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VITAMIN D IN THE PREVENTION OF CEREBROVASCULAR PATHOLOGIES: RESULTS OF NEW CLINICAL TRIALS IN LIGHT OF UNEXPECTED DEVELOPMENTS AND PROBABILITIES

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INTRODUCTION

Ischemic stroke is the main cause of long-term disability and the fourth cause of mortality globally. The World Health Organization (WHO) estimates that approximately 15 million new cases of stroke occur each year, of which 5 million have fatal outcomes and another 5 million produce serious and permanent disability, with significant social costs. It is believed that over the next few years aging populations and the reduction of mortality by stroke will lead to a progressively increasing prevalence of this pathology. Researchers have attempted to create validated systems of risk calculation: they aim to identify both high-risk patients in order to reduce the possibility of the onset of stroke and risk thresholds that make possible the implementation of effective preventive therapies [1,2].

Alongside the study of noted risk factors for cerebrovascular pathologies – hypertension, diabetes, dyslipidemia, smoking, and atrial fibrillation – in the last few years particular attention has been paid to identifying new potential risk factors, among which nutritional and dietary factors have become especially important.

Widely used in the prevention and treatment of bone pathologies [3], in recent years vitamin D has been introduced for the possible prevention of cerebrovascular diseases as well. For over a decade, sales of vitamin D in the U.S. have grown exponentially, making it one of the most commonly used supplements [4,5]. Its potential benefits have been upheld by ecological studies – both laboratory and observational – although these data have turned out to be inconsistent and insufficient to establish a causal connection [3,6,7]. Studies on the usefulness of vitamin D in preventing cerebrovascular diseases, conducted together with secondary or post hoc analyses, have largely produced invalid results. Indeed, all these studies were marred by several limitations: low dosages, inadequate type of study, short duration, and less than optimal verification of the endpoints [3]. No large-scale studies with significantly high doses of vitamin D have been carried out whose primary endpoint is the prevention of cerebrovascular diseases. For this reason, the Institute of Medicine [3] and the Preventive Services Task Force in the U.S. [8] have reached the conclusion that available data do not allow us to definitively verify the efficiency of the use of vitamin D for this purpose or to establish a risk-benefit relationship. The Institute of Medicine has asked the scientific community to undertake clinical trials with high doses of vitamin D (at least double the daily dose of 600-800 IU/day recommended for bone health) in different populations, including African Americans, who tend to have less cutaneous synthesis of vitamin D through exposure to sun with respect to other ethnic groups [9].

NEW CLINICAL TRIALS (TABLE 1)

The VITamin D and OmegA-3 TriaL (VITAL) was the first trial on a large scale [10,11]. Conducted in the U.S., this was a randomized, double-blind, placebo-controlled clinical trial which evaluated the risks and benefits

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Conflict of interest
The Authors declare that they have no conflicts of interest.

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of dietary supplementation of vitamin D_3 (2,000 IU/day) and omega-3 fatty acids (1 g/day of Omacor® fish oil capsules with 840 mg omega-3 fatty acids, comprising eicosapentaenoic acid [EPA, 460 mg] + docosahexaenoic acid [DHA, 380 mg]) for the primary prevention of cancer and of cerebrovascular diseases. It involved 25,871 men and women in the U.S., aged ≥ 50 and ≥ 55, respectively. The study design called for a similar number of men and women and a broad sample of African Americans. The study lasted 5.3 years. The results of VITAL showed that vitamin D does not cause a reduction of the co-primary endpoints of cerebrovascular pathologies (consisting of heart attack, cerebrovascular stroke, and mortality; HR = 0.97 [0.86-1.08]).

Nor does vitamin D reduce the specified secondary cardiovascular endpoints, which include a wide array of major cerebrovascular events in addition to coronary revascularization (HR = 0.96 [0.86-1.08]), heart attack (HR = 0.96 [0.78-1.19]), stroke (HR = 0.95 [0.76-1.20]) and cerebrovascular mortality (HR = 1.11 [0.88-1.40]), when taken individually. Vitamin D does not affect all causes of mortality (HR = 0.99 [0.87-1.12]). Similar results were seen in analyses which excluded the first or the first two years of follow-up exams or which eliminated non-compliance. No significant increases associated with the treatment were noted with regard to the risk of hypercalcemia, renal calculi, or gastrointestinal symptoms. Vitamin D does not influence one-year changes of lipid-related or inflammatory markers. The association between vitamin D and the risk of cerebrovascular endpoints or mortality for all causes did not differ significantly for race or ethnic group, cardiovascular risk factors, serum 25(OH)D levels, simultaneous randomization for omega-3 fatty acids, or other characteristics specified as potential modifying effects: vitamin D did not significantly reduce these endpoints in any subgroup.

The Vitamin D Assessment Study (ViDA) was a randomized, double-blind, placebo-controlled trial conducted in New Zealand [12]. The 5,110 participants were divided into two groups, the first (n = 2,558) receiving an initial dose of vitamin D of 200,000 IU, followed a month later by a monthly dose of 100,000 IU, and the second (n = 2,552) receiving a placebo, for a median duration of 3.3 years (range = 2.5-4.2 years). No significant percentage difference was observed in the range of the above-mentioned cerebrovascular events between the vitamin D (11.8%) and the placebo (11.5%) groups (HR = 1.02 [0.87-1.20]). Likewise, sub analysis for heart attack (RR = 0.90 [0.54-1.50]) and stroke (RR = 0.95 [0.55-1.62]) did not produce significant results. The same results were obtained in the subgroup of vitamin D deficient participants (HR = 1.00 [0.74-1.35]) and when participants were divided for previous vascular events. No difference was noted between the vitamin D and placebo groups at the time of the first vascular event or in the frequency of secondary, pathology-specific outcomes. Like the VITAL study, the ViDA trial showed that vitamin D does not reduce the risk of mortality for all causes.

The short duration of the study and the bolus administration of vitamin D (100,000 IU/month) represent important limitations of this trial.

The Women's Health Initiative (WHI) was a randomized double-blind trial with placebo which involved 36,282 postmenopausal women between the ages of 51 and 82 from 40 clinical centers in the U.S. [13] The participants were divided into two groups, the first receiving 1,000 mg of calcium carbonate + 400 IU of vitamin D_3/day and the second a placebo. The average follow-up period was 7 years. The results of this study for coronary heart disease (HR = 1.04 [0.92-1.18]), stroke (HR = 0.95 [0.82-1.10]), and death for vascular diseases (HR = 0.92 [0.77-1.10]) were not statistically significant.

The RECORD Trial (Randomized Placebo-Controlled Trial of Vitamin D_3 and/or Calcium) was a pragmatic, randomized, placebo-controlled and factorial design study of supplementation with calcium and/or vitamin D_3 for the secondary prevention of bone fragility fractures [14]. The research was conducted on 5,292 subjects with an average age of 77 years. The average duration of the follow-up exam was 6.2 years. Participants were vitamin D deficient at the start of the trial and were divided into four groups, which received vitamin D_3 (800 IU/day), calcium (1,000 mg/day), both, or a placebo. The main outcomes were death for all causes, death for vascular pathologies, death for neoplasms, and incidence of neoplasms. The hazard ratios for heart attack (HR = 0.97 [0.75-1.26]), stroke (HR = 1.06 [0.85-1.32]), and vascular mortality HR = 0.91 [0.79-1.05]) were not significant. A post hoc statistical analysis adjusted for compliance and which therefore had a lower number of participants showed accentuated trends for reduced mortality in the group treated with vitamin D and increased mortality in that taking calcium only, even if the overall results did not attain statistical significance.

Trivedi et al. conducted a study to determine the effect of vitamin D supplementation every four months on the fracture rate in men and women aged ≥ 65 years [15]. This randomized double-blind trial involved administration of 100,000 IU/die of vitamin D_3 or of a placebo every four months for a period of five years. Participants numbered 2,686 (2,037 men and 649 women) aged between 65 and 85 years. The hazard ratios for incidence of coronary disease (HR = 0.94 [0.77-1.15]), coronary mortality (HR = 0.84 [0.56-1.27]), incidence of cerebrovascular pathologies (HR = 0.90 [0.77-1.06]), and vascular mortality (HR = 0.84 [0.65-1.10]) did not reach statistically significant levels.

The Finnish Vitamin D Trial (FIND) for the primary prevention of neoplasms and cerebrovascular pathologies, lasting five years, saw the participation of 2,495 subjects (men aged ≥ 60 years and women ≥ 65 years) [16]. Participants were divided into three groups, which received 1,600 or 3,200 IU/day of vitamin D or a placebo. Initially, researchers planned to involve 18,000 participants, but the study group was later reduced because of recruiting difficulties and funding limitations. The primary outcomes included incidence of neoplasms and vascular pathologies. The results of the trial were expected for June 2018 but have not been published yet.

At present, the VITAL trial is the only one that was conducted on a broad population sample and whose primary endpoints were cancer and cerebrovascular pathologies. Indeed, the other two studies conducted on a vast scale – the Australian D-Health [17] and the British Vitamin D and Longevity (VIDAL) [18] trials – which planned to involve 25,000 and 20,000 participants, respectively, posit total deaths and incidence of neoplasms as their endpoints. Only the D-Health study is studying the incidence of cerebrovascular pathologies: results of this trial are expected in 2021.

A recent meta-analysis of vitamin D trials [19], which also included the VITAL and ViDA studies, showed that vitamin D does

TABLE I. New clinical trials.

Trial	Sample	Age range	Duration (years)	Vit. D dose	Outcomes
Vitamin D and Omega-3 Trial (VITAL), USA	25.875	≥ 50 men ≥ 55 women	5	2.000 UI/day	Neoplasms, vascular pathologies
Vitamin D Assessment Study (ViDA), New Zealand	5.110	50-84	3.3 (median)	100.000 UI/month	Vascular pathologies
Women's Health Initiative (WHI)	36.282	51-82	7 (average)	400 UI/die	Femur fractures, other fractures, colorectal cancer, total mortality and by cause
Randomized Placebo-Controlled Trial of Vitamin D_3 and/or Calcium (RECORD)	5.292	77 (average)	6.2 (average)	800 UI/day	Total mortality, by vascular cause and by neoplasms, incidence of neoplasms
Trivedi et al.	2.686	65-85	5	100.000 UI every 4 months	Incidence of fractures, total mortality
Finnish Vitamin D Trial (FIND), Finland	2.495	≥ 60 men ≥ 65 women	5	1.600 UI/day or 3.200 UI/day	Neoplasms, vascular pathologies
D-Health, Australia	21.315	60-84	5	60.000 UI/month	Total mortality, neoplasms
Vitamin D and Longevity (VIDAL), UK	20.000	65-84	5	100.000 UI/month	Total mortality, neoplasms

not reduce the risk of major adverse cardiovascular events (10 trials, 6,243 events, 79,111 participants; RR = 1.00 [0.95-1.06]), of heart attack (18 trials, 2,550 events, 82,576 participants; RR = 1.00 [0.93-1.08]), of stroke (15 trials, 2,354 events, 82,239 participants; RR = 1.06 [0.98-1.15]), or of cardiovascular mortality (10 trials, 2,202 events, 76,783 participants; RR = 0.98 [0.90-1.07]).

CONCLUSIONS

The results of in vitro and in vivo experimental studies suggest that $1,25(OH)_2D$ inhibits the proliferation of vascular smooth muscle cells and vascular calcification, has a beneficial impact on the homeostasis of blood volume and pressure by regulating the renin-angiotensin-aldosterone system, reduces inflammation, and improves insulin sensitivity [20-23]. In prospective observational studies, 25(OH)D levels are inversely correlated to risk factors and to cerebrovascular events [24-26]. Nonetheless, the results of currently available clinical trials have generally failed to demonstrate significant improvement in endpoints of preventing vascular pathologies. This contradiction in the results, however, rather than casting a shadow over the matter, provides the premises for further study on the role of vitamin D in preventing cerebrovascular pathologies. Indeed, analysis of outcome data from the trials does not allow us to definitively exclude the possible beneficial effect of vitamin in the prevention of cerebrovascular diseases. It is possible to identify a threefold order of factors responsible for the negative results: study populations which did not show high cerebrovascular risk, which were not vitamin D deficient, and which had co-factors that were not adequately assessed.

For these reasons, it is necessary to identify populations with vascular risk factors which could effectively benefit from vitamin D. It is possible to hypothesize that protective levels of vitamin D for vascular pathologies are lower than those for other pathologies, such as neoplasms. It is quite probable that in clinical trials whose principal endpoints are the incidence of neoplasms and vascular conditions patients already had a protective base level of vitamin D for these pathologies. In this light, it would be necessary to focus attention on population subgroups with high cerebrovascular risk and severe vitamin D deficiency (≤ 10 ng/mL).

Rather than a single risk factor, vitamin D deficiency should be considered from the point of view of a complex nutritional alteration which causes some dysfunction – at the endothelial level – of the homeostasis of blood circulation and coagulation as well as of glucose and lipid metabolism, with the resulting possibility of an increase in the risk for major vascular diseases.

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