ALIMENTAZIONE E VITAMINA D

Roma – Hotel Mediterraneo - 2 dicembre 2022

III° Modulo formativo
Modalità di supplementazione con vitamina D

10.45 Registrazione ECM

11.00 Presentazione dei lavori – **R. Nuti**

11.15 Moderazione: **B.Frediani** - **G.Minisola**

Ia Sessione
Fabbisogno ed utilizzo della vitamina D

Progetto SAD - "Studio sull'introito Alimentare della vitamina D "
Presentazione del Diario e del Questionario definitivi
R. Nuti

E' possibile correggere l'ipovitaminosi D con la sola dieta?
S.Giannini

I pro e i contro degli alimenti contenenti Vit.D
S.Gonnelli

Quando "suggerire" una terapia con Vit.D in "soggetti sani "
I.Chiodini

Considerazioni conclusive della Ia Sessione
B.Frediani

13.00 Buffet lunch

OSPEDALE NIGUARDA CA' GRANDA
Dpt of Medical Biotechnology and Translational Medicine, University of Milan. Unit for Endocrinology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
UNIVERSITÀ DEGLI STUDI DI MILANO

DICHIARAZIONE DI POTENZIALE CONFLITTO DI INTERESSI

Ai sensi dell'art. 4.5 su "Docenti e moderatori dell'evento", pag. 8 del Manuale Nazionale di Accreditamento per l'erogazione di eventi ECM del 06/12/2018, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Theramex
- HRA Pharma
- Corcept Therapeutics
- UCB
- Amgen
- Sandoz
- Eli-Lilly
- Recordati

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MDPI

Review

Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS)

Francesco Bertoldo [1], Luisella Cianferotti [2], Marco Di Monaco [3], Alberto Falchetti [4,*], Angelo Fassio [5], Davide Gatti [5], Luigi Gennari [6], Sandro Giannini [7], Giuseppe Girasole [8], Stefano Gonnelli [6], Nazzarena Malavolta [9], Salvatore Minisola [10], Mario Pedrazzoni [11], Domenico Rendina [12], Maurizio Rossini [5] and Iacopo Chiodini [13,14]

AGENDA

- Who are the subjects at risk of hypovitaminosis D?

- Should the biochemical assessment of serum 25(OH)D levels be conducted in the general population?

- Should the biochemical assessment of serum 25(OH)D levels be conducted in the population at risk of hypovitaminosis D?

  ✓ Is there any direct evidence that basal 25(OH)D levels represent an essential parameter for prescribing vitamin D supplementation?

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- Should the general population be supplemented with vitamin D?

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«Normal» Vitamin D levels

The definition of a sufficient 25(OH)D level in the general population, **the association between vitamin D deficiency and fractures** has been considered as the **most relevant indicator** by members of this task force.

There is a good but not unanimous consensus on the **association** between serum values of **25(OH)D less than 20 ng/mL and increased risk of fracture**:

- For values less than 20 ng/mL (50 nmol/L) there is a 40% increase in the risk of femoral fracture for each SD decrease of 25(OH)D[a].

- The risk of fracture is linearly reduced to a value of **25(OH)D of ~24 ng/mL** while for values higher than this **threshold** the fracture risk would no longer decrease

- However, other data show that the reduction of the risk of femoral and non-vertebral fractures by vitamin D supplementation was obtained in patients with **25(OH)D >30 ng/mL[c]**

[a]Feng, Y. Et al, Osteoporos. Int. 2017, 28, 1641–1652.
[b]Lv, Q.B. et al, A meta-analysis of prospective cohort studies. Oncotarget 2017, 8, 39849–39858
[c]Bischoff-Ferrari et al JAMA 2005, 293, 2257–2264; Carmel, A.S. et al Osteoporos. Int. 2012, 23, 2479–2487

Definition of Vitamin D Status

	Deficiency *	Insufficiency *	Optimal * Optimum *
GENERAL POPULATION	<10 ng/mL	<20 ng/mL	**20–50 ng/mL**
POPULATION AT RISK ** OR ON TREATMENT WITH *BONE MODIFYING AGENTS*	<10 ng/mL	<30 ng/mL	**30–50 ng/mL**

* Reported cut-off values should be considered with a margin of variability of +/−10%, considering the analytical variability of the 25(OH)D dosage. Moreover, due to the seasonal variability of 25(OH)D levels, a dosage performed at the end of winter/early spring should be particularly considered. A serum value of <10 ng/mL (25 nmol/L) is associated with rickets and osteomalacia, if long lasting. From ng/mL to nmol/L: ng/mL × 2.5.
** The population at risk of hypovitaminosis is shown in Table 2.

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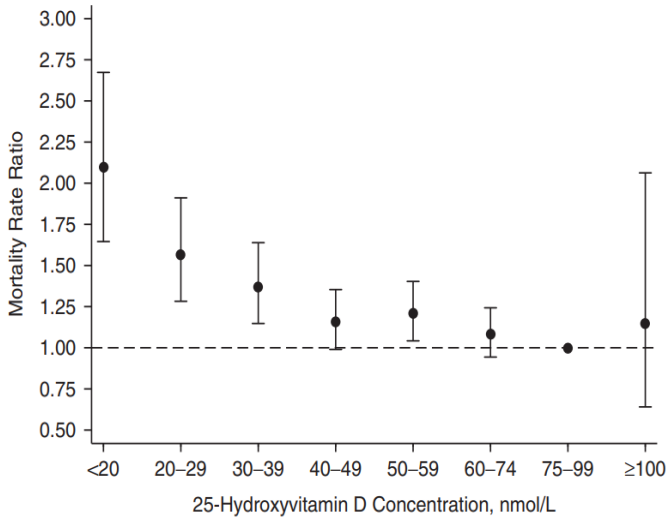
- Falls and mortality: A U-shaped curve defining the beneficial effects of serum 25(OH)D, as if for **25OHD levels above 50 ng/ml** there may be the resumption of negative outcomes.
- But studies with standardized of 25(OH)D dosages showed **a J-shape correlation curve** between vitamin D levels and mortality with a **plateau at values around 18–20 ng/mL**[b]
- So: **in the general population 25(OH)D levels ≥ 20 ng/mL should be considered as adequate**.
- But: **reaching 25(OH)D levels >30 ng/mL is not of particular relevance for the general population, but it is relatively safe**.
- In patients with osteoporosis and in subjects at risk for hypovitaminosis D, a value of ≥30 ng/mL is "optimal"



[b]Durazo-Arvizu, R.A. et al. Am. J. Epidemiol. 2017, 185, 720–726

Population/condition at risk of hypovitaminosis D

- Old people (≥75 years)
- Institutionalized subjects or conditions associated with inadequate solar exposure
- Obesity
- Pregnancy and breast-feeding

Soggetti Normali!

- Metabolic bone diseases and other skeletal disorders
- Vegan diet
- Anorexia nervosa
- Chronic renal failure
- Cancer (in particular breast, prostate, and colon)
- Type 2 diabetes mellitus
- Intestinal malabsorption and bariatric surgery
- Drugs that interfere with the absorption or hepatic metabolism of vitamin D (antiepileptics, glucocorticoids, antiviral AIDS, antifungal agents, cholestyramine)
- Cystic fibrosis

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- Who are the subjects at risk of hypovitaminosis D?
- **Should the biochemical assessment of serum 25(OH)D levels be conducted in the general population?**
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  - ✓ Is there any direct evidence that basal 25(OH)D levels represent an essential parameter for prescribing vitamin D supplementation?
  - ✓ Is the 25(OH)D measurement cost-effective, in a population at risk of hypovitaminosis D?
  - ✓ Is there any evidence that, in a population at risk of hypovitaminosis D, the basal 25(OH)D measurement may contribute to prevent potential toxicity?
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Should the Biochemical Assessment of Serum 25(OH)D Levels Be Conducted in the General Population?

- The **measurement of 25(OH)D**, widely available although qualitatively questionable **has drastically increased** worldwide **in the last decade**.
- This has clearly **increased health expenditure** for both public and private systems
- This imposes primarily the **selection of patients to be screened** for hypovitaminosis D
- **No** evidence that a **mass hypovitaminosis D screening** and the consequent treatment of vitamin D deficient cases, would represent a **cost-effective** procedure
- **Therefore, at this stage, we do not recommend the extensive screening for hypovitaminosis D in the adult general population (Table 3).**

	Evidence Level
It is recommended not to perform the 25(OH)D measurement in the general population.	⊕

Sattar, N. et al, Lancet 2012, 379, 95–96; Bilinski, K et al, J. Am. Med. Inform. Assoc. 2017, 24, 776–780; LeBlanc, E.S. et al, Ann. Intern. Med. 2015, 162, 109–122; Minisola, S. et al Eur. J. Endocrinol. 2019, 180, D1–D7. Kahwati, L.C. et al JAMA 2021, 325, 1443–1463; Caillet, P. et al Sci. Rep. 2017, 7, 10361

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Is there any direct evidence that basal 25(OH)D levels represent an essential parameter for prescribing vitamin D supplementation?

- Although the majority guidelines consider the measurement of serum 25(OH)D levels as highly recommendable, at least in subjects defined at risk of hypovitaminosis D, **there is no direct evidence supporting a clear advantage in performing an assessment of the basal vitamin D status.**
- Available information shows that the **basal assay of vitamin D has little or no influence at all on the 25(OH)D levels reached with supplementation**.
- A systematic review including 144 cohorts from 94 independent studies showed that **the basal 25(OH)D levels would explain only a minimal proportion of the response to vitamin D supplementation (1.9%)**
- Other studies suggested that **it is possible to predict vitamin D deficiency with simple algorithms without dosing 25(OH)D, using indirect data only**

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Is there any direct evidence that basal 25(OH)D levels represent an essential parameter for prescribing vitamin D supplementation?

Indirect predictors of hypovitaminosis D

- black race
- BMI
- suntan within the past year
- sun exposure in the past 3 months
- sunscreen use
- supplemental vitamin D intake

From these six items, a composite score of ≤2.25 demonstrated ≥89% sensitivity but ≤35% specificity

Nabak, A.C et al, Public Health Nutr. 2014, 17, 739–746

Is there any direct evidence that basal 25(OH)D levels represent an essential parameter for prescribing vitamin D supplementation?

- in the suspicion of signs/symptoms referable to osteomalacia, it is advisable to quantify serum 25(OH)D levels mainly for supporting the diagnosis and for the differential diagnosis.
- 25(OH)D levels persistently below 10–12 ng/mL (25–30 nmol/L) generally support the diagnosis of vitamin D-dependent osteomalacia (especially if associated with high values of alkaline phosphatase).

Bouillon, R & Carmeliet, G. Best Pract. Res. Clin. Endocrinol. Metab. 2018, 32, 669–684.
Fukumoto, S et al, J. Bone Miner. Metab. 2015, 33, 467–473.

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Is there any evidence that, in a population at risk of hypovitaminosis D, the basal 25(OH)D measurement may contribute to prevent potential toxicity?

- There are **no direct data** exploring whether baseline assessment of **25(OH)D** is a **predictor** for the risk of **toxicity** during supplementation.
- Many studies showed that supplementation with **high doses of vitamin D are safe** also in subjects with 25(OH)D levels in the range of sufficiency (>20 ng/mL, 50 nmol/L).
- In institutionalized women with values >20 ng/mL (50 nmol/mL), doses of **500,000 IU cholecalciferol** in bolus **followed by 50,000 IU/month** did **not** lead to **hypercalcemia** or other adverse events.
- Supplementation with cholecalciferol **100,000 IU/month** in institutionalized women with a mean baseline 25(OH)D level of 22 ng/mL (55 nmol/L) **did not result in toxicity**.

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Is the 25(OH)D measurement cost-effective, in a population at risk of hypovitaminosis D?

- There are **no data on the cost/effectiveness** of determining the basal 25(OH)D level in the categories of subjects at risk for hypovitaminosis D
- The National Institute for Health and Care Excellence (NICE) guidelines indicate that, although the dosage of 25(OH)D should be performed only in the population at risk, further studies are required to define the cost/benefit ratio of the dosage itself.
- The Ontario Health Technology Advisory Committee (OTACH) 2010 report also concluded that **the clinical benefit, the social, ethical and economic values of the dosage in subjects at risk of hypovitaminosis D are not yet well defined**, even if the approach is very feasible.

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Evidence levels supporting the suggestion and recommendation regarding the measurements of 25(OH)D levels in specific categories of subjects

	Evidence Levels
It is suggested not to indiscriminately measure the levels of 25(OH)D in patients with conditions/pathologies at risk of hypovitaminosis D	⊕⊕
It is recommended the measurement of 25(OH)D levels only when it is deemed necessary for the clinical management of the patient (i.e., when osteomalacia is suspected)	⊕⊕

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Should the general population be supplemented with vitamin D?

The rationale for a potential supplementation with vitamin D to all subjects in a primary prevention strategy arises from the following considerations:

- wide prevalence of subjects with 25(OH)D below the “sufficient” threshold
- potential benefits on multiple (skeletal and extra-skeletal) outcomes
- safety profile of supplementation with cholecalciferol
- simple and economic treatment

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Should the general population be supplemented with vitamin D?

But: does the administration of vitamin D to the general population reduce the risk of skeletal fractures or provide extra-skeletal benefits?

- Metanalytic data show that in **non-hospitalized adult subjects, vitamin D supplementation (alone or with calcium) do not change the risk for femoral fractures nor for all fractures** versus placebo/no treatment.
- Recent meta-analysis focused **on the general population (with the explicit exclusion of subjects hospitalized, or known to have vitamin D deficiency, osteoporosis or previous fractures)**, assessing specifically the fracture and mortality endpoints shows that there are **no effects of vitamin D alone or in combination with calcium on the incidence of fractures, on all-cause mortality and on incident cardiovascular disease**

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No evidence-based conclusions can currently be drawn on potential benefits of vitamin D in the general population, both in terms of cost-effectiveness and in terms of mortality or on skeletal and extra-skeletal outcomes

	Evidence Levels
It is recommended not to administer vitamin D supplements in the general population, since there is no definite evidence of cost-effective benefits, either on mortality or on skeletal and extra-skeletal outcomes.	⊕⊕⊕

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Nota AIFA 96

Farmaci inclusi nella Nota AIFA:

- **colecalciferolo**
- **colecalciferolo/Sali di calcio**
- **calcifediolo**

*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 immotivate)
- persone con diagnosi di iperparatiroidismo secondario a ipovitaminosi D
- persone affette da osteoporosi di 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 della ipovitaminosi D.

Jacques de La Palice (n. 1470)

«se non fosse morto, sarebbe ancora in vita»

REVIEW

JBMR PLUS Open Access ASBMR

Vitamin D: Giveth to Those Who Needeth

Paul Lips,[1] John P Bilezikian,[2] and Roger Bouillon[3]

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OSPEDALE NIGUARDA CA' GRANDA

UNIVERSITÀ DEGLI STUDI DI MILANO
LA STATALE

Dept. of Medical Biotechnology and Translational Medicine

Director, Unit of Endocrinology,
Ospedale Niguarda Cà Granda, Milan, Italy

Associate Professor of Endocrinology,
University of Milan, Milan, Italy

THANK YOU