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The Enigma of Vitamin D supplementation in Aging with Obesity

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Editorial revision form

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QUESTIONS

-pag 1/8 line 44 to add to reference number 4 the paper by Curic et al "MINERVA MEDICA " Volume: 109 Issue: 2 Pages: 79-87

-page 4/8 line 16 to add to reference 21 the following Riobaldone et al. MINERVA GASTROENTEROLOGICA E DIETOLOGICA 2020;â€□: 66 2 Pages: â€□ 106-112

Riobaldone, D.G., Astegiano, M., Actis, G.C. and Pellicano, R., 2020. Management of inflammatory bowel disease during COVID-19 pandemic.

ANSWERS. I included / replaced the following references.

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Abstract

INTRODUCTION: The American Geriatrics Society recommends a minimum daily supplement of 1,000 IU and underlines that a dosage lower than 600 IU do not prevent falls in elderly people.

EVIDENCE ACQUISITION: Review author searched on PubMed, Medline, Embase, Scopus database (last search May 30, 2021), with the MeSH terms and keywords of vitamin D, (25(OH)D), elderly and obesity. This review article aims to support the rationale on the correct vitamin D supplementation in elderly people with obesity and overweight.

EVIDENCE SYNTHESIS: 10 studies were found suitable for consideration in writing this comprehensive evidence-based rapid review. The supplementation of vitamin D included 1500 elderly subjects with Body Mass Index (BMI) over 25 kg/m2. This article shows that the daily vitamin D supplementation from 2000 to 4000 UI is highly recommended in elderly people with obesity because 1) sequestration of vitamin D by the adipose tissue

2) increased catabolism of vita-in D in the adipose tissue 3) decreased synthesis of serum 25 hydroxyvitamin D (25(OH)D) in the liver 4) reduced sun-exposure. 5) Dosages equal at 1000 UI or lower do not show and important effect on vitamin d deficiency and related comorbidities in elderly people with obesity.

CONCLUSIONS: Gender, baseline levels of serum (25(OH)D) concentration, ethnicity and severity of BMI should be accounted for the correct supplementation of vitamin D in elderly population for the precision medicine goal.

Key words: vitamin D; elderly; sarcopenia, serum 25 hydroxyvitamin D

INTRODUCTION.

The vitamin D system includes a group of fatty-soluble prohormones and their corresponding metabolites. [1]. There are two main forms of vitamin D in nature: vitamin D2 (ergocalciferol), photochemically synthesized in plants, and vitamin D3 (cholecalciferol), synthesized by the skin in response to exposure to sunlight. The levels of vitamin D derive mainly from the endogenous skin production stimulated by sunlight and by oral intake [2-3]. In elderly people have been demonstrated that there is an inverse association between serum 25 (OH) D concentration and a Body Mass Index (BMI) greater than 25 kg/ m2 [4].

It is unclear whether this association is due to increased fat deposition, a sedentary lifestyle, low sun exposure, direct vitamin D deficiency, genetic changes in vitamin D metabolism, or other unknown factors [5].

The presence of a vitamin D deficiency in obese people shows a negative relationship between (25(OH)D) and body fat percentage. This marked unbalanced ration is higher for some ethnicities, and the relationship is more evident in older people rather than young [6]. Furthermore, some studies have shown that the reduction on body weight and percentage of fat mass are associated with an increase in circulating levels of (25(OH)D) [7,8]. There are several reasons behind of this situation: 1) the volumetric dilution, in particular, the serum levels of vitamin D are reduced as well as body mass and therefore the amount stored in fat increases, 2) different lifestyles between obese and underweight people 3) different ability to activate vitamin D between obese and underweight people due to the levels of the enzymes activating vitamin D, 25-hydroxylase CYP2J2 and 1a-hydroxylase CYP27B1, 4) the sequestration of vitamin D into the adipose tissue [9].

The aim of this review is to shed in light and define the dose-efficacy of the vitamin D supplementation in elderly patients with overweight and obesity.

EVIDENCE ACQUISITION

This systematic review was performed according to the following steps suggested by Egger [10]: (i) configuration of a working group; (ii) formulation of the revision question on the basis of considerations made in the abstract; (iii) identification of relevant studies. The search involved all the studies published from the 1st of January 2010 the 30th May 2021. English written articles were identified by searching on PubMed, Medline, Embase, Scopus database (last search May 30, 2021), with the MeSH terms and keywords of vitamin D, (25(OH)D), elderly and obesity.

(SP) independently reviewed each report. For each of the relevant abstracts, full publications were retrieved for evaluation on the basis of criteria established a priori.

Original clinical trials investigating the effects of vitamin D supplementations (divided for dose intervention) in elderly patients were evaluated. The change of vitamin D level (t1 minus t0 basal level) was the primary outcome considered. Only elderly patients with age over 65 years old were included with overweight and obesity. The eligible studies were required to report baseline and follow-up values, i.e. the mean change from baseline (Δ-change) and/or the mean difference Δ-changes (MDΔ) between intervention groups for Vitamin D outcome.

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Table 1 shows 10 studies with more than 1500 elderly subjects with overweight and obesity. All studies showed a clinical effect of vitamin D supplementation compared to placebo, but significsnt effects “between groups” were reported in studies with daily supplementation from 2000 to 4000 UI. Sollid, 2014 et al (11) reported an increase of 45.8 nmol/L in intervention group with vitamin D 20.000 UI/weekly compared with placebo 3.4 nmol/L, respectively, nevertheless a situation of obesity.

Similar effects were reported in the study of Tomi-Pekka with a supplementation of 80 μg/d vitamin D3 daily (12), but not in the study of Macdonald with a lower supplementation (1000 UI daily). (13).

In 2017, Levis at al, showed that daily cholecalciferol 4,000 IU for 9 months increased the (25(OH)D) concentrations, nevertheless the population was with obesity (14).

There was not recorded any improvement in (25(OH)D) on recent clinical trials with low dosages (15-17). Very interesting data were reported by 3 recent studies (18-20) that reported an high efficacy of vitamin D supplementation ((25(OH)D) increased +50% from baseline) in obese patients at dosages of vitamin D (from 2000 to 300.000 IU).

CONCLUSIONS

This review shows that in elderly patients with a BMI over 25 kg / m2 (both in overweight and obese) a daily vitamin D supplementation from 2000 IU and above could be a real effective treatment for raising the levels of (25(OH)D) instead the normal recommended dosage of 1000-800 IU daily.

In this category of patients, the areas of effectiveness of vitamin D intake are multiples such as the quality of life, the prevention of sarcopenia, the reduction of depression, the reduction in the incidence of fractures, pain reduction, the reduction in the incidence of infections and the improvement of physical function (21-23)

Considering the positive effects of vitamin D in elderly on the following areas, the identified dosage must be standardized whenever possible, at 2000 IU / day and above when it is possible.

No effects of vitamin D supplementation was found in situations of sarcopenia (at the dose of 800 IU [16]), to improve physical functions at the dose of 400 IU [22]), cytokine suppression at the dose of 750 IU [23]), blood pressure and glucose homeostasis (from 250 to 400 IU [24-26]).

Furthermore the patients with obesity (BMI over 30Kg / m2) have found positive effects (at doses ranging from 2000 to 4000 IU daily) in improving physical functions, in association between protein intake and bone mineral density, and increased concentration of serum 25 (OH) D levels, the latter factor is of great scientific interest and of current importance, as it can determine (through the presence of fat mass) a sequestration of the supplemented vitamin D. (27)

It is known that the concentrations of serum (25(OH)D) are less in obese individuals and in particular in elderly. There are several mechanisms described in the literature that shows the involvement of vitamin D in adipose

tissue metabolism and catabolism in elderly. Summarizing this founding, the vitamin D supplementation over 2000 UI is highly recommended in elderly obese because 1) sequestration of vitamin D by the adipose tissue 2) increased catabolism of vitamin D in the adipose tissue 3) decreased synthesis of 25(OH)D in the liver 4) reduced sun-exposure.

This study lays the foundation for identifying the effectiveness of proper vitamin D supplementation in elderly patients with obesity. The importance of supplementation must be assessed by taking into consideration various determining factors such as: the basal serum dose, gender, age and the BMI

Author Contributions: SP is full responsible for “Conceptualization; methodology; resources; writing—original draft preparation, andreview and editing,

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Conflicts of Interest: The authors declare no conflict of interest.”

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Table 1. Effect of vitamin D supplementation in elderly with obesity and overweight (Main studies from 2010 to 2020)

Author (year of pubblication)	Participants	Design of the study	Mean age	Mean BMI	Dosage	Treatment duration	Serum Vit D DELTA + ds
Sollid, 2014	511	Randomized double blind placebo-controlled trial	65.1 years	29.9 kg/m2	20.000 UI per week or placebo	1 year	Treat: 45.8 +/-24.2 nmol/l Placebo: 3.4 +/-16.9 nmol/l
Tomi-Pekka, 2015	73	Randomized placebo double blinded trial	65.7 years	29.4 kg/m2	40 mcg 80 mcg	5 months	PLACEBO: 4.1 +/-17.3 nmol/l. TREAT 40: +27.7 +/-17.2 nmol/l. TREAT 80: +45.0 +/-23.4 nmol/l.
Macdonald, 2013	305	Double blind placebo controlled trial	60-70 ys	>25.0 kg/m2	400 UI 1000 UI daily	1 year	400 UI: +31.6 +/-19.8 nmol/l 1000 UI: +42.6 +/-18.9 nmol/l PLACEBO: -4.1 +/-11.5
Zevis, 2017	130	Randomized double	72.4 years	30.7 kg/m2	4000 UI daily	9 months	TREAT: + 23.0 +/-14.2 ng/ml.

		blinded placebo trial					PLACEBO: 1.2 +/-5.8 ng/ml.
Vijnen, 2015	30	Randomized	> 65 years	31 kg/m2	LD: 2 gruppi, entrambi treat. Loading dose 50.000 UI	6 months	LD: 61 nmol/l (54-72). DD: 44 nmol/l (26-50).
Delomas, 2017	111	Randomized single blinded controlled study	85.1 years	25.0 kg/m2	4 x 100.000 UI vs individualized load (400.000 o 300.000 o 200.000)	2 months	TREAT: 50.2 +/- 15.4 ng/ml PLACEBO: 35.8 +/- 6.5 ng/ml
Sagari, 2013	86	Randomized trial	73.4 years	25.9 kg/m2	400 o 2000 UI daily	6 months	+ 2.4 +/-12.0 ng/ml M 400: -1.2 +/-5.9 M 2000: 6.1 +/-12.6 F 400: -3.4 +/-10.8 F 2000: 5.3 +/-12.3
Pirotta, 2015	26	Double blinded placebo controlled randomized trial	> 65 years		2000 UI	10 weeks	TREAT: +34 +/- nmol/l PLACEBO: -1.2 +/- nmol/l

Flodin, 2014	79	Randomized trial	79 years	28 kg/m2	800 UI/d	12 months	Placebo: 17 +/-22 nmol/l G1: 18 +/-37 nmol/l G2: 20 +/-24 nmol/l
Bauer, 2015	380	Multicenter randomized double blind trial	77.7 years	26.1 kg/m2	Twice daily 800 UI	13 weeks	TREAT: +25.0 (14.0-39.0) nmol/l PLACEBO: -6.0 (-11.0-0.0) nmol/l

The Enigma of Vitamin D supplementation in Aging with Obesity

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Author Contributions: SP is full responsible for “Conceptualization; methodology; resources; writing—original draft preparation, andreview and editing,

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Table 1. Effect of vitamin D supplementation in elderly with obesity and overweight (Main studies from 2010 to 2020)

Author (year of pubblication)	Participants	Design of the study	Mean age	Mean BMI	Dosage	Treatment duration	Serum Vit D DELTA + ds
Sollid, 2014	511	Randomized double blind placebo-controlled trial	65.1 years	29.9 kg/m2	20.000 UI per week or placebo	1 year	Treat: 45.8 +/-24.2 nmol/l Placebo: 3.4 +/-16.9 nmol/l
Tomi-Pekka, 2015	73	Randomized placebo double blinded trial	65.7 years	29.4 kg/m2	40 mcg 80 mcg	5 months	PLACEBO: 4.1 +/-17.3 nmol/l. TREAT 40: +27.7 +/-17.2 nmol/l. TREAT 80: +45.0 +/-23.4 nmol/l.
Macdonald, 2013	305	Double blind placebo controlled trial	60-70 ys	>25.0 kg/m2	400 UI 1000 UI daily	1 year	400 UI: +31.6 +/-19.8 nmol/l 1000 UI: +42.6 +/-18.9 nmol/l

							PLACEBO: -4.1 +/-11.5
Levis, 2017	130	Randomized double blinded placebo trial	72.4 years	30.7 kg/m2	4000 UI daily	9 months	TREAT: + 23.0 +/-14.2 ng/ml. PLACEBO: 1.2 +/-5.8 ng/ml.
Wijnen, 2015	30	Randomized	> 65 years	31 kg/m2	LD: 2 gruppi, entrambi treat. Loading dose 50.000 UI	6 months	LD: 61 nmol/l (54-72). DD: 44 nmol/l (26-50).
Delomas, 2017	111	Randomized single blinded controlled study	85.1 years	25.0 kg/m2	4 x 100.000 UI vs individualized load (400.000 o 300.000 o 200.000)	2 months	TREAT: 50.2 +/- 15.4 ng/ml PLACEBO: 35.8 +/- 6.5 ng/ml
Lagari, 2013	86	Randomized trial	73.4 years	25.9 kg/m2	400 o 2000 UI daily	6 months	+ 2.4 +/- 12.0 ng/ml M 400: -1.2 +/-5.9 M 2000: 6.1 +/-12.6

							F 400: -3.4 +/-10.8 F 2000: 5.3 +/-12.3
Pirotta, 2015	26	Double blinded placebo controlled randomized trial	> 65 years		2000 UI	10 weeks	TREAT: +34 +/- nmol/l PLACEBO: -1.2 +/- nmol/l
Flodin, 2014	79	Randomized trial	79 years	28 kg/m2	800 UI/d	12 months	Placebo: 17 +/-22 nmol/l G1: 18 +/- 37 nmol/l G2: 20 +/- 24 nmol/l
Bauer, 2015	380	Multicenter randomized double blind trial	77.7 years	26.1 kg/m2	Twice daily 800 UI	13 weeks	TREAT: +25.0 (14.0-39.0) nmol/l PLACEBO: -6.0 (-11.0-0.0) nmol/l

Supplementary Digital Material

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