VITAL Study: lights and shadows

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INTRODUCTION

Vitamin D is a fat-soluble hormone that plays a key role in regulating calcium absorption in the intestine. Cholecalciferol is converted into calcifediol by the liver enzyme 25-hydroxylase and subsequently, under the control of the parathormone (PTH), by the kidney enzyme 1-25-hydroxylase into the biologically active form, calcitriol. Because calcitriol directly regulates the absorption of elemental calcium from the gut, it is therefore essential to ensure an adequate substrate for bone formation.

Under conditions of low vitamin D levels, calcium absorption in the intestine is reduced and the calcium required for blood homoeostasis is drawn from the skeleton under the influence of PTH [1]. Therefore, as is well known in physiology, severe vitamin D deficiency leads to the development of osteomalacia (in adults) and rickets (in children) [2].

The earliest clinical/historical confirmation of vitamin D's fundamental role in the development of osteomalacia and in bone metabolism comes from ancient finds of skeletons of individuals with deformities and multiple bone fractures as well as from empirically garnered evidence.

It is also well known that populations living above the 37th parallel are at higher risk of developing rickets/osteomalacia. Humans are able to synthesise vitamin D_3 through photochemical conversion. Ultraviolet B radiation leads the conversion of 7-dehydrocholesterol into cholecalciferol by the skin. However, in the earth's northern and southern regions UVB radiation with the wavelength required for vitamin D synthesis does not reach the surface. It has also been found that when rachitic children are exposed to the sun their clinical picture improves until complete recovery.

Vitamin D, which is present in moderate amounts in animal fats, can also be absorbed from the diet. Among Scandinavian populations, it has been shown that the risk of vitamin D deficiency was particularly high for those who lived inland and therefore had a diet low in or even devoid of fish, which is the main animal source of dietary vitamin D. For centuries, cod liver, which is extremely rich in vitamin D, has protected Nordic populations from developing osteomalacia or rickets.

It has therefore been widely accepted that vitamin D is a fundamentally important nutrient/hormone for bone health. In recent years, evidence for this assertion has been further strengthened. There have been many studies published, especially observational but also interventional investigations, that confirm the importance of vitamin D and, in particular, that emphasise the marked deleterious effect of low levels of vitamin D or its deficiency on bone.

Interestingly, observational studies conducted on populations at risk of fracture are essentially all in agreement in pointing out the negative role of vitamin D deficiency in increased fracture risk. In contrast, the data from interventional studies has introduced a fair amount of uncertainty. Indeed, some clinical trials were unable to demonstrate a positive effect of vitamin D on the reduction of fracture risk. Nevertheless, although these studies were conducted with extreme scientific rigour and on large populations, their limitations should not be disregarded. Therefore, we cannot, we must not allow them to negatively influence our clinical choices [3]. Specifically, I will focus on the inherent weaknesses of the recent "Vitamin D and OmegA-3 TriaL (VITAL)" randomised clinical trial whose ancillary study results on fragility fractures [3], were recently published.

THE "VITAMIN D AND OMEGA-3 TRIAL (VITAL)"

The VITAL study was a pragmatic, randomised, blinded clinical trial in which vitamin D, omega-3 or placebo were administered according to a factorial design.

Summing up, participants (over 25,000 individuals residing in the United States of America) could receive either a tablet containing a combination of vitamin D and omega-3, vitamin D and placebo, omega-3 and placebo, or just placebo [4]. The main aim of the study, which was begun in 2010 at Harvard University, was to show a possible effect of vitamin D and omega-3 on the incidence of autoimmune diseases and cancer (Figs. 1, 2).

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Conflict of interest
The author states that there are no conflicts of interest.

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However, numerous other ancillary investigations were also planned, including studies targeting bone health and fractures. Serum, for biomarker analysis, was also collected from a proportion of the patients enrolled who were also given diagnostic examinations to assess bone density and fragility.

SUPPOSITIONS, CONTEXT AND THE VITAL-STUDY POPULATION

Before delving into the study details, one should recall the investigators' motivation to conduct this mega-trial. In the United States, it is extremely common for vitamin D to be administered together with so-called "over-the-counter" (OTC) preparations, which are by definition easy to find in ordinary supermarkets.

This widespread usage arose and was developed as a result of the strongly rooted belief in American society that regular multivitamin supplementation (often containing high doses of vitamin D) is essential for the health of people at all ages. The habit of taking OTC preparations is so ingrained that the market has shown continuous growth, having reached a staggering $30 billion/year in the US in 2023. This premise is crucial to understanding the context in which the VITAL study was conducted.

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Middle-aged subjects with certain peculiar characteristics were enrolled in the VITAL study. The most important of these was certainly the subjects' high level of education. Enrolment was implemented through a letter, which included complex questionnaires that required suitable medical and scientific knowledge, which was sent to each subject's home address. This presupposition, together with informative brochures on vitamin D and omega-3 being mailed to the subjects, led to the enrolment of a considerable proportion of patients who were already taking vitamin D, before the study (42.6% of the patients enrolled had been taking vitamin D outside the study). In fact, before entering the study. this share of patients was found to have average 25-hydroxy-vitamin D [25(OH)D] levels of 34.9 ng/mL. Furthermore, subjects were also allowed to continue taking up to 800 IU of vitamin D supplements per day during

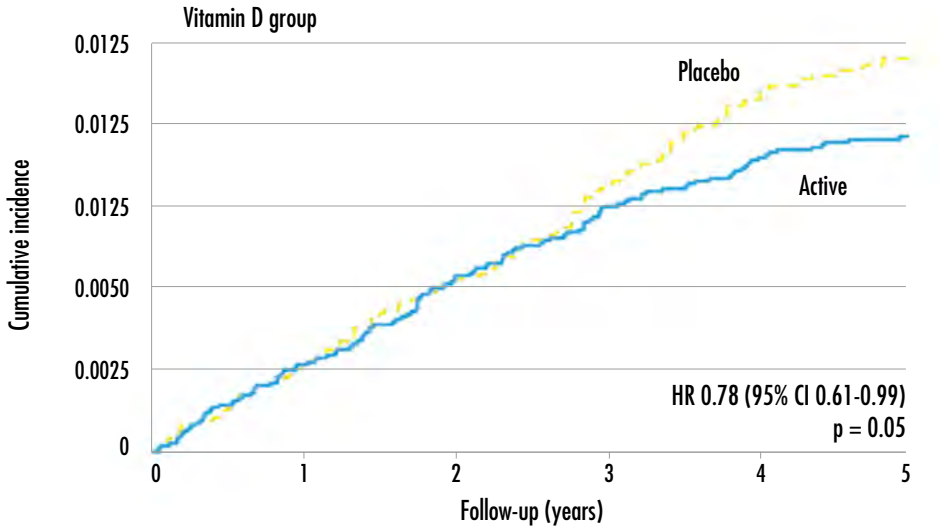

FIGURE 1.
Incidence of autoimmune diseases in the VITAL study (from Hahn et al., 2022, mod.) [6].

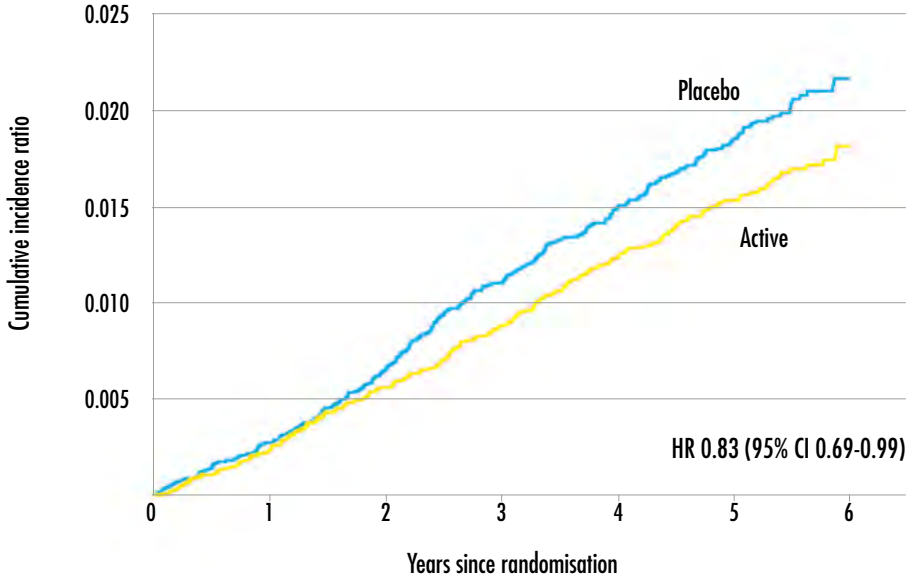

FIGURE 2.
Incidence of advanced cancer in the VITAL study (from Chandler et al., 2020, mod.) [7].

TABLE I.
Baseline characteristics of the population enrolled in the VITAL study (from LeBoff et al., 2022, mod.) [8].

Characteristic	Total (N = 25,871)	Vitamin D group (N = 12,927)	Placebo group (N = 12,944)
Women no. (%)	13,085 (50.6)	6,547 (50.6)	6,538 (50.5)
Age, years	67.1 ± 7.1	67.1 ± 7.0	67.1 ± 7.1
Body mass index (BMI)	28.1 ± 5.7	28.1 ± 5.7	28.1 ± 5.8
Diabetes no./total no. (%)	3,537/25,824 (13.7)	1,804/12,900 (14.0)	1,733/12,924 (13.4)
Family history of hip fracture, no./total no. (%)	3,704/23,979 (15.4)	1,809/11,970 (15.1)	1,895/12,009 (15.8)
Rheumatoid arthritis no./total no. (%)	1,118/25,512 (4.4)	556/12,749 (4.4)	562/12,763 (4.4)
Family history of fragility fracture no./total no. (%)	2,578/25,023 (10.3)	1,287/12,513 (10.3)	1,291/12,510 (10.3)
Falls in the last year no./total no. (%)	6,921/25,715 (26.9)	3,521/12,848 (27.4)	3,400/12,867 (26.4)
Use of anti-osteoporosis drugs no./total no. (%)	1,240/25,690 (4.8)	609/12,835 (4.7)	631/12,855 (4.9)
Smokers no./total no. (%)	1,835/25,488 (7.2)	921/12,732 (7.2)	914/12,756 (7.2)
Use of vitamin D supplements no./total no. (%)	11,030 (42.6)	5,497 (42.5)	5,533 (42.7)
Use of glucocorticoids no./total no. (%)	461/25,427 (1.8)	239/12,705 (1.9)	222/12,722 (1.7)
Milk intake (units)	0.71 ± 0.91	0.71 ± 0.89	0.72 ± 0.92
Basal 25(OH)D levels, ng/mL	30.7 ± 10.0	30.7 ± 10.0	30.7 ± 10.0
Basal calcaemia levels, mg/dL	9.00 ± 1.61	9.00 ± 1.61	9.00 ± 1.61

the VITAL trial. It was also surprising to note that subjects not taking vitamin D at the beginning of the study were found to have average blood 25(OH)D levels measuring 27.4 ng/mL, which is more than adequate for bone health maintenance.
Summing up, on average, patients who would never have been treated with additional doses of vitamin D in clinical practice were enrolled in the VITAL trial. Moreover, this population was already at low risk of fracture at baseline. Only 1 in 10 patients had a history of fragility fracture and only 1 in 20 were treated with osteoporosis drugs. Table I shows the baseline characteristics of the VITAL study population [8].

VITAL STUDY RESULTS, *PRIMARY* ENDPOINTS, AND INCIDENCE OF FRACTURES

After being randomised, the VITAL study subjects enrolled were followed up with annual questionnaires for more than 5 years, whilst several outcomes were evaluated each year and at the end of the study.
The primary endpoint (incidence of fragility fractures in the two randomisation groups) was not achieved: the fracture incidence rates overlapped in the two groups.
Before going into the detail on the results of the ancillary study on fractures it is important to establish the observed fracture rate, i.e., the number of fractures the patients had during the follow-up. once again, this will allow us to better understand the characteristics of the individuals enrolled in the study. A total of 865 fragility fractures (excluding pathological, traumatic, periprosthetic fractures, etc.) were observed during a median follow-up period of 5.3 years. This rate corresponds to a fracture risk of 3.3% at 5 years, coming to, approximately, a 6.6% risk at 10 years, which is well below the pharmacological treatment threshold for osteoporosis. Similarly, the 0.8% 10-year femoral fracture incidence rate that was observed was still well below the treatment threshold, which is usually set at 3%. Clearly, the enrolled population was already at a low risk of fracture even before entering the study and remained so throughout the duration of the investigation.

VITAMIN D *SAFETY*

The incidence of hypercalcaemia, kidney stones and adverse events in general was similar among all the patients. Nevertheless, there was a reduction in gastrointestinal bleeding events and skin rash among the patients treated with vitamin D.
The safety profile was therefore found to be favourable in the active vitamin D treatment arm.

SUBGROUP ANALYSIS AND VITAMIN D LEVELS

In one of the subgroups of the study population, 25(OH) D values were analysed after 2 years (besides at baseline). As expected, 25(OH)D levels increased significantly (statistically but not clinically) in the subgroup treated with vitamin D (29.2 ng/mL→ 41.2 ng/ mL). Still, not very surprisingly, patients in the placebo arm also maintained adequate vitamin D levels, achieving values of 29.4 ng/mL at year 2. Once again, this indicates how the patients enrolled were largely already on supplementation and how they continued using it during follow-up. Therefore, though several sub-analyses were conducted on the basis of the baseline 25(OH)D levels, still again no (significant) reduction in fracture risk was found. Nonetheless, laboratory data were available from only a small portion of the cohort. Of these, only a minority had insufficient vitamin D

TABLE II
Hazard Ratio in subgroups of patients in the VITAL study (from LeBoff et al., 2022, mod.) [3].

Subgroup	Total	Vitamin D group	Placebo group	Hazard Ratio (95% CI)	Hazard Ratio if patients are doubled & equal fracture incidence
Anti-osteoporosis drugs					
Yes	1,240	62	79	0.74 (0.53-1.03)	**0.74 (0.62- 0.97)**
No	24,450	704	697	1.01 (0.91-1.12)	1.01 (0.96-1.11)
History of fragility fractures					
Yes	2,578	146	161	0.87 (0.69-1.09)	**0.87 (0.74-0.99)**
No	22,445	598	595	1.01 (0.90-1.14)	1.01 (0.93-1.08)

levels. Furthermore, among the 401 subjects whohad 25(OH)D levels below 12 ng/mL, the incidence of fractures was 3.7% at 5 years, which was extremely similar to the entire cohort. Even so, this apparently counter-intuitive finding can be explained by the admission of up to 800 IU/day of vitamin therapy outside the study. Whilst 25(OH)D dosages were also allowed outside the study according to current clinical practice, it cannot be ruled out that a major bias (exclusion of patients from the analysis or increased vitamin D levels even in the placebo group) may have been caused once patients with very low levels started vitamin D supplementation. Also, to be noted was that PTH and calcaemia levels in the study population were found to be normal as they were also in the subgroup with vitamin D deficiency (the presence of hyperparathyroidism of any nature was one of the exclusion criteria). This implies that the vitamin D deficient patients had most likely been so for just a short time and/or that their homeostatic compensation mechanisms of their PTH/calcaemia/25(OH)D axis had not yet been established or were not yet fully evident. No stratified analyses were conducted on the basis of 25(OH)D values at the end of the study. Sub-analyses were conducted in subgroups at particular risk of fracture, such as those patients with previous fractures or those treated with osteoporosis drugs. In these subgroups (in any event in the minority) the risk of fracture was no different between the placebo and the vitamin D groups. Yet, a numerically lower fracture incidence rate was shown in the active treatment group (Tab. II). It is interesting to note that among these many subgroups there was insufficient proof to show any reduction in fracture risk.

In addition, the fracture incidence rate was not especially high. This rate was 11.3% at 5 years (about 22% at 10 years) for those patients being treated for osteoporosis, whilst it was 11.9% at 5 years (about 23-24% at 10 years) among those subjects with previous fractures. For comparison, in the 10-year extension of the FREEDOM study (clinical trial with denosumab), which was very similar to the VITAL study, the 10-year cumulative overall incidence rate for fragility fractures among patients treated with denosumab was 16.3% *vs* 26% in the "virtual" placebo arm. It would therefore be difficult to believe that vitamin D alone could have a clear anti-fracture effect among so few patients who were at such low risk. Nonetheless, it would be sufficient to assume that a doubling of the number of cases (keeping the fracture incidence rates the same) in these subgroups could achieve statistical significance in favour of vitamin D (Table II). Indeed, it is a well-known fact that it is even more crucial to achieve and maintain adequate vitamin D levels (probably above the threshold of 20-30 ng/mL) among patients being treated with anti-osteoporosis drugs in order to maximise the anti-fracture effect of the drugs [5]. This finding is further confirmed by evidence from another sub-analysis still from the VITAL trial that showed a significant reduction in the risk of major osteoporotic fracture (MOF) among patients being treated with anti-osteoporosis drugs [HR 0.54 (95% CI 0.29-0.99)].

CONCLUSIONS

Regardless of its limitations, VITAL is a crucially important study. The trial was conducted meticulously, on a very large population, who were studied over an extended period of time. Additionally, the study brought to light an important confirmation of vitamin D's potential extra-skeletal effects. Nevertheless, in the ancillary study on fragility fractures, the group treated with vitamin D showed no reduction in the incidence of fractures. This result was largely to be expected considering the study's significant limitations as well as the low-risk population enrolled. Among selected patients, such as those with osteoporosis, vitamin D treatment is and remains essential to preserve bone health. Moreover, this important observation was also reiterated by the same VITAL study authors, who suggested that thresholds of 25(OH)D ≥30 ng/mL [8] should be achieved and maintained in all patients with osteoporosis.

In conclusion, the effects of vitamin D on bones appear to be more pronounced in vitamin-D deficient individuals at risk of fracture or of osteomalacia.

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