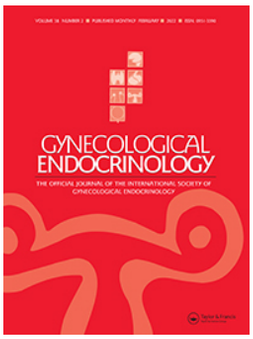

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EDITORIAL
VITAMIN D

Disentanglement among vitamins D

Vitamin D is essential for intestinal calcium absorption and therefore crucial for skeletal health. In addition, its beneficial effects extend outside bone tissue. The list of putative non-skeletal effects for which vitamin D adequacy is needed ranges from diseases at birth to those causing death. Associations between a poor vitamin D status and endometriosis, uterine myoma, dysmenorrhea, abnormal PAP smear results, and high-risk HPV infection of the cervix have also been described. Just to stay in our days, a possible favorable role of "vitamin D" in modulating SARS-COV-2 infection has been demonstrated by some [1] but not all researchers. However, hypovitaminosis D (a term we would prefer to indicate both deficiency and insufficiency, in analogy with other clinical conditions, i.e. hypomagnesemia, hypocalcemia, hyposideremia) is highly prevalent in the world.

It is well established that hypovitaminosis D is causally linked to decreased intestinal calcium absorption with secondary compensatory increased parathyroid hormone secretion. This determines increased bone resorption, bone loss, osteoporosis that finally causes an increased fracture risk [2]. Basically, there are two main strategies for correcting hypovitaminosis D: (1) following the discovery in 1919 that sunlight was able to cure rickets, regular exposure to sunlight or artificial ultraviolet B radiation is an inexpensive way to reach vitamin D sufficiency; or (2) following the observation in 1924 that an inactive lipid in the diet and skin could be converted by ultraviolet light into an anti-rachitic substance, increasing the dietary intake of ergocalciferol, cholecalciferol and corresponding 25(OH)D derivatives could be an alternative way. Despite this, for a number of reasons (for which the reader could refer to reference [3]), these strategies are difficult to be followed on a regular basis or difficult to implement as a basic salutary approach by public health authorities.

Supplementation with vitamin D represents the third and most used strategy to correct hypovitaminosis D. It is important to emphasize that '*Vitamin D*' is mistakenly used as a generic term to indicate all the metabolites generated from precursors (7-dehydrocholesterol and ergosterol) and even for any other molecule based upon vitamin's secosteroid (disrupted steroid ring) [4]. The most frequently vitamin D employed in the context of supplementation in normal subjects are: ergocalciferol (D_2), cholecalciferol (D_3) calcifediol [25(OH)D] alpha-calcidol [1α(OH)D] and calcitriol [$1,25(OH)_2D$]. Ergocalciferol (as 50,000 IU capsules and in a liquid form at 8,000 IU/mL) is mainly used in the United States, but rarely used in Europe. Cholecalciferol in relatively low doses (1,000–2,000 IU) is available in the United States as over the counter product. The larger utilization of cholecalciferol outside the United States can be probably ascribed to fewer published studies and demonstrated convincing benefits of ergocalciferol in respect to cholecalciferol [4]. Alphacalcidol and calcitriol are rarely used in normal subjects for the sake of supplementation and mostly employed in specific diseases (i.e., in patients with renal failure or hypoparathyroidism). At the end, cholecalciferol and calcifediol are the most utilized '*Vitamin D*' products for reaching sufficiency in normal subjects, whatever the threshold chosen (20 vs 30 ng/mL). Some of the most relevant differences between cholecalciferol and calcifediol are reported in Table 1.

Table 1. Differences between cholecalciferol and calcifediol.

	Cholecalciferol	Calcifediol
Presence in foods	Abundant in oily fish	Low in eggs and meat
Production	Skin	Liver
Absorption efficiency	79%	93%
Transportation	Chylomicrons	Porta vein
Volume of distribution	Larger than body size	Larger than plasma volume
Circulating half-life	2 days	2 weeks
Functional half-life	2–3 months	2–3 months
Conversion into IU	Yes	No
Minimal toxic dose per day	>1000 mcg/day	Unknown

These dissimilarities give the rationale for using calcifediol in specific clinical conditions. The most relevant are represented by clinical conditions in which a rapid normalization of vitamin D sufficiency is needed (mainly because the mean increase in serum after intake of 1 µg cholecalciferol is 1.53 nmol/L whereas the mean increase is 4.76 nmol/L with calcifediol) [5]; in obese individuals, in patients with hepatic failure, in patients with inactivating mutations of genes encoding CYP2R1 (the principal enzyme which is responsible for vitamin D 25-hydroxylase) or in patients taking drugs that could influence the activity of cytochrome enzymes (i.e., anti-retroviral or anti-tubercular and so on). However, the field of vitamin D pharmacology is a rapidly evolving one with new compounds on the horizon, now utilized in patients with renal failure. Their utilization may overcome some of the inconveniences observed with commercially available preparations [6].

Disclosure statement

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