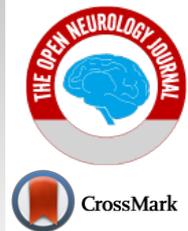




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RESEARCH ARTICLE

Vitamin D Serum Level in Elderly Patients with Alzheimer's Disease: Preliminary Analysis from Cilento Region

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Abstract:

Introduction:

It is estimated that 46 million people in the world live with dementia and it is estimated that this number will increase 3-fold by 2050, being a leading cause of disability worldwide and major welfare and economic problem. The aging of the general population increase these problems, especially in regions, such as Cilento (Southern Italy), where we can register higher longevity. Preserving cognitive health is one of the most important aims of the current research, also through the identification of possible preventative life-style strategies. Recent meta-analyses suggest that low serum vitamin D concentrations could be associated with Alzheimer's disease (AD) and cognitive impairment. The specific role of Vitamin D, however, is still controversial. There is a growing evidence of high rates of vitamin D deficiency in the elderly and there is still much uncertainty about the cause of AD and other forms of dementia. On the other hand, there is no definitive evidence is not conclusive and vitamin D could be involved in many other physiological and pathological mechanisms.

Objective:

Our aim is to investigate vitamin D serum levels in a small preliminary sample of AD patients from the Cilento area.

Materials and Methods:

Patients were recruited from the AD centre of the San Luca Hospital, in Vallo della Lucania (SA). We enrolled 25 consecutive patients, 13 women, and 12 men. The mean age was 78.5±8.3 years, the mean duration of the disease was 3.5±1.8 years. The average school-age of the patients was 6.1 +/- 3.5 years, the average disease age was 6.3 +/- 1.7 years, the average basal Mini-Mental Score Examination (MMSE) score was 17.6 +/- 3.6. We determined serum 25-hydroxyvitamin D (25[OH]D) in 25 consecutive AD patients.

Results:

The mean vitamin D serum level was 17.9±7.9 **UI/ml**, denoting a state of insufficiency. Among our 25 patients, only 3 had serum level above 30 UI/ml; most patients (17 out of 25) showed serum level among 10 and 30 UI, while in 5 patients, serum level was less than 10 UI.

Conclusion:

Our preliminary data showed that Vitamin D deficiency was, in our patients, independently associated with AD, even in a special population, high rate of centenarians, like Cilento people. However, our preliminary study has different limitations. The vitamin D deficiency has been evaluated through a single time-point of measurement (or in different periods of the year), that may be susceptible to bias. Even the differences in age and level of education should be taken into consideration. Nevertheless, these data in the Cilento region are original (there are no similar reports to our knowledge). However, our results confirm the necessity of other study, and this result is an important opportunity to introduce a modifiable risk factor and, consequently, a new treatment for AD.

Keywords: Alzheimer Disease, Cilento Region, Vitamin D, Cognitive impairment, Mini-Mental Score Examination (MMSE) score, Dementia.

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1. INTRODUCTION

Dementia is defined as the progressive decay of cognitive functions and behavioral changes capable of determining the

reduction of an individual's functioning capacity. It is an acquired and progressive degenerative disease enough to impact on the activities of daily living. Everyday activities, in fact, are greatly impaired from dementia, that is a major cause

of dependence, disability, and death. It mainly affects older people, with a mean age, at diagnosis of dementia, of 80 years of age [1] although it is not a normal part of ageing [2].

Dementias are chronic, in most degenerative and require a complex management and the involvement of multiple healthcare professionals. The definition of dementia as we know now was established in 2011. Based on this definition, at least two neuropsychiatric or cognitive domains must be impaired without no better explanation by nondegenerative or primary psychiatric disorders, or other systemic conditions. The diagnosis of dementia is based on clinical characteristics, mostly reported by parents, and objective evaluation of cognitive loss through a neuropsychiatric and neuropsychological assessment [3].

In the last years, the World Health Organization (WHO) indicates dementia as a public health priority. About 50 million people worldwide are affected by dementia nowadays; among these patients, about 60% live in low- and middle-income countries. The total number of people with dementia is estimated to increase to 82 million in 2030 and 152 million in 2050 [2]. Every year, about 10 million people progress to dementia [1]. These data imply a large expenditure of resources in terms of the direct costs of medical, social and informal care associated with dementia and indirect cost due to the constant commitment of patients' family members. Assistance is needed from the health, social, financial and legal systems for both people with dementia and their parents, to support them from the economic and emotional point of view [2]. In the USA, the annual cost of dementia is estimated to be about \$818 billion in 2015, an increase of 35% since 2010, and a \$ 1 trillion threshold increase in 2018. It is an enormous sum. The global costs seem to be similar, in magnitude, to the GDP of countries like Indonesia, The Netherlands, and Turkey. These examples verify how enormous is the cost of dementia [4, 5]. Dementia has huge economic impacts also in England, where about 690 000 people with dementia live at present and where the total annual cost of dementia is estimated to be £24.2 billion in 2015 [6]. In Italy, mean total monthly societal costs per patient is up to €2728 for patients and societal costs generally increased with increasing dementia severity [7].

In all forms of dementia, Alzheimer's disease (AD) is the most common and represents one of the most impactful diseases for public health with enormous health and economic implications for contemporary society. Countless progress in AD knowledge has been made in the last years but they were not sufficient to lead to the development of disease-modifying treatments. AD is the most common type of dementia, accounting for 50%–75%, and is primarily a condition of later life [5].

AD is caused by the complex interplay of various genetic, environmental and lifestyle factors, whose consequence is the degeneration of neuronal cells over the period of time. Among genetic, the APOE gene seems to have a key role; moreover, genome-wide association studies using many thousands of samples have identified more than 20 genetic risk factors,

implicating inflammatory, cholesterol metabolism and endosomal vesicle recycling pathways that could be involved in AD pathogenesis [8]. Genetic alteration can determine neuronal loss, abnormal accumulation of Amyloid- β (A β) and neurofibrillary tangles (NFTs) which lead to loss of synapses and neuronal death, macroscopic atrophy and, clinically, severe memory impairments and other cognitive dysfunctions and eventual demise of the individual. Other risk factors for AD could be overweight, smoking, diabetes. Vascular risk factors may increase the risk of clinical AD through a 'double-hit' with superimposed cerebrovascular damage, or vascular damage might influence the development of AD pathology directly [8].

Recently, a potential role has been proposed also for vitamin D. During the last 25 years, vitamin D has been suggested as a candidate in nervous system development and function and a therapeutic tool in different neurological pathologies. Vitamin D could play an important role in the pathophysiology of dementia and therefore of Alzheimer's disease and could be considered in this sense a potential risk factor.

The Cilento region is particularly interesting because, in this area we can record high longevity.

In particular, the centenarians of Cilento had a healthy metabolic profile and a low prevalence of clinical cardiovascular diseases and even in centenarians with structural cardiac anomalies, there is little evidence of objectionable symptoms [9].

Furthermore, in an over ninety year old population of Cilento it has been shown how the nutritional status and the oxidative balance are correlated to a better cognitive profile [10].

In our work, we have determined the serum values of vitamin D in a population of patients with Alzheimer's disease, all of which are native and resident in Cilento.

2. MATERIALS AND METHODS

This cross-sectional study was conducted at the Alzheimer Disease Center of the San Luca Hospital, in Vallo della Lucania (SA), a village in the National Park of Cilento, Vallo di Diano and Alburni (Salerno, Southern Italy). We enrolled 25 consecutive patients, 13 women and 12 men. The mean age is 78.5 ± 8.3 years and the mean duration of the disease is 3.5 ± 1.8 years. The average school age of the patients was 6.1 ± 3.5 years, the average disease age 6.3 ± 1.7 years, the average basal Mini Mental Score Examination (MMSE) score was 17.6 ± 3.6 . Each subject completed clinical and neuropsychological evaluations between January 2018 and June 2018. Subjects who fulfilled criteria for the diagnosis of AD were enrolled. For this study, we excluded subjects with a diagnosis of major depressive disorder, non-AD dementias, other neurological disorders affecting cognitive functions and vascular dementia. Subjects who were currently receiving Vitamin D supplements were also excluded. We also collected demographic information, specific geographical area of origin, educational level, presence or absence of other pathologies, presence or absence, in the same family, of other people with

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AD. All patients underwent the neuropsychological evaluation with the mini-mental state examination (MMSE), functional capacity measured by Katz Index (Basic Activities of Daily Living) and Lawton-Brody (Instrumental Activities of Daily Living) scale. The diagnosis of probable AD was made according to the DSM-5 Criteria [11].

Serum 25-hydroxyvitamin D [25(OH)D] levels were measured by MicroVue™ 25-OH Vitamin D EIA Kit (Quidel, San Diego, CA, US).

All patients provided written informed consent prior to enrolment in the study.

3. RESULTS AND CONCLUSION

We enrolled 25 consecutive patients, 13 women and 12 men. The mean age is 78.5 ± 8.3 years, the mean duration of the disease is 3.5 ± 1.8 years. Mean vitamin D serum level is 17.9 ± 7.9 ng/ml, denoting a state of insufficiency. Among our 25 patients, only 3 had serum level above 30 ng/ml; most patients (17 out of 25) showed serum level among 10 and 30 ng/ml, while in 5 patients serum level is less than 10 ng/ml.

Vitamin D principal sources are fish, lipids and full-fat dairy products, as well as sunlight exposure, that can produce substantial amounts of vitamin D in the epidermis [12]. After its production in the skin, vitamin D is subsequently metabolized to its hormonally active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), in two steps: hydroxylation in the liver to 25-hydroxyvitamin D [25(OH)D] followed by 1 α -hydroxylation in the renal proximal tubule to 1,25-dihydroxyvitamin D (1,25(OH)2D-calcitriol) [13, 14].

Vitamin D has a key role in stimulating calcium absorption from the gut and promoting skeletal health, as well as many other important physiological functions, with effects on bone marrow, brain, colon, breast, malignant cells, and immune system [15].

Some authors define vitamin D as the “forgotten neurosteroid”, indicating the term vitamin as wrong [16].

Vitamin D deficiency could be implicated in different chronic pathologies. For example, it has been hypothesized that Vitamin D could have a role in age-related macular degeneration (AMD), a chronic, late-onset degeneration of the macula, that represents the first cause of vision loss in adults in developed countries [17]. Among the etiopathogenetical hypothesis, it has been shown that 25(OH)D3 reduces the proliferation of cells of the immune system and the proliferation of endothelial cells and angiogenesis. Taken together, these data suggest a possible anti-inflammatory role and Vitamin D deficiency could be implicated in several conditions sharing, as a key role, inflammation [18 - 20].

So, there is a negative relationship between 25(OH)D3 levels and several chronic conditions associated with inflammation, such as type 1 diabetes, cancer, heart diseases and rheumatoid arthritis [21, 22].

Recently, a role has been proposed also in the development of depression [23]. Growing evidence, in fact, points to the role of vitamin D in the pathobiology and treatment of depression. Serum vitamin D levels inversely correlate with clinical

depression, but there is not enough evidence to suggest universal supplementation in depression. Enriching depression treatment trials with subjects having concurrent vitamin D deficiency appears to be a potential step forward in this field.

Recent studies indicate that vitamin D deficiency could have a role also in dementia pathogenesis. Vitamin D deficiency, in fact, is more frequent in patients with dementia, that have a lower level of vitamin D (25-hydroxyvitamin D (25(OH) D)) compared with the control group healthy age-matched patients [24] However, we still do not know if vitamin D deficiency may be only a marker or potential risk factor for developing dementia [25 - 27] Within the prospective Rotterdam Study, it has been evidenced that lower serum vitamin D concentrations are associated with a higher incidence of dementia [28]. This is a very interesting result, since vitamin D could be a potentially modifiable risk factor for dementia thanks to its possible neuroprotective action. However, different studies examining the association between vitamin D and dementia have provided conflicting results and further studies are needed.

Our preliminary data showed that Vitamin D deficiency was, in our patients, independently associated with AD. However, several studies do not agree on the role of vitamin d in dementia pathogenesis. The “Canadian Study of Health and Aging”, for example, is a 10-year cohort study that did not demonstrate a significant association found between Vitamin D level and cognitive decline, dementia or AD [29]. On the contrary, these authors demonstrated that higher Vitamin D concentrations were associated with an increased risk of dementia and AD in women, but not in men. They conclude that, even if this study does not support a protective effect of vitamin D status on cognitive function, further research is needed, especially to clarify the relation by sex. Other studies, however, support a protective role of vitamin D in dementia development and a negative association between Vitamin D serum level and cognitive decline. Littlejons *et al.* [27] confirm that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer's disease, adding to the ongoing debate about the role of vitamin D in nonskeletal conditions. Moreover, Low 25OHD concentrations were associated with mild cognitive impairment (MCI) status in older non-demented community-dwellers with a subjective memory complaint [30].

Vitamin D deficiency has been classically associated with skeletal disorders, but it could play a role in different chronic disease since vitamin D receptors have been described on multiple types of cells. In 2005, Eyles and coll reported, for the first time, the distribution of the 1,25-dihydroxyvitamin D3 receptor (VDR), and 1 α -hydroxylase (1 α -OHase), the enzyme responsible for the formation of the active vitamin in the human brain. Multiple different areas of the brain, including hypothalamus and the large neurons within the substantia nigra, host both the receptor and enzyme, while the nucleus basalis of Meynert and the Purkinje cells in the cerebellum expressed 1 α -OHase in the absence of VDR. The observed distribution of the VDR is consistent with the proposal that Vitamin D operates in a similar fashion to the known neurosteroids [31].

In other words, the presence of the receptor and / or enzyme in specific areas related to memory could explain the possible association between vitamin d levels and dementia.

Our preliminary data showed that Vitamin D deficiency was, in our patients, independently associated with AD, even in a special population, high rate of centenarians, like Cilento people. However, our preliminary study has different limitations. The vitamin D deficiency has been evaluated through a single time-point of measurement (or in different periods of the year), that may be susceptible to bias. Even the differences in age and level of education should be taken into consideration. Nevertheless, these data in the Cilento region are original (there are no similar reports to our knowledge). However, our results confirm the necessity of other study and this result is an important opportunity to introduce a modifiable risk fact and, consequently, a new treatment for AD.

AUTHOR CONTRIBUTIONS

Study concept and design: Vincenzo Pizza.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: All authors.

Study supervision: Anna Capasso.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent has been obtained form all participants.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the [V.P], upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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