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# Why modest but widespread improvement of the vitamin D status is the best strategy?

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Vitamin D is a precursor for a secosteroid ligand of a major transcription factor, VDR, and is vital for normal bone mineralization. It also regulates many other genes so that it may be involved in many extra skeletal health effects. The optimal vitamin D status is controversial but there is a wide unanimity that the vitamin D status can and should be improved for some risk groups. To normalize serum calcium homeostasis as based on normal levels of serum $1,25(OH)_2D_3$ or parathyroid hormone, or to optimize intestinal calcium absorption or bone mineral density in adults or elderly subjects, serum 25OHD should be 20 ng/ml or higher. A daily vitamin D supplement of at least 400 IU or preferably 800 IU of vitamin $D_3$ can reduce the risk of fractures and probably also falls in elderly subjects, especially when combined with an optimal calcium intake. There is no formal proof of causality to define an optimal vitamin D intake or serum 25OHD based on its presumed extra skeletal health effects but the guidelines for bone health would probably eliminate also most negative extra skeletal health effects. The recommended vitamin $D_3$ supplement of 400–800 IU/d for adults also corresponds to the daily replacement dose calculated from metabolic clearance studies.



During the evolution of man, mammals and probably all vertebrates with a calcified skeleton, dietary intake of vitamin D was of minor importance. The endogenous vitamin D synthesis by converting provitamin $D_3$ into previtamin $D_3$ during exposure to UV-B was indeed the major origin of vitamin D. Vitamin D from food sources contributed little to the overall vitamin D status, with very few exceptions of species that consumed vitamin D rich fish. Vitamin D deficiency rickets was probably a rare disease until it

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became a major health problem in some areas of the world from the 17th century onwards. The most obvious reason was the lack of exposure to UV-B due to poor living conditions in industrialized cities. We now also know that voluntary and strict avoidance of exposure to sunlight because of social, religious or other reasons creates a low vitamin D status. Therefore exposure to UV-B light was nature's solution to prevent rickets and this is still today's solution in major parts of the world. From careful studies in the beginning of the 20th century we know that lack of sun exposure can be compensated by sufficient oral vitamin D intake by either vitamin D rich food or vitamin D supplementation. The daily amount of vitamin D needed to prevent rickets has been explored, mostly empirically, in the first half of the 20th century and 200–400 IU of vitamin $D_3$ was found to be highly efficient. Most agencies responsible for defining nutritional guidelines therefore recommend a daily vitamin D supplement of 200 IU and more recently 400 IU for infants and children (see chapter Pettifor in this volume). Whether higher amounts of vitamin D for infants and children would have long term extra-skeletal effects is presently not established.

There is less consensus about the vitamin D requirements of adults and elderly subjects. This is largely due to a combination of events. First, although endogenous synthesis of vitamin D was nature's solution to provide a sufficient vitamin D status, we now know that exposure to UV-B or sunlight in general can increase, albeit with a long lag time, the risk of several skin cancers and can cause premature photo aging of the skin, especially in subjects with a fair skin phenotype.[1] Therefore exposure to sunlight as the major source of vitamin D cannot be considered to be the solution and here opinion differs with regard how much exposure to sunlight might be acceptable. Most dermatologists think that due to the cumulative "oncogenic" effects of UV-B maximal protection is needed and therefore oral intake of vitamin D is the only alternative to achieve a satisfactory vitamin D status. Others however think that modest exposure to sunlight can contribute to maintaining a normal vitamin D status but the implementation of such strategy requires a difficult message[2] as the potential "safe" exposure time to sunlight depends on many factors (skin phenotype, intensity of UV-B irradiation). Secondly, we know that the normal food intake according to very variable nutritional habits does not provide the necessary amount of vitamin D unless vitamin D rich food (especially fatty fish) is frequently used. Therefore, restriction to UV-B exposure, certainly of people with a fair skin phenotype, and the low vitamin D content of natural food make access to vitamin D-enriched food or vitamin D supplements desirable and sometimes necessary well beyond the early life period.

How can we then define the optimal vitamin D status? One should make a distinction between vitamin D's effects on bone (which are well established) and its possible extra-skeletal effects, which are based on a plausible hypothesis but not (yet?) proven by randomized supplementation trials. Different strategies can be used to try to define the minimal 25OHD level necessary to avoid the contribution of vitamin D status to so many diseases taking into account that the minimal threshold may differ from disease to disease. One method would be to use cross sectional, retrospective or preferably prospective studies or case control studies, as to define the level of 25OHD associated with the greatest risk and the plateau 25OHD level above which no further improvement can be identified. As always true randomized control trials are the best method to distinguish coincidence from causality and to define the vitamin D intake or dose or serum 25OHD level needed to obtain a beneficial effect on bone or extra-skeletal tissues.

There is at present by far no unanimity about the answers to these questions. In this chapter/volume two different opinions are presented. Elsewhere in this volume R. Vieth (see *Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml)*) argues that a generous supply of vitamin D as to achieve 25OHD levels above 30 ng/ml is needed. In this chapter, however, I will argue that there is reasonable evidence that vitamin D has beneficial effects on bone health and that this can be achieved by serum levels of 25OHD above 20 ng/ml. There are very strong preclinical data that suggest a wide spectrum of extra-skeletal effects of vitamin D but such actions have not been convincingly demonstrated in men so that defining optimal 25OHD levels for such potential health effects is yet largely speculative.

## Defining the optimal vitamin D status for bone health of adults and elderly subjects

Overt osteomalacia is a rare disease in otherwise healthy subjects indicating that the normal access to combined nutritional and endogenous vitamin D supply is usually sufficient to avoid this disease.