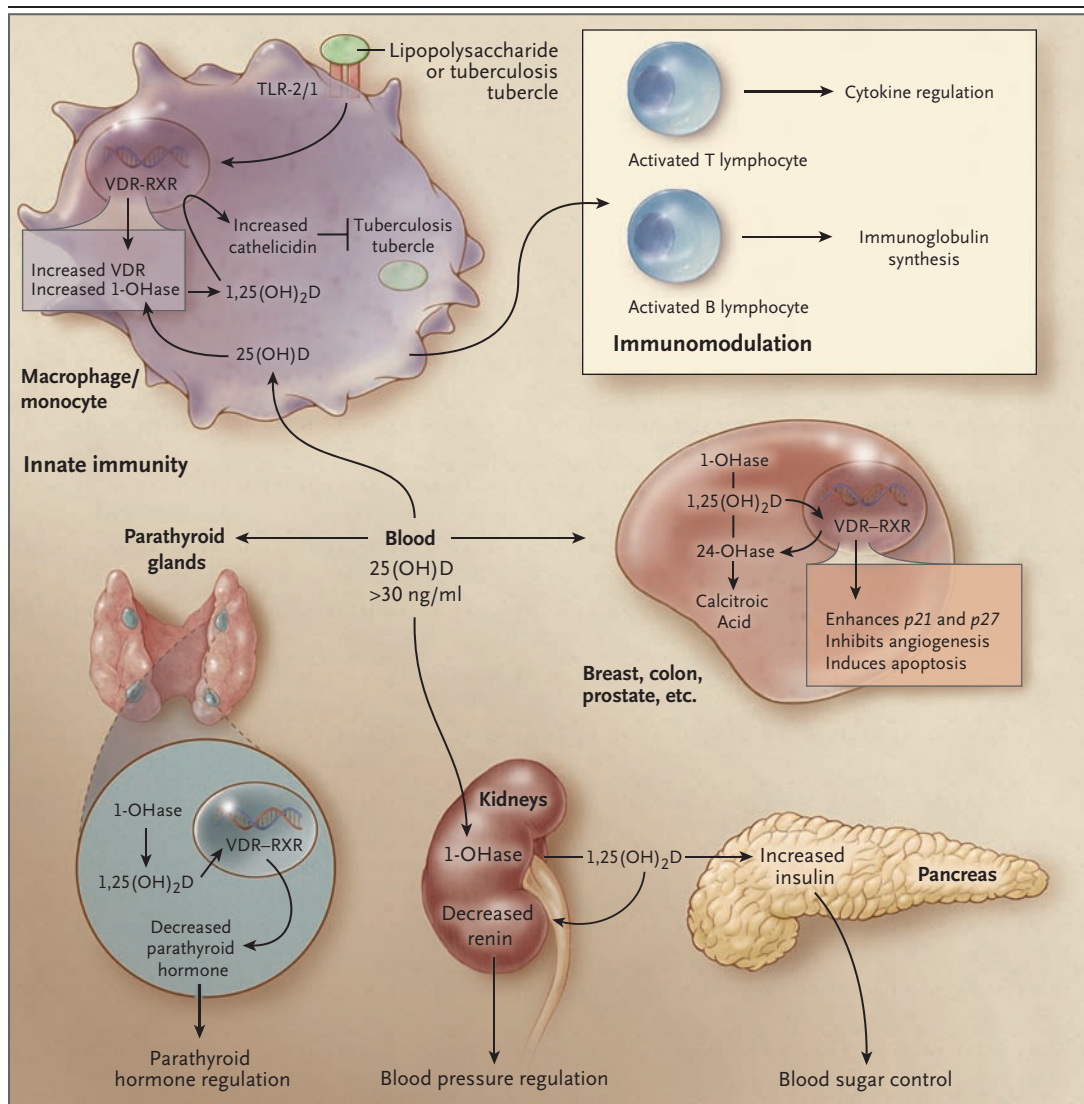
Figure 2. Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions.

When a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or its lipopolysaccharide, the signal up-regulates the expression of vitamin D receptor (VDR) and 25-hydroxyvitamin D-1α-hydroxylase (1-OHase). A 25-hydroxyvitamin D [25(OH)D] level of 30 ng per milliliter (75 nmol per liter) or higher provides adequate substrate for 1-OHase to convert 25(OH)D to its active form, 1,25 dihydroxyvitamin D [1,25(OH)$_2$D]. 1,25(OH)$_2$D travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*. It is also likely that the 1,25(OH)$_2$D produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng per milliliter, the risk of many common cancers is reduced. It is believed that the local production of 1,25(OH)$_2$D in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including *p21* and *p27,* as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once 1,25(OH)$_2$D completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (24-OHase), which enhances the catabolism of 1,25(OH)$_2$D to the biologically inert calcitroic acid. Thus, locally produced 1,25(OH)$_2$D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of 1,25(OH)$_2$D inhibits the expression and synthesis of parathyroid hormone. The 1,25(OH)$_2$D produced in the kidney enters the circulation and can down-regulate renin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas.

of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors.[63] Pooled data for 980 women showed that the highest vitamin D intake, as compared with the lowest, correlated with a 50% lower risk of breast cancer.[64] Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma[65] and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.[66]

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.[1-3] Furthermore, in a vitamin D–insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated.[1,3,6,7] The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1α-hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check.[1-3,47,56,58] It has been suggested that if a cell becomes malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.[2,3,7,67] Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the *CYP24* gene to produce the inactive calcitroic acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism (Fig. 1).[1-4] This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.[56-65]

AUTOIMMUNE DISEASES, OSTEOARTHRITIS, AND DIABETES

Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crohn's disease.[68,69] Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.[69,70] Among white men and women, the risk of multiple sclerosis decreased by 41% for every increase of 20 ng per milliliter in 25-hydroxyvitamin D above approximately 24 ng per milliliter (60 nmol per liter) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; P=0.04).[71] Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multi-

ple sclerosis.[72] Similar observations have been made for rheumatoid arthritis[73] and osteoarthritis.[74]

Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.[53] For 10,366 children in Finland who were given 2000 IU of vitamin D_3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89).[75] Among children with vitamin D deficiency the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.[53] Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.[76]

CARDIOVASCULAR DISEASE

Living at higher latitudes increases the risk of hypertension and cardiovascular disease.[54,77] In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).[78] Vitamin D deficiency is associated with congestive heart failure[54] and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.[54,79]

VITAMIN D DEFICIENCY AND OTHER DISORDERS

SCHIZOPHRENIA AND DEPRESSION

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression.[80,81] Maintaining vitamin D sufficiency in utero and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.[82]

LUNG FUNCTION AND WHEEZING ILLNESSES

Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 nmol per liter) had

Table 2. Causes of Vitamin D Deficiency.*

Cause	Effect
Reduced skin synthesis	
Sunscreen use — absorption of UVB radiation by sunscreen[1-3,7,85]	Reduces vitamin D_3 synthesis — SPF 8 by 92.5%, SPF 15 by 99%
Skin pigment — absorption of UVB radiation by melanin[1-3,7,85]	Reduces vitamin D_3 synthesis by as much as 99%
Aging — reduction of 7-dehydrocholesterol in the skin[2,7,85]	Reduces vitamin D_3 synthesis by about 75% in a 70-year-old
Season, latitude, and time of day — number of solar UVB photons reaching the earth depending on zenith angle of the sun (the more oblique the angle, the fewer UVB photons reach the earth)[1-3,85]	Above about 35 degrees north latitude (Atlanta), little or no vitamin D_3 can be produced from November to February
Patients with skin grafts for burns — marked reduction of 7-dehydrocholesterol in the skin	Decreases the amount of vitamin D_3 the skin can produce
Decreased bioavailability	
Malabsorption — reduction in fat absorption, resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption, and other causes[86,87]	Impairs the body's ability to absorb vitamin D
Obesity — sequestration of vitamin D in body fat†	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications — binding to the steroid and xenobiotic receptor or the pregnane X receptor[1-3,7,88]	Activates the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive calcitroic acid
Breast-feeding	
Poor vitamin D content in human milk[1,33,89]	Increases infant risk of vitamin D deficiency when breast milk is sole source of nutrition
Decreased synthesis of 25-hydroxyvitamin D	
Liver failure	
Mild-to-moderate dysfunction	Causes malabsorption of vitamin D, but production of 25-hydroxyvitamin D is possible[2,3,6,7,90]
Dysfunction of 90% or more	Results in inability to make sufficient 25-hydroxyvitamin D
Increased urinary loss of 25-hydroxyvitamin D	
Nephrotic syndrome — loss of 25-hydroxyvitamin D bound to vitamin D–binding protein in urine	Results in substantial loss of 25-hydroxyvitamin D to urine[2,3,6,91]
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease	
Stages 2 and 3 (estimated glomerular filtration rate, 31 to 89 ml/min/1.73 m²)	
Hyperphosphatemia increases fibroblast growth factor 23, which decreases 25-hydroxyvitamin D-1α-hydroxylase activity[5,6,91-94]	Causes decreased fractional excretion of phosphorus and decreased serum levels of 1,25-dihydroxyvitamin D
Stages 4 and 5 (estimated glomerular filtration rate <30 ml/min/1.73 m²)	
Inability to produce adequate amounts of 1,25-dihydroxyvitamin D[2,3,6,91-96]	Causes hypocalcemia, secondary hyperparathyroidism, and renal bone disease

a 176-ml increase in the forced expiratory volume in 1 second.[83] Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.[84]

CAUSES OF VITAMIN D DEFICIENCY

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of

Table 2. (Continued.)

Cause	Effect
Heritable disorders — rickets	
Pseudovitamin D deficiency rickets (vitamin D–dependent rickets type 1) — mutation of the renal 25-hydroxyvitamin D-1α-hydroxylase gene (CYP27B1)[1-3,97]	Causes reduced or no renal synthesis of 1,25-dihydroxyvitamin D
Vitamin D–resistant rickets (vitamin D–dependent rickets type 2) — mutation of the vitamin D receptor gene[1-3]	Causes partial or complete resistance to 1,25-dihydroxyvitamin D action, resulting in elevated levels of 1,25-dihydroxyvitamin D
Vitamin D–dependent rickets type 3 — overproduction of hormone-responsive-element binding proteins[98]	Prevents the action of 1,25-dihydroxyvitamin D in transcription, causing target-cell resistance and elevated levels of 1,25-dihydroxyvitamin D
Autosomal dominant hypophosphatemic rickets — mutation of the gene for fibroblast growth factor 23, preventing or reducing its breakdown[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
X-linked hypophosphatemic rickets — mutation of the PHEX gene, leading to elevated levels of fibroblast growth factor 23 and other phosphatonins[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Acquired disorders	
Tumor-induced osteomalacia — tumor secretion of fibroblast growth factor 23 and possibly other phosphatonins[1-3,5,6,92,99]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Primary hyperparathyroidism — increase in levels of parathyroid hormone, causing increased metabolism of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D[2,3,6]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels that are high-normal or elevated
Granulomatous disorders, sarcoidosis, tuberculosis, and other conditions, including some lymphomas — conversion by macrophages of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D[100]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels
Hyperthyroidism — enhanced metabolism of 25-hydroxyvitamin D	Reduces levels of 25-hydroxyvitamin D

* UVB denotes ultraviolet B, SPF sun protection factor, and HAART highly active antiretroviral therapy.
† There is an inverse relationship between the body-mass index and 25-hydroxyvitamin D levels.[2,7,85]

vitamin D metabolism and responsiveness.[2,3,6] Table 2 lists causes and effects of vitamin D deficiency.

VITAMIN D REQUIREMENTS AND TREATMENT STRATEGIES

CHILDREN AND ADULTS

Recommendations from the Institute of Medicine for adequate daily intake of vitamin D are 200 IU for children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for adults 71 years of age or older.[101] However, most experts agree that without adequate sun exposure, children and adults require approximately 800 to 1000 IU per day.[1-3,8,15,16,20,102,103] Children with vitamin D deficiency should be aggressively treated to prevent rickets (Table 3).[1,28,105-107] Since vitamin D_2 is approximately 30% as effective as vitamin D_3 in maintaining serum 25-hydroxyvitamin

D levels,[117,118] up to three times as much vitamin D_2 may be required to maintain sufficient levels. A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients a 50,000-IU capsule of vitamin D_2 once a week for 8 weeks, followed by 50,000 IU of vitamin D_2 every 2 to 4 weeks thereafter (Table 3).[2,7,9] Alternatively, either 1000 IU of vitamin D_3 per day (available in most pharmacies) or 3000 IU of vitamin D_2 per day is effective.[2,7,102,103] Strategies such as having patients take 100,000 IU of vitamin D_3 once every 3 months have been shown to be effective in maintaining 25-hydroxyvitamin D levels at 20 ng per milliliter or higher and are also effective in reducing the risk of fracture.[119]

BREAST-FED INFANTS AND CHILDREN

Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D–deficient provide even less to their breast-

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,109,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D,[2,3,86,87] inadequate sun exposure[2,3,6,7] or supplementation[2,3,6,7])	Adequate exposure to sun or ultraviolet radiation,[7,113] 50,000 IU of vitamin D_2 every day, every other day, or every wk,† up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU of vitamin D_2 every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp),[111-114] 50,000 IU of vitamin D_2 every day or every other day‡
Drugs that activate steroid and xenobiotic receptor,[88] and drugs used in transplantation[116]	50,000 IU of vitamin D_2 every other day or every week, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every 2 wk for 8–10 wk, or every wk if 25-hydroxyvitamin D <30 ng/ml‡
Obesity[2,7]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 1 or 2 wk, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every wk for 8–12 wk; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Nephrotic syndrome[2,3,6,7,91-94]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 once or twice/wk,[2,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[2]‡	50,000 IU of vitamin D_2 twice/wk for 8–12 wk[2,94]; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate,[6] 1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk,[91,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D_2 once/wk for 8 wk[91,94]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D_3/day,[51] 50,000 IU of vitamin D_2 every 2 wk, need to treat with 1,25-dihydroxyvitamin D_3 or active analogue‡	0.25–1.0 µg of 1,25-dihydroxyvitamin D_3 (calcitriol)[2,6,91,93,94] by mouth twice a day or one of the following: 1–2 µg of paricalcitriol IV every 3 days,[6,91,93,94] 0.04–0.1 µg/kg IV every other day initially and can increase to 0.24 µg/kg, 2–4 µg by mouth three times/wk,[6,91,93,94] or doxecalciferol[6,91,93,94] 10–20 µg by mouth three times/wk or 2–6 µg IV three times/wk

Table 3. (Continued.)

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Adults		
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk (serum calcium levels will not increase),[115] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk‡	50,000 IU of vitamin D_2 once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Granulomatous disorders and some lymphomas	400 IU of vitamin D_3/day, maintenance dose is 50,000 IU of vitamin D_2/mo‡	50,000 IU vitamin D_2 once a wk for 4 wk or every 2 to 4 wk, need to keep 25-hydroxyvitamin D between 20 and 30 ng/ml (level above 30 ng/ml can result in hypercalciuria and hypercalcemia)‡

* These recommendations are based on published literature and the author's personal experience. IV denotes intravenously. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.
† For the specific mechanism of deficiency, see Table 2.
‡ The goal is to achieve concentrations of 25-hydroxyvitamin D at about 30 to 60 ng per milliliter. Physicians should use these guidelines in combination with their clinical judgment according to the circumstances.
§ In stages 2 and 3 of chronic kidney disease, the estimated glomerular filtration rate is 31 to 89 ml per minute per 1.73 m^2; in stages 4 and 5, the estimated rate is <30 ml per minute per 1.73 m^2.

fed infants.[33,89] Lactating women given 4000 IU of vitamin D_3 per day not only had an increase in the level of 25-hydroxyvitamin D to more than 30 ng per milliliter but were also able to transfer enough vitamin D_3 into their milk to satisfy an infant's requirement.[89]

In Canada, to prevent vitamin D deficiency, current guidelines recommend that all infants and children receive 400 IU of vitamin D_3 per day (Table 3).[104]

PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with any stage of chronic kidney disease, 25-hydroxyvitamin D should be measured annually, and the level should be maintained at 30 ng per milliliter or higher, as recommended in the Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation.[6,91,93,94] It is a misconception to assume that patients taking an active vitamin D analogue have sufficient vitamin D; many do not. Levels of 25-hydroxyvitamin D are inversely associated with parathyroid hormone levels, regardless of the degree of chronic renal failure.[2,6,93-96] Parathyroid glands convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which directly inhibits parathyroid hormone expression.[6,93-96,120] Patients with stage 4 or 5 chronic kidney disease and an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, as well as those requiring dialysis, are unable to make enough 1,25-dihydroxyvitamin D and need to take 1,25-dihy-droxyvitamin D_3 or one of its less calcemic analogues to maintain calcium metabolism and to decrease parathyroid hormone levels and the risk of renal bone disease (Table 3).[6,91,93,94]

MALABSORPTION AND MEDICATION

Patients with mild or moderate hepatic failure or intestinal fat-malabsorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that activate steroid and xenobiotic receptor, require higher doses of vitamin D (Table 3).[7,88] Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B–emitting device is also effective.[7,113,115]

SUNLIGHT AND ARTIFICIAL ULTRAVIOLET B RADIATION

Sensible sun exposure can provide an adequate amount of vitamin D_3, which is stored in body fat and released during the winter, when vitamin D_3 cannot be produced.[7,15,85,108-110] Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.[2,7,108-110] Exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20,000 IU of vitamin D_2.[1,2,7,85] The skin has a great capacity to make vitamin D_3, even in the elderly, to reduce the risk of fracture.[109-111] Most tanning beds

emit 2 to 6% ultraviolet B radiation and are a recommended source of vitamin D_3 when used in moderation.[111-113,115] Tanners had robust levels of 25-hydroxyvitamin D (approximately 45 ng per milliliter [112 nmol per liter]) at the end of the winter and higher bone density as compared with nontanners (with levels of approximately 18 ng per milliliter [45 nmol per liter]).[112] For patients with fat malabsorption, exposure to a tanning bed for 30 to 50% of the time recommended for tanning (with sunscreen on the face) is an excellent means of treating and preventing vitamin D deficiency (Table 3).[113] This reduces the risk of skin cancers associated with ultraviolet B radiation.

VITAMIN D INTOXICATION

Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.[1-3,27,121,122] Doses of 10,000 IU of vitamin D_3 per day for up to 5 months, however, do not cause toxicity.[27] Patients with chronic granulomatous disorders are more sensitive to serum 25-hydroxyvitamin D levels above 30 ng per milliliter because of macrophage production of 1,25-dihydroxyvitamin D, which causes hypercalciuria and hypercalcemia.[1-3,100] In these patients, however, 25-hydroxyvitamin D levels need to be maintained at approximately 20 to 30 ng per milliliter to prevent vitamin D deficiency and secondary hyperparathyroidism (Table 3).[1-3,100]

CONCLUSIONS

Undiagnosed vitamin D deficiency is not uncommon,[1-3,6-20,123] and 25-hydroxyvitamin D is the barometer for vitamin D status. Serum 25-hydroxyvitamin D is not only a predictor of bone health[8] but is also an independent predictor of risk for cancer and other chronic diseases.[8,54,59-64,71-75,83-85]

The report that postmenopausal women who increased their vitamin D intake by 1100 IU of vitamin D_3 reduced their relative risk of cancer by 60 to 77% is a compelling reason to be vitamin D–sufficient.[124] Most commercial assays for 25-hydroxyvitamin D are good for detecting vitamin D deficiency. Radioimmunoassays measure total 25-hydroxyvitamin D, which includes levels of both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3. Some commercial laboratories measure 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 with liquid chromatography and tandem mass spectroscopy and report the values separately. As long as the combined total is 30 ng per milliliter or more, the patient has sufficient vitamin D.[7,14,27] The 1,25-dihydroxyvitamin D assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism. Because the 25-hydroxyvitamin D assay is costly and may not always be available, providing children and adults with approximately at least 800 IU of vitamin D_3 per day or its equivalent should guarantee vitamin D sufficiency unless there are mitigating circumstances (Table 2).

Much evidence suggests that the recommended adequate intakes are actually inadequate and need to be increased to at least 800 IU of vitamin D_3 per day. Unless a person eats oily fish frequently, it is very difficult to obtain that much vitamin D_3 on a daily basis from dietary sources. Excessive exposure to sunlight, especially sunlight that causes sunburn, will increase the risk of skin cancer.[125,126] Thus, sensible sun exposure (or ultraviolet B irradiation) and the use of supplements are needed to fulfill the body's vitamin D requirement.

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The Vitamin D Deficiency Pandemic:
a Forgotten Hormone Important for Health

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ABSTRACT

Early in the twentieth century more than 80 percent of children in industrialized Europe and North America were ravaged by the devastating skeletal consequences of rickets. Finding that exposure to ultraviolet radiation or sunlight treated and prevented rickets led to the ultraviolet irradiation of foods including milk. These practices along with the fortification of a variety of foods including dairy products with vitamin D and widespread use of cod liver oil eradicated rickets as a significant health problem by the late 1930s. Many countries mandated the fortification of milk with vitamin D to prevent rickets during wartime shortages. In the 1950s, in Europe, many countries forbid fortification of dairy and food products except breakfast cereals and margarine because of an outbreak of vitamin D intoxication in neonates.

Vitamin D deficiency has again become a major public health interest with its association with osteoporosis, osteomalacia, fractures, and more recently with prevention of cancer, diabetes, heart disease and other chronic illnesses. Regular sun exposure has decreased due to changing lifestyles. Vitamin D deficiency is especially prevalent in dark skinned children and adults living in Northern latitudes, and obese children and adults. Improving the vitamin D status worldwide would have dramatic effects on public health, and reduce healthcare costs for many chronic diseases. The most cost-effective way to remedy this deficiency is to increase food fortification with higher levels of vitamin D along with sensible sun exposure, and adequate vitamin D supplementation. I review the pathophysiology of vitamin D deficiency and its health consequences and provide recommendations for a new policy approach to this vital public health issue.

Key Words: vitamin D deficiency, micronutrient deficiency conditions, pandemic, global health, 25-hydroxyvitamin D, osteoporosis, rickets

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INTRODUCTION: HISTORICAL PERSPECTIVE

At the early part of the 20th century, rickets remained one of the most devastating health consequences of the Industrial Revolution.[1,2] It was estimated that more than 90 percent of children in Northern Europe and 80 percent of children in Boston and New York City showed evidence of this bone deforming disease. As early as 1822 Sniadecki identified the importance of sun exposure for preventing growth retardation and skeletal deformities associated with rickets noting that children living in the inner city of Warsaw had a high incidence of rickets whereas children living in adjacent rural areas did not.[3] This was followed by the insightful observations in 1889 by Palm that children living in London and Glasgow were plagued with rickets while children who lived in squalor in Asia and India were free of the disease.[1] He recommended that children from the inner cities should be exposed to sunlight and encouraged sunbathing as a preventive and treatment strategy. However, the medical community found it inconceivable that skin exposure to sunlight could have any beneficial effect for bone health. In 1919, Huldschinsky exposed children to a mercury arc lamp and demonstrated radiologic healing of rickets.[4] He promoted the use of ultraviolet irradiation as an infallible cure for rickets. Pharmacies in the United States and Europe sold ultraviolet lamps to parents so that they could expose their children to the anthracitic ultraviolet radiation. In 1921, Hess and Unger exposed several children who had rickets to sunlight on the roof of a New York City hospital and demonstrated dramatic improvement in their rickets.[1]

Common folklore, especially in Scandinavian countries and on the coastline of Great Britain, had known that cod liver oil was effective in preventing and treating rickets. Studies conducted on rachitic rodents demonstrated that when they were irradiated with an ultraviolet lamp, the healing of rickets was similar to that of rachitic rodents that received cod liver oil, suggesting that the antirachitic factor was both a nutrient and a hormone. These observations prompted Steenbock to introduce the concept of irradiation of people and animals to induce antirachitic activity, and to then suggest the irradiation of food. He and his colleagues demonstrated that irradiating a wide variety of foods with ultraviolet radiation imparted antirachitic activity. This led them to irradiate milk with ultraviolet radiation as a simple way to prevent rickets in children. The practice of using ultraviolet radiation of milk was quickly implemented throughout the US, Canada and Europe as a means of preventing rickets in children.

In the 1920s, irradiation of yeast was found to promote antirachitic activity. Ergosterol was identified as the sterol in yeast that had antirachitic activity when irradiated; ergosterol was called provitamin D_2 and its

irradiation product, vitamin D_2. Ergosterol was added to milk, followed by ultraviolet irradiation to enhance the antirachitic activity of the milk. Windaus and colleagues developed an analog of ergosterol that had a side chain for cholesterol which had similar antirachitic activity as irradiated ergosterol. This new provitamin D was called 7-dehydrocholesterol and its resulting vitamin D was called vitamin D_3.[1,2]

Once vitamin D_2 was easily made from ergosterol, it was added to milk directly and replaced the irradiation process. Within a few years after this process of fortifying milk with vitamin D was implemented in the 1930s, rickets was eradicated as a health problem.[5] This was implemented in the 1930s along with widespread use of cod liver oil, within a few years, eradicating rickets as a public health problem.[4] Vitamin D fortification became so popular that it was added to custard, hotdogs and even beer in the US.

In the early 1950s, in Great Britain, an outbreak of hypercalcemia in infants was thought to be due to the over fortification of milk with vitamin D. Although this was never proven, the resulting hysteria about children becoming intoxicated with vitamin D from milk prompted Great Britain to ban vitamin D fortification of most foods, and all other European countries soon followed suit. Vitamin D fortification of margarine was eventually introduced in Europe as a way of preventing vitamin D deficiency in children and today many breakfast cereals are also fortified with vitamin D in most European countries. Finland and Sweden began to fortify their milk with vitamin D in the 1990s, but overall, fortification is not widely practiced in Europe.

BIOLOGIC FUNCTIONS OF VITAMIN D FOR BONE HEALTH

During exposure to sunlight, 7-dehydrocholesterol in the epidermis and dermis absorb ultraviolet B radiation resulting in the production of pre-vitamin D_3. Previtamin D_3 is rapidly converted by thermally induced rearrangement of the double bonds to form vitamin D_3. Vitamin D_3 enters the circulation and is bound to the vitamin D binding protein. It enters the liver where it is converted to 25-hydroxyvitamin D_3 [25(OH)D_3] (Figure 1).[6] Both vitamin D_2 and vitamin D_3 are converted to their respective 25-hydroxymetabolites, and are known collectively as total 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is the major circulating form of vitamin D that is measured by clinical laboratories to determine a patient's vitamin D status.[6] 25(OH)D is biologically inactive and is transported on the vitamin D binding protein to the kidneys where it is

converted to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] which is considered to be the biologically active form of vitamin D. It is responsible for regulating calcium and bone metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton (Figure 1).[6]
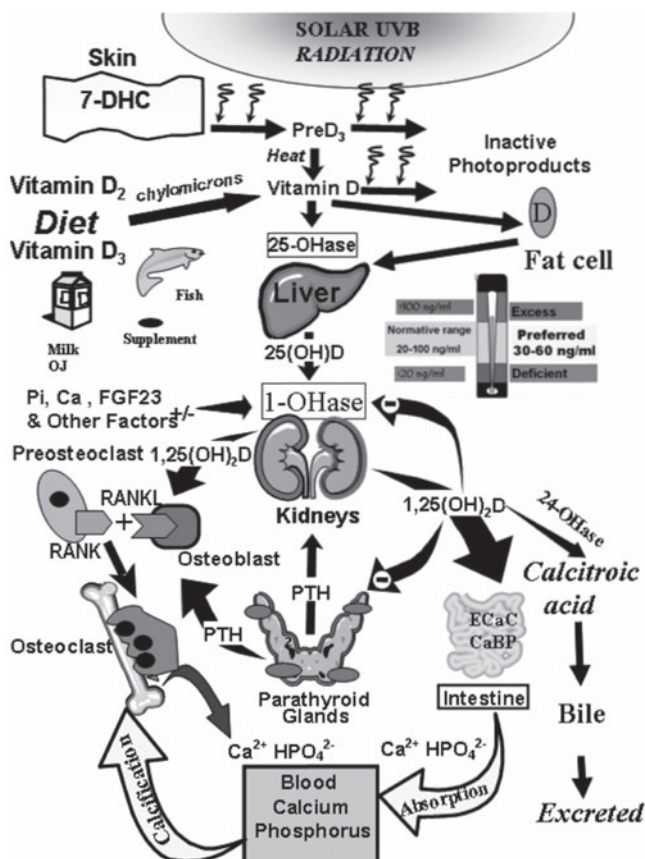
Fig. 1. Schematic representation of the synthesis and metabolism of vitamin D for regulating calcium, phosphorus and bone metabolism.

Note: During exposure to sunlight, 7-dehydrocholesterol in the skin is converted to previtamin D$_3$. PreD$_3$ immediately converts by a heat dependent process to vitamin D$_3$. Excessive exposure to sunlight degrades previtamin D$_3$ and vitamin D$_3$ into inactive photoproducts. Vitamin D$_2$ and vitamin D$_3$ from dietary sources is incorporated into chylomicrons, transported by the lymphatic system into the venous circulation. Vitamin D (D represents D$_2$ or D$_3$) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D binding protein which transports it to the liver where vitamin D is converted by the vitamin D-25-hydroxylase to

25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to measure vitamin D status (although most reference laboratories report the normal range to be 20-100 ng/ml, the preferred healthful range is 30-60 ng/ml). It is biologically inactive and must be converted in the kidneys by the 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to its biologically active form 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. Serum phosphorus, calcium fibroblast growth factors (FGF-23) and other factors can either increase (+) or decrease (-) the renal production of 1,25(OH)$_2$D. 1,25(OH)$_2$D feedback regulates its own synthesis and decreases the synthesis and secretion of parathyroid hormone (PTH) in the parathyroid glands. 1,25(OH)$_2$D increases the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)$_2$D to the water soluble biologically inactive calcitroic acid which is excreted in the bile. 1,25(OH)$_2$D enhances intestinal calcium absorption in the small intestine by stimulating the expression of the epithelial calcium channel (ECaC) and the calbindin 9K (calcium binding protein; CaBP). 1,25(OH)$_2$D is recognized by its receptor in osteoblasts causing an increase in the expression of receptor activator of NFκB ligand (RANKL). Its receptor RANK on the preosteoclast binds RANKL which induces the preosteoclast to become a mature osteoclast. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. Adequate calcium and phosphorus levels promote the mineralization of the skeleton.[6]

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Patients who are vitamin D deficient absorb only about 10 to 15 percent of their dietary calcium and 60 percent of their dietary phosphorus. When vitamin D deficiency is corrected, intestinal calcium absorption increases to about 30-40 percent and phosphorus absorption is increased to about 80 percent. Vitamin D's major function for bone health, therefore, is to maintain an adequate calcium-phosphorus product which results in the mineralization of osteoid laid down by osteoblasts.

CONSEQUENCES OF VITAMIN D DEFICIENCY ON CALCIUM AND BONE METABOLISM

Vitamin D deficiency causes a decrease in the efficiency of intestinal calcium absorption and results in a decrease in ionized calcium. The calcium sensor in the parathyroid glands immediately recognizes the decrease causing the parathyroid glands to increase the production and secretion of parathyroid hormone (PTH) (Figure 1).[6,7] PTH maintains serum calcium levels by increasing tubular reabsorption of calcium in the kidneys. Through its receptor on osteoblasts, PTH stimulates the formation of osteoclasts, which in turn dissolves the bone matrix and mineral to release the calcium into the extracellular space (Figure 1).[6] This process, known as secondary hyperparathyroidism, can precipitate and exacerbate both osteopenia and osteoporosis, increasing risk of fracture.[6,8] PTH also causes phosphorus loss in the urine resulting in a low-normal serum phosphorus level.

The net result is in an inadequate calcium-phosphate product necessary for the mineralization of the collagen matrix leading to osteomalacia.[1,6] In children, poorly mineralized matrix and abnormal chondrocyte maturation leads to the classic skeletal deformities of rickets including the inward or outward bowing of the legs, widened epiphyseal plates at the end of the long bones and costochondral junctions, frontal bossing of the skull, craniotabes and a delay in tooth eruption.[1,2] In adults, there is enough mineral in the long bones and the epiphyseal plates are closed; thus, there are no obvious skeletal deformities. However, the unmineralized matrix underneath the periosteal membrane that is heavily innervated with sensory fibers is hydrated and pushed upwards, often being perceived by the patient as throbbing aching bone pain. These patients are often misdiagnosed as having fibromyalgia, chronic fatigue syndrome or arthritis. Neither a skeletal x-ray nor a bone density scan can distinguish between osteomalacia, osteopenia and osteoporosis. They look the same i.e., decreased bone mineral (calcium) content that can increase risk of fractures.[6,8]

NON-CALCEMIC FUNCTIONS OF VITAMIN D

The association of living at upper (and lower) latitudes (i.e., above or below the 35th parallels of latitude) with increased risk of dying from cancer, type 1 diabetes, multiple sclerosis and hypertension is well documented.[6,8,9] It has been assumed that living beyond the temperate zone at higher latitudes increases risk of vitamin D deficiency because of decreased sun exposure on account of longer winters and the angle of sun, which is such that there is decreased ultraviolet B radiation. It is also recognized that every tissue and cell in the body including immune, brain, colon, prostate, and breast cells, among many others, have a vitamin D receptor (VDR).[6-10] Studies have revealed that upwards of 2000 genes are either directly or indirectly regulated by $1,25(OH)_2D$.[6,11] Initially, it was thought that increasing your vitamin D intake or exposure to sunlight raised your blood levels of $25(OH)D$, which resulted in increased blood levels of $1,25(OH)_2D$, which in turn could interact with a wide variety of genes in a multitude of cells and organs to maintain cells and organ health, thereby reducing risk of chronic diseases. However, the conundrum was that the kidneys only produced a finite amount of $1,25(OH)_2D$ that was tightly regulated by the serum calcium, phosphorus and PTH levels in the circulation. The realization that many tissues and cells in the body including among others the skin, breast, prostate, brain, and activated macrophages have an enzymatic process that is identical to the kidneys converting $25(OH)D$ to $1,25(OH)_2D$, provided a

new insight as to how vitamin D could have all of the other health benefits not related to calcium and bone metabolism Figure 2.[6,12]
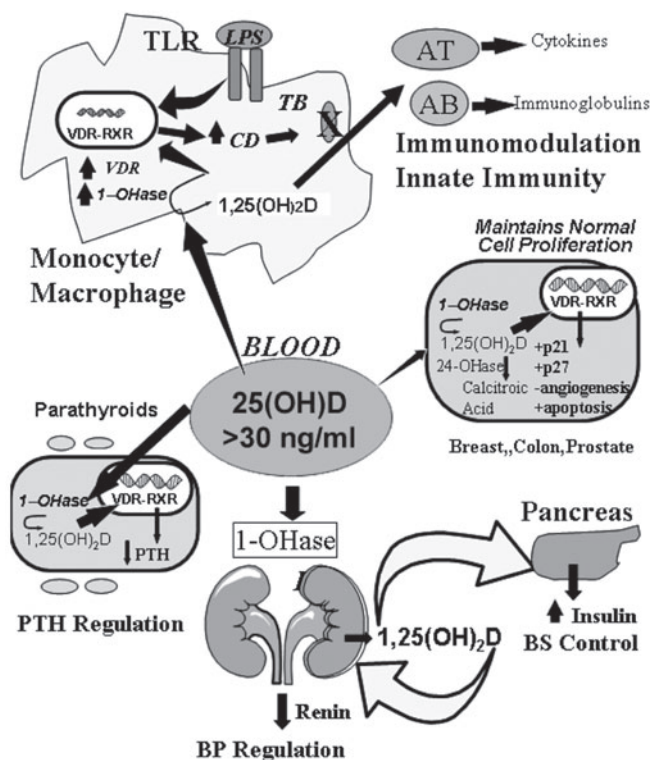
Fig. 2. Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxyvitamin D 1,25(OH)$_2$D for non-skeletal functions.

Note: When a monocyte/macrophage is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infective agent such as *Mycobacterium tuberculosis* (TB), or its lipopolysaccharide (LPS) the signal upregulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase). 25(OH)D levels > 30 ng/ml provides adequate substrate for the 1-OHase to convert it to 1,25(OH)$_2$D. 1,25(OH)$_2$D returns to the nucleus where it increases the expression of cathelicidin (CD) which is a peptide capable of promoting innate immunity and inducing the destruction of infective agents such as TB. It is also likely that the 1,25(OH)$_2$D produced in the monocytes/macrophage is released to act locally on activated T (AT) and activated B (AB) lymphocytes which regulate cytokine and immunoglobulin synthesis respectively. When 25(OH)D levels are $\approx$ 30 ng/ml, it reduces risk of many common cancers. It is believed that the local production of 1,25(OH)$_2$D in the breast, colon, prostate, and other cells regulates a variety of genes that control proliferation including p21 and p27 as well as genes that inhibit angiogenesis and induced apoptosis. Once 1,25(OH)$_2$D completes the task of maintaining normal cellular proliferation and differentiation,

it induces the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). The 24-OHase enhances the metabolism of 1,25(OH)$_2$D to calcitroic acid which is biologically inert. Thus, the local production of 1,25(OH)$_2$D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity and the local production of 1,25(OH)$_2$D inhibits the expression and synthesis of PTH. The production of 1,25(OH)$_2$D in the kidney enters the circulation and is able to down regulate renin production in the kidney and to stimulate insulin secretion in the β-islet cells of the pancreas.

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THE VITAMIN D DEFICIENCY PANDEMIC

In the 1940s, 100 IU of vitamin D/day was considered sufficient to prevent overt skeletal deformities associated with rickets.[6] Regulatory agencies in the US and Europe later increased the dose two-fold and recommended that 200 IU of vitamin D/day be required to satisfy the requirement for children. It was assumed that the same was true for adults. Since rickets is not commonly seen, physicians, regulatory and healthcare agencies and the general public concluded that vitamin D deficiency was conquered. In Canada, following the end of mandatory regulations after World War II, when routine vitamin D fortification of milk was stopped in many dairies, cases of rickets were reported as increased in admissions to Montreal hospitals, leading to reintroduction of mandatory milk fortification with vitamin D by federal regulation in 1979. In the 1950s, an outbreak of hypercalcemia in Great Britain was attributed to vitamin D intoxication and led to laws forbidding the fortification of dairy products and most food products with vitamin D, except cereals and margarine.

In the 1970s, clinical assays were developed for 25(OH)D in the serum. To determine the normal range for the assay, blood was collected from healthy adults who were presumed to be vitamin D sufficient and the mean ± two standard deviations was used as the normal range (10-55 ng/mL) at that time. In 1998, healthy adults with a blood level of 25(OH)D between 11 and 25 ng/mL were considered to be vitamin D sufficient. When they received 50,000 IU of vitamin D$_2$ weekly for eight weeks, there was a substantial decrease in their PTH levels. On average, there was a 35 percent decrease in PTH levels in the adults who had blood levels less than 20 ng/mL. Thus it was concluded that vitamin D deficiency should be defined as a 25(OH)D < 20 ng/mL.[13] It was also observed that PTH levels began to plateau when 25(OH)D levels were between 30 and 40 ng/mL.[14] Postmenopausal women who had their blood level of 25(OH)D increased from 20 to 30 ng/ml had a 65 percent increase on average in their efficiency of intestinal calcium absorption.[15] Based on all of these data, it has been

suggested that vitamin D deficiency be defined as 25(OH)D < 20 ng/mL and vitamin D insufficiency as 21-29 ng/mL (Figure 1).[6,8]

Based on the new definitions for vitamin D deficiency and insufficiency, it has been estimated that more than one billion people worldwide are either vitamin D deficient or insufficient.[6,8,9] A multitude of studies have reported that 50-100 percent of the elderly men and women in the US and Europe are vitamin D deficient.[6] Children, pregnant and lactating women, and young adults are at equally high risk. At the time of birth, 76 percent of mothers and 81 percent of newborns were vitamin D deficient even though the women were ingesting ~600 IU of vitamin D/day during pregnancy.[6] It has been estimated that more than 50 million teenagers in the US are either vitamin D deficient or insufficient.[16] Fifty percent of children ages 1 to 5 and 70 percent of children 6 to 11 years of age were found to be vitamin D deficient or insufficient in the US.[17] Thirty to more than 50 percent of children living in India, China and Saudi Arabia were vitamin D deficient.[6] Thirty-two percent of healthy physicians and medical residents at a Boston hospital who took a multivitamin containing 400 IU of vitamin D/day and drank a glass of vitamin D fortified milk/day were found to be vitamin D deficient. In Europe, very few foods are fortified with vitamin D and therefore both children and adults are at high risk for this vitamin deficiency. In the US, a 20 percent decline was reported in the serum 25(OH)D levels as measured by the national database NHANES III between 1994 and 2004. The major causes were obesity, lifestyle changes, decreased milk consumption and increased use of sun protection.[18]

Reports of Vitamin D deficiency from countries as diverse as Great Britain[19] Austria,[20] Germany,[21] Finland,[22] New Zealand[23] and India[24] indicate the scope of the pandemic. Even sunny Australia reports 30 to 50 percent of children and adults as being vitamin D deficient.[6] The age groups included in studies of these countries include young adults and the elderly with wide variation by country of residence.[25] Even where vitamin D fortification of milk has been in place for many decades, as in the US and Canada, there are still major deficiencies related to season, latitude of residence, age, gender and social conditions.[26] Adequate exposure to summer sunlight is the essential means to ample supply, but oral intake augmented by both fortification and supplementation is necessary to maintain baseline stores.

CONSEQUENCES OF VITAMIN D DEFICIENCY ON HEALTH

The skeletal consequences of vitamin D deficiency on bone health include osteoporosis and increased risk for fractures, especially of the hip, vertebrae

and forearm with serious impact on quality of life and survival.[6,8] What is less appreciated is that vitamin D deficiency causes muscle weakness, increasing risk of swaying and falling, thus further increasing risk of fracture in the frail elderly.[6,8]

Vitamin D deficiency has been associated with increased risk for cancer, including that of the breast, prostate, colon and ovaries.[6-10] Women who had a blood level of 25(OH)D ~ 48 ng/mL reduced their risk of developing breast cancer by 50 percent.[27] This is consistent with the observation that women who had the most sun exposure as teenagers and young adults reduced their risk of developing breast cancer later in life by more than 60 percent.[28] A retrospective analysis of postmenopausal women receiving 1500 mg of calcium and 1100 IU of vitamin D a day revealed a decrease of more than 60 percent in the development of all cancers compared to women who either took calcium without vitamin D or a placebo.[29] The International Agency for Research on Cancer 2008 review of evidence of vitamin D and cancer show evidence for an increased risk of colorectal cancer and colorectal adenoma with low serum 25-hydroxyvitamin D levels.[30]

Osteoporosis and vitamin D deficiency have also been linked with increased risk of many chronic diseases including: heart disease, type 2 diabetes, autoimmune and infectious diseases, asthma and other wheezing disorders. It is well documented that living at upper and lower latitudes increases risk for multiple sclerosis and type 1 diabetes. Women who had the highest blood levels of 25(OH)D had a 42 percent reduced risk of developing multiple sclerosis as compared to women with the lowest blood levels.[6,8] Similarly, women who had the highest intake of vitamin D reduced their risk of developing rheumatoid arthritis by more than 40 percent.[6] Children in Finland who received 2000 IU of vitamin D/day during their first year of life and followed for 31 years were found to have a 78 percent reduced risk of developing type 1 diabetes.[31]

Vitamin D deficiency has been associated with a 50 percent increased risk of having a myocardial infarction.[32] Hypertension, congestive heart failure and peripheral vascular disease have been associated with vitamin D deficiency.[6] Vascular smooth muscle, and cardiomyocytes have a vitamin D receptor, and it has been estimated that up to 200 genes related to cardiovascular health may be directly or indirectly influenced by $1,25(OH)_2D$. Furthermore, renin production is down-regulated by $1,25(OH)_2D$.[6]

Activated macrophages can convert 25(OH)D to $1,25(OH)_2D$. When the macrophage produces $1,25(OH)_2D$, it instructs the cell to produce cathelicidin which is a member of the defensin protein family whose purpose is to kill infective agents such as tuberculosis.[6,33] This led to the suggestion

that the reason why upper respiratory tract infections and influenza are most common during the winter is that that is the time when the 25(OH)D levels are at their lowest. It has been reported that adults in the United States with the highest blood levels of 25(OH)D had the lowest risk for developing upper respiratory tract infections compared to adults with the lowest blood levels.[34] A study in postmenopausal women who received 2000 IU of vitamin D/day indicated a risk of upper respiratory tract infections reduced by 90 percent in one year.[6]

People tend to reduce their sun exposure when given advice to avoid the sun to prevent risk of skin cancers. Adults work mainly indoors, and children and adolescents are spending increasing amounts of time indoors playing on computers instead of being out of doors. The use of sunscreens promoted by advertising such as the "slip slap slop" message in Australia has resulted in a marked increase in vitamin D deficiency in children and adults. Eighty seven percent of Australian dermatologists had a deficient blood level of 25(OH)D < 20 ng/mL at the end of the summer.[35]

PREVENTION AND TREATMENT FOR VITAMIN D DEFICIENCY AND INSUFFICIENCY

There have been two reports suggesting that vitamin D_2 is less effective than vitamin D_3 in maintaining vitamin D status, and that vitamin D_2 increases the destruction of $25(OH)D_3$. However, there are several other studies that have reported that vitamin D_2 is as effective as vitamin D_3 in maintaining vitamin D status in both children and adults.[6,36,37] In children, 2000 IU of vitamin D_2/day was as effective as giving 2000 IU of vitamin D_3/day in maintaining their serum 25(OH)D levels.[37] Healthy adults who received 1000 IU of vitamin D_2 or 1000 IU of vitamin D_3 or 500 IU of vitamin D_2 +500 IU of vitamin D_3 were able to raise their blood levels of 25(OH)D by 10 ng/mL.

It has been estimated that for every 100 IU of vitamin D/day that is taken, the blood level of 25(OH)D is increased by 1 ng/mL (2.5 nmol/L).[6,36] Healthy adults receiving 1000 IU of vitamin D a day for three months during the winter in Boston and who had an average serum 25(OH)D of 18 ng/mL raised their blood level to 28 ng/mL and thus did not achieve vitamin D sufficiency.[36] To treat vitamin D deficiency, pharmacologic doses of vitamin D are often required. A simple strategy is to fill up the empty vitamin D tank by giving 50,000 IU of vitamin D_2 once a week for eight weeks. This is equivalent to taking 6000 IU of vitamin D a day. However, to prevent a recurrence of vitamin D deficiency, an effective strategy is to

then give 50,000 IU of vitamin D_2 once every two weeks indefinitely. Recently, after keeping study subjects on this medical regimen for six years, it was reported that men and women were able to maintain a blood level of 25(OH)D > 30 ng/mL (range ~ 40-60 ng/mL).[38] The serum calcium remained normal throughout the study and no toxicities or increased incidences of kidney stones were reported.

There are now several reports of both children and adults receiving 2000 IU of vitamin D a day for up to a year with the result of maintaining their blood levels at 25(OH)D > 30 ng/mL. In one study, prepubertal and teenage girls who received 2000 IU of vitamin D_3 a day for one year showed improvement in bone mineral density.[39] It has been estimated that adults who received at least 800 IU of vitamin D a day can reduce their risk of fracture by more than 50 percent and risk of falling by as much as 72 percent.[40,41]

VITAMIN D TOXICITY

There has been great concern about increasing vitamin D intake for children and adults because of potential vitamin D toxicity which causes hypercalcemia, hyperphosphatemia, nephrocalcinosis, and soft tissue calcification, all of which can contribute to increased risk of death. Studies have shown that adults can take up to 10,000 IU of vitamin D a day for at least five months without altering their serum calcium or urinary calcium output.[42] One method for preventing rickets in neonates in the inner cities of Europe was to give a single 200,000 IU injection of vitamin D.[1,6] Studies in children and adults receiving 2000 IU of vitamin D a day have not reported any toxicity.

Vitamin D intoxication is one of the rarest medical conditions that may be caused either by intentional or inadvertent exposure to excessively high amounts of vitamin D attained by ingesting an average of more than 10,000 IU of vitamin D a day for more than six months. In one case report, a man took 2 teaspoons a day of a product thinking it contained 1000 IU of vitamin D per teaspoon for more than six months. When he presented with vitamin D intoxication, an analysis of his vitamin D preparation was made and found to be undiluted and containing 1 million IU of vitamin D in 2 teaspoons.[6]

CONCLUSION AND RECOMMENDATIONS

Vitamin D deficiency and insufficiency is pandemic and is seen in essentially every country in the world. There are many causes (Figure 3), but lack of

awareness of the importance of this deficiency is crucial in individual and public health. Oily fish, cod liver oil and mushrooms exposed to sunlight or ultraviolet radiation are the only natural sources. The need for fortifying basic foods with vitamin D is now ever more important since excess sun exposure, a major source of this vital hormone/nutrient, is related to skin cancers and lifestyle changes reduce outdoor exposure for children and many other age groups. Since very few foods are fortified with vitamin D and there is typically only 100 IU of vitamin D in a serving, natural foods provide only a small portion of what is required to satisfy either a child's or adult's vitamin D requirement. The worldwide concern about sun exposure and skin cancer has also exacerbated the problem.[6,8,35]
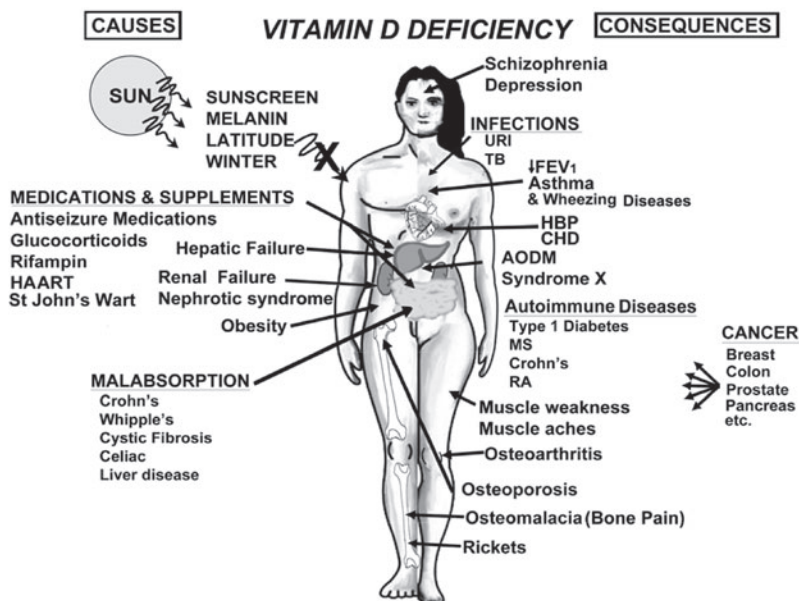
Fig. 2. A Schematic Representation of the Major Causes for Vitamin D Deficiency and Potential Health Consequences.

Source: Reference [6] Holick copyright 2007. Reproduced with permission.

The vitamin D deficiency pandemic increases the entire world's population risk of the most serious chronic illnesses including deadly cancers, type 2 diabetes, heart disease, stroke, autoimmune diseases, asthma and infectious diseases (Figure 3). There is no drawback to increasing your vitamin D intake unless you have a granulomatous disorder. Thus there

needs to be increased awareness on the part of the medical community and public about the insidious consequences of vitamin D deficiency.

In 2008, the American Academy of Pediatrics increased its recommended daily supplements recommendation from 200 to 400 IU/day for infants, children and adolescents.[43,44] Recommended daily intake for elderly adults was also increased to 1,000 IU/day. New recommendations continue to emerge, substantially increasing the adequate intakes for children and adults as well as what is considered to be the safe upper limit of intake. Recommendations for sensible daily sun exposure and adequate vitamin D supplementation are both in a state of flux. Food fortification policies are needed to assure a basic level of vitamin D intake. People in long-term care and custodial situations should be given daily supplements of vitamin D perhaps in the form of multivitamins to ensure adequacy of essential elements, especially vitamin D.

Public policies to ensure adequate vitamin D intake in public health nutrition are vital for all countries including the industrialized countries as well as former Soviet countries in transition and developing countries. Migrant population groups with dark skin migrating to northern latitudes and especially those who cover themselves for religious reasons are at high risk for vitamin D deficiency, as are their breastfed babies unless adequately supplemented with vitamin D. Teenagers and young adults are less exposed to the sun due to work and lifestyle changes. Precautions regarding overexposure to the sun are justified, but moderate sun exposure during midday is especially important for older adults.

Vitamin D deficiency is so widespread that a combination of food fortification for the total population and individual screening for people in groups at risk for this important deficiency is needed. Clinical testing and population surveys of 25(OH)D levels should be integral to population health monitoring. Awareness by the general public, healthcare providers and health insurance systems of the importance of vitamin D adequacy could have a dramatic impact on the health and welfare of all children and adults.

All countries in Europe and globally should mandate fortification of milk, (including milk formulas, powders and evaporated milk), soft milk products (yoghurts, cottage cheeses and others) as a key vehicle for prevention of deficiency of vitamin D, including in sunny countries. International agencies such as the World Health Organization, UNICEF and the major donors should promote fortification as an essential element of the New Public Health. Further, all health systems should incorporate routine clinical testing of 25(OH)D levels for those at risk and vitamin D supplementation as routine preventive measures among age groups as

discussed above. Recognition of the pandemic of vitamin D deficiency obliges governments to lead in regulation of mandatory fortification and monitoring of compliance by industry.

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ELSEVIER

Prevalence and correlates of vitamin D deficiency in US adults

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Abstract

Mounting evidence suggests that vitamin D deficiency could be linked to several chronic diseases, including cardiovascular disease and cancer. The purpose of this study was to examine the prevalence of vitamin D deficiency and its correlates to test the hypothesis that vitamin D deficiency was common in the US population, especially in certain minority groups. The National Health and Nutrition Examination Survey 2005 to 2006 data were analyzed for vitamin D levels in adult participants (N = 4495). Vitamin D deficiency was defined as a serum 25-hydroxyvitamin D concentrations ≤20 ng/mL (50 nmol/L). The overall prevalence rate of vitamin D deficiency was 41.6%, with the highest rate seen in blacks (82.1%), followed by Hispanics (69.2%). Vitamin D deficiency was significantly more common among those who had no college education, were obese, with a poor health status, hypertension, low high-density lipoprotein cholesterol level, or not consuming milk daily (all $P < .001$). Multivariate analyses showed that being from a non-white race, not college educated, obese, having low high-density lipoprotein cholesterol, poor health, and no daily milk consumption were all significantly, independently associated with vitamin D deficiency (all $P < .05$). In summary, vitamin D deficiency was common in the US population, especially among blacks and Hispanics. Given that vitamin D deficiency is linked to some of the important risk factors of leading causes of death in the United States, it is important that health professionals are aware of this connection and offer dietary and other intervention strategies to correct vitamin D deficiency, especially in minority groups.

1. Introduction

Vitamin D has been traditionally considered as important in skeletal health. However, during the past decade, numerous research findings have revealed that vitamin D produces beneficial effects on extraskeletal tissues as well [1-3]. Some evidence suggests that vitamin D helps to regulate cell growth and prevent cancer progression [4-6]. Epidemiological studies have reported that higher vitamin D levels were associated with reduced cancer incidence and decreased cancer-related mortality [7-9]. Vitamin D was found to be involved in controlling the production of renin, one of the most important hormones for regulating blood pressure [10]. Thus, Vitamin D deficiency might contribute to development and progression of hypertension and cardiovascular disease [11-14]. Furthermore, vitamin D deficiency has been linked to the development of type 1 diabetes [1-3,15], multiple sclerosis [16,17], rheumatoid arthritis [18], and other autoimmune conditions [1-3,19,20].

Vitamin D can be synthesized by the skin through exposure to ultraviolet light of wavelength 290 to 315 nm that stimulates the conversion of 7-dehydrocholesterol to

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previtamin D [21]. The other source of vitamin D is from the diet. Vitamin D from food undergoes hydroxylation in the liver to 25-hydroxyvitamin D—the major circulating form— and then in the kidney to 1,25-dihydroxyvitamin D, which optimizes calcium and phosphate absorption from the intestine, as well as having direct effects on bone cells [1,3]. The recommended adequate intake of vitamin D used to be 200 IU/d for all children and adults 50 years or younger, 400 IU/d for people aged 51 to 70 years, and 600 IU/d for those older than 70 years [22]. However, due to its beneficial effects, the amounts of vitamin D needed for optimal health are probably higher than previously thought [2,23]. On November 30, 2010, the Institute of Medicine released updated recommendations regarding vitamin D intake: 600 IU/d for people aged 1 to 70 years and 800 IU for people aged 71 and older [24].

Although vitamin D deficiency is commonly defined as a 25-hydroxyvitamin D level ≤20 ng/mL (50 nmol/L) [20,25], published studies have used different definitions for vitamin D deficiency. By different cutoff points, vitamin D deficiency was found to be common in certain subpopulations, including elder adults (41% using 25-hydroxyvitamin D level ≤20 ng/mL) [20], African Americans (61% using 25-hydroxyvitamin D level ≤15 ng/mL) [26], and women with osteoporosis (64% using 25-hydroxyvitamin D level ≤30 ng/mL [27]. Given that low vitamin D levels are linked to all major health problems in populations, such as cardiovascular disease, cancers, and diabetes, it is of importance to identify how prevalent this condition is and what factors are associated with this condition in the US population. This study analyzed the data from the 2005 to 2006 National Health and Nutrition Examination Survey (NHANES) to describe the epidemiology of vitamin D deficiency in US adults, including prevalence patterns of vitamin D deficiency and its correlates. Based on the findings from the literature, it was hypothesized that vitamin D deficiency was common in the US population, especially certain minority groups. The objective of this study was to examine and compare the prevalence rate of vitamin D deficiency by age, race, other demographic factors, as well as by certain health conditions, using serum 25-hydroxyvitamin D level, the best indicator of vitamin D status.

2. Methods and materials

2.1. Study population

The NHANES is an ongoing program conducted by the National Center for Health Statistics to assess the health and nutritional status in the noninstitutionalized US population and track changes over time [28]. The survey combines interviews and physical examinations. The interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical and physiologic measurements, as well as laboratory tests.

The NHANES uses a stratified multistage probability sampling design and constructs sample weights to produce nationally representative data. The NHANES data are available in the public domain. The 2005 to 2006 NHANES oversampled certain subgroups of the US population, including low-income persons, older adults aged 60 years or older, African Americans, and Mexican Americans, to provide a more in-depth snapshot of these population groups. A total of 12 862 individuals were sampled into the 2005 to 2006 NHANES. Among the sampled individuals, 10 348 (80.5%) participated in the interview, 9950 (77.4%) were involved in the examination, and 8306 (65%) provided valid data on vitamin D measurement. The current analysis only included individuals who provided vitamin D data and were aged 20 years or older (N = 4495). The NHANES was approved by its institutional review board, and analyzing the public domain data from NHANES does not require additional institutional review board approval.

2.2. Measurements

2.2.1. Demographic variables

Age was recoded into 5-year age groups. Race was classified as white, black, Hispanic, and other races combined. Education level was dichotomized as yes or no for any postsecondary or college education.

2.2.2. Health-related variables

Smoking status was classified as never, former, and current. Overweight was defined by body mass index (BMI) (kg/m^2) between 25.0 and 29.9, and obesity was defined by BMI of ≥30.0. Total cholesterol is measured enzymatically in serum in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol [29]. A total cholesterol level that is ≥200 mg/dL was considered as elevated. High-density lipoprotein (HDL) was measured directly in serum [29], and a level less than 40 mg/dL was classified as low. Hypertension was assessed by self-reporting in answer to the question "has a physician ever told you that you have high blood pressure." Milk consumption was coded as daily use yes or no. Health status was self-reported as good/ excellent and poor/fair.

2.2.3. Vitamin D measures

Serum 25-hydroxyvitamin D concentration was measured at the National Center for Environmental Health, Center for Disease Control, using a radioimmunoassay kit (DiaSorin, Stillwater, MN) [29], and a level that was ≤20 ng/mL (50 nmol/L) was defined as vitamin D deficiency.

2.3. Statistical analyses

Data analysis was performed using SAS Release 8.2 (SAS Institute Inc, Cary, NC) and SUDAAN Release 9.0.1 (Research Triangle Institute, Research Triangle Park, NC). SAS was used for data management to sort data, recode variables, and run frequencies for examining the data.

SUDAAN was designed to analyze survey data because this statistical software can account for the complex multistage sample design, such as NHANES. The PROC CROSSTAB procedure in SUDAAN was used for calculating prevalence rates of vitamin D deficiency presented as percentages (%) and 95% confidence intervals (CI). A prevalence rate was calculated as the percentage of the number of people who were classified as vitamin D deficiency by the total number of people in the corresponding category. Serum vitamin D concentrations were reported as mean ± SD. χ^2 Test was used to assess bivariate associations between vitamin D deficiency and other variables. Multiple logistic regression analyses (the PROC LOGISTIC procedure in SUDAAN) were used to examine the relationship between vitamin D deficiency and a set of explanatory variables to identify independent correlates of vitamin D deficiency and to calculate adjusted odds ratios and 95% CI. All variables with a significant bivariate association with vitamin D deficiency ($P < .05$) were examined in a multivariate logistic regression model. Dummy variables were created for each race to assess the individual minority group's risk for vitamin D deficiency. Taylor series linearization methods were used for variance estimation. All analyses were based on weighted data to adjust for nonresponse and to make the data representative of the US population. These adjustments were made by applying the examined sample weight variable provided by the NHANES. Weighted prevalence rate estimates were reported.

3. Results

A total of 4495 individuals aged 20 years or older were included in this study. About 17% of the study population were 65 years or older. Table 1 showed the characteristics of the study population. Fifty-two percent of the study participants were women. The race distribution was 72.5%, 11.1%, 11.3%, and 5.1% for white, black, Hispanic, and other races, respectively. More than 57% of study participants received at least some postsecondary education. Most individuals (83.8%) reported to have a good or excellent health status. Twenty-four percent of the study participants were current smokers, and 25% were former smokers. About one third of the study participants were overweight, and another one third were obese. Thirty percent of individuals had hypertension, 45.4% had a high total cholesterol level, and 15.5% had a low HDL cholesterol level. Less than half (43.3%) of the study population reported consuming milk products daily.

The mean ± SD of vitamin D levels were 19.9 ± 8.5 ng/mL in the study population and were 20.1 ± 7.9 ng/mL in men and 19.8 ± 9.0 ng/mL in women. The overall prevalence rate of vitamin D deficiency (≤20 ng/mL) was 41.6% (95% CI, 36.6%-46.8%). Examination of the prevalence rate of vitamin D deficiency by age showed insignificant variations between age groups (Fig. 1). The age groups of 55 to 59 and

Table 1
Characteristics of study population and prevalence rate (%) of vitamin D deficiency

Characteristics	n[a] (%)	Prevalence rate (%) (95% CI)
Age (y)		
<65	3432 (82.8)	41.7 (36.0-47.6)
≥65	1063 (17.2)	41.1 (37.4-44.6)
Sex		
Male	2158 (48.0)	41.1 (36.6-45.8)
Female	2337 (52.0)	42.0 (36.2-48.1)
Race		
White	2271 (72.5)	30.9 (26.2-36.2) **
Black	1002 (11.1)	82.1 (76.5-86.5)
Hispanic	1049 (11.3)	62.9 (53.2-71.7)
Other	173 (5.1)	57.6 (46.9-67.4)
Any college education		
Yes	2182 (57.6)	36.7 (32.1-41.5) **
No	2308 (42.4)	48.2 (42.2-54.2)
Health status		
Good/excellent	3289 (83.8)	37.4 (32.4-42.7) **
Poor/fair	897 (16.2)	59.5 (51.3-67.2)
Smoking status		
Never	2365 (51.0)	42.4 (37.0-48.0)
Former	1147 (25.0)	37.8 (31.6-44.5)
Current	983 (24.0)	43.7 (37.9-49.7)
Body weight		
Normal	1413 (33.7)	33.0 (28.4-37.9) **
Overweight	1519 (32.5)	37.7 (32.1-43.7)
Obese	1563 (33.9)	53.8 (46.7-60.8)
Hypertension		
Yes	1482 (30.0)	46.3 (41.0-51.8) **
No	3054 (70.0)	39.5 (34.3-44.9)
High total cholesterol		
Yes	2043 (45.4)	40.3 (34.6-46.2)
No	2452 (54.6)	42.7 (37.5-48.0)
Low HDL cholesterol		
Yes	683 (15.8)	49.9 (43.1-56.7) *
No	3812 (84.2)	40.0 (34.8-45.5)
Consume milk products daily		
Yes	1967 (43.3)	33.2 (28.5-38.3) **
No	2528 (56.7)	48.0 (42.4-53.6)

[a] n indicates sample size.
* $P < .01$.
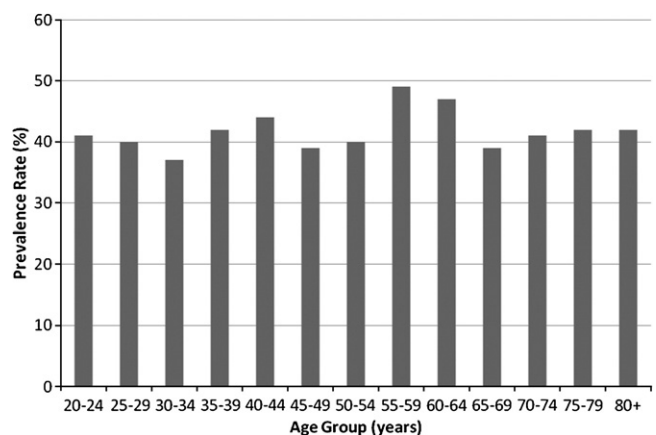** $P < .001$ for difference between groups.

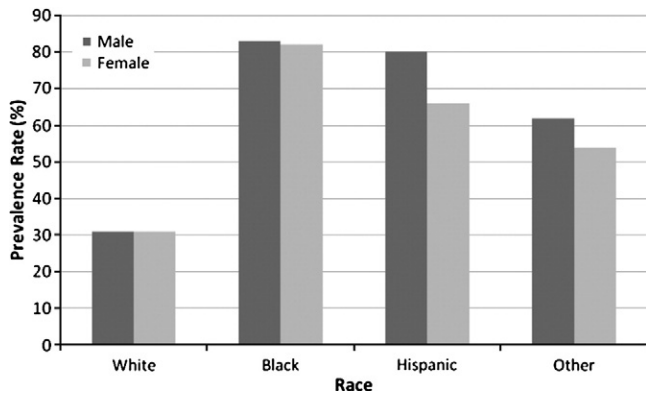Fig 1. Prevalence rate (%) vitamin D deficiency by age.

Fig 2. Prevalence rate (%) vitamin D deficiency by race and gender.

60 to 64 years had the highest prevalence rate of vitamin D deficiency (49.0% and 47.0%, respectively). The age patterns of vitamin D deficiency between men and women were not significantly different. Fig. 2 shows the prevalence rate of vitamin D deficiency by race and sex. Black adults had the highest prevalence rate of vitamin D deficiency (82.1%; 95% CI, 76.5%-86.5%), followed by Hispanic adults (62.9%; 95% CI, 53.2%-71.7%). Among Hispanic and other races, men were significantly more likely to have vitamin D deficiency than women (P < .001). When examining by other factors (Table 1), the prevalence rate of vitamin D deficiency was significantly more common among those who had no college education, were obese, with a poor health status, hypertension, low HDL cholesterol level, or not consuming milk products daily (all P < .001).

A comparison between individuals who had vitamin D deficiency and those who had a normal vitamin D level revealed several significant differences (Table 2). In demographic aspects, individuals with vitamin D deficiency

were significantly more likely to be black (21.9% vs 3.4%; P < .0001) or Hispanic (17.1% vs 7.2%; P < .0001), without any college education (49.2% vs 37.6%; P < .0001), and not in good health (23.6% vs 11.2%; P < .0001). For cardiovascular disease–related risk factors, individuals with vitamin D deficiency were more likely to be overweight (73.3% vs 61.4%; P < .0001) or obese (43.9% vs 26.8%; P < .0001), have hypertension (33.5% vs 27.6%; P < .001), and have a low HDL cholesterol level (18.9% vs 13.5%; P < .01). A high percentage of the individuals with vitamin D deficiency did not consume milk products daily (65.4% vs 50.5%; P < .0001).

Table 3 shows the results from multivariate analyses. After adjusting for all related factors, the multivariate model revealed that being black or Hispanic, no college education, not in a good health status, being obese, low HDL cholesterol, and not consuming milk products daily were all significant independent correlates of vitamin D deficiency. Among the independent correlates, being a minority was the strongest indicator for vitamin D deficiency; compared with whites, blacks had 9.6 times and Hispanics had 3.2 times increased risk for vitamin D deficiency. Obese individuals showed nearly double the risk for vitamin D deficiency than nonobese individuals.

4. Discussion

From the results of the current study, the hypothesis was accepted that vitamin D deficiency was common in US adults, especially among minority groups. Although

Table 2
Univariate association between vitamin D deficiency and other variables

	Vitamin D deficiency		P [a]
	Yes (n = 2,257) % (95% CI)	No (n = 2,238) % (95% CI)	
Being female	52.5 (50.1-54.9)	51.6 (49.8-53.4)	.5584
65 years or older	17.0 (13.9-20.6)	17.4 (14.1-21.3)	.7721
Being black	21.9 (15.3-30.3)	3.4 (2.2-5.2)	<.0001
Being Hispanic	17.1 (12.8-22.5)	7.2 (5.3-9.7)	<.0001
No college education	49.2 (45.4-32.0)	37.6 (33.3-42.1)	<.0001
Poor/fair health status	23.6 (21.1-26.3)	11.2 (9.2-13.4)	<.0001
Being current smoker	25.2 (22.8-27.7)	23.1 (19.8-26.7)	.1204
Being former smoker	22.7 (20.7-24.9)	26.6 (23.7-29.8)	.0902
Being overweight	73.3 (70.2-76.2)	61.4 (57.6-65.1)	<.0001
Being obese	43.9 (40.2-47.6)	26.8 (23.4-30.6)	<.0001
Hypertension	33.5 (30.6-36.5)	27.6 (25.0-30.3)	.0009
High total cholesterol	44.0 (40.3-47.7)	46.4 (44.0-48.9)	.2291
Low HDL cholesterol	18.9 (16.4-21.7)	13.5 (11.3-15.8)	.0047
Not consume milk products daily	65.4 (61.2-69.4)	50.5 (47.1-54.0)	<.0001

[a] P values are for the difference between the 2 groups of vitamin D deficiency status.

Table 3
Independent correlates of vitamin D deficiency

	Odds ratio	95% CI	P
Being black			
No (white)	1.0		
Yes	9.6	6.3-14.5	<.001
Being Hispanic			
No (white)	1.0		
Yes	3.2	2.1-4.9	<.001
No college education			
Yes	1.0		
No	1.3	1.1-1.5	.01
Poor/fair health status			
No	1.0		
Yes	1.8	1.4-2.3	<.001
Being obese			
No	1.0		
Yes	1.9	1.6-2.3	<.001
HDL Cholesterol <40 mg/dL			
No	1.0		
Yes	1.4	1.1-1.8	.03
Not consuming milk products daily			
No	1.0		
Yes	1.6	1.4-1.9	<.001

Note: Other covariates adjusted but not significant in the model included hypertension, health status, and education level.

different cutoff points have been used to define vitamin D deficiency, several studies have reported a high prevalence rate of vitamin D deficiency in non-Hispanic blacks [30-33]. Using the definition of serum 25-hydroxyvitamin D concentrations ≤20 ng/mL, we found that over 80% of black adults, both men and women, would be categorized as vitamin D deficient. Compared with white adults, other minorities were also at a higher risk for vitamin D deficiency, especially Hispanic men, which confirmed the results from other studies [31,34-36]. Because the skin pigment melanin absorbs sunlight [37], an important source of erethymal vitamin D, people of color are at particularly high risk for vitamin D deficiency [2,38]. The association between race and vitamin D deficiency may be related to several factors. Sun exposure is the primary determinant of vitamin D status [3] and non-whites require more sunlight exposure to obtain adequate vitamin D levels because of skin pigmentation. Another possible explanation could be because of the different dietary patterns, particularly the intake of dairy products in different population groups. Lower socioeconomic status among minority populations could also impact on food choices, for example, less likely to purchase fish that provide a good source of vitamin D. Kakarala et al [39] reported that underserved individuals, who were not medically insured and were mostly non-whites, were 3 times more likely than whites to have vitamin D deficiency and had a low-dietary vitamin D intake. Our analysis confirmed the finding that lower education level, a marker of low socioeconomic status, was associated with vitamin D deficiency.

Several important cardiovascular disease risk factors were found to be significantly associated with vitamin D deficiency in this study, including obesity and low HDL level. Obesity has been shown to be independently correlated with vitamin D deficiency in other studies [20]. Our analyses confirmed that the risk of vitamin D deficiency was almost double among obese adults compared with those who had a normal weight. Similar patterns have been reported world-wide. Research on 3100 women in northeast Scotland found that those with an average BMI of 34 produced 10% less vitamin D than those of average weight [40]. A Spanish study showed that over half of the morbidly obese patients (BMI ≥ 40) were diagnosed with vitamin D deficiency [41]. In an Italian study, BMI was also significantly correlated with 25-hydroxyvitamin D concentration after adjusting for insulin-sensitivity, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides [42]. The relationship between vitamin D deficiency and obesity is still unknown, and the temporal relationship is not clear, for example, vitamin D deficiency causes obesity or the other way around. Excess body fat tissue could absorb and retain vitamin D, and thus, circulatory vitamin D is decreased and unavailable to the body [43]. The absence of vitamin D could create interference with the functioning of a hormone called leptin, which signals the brain when the stomach is full, therefore, stop eating [44]. In addition, overweight people may tend to spend more time indoors and receive less ultraviolet rays of the sun that spur the production of vitamin D [45].

The association between vitamin D deficiency and weight might be also because of the link between vitamin D and the metabolic syndrome, as overweight is a major component of the metabolic syndrome. Previous studies have shown an inverse relationship between vitamin D concentrations and the prevalence of the metabolic syndrome, including insulin resistance, high total cholesterol and triglyceride levels, low LDL cholesterol level, and high blood pressure [46-48]. Observational studies have suggested an association between vitamin D deficiency and the onset of type 2 diabetes, a common consequence of the metabolic syndrome [46,48]. Vitamin D has important effects on insulin action and may impact on several pathways, which may be of importance in the development of type 2 diabetes [49]. Among obese individuals, vitamin D deficiency was associated with other metabolic syndrome risk factors [41]. Our findings also supported this association that low HDL cholesterol was independently and significantly correlated with vitamin D deficiency.

The strength of this study was the large sample size and the population-based data on vitamin D. There were some limitations recognized in this study. Cross-sectional data do not permit determination of the causative nature of the association between vitamin D deficiency and its correlates. This study was based on a one-time measurement of vitamin D, and it could not show the variation of vitamin D concentration during different seasons because there is a seasonal impact on vitamin D level. There was a lack of the information on sun exposure, such as time spent outdoors and sunscreen use. Different regions have different altitudes, which can affect the strength of ultraviolet rays, and this study did not have region-specific data on vitamin D deficiency. In addition, vitamin D supplement use can influence the vitamin D level, but this factor could not be evaluated in the current study.

In conclusion, vitamin D deficiency was common in both men and women across different age groups in the US adult population, especially among minority groups. Due to the link between vitamin D deficiency and major chronic diseases and all-cause mortality [50], it might underscore the necessity to identify vitamin D deficiency as part of screening for risk factors. It may be prudent for registered dietitians and other health professionals to advise clients on ways to increase dietary vitamin D or recommend supplementation. Traditional sources of vitamin D are fatty fish and their oils and fortified milk. The expansion of vitamin D fortified food products has given consumers a wider variety of sources for vitamin D, such as juices, ready-to-eat cereal, and yogurt. Although many of these food sources are low-cost solutions for vitamin D deficiency, even supplemental vitamin D is a relatively inexpensive source [51]. Correcting vitamin D deficiency by supplementation is less challenging than asking people to change dietary patterns. Given that minority populations experience a higher prevalence of

cardiovascular disease, hypertension, and metabolic syndrome, as well as vitamin D deficiency, proactive health professionals could be instrumental in correcting vitamin D deficiency in minority groups. Using diet, supplements, or even safe sun exposure could be a public health strategy, which is simple, effective, and low cost, for risk reduction of vitamin D deficiency.

Acknowledgment

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EDUCATION AND TRAINING

Master in "Management e Marketing Farmaceutico" - Alma Laboris (November 2014 - January 2015) with the following rules:

- *PHARMACEUTICAL MARKETING*
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- *PHARMACEUTICAL BUSINESS & MANAGEMENT*
- *PHARMACEUTICAL FINANCE AND CONTROL*
- *MANAGEMENT AND HR IN THE PHARMACEUTICAL COMPANIES*

- **PhD in Neurobiology** - 'University of Catania(site of Rome);
- **Master** *Programma Scienziati in Azienda* – ISTUD Foundation of Stresa (November 2006 - July 2007);
- **Pharmacist Licence**;
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WORK EXPERIENCE
Actually

Society:	**GUNA S.p.A –Milan**
Dates from - to:	23/02/2015 – current
Type of sector	Homeopathic medicinal products for Human and Veterinary use, Medical Device, Food Supplements, Cosmetics
Occupation and position held:	**Regulatory Affairs Manager**
	Team of 8 people

Main activities and responsibilities:

Assess, plan and execute the registration process/renewal/variation for homeopathic medicinal products for human and veterinary use, cosmetics and medical devices, food supplements in new markets opened by the Export department.

Coordinator of the regulatory and Module 4 team involved in the registration procedure for homeopathic medicinal products.

Effectively interact and communicate with Manufacturers, external Regulatory Agencies and Local Distributors to collect the documentation needed to submit for registration.

Request and prepare supporting technical and non-technical data from manufacturers and work closely with the QA, documentation and compliance colleagues form our manufacturing dept.

Responsible for confirming Artwork acceptability, as well as the receipt of necessary licenses, prior to approving the product to the 'Production' cycle.

Responsible for Product Labels and Artworks, and as such to assess the feasibility of Labels and Artworks for specific Regions in accordance with Marketing, Supply and Business Development.

Responsible for feed (evaluation and creation of labels, notification to the relevant authorities).

Direct the preparation and submission of regulatory agency applications, reports, or correspondence.

Review all regulatory agency submission materials to ensure timeliness, accuracy, comprehensiveness, or compliance with regulatory standards.

Provide regulatory guidance to departments or development project teams regarding design, development, evaluation, or marketing of products. Develop and maintain positive rapport and working relationships within and across all the departments, including being the first local interface with GCMC. Cooperate with the team to evaluate e promote regulatory strategies and compliance support to company's corporate objectives.

Participate in and assists with facility inspections, Notified Body Audits and other governmental inspections as directed.

Support to the pharmacovigilance dept. and clinical dept. (IMPD dossier, support for implementing the new regulamentation).

Formulate or implement regulatory affairs policies and procedures to ensure that regulatory compliance is maintained or enhanced.

Communicate regulatory information to multiple departments and ensure that information is interpreted correctly.

Society: **GUNA S.p.A –Milan**
Dates from - to: 18/10/2014 – 22/02/2015
Type of sector Homeopathic medicinal products for Human and Veterinary use, medical Device, Food Supplements, Cosmetics

Occupation and position held:	**Regulatory Affairs Coordinator Senior** **Coordinator of a team of 4 people**
Main activities and responsibilities:	Assist in and coordinate preparation of all regulatory submissions. Coordinate submission components, perform final preparation, assembly, formatting, editing, proofreading, and QA of regulatory documents. Back up for managing the regulatory database. Input data and archive as needed. Organize and retrieve submissions from regulatory archives Coordinate department projects, meetings, and conferences both internal and outside with other departments, regulatory agencies, partners, and consultants. Back up for editing regulatory documents in preparation for final submissions Oversee completion of general department activities Homeopathic medicinal products: Owner for the registration submission of CTD regulatory dossier, variations, module 3 and module 1. Revisions of module 2.5, 5, 2.4 and 4. Preparation of export dossiers. Cosmetics: chemical / product regulation implementation, ingredient restriction review, product labelling Regulatory compliance, claims substantiation for pack copy and brochure/printed material content on a regional basis, registration and notification where applicable and consumer complaints monitoring. Class III Medical Devices: Compilation of documentation and liaison with Corporate RA & Subcommittees; Compilation of global regulatory submissions; Co-ordination of the licenses for controlled substances and other; Implement regulatory/quality system requirements as per IVD Directive (CE); Control of distribution of product from regulatory perspective through regulatory; Provision of Regulatory affairs advice when requested internally and from; Participation in Internal and External Quality Audit as required; Participation in Management Reviews of the Quality & Environment System as required; Communication to management on Regulatory affairs issues, which require addressing; Approval of Printed material from a regulatory affairs perspective; CE Marking – Regulatory requirements (ref. CE Technical Files);Dealing with European Competent Authorities as needed regarding vigilance and registration.
Society:	**GUNA S.p.A –Milan**
Dates from -to:	11/11/2013 - 17/10/2014
Type of sector	Homeopathic medicinal products for Human and Veterinary use, medical Device, Food Supplements, Cosmetics
Occupation and position held:	**Regulatory Affairs Associate** **Coordinator of 2 people**
Main activities and responsibilities:	Homeopathic medicinal products: Owner for the registration submission of CTD regulatory dossier, variations, module 3 and module 1. Revisions of module 2.5, 5, 2.4 and 4. Preparation of export dossiers. Cosmetics: chemical / product regulation implementation, ingredient restriction review, product labelling Regulatory compliance, claims substantiation for pack copy and brochure/printed material content on a regional basis, registration and notification where applicable and consumer complaints monitoring. Class III Medical Devices: Compilation of documentation and liaison with Corporate RA & Subcommittees; Compilation of global regulatory submissions; Co-ordination of the licenses for controlled substances and other; Implement regulatory/quality system requirements as per IVD Directive (CE); Control of distribution of product from regulatory perspective through regulatory; Provision of Regulatory affairs advice when requested internally and from; Participation in Internal and External Quality Audit as required; Participation in Management

Reviews of the Quality & Environment System as required; Communication to management on Regulatory affairs issues, which require addressing; Approval of Printed material from a regulatory affairs perspective; CE Marking – Regulatory requirements (ref. CE Technical Files); Dealing with European Competent Authorities as needed regarding vigilance and registration.

Society:	**Mediolanum farmaceutici S.p.A –Milan**
Dates form - to:	01/09/2011- 03/09/2013
Type of sector	Ethics Medicinal products such as Antibiotics, Anti-inflammatory, Anticoagulants, etc.
Occupation and position held:	**Regulatory Affairs Specialist** **Coordinator of 1 person**
Main activities and responsibilities:	Preparation of documentation and submission to AIFA and Ministry of Health in compliance with current legislation to ensure efficient registration and maintenance of the registrations in accordance with business strategies; -Variations, Marketing Authorisation renewals, labelling updates, artwork revision and approval; -Lifecycle management of medicinal products; -Ensure advertising and promotional activities meet applicable regulatory requirements and prepare submission for approval to AIFA -Maintaining and processing of local regulatory database - Revision and updating registration dossier (CTD and e-CTD), gap-analysis and consequent evaluation of the regulatory strategy - Regulatory Compliance

Society:	**Keypharma Srl –Milan**
Dates form – to:	21/10/2010 - 23/07/2011
Type of sector	Pharmaceutical Regulatory Affairs Consultant Society
Occupation and position held:	**Regulatory Affairs Specialist**
Main activities and responsibilities:	Assist companies (for example: Schering-Plough) to plan and manage their pharmaceutical and medical product development programs and regulatory requirements Schering-Plough) -Variations, Marketing Authorisation renewals, labelling updates, artwork revision and approval; -Lifecycle management of medicinal products; -Ensure advertising and promotional activities meet applicable regulatory requirements and prepare submission for approval to AIFA -Maintaining and processing of local regulatory database - Revision and updating registration dossier (CTD and e-CTD), gap-analysis and consequent evaluation of the regulatory strategy - Regulatory Compliance

PHARMACOVIGILANCE:

Validated Pharmacovigilance database;

Daily checks of the National Network of Pharmacovigilance (RNF);

Periodic inspection of national and international scientific literature for medicinal products and active substances;

Inclusion of cases of Italian literature in the National Network of Pharmacovigilance (RNF);

Information requests for follow-ups;

Translation into English of ADRs in CIOMS format and / or in xml format;

Inserting ICSRs in EudraVigilance;

Insertion and update of medicinal products in the European database Extended EudraVigilance Medicinal Product Dictionary (XEVMPD);

Audits and preparation for inspections by regulatory authorities;

Preparation of Periodic Safety Update Reports (PSURs);

Preparation of Standard Operating Procedures (SOPs);
Data Entry.

Society:	**GB Pharma – Pavia**
Dates form - to:	01/03/2010 - 20/10/2010

Type of sector	CRO and Pharmaceutical Regulatory Affairs Consultanting Society
Occupation and position held:	**Regulatory and Pharmacovigilance Affairs Specialist**
Main activities and responsibilities:	Assist companies to plan and manage their pharmaceutical and medical product development programs and regulatory requirements Schering-Plough)

-Variations, Marketing Authorisation renewals, labelling updates, artwork revision and approval;
-Lifecycle management of medicinal products;
-Ensure advertising and promotional activities meet applicable regulatory requirements and prepare submission for approval to AIFA
 -Maintaining and processing of local regulatory database
 - Revision and updating registration dossier (CTD and e-CTD), gap-analysis and consequent evaluation of the regulatory strategy
- Regulatory Compliance
Medical Devices: Prepare of Technical files.

PHARMACOVIGILANCE:
Validated Pharmacovigilance database;
Daily checks of the National Network of Pharmacovigilance (RNF);
Periodic inspection of national and international scientific literature for medicinal products and active substances;
Inclusion of cases of Italian literature in the National Network of Pharmacovigilance (RNF);
Information requests for follow-ups;
Translation into English of ADRs in CIOMS format and / or in xml format;
Inserting ICSRs in EudraVigilance;
Insertion and update of medicinal products in the European database Extended EudraVigilance Medicinal Product Dictionary (XEVMPD);
Audits and preparation for inspections by regulatory authorities;
Preparation of Periodic Safety Update Reports (PSURs);
Preparation of Standard Operating Procedures (SOPs);
Data Entry.

Society:	**Pfizer Italia - ROME**
Dates form - to:	18/06/2009 - 17/12/2009

Type of sector:	Ethics Medicinal products such as: Oncologic, Anti-Inflammatory, etc.
Occupation and position held:	**Regulatory Affairs Specialist**
Main activities and responsibilities:	Preparation of documentation and submission to AIFA and Ministry of Health in compliance with current legislation to ensure efficient registration and maintenance of the registrations in accordance with business strategies;

-Variations, Marketing Authorisation renewals, labelling updates, artwork revision and approval;
-Lifecycle management of medicinal products;
-Ensure advertising and promotional activities meet applicable regulatory requirements and prepare submission for approval to AIFA

-Maintaining and processing of local regulatory database
- Revision and updating registration dossier (CTD and e-CTD),
gap-analysis and consequent evaluation of the regulatory strategy
- Regulatory Compliance

Society:	**Pharmades** - **Rome**
Dates from - to:	14/04/2009 - 17/06/2009
Type of sector:	Pharmaceutical Regulatory Affairs Consultanting Society
Occupation and position held:	**Regulatory Compliance** for **Bristol Myers Squibb (Anagni (FR)**
Main activities and responsibilities:	CMC Regulatory Activities

Society:	**Allergan S.p.A** - **ROME**
Dates form - to:	14/02/2007 - 27/02/2009
Type of sector: :	Ethics Medicinal products such as: Ophtalmology products, BOTOX. Medical Devices
Occupation and position held:	**Regulatory affairs and Pharmacovigilance specialist**
Main activities and responsibilities:	Centralized procedure: translation of texts endorsed by EMEA and send to AIFA in the timing appropriate;

Renewals (for national and MRP products);
Gap - analyses of registration dossier (to evaluate the needs to submit national variations as well as local feed-back for the Core European for the preparation of local documentation);
Convert the dossier from NTA to CTD format (all modules);
Management information;
Preparation of printed texts (SmPC, leaflets and labels) for all types of procedures;
Implementation and control of the packaging material (management of AW)
Managing of local and global Archives (paper and electronic) and all computer systems with the insertion of local documentation;
Information of regulatory updates of P , pharmaceutical legislation (control and constant updating of the various links regulators and send the information related to the offices / departments concerned);
Management computer systems on regulatory matters (managed globally and locally control and update);
Parallel imports (contacts with AIFA for parallel imports);
Payback (flow management for payments and sending the appropriate documentation to AIFA within the time frame indicated);
Braille codes (request and obtain the codes Braille);
Type IA , IB and II variations (according to Regulation 1084/2003/EC) for national, MRP and DCP procedures;
Implementation of an electronic System for Regional newsletters
Pharmacovigilance activities : Pharmacovigilance Back- up;
Management of adverse events and filling in forms to be sent to the parent or to the national PV.

Other skills and competences
PC skills: windows, power point, internet and graphic programs

Laboratory skills: Biomedical processes, HPLC, Spettrophotometer.

Mother tongue: Italian

Other languages:

French: elementary.

English: Good.

Spanish: elementary.

References:

- G. De Luca, Di Giorgio RM, Macaone S, Calpona PR, Costantino S, Di Paola ED, Costa N, Rotiroti D, Ibbadu GF, Russo E , De Sarro G . *Amino acid levels in some lethargic mouse brain areas before and after pentylenetetrazole kindling* Pharmacol Biochem Behav. 2005 May;81(1):47-53

- G. De Luca, G.B. De Sarro, S. Costantino, V. Macaione, P. R. Calpona, G. Ciliberto and R.M.Di Giorgio *Susceptibility to audiogenic seizure and neurotransmitter amino acid levels in brain areas of IL-6 deficient mice* Pharmacology, Biochemistry and Behavior 78, p 75-81, 2004.

- Cappuccio I, Verani R, Spinsanti P, Niccolini C, Gradini R, Costantino S, Nicoletti F, Melchiorri D. *Context-dependent regulation of embryonic stem cell differentiation by mGlu4metabotropic glutamate receptors.* Neuropharmacology. 2006 Jun 24;

HOBBIES

Books ; kitchen; Sports: tennis and swimming (for seven years at a competitive level); volunteering; Theatre.

Good interpersonal relationships, ability to work in team, autonomous , strongly results-oriented, reliable and serious; problem-solving.

Updated Curriculum on 24/06/2016

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