Vitamin D Nutritional Policy is at a Crossroads

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The recent 2011 Institute Of Medicine (IOM) report on vitamin D nutritional guidelines is not significantly different from the 1998 IOM report. In addition there are a number of concerns with several aspects of the 2011 IOM report that require discussion.. This abstract summarizes the recent dramatic increase in understanding of the many biological actions of vitamin D which make it essential, from a responsible medicine perspective, to reconsider the present vitamin D nutritional guidelines and to formulate new world-wide policy changes that will maximize vitamin D's contributions to improve life long good health at minimal cost. In spite of many government and medical associations world-wide guidelines for the reference daily intake (RDI) of vitamin D, scientists and nutritionists from many countries agree that at present about half of elderly North Americans and Western Europeans and probably also two-thirds of the rest of the world are not receiving enough vitamin D to maintain healthy bone. Consequently, evidence has accumulated that beside intestine and bone, there are five additional physiological systems where the VDR with 1α,25$(OH)_2$D generates biological responses; these include the immune system (both the innate and adaptive), pancreas and metabolic homeostasis, heart-cardiovascular, muscle and brain systems as well as the control of the cell cycle and thus of the disease process of cancer. Responsible medicine demands that world-wide vitamin D nutritional guidelines reflect current scientific knowledge about vitamin D's spectrum of activities. Also there should be more focus on encouraging individuals to make their own informed decision as to their daily vitamin D_3 dose. In summary, world-wide vitamin D nutritional policy is now at a crossroads.

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****** BACKGROUND INFORMATION ******

TISSUES EXPRESSING THE VITAMIN D RECEPTOR (VDR)

Adipose	Adrenals	Bone, osteoblasts	Brain, general
Brain, amygdala	Brain hypothalamus	Brain, glial cells	Breast
Cartilage	Colon	Eggshell gland (birds)	Epididymus
Gills (fish)	Hair follicle	Intestine	Kidney
Liver	Lung	Lymphocytes	Muscle, cardiac
Muscle, embryonic	Muscle, smooth	Ovary	Pancreas βcells
Parathyroid	Parotid	Pituitary	Placenta
Prostate	Retina	Seminiferous tubule	Skin
Sperm	Stomach	Testis	Thymus
Thyroid	Tonsils Dendritic	Yolk sac (birds)	

A cell that contains the VDR can respond to the steroid hormone 1α,25$(OH)D_3$ by generation of biological response(s). Thus the expansion of the vitamin D endocrine system beyond intestine, bone, and kidney (calcium homeostasis) to the immune, cardiovascular, pancreas, muscle and, ultimately to the brain is not surprising, since the presence of VDR in these tissues has been known for some time.

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****** BACKGROUND INFORMATION ******

Sites of Extra-Renal Production of 1α,25$(OH)_2D_3$ in Man as Marked by the Presence of the 25$(OH)D_3$-1α-Hydroxylase Enzyme

Colon	Dendritic cells	Brain, Schwann Cells
Breast, mammary	Pancreatic islets	Parathyroid gland
Placenta, decidua	Prostate	Skin, keratinocytes

The 25$(OH)D_3$ -1α-hydroxylase enzyme converts 25$(OH)D_3$ into the steroid hormone 1α,25$(OH)_2D_3$. The primary location of the enzyme is in the kidney proximal convoluted tubule and it is responsible for maintaining the serum concentration of 1α,25$(OH)_2D_3$ at 30 – 70 pg/ml. In addition, the 1α-hydroxylase is present in at least nine extra-renal sites (see table above) where it produces small amounts of 1α,25$(OH)_2D_3$ that generates biological responses in that 'local neighborhood' (i.e. a paracrine action.

****** BACKGROUND INFORMATION ******

Over the past decade there has been a dramatic increase in our understanding of the many biological actions that result from vitamin D acting through its metabolite 1α,25$(OH)D_3$ in collaboration with its cognate vitamin D receptor (VDR). Consequently, evidence has accumulated that besides the intestine and bone, there are at least five additional physiological systems in which the VDR with 1α,25$(OH)D_3$ generates biological responses. These include the immune system (both the innate and adaptive), pancreas and metabolic homeostasis, heart-cardiovascular, muscle and brain systems as well as the control of the cell cycle, and thus of the disease process of cancer. Acting through the VDR 1α,25$(OH)D_3$ can produce a wide array of favorable biological effects that collectively are projected to contribute to the improvement of human health.

[Norman & Bouillon, Exper. Biol. & Med. 235:1034 (2010)].

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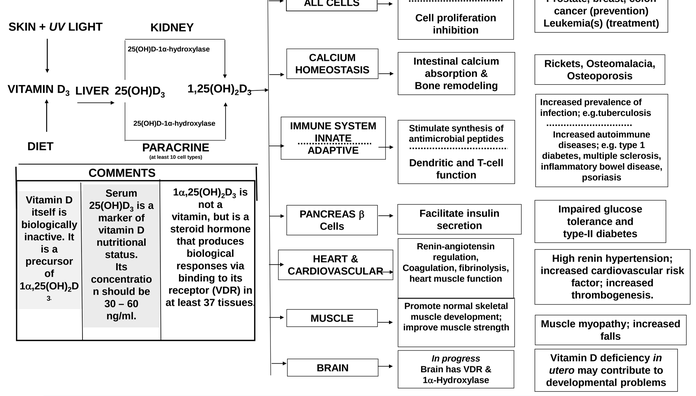
CONTRIBUTIONS OF VITAMIN D TO GOOD HEALTH



COMMENTS		
Vitamin D itself is biologically inactive. It is a precursor of 1α,25$(OH)_2D_3$	Serum 25$(OH)D_3$ is a marker of vitamin D nutritional status. Its concentration should be 30 – 60 ng/ml.	1α,25$(OH)_2D_3$ is not a vitamin, but is a steroid hormone that produces biological responses via binding to its receptor (VDR) in at least 37 tissues

PHYSIOLOGICAL SYSTEMS	BIOLOGICAL RESPONSES	D DEFICIENCY ASSOCIATED DISEASES
ALL CELLS	Cell cycle regulation Cell proliferation inhibition	Cancer Prostate, breast, colon cancer (prevention) Leukemia(s) (treatment)
CALCIUM HOMEOSTASIS	Intestinal calcium absorption & Bone remodeling	Rickets, Osteomalacia, Osteoporosis
IMMUNE SYSTEM INNATE ADAPTIVE	Stimulate synthesis of antimicrobial peptides Dendritic and T-cell function	Increased prevalence of infection; e.g.tuberculosis Increased autoimmune diseases; e.g. type 1 diabetes, multiple sclerosis, inflammatory bowel disease, psoriasis
PANCREAS β Cells	Facilitate insulin secretion	Impaired glucose tolerance and type-II diabetes
HEART & CARDIOVASCULAR	Renin-angiotensin regulation, Coagulation, fibrinolysis, heart muscle function	High renin hypertension; increased cardiovascular risk factor; increased thrombogenesis.
MUSCLE	Promote normal skeletal muscle development; improve muscle strength	Muscle myopathy; increased falls
BRAIN	*In progress* Brain has VDR & 1α-Hydroxylase	Vitamin D deficiency *in utero* may contribute to developmental problems

New evidence indicates that vitamin D3 intake should be in the range of 2000 – 4000 IU/day. Everyone should have their serum 25(OH)D levels determined at least once yearly . Vitamin D3 soft gel capsules (1000 or 2000 IU), Codes 1452 or 1463, can be obtained from the J.R.Carlson Laboratories or other vendors. More vitamin D-related health information is available at both the Vitamin D Workshop website http://vitamind.ucr.edu/ and the GrassrootsHealth web site http://www.grassrootshealth.net/

****** MORE BACKGROUND INFORMATION ******

In spite of the guidelines for the reference daily intake (RDI) for vitamin D published by governments and medical associations worldwide, scientists and nutritionists from many countries agree that at present about half of elderly North Americans and Western Europeans are vitamin D deficient; in the rest of the world about two-thirds of the total population are not receiving enough vitamin D to maintain bone health.

(a) Proc. 13th Vitamin D Workshop in Victoria, BC(2006); JSBMB 103: 204 - 205 (2007).
(b) Proc. 14th Vitamin D Workshop in Brugge, BE (2009); JSBMB 121:4 – 6 (2010).

Institute of Medicine (IOM) Recommendations For Daily Intake of Vitamin D

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Age Category	2011 Recommended Dietary Allowance (RDA) of Vitamin D [IU/day]	1998 Adequate Intake (AI) of Vitamin D [IU/day]
Infants 0 – 12 months	400	200
1 – 51 years	600	200
51 - 70 years	600	400
➢ 70 years	800	600
Pregnant & Lactating	600	No advice
A safe high dose, i.e Tolerable Upper Level of Intake (TULI) From age 1 on…	4000 (see below)	2000

Others have argued that the TULI should be 10,000 IU/day. This value was derived from evaluation of a series of human clinical trials in which no vitamin D toxicity occurred. [Hathcock JN, Shao A, Vieth R, Heaney R 2007 "Risk assessment for vitamin D". Am J Clin Nut.r 85:6-18]

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****** PROPOSED 25(OH)D GUIDELINES *****

Serum 25$(OH)D_3$ is a Marker of Vitamin D Nutritional Status

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Serum 25(OH)D (ng/ml)	Serum 25(OH)D (nmoles/L)	Nutritional Descriptor
< 5	< 12	Severe D deficiency
< 10	< 25	Vitamin D deficiency
10-20	25 - 50	Vitamin D insufficiency
20-30	50 - 75	Marginal vitamin D insufficiency
30 - 60	75 - 150	VITAMIN D SUFFICIENCY
> 150	> 375	Risk for vitamin D toxicity

The 1998 IOM Report urged that serum 25(OH)D levels be used as a marker of vitamin D nutritional status. By 2005 the routine availability of LC/MS/MS 25(OH)D assays made it possible to adopt this recommendation. This has facilitated a dialog on what levels should be the cutoff for defining **VITAMIN D SUFFICIENCY**: should it be 20ng/ml, > 20 ng/ml, >30 ng/ml or > 40 ng/ml? In its January 2011 report, the IOM states that a 25(OH)D serum level of 20ng/ml (50 nmoles/L) is "adequate to assure good bone health". Many scientists in the vitamin D field support a higher serum value of 25(OH)D; e.g. 30 – 60 ng/ml (75 – 150 nmoles/L) or 40 – 75 ng/ml (100 – 185 nmoles/L). The authors of this poster support the 30 – 60 ng/ml (75 – 150 nmoles/L) cut point.

EXAMPLES OF SERUM 25(OH)D LEVELS (Exposure to sunlight/UV or vitamin D_3 over-dose)

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Serum 25(OH)D (ng/m)	Serum 25(OH)D (nmoles/L)	Nutritional Descriptor
30 - 60	75 - 150	VITAMIN D SUFFICIENCY
~ 50	125	Summer workers, Omaha, NB (a)
58	148	Beach life guards in St. Louis in summertime (b)
65	162	Beach life guards in summertime in Israel (c)
> 150	> 375	Risk for Toxicity (d)
~ 300	~ 750	Example of symptomatic toxicity (e)

(a) Barger-Lux & Heaney JCEM **87**:4952 (2002).
(b) Better, OS *et al.* in Phosphate & Minerals in Health Disease, pp 467 (2002)
(c) Haddad, JG JCEM **33**:992 (1971).
(d) Norman, AW & Bouillon, R. Exp. Biol. Med **235**: 1034 (2010).
(e) Jacobus, CH *et al.* "Hypervitaminosis D associated with drinking milk" NEJM **326**: 1173 (1992).Extrem hypercalcemia from daily consumption of milk with 5.7 mg of vitamin D_3 per liter or 2030,000 IU/L.

VITAMIN D_3 DOSE RESPONSE IN HUMANS

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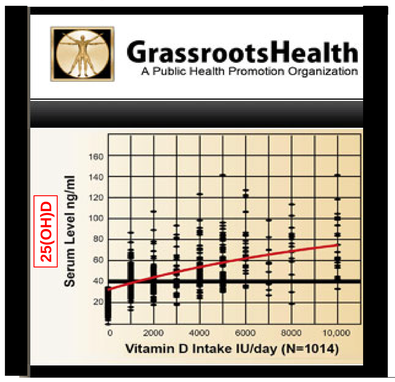

➢ A daily supplementation of 1000 IU of vitamin D_3, produces a serum 25(OH)D range from 15 – 85 ng/ml (38 – 212 nmoles/L).
➢ At 10,000 IU/day, no one was above 200 ng/ml (500 nmoles/L).
➢ The red line shows a potential 'flattening' at higher levels.
➢ The serum 25(OH)D data for 1014 people are in this chart.
➢ The URL to the GrassRootsHealth web site is http://www.grassrootshealth.net/

Another viewpoint is that "For every 1000 IU of vitamin D_3 taken in, there is an increase of roughly 7 – 10 ng/ml (17 - 30 moles/L) in the serum 25(OH)D levels". R. P. Heaney *et al.* "Vitamin D_3 is more potent that vitamin D_2 in humans" Endocrinology 152, (2011) *in press.*

VITAMIN D NUTRITIONAL POLICY IS AT A FORK IN THE ROAD !!

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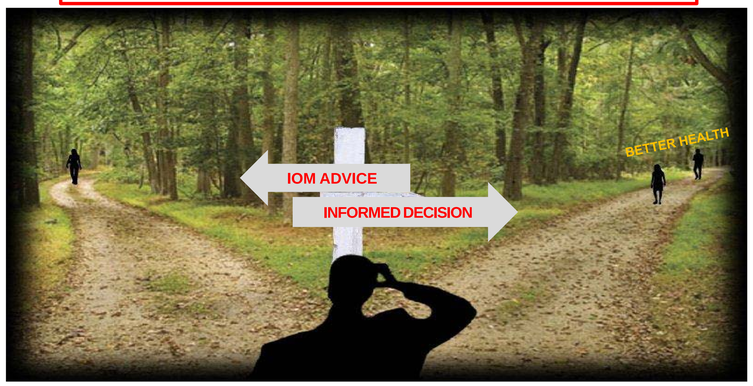

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CONCLUSIONS

Vitamin D Policy is at a Crossroads

(1) The 2011 IOM report on vitamin D nutritional guidelines is not significantly different from the 1998 IOM report. For example, in 1998 the recommended vitamin D intake for adults was 400 IU/day; the 2011 recommended doses were just 600 IU/day; a mere 50% increase.

(2) Both IOM reports on vitamin D nutritional guidelines only specify a generic vitamin D, rather than either vitamin D_3 or vitamin D_2. It is appropriate to specify the natural form of vitamin D that is made from 7-dehydrocholesterol by UVB irradiation, namely vitamin D_3. This is especially true since there is now some evidence in humans that the unnatural vitamin D_2 is less biologically active than the natural vitamin D_3.

(3) The 2011 IOM guidelines focus only on bone health. There is no explicit acknowledgement of the four other physiological systems responsibilities of vitamin D (immune, pancreas, heart and cardiovascular, and muscle) where vitamin D_3 clearly contributes to Good Health.

(4) The IOM report does approve raising the TULI (highest *safe* dose) from the 2000 IU/day in 1998 to the 2011 intake of 4000 IU/day.

(5) Both IOM reports define official nutrition policy and provide guidelines to governmental agencies for both Canada and the USA.

(6) The IOM report offers little advice or encouragement for the individual citizens of both countries who are willing to make their own personal informed decision with regard to their daily vitamin D_3 intake.

WHICH ROAD TO TAKE ?

Our Recommendation focuses on encouraging individuals to make their own informed decision as to their daily vitamin D_3 dose of approximately 4000 IU/day with a documented annual serum 25(OH)D level in the 30 – 60 ng/ml (75 – 150 nmoles/L) range. Collectively this will make significant and useful contributions to each individual's PERSONAL GOOD HEALTH.