Review

Vitamin D insufficiency and disease risk in the elderly

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(Received 19 July, 2023; Accepted 8 August, 2023; Released online in J-STAGE as advance publication 26 August, 2023)

Vitamin D insufficiency, milder than deficiency, is common, and a risk of various diseases. Since vitamin D exert diverse actions, both skeletal and non-skeletal, its insufficiency is a risk of various diseases including osteoporosis, sarcopenia, cardiovascular disease, cancer, and even mortality. Regarding the association of vitamin D status and disease risk, a marked discrepancy exists between the results from the observational studies and intervention studies, mostly yielding the positive and negative results in the former and latter, respectively. Such inconsistency probably arises from methodological problems, of which the baseline vitamin D status would be the most important. Vitamin D intervention would be effective in the deficient/insufficient subjects, but not in sufficient subjects. Since the elderly subjects, especially the institutionalized people, are mostly vitamin D deficient/insufficient, they are likely to benefit from improvement of vitamin D status. Vitamin insufficiency is a risk of various diseases, and correcting the vitamin status alone would reduce the risk of many diseases, and favorable to avoid the undesirable consequences of polypharmacy in the elderly. Additionally, disease prevention by nutritional improvement is cheap and free from side effects, and suited for the primary prevention of diseases.

***Key Words*: vitamin D insufficiency, disease risk, vicious cycle, fracture, non-skeletal action**

The discovery of vitamins and the elucidation of the pathogenesis of their deficiency diseases were the landmark in the modern nutrition, the best known example of which would be the beriberi due to vitamin B_1 deficiency.(1) Vitamin D was identified as the anti-rickets vitamin, and has long been considered to the vitamin solely associated with calcium and bone homeostasis. Recent studies have shown, however, that vitamin D has numerous extra-skeletal actions including cardiovascular, immune, and anti-cancer ones, and is considered to be an omnifarious vitamin.(2,3) Thus, the consequence of vitamin D deficiency/insufficiency (vide infra for the distinction of deficiency and insufficiency) is not limited to the skeletal manifestations, but associated with increased risk for various diseases including the non-skeletal ones.(2,3) Additionally, the prevalence of vitamin D deficiency/insufficiency is known to be extremely high worldwide.(4,5)

Multimorbidity, which is defined as the co-existence of two or more chronic health conditions, is quite common in the elderly subjects.(6) Individually prescribing therapeutic drugs to each disease causes polypharmacy, which is associated with various adverse outcomes such as mortality, falls, adverse drug reactions through drug-drug interactions and drug-disease interactions.(6) Furthermore, the elderly subjects are at much higher risk of experiencing the unfavorable consequence of polypharmacy due to such age-related factors as decreased renal and hepatic function.

Given the omnifarious actions of vitamin D and increased risk of various diseases due to its deficiency/insufficiency, the elderly subjects with vitamin D deficiency/insufficiency will benefit from the improvement of vitamin D status with resultant decreased disease risk. As will be detailed below, unlike the drug treatment, improving the vitamin D status alone could simultaneously decrease the multiple risks for diseases, and can be a good alternative as a preventive strategy to the elderly subjects.

In this narrative review, we will give some description on vitamin D deficiency/insufficiency, disease risks associated with it, and its societal consequences. Additional consideration will be made on the methodological issues in studying and interpreting the relationship between the vitamin D status and disease risk.

Vitamin Deficiency and Insufficiency

Vitamin deficiency is associated with characteristic phenotypic changes. Examples with the responsible vitamins in the parentheses include beriberi (vitamin B_1), rickets and osteomalacia (vitamin D), scurvy (vitamin C), pellagra (niacin), and coagulation abnormality (vitamin K).(1) These deficiency diseases, which once caused disastrous consequence to the society, are now considered to be mostly overcome in developed countries, and the significance of vitamins in health promotion does not seem to be receiving much attention any more, which, however, is not the case.(7) Vitamins' roles in health promotion must be considered from the much wider perspectives including their possible contribution in the prevention of non-communicable diseases (NCDs).(8) For their prevention, life-style modification can play important roles, and the significance of vitamins in health promotion must be considered from such viewpoint.

Recently, vitamin insufficiency, sometimes alternatively called subclinical deficiency, has been receiving increasing concern. It refers to a state in which inadequate vitamin status is milder than deficiency. Vitamin insufficiency does not cause classical deficiency diseases describe above, but is associated with the increased risk of various diseases. Patients with vitamin deficiency have typical phenotypic changes, and can be individually diagnosed. In contrast, although vitamin insufficiency is related to the increased disease risk, it is not accompanied by the phenotypic abnormalities in each subject. Therefore, it cannot be diagnosed individually, and its significance is quite likely to be overlooked.(7) Vitamin insufficiency may be comparable to elevated serum LDL-cholesterol level, which is asymptomatic but associated with increased cardiovascular disease risk.

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doi: 10.3164/jcbn.23-59

The distinction of vitamin deficiency and insufficiency also has great impact on the vitamin requirement. Much more amount of vitamin is needed for the prevention of insufficiency than that of deficiency. "How much vitamins are needed for health promotion?" is a fundamental question, and the answer is greatly influenced by the indices based on which we define the required vitamin amount; deficiency or insufficiency. Considering the social background that NCDs are the leading cause of morbidity and mortality in developed countries, disease risk due to vitamin insufficiency is of great clinical and societal significance.

Sources of Vitamin D

Vitamin D consists of ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). The former is from plant-based food, and the latter is either synthesized in the skin under the influence of ultraviolet (UV)-B or taken from animal food.[5] Vitamin is an organic compound distinct from fat, carbohydrate, and protein, a natural food component usually present in minute amounts and essential for normal physiological functions.[1] Vitamin D is unique in that significant amount is produced in the skin under the influence of UV-B.

Pro-vitamin D (7-dehydrocholesterol; 7-DHC) in the skin is the precursor of vitamin D_3, and the B ring of its sterol nucleus is opened by the action of UV-B, yielding pre-vitamin D_3, which then is converted to cholecalciferol (vitamin D_3) by thermal isomerization. An estimate states that adults can biosynthesize as much as 600 IU vitamin D_3 per day. Amount of vitamin D_3 synthesized in the skin is influenced by various factors. Environmental factors such as season, latitude, and time of the day all exert major contribution to the dermal vitamin D_3 production. It has been reported that subjects living above 40 degrees N/S cannot expect vitamin D_3 production in the skin during wintertime. Vitamin D_3 production in the skin is much higher during summertime than that during wintertime, and highest at midday, since UV-B irradiation depends on the zenith angle of the sun.[1] Dermal vitamin D_3 production is also influenced by the skin types. In subjects with darker skin, vitamin D_3 production in the skin is much lower than in those with lighter skin, and the black subjects are more susceptible to vitamin D deficiency/insufficiency. Vitamin D_3 production in the skin is diminished by clothing, sunscreen use, and living indoors, since UV-B is absorbed by window glass. Foods with the abundance of vitamin D are quite limited. Next to the fish liver and oils with extremely high content of vitamin D_3, fatty fishes are rich source of vitamin D_3 because of food chain. Vitamin D_3 is produced in plankton by UV-B, which is taken up by fish, and further by larger fish. Mushrooms are rich in ergosterol, and can be a rich source of vitamin D_2 after exposure to sunlight or UV-B.[1]

Of note, breast milk is not a good source of vitamin D.[9] Yorifuji *et al.*[10] have reported that breast feeding is s significant risk of craniotabes, a rickets-like condition. Recently, Tsugawa *et al.*[11] have shown that vitamin D concentration in breast milk is much lower during wintertime than during summertime, and it is far lower in breast milk obtained in 1996 to 1997 than that in 1989.

Metabolism and Action of Vitamin D

Vitamin D, either from dermal production or intake from food, undergoes two hydroxylation, first to 25-hydroxy vitamin D [25(OH)D] (calcidiol) in the liver by such enzymes as CYP27A1, then to the active form of vitamin D, 1,25-dihydroxy vitamin D [$1,25(OH)_2D$] (calcitriol) in the kidney catalyzed by CYP27B1. CYP27B1 activity is under strict control; stimulation by parathyroid hormone (PTH) and inhibition by increased $1,25(OH)_2D$ level.[3]

Actually, $1,25(OH)_2D$ is not merely a vitamin, but a hormone. It binds to vitamin D receptor (VDR), heterodimerize with retinoid X receptor (RXR), binds to vitamin D responsive element (VDRE), and regulate the expression of hundreds of genes both related and unrelated to calcium homeostasis. VDR is ubiquitously present, the presence of which is not limited to organs related to calcium regulation. VDR-knockout mice exhibit various manifestations unrelated to calcium metabolism.[3] Additionally, CYP27B1 is present in some extra-renal organs. Renally produced $1,25(OH)_2D$ is responsible for the maintaining of its circulating level, and extra-renally produced $1,25(OH)_2D$ is considered to be involved in the local action of vitamin D. These recent findings have highlighted the significance of vitamin D in the non-classical organs, and is the basis for the extra-skeletal action of vitamin D.[3]

Biomarkers of Vitamin D

Although it is a general consensus that serum 25(OH)D concentration is the best indicator of vitamin D status, the reference values for serum 25(OH)D are still controversial.[12,13] It is known that serum 25(OH)D concentration below the cut-off value of 10 to 12 ng/ml dramatically increases the risk of severe vitamin D deficiency and mineralization defect; rickets and osteomalacia, and serum level higher than this level is required for the prevention of mineralization defects.

Regarding unfavorable outcomes other than mineralization defects, the cut-off values are still under debate. The Dietary Reference Intakes (DRIs) by the Institute of Medicine (IOM, USA) has employed the cut-off value for the serum 25(OH)D concentration of 20 ng/ml as the basis to establish the reference values.[14] The EFSA (European Food Safety Authority) has similarly determined the threshold of serum 25(OH)D level to be 20 mg/ml.[15] Cut-off value of serum 25(OH)D has also been set to be 20 ng/ml in Japanese DRIs.[16]

The Endocrine Society (USA), however, has defined vitamin D deficiency and insufficiency as serum 25(OH)D level below 20 ng/ml and 21–29 ng/ml, respectively.[13] Recently a guideline was published in Japan by the Japan Endocrine Society and Japanese Society for Bone and Mineral Metabolism regarding its judgement as below.[17]

Sufficiency:	Serum 25(OH) level, equal to or higher than 30 ng/ml
Insufficiency:	Serum 25(OH) level, between 20 and 30 ng/ml
Deficiency:	Serum 25(OH)D level, less than 20 ng/ml

Other reference values for serum 25(OH)D levels have also been described as below: sufficiency being defined as 25(OH)D >20 ng/ml (>50 nmol/L), insufficiency when the 25(OH)D are between 12 and 20 ng/ml (30–50 nmol/L), and deficiency when the 25(OH)D is <12 ng/ml (30 nmol/L).[18]

High Prevalence of Vitamin D Deficiency/Insufficiency

There have been numerous publications demonstrating that the prevalence of vitamin D deficiency/insufficiency is extremely high worldwide.[5] Even a term "vitamin D deficiency pandemic" is advocated by some researchers.[4] In a Vitamin D Standardization Program (VDSP), serum 25(OH)D concentration was evaluated in US (n = 15,652), Canada (n = 11,336), and Europe (n = 55,844).[9] It was lower than 12 ng/ml in 5.9%, 7.4%, and 13% in US, Canada, and Europe, respectively. Prevalence of serum 25(OH)D level less than 20 ng/ml was 24.0%, 36.8%, and 40.4% in US, Canada, and Europe, respectively. The prevalence was different among the ethnic groups. Analysis of US data, which is from National Health and Nutrition Examination surveys (NHANES) 2007–2010, has shown that the prevalence of serum 25(OH)D lower than 12 ng/ml was 2.3%, 6.4%, and 24% in non-Hispanic white, Hispanic, and non-Hispanic blacks,

doi: 10.3164/jcbn.23-59

respectively, highlighting the importance of skin color.

Since vitamin D is derived from dermal production by the action of UV-B (290–315 nm) or intake from food, vitamin D deficiency/insufficiency can arise from insufficient supply of vitamin D from either source or combination of both. Dermal production makes much more contribution, and it can be reduced by such reasons as high latitude, winter season, darker skin color, use of sunscreen, and age-related decreased dermal production of vitamin D.

Consequences of Vitamin D Deficiency and Insufficiency: Observational Studies

In this article, we will separately describe the results from the observational and intervention studies regarding the health consequences of vitamin D deficiency/insufficiency, since results from these two types of study designs are largely discrepant; mostly favoring the significant association of vitamin D deficiency/insufficiency and disease risks in the observational studies, whereas quite often showing the negative results in the intervention studies.

As described above, VDR is widely distributed, and vitamin D deficiency/insufficiency is a risk for many diseases (Fig. 1). However, only diseases which is common in the elderly subjects is described in this article. For example, involvement of vitamin D in the early development or in the pathogenesis of autoimmune or allergic diseases are not dealt with.

Fracture. Bone is formed by the calcium phosphate deposition onto a proteinous matrix (mineralization). Since the most fundamental role of vitamin D is to enhance the intestinal absorption of calcium and phosphorus, its deficiency causes mineralization defect; rickets and osteomalacia.

In vitamin D insufficiency, the unfavorable consequence of vitamin D insufficiency is considered to be mainly caused by the increased serum parathyroid hormone (PTH) level. Because of the impaired intestinal calcium and phosphorus absorption, serum calcium level decreases. Since maintaining serum calcium concentration is of vital importance, secondary hyperparathyroidism with resultant exaggerated bone resorption occurs, leading to the increased fracture risk.[2] In a Swedish cohort study, 1,504 women aged 75 years were measured for their serum 25(OH)D levels at the age of 75 and 80, and evaluated for the 10-year fracture incidence.[19] They were divided into three groups according to their serum 25(OH)D level; <20 (low), 20 to 30 (intermediate), and >20 ng/ml (high). Compared to the high group, hip fracture incidence in the low group was significantly higher between 80 to 85 years of age [22.2% (low) vs 6.6% (high); $p = 0.003$], which was more marked between 80 to 90 years of age. In contrast, another Swedish cohort study has reported negative results.[20] Swedish women ($n = 66,651$) completed the food frequency questionnaire, and were followed up. In the multi-variate analysis, the hazard ratio (HR) for total fracture or hip fracture was not significantly different from unity among the tertiles of vitamin D intake. The authors have concluded that dietary intake of vitamin D is of minor importance. Caution is needed, however, in the interpretation of these results. Vitamin D status was evaluated by serum 25(OH)D level in the former, and dietary vitamin D intake in the latter. Considering the much larger contribution of dermal production than intake from food to the vitamin D status, above results are conceivable. In a recent meta-analysis including 20 cohort studies, higher serum 25(OH)D level was associated with lower risk of hip fracture with the relative risk (RR) of 0.89 (95% CI; 0.80, 0.98), but not associated with the risk of total fracture.[21] Such apparently discrepant results are understandable taking the pathophysiology of osteoporosis into account. Vitamin D insufficiency causes increased secretion of PTH, which enhances the resorption of cortical bone rather than trabecular bone. Since trabecular bone predominate in the vertebrae, and distal femur consists of both components, vitamin D insufficiency is a risk of hip fracture.[22] Lack of association between serum 25(OH)D and the risk of total fracture could be explained by that vertebral fracture is the most prevalent fracture in osteoporosis.

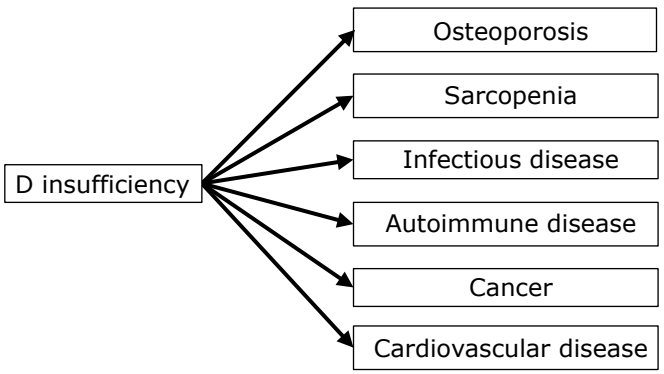

Fig. 1. Vitamin D insufficiency as a risk of various diseases. Vitamin D insufficiency increases the risk of various diseases including osteoporosis, sarcopenia, infectious disease, autoimmune disease, cancer, and cardiovascular disease.

Muscle weakness and falling. Essential involvement of vitamin D in the muscle is illustrated by the finding that systemic VDR knockout mice exhibited smaller and immature muscle cells especially of fast-twich fibers and cardiomyocyte selective VDR deletion caused hypertrophy and fibrosis.[3]

In humans also, severe vitamin D deficiency with long duration is known to be associated with muscle weakness and cardiomyopathy.[23] In an Italian study involving 976 subjects aged 65 years or older, percentage of subjects with their serum 25(OH)D level less than 10 ng/ml was 28.8% in women and 13.6% in men, and serum 25(OH)D level was less than 20 ng/ml in 74.9% of women and 51.0% of men. Subjects with serum 25(OH)D level less than 10 ng/ml had worse short physical performance battery (SPPB) score, and those with serum 25(OH)D level less than 20 ng/ml had lower handgrip strength.[24] Similar findings have also been reported from many cross-sectional studies.[23] In a prospective study, authors of the Newcastle 85+ Study have studied the contribution of season-specific quartiles (SQ1 to SQ4) of serum 25(OH)D level and grasp strength and index of physical activity (Timed Up-and-Go test; TUG) for 5 years.[25] Men in SQ1 had a significant annual decline in grasp strength which accelerated over time after full adjustment. The authors have concluded that low baseline 25(OH)D may contribute to muscle strength decline in the very old people and particularly in men. The overall results from many papers, however, are somewhat inconsistent, probably because of the heterogenous population of the study subjects such as the inclusion of very old subjects or not, and their vitamin D status as well as the assessment method of muscle strength.[23]

Cancer. The roles of vitamin D in reducing the incidence of cancer has long been studied with increasing number of recent publications.[26] The first report suggesting the vitamin D status and cancer came from the ecological studies showing the association of latitude and sun exposure and cancer mortality,[26] which has prompted the laboratory studies on the vitamin D action on cancer cells. Of interest is the observation that VDR expression is decreased or absent in cancer cells. Later on, papers from many observational studies appeared on the relationship between vitamin D status and the risk of various cancer. Regarding colorectal cancer, in the combined analysis of the results from Health Professionals Follow-up Study (HPFS)

including 18,225 men and Nurses' Health Study (NHS) including 32,826 women, the pooled odds ratio (OR) for colorectal cancer was 0.66 (p for trend, 0.01).[27]

A few words of caution deserve to be addressed. In the observational studies on the relationship between vitamin D and cancer, serum 25(OH)D is used as an indicator of vitamin D status. Reports employing dietary vitamin D intake have yielded much lower correlation than those using serum 25(OH)D level, reflecting that dietary intake makes only minor contribution to the vitamin D status. Using serum 25(OH)D is still problematic, since it exhibits both seasonal and long-term variation. Thus, in the observational studies, longer follow-up time is associated with less marked vitamin D effects. Generally, the relationship that higher serum 25(OH)D concentration is associated with lower cancer risk than its lower level is more prominent in case control and nested case control studies than in cohort studies, probably reflecting the longer study duration in the latter.[26]

Cardiovascular disease. Vitamin D exerts beneficial effects on endothelial, vascular smooth muscle, and cardiac muscle cells.[3] It also negatively affects renin-angiotensin-aldosterone (RAA) system. Indeed, high RAA and cardiac hypertrophy were observed in VDR-knockout mice. Observational studies have unequivocally shown the inverse relationship between vitamin D status and cardiovascular risk factors and cardiovascular events. Besides cross-sectional studies, such relationship was confirmed in the cohort studies. In the Framingham Offspring Study, subjects with their serum 25(OH)D concentration below 15 ng/ml had higher risk of developing their first cardiovascular event (HR 1.62; 95% CI 1.11 to 2.36). A meta-analysis of 19 prospective studies including 65,944 subjects, the relative risk of cardiovascular disease was 1.05; 95% CI 1.00 to 1.60 per 10 ng/ml decrease in serum 25(OH)D level.[3,28]

Consequences of Vitamin D Deficiency and Insufficiency: Intervention Studies

Fracture. Regarding the fracture prevention by vitamin D, results from intervention studies are rather conflicting, in contrast to the reports from observational studies mostly favoring the increased risk in vitamin D deficiency/insufficiency. Diverse study designs have been adopted in the intervention trials, e.g., vitamin D alone or in combination with calcium, and administration of daily smaller dose or intermittent larger dose, which are known to affect the treatment effects. A recent meta-analysis by Bolland *et al.*[29] have evoked a controversy. They have concluded that vitamin D intervention does not decrease the fracture incidence, and it should not be given for the fracture prevention. Criticism against their systematic review includes exclusion of trials employing the intervention with vitamin D plus calcium, which is considered to be more effective than vitamin D alone, inclusion of trials with short duration, inclusion of trials employing the annual intervention with very high dose, which is suspected to rather increase the fracture risk.[30]

In their earlier work by Chapuy *et al.*,[31] daily supplementation with 800 IU of vitamin D and 1,200 mg of calcium decreased the incidence of hip, and other non-vertebral fractures by 43% and 32%, respectively. Of note, the study subjects in their study were nursing home or apartment dwelling elderly women with their mean serum 25(OH)D level only 13 to 16 ng/ml. Additionally, serum 25(OH)D level was measured by the older competitive protein binding assay (CPBA), which is reported to give much higher value than HPLC.[32] Thus, the subjects in their study are considered to be even more vitamin D deficient. Vitamin D intervention is quite likely to be effective in those with vitamin D deficiency, but not in vitamin D sufficient subjects.[32]

Younger, well-nourished subjects, who are likely to be vitamin D sufficient, are unlikely to benefit from vitamin D supplementation, but elderly subjects are expected to be improved, since they are quite likely to be vitamin D deficient/insufficient because of decreased dermal production, deficient consumption of vitamin D-rich food.[32,33] Indeed, in a recent RCT, vitamin D supplementation decreased the hip and other non-vertebral fracture by approximately 15%, and the effects were more marked in subjects in seventies or eighties than those in sixties, and in the institutionalized subjects than those with community-dwelling.[34]

Muscle weakness and falling. Previous results on the vitamin D supplementation are conflicting.[23] Regarding the various interventions for preventing falls in older people, two Cochrane reviews are available, one for those in care facilities and hospitals,[35] and the other for the community-dwelling elderly.[36] In the former, 95 trials (138,164 participants), 71 (40,374 participants; mean age 84 years; 75% women) in care facilities and 24 (97,790 participants; mean age 78 years; 52% women) in hospitals were included.[35] Regarding vitamin D, there is moderate-quality evidence that vitamin D supplementation (4,512 participants, 4 studies) probably reduces the rate of falls (RR 0.72, 95% CI, 0.55 to 0.95), but not the risk of falling (RR 0.92, 95% CI 0.76 to 1.12). In contrast, vitamin D intervention did not reduce the falls in the latter in community-dwelling elderly as a whole.[36] Interestingly, the rate of falls and the risk of falling were reduced by the intervention; RR 0.81 (95% CI 0.68 to 0.97) for the former and RR 0.88 (95% CI 0.80 to 0.96) for the latter, even in the community-dwelling subjects with serum 25(OH)D level below 20 ng/ml.[36]

Bouillon *et al.*[3] have concluded that there is at present no consensus regarding the potential beneficial effects of vitamin D supplementation on muscle function, balance, and risk of falls. Thus, the observational data favor the relationship between vitamin D status and muscle strength and physical performance, the results from the intervention studies are conflicting. At present, the conclusion by Remelli *et al.*[22] would be the acceptable one from the practical viewpoint that clinicians should screen vitamin D levels in sarcopenic patients and advocate oral supplementation to any older person with vitamin D deficiency/insufficiency, since vitamin D deficiency is very common in older people and vitamin D has many other biological effects.

Caution is needed, however, that very high dose of vitamin D supplementation may increase the risk of falling.[3] Sanders have conducted an RCT in 2,256 community-dwelling women aged 70 years or over with the annual oral administration of 500,000 IU vitamin D_3. In the intervention group, the RR of falling and fracture was 1.15 (95% CI, 1.02–1.30), and 1.26 (95% CI, 1.00–1.59), respectively.[37] Similar findings have repeatedly been reported.[3]

Cancer. In large-scale, intervention trials, vitamin D intervention was not associated with decreased cancer incidence.[2] In VITAL study including 25,874 subjects, daily supplementation with vitamin D (2,000 IU/day) did not reduce the incidence of invasive cancer. In the ViDA study, monthly vitamin D supplementation did not affect the cancer incidence. Of note, however, participants in these studies were mostly vitamin D sufficient with serum 25(OH)D concentration 30.8 ± 10 ng/ml in VITAL and 26.5 ± 9 ng/ml in ViDA. Large-scale intervention study including vitamin D deficient/insufficient subjects is unavailable. Thus, vitamin D supplementation is quite unlikely to exert beneficial effects in vitamin D sufficient subjects.

Cardiovascular disease. In two large-scale trials (VITAL and ViDA), no significant reduction in cardiovascular events was observed.[2] In the former, the HR for the major cardiovascular events and cardiovascular death was 0.97 (95% CI, 0.85 to 1.12) and 1.11 (95% CI, 0.88 to 1.40) during the 5.3 years of follow-up. Similarly in the latter, HR for major cardiovascular events was 1.02 (95% CI, 0.87 to 1.20). In a meta-analysis including 21 RCTs (83, 291 patients) aged 65.8 ± 8.4 years, vitamin D supplementation did not reduce the major adverse cardiovascular events (RR, 1.00, 95% CI, 0.95–1.06), myocardial infarction

doi: 10.3164/jcbn.23-59

(RR, 1.00, 95% CI, 0.93–1.08), stroke (RR, 1.06, 95% CI, 0.98–1.15), CVD mortality (RR, 0.98. 95% CI, 0.90–1.07), or all-cause mortality (RR, 0.97, 95% CI, 0.93–1.02).[28] Such null results were unaffected by the baseline vitamin D status, but only few subjects are included in large-scale trials.[2]

Methodological Considerations Regarding the Intervention Studies

Methodological consideration is warranted regarding the interpretation of intervention studies by vitamin D. Recently, a review has been published summarizing the recent human studies with emphasis on extra-skeletal effects of vitamin D.[2] In this review, recent publications from randomized controlled trials (RCTs) and Mendelian randomization studies have been reviewed regarding type 2 diabetes mellitus (T2DM), cancer, cardiovascular events, musculoskeletal effects and falls, lung function and respiratory effects, autoimmune diseases, pregnancy, and mortality. Although only the small-scale RCTs have been available before, large-scale RCTs have been published in recent several years, and such RCTs between 2017 to 2020 are reviewed here.

VITAL study recruited more than 25,000 subjects, and studied the effects of 2,000 IU/day of vitamin D supplementation for the average duration of 5.3 years,[38] but the results were negative with the HR for invasive cancer incidence of 0.96 (95% CI 0.88–1.06). Vitamin D Assessment (ViDA) study has studied the effects of monthly high-dose (100,000 IU/day) of vitamin D supplementation including 5,108 subjects with the mean duration of 3.3 years. The results were also negative with the HR for cancer incidence of 1.01 (95% CI 0.81–1.25).[39] In Vitamin D and type 2 diabetes (D2d) study, 2,423 subjects with high risk of progressing to T2DM were given 4,000 IU/day of vitamin D for the mean duration of 2.5 years.[40] Vitamin D supplantation was associated with non-significant effect for reducing the developing T2DM with the HR of 0.88 (95% CI 0.75–1.04). In DO-HEALTH study, 2,157 subjects were given 2,000 IU/day of vitamin D with the mean duration of three years.[41] Vitamin D supplementation was without significant effects. Among adults without major comorbidities aged 70 years or older, treatment with vitamin D_3, omega-3 fatty acids, or a strength-training exercise program did not result in statistically significant differences in improvement in systolic or diastolic blood pressure, nonvertebral fractures, physical performance, infection rates, or cognitive function.

Consequences of Vitamin D Deficiency and Insufficiency: Mendelian Randomization Studies

Mendelian Randomization Studies (MR) is another novel study design enabling to reduce the bias inherent in observational studies such as confounders and reverse causation.[2] In MR, single nucleotide polymorphisms (SNPs) associated with serum 25(OH)D level is employed. Although many papers using MR have been published with regard to vitamin D, they have not been promising. In an earlier study, SNPs in four genes related to vitamin D production and metabolism were used, which, however, could explain only 2.4% of variance in serum 25(OH)D level.[3] The accountability was probably too low to detect the association. A recent study has identified more than 150 related SNPs explaining 10.5% of variance in serum 25(OH)D level, which will enhance the studies on MR related to vitamin D.[2]

Disease Risk and Vitamin Insufficiency from the Disease Point of View

Let us take the osteoporotic fracture risk as an example (Fig. 2). Insufficiency of various vitamins, including those other than vitamin D, are known to be risk factors of osteoporotic fracture. For example, vitamin K insufficiency is a risk of osteoporotic fracture.[8] Vitamin K is a cofactor of γ-carboxylase in the liver, which introduces additional carboxyl group to the glutamic acid residue in four of the blood coagulation factors, providing the calcium ion binding capacity. Thus, vitamin K deficiency causes blood coagulation abnormality, but there are many proteins which are vitamin K-dependently γ-carboxylated other than blood coagulation factors. Vitamin K insufficiency is associated with undercarboxylation of osteocalcin, which is an abundant non-collagenous bone matrix protein, and a risk of osteoporotic fracture.

Additionally, hyperhomocysteinemia (HHcy) is a risk of osteoporotic fracture. Folate, vitamin B_{12}, vitamin B_6, and vitamin B_2 are involved in one-carbon metabolism in their co-enzyme forms.[42] Homocysteine (Hcy) is an intermediate in the methionine cycle, and metabolized either by re-methylation to methionine or to cysteine by trans-sulfation. Re-methylation to methionine is catalyzed by methionine synthase with 5-methyltetrahydrofolate as a methyl group donor and vitamin B_{12} (methylcobalamin) as a cofactor. Alternative fate of Hcy is the trans-sulfation to cysteine in a vitamin B_6-dependent way. Therefore, inadequate status of these vitamins causes elevated plasma Hcy concentration; HHCy. HHCy has been reported to exert various detrimental effects on the endothelial cells, and has been reported to be associated with the risk for CVD.[43] There have been observational studies showing the positive strong association between HHCy and the risk of osteoporotic fractures.[44,45] Osteoporosis refers to a state with increased fracture risk, which is caused by either decreased bone mineral density or compromised bone quality. HHCy is considered to increase the fracture risk by interfering the collagen structure and impairing the bone quality.

Although vitamin D deficiency/insufficiency is a risk of osteoporotic fracture, it is not the only vitamin associated with fracture risk. Thus, when considering the health effects of vitamin D, other vitamins' nutritional status must be also considered. There

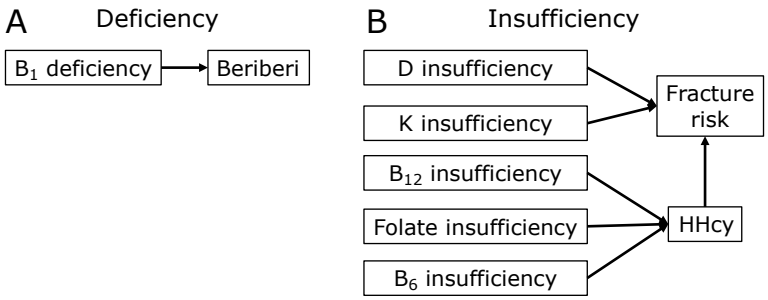

Fig. 2. Relationship between disease and vitamin deficiency and insufficiency. Vitamin deficiency causes a classical deficiency disease, e.g., beriberi due to vitamin B_1 deficiency (A). In contrast, multiple vitamins increase the disease risk (B).

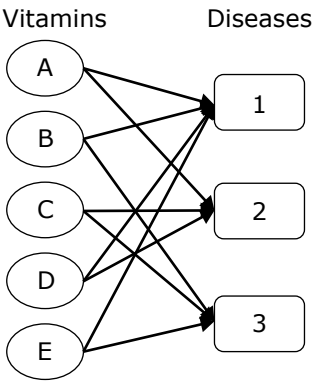

Fig. 3. Complex relationship between vitamins insufficiency and diseases risk. Vitamin insufficiency is a risk of various diseases, and multiple vitamins contribute to the increased disease risk, showing the multiple to multiple relationship.

appeared a paper from the cohort study investigating the effects of multiple vitamin deficiencies on the incident fracture risk.[46] The subjects were evaluated for their status regarding vitamin D, vitamin K, and B vitamins related to HHCy, and divided into 0, 1, 2, and 3 depending on the number of deficient vitamins. The number of deficient vitamins was significantly associated with incident fracture with the HR of 1.25 (95% CI 1.04–1.50). In the case of vitamin deficiency, single vitamin deficiency causes a classical deficiency disease, but in insufficiency, multiple vitamin insufficiency is associated with multiple disease risks (Fig. 3).

Vitamin D Deficiency/Insufficiency and Elderly Health

Vitamin D deficiency is known to be a risk of many diseases prevalent in the elderly. Elderly subjects have various conditions which make them susceptible to vitamin D deficiency/insufficiency.[32] In the skin, 7-DHC is converted to previtamin D_3 by the action of UV-B. Both dermal content of 7-DHC and dermal capacity to produce vitamin D has been reported to be markedly decreased in the elderly. A recent study has shown that 13% reduction of dermal production per decade, which means that vitamin D production in subjects of 70 years of age is approximately half of that in those at 20 years of age.[30] Decreased dermal vitamin D production would be more marked in the institutionalized elderly. Additionally, the elderly subjects are likely to be vitamin D-resistant. Conversion of 25(OH)D to the active form, $1,25(OH)_2D$ by renal CYP27B1 is decreased in the elderly.

Multimorbidity is quite common in the elderly subjects.[6] Individually prescribing therapeutic drugs to each disease causes polypharmacy, which is associated with various adverse outcomes such as mortality, falls, adverse drug reactions through drug-drug interactions and drug-disease interactions.[6] Vitamin insufficiency is a risk of various diseases, and correcting the vitamin status alone would reduce the risk of many diseases, and is favorable to avoid the undesirable consequences of polypharmacy in the elderly.

Possible Vicious Cycle between Vitamin D deficiency/insufficiency and Disease Risk

Vitamin D deficiency/insufficiency and diseases prevalent in the elderly can form a vicious cycle, the good example of which would be its relation to osteoporosis and sarcopenia (Fig. 4).[22] Hypovitaminosis D is a risk of sarcopenia and osteoporosis. Once sarcopenic and osteoporotic, the affected subjects are associated with slower walking speed, decline in morbidity, increased risk of falling and fracture, and institutionalization, which would further aggravate malnutrition and hypovitaminosis D. Additionally, the elderly subjects have quite often such chronic diseases as cardiovascular disease, stroke, diabetes mellitus, chronic kidney disease, and chronic lung disease, which are associated with

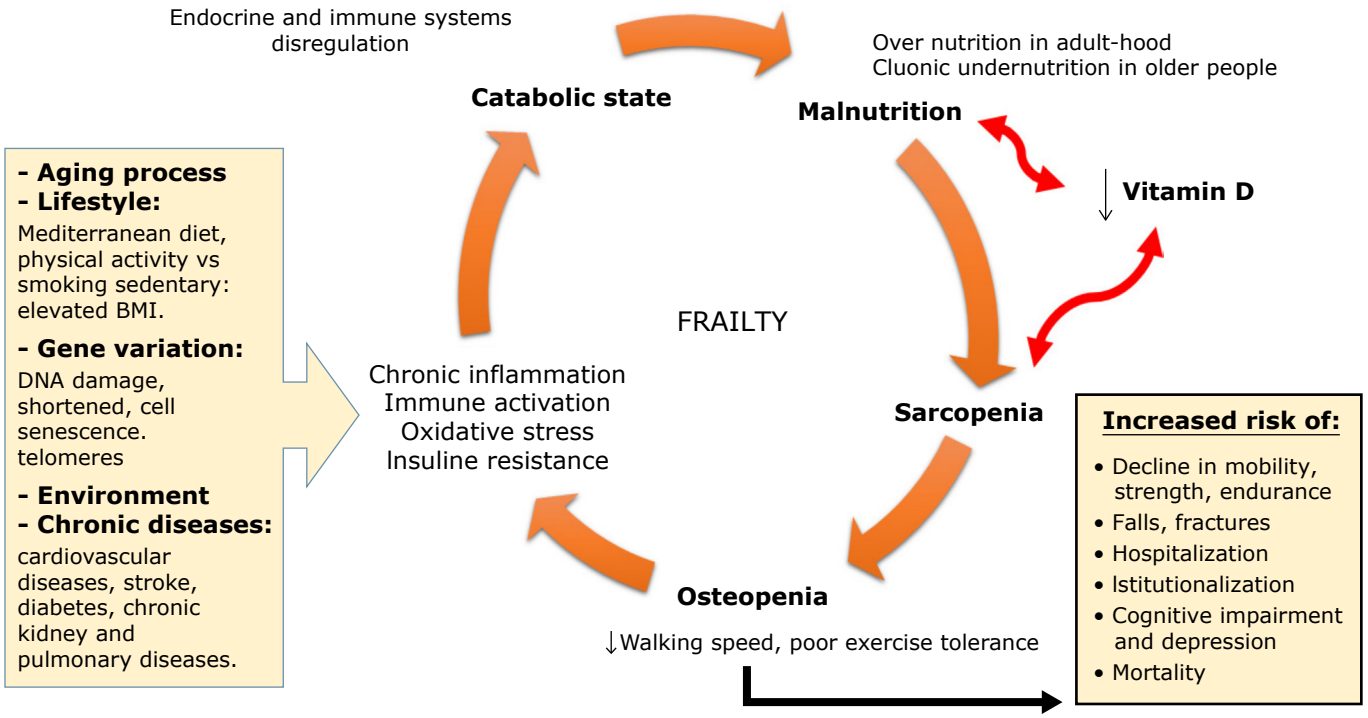

Fig. 4. Vicious cycle of vitamin D and frailty. Vitamin D evokes a vicious cycle in sarcopenia, osteoporosis, and malnutrition. Adopted from reference (23) with the Creative Commons, CC BY license.

doi: 10.3164/jcbn.23-59

unfavorable conditions including chronic inflammation, enhanced immune activation, increased oxidative stress, and insulin resistance, all contributing to the catabolic state and worsening the malnutrition. These conditions would further worsen the vitamin D deficiency/insufficiency, and aggravate the sarcopenia and osteoporosis.

How can We Improve the Vitamin D Nutritional States in the Elderly?

In a recent review, three strategies besides dietary intake, have been suggested for improving the vitamin D status; sunshine exposure, food fortification, and supplementation.[32]

Even if the dermal vitamin D production is compromised in the elderly as described above, they can still synthesize significant amount of vitamin D in the skin.[5] Higher UV exposure would surely enhance the dermal production, and staying longer time outdoors will be of additional health benefits. However, encouraging the elderly subjects to increase their UV exposure as a measure to improve their vitamin D status is controversial, considering the association of UV exposure and non-melanoma skin cancer.[32] In areas where fish is not often consumed, the natural food source of vitamin D is scarce. Food fortification can be a promising alternative, but is under legal registry in many countries. Giustina *et al.*[32] have concluded that supplementation would be the easiest way in the elderly and institutionalized subjects. Then, how much dose is needed? Cashman *et al.*[9] have performed a meta-regression analysis of an individual subjects from RCTs during winter, and concluded that for avoiding severe deficiency (10 ng/ml), daily dose of 400 IU is needed, and for achieving 20 ng/ml, daily dose of 1,000 IU is required.

Conclusion

Vitamin D insufficiency, milder than deficiency, is quite common. Since vitamin D has various skeletal and non-skeletal roles, its insufficiency is a risk of diversity of diseases such as osteoporosis, sarcopenia, cardiovascular disease, cancer. The association of vitamin D status and disease risk is mostly positive in the observational studies, but conflicting in the intervention studies. Such discrepancy probably arises from various methodological problems, the most important of which would be the baseline vitamin D status. The title of a recent review is very informative, which is entitled, "Vitamin D: Giveth to those who needeth".[30] Thus, vitamin D intervention would be effective in the deficient/insufficient subjects, but not sufficient subjects. Since the elderly subjects, especially the institutionalized people, are quite likely to be vitamin D deficient/insufficient, they are likely to benefit from improvement of vitamin D status. Since vitamin D deficiency/insufficiency induces a vicious cycle, its correction is of even more importance.

Unlike vitamin deficiency, vitamin insufficiency is a risk of various diseases, and correcting the vitamin status alone would reduce the risk of many diseases, and is favorable to avoid the undesirable consequences of polypharmacy. Additionally, disease prevention by nutritional improvement is cheap and free from side effects, it is suited for the primary prevention of diseases.

Author Contributions

KT has constructed the overall design, and critically reviewed the papers on diseases associated with vitamin D deficiency/insufficiency. MA and AK have searched the papers regarding vitamin D and disease risk, and reviewed them independent of KT. JT has searched the papers on elderly nutrition, and reviewed them. KT has mainly prepared the original manuscript, which was revised several times after in-depth discussion with MA, JT, and AK. All authors have agreed with the final version of the manuscript.

Acknowledgments

This work was supported by JSPS KAKENHI 19K11755 (KT), 20K23303 (MA), 23K01834 (JT), and 19K11747 (AK), and Health, Labor and Welfare Science Research 22FA2022 (KT as a co-investigator).

Conflict of Interest

No potential conflicts of interest were disclosed.

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doi: 10.3164/jcbn.23-59