Humans acquire vitamin D through skin photosynthesis and digestive intake. Two hydroxylations are needed to obtain the bioactive compound, the first produces 25-hydroxyvitamin D [25(OH)D], and the second 1,25-dihydroxyvitamin D [1,25(OH)₂D]. There is no consensus regarding the appropriate cut-off level to define the normal serum 25(OH)D range. Experimental, epidemiological and clinical studies have related low vitamin D status with longevity. Although some results are controversial, low serum 25(OH)D levels have been linked to all-cause, cardiovascular, cancer and infectious related mortality.

Throughout life span a significant proportion of human beings display insufficient (20-30 ng/mL) or deficient (<20 ng/mL) serum 25(OH)D levels. Appropriate lifestyle changes, such as regular short exposures to sunlight (15 min a day), and an adequate diet that includes vitamin D rich components, are not always easily accomplished. Studies relating to vitamin D supplementation have methodological limitations or are based on relatively low doses. Therefore, dosages used for vitamin D supplementation should be higher than those traditionally suggested. In this sense, there is an urgent need for prospective controlled studies using high daily vitamin D doses (2,000 IU or higher) including cardiovascular, cancer, infectious and other endpoints. Relationship between vitamin D and health outcomes is not linear, and there are probably various optimal vitamin D levels influencing different endpoints.

Key words: Vitamin D - Mortality - Longevity - Cancer.

Steroid hormones display pleiotropic functions through specific receptors and non-genomic mechanisms. Vitamin D is a secosteroid that was initially classified as an essential compound that should be provided through the diet. However, vitamin D production in mammals – including humans — is a complex process including skin photosynthesis and two metabolic hydroxylations: one in the liver to produce 25-hydroxyvitamin D [25(OH)D] or calcidiol (1 ng/mL=2.5 nmol/L) and a second at different tissues to render 1,25-dihydroxyvitamin D [1,25(OH)₂D] or calcitriol. Under optimal conditions, humans may synthesize 90% of their vitamin D requirements.
Vitamin D is produced by plankton and several fish which are included in the alimentary chain. Human beings acquire 10% of the daily required vitamin D from intestinal absorption. Food rich in vitamin D include fish (catfish, salmon, mackerel, sardines, tuna fish), ultraviolet B radiated mushrooms and few other vegetables. Vitamin D is also obtained from fortified foods or through vitamin D supplements. In women, vitamin D dietary intake may range from 2.4 (Spain) to 10.5 µg/day (Finland). Higher serum levels observed in Finland, especially in men, are relate to the fact that milk is vitamin D fortified, a semi-mandatory regulation in this country. Early studies using autoradiographic and histochemical methods demonstrated vitamin D cell nuclear binding in a wide range of organs and systems, and that the regulation of calcium homeostasis is only one of its many functions. Vitamin D participates in numerous biological processes: mineral and bone metabolism, direct genomic actions, cell functions, and immune responses. In addition, vitamin D is involved in the lysosome-mediated catabolic pathway of autophagy associated to anti-aging, antimicrobial effects, and tumor suppression. The present review will discuss aspects of vitamin D related to mortality and longevity, beyond its participation in mineral metabolism.

**Longevity and prevalence of low vitamin D status**

Longevity and aging are mutually related complex processes which are genetically determined and environmentally altered. From ancient time humans have searched for the “Fountain of Youth” to counteract the ageing process (increase longevity), as one can observe from the writings of Herodoto, the desperate search in Florida by Ponce de Leon and even in recent times by the pirate Jack Sparrow who supposedly found the fountain. The antithesis of the mythical site could be the Fountain of Death described in “The Immortal” a short story by Jorge Luis Borges. Although there are no such fountains, the genome and cells are quite sensible to dietary components and environmental factors. Thus, caloric intake, antioxidants, and micronutrients may influence both longevity and mortality through different mechanisms. Endogenous vitamin D status has been associated to all-cause mortality and the prevalence of different age-related diseases.

25(OH)D has a long half life, represents the endogenous vitamin D status, and is the precursor of the bioactive compound: 1,25(OH)2D. Very low serum levels of 25(OH)D (<10 ng/mL) are associated with rickets in children or osteomalacia in adults, and increased serum parathyroid hormone (PTH) levels. Low serum 25(OH)D levels (10-30 ng/mL) have been associated to osteoporosis, neuromuscular alterations, falls and other diseases. Although there is no definitive consensus, optimal serum 25(OH)D levels seem to be around 30 to 50 ng/mL or even higher. More than a quarter of the world population has low serum vitamin D levels. This situation is the consequence of dietary and lifestyle factors which reduce both normal synthesis and digestive intake. Currently, a great deal of individuals do not receive enough sunlight and others have pigmented skin or are sunscreen users which may interfere with vitamin D synthesis. Aging reduces skin vitamin D production, with a gender disadvantage observed among women. Indeed, mild to severe degrees of hypovitaminosis D may occur from early (intrauterine) life to advanced age. Elder, obese and those with pigmented skin are vulnerable populations. Even in the sunniest locations, the prevalence of insufficient (20-30 ng/mL) or deficient (<20 ng/mL) serum 25(OH)D levels is high in relation to age, race, lifestyles, and adiposity among others.

**Serum vitamin D levels and mortality: all-cause and cardiovascular**

After a median follow-up of 3.8 years, the National Health and Nutrition Examination...
Survey (NHANES) 2001-2004 provided evidence relating serum 25(OH)D levels and all-cause mortality among general adults. Mean vitamin D levels were significantly lower in subjects who died (21 ng/mL) than those who survived (24.3 ng/mL). After adjusting for several confounders, vitamin D levels were weakly and inversely associated to all-cause mortality. Cause-specific mortality of the NHANES cohort (1988-1994) was analyzed in 2001, showing that individuals with serum 25(OH)D levels in the lowest quartile had a higher risk for cardiovascular death. The higher age- and sex-adjusted cardiovascular mortality observed in blacks vs. whites was attenuated by 25(OH)D adjustment, and fully eliminated when income adjustment was included.

Studies performed in Europe have confirmed the association between serum 25(OH)D and all-cause and cardiovascular mortality. The Italian prospective InCHIANTI (Invecchiare in Chianti, Aging in the Chianti Area) cohort study reported a link between low serum 25(OH)D levels and all cause and cardiovascular disease (CVD) mortality among 1,006 adults (65 years or more) followed-up for a median of 6.5 years. Subjects with 25(OH)D levels in the lowest quartile (<10.5 ng/mL) displayed a significant higher risk for all-cause and CVD mortality. After an 11.7 year follow-up, the Tromso study also reported a significant higher risk for all-cause mortality among non-smokers with 25(OH)D levels in the lowest quartile as compared to the highest one, with no differences observed for smokers.

The Mini-Finland Health Survey evaluated the value of 25(OH)D serum determination in predicting CVD mortality in subjects aged 30 or more free of CVD at baseline. The hazard ratios (HRs) for global CVD and cerebrovascular death were significantly lower for individuals with 25(OH)D levels in the highest quintile in comparison to the lowest one. However, no differences were observed for coronary-related death. More recently, a population-based Finnish cohort reported that serum 25(OH)D concentrations were associated to all cause and cardiovascular mortality. The cohort included individuals free of CVD and cancer at baseline. After a mean 9.1 year follow-up and confounder adjustments, hazard ratios (HRs) for all-cause death was greater in the lower 25(OH)D tertile. The association between 25(OH)D levels and total mortality was reported in a Uppsala community-based cohort of elderly men (mean 71 years at baseline) who were followed-up for 12.7 years. Mortality cases increased at the lowest and highest levels of 25(OH)D (U-shape).

After 15 years of follow-up, diabetic patients with serum 25(OH)D levels below 13.9 nmol/L (the lowest 10th percentile) displayed a two-fold higher risk for all-cause and cardiovascular mortality even after adjusting for diabetes duration, glycated hemoglobin status, kidney function and cardiovascular risk (CVR) factors. In patients with heart failure, serum vitamin D and PTH levels are markers of cardiovascular and all-cause mortality in multivariate regression analyses adjusted for other independent prognostic variables. In this study, HRs for vitamin D deficiency (<20 ng/mL) was 1.9.

Low serum 25(OH)D levels measured before hospitalization of critically ill patients to intensive care units were associated to all-cause and cardiovascular mortality. In this ill population, when 25(OH)D levels were categorized as deficient (<15 ng/mL), insufficient (16-29 ng/mL), and sufficient (≥30 ng/mL), logistic regression analysis showed that 25(OH)D deficiency prior to hospital admission was a significant predictor of short- and long-term all-cause patient mortality and blood culture positivity.

**Vitamin D and cancer**

Vitamin D has pivotal roles in a wide range of cellular mechanisms involved in cancer development. Experimental and preclinical studies indicate that vitamin D metabolites may delay tumor progression.
through cell cycle intervention and apoptosis. These effects may be mediated through vitamin D receptors (VDRs) expressed in cancer cells. VDR polymorphisms have been associated to a higher risk for breast, prostate, colon and other cancers. Vitamin D may protect from tumor progression by modulating p53 protein, fact that provides vitamin D the profile of an anti-apoptotic agent.

Sunlight and latitude of residency have been related to a higher risk for some types of cancer. A meta-analysis addressed the relationship between vitamin D levels and cancer incidence and mortality. Twenty of 30 studies assessing vitamin D and colon cancer showed that individuals with higher vitamin D levels had either a lower colon cancer incidence or decreased mortality. Similarly, 9 of 13 studies regarding breast cancer and 13 of 26 related to prostate cancer evidenced the beneficial effects of sufficient vitamin D levels over incidence or mortality.

In the NHANES III cohort, total cancer mortality was unrelated to serum 25(OH)D levels in the entire population. Contrarily, colorectal cancer mortality was inversely related to serum 25(OH)D levels. Thus, individuals with 25(OH)D levels ≥80 nmol/L or higher displayed lower cancer mortality rates as compared to those with levels below 50 nmol/L. This study has been reinterpreted as a significant lower breast cancer mortality rate found in women presenting 25(OH)D serum levels above 62.5 nmol/L.

Assessment of dose-response effects of vitamin D over colorectal, breast and prostate cancer has been reviewed in a recent meta-regression analysis of 35 studies that included 25(OH)D measurements. The relative risk for a 10 ng/mL increase in serum 25(OH) D was 0.85 for colorectal cancer, 0.89 for breast cancer, and 0.99 for prostate cancer. Thus, it seems that 25(OH)D levels display a consistent inverse relationship with colorectal cancer.

Serum 25(OH)D and 1,25(OH)₂D levels have been related to prostate cancer mortality. In regression models adjusted for different factors, the HR was significantly higher for total mortality in subjects (men and women) in the lowest quartile of 25(OH)D as compared to those in the highest while there was no association between 1,25(OH)₂D and total mortality.

A research of the French National Institute for Health and Medical Research including 70,000 women studied over a 10-year period concluded that sufficient ultraviolet B exposure is a key element in boosting vitamin D production while diet or nutritional supplements play a secondary role only. Thus, regular sun exposure and a vitamin D rich diet reduce breast cancer risk 32% to 43%. They also surmise that the deciding factor in breast cancer prevention is exposure to adequate amount of ultraviolet B rays. Admittedly, food that is rich in vitamin D, such as fish, dairy products, eggs and certain types of oils or food supplements, can boost the solar effects; however, researchers believe the latter may have little effect on the occurrence or progression of the disease if applied alone.

Cancer risk among participants included in the NHANES III was analyzed according to 25(OH)D levels, season at sampling and latitude of residency. In this cohort the relative risk (RR) was higher (1.85) for men having 25(OH)D levels ≥100 nmol/L as compared to those having levels <37.5 nmol/L. Although in women the risk was unrelated to 25(OH)D levels, combined risk decreased as 25(OH)D increased in the summer/higher latitude group (RR= 0.52 for ≥100 nmol/L as compared to <37.5 nmol/L). In addition, there was a trend for an inverse association between 25(OH)D levels and colorectal cancer mortality, and a positive association between 25(OH)D and male lung cancer mortality.

A meta-analysis of eight prospective studies determined the association of circulating 25(OH)D levels and colon and/or rectal cancer, showing a significant inverse association for colorectal cancer. The association was stronger for rectal than colon cancer.

Despite the aforementioned, relationship between vitamin D and cancer seems to be complex and not a question of a simple inverse relationship.
Vitamin D and infections

Differences in vitamin D status may contribute to the susceptibility to microbial infection. Vitamin D status may relate to a higher risk for some types of infections, including tuberculosis, influenza, upper respiratory tract viral illness and other viral infections. T cells exposed to a foreign pathogen induce VDRs which in turn increase the activity of natural killer cells and enhance the phagocytic activity of macrophages. In addition, vitamin D increases the production of the antimicrobial peptide cathelicidin which is induced by bacteria, viruses and fungi.

The association of rickets, low vitamin D and pneumonia has long been documented. Rickets predict a worse response to pneumonia treatment (including lower neutrophil response and oxygen saturation) as compared to those without the disease. Low vitamin D has been associated to the development of tuberculosis. In fact, before the introduction of tuberculostatic agents, sunlight exposition and vitamin D supplementation were very common methods to treat the disease. Mortality related to tuberculosis increases as serum 25(OH)D levels decrease. However, low serum vitamin D levels may in fact be the result of the disease process and not the cause. Severity of tuberculosis predicts a higher mortality rate and greater vitamin D dysfunction.

Adequate vitamin D status contributes to sputum clearance, clinical improvement and mortality reduction among patients with tuberculosis associated to immunodeficiency virus infection (HIV). During Mycobacterium tuberculosis stimulation, 1,25(OH)2D modulates cytokine production and increases cathelicidin secretion; hence reducing proinflammatory cytokine related tissue damage.

Finish young men with serum 25(OH)D levels <40 nmol/L have significantly more days of absence during respiratory infections than controls. A recent prospective study performed among patients with pneumonia reported that severe 25(OH)D deficiency related to higher mortality rates when compared to those with sufficient levels. Increased mortality was not related to comorbid conditions, age or severity of the acute illness, and 25(OH)D levels did not correlate to blood cathelicidin and beta-defensin levels.

Serum 25(OH)D levels have been related to a higher mortality risk in patients infected with type 1 HIV. Recently the EuroSIDA Study Group compared serum 25(OH)D levels and clinical progression. During follow-up, subjects in the lowest 25(OH)D tertile had a significantly higher risk of clinical progression, all-cause mortality and acquired immunodeficiency syndrome events. It may seem that 1,25(OH)2D induces favorable immunological changes, including cathelicidin and beta defensin 2 synthesis and autophagy.

Vitamin D is an important factor in the prevention of respiratory infections. In a probability survey of the NHANES cohort which included subjects 12 years and older, lower 25(OH)D levels were independently associated to upper respiratory tract infections. The association between 25(OH)D levels and these respiratory infections appeared to be strong among subjects with asthma and chronic obstructive pulmonary disease. Vitamin D supplementation during pregnancy reduces the prevalence of neonatal asthma.

Appropriate vitamin D levels during intrauterine life may determine the posterior immune response. Umbilical cord levels of serum 25(OH)D were lower in neonates who subsequently developed respiratory syncytial virus bronchiolitis as compared to those who did not. Neonates born with serum 25(OH)D concentrations <20 ng/mL had a six-fold higher risk of this viral infection in the first year of life as compared to those with levels ≥30 ng/mL.

Although evidence may have some limitations and 25(OH)D may be a marker of poor health, exploring the importance of vitamin D in other infections and circumstances seems reasonable and interesting.

Sunlight and vitamin D supplementation could improve longevity

There is a growing body of evidence suggesting that sufficient vitamin D levels may
Sunlight exposure

Vitamin D supplements and skin biosynthesis may display different responses in terms of circulating 25(OH)D. Thus, vitamin D synthesized in the skin is almost exclusively bound to the vitamin D-binding globulin protein which produces a slower vitamin D hepatic delivery and a more sustained increase in plasma 25(OH)D levels as compared to vitamin D oral intake. Regular and modest sunlight exposure could naturally stimulate vitamin D skin photosynthesis. Hence, sun exposure of 10-15 minutes, three times a week, during the spring, summer and fall, over face and arms is sufficient to maintain adequate vitamin D status.

Reports indicate that sun ultraviolet radiation or an unidentified associated factor may reduce all-cause mortality and cardiovascular-related mortality. The effect of ultraviolet exposure on mortality (all-cause, cancer and CVD) was studied in the Swedish Women’s Lifestyle and Health cohort with a 15 year follow-up. Sun ultraviolet exposure was associated to reduced all-cause and CVD mortality, while artificial ultraviolet exposure was associated with all-cause and cancer mortality.

A case-control study has recently assessed the influence of ultraviolet sunlight exposure during adolescence and adulthood on future breast cancer risk. The study compared the risk of breast cancer between the women who spent more than 21 hours/week under sunlight and those less than 6 hours/week. Women who spent more time outdoors in their teens had significantly lower risk of breast cancer (OR 0.71). The risk was also reduced spending more time in outdoors in their 20s and 30s (OR 0.64), their 40s and 50s (OR 0.74), and between 60 and 75 (OR 0.50).

It seems that small amount of sunlight exposure may contribute to maintain a healthy life, although it remains to be determined if the benefits are due to vitamin D photosynthesis or another ultraviolet-related effect.

Vitamin D supplements

According to pooled data from 7 randomized controlled trials including 68,517 patients (mean age 69.9 years), combined supplementation of vitamin D 400-800 IU plus calcium reduced overall fracture risk by 8% (HR 0.92), and hip fracture risk by 16% (HR 0.84). Contrarily, vitamin D alone had no effects on fracture risk as compared to placebo; however, important to mention is that used vitamin D doses was in fact low. In this study, there was also no head-to-head comparison between vitamin D alone and the combination: calcium plus vitamin D. Under this scenario, it may seem rather that vitamin D increases muscle strength which indirectly reduces the risk of falls and thus fractures.

Cumulative mortality was assessed in a nationwide Finnish cohort study of patients (50 or more years) discharged after hip fracture. Mortality after one year was significantly lower in patients who purchased vitamin D and calcium or vitamin D supplements and anti-osteoporotic treatments than those who did not (HR 0.74). The advantage of treatment was maintained for five years in individuals who purchased the treatment.
A meta-analysis of 18 studies reported that vitamin D supplementation at daily doses ranging from 300 to 2,000 IU for an average of 5.7 years reduced the risk of all cause death by 7%. A systematic review of 17 prospective studies and randomized trials examining vitamin D and calcium supplementation, concluded that vitamin D supplementation may reduce CVR while calcium supplementation has no or minimal effect on CVR.

A four-year prospective randomized placebo-control trial analyzing fracture incidence, reported as a secondary outcome the incidence of breast cancer in postmenopausal women who were assigned to receive 1,400-1,500 mg supplemental calcium/day alone, supplemental calcium plus 1,100 IU vitamin D3/day, or placebo. In multiple logistic regression models, both, treatment and serum 25(OH)D levels, were independent predictors of cancer risk.

Another study suggests that high doses of vitamin D supplements may prevent breast cancer recurrence and death. In a group of 512 patients with early breast cancer, only 24% had sufficient 25(OH)D levels while 37.5% were vitamin D deficient (<20 ng/mL) and 38.5% insufficient (20-28.8 ng/mL). During a mean 11.6 year follow-up, 116 women had distant recurrences and 106 died. Women with deficient 25(OH)D levels had a significant higher risk of distant recurrences and death than those with sufficient levels.

A case-control study explored the association of serum 25(OH)D levels and breast cancer risk, reporting that vitamin D was inversely related to breast cancer risk in a dose-dependent manner. Comparing women with levels <20 ng/mL and those with levels >40 ng/mL, there was a higher breast cancer risk in those with lower levels. Effect was more evident in relation to menopausal and tumor receptor status.

CVD risk in relation to vitamin D intake (food and supplements) has been analyzed in two cohorts (Nurses’ Health Study and the Health Professionals Follow-Up Study) including 118,864 subjects free of CVD and cancer at baseline. Subjects were prospectively followed-up for cardiovascular outcomes. Higher vitamin D intake (≥600 IU/d) was associated to a lower CVD risk in men but not in women.

A more recent report pointed out to the fact that vitamin D insufficiency may be a factor related to a decreased response to bisphosphonates observed in clinical practice. Thus, postmenopausal women who had serum 25(OH)D levels above 33 ng/mL were 7 times more likely to respond to osteoporosis therapy than those with lower levels (OR 7.24). In this study, bisphosphonates responders displayed lower rates of vitamin D insufficiency than non responders (16.8% vs. 54.9%).

**Conclusions**

Due to different medical and social factors low vitamin D levels are very prevalent worldwide. Although vitamin D is currently considered as a hormone rather than a vitamin, *sensu strictu*, changes in lifestyle of the past decade has made us reconsider its important role from a nutritional point of view. Prospective randomized studies analyzing vitamin D supplementation with higher dosages, controlled conditions and appropriate endpoints are still lacking. “Normal” vitamin D levels required for optimal cell functioning are still unknown. In addition, causes of death may be confounded or poorly specified and hence result in bias. Nevertheless, low 25(OH)D levels may be seen as a marker of poor health. The ongoing **Vitamin D and Omega-3 Trial** (VITAL) will provide answers to many questions and hopefully confirm the benefits of vitamin D supplementation. In the meantime a traditional lifestyle with a vitamin D enriched natural diet, exposure to sunlight in a responsible manner and regular outdoor activities should be highly recommended.

Finally, 25(OH)D should be considered a prohormone, with genomic and non genomic actions and synergistic actions with 1,25(OH)2D and antiproliferative effects. Therefore, under this profile future research will define its clinical and therapeutical relevance.
**Riassunto**

**Vitamina D, luce solare e longevità**

Gli esseri umani assumono vitamina D attraverso la fotosintesi cutanea e l’apporto dietetico. Sono necessarie due idrossilazioni per ottenere il composto bioattivo: la prima produce 25 idrossivitamina D [25(OH)D], e la seconda 1,25 didrossivitamina D [1,25(OH)2D]. Non vi è accordo sull’appropriato livello di cut-off per definire il normale intervallo sierico di 25(OH)D. Studi sperimentali, epidemiologici e clinici hanno correlato un basso livello di vitamina D alla longevità. Sebbene alcuni risultati siano controversi, bassi livelli sierici di 25(OH)D sono stati correlati a mortalità dovuta a patologie tumorali, cardiovascolari, infettive o a cause generali. Nel corso della vita, una percentuale significativa di esseri umani mostra livelli sierici insufficienti (20-30 ng/ml) o carenti (<20 ng/ml) di 25(OH)D. Cambiamenti appropriati dello stile di vita, come un’esposizione breve e regolare alla luce solare, possono essere altamente benefici. Gli studi sull’integrazione con vitamina D presentano limiti metodologici oppure si basano su dosi relativamente basse. Per tale motivo, i dosaggi usati per l’integrazione con vitamina D dovrebbero essere più elevati rispetto a quelli comunemente consigliati. In tal senso, c’è un urgente bisogno di studi prospettici controllati che utilizzino elevati dosi giornaliere di vitamina D (2.000 IU o più) che includano endpoint relativi a patologie cardiovascolari, infettive o tumorali. La correlazione tra vitamina D ed esiti clinici non è lineare e vi sono probabilmente vari livelli ottimali di vitamina D in grado di influenzare endpoint diversi.


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