EDITORIAL

Maurizio Rossini

Department of Medicine, Section of Rheumatology, University of Verona

Dear Colleagues,

The fear I expressed in my editorial for the second issue of 2019 of the Journal has unfortunately turned out to be well founded, given that there have been no occasions for an exchange with Health Board officials with regard to a cost-benefit analysis of vitamin D supplementation and for bringing operators in the health field up to date on the best ways of using it. Now, in my opinion, we run the risk that many patients will lack proper access to vitamin D treatment. As you know, faced with the exorbitant – and admittedly unjustifiable – costs for vitamin D in Italy, the national drug administration (AIFA) has indeed recently taken measures to limit prescriptions paid by the national health service (SSN) for some vitamin D-based drugs (cholecalciferol, cholecalciferol in capsules, cholecalciferol /calcium salts) for the “prevention and treatment of vitamin D deficiency in adults” (note 96, see this and future issues).

The contents of the note acknowledge the importance of vitamin D supplementation in the case of deficiency, particularly for musculoskeletal health. Yet its statements, I believe, are prone to unsure if not ambiguous interpretations, which could give rise to numerous doubts, in spite of clarifications subsequently issued by the AIFA for health workers and citizens. The implementation of this measure will certainly reduce the costs borne by the SSN for vitamin D supplementation. Yet the Health Board will not be able to attribute these savings to an improved suitability of its use: to my mind, the note lends itself to restrictive interpretations which may negatively affect patients who should have the right to use and benefit from supplementation. Costs for the SSN may actually increase, in terms of diagnosis and above all for lack of prevention.

In my opinion, the critical parts of note 96 are as follows:

1. While recognizing that vitamin D deficiency may be asymptomatic (point 3, vitamin D chart – for citizens), its measurement is recommended only for persons with symptoms, those clearly affected by severe deficiency and above all patients with serious hypovitaminosis D complications such as osteomalacia. This recommendation seems to contradict one of the principles of the AIFA, which has always been concerned with encouraging prevention of diseases rather than the use of drugs for their treatment. Another statement, found in the measurement guidelines in Attachment 1 to the note, is likewise open to ambiguous interpretation in clinical practice: this says that determining 25(OH)D levels is not necessarily recommended in all possible risk categories. Yet does this mean that a doctor may choose to ignore those risk conditions, or, as I understand it, that in that case measuring vitamin D levels is superfluous and wasteful because it is in any case recommended for purposes of prevention?

2. Symptoms that can be attributed to hypovitaminosis D (asthenia, myalgia, diffused or localized pain, bone soreness, lumbosacral, pelvic or lower limb pain, sensory impairment, muscle weakness mainly in the quadriceps and glutes with difficulty standing up and sitting down, unsteady gait, susceptibility to falls, etc.) are varied and nonspecific. More often than not, these symptoms are attributable not to hypovitaminosis D but to many other...
conditions, some of which are more severe. Should we not believe that such a scenario might disorient doctors, leading them to overprescribe ineffective and costly doses of 25(OH)D? Should we not further imagine that unrealistic expectations will thereby be created regarding the symptomatic benefits of vitamin D supplementation, including in conditions in which a possible associated deficiency does not play a pathogenetic role?

### 3. The note recommends measuring 25(OH)D levels in persons with secondary hyperparathyroidism by means of a dose of parathormone (PTH), which leading international guidelines do not recommend, as it is notoriously subject to great analytical and biological variability, costly (€22) and physiopathologically altered in most elderly patients. In addition, it is known that most individuals with vitamin D deficiency do not have above average PTH concentrations.

### 4. The note also recommends measuring vitamin D levels in individuals affected by osteoporosis due to any cause or osteopathic diagnosed diseases that require mineralizing therapy, for which correction of hypovitaminosis should be propaedeutic for the beginning of therapy. And what about patients already undergoing therapy? And, further, why administer doses of 25(OH)D, given that even if these are above 20 ng/mL supplementation is recommended for recognized bone pathologies (as shown in the algorithm of Attachment 1)? It seems to me that the current text of the note does not clearly state what can be legitimately assumed from application of the algorithm, namely, that in all conditions of osteoporosis or of verified osteopathic diseases, including in those candidate to a mineralizing therapy, vitamin D supplementation is nonetheless recommended (as stated in note 79) and therefore reimbursed. In addition, in clinical practice, whether before or at the start of a mineralizing therapy, supplementation with higher or more generous doses of vitamin D is called for, such that measuring 25(OH)D levels is not in most cases indispensable in the clinical management of patients.

### 5. Given that exposure to sunlight – as has been rightly recognized – represents the principal mechanism of vitamin D production (80%), how is it that among the risk conditions for hypovitaminosis D the most frequent ones are not given? These are conditions resulting from circumstances that necessitate reduced exposure to sunlight (for example, for reasons of work, disability, cultural prohibitions or side effects linked to UVB exposure), or from those linked to an inability to produce adequate quantities of vitamin D in spite of sun exposure, such as often occurs in the elderly. It does not seem proper to limit discussion of this point to a mere acknowledgement of the risk conditions generated by long-term therapy with drugs that interfere with vitamin D metabolism or of those diseases which can result in poor absorption.

### 6. In my Region, testing for 25(OH)D levels in a single patient costs €17. Using cheaper pharmaceutical formulations, I can treat three patients with vitamin D for a year for this amount. Given that note 97 encourages the widespread and general usage of vitamin D – not to mention the frequent cases in which it demands it – do we not run the risk of shifting expense from prescription to diagnosis?

### 7. The note states that doses higher than 40 ng/mL may be associated with additional risks, among which – as is specified in the relevant clarifications – that of neoplasms. This claim is based on several reports, upon which doubt has been cast by the very source cited in the note, and which other studies have contradicted. As far as I know, so far EU regulatory agencies have not issued any alerts on the risk of oncological pathologies. In any case, exceeding the limit of 40 ng/mL can easily be caused by following commonly recommended dosages … or even by a nice sunny day. At present, this limit therefore appears to be unnecessarily alarmist, which among other things may result in doctors and patients further requesting repeated and useless tests for measuring 25(OH)D levels for fear of having exceeded them. It is known that before running the risk of the most certain side effect of vitamin D supplementation, hypercalcemia, over 100 ng/mL must be taken. In light of our current knowledge, I believe that in any case it would be more appropriate to warn of possible side effects with levels above 50 ng/mL, as stated in many guidelines.

### 8. The minimum threshold of 20 ng/mL of 25(OH)D is deemed sufficient in the general population, though not for some particular risk conditions: in the elderly, in patients with secondary hyperparathyroidism or in those in mineralized therapy for osteoporosis, as is in part recognized on the basis of scientific evidence in point 5 of AIFA clarifications for health workers. Some authoritative scientific societies, which are not mentioned in the background section of the note, maintain that in such conditions 25(OH)D levels above 30 ng/mL provide greater guarantees.

### 9. The note recommends interrupting corrective treatment once symptoms of the deficiency have disappeared, except in the case that they should resurface. But if they persist, perhaps because the conditions that expose patients to the risk of hypovitaminosis D cannot be modified, must I wait until my patient becomes ill again before treating him or her at the SSN’s expense? What has happened to the appreciation for the benefits of prevention and in that sense respect for SPC recommendations for cholecalciferol?

### 10. All notes issued by the AIFA essentially aim to define the criteria for the reimbursement of drugs for optimal therapeutic suitability. As note 79 reminds us, prescriptions should nonetheless be written following the recommendations and warnings of the information sheets for each drug. Not only is this principle not repeated in note 96, it is even, I believe, sometimes not even respected. A possible consequence of this neglect is that it could encourage, for example, the use of some known medications even if these present side effects or are not recommended. Furthermore, Attachment 1 provides indications for the use of specific doses and not for all uses authorized by the SPC. In addition, certain studies indicate that the doses recommended in the note are insufficient for certain types of patients.

### 11. The note (in particular Attachment 1) recommends the need for specialist evaluation for certain conditions, such as kidney failure (I assume, by the way, that the incorrect unit of measure used for its definition is due to a typographical error); yet if fails to indicate whether there are criteria for vitamin D reimbursement in these conditions.
12. With regard now to the statement in the background section about the extra skeletal effects of vitamin D, according to which results of randomized clinical trials (RCTs) with high numbers of participants have not confirmed the hypothesis of benefits resulting from supplementation and have in particular identified areas of documented ineffectiveness in oncology and cardiology: it seems that the authors of this statement have not considered that currently available RCTs were largely conducted on non-deficient subjects and are therefore not able to exclude possible benefits in conditions of deficiency (as one could rationally expect and as has in fact been observed in some sub analyses). And on the subject of recognized immunological effects: in this issue we feature an update from a well-known institute in Genoa on the role of vitamin D in rheumatological diseases. The authors conclude that even if the complexity of rheumatological and autoimmune diseases as well as several methodological limits of published studies significantly circumscribe the possibility of making generalizations as to the therapeutic potential of cholecalciferol in these pathologies, preliminary data from these studies, together with the safety and low cost of cholecalciferol, strongly support its use in patients affected by these diseases, considering the potential and relevant clinical benefits.

What do you think? I hope you enjoy reading this issue.
Nota 96

La prescrizione a carico del SSN dei farmaci con indicazione “prevenzione e trattamento della carenza di vitamina D” nell’adulto (>18 anni) è limitata alle seguenti condizioni:

Prevenzione e trattamento della carenza di vitamina D nei seguenti scenari clinici:
- indipendentemente dalla determinazione della 25(OH) D
- persone istituzionalizzate
- donne in gravidanza o in allattamento
- persone affette da osteoporosi da qualsiasi causa o osteopatie accertate non candidate a terapia remineralizzante (vedi nota 79) previa determinazione della 25(OH) D (vedi algoritmo allegato)
- persone con livelli sierici di 25OHD < 20 ng/mL e sintomi attribuibili a ipovitaminosi (astenia, mialgie, dolori diffusi o localizzati, frequenti cadute immotive)
- persone con diagnosi di iperparatiroidismo secondario a ipovitaminosi D
- persone affette da osteoporosi da qualsiasi causa o osteopatie accertate candidate a terapia remineralizzante per le quali la correzione dell’ipovitaminosi dovrebbe essere propedeutica all’inizio della terapia *
- una terapia di lunga durata con farmaci interferenti col metabolismo della vitamina D
- malattie che possono causare malassorbimento nell’adulto

* Le terapie remineralizzanti dovrebbero essere iniziate dopo la correzione dell’ipovitaminosi D.

Farmaci inclusi nella Nota AIFA:
- colecalciferolo
- colecalciferolo/Sali di calcio
- calcifediolo

Per guidare la determinazione dei livelli di 25OH vitamina D e la conseguente prescrizione terapeutica è possibile fare riferimento alla flow-chart allegata.

Background
La vitamina D viene prodotta per effetto sulla cute dei raggi ultravioletti di tipo B (lunghezza d’onda 290 - 315 nm) che trasformano un precursore, il 7 deidrocolesterolo (la pro-vitamina D), in pre-vitamina D e successivamente in colecalciferolo (vitamina D3). La vitamina D può essere quindi depositata nel tessuto adiposo o trasformata a livello epatico in 25OH vitamina D (calcidiolo o calcifediolo) che, veicolata da una proteina vettrice, rappresenta il deposito circolante della vitamina D. Per esercitare la propria attività biologica il 25OH colecalciferolo deve essere trasformato in 1-25 (OH)₂ colecalciferolo o calcitriolo, ligando naturale per il recettore della vitamina D. La sede principale della 1-idrossilasi è il rene ma questo enzima è presente anche nelle paratiroidi, ed in altri tessuti epiteliiali.
La funzione primaria del calcitriolo è di stimolare a livello intestinale l’assorbimento di calcio e fosforo, rendendoli disponibili per una corretta mineralizzazione dell’osso. In ambito clinico, esiste una generale concordanza sul fatto che la vitamina D promuova la salute dell’osso e, insieme al calcio (quando indicato), contribuisca a proteggere dalla demineralizzazione (in particolare negli anziani).


Le indicazioni all’esecuzione del dosaggio tuttavia differiscono tra i vari documenti di consenso. Esiste sostanziale concordanza sul concetto che la determinazione dei livelli di 25(OH)D dovrebbe essere eseguita solo quando risulti indispensabile nella gestione clinica del paziente (diagnostica differenziale o scelta della terapia).

Secondo i documenti prodotti da organismi regolatori, il dosaggio dovrebbe essere eseguito in un ristretto numero di pazienti con sintomi persistenti di profonda astenia, mialgie, dolori ossei diffusi o localizzati sospetti per osteomalacia o con PTH elevato o predisposizione alle cadute immotivate o in particolari condizioni di rischio (NHS 2018, NICE 2016). I documenti prodotti da Società Scientifiche riportano invece elenchi di categorie di persone a rischio di ipovitaminosi D tra le quali eseguire il prelievo; per esempio soggetti obesi includendo di fatto ampi strati della popolazione. (Cesareo R et al. AME 2018). Pare ragionevole limitare l’indagine a categorie ristrette notoriamente a rischio elevato come persone sintomatiche o chi assumano cronologicamente alcune categorie di farmaci (antiepilettici, glucocorticoidi, antiretrovirali, anti-micotici, colesteramia, orlistat etc.).

A scopo esemplificativo è stato elaborato un diagramma di flusso allegato.

Il valore di 25OHD pari a 20 ng/ml (50 nmol/l) è ritenuto, come supportato dalla letteratura scientifica, il limite oltre il quale viene garantito un adeguato assorbimento intestinale di calcio e il controllo dei livelli di paratormone nella quasi totalità della popolazione; per tale motivo esso rappresenta il livello sotto il quale iniziare una supplementazione (IOM 2011). L’intervallo dei valori compresi tra 20 e 40 ng/mL viene considerato come “desirable range” in base a motivazioni di efficacia, garantita oltre i 20 ng/mL, e sicurezza, non essendovi rischi aggiuntivi al di sotto dei 40 ng/mL (El-Hajj Fuleihan G et al. 2015).

**Evidenze disponibili**

L’apporto supplementare di vitamina D è uno dei temi più dibattuti in campo medico, fonte di controversie e di convinzioni tra loro anche fortemente antitetiche.


Diversi studi osservazionali hanno riportato in varie situazioni patologiche (cardiopatie, neoplasie, malattie degenerative, metaboliche respiratorie etc.) peggiori condizioni di salute in popolazioni con bassi livelli di vitamina D, questo ha portato a valutare con opportuni studi sperimentali l’efficacia della

**Particolari avvertenze**


L’approccio più fisiologico della supplementazione con vitamina D è quello giornaliero col quale sono stati realizzati i principali studi che ne documentano l’efficacia; tuttavia al fine di migliorare l’aderenza al trattamento il ricorso a dosi equivalenti settimanali o mensili è giustificato da un punto di vista farmacologico (Chel V et al. 2008). In fase iniziale di terapia, qualora si ritenga opportuno ricorrere alla somministrazione di dosi elevate (boli), si raccomanda che queste non superino le 100.000 UI, perché per dosi superiori si è osservato un aumento degli indici di riassorbimento osseo, ed anche un aumento paradosso delle fratture e delle cadute (Smith H et al 2007, Sanders KM et al 2010). Una volta verificato il raggiungimento di valori di normalità essi possono essere mantenuti con dosi inferiori, eventualmente anche in schemi di somministrazione intervallati con una pausa estiva. **Il controllo sistematico dei livelli di 25OH-D non è raccomandato a meno che cambino le condizioni cliniche.**

Si rappresenta infine l’importanza della segnalazione delle reazioni avverse che si verificano dopo la somministrazione dei medicinali, al fine di consentire un monitoraggio continuo del rapporto beneficio/rischio dei medicinali stessi. Agli operatori sanitari è richiesto di segnalare, in conformità con i requisiti nazionali, qualsiasi reazione avversa sospetta tramite il sistema nazionale di farmacovigilanza all’indirizzo [http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali](http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali).
Bibliografia


Chel V, Wijnhoven HAH, Smit JH et al. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents Osteoporos Int. 2008; 19: 663–671.


Sanders KM, Stuart AL, Williamson EJ. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010; 303: 1815-1822.


Allegato 1. Guida alla misurazione della 25OHD e alla successiva prescrizione della Vitamina D

Diagramma di flusso applicabile a persone > 18 anni per la determinazione della 25OH Vit D
La flowchart non è applicabile nelle seguenti condizioni per le quali è indicata una valutazione specialistica:
- insufficienza renale (eGFR<30 mmol/L),
-  urolitiasi,
- ipercalcemia,
- sarcoidosi,
- neoplasie metastatiche, linfomi,

NB: La determinazione dei livelli di 25OHD NON deve essere intesa come procedura di screening è NON è indicata obbligatoriamente in tutte le possibili categorie di rischio.

(adattato da NICE 2018)

1. Esiste almeno un sintomo persistente fra quelli elencati suggestivo per carenza di vitamina D ?
   - Sintomi di osteomalacia come dolenza in sedi ossee o dolore (anche pulsante) lombosacrale, pelvico o agli arti inferiori; senso di impedimento fisico; dolori o debolezza muscolare (anche di grado elevato) soprattutto ai quadricipi ed ai glutei con difficoltà ad alzarsi da seduto o andatura ondeggiante;
   - Dolori diffusi di lunga durata;
   - Propensione alle cadute immotivate.

2. È prevista una terapia di lunga durata con farmaci interferenti col metabolismo della vitamina D (ed es. antiepilettici, glucocorticoidi, anti-retrovirali, anti-micotici, colestrammina, orfisitato etc.) oppure esiste una condizione di malassorbimento (ad es. fibrosi cistica, celiaquia, m. Crohn, chirurgia bariatrica, etc) ?

3. Esiste una patologia ossea accertata (osteoporosi, osteomalacia o malattia di Paget) che può beneficiare dal trattamento con vitamina D oppure necessita di terapia remineralizzante?

4. Esiste un riscontro di PTH elevato con calcemia normale o bassa?

<table>
<thead>
<tr>
<th>Livelli di 25 (OH) D</th>
<th>Prescrizione di:</th>
<th>Prescrizione di:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 12 ng/mL (0-30 nmol/L)</td>
<td>colecalciferolo in dose cumulativa di 300.000 UI somministrabile in un periodo massimo di 12 settimane, suddivisi in dosi giornaliere, settimanali o mensili (non oltre le 100.000 UI/dose per motivi di sicurezza)</td>
<td>calcifediolo 1cps 2 volte al mese</td>
</tr>
<tr>
<td>13-20 ng/mL (30-50 nmol/L)</td>
<td>colecalciferolo in dose giornaliera di 750-1.000 UI o in alternativa dosi corrispondenti settimanali o mensili.</td>
<td>calcifediolo 1cps/mese</td>
</tr>
<tr>
<td>&gt;20 ng/mL (50 nmol/L)</td>
<td>Considerare altre possibili cause dei sintomi.</td>
<td>La determinazione della 25(OH) D, NON è appropriata.</td>
</tr>
</tbody>
</table>

Verifica dei livelli della 25OH D a tre mesi nel caso non vi sia risoluzione del quadro clinico di partenza

La supplementazione con vitamina D, dopo la eventuale fase intensiva iniziale di 3 mesi, prevede:
- l’interruzione del trattamento a correzione avvenuta dei sintomi da carenza salvo ricomparsa degli stessi
- la prosecuzione per tutta la durata delle terapie remineralizzanti,
- la prosecuzione per la durata delle terapie interferenti col metabolismo della vitamina D (antiepilettici etc.)
- la prosecuzione in caso di osteomalacia, osteoporosi e malattia di Paget
INTRODUCTION

Traditionally, the two primary functions of vitamin D are regulation of calcium and phosphorus homeostasis and control of skeletal mineral metabolism, which are commonly defined as “skeletal effects” [1-3]. In this context, the effect of vitamin D on calcium homeostasis is important not only for bone health but also for some metabolic, cellular and neuromuscular functions.

In the last thirty years, some other functions of vitamin D have emerged, such as its effect on the homeostasis/metabolism of many tissues and organs. These effects are usually defined as “extra-skeletal”. It has been suggested that vitamin D has a role in cellular proliferation and differentiation, on the cardiovascular system and on the modulation of the immune system as well [1-3].

These “extra-skeletal effects”, originally hypothesized on the basis of evidence from animal models [4], were subsequently confirmed by several epidemiological studies [5]. However, even though multiple and significant epidemiological studies have confirmed the correlation between appropriate levels of serum 25-hydroxyvitamin D [25(OH)D] and a lower incidence of some pathologies, data from randomized controlled studies (RCTs) are quite heterogeneous and in some cases even contradictory [5].

The aim of this review is to describe the existing relationship between vitamin D and some inflammatory/autoimmune rheumatic diseases (IRDs) and to summarize scientific findings related to the benefits of cholecalciferol supplementation in IRDs.

VITAMIN D AND THE IMMUNE SYSTEM

Clinical observations and experimental data suggest that vitamin D plays a critical role in the modulation of immune system functions (6-8). Through its active metabolite – calcitriol [1,25(OH)2D] – vitamin D indeed seems to be able to affect the activity of most immune system cells.
Two observations support this hypothesis:
[6-8]
- the vitamin D receptor (VDR) is expressed in most immune cells, including B and T lymphocytes, monocytes, macrophages and dendritic cells;
- some immune cells seem to be able to convert 25(OH)D to 1,25(OH)2D, the active metabolite that produces the final effect of vitamin D at the cellular level.

The modulatory activity of vitamin D seems to apply both to innate and adaptive immunity [6-8].

The role of vitamin D as regulator of innate immunity has been widely characterized [6-8]. Calcitriol is able to trigger the production of antimicrobial peptides from macrophages/monocytes and to increase chemotaxis, autophagy and immune system phagolysosome fusion. In addition, 1,25(OH)2D seems able to affect gut microbiota, to reduce intestinal permeability and, more generally, to "facilitate" the barrier function of tissues against pathogens [6].

Regarding the adaptive immune system, experimental data appear more heterogeneous, even while supporting an effect on the immune function [6-8]. Calcitriol seems capable of suppressing T helper 1 (Th1) activation and to modulate activity of Th2 cells (upregulation), Th17 cells (suppression) and Treg cells (function stimulation) [6]. Moreover, 1,25(OH)2D has proved to be able to reduce the proliferation and differentiation of B lymphocytes, causing less expression of autoantibodies [6-8].

In conclusion, even though available data are not always supported by solid scientific evidence, overall they seem to indicate that vitamin D may play a protective role against pathogens and in the reduction of inflammatory/autoimmune processes, phenomena that essentially require immunomodulatory action.

HYPOVITAMINOSIS D IN INFLAMMATORY/AUTOIMMUNE RHEUMATIC DISEASES

Epidemiological studies have unequivocally confirmed a high incidence of hypovitaminosis D in several IRDs. On average, patients with rheumatoid arthritis (RA), psoriatic arthritis (PA), ankylosing spondylitis (AS), systemic sclerosis (SS) and lupus (SLE) appear to have 25(OH)D values lower by at least 8-10 ng/ml compared to those of healthy control groups [9-14].

In a post-hoc analysis of the CARMA study (Fig. 1) [9], the vitamin D status of 2,234 patients with RA, PA and AS was compared with that of 667 healthy subjects. Vitamin D deficiency (< 20 ng/ml) fluctuated between 40 and 41% in patients with RA, PA and AS and was found in 27% of healthy subjects (P < 0.001). These results are even more significant if we consider that the average age of the population was well below 60 years and that patients were treated with vitamin D supplements in varying percentages. In patients affected by RA – the group with the highest percentage of patients treated with cholecalciferol (42%) – the relationship between RA and hypovitaminosis D was particularly strong in the multivariate analysis as well [OR = 1.5 - 95% CI 1.1-2.0] [9].

The high incidence of hypovitaminosis D in patients with RA was clearly confirmed by a recent meta-analysis performed on 15 observational studies (1,100 RA patients and 1,000 healthy controls) [12]. The authors observed considerably lower average 25(OH)D values in RA patients compared to those in the control group and further found that deficiency was significantly higher in patients with RA (55% in RAs vs. 33% in healthy subjects; OR = 2.5 - 95% CI 1.1-5.3). Similar studies on patients with SLE or SS produced the same results [10, 11, 13, 14].

Recently, Islam et al. conducted a review of several studies on the prevalence of hypovitaminosis D in patients with SLE [13]. In total they analyzed 34 studies (2,265 patients with SLE and 1,846 healthy subjects). The average 25(OH)D value in SLE patients was generally about 10 ng/ml lower compared to the control group. In the absence of appropriate vitamin D supplementation, the difference between SLE patients and the control group becomes particularly important in patients treated with hydroxychloroquine, corticosteroids or other immunosuppressive medications (average difference compared to healthy subjects: 1.6 ng/ml) [13].

Analogous results were found in another meta-analysis conducted on data regarding SS and hypovitaminosis D [6 studies, 554 SS patients and 321 healthy subjects] [14].

The standardized average difference between patients with SS and healthy subjects was about 9 ng/ml, with some variability linked to the characteristics of the SS.

% of patients with 25(OH)D < 20 ng/mL (histograms)

mean value of 25(OH)D (ng/mL) (dots and lines)

FIGURE 1.
Percentage of patients with vitamin D deficiency [25(OH)D < 20 ng/mL] (histograms) and mean value (95% CI) of 25(OH)D (ng/mL) (dots and lines) in healthy subjects and those with RA, AS and PA (CARMA study) [Urruticoechea-Arana et al., 2015] [9].
in healthy subjects as a function of either the baseline levels of 25(OH)D or of cholecalciferol intake are definitely insufficient. Two studies have shown a correlation between exposure to UVB or intake of vitamin D3 (from food or supplements) and the risk of developing RA [15,16]. The Nurses’ Health Study (NHS), conducted on a population of more than 100,000 women, showed a lower incidence of RA in subjects who had a higher cumulative average exposure to UVB compared to women who had a lower exposure (HR = 0.8, 95% CI, 0.7-0.9) [15].

These results were not confirmed in the duplicate study NIHSSL [15].

Results from the Iowa Women’s Health Study, which investigated the incidence of RA as a function of vitamin D intake in a population of more than 29,000 women, showed that higher vitamin D intake (both via diet and supplementation) was associated with a reduced risk of RA (RR = 0.7, 95% CI, 0.4-1.0) [16].

Contrary to what has just been described, it should be noted that post-hoc analysis of these two studies and of others failed to confirm the relationship between vitamin D and RA or SLE risk [17,19]. Therefore, ad hoc studies need to be designed and carried out to further investigate the cause-effect relationship between hypovitaminosis D and IRDs occurrence.

**VITAMIN D STATUS AND DISEASE ACTIVITY/SEVERITY**

The existence of a relationship between vitamin D status [serum 25(OH)D] and disease activity or severity has been reported in several studies that were primarily (but not exclusively) carried out on patients with RA, SLE and SS [10-12,20-23]. Most studies that examined the relationship between 25(OH)D and disease activity in patients with RA showed an inverse correlation between vitamin D status and DAS28, VAS and/or VES [12, 20-22]. In the COMORA study, for instance, performed on 1,413 RA patients, average DAS28 values in subjects with normal vitamin D levels were considerably lower compared to subjects with hypovitaminosis D (Fig. 2) [22]. A similar relation (inverse correlation) was also found for ACPAs by Wang et al. [21].

Also for SS and SLE patients, clinical data showed an inverse correlation between 25(OH)D and disease activity or clinical outcomes (scleroderma ulcers) [10,11,23]. Regarding SS patients, for example, Caimi et al. analyzed the relationship between variation of 25(OH)D values over time and the incidence of digital ulcers in 65 SS patients. They found that a 25(OH)D reduction (in 48% of patients) during a 5-year follow-up was associated with higher risk for developing digital ulcers (OR = 16.6, 95% CI, 1.7-164.5) [11]. Another study, which investigated average 25(OH)D values as a function of disease activity measured by the SLEDAI index in 199 SLE patients, found a progressive decrease of 25(OH)D in tandem with a progressive worsening of the SLEDAI (Fig. 3) [10].

**USE OF VITAMIN D TO TREAT INFLAMMATORY/AUTOIMMUNE RHEUMATIC DISEASES**

Overall, the epidemiological and clinical findings described here have opened the way toward the hypothesis that reduction of disease activity and perhaps even improved clinical results can be attained by using cholecalciferol supplementation in IRDs patients with vitamin D deficiency [7].

A recent literature review describing the main RCTs performed on patients with SLE, RA, Crohn’s Disease, multiple sclerosis and type 1 diabetes has highlighted the therapeutic potential of cholecalciferol and its metabolites with regard to IRDs [7].

In the case of SLE patients, studies were conducted using cholecalciferol doses between 2,000 IU and roughly 7,000 IU daily for 3 to 12 months versus placebo. Two of these studies, namely that with the greatest duration (12 months) and that in which the highest doses of cholecalciferol were given (50,000 IU per week), clearly showed beneficial effects of cholecalciferol on disease activity (SLEDAI and ECLAM), on VES and on clinical symptoms. The only study which did not confirm these results was compromised by various shortcomings, such as the short period in which supplementation was given and the inclusion of patients in which the disease was not active [7].

Less solid though very promising data were obtained from RCT studies that used cholecalciferol supplementation or its metabolites in RA patients. The weakness of the data in these cases is probably due to several limitations of the RCTs (number of patients, duration of the follow-up and relatively high baseline 25(OH)D values) [7].

In general, these RCT studies highlighted positive trends regarding DAS28, VES and clinical symptoms; yet these did not achieve statistically significant results [7].

On the other hand, a more recent prospective study that administered cholecalciferol 100,000 IU per month in RA patients showed beneficial effects on VAS and DAS28 [24]. The most important point of this study is that it demonstrated different effects of cholecalciferol on DAS28 and VAS depending on baseline 25(OH)D levels. The most beneficial effects of cholecalciferol on
DAS28 were found in patients with baseline 
25(OH)D > 20 ng/mL, while its greatest 
effects on VAS were in patients with baseline 
25(OH)D < 20 ng/mL [24].

CONCLUSIONS

Within the limits dictated by the complexity and heterogeneity of the IRDs, data from the literature appear to unambiguously confirm a role of vitamin D in diseases such as RA, SS and SLE. Its effect with regard to other IRDs (PA and AS) seems less clear, mainly because of the scarcity of published studies and their modest quality. It is therefore possible that vitamin D plays a relevant role in these diseases as well [20]. In general, we can state that serum 25(OH)D levels seem to influence the activity and severity of some IRDs and can possibly also have an effect on certain clinical outcomes; less clear is the cause-effect relationship in IRDs pathogenesis.

Based on data from RCTs, cholecalciferol supplementation should be offered to all patients with IRDs who do not have optimal 25(OH)D baseline values. Meanwhile, for IRDs patients with normal vitamin D values, well-designed RCTs conducted on specific populations will be necessary to determine the possible use of cholecalciferol, with the aim of improving the clinical evolution and outcome of the disease.

Reference


plantation by vitamin D. Front Immunol 2019;10:2586.


BIBLIOGRAPHIC SELECTION

**CARDIOLOGY**

- Bouillon R. Vitamin D and cardiovascular disorders. Osteoporos Int 2019 - Review. PMID 31402402
- Cha JJ and Wi J. Association of Vitamin D Deficiency with Profound Cardiogenic Shock In Patients Resuscitated from Sudden Cardiac Arrest. Shock 2019. PMID 31490356
- Cheru LT, et al. Low vitamin D is associated with coronary atherosclerosis in women with HIV. Antivir Ther 2019. PMID 31742564
- Cui C, et al. Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of renin-angiotensin system. Redox Biol 2019. PMID 31421410
- Djoussé L, et al. Supplementation with Vitamin D and/or Omega-3 Fatty Acids and Incidence of Heart Failure Hospitalization: VITAL-Heart Failure. Circulation 2019. PMID 31709816
- Dogdus M, et al. Cardiac autonomic dysfunctions are recovered with vitamin D replacement in apparently healthy individuals with vitamin D deficiency. Ann Noninvasive Electrocardiol 2019. PMID 31339201
- Fonseca Valle D and Giannini DT. Correlation between vitamin D and blood pressure in adolescents. Int J Adolesc Med Health 2019. PMID 31562802
- Keskin Ü and Basat S. The effect of vitamin D levels on gastrointestinal bleeding in patients with warfarin therapy. Blood Coagul Fibrinolysis 2019. PMID 31415247
- Keskin Ü and Basat S. The effect of vitamin D levels on gastrointestinal bleeding in patients with warfarin therapy. Blood Coagul Fibrinolysis 2019. PMID 31415247
- Laird EJ, et al. Vitamin D Status Is Not Associated With Orthostatic Hypotension in Older Adults. Hypertension 2019. PMID 31327261

© Copyright by Pacini Editore srl

This is an open access article distributed in accordance with the CC-BY-NC-ND (Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International) license. The article can be used by giving appropriate credit and mentioning the license, but only for non-commercial purposes and only in the original version. For further information: https://creativecommons.org/licenses/by-nc-nd/4.0/deed.en

Lim GB. Vitamin D supplementation and CVD. Nat Rev Cardiol 2019. PMID 31273304


Orkaby AR, et al. Vitamin D supplements and prevention of cardiovascular disease. Curr Opin Cardiol 2019. PMID 31425172


Perge P, et al. Vitamin D Deficiency Predicts Poor Clinical Outcomes in Heart Failure Patients Undergoing Cardiac Resynchronization Therapy. Dis Markers 2019. PMID 31737126

Peters KM and Borraldaile NM. Microarray data and pathway analyses for human microvascular endothelial cells supplemented with low dose vitamin D or niacin during lipotoxicity. Data Brief 2019. PMID 31667254

Playford MP, et al. Serum active 1,25(OH)2D, but not inactive 25(OH)D vitamin D levels are associated with cardiometabolic and cardiovascular disease risk in psoriasis. Atherosclerosis 2019. PMID 31450013


Talari HR, et al. Long-term vitamin D and high-dose n-3 fatty acids’ supplementation improve markers of cardiometabolic risk in type 2 diabetic patients with CHD. Br J Nutr 2019. PMID 31481139


Well RB. Beneficial Effects of Sunlight May Account for the Correlation Between Serum Vitamin D Levels and Cardiovascular Health. JAMA Cardiol 2019. PMID 31721977


• Robertson C, et al. Scope and limitations of nuclear magnetic resonance techniques for characterisation and quantitation of vitamin D in complex mixtures. Skin Res Technol 2019. PMID 31549460


• Wolf P. Vitamin D: one more argument for broad-spectrum ultraviolet A + ultraviolet B sunscreen protection. Br J Dermatol 2019. PMID 31674668

• Young AR, et al. Optimal sunscreen use, during a sun holiday with a very high ultraviolet index, allows vitamin D synthesis without sunburn. Br J Dermatol 2019. PMID 31069787


EPIDEMIOLOGY


• Anwar M, et al. The sunshine under our skin: public knowledge and practices about vitamin D deficiency in Al Ain, United Arab Emirates. Arch Osteoporos 2019. PMID 31758340

• Azizi S and Tariq TM. Vitamin D Deficiency Among Afghan Adolescents in Kabul. J Coll Physicians Surg Pak 2019. PMID 31659965


• Bouillon R. Vitamin D status in Africa is worse than in other continents. Lancet Glob Health 2019. PMID 31786116

• Caristia S, et al. Vitamin D as a Biomarker of Ill Health among the Over-50s: A Systematic Review of Cohort Studies. Nutrients 2019 - Review. PMID 31590434


• Cembranel F, et al. Obesity and 25(OH)D Serum Concentration Are More Important than Vitamin Dintake for Changes in Nutritional Status Indicators: A Population-Based Longitudinal Study in a State Capital City in Southern Brazil. Nutrients 2019. PMID 31590272

• Corrêa MP, et al. Changes in the total ozone content over the period 2006 to 2100 and the effects on the erythemal and vitamin D effective UV doses for South America and Antarctica. Photochem Photobiol Sci 2019. PMID 31696195


• Enlund-Cerullo M, et al. Genetic Variation of the Vitamin D Binding Protein Affects Vitamin D Status and Response to Supplementation in Infants. J Clin Endocrinol Metab 2019. PMID 31365099


• Rabuetti A, et al. Vitamin D Status Among Male Late Adolescents Living in Southern Switzerland: Role of Body Composition and Lifestyle. Nutrients 2019. PMID 31717911

• Religi A, et al. Correction to: Estimation


• Tanabe S, et al. Physical inactivity and vitamin D deficiency in hospitalized elders. J Bone Miner Metab 2019. PMID 30915552


• Zhu XL, et al. Associations of vitamin D with novel and traditional anthropometric indices according to age and sex: a cross-sectional study in central southern China. Eat Weight Disord 2019. PMID 31728924

ENDOCRINOLOGY


• Aktaş BY and Öztürk Aktaş O. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med 2019. PMID 31665587

• Aktaş Ş. Vitamin B12 and vitamin d levels in patients with autoimmune hypothyroidism and their correlation with the antithyroid peroxidase antibodies. Med Princ Pract 2019. PMID 31779003


• Barros-Oliveira CS, et al. Sweat and vitamin D status in congenital, lifetime, untreated GH deficiency. Endocrine 2019. PMID 31292841


• Cadario F, et al. Vitamin D and e3 Supplementation in Mediterranean Diet During the 1st Year of Overt Type 1 Diabetes: A Cohort Study. Nutrients 2019. PMID 31505819

• Canat HI, et al. Is high levels of vitamin D a new risk factor for Peyronie’s disease? Andrologia 2019. PMID 31482615

• Chen C, et al. The vitamin D receptor (VDR) protects pancreatic beta cells against Forkhead box class O1 (FOXO1)-induced mitochondrial dysfunction and cell apoptosis. Biomed Pharmacother 2019. PMID 31261027


• Cheung MM, et al. Low dietary magnesium intake alters vitamin D-parathyroid hormone relationship in adults who are overweight or obese. Nutr Res 2019. PMID 31675537


• Câmara AB and Brandão IA. The relationship between vitamin D deficiency and oxidative stress can be independent of age and gender. Int J Vitam Nutr Res 2019. PMID 31711376

• de Boer IH, et al. Effect of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA 2019. PMID 31703120

• Denova-Gutiérrez E, et al. Low Serum Vitamin D Concentrations Are Associated with Insulin Resistance in Mexican Children and Adolescents. Nutrients 2019. PMID 31491877
• Ekborn K, et al. Follow-up study found that vitamin D deficiency and weight gain increased the risk of impaired fasting glycemia. Acta Paediatr 2019. PMID 31483890


• Formenti AM, et al. Body mass index predicts resistance to active vitamin D in patients with hypoparathyroidism. Endocrine 2019. PMID 31655979

• Fu J, et al. Vitamin D levels are associated with metabolic syndrome in adolescents and young adults. The BCAMS study. Clin Nutr 2019. PMID 30236482


• Ganji V, et al. Serum vitamin D concentrations are inversely related to prevalence of metabolic syndrome in Qatari women. Biofactors 2019. PMID 31512799


• Gröber U and Holick MF. Diabetes Prevention: Vitamin D Supplementation May Not Provide Any Protection If There Is No Evidence of Deficiency! Nutrients 2019. PMID 31689953


• Koehler VF, et al. Vitamin D Status and Thyroid Autoantibodies in Autoimmune Thyroiditis. Horm Metab Res 2019. PMID 31766063


• Mansur JL. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med 2019. PMID 31665589


• Niroomand M. Magnitude of benefit of vitamin D supplementation and the stage of impaired glucose metabolism: Area for future studies. Diabetes Res Clin Pract 2019. PMID 31325542


• Nodehi M, et al. Effects of vitamin D supplements on frequency of CD4+ Tcell subsets in women with Hashimoto’s thyroiditis.


- Parsanathan R and Jain SK. Glutathione deficiency induces epigenetic alterations of vitamin D metabolism genes in the livers of high-fat diet-fed obese mice. Sci Rep 2019. PMID 31616013


- Yang YY and Liu JM. What can we learn from the Vitamin D and Type 2 Diabetes (D2d) Study? J Diabetes 2019. PMID 31755248


EPIDEMIOLOGY


GASTROENTEROLOGY


- Cimini FA, et al. Overview of studies of the vitamin D/vitamin D receptor system in the development of non-alcoholic fatty liver disease. World J Gastrointest Pathophysiol 2019. PMID 31559105


- Dong B, et al. Vitamin D receptor activation in liver macrophages ameliorates hepatic inflammation, steatosis, and insulin resistance in mice. Hepatology 2019. PMID 31506976


• Durak Ş, et al. The effects of serum levels, and alterations in the genes of binding protein and receptor of vitamin D on gastric cancer. Mol Biol Rep 2019. PMID 31549372


• Fu L, et al. [Correlation between serum 25(OH) vitamin D and liver fat content in nonalcoholic fatty liver disease]. Nan Fang Yi Ke Da Xue Xue Bao 2019. PMID 31640966 Chinese.


• Hu CQ, et al. Vitamin D Deficiency Attenuates Acute Alcohol-Induced Hepatic Lipid Accumulation in Mice. Lipids 2019. PMID 31463983


• Joanna B, et al. Vitamin D, linoleic acid, arachidonic acid and COX-2 in colorectal cancer patients in relation to disease stage, tumor localisation and disease progression. Arab J Gastroenterol 2019. PMID 31272909


• Limketkai BN, et al. Levels of Vitamin D are Low After Crohn’s Disease is Established But Not Before. Clin Gastroenterol Hepatol 2019. PMID 31589971

• Liu Y, et al. Active vitamin D supplementation alleviates initiation and progression of nonalcoholic fatty liver disease by repressing the p53 pathway. Life Sci 2019. PMID 31756344


• Lu R, et al. Imbalance of autophagy and apoptosis in intestinal epithelium lacking the vitamin D receptor. FASEB J. 2019. PMID 31361973


• Mechie NC, et al. Distinct Association of Serum Vitamin D Concentration with Disease Activity and Trough Levels of Infliximab and Adalimumab during Inflammatory Bowel Disease Treatment. Digestion 2019. PMID 31536991

• Mentella MC, et al. The Association of Disease Activity, BMI and Phase Angle with Vitamin D Deficiency in Patients with IBD. Nutrients 2019. PMID 31717788

• Mohamed AA, et al. Serum Vitamin D Levels in Chronic Hepatitis B Patients Before and During Treatment. Infect Disord Drug Targets 2019. PMID 31721718


• Qu B, et al. Role of Circulating and Supplemental Calcium and Vitamin D in the Occurrence and Development of Colorectal Adenoma or Colorectal Cancer. J Clin Gastroenterol 2019. PMID 28134636


• Scott MJ. The upside-downside nature of Vitamin D signaling in liver. J Leukoc Biol 2019. PMID 31379001

• Sharifi A, et al. Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMS 2019 - Clinical Trial. PMID 31274211


Yao B, et al. The protective effect of lithocholic acid on the intestinal epithelial barrier is mediated by the vitamin D receptor via a SIRT1/Nrfl2 and NF-kB dependent mechanism in Caco-2 cells. Toxicol Lett 2019. PMID 31472180

Zhang YH, et al. The effects of oral vitamin D supplementation on the prevention of periuteal dialysis-related peritonitis: study protocol for a randomized controlled clinical trial. Trials 2019. PMID 31779675

Zhang Z, et al. Vitamin D and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care 2019. PMID 31589177


HEMATOLOGY


Arain A and Matthiesen C. Vitamin D deficiency and graft-versus-host disease in hematopoietic stem cell transplant population. Hematol Oncol Stem Cell Ther 2019 - Review. PMID 30213260


IMMUNOLOGY


Aguilar-Jimenez W, et al. Genetic associations of the vitamin D and antiviral pathways with natural resistance to HIV-1 infection are influenced by interpopulation variability. Infect Genet Evol 2019. PMID 31103723


Carlberg C. Vitamin D Signaling in the Context of Innate Immunity: Focus on Human Monocytes. Front Immunol 2019 - Review. PMID 31572402


Cruz JRS, et al. Assessment of vitamin D status in common variable immunodeficiency or ataxia-telangiectasia patients. Allergol Immunopathol (Madr) 2019. PMID 31377030

Eroglu C, et al. The relation between serum vitamin D levels, viral infections and severity
of attacks in children with recurrent wheezing. Allergol Immunopathol (Madrid) 2019. PMID 31477398


Jonas MI, et al. Vitamin D Receptor Gene Expression in Adipose Tissue of Obese Individuals is Regulated by miRNA and Correlates with the Pro-Inflammatory Cytokine Level. Int J Mol Sci 2019. PMID 31652924


Lin LY, et al. Vitamin D deficiency or supplementation and the risk of human herpesvirus infections or reactivation: a systematic review protocol. BMJ Open 2019. PMID 31594899


Martinez-Moreno J, et al. Effect of high doses of vitamin D supplementation on dengue virus replication, TollHike receptor expression, and cytokine profiles on dendritic cells. Mol Cell Biochem 2019. PMID 31758375

McKinley MC. Effect of Vitamin D and Omega-3 Supplements on Systemic Inflammation. Clin Chem 2019. PMID 31699703

Mousavi S, et al. Vitamin D in Acute Campylobacteriosis Results From an Intervention Study Applying a Clinical Campylobacter jejuni Induced Enterocolitis Model. Front Immunol 2019. PMID 31552040


Shabana MA, et al. Predictive role of IL-17A/IL-10 ratio in persistent asthmatic patients on vitamin D supplementation. Immunobiol 2019. PMID 31570180

Sopo SM, et al. The unpredictability of seasonal variations in serum vitamin D levels in children with asthma and/or rhinitis. Allergol Immunopathol (Madrid) 2019. PMID 30940418


Yalcin AD and Uzun R. Anti-IgE Significantly Changes Circulating Interleukin-25, Vitamin D and Interleukin-33 Levels in Patients with Allergic Asthma. Curr Pharm Des 2019. PMID 31566129


Zhou Q, et al. Vitamin D supplementation could reduce the risk of acute cellular rejection and infection in vitamin D deficient liver allograft recipients. Int Immunopharmacol 2019. PMID 31422183

Zhu DC, et al. [Research progress on the relevance between serum vitamin D and IL-33/ST2 levels and allergic rhinitis]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2019 - Review. PMID 31446716 Chinese.

LABORATORY


dehydroepiandrosterone sulphate and vitamin D as examples. Ann Clin Biochem 2019. PMID 30974962


Chun RF, et al. Vitamin D Binding Protein and the Biological Activity of Vitamin D. Front Endocrinol (Lausanne) 2019 · Review. PMID 31708871


Duchow EG, et al. Vitamin D binding protein is required to utilize skin-generated vitamin D. Proc Natl Acad Sci U S A 2019. PMID 31748273

Francic V, et al. The Effect of Vitamin D Supplementation on its Metabolism and the Vitamin D Metabolite Ratio. Nutrients 2019. PMID 31640241


Viraraghavan VR. Importance of the method used to estimate 25(OH)D and the definition used for vitamin D status classification in a clinical trial on vitamin D metabolism. Paediatr Int Child Health 2019. PMID 31094295


MISCELLANEOUS

Amrein K, et al. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: a study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). BMJ Open 2019. PMID 31722941

Atalay K, et al. Serum levels of thyroid hormone, vitamin D, vitamin B12, folic acid, C-reactive protein, and hemoglobin in Pseudoexfoliation and primary open angle Glaucoma. J Fr Ophtalmol 2019. PMID 31103354

Aykan DA and Seyithanoglu M. The Effects of Administration of Vitamin D, Infliximab, and Leflunomide on Testosterone Concentrations in Rats under Atorvastatin Therapy. Eurasian J Med 2019. PMID 31692672


Beauchet O, et al. Effects of Vitamin D and Calcium Fortified Yogurts on Cognition, Cognitive Performances, and Serum 25-Hydroxyvitamin D Concentrations in Older Community-Dwelling Females: Results from the GAit, MEmory, and Dietary Vitamin D (GAME-D2) Randomized Controlled Trial. Nutrients 2019. PMID 31779179

Bezrati I, et al. A single mega dose of vitamin D3 improves selected physical variables in vitamin D insufficient young amateur soccer players: a randomized controlled trial. Appl Physiol Nutr Metab 2019. PMID 31597046


Boucher BJ. Validating the effects of correcting vitamin D deficiency; time for reappraisal of clinical trial design. QJM 2019. PMID 31020315

Bouillon R and Bikle D. Vitamin D Metabolism Revised: Fall of Dogmas. J Bone Miner Metab 2019. PMID 31589774

Bouillon R and Quesada-Gomez JM. Calcifedoral or vitamin D to optimize vitamin D status: Reply to letter of M Sosas. Osteoporos Int 2019. PMID 31612250

Bratlie M, et al. Five salmon dinners per week was not sufficient to prevent the reduction in serum vitamin D in autumn at 60º north latitude: a randomised trial. Br J Nutr 2019. PMID 31760958


Casado Burgos E. [Response to the Editorial «Vitamin D: The new suit of the Sun King»]. Aten Primaria 2019. PMID 31672249

Spanish.

Chabrol T and Wion D. Randomized clinical trials of oral vitamin D supplementation in need of a paradigm change. The vitamin D autacoid paradigm. Med Hypotheses 2019. PMID 31627120


Dong W, et al. Multiple genome analyses reveal key genes in Vitamin C and Vitamin D synthesis and transport pathways are shared. Sci Rep 2019. PMID 31727908


Ebrell MH. Vitamin D Is Not Effective as Primary Prevention of Cardiovascular Disease or Cancer. Am Fam Physician 2019. PMID 31524368


Fraser WD, et al. Vitamin D Measurement, the Debates Continue, New Analyses Have Emerged, Developments Have Variable Outcomes. Calcif Tissue Int 2019 - Review. PMID 31741016


Grant WB and Boucher BJ. A Review of the Potential Benefits of Increasing Vitamin D Status in Mongolian Adults through Food Fortification and Vitamin D Supplementation. Nutrients 2019 - Review. PMID 31615079

Grant WB and Boucher BJ. Why Secondary Analyses in Vitamin D Clinical Trials Are Important and How to Improve Vitamin D Clinical Trial Outcome Analyses-A Comment on “Extra-Skeletal Effects of Vitamin D, Nutrients 2019, 11, 1460”. Nutrients 2019. PMID 31514355


Jiang X, et al. The genetics of vitamin D. Bone 2019. PMID 30316967


Khayyatzadeh SS, et al. What is the best solution to manage vitamin D deficiency? IUBMB Life 2019 - Review. PMID 30932323

Kim DK, et al. The Relationship between Vitamin D Status and Rotator Cuff Muscle Strength in Professional Volleyball Athletes. Nutrients 2019. PMID 31739527


Kühn J, et al. Feasibility of artificial light regimes to increase the vitamin D content in indoor-laid eggs. Poult Sci 2019. PMID 31041442

Larson-Meyer DE, et al. Validation of a Vitamin D Specific Questionnaire to Determine Vitamin D Status in Athletes. Nutrients 2019. PMID 31717985


Lippi G and Targher G. Are we overrating the extra-skeletal benefits of oral vitamin D supplementation? Ann Transl Med 2019. PMID 31700935

Lucas A and Wolf M. Vitamin D and Health Outcomes: Then Came the Randomized Clinical Trials. JAMA 2019. PMID 31703117

Luttmann-Gibson H, et al. Serum 25-hydroxyvitamin D in the ViTAMin D and Ome-ga-3 Trial (VITAL): Clinical and demographic characteristics associated with baseline and change with randomized vitamin D treatment. Contemp Clin Trials 2019. PMID 31669447


Manousaki D and Richards JB. Commentary: Role of vitamin D in disease through the lens of Mendelian randomization—Evidence from Mendelian randomization challenges the benefits of vitamin D supplementation for disease prevention. Int J Epidemiol 2019. PMID 31518416

Manson JE, et al. Principal Results of the ViTAMin D and Omega-3 Trial (VITAL) and Updated Meta-analyses of Relevant Vitamin D Trials. J Steroid Biochem Mol Biol 2019 - Review. PMID 31733345


Moyersoen I, et al. A Novel Approach to Optimize Vitamin D Intake in Belgium through Fortification Based on Representative Food Consumption Data. J Nutr 2019. PMID 31204779

Munshi RP, et al. Assessing the Effectiveness of Panchatikta Ghrita, a Classical Ayurvedic Formulation as Add-on Therapy to Vitamin D(3) and Calcium Supplements in Patients with Osteopenia: A Randomized, Open-Labeled, Comparative, Controlled Clinical Study. J Aliment Complement Med 2019. PMID 31460771


Nikooyeh B, et al. Vitamin D-fortified cooking oil is an effective way to improve vitamin D status: an institutional efficacy trial. Eur J Nutr 2019. PMID 31606753


Orces C. The Association between Body Mass Index and Vitamin D Supplement Use among Adults in the United States. Cureus 2019. PMID 31720189


Reyes-García R, et al. Factors Predicting the Response to a Vitamin D-Fortified Milk in Healthy Postmenopausal Women. Nutrients 2019. PMID 31689902

Roizen JD and Levine MA. Vitamin D therapy and the era of precision medicine. J Clin Endocrinol Metab 2019. PMID 31665328


PMID 31706679
Ergosterol to Vitamin D(2), Physiochemical Trafine-grinding on the Biotransformation of Eur J Clin Nutr 2019. PMID 31548595

Gual and capsular vitamin D preparations. Ratios 25-hydroxyvitamin D following sublingual. Williams CE, et al. Rate of change of circu

31752277

PMID 31776371


Boucher BJ and Grant WB. Letter by Boucher and Grant Regarding Article, “Vitamin D Status and Risk of Stroke: The Rotterdam Study”. Stroke 2019. PMID 31690253


Fashanu OE, et al. Mid-Life serum Vitamin D concentrations were associated with incident dementia but not late-life neuropsychological performance in the Atherosclerosis Risk in Communities (ARIC) Study. BMC Neurol 2019. PMID 31640594

Feng X, et al. Vitamin D enhances responses to interferon-β in MS. Neural Neuroimmunol Neuroinflamm 2019. PMID 31582399

• Bentata Y. Benefit-risk balance of native vitamin D supplementation in chronic hemodialysis: what can we learn from the major clinical trials and international guidelines? Ren Fail 2019. PMID 31267807 Free PMC article.


• Kara AV and Soylu YE. The relationship between vitamin D and inflammatory markers in maintenance hemodialysis patients. Int Urol Nephrol 2019. PMID 31385179


• Kyun Choi C, et al. Serum level vitamin D and parathyroid hormone, and mortality, with or without chronic kidney disease. J Bone Miner Metab 2019. PMID 30553953

• Li A, et al. LC3 promotes the nuclear translocation of the vitamin D receptor and decreases fibrogenic gene expression in proximal renal tubules. Metabolism 2019. PMID 31226352


• Pereira RC, et al. Vitamin D sterols increase FGF23 expression by stimulating osteoblast and osteocyte maturation in CKD bone. Bone 2019. PMID 31377240 Free PMC article.

• Sasak G and Bakan A. Is Vitamin D Deficiency Associated With Metabolic Syndrome in Renal Transplant Recipients? Transplant Proc 2019. PMID 31474294


• Wu CC, et al. Antiproteinuria Effect of Calcitriol in Patients With Chronic Kidney Disease and Vitamin D Deficiency: A Randomized Controlled Study. J Ren Nutr 2019. PMID 31704188

• Xiaowei L, et al. Comparison of the effects of valsartan plus activated vitamin D versus valsartan alone in IgA nephropathy with moderate proteinuria. Int Urol Nephrol 2019. PMID 31768803


• Yajima A, et al. The Importance of Biologically Active Vitamin D for Mineralization by Osteocytes After Parathyroidectomy for Renal Hyperparathyroidism. JBMR Plus 2019. PMID 31768492

• Yang SK, et al. Association of Vitamin D Receptor Gene Polymorphism With the Risk of Nephrolithiasis. Ther Apher Dial 2019. PMID 30701705


**ONCOLOGY**

• Alkan A and Köksel EB. Vitamin D deficiency in cancer patients and predictors for screening (D-ONC study). Curr Probl Cancer 2019. PMID 30683325


• Blajszczak CC and Nonn L. Vitamin D regulates prostate cell metabolism via genomic and non-genomic mitochondrial redox-dependent mechanisms. J Steroid Biochem Mol Biol 2019. PMID 31574299

• Brown RB. Author Response to "In Defense of the UVB-Vitamin D-Cancer Hypothesis.". Endocrine 2019. PMID 31493272


• Grant WB. In defense of the UVB-vitamin D-cancer hypothesis. Endocrine 2019. PMID 31392627

• Grant WB and Moukayed M. Vitamin D(3) from Ultraviolet-B Exposure or Oral Intake in Relation to Cancer Incidence and Mortality. Curr Nutr Rep 2019. Review. PMID 31055734

• Horas K, et al. Loss of the Vitamin D Recep-
• Treatment patterns: investigating the association between de novo vitamin D supplement use post breast cancer diagnosis and all-cause mortality using linked pharmacy claim and registry data. Am J Epidemiol 2019. PMID 31673702


• Mittal S, et al. Vitamin D Receptor and Role of Vitamin D Supplementation in Advanced Gallbladder Cancer: A Prospective Study from Northern India. Gulf J Oncolog 2019. PMID 31591986


• Song J, et al. The correlation between low vitamin D status and renal interleukin-6/STAT3 hyper-activation in patients with clear cell renal cell carcinoma. Steroids. 2019. PMID 31295461

• Toprak B, et al. No association of serum PSA with vitamin D or total oxidant-antioxidant capacity in healthy men. Aging Male 2019. PMID 30084276


• Yonaga H, et al. Effect Modification of Vitamin D Supplementation by Histopathological Characteristics on Survival of Patients with Digestive Tract Cancer: Post Hoc Analysis of the AMATERASU Randomized Clinical Trial. Nutrients 2019. PMID 31652554

• Zhang X and Niu W. Meta-analysis of randomized controlled trials on vitamin D supplement and cancer incidence and mortality. Biosci Rep 2019. PMID 31696224


**OBSTETRICS GYNECOLOGY**


• Behmanesh N, et al. Effects of vitamin D supplementation on follicular development, gonadotropins and sex hormone concentrations, and insulin resistance in induced polycystic ovary syndrome. Turk J Obstet Gynecol 2019. PMID 31673465


• Ding L, et al. Toxicity of cooking oil fume derived particulate matter: Vitamin D(3) protects tubule formation activation in human umbilical vein endothelial cells. Ecotoxicol Environ Saf 2019. PMID 31706245

• Eftekhar M, et al. Is there any association between vitamin D levels and polycystic ovary syndrome (PCOS) phenotypes? Arch Endocrinol Metab 2019. PMID 31576965


• Heidari H, et al. Vitamin D Supplementation for Premenstrual Syndrome-Related inflammation and antioxidant markers in students with vitamin D deficient: a randomized clinical trial. Sci Rep 2019. PMID 31624297


• Leere JS and Vestergaard P. Calcium Metabolic Disorders in Pregnancy: Primary Hyperparathyroidism, Pregnancy-Induced Osteoporosis, and Vitamin D Deficiency in Pregnancy. Endocrinol Metab Clin North Am 2019 - Review. PMID 31345528


• Muyayalo KP, et al. Low circulating levels of vitamin D may contribute to the occurrence of preeclampsia through deregulation of Treg /Th17 cell ratio. Am J Reprod Immunol 2019. PMID 31299118


• Paffoni A, et al. Effect of vitamin D supplementation on assisted reproduction technology (ART) outcomes and underlying biological mechanisms: protocol of a randomized clinical controlled trial. The “supplementation of vitamin D and reproductive outcome” (SUNDRO) study. BMC Pregnancy Childbirth 2019. PMID 31675919


• Wu L, et al. Poor ovarian response is associated with serum vitamin D levels and pro-inflammatory immune responses in women undergoing in-vitro fertilization. J Reprod Immunol 2019. PMID 31604165


• Yin W, et al. [Effect of vitamin D supplementation on gestational diabetes mellitus: a Meta-analysis]. Wei Sheng Yan Jiu 2019. PMID 31601326 Chinese


• Zeynali M and Haghighian HK. Is there a relationship between serum vitamin D with dysmenorrhea pain in young women? J Gynecol Obstet Hum Reprod 2019. PMID 30898624


**PEDIATRICS**


• Asghari G, et al. The relation between circulating levels of vitamin D and parathyroid hormone in children and adolescents with overweight or obesity: Quest for a threshold. PloS One 2019. PMID 31770397


• Ercan N, et al. Is there an association between vitamin D levels and cow’s milk protein allergy at infancy? Arch Argent Pediatr 2019. PMID 31560486

• Esmaeili Dooki MR, et al. Vitamin D status in preschool children: should vitamin D supplementation, preventing vitamin D deficiency be continued in children over 2 years? J Public Health (Oxf) 2019. PMID 30137506


• Jaksic M, et al. Association between inflammation, oxidative stress, vitamin D, copper and zinc with pre-obesity and obesity in school children from the city of Podgorica, Montenegro. J Pediatr Endocrinol Metab 2019. PMID 31444965


• Linden MA, et al. DEFINITION OF VITAMIN D DEFICIENCY IN SCHOOLCHILDREN: SYSTEMATIC REVIEW WITH META-ANALYSIS. Arq Gastroenterol 2019. PMID 31721968

• Mandlik RM, et al. Paradoxical Response of Parathyroid Hormone to Vitamin D-Calcium Supplementation in Indian Children. J Pediatr 2019. PMID 31704050

• McClory S, et al. Effectiveness of vitamin D supplementation in Swedish children may be negatively impacted by BMI and se-

• Midtba UK, et al. Vitamin D status in preschool children and its relations to vitamin D sources and body mass index. Fish Intervention Studies-KIDS (FIN-S-KIDS). Nutrition 2019. PMID 31739173

• Nalbantoglu B and Nalbantoglu A. Vitamin D Levels in Children With Recurrent Aphthous Stomatitis. Ear Nose Throat J 2019. PMID 31631677


• Sakamoto Y, et al. Physiologic Leg Bowing is not a Physiologic Condition but Instead is Associated with Vitamin D Disorders in Toddlers. Calcif Tissue Int 2019. PMID 31595325


• Zisi D, et al. The association between vitamin D status and infectious diseases of the respiratory system in infancy and childhood. Hormones (Athens) 2019 - Review. PMID 31768940

PNEUMOLOGY


• Garcia-Marcos L. The unpredictable levels of vitamin D and their effects on asthma. Allergol Immunopathol (Madr) 2019. PMID 31401986

• Gupta SK and Ramadas S. Vitamin D in chronic obstructive pulmonary disease and asthma in Indian population. Lung India 2019. PMID 31670293

• Hirai K, et al. Comparison of the Association between Circulating Vitamin D(3) Levels and Clinical Outcomes in Patients with Asthma and Chronic Obstructive Pulmonary Disease: A Prospective Observational Study. Biol Pharm Bull 2019. PMID 31484846


• Kelly RS, et al. The role of the 17g21 genotype in the prevention of early childhood asthma and recurrent wheeze by vitamin D. Eur Respir J 2019. PMID 31439681

• Leclair TR, et al. Vitamin D Supplementation in Mechanically Ventilated Patients in the Medical Intensive Care Unit. JPEN J Parenter Enteral Nutr 2019. PMID 30756402


• Li SR, et al. Vitamin D deficiency exacerbates bleomycin-induced pulmonary fibrosis partially through aggravating TGF-β/Smad2/3-mediated epithelial-mesenchymal transition. Respir Res 2019. PMID 31775746


• Mathysen C, et al. Vitamin D Modulates the Response of Bronchial Epithelial Cells Exposed to Cigarette Smoke Extract. Nutrients 2019. PMID 31500220

• Mishra NK, et al. Should vitamin D be routinely checked for all chronic obstructive pulmonary disease patients? Lung India 2019. PMID 31670296

• Mohammadi A, et al. Vitamin D receptor Apal (rs7975322), Bsml (rs1544410), Fok1 (rs2228570), and TaqI (rs731236) gene polymorphisms and susceptibility to pulmonary tuberculosis in an Iranian population: A systematic review and meta-analysis. J Microbiol Immunol Infect 2019 - Review. PMID 31740220

• Munkhbayaralk S, et al. Vitamin D plasma concentration and vitamin D receptor genetic variants confer risk of asthma: A comparison study of Taiwanese and Mongolian populations. World Allergy Organ J 2019. PMID 31719947


• Rajaram M, et al. Effects of genetic polymorphisms in Vitamin D metabolic pathway on Vitamin D level and asthma control in South Indian patients with bronchial asthma. Lung India 2019. PMID 31670295


• Xu Y, et al. Budesonide up-regulates vitamin D receptor expression in human bronchial fibroblasts and enhances the inhibitory effect of calcitriol on airway remodeling. Allergol Immunopathol (Madr) 2019. PMID 31204163


• Özdoğan Ş. Seasonal, sex variations in vitamin d levels and their association with pulmonary function in children with asthma. Turk J Med Sci 2019. PMID 31651126

• PSYCHIATRY


• Alzghoul L. Role of Vitamin D in Autism Spectrum Disorder. Curr Pharm Des 2019. PMID 31755381


• de Koning EJ, et al. Vitamin D supplementation for the prevention of depression and poor physical function in older persons: the D-Vitaal study, a randomized clinical trial. Am J Clin Nutr 2019. PMID 31340012


• Faivre S, et al. Vitamin D deficiency in a psychiatric population and correlation between vitaminD and CRP. Encephale 2019. PMID 30885444


• Gan J, et al. The Effect of Vitamin D Supplementation on Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Child Adolesc Psychopharmacol 2019. PMID 31368773


• Ikonen H, et al. Vitamin D status and correlates of low vitamin D in schizophrenia, other psychoses and non-psychotic depression - The Northern Finland Birth Cohort 1966 study. Psychiatry Res 2019. PMID 30876732

• Jorde R and Grimnes G. Vitamin D: no cure for depression. Am J Clin Nutr 2019. PMID 31504098


• Kotsi E, et al. Vitamin D levels in children and adolescents with attention-deficit hyperactivity disorder (ADHD): a meta-analysis. Atten Defic Hyperact Disord 2019 - Review. PMID 30367389


• Vyas CM and Okereke OI. Vitamin D and Psychosis in Alzheimer Disease: New Insights From Pharmacogenomics Research. Am J Geriatr Psychiatry 2019. PMID 31262684


• Woodward G, et al. Serum Vitamin D and Magnesium levels in a psychiatric cohort. Psychiatr Danub 2019. PMID 31488730

• RHEUMATOLOGY


• Chang E and Kim Y. Vitamin D Ameliorates Fat Accumulation with AMPK/SIRT1 Activity in C2C12 Skeletal Muscle Cells. Nutrients 2019. PMID 31744213

• Chung JS, et al. Concurrent Bilateral Anterior Tibial Stress Fractures and Vitamin D Deficiency in an Adolescent Female Athlete: Treatment With Early Surgical Intervention. Front Pediatr 2019. PMID 31637224

• Conaway HH, et al. Glucocorticoids employ the monomeric glucocorticoid receptor to potentiate vitamin D[3] and parathyroid hormone-induced osteoclastogenesis. FASEB J 2019. PMID 31675485


• Dretakis K and Igoumenou VG. The role of parathyroid hormone (PTH) and vitamin D in falls and hip fracture type. Aging Clin Exp Res 2019. PMID 30701437


• Faber J, et al. Long-Term Impact of Calcium and Vitamin D Supplementation on Bone Density in HIV[+] Patients with Documented Deficiencies. AIDS Res Hum Retroviruses 2019. PMID 31523978

• Fan H and Xiao J. Critical thinking about three meta-analyses: can vitamin D alone or with calcium prevent fractures? Curr Med Res Opin 2019. PMID 31670980

• Fraissler L, et al. Vitamin D Deficiency in Patients With Idiopathic and Traumatic Osteochondritis Dissecans of the Talus. Foot Ankle Int 2019. PMID 31370694


• Hu CZ, et al. Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomised controlled trials. BMJ Open 2019. PMID 31619412


• Lodha S, et al. Spontaneous simultaneous bilateral quadriceps tendon rupture associated with severe vitamin D deficiency. Clin Endocrinol (Oxf) 2019. PMID 31368123

• Martinez-Aguilar MM, et al. Serum Pro- teomic Analysis Reveals Vitamin D-Binding Protein (VDBP) as a Potential Biomarker for Low Bone Mineral Density in Mexican Postmenopausal Women. Nutrients 2019. PMID 31766436


• Oliar Araghi S, et al. Do Vitamin D Level and Dietary Calcium Intake Modify the Association Between Loop Diuretics and Bone Health? Calcif Tissue Int 2019. PMID 31608419


• Pennisi M, et al. Decrease in Serum Vitamin D Level of Older Patients with Fatigue. Nutrients 2019. PMID 31635199


• Rendina D, et al. Vitamin D Status in Paget Disease of Bone and Efficacy-Safety Profile of Cholecalciferol Treatment in Pagetic Patients with Hypovitaminosis D. Calcif Tissue Int 2019. PMID 31236621


• Sadie-Van Gijsen H. The Regulation of Marrow Fat by Vitamin D: Molecular Mechanisms and Clinical Implications. Curr Osteoporos Rep 2019. Review. PMID 31749086


• Shevchenko N and Khadzhynova Y. JUVENILE IDIOPATHIC ARTHRITIS AND VITAMIN D STATUS IN UKRAINIAN PATIENTS. Georgian Med News 2019. PMID 31687956

• Sosa-Henríquez M. Cholecalciferol and calcifediol for vitamin D supplementation. Osteoporos Int 2019. PMID 31673732

• Sprague S, et al. Study protocol: design and rationale for an exploratory phase II randomized controlled trial to determine optimal vitamin D(3) supplementation strategies for acute fracture healing. Pilot Feasibility Stud 2019. PMID 31768262

• Sun J, et al. Vitamin D receptor expression in peripheral blood mononuclear cells is inversely associated with disease activity and inflammation in lupus patients. Clin Rheumatol 2019. PMID 31104216


• Ying L. A case of pathological fracture caused by vitamin D insufficiency in a young athlete and a review of the literature. J Clin Orthop Trauma 2019. PMID 31708637


• Zhou T and Qi L. Vitamin D, genetics, and bone mineral density during weight loss. Curr Opin Clin Nutr Metab Care 2019. PMID 31577641

• Zhu K, et al. Low Vitamin D Status Is Associated With Impaired Bone Quality and Increased Risk of Fracture-Related Hospitalization in Older Australian Women. J Bone Miner Res 2019. PMID 31233633