https://doi.org/10.31925/farmacia.2023.6.6 **ORIGINAL ARTICLE**

VITAMIN C TREATMENT IMPROVES RECALLING SCORES IN MINI-MENTAL STATE EXAMINATION IN PATIENTS WITH COGNITIVE IMPAIRMENT

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Abstract

The primary purpose of the current study was to test the hypothesis that vitamin C would improve the Mini-Mental State Examination (MMSE) total score and/or either of its domains. In order to measure the influence of vitamin C on MMSE total scores and its domains, our experimental design consisted of two comparisons of four groups of patients. Firstly, we compared 25 patients who received no treatment with 25 patients who received only vitamin C treatment over four timelines: after 2, 6 and 12 months. Secondly, we compared 25 patients who received normal dementia treatment with 25 patients who received dementia treatment supplemented with vitamin C over the same three timelines. Our statistical analysis demonstrated that there was a significant interaction between the type of treatment and time in terms of MMSE total scores ($F(3, 144) = 7.794$, $p < 0.001$ and $\eta p2 = 0.140$) for the dementia treatment - dementia treatment plus vitamin C comparison and ($F(3, 144) = 2.437$, $p = 0.049$ and $\eta p2 = 0.048$) for the vitamin C - no treatment comparison. Across the twelve months of treatment with vitamin C in addition to dementia treatment, patients significantly improved their mean MMSE score in comparison to the group of patients that received only the dementia treatment.

Rezumat

Scopul prioritar al studiului actual a fost de a testa ipoteza că vitamina C ar îmbunătăți scorul total al Examenului de Stare Mini-Mentală (MMSE) și/sau oricare dintre domeniile sale. Am comparat, în primul rând, 25 de pacienți care nu au primit niciun tratament cu 25 de pacienți care au primit doar tratament cu vitamina C în patru intervale de timp: după 2, 6 și 12 luni. În al doilea rând, am comparat 25 de pacienți care au primit un tratament normal pentru demență cu 25 de pacienți care au primit un tratament pentru demență suplimentat cu vitamina C, pe aceleași trei perioade de timp. Analiza noastră statistică a demonstrat că a existat o interacțiune semnificativă între tipul de tratament și timp în ceea ce privește scorurile totale MMSE ($F(3, 144) = 7,794$, $p < 0,001$ și $\eta p2 = 0,140$) pentru comparația tratament pentru demență - tratament pentru demență plus vitamina C și ($F(3, 144) = 2,437$, $p = 0,049$ și $\eta p2 = 0,048$) pentru comparația vitamina C - fără tratament. Pe parcursul celor douăsprezece luni de tratament cu vitamina C în plus față de tratamentul pentru demență, pacienții și-au îmbunătățit semnificativ scorul mediu MMSE în comparație cu grupul de pacienți care a primit doar tratamentul pentru demență.

Keywords: vitamin C, MMSE, memory, recall, cognitive decline, dementia

Introduction

Vitamin C is soluble in water and is used as an electron donor in various vital biological processes in the body. The active form of the vitamin is named l-ascorbic acid, and it exists mainly as the monoanion ascorbate at physiological pH [1]. Most animal species are capable of biosynthesizing vitamin C from glucose

in the liver. However, humans, as well as guinea pigs and some species of fish and birds, rely on a sufficient dietary intake of vitamin C. This inability to synthesise vitamin C from the glucose in the liver is explained by some mutations and deletions in the gene encoding for l-gulono-1,4-lactone oxidase that happened in the evolution of these species, causing it to become non-functional [2]. Therefore, this inability to catalyse the final step in vitamin C biosynthesis results in a total dependence on dietary intake for the affected species [3, 4].

Regarding vitamin C in the brain, the sodium-ascorbate co-transporter (SVCT2) receptor controls active vitamin C transport over the choroid plexus to the extracellular fluid of the brain and beyond on to neuronal cells [5]. Interestingly, for dehydroascorbic acid (DHA) transport, neuroglia is thought to rely on passively facilitated diffusion through GLUT-transporters, given that it does not express the SVCT2 transporter. Furthermore, the DHA is subsequently reduced to ascorbate intracellularly [6]. In addition, vitamin C is also distributed in specific regions, with the hippocampus, occipital and frontal cortex showing elevated concentrations [7]. Nonetheless, some authors have attributed these apparent regional differences to variations in neuronal density. Furthermore, glia has particularly low vitamin C concentrations (about 1 mM) compared to neurons (about 10 mM), and for example, the hippocampus and frontal cortex both display elevated levels of neurons in comparison to other brain areas [8]. Moreover, SVCT2 expression is also associated with a 10-fold higher metabolism and, hence, reactive oxygen species (ROS) formation [9, 10].

Therefore, the various roles of vitamin C related to the structural and functional integrity of the brain fuel the question of whether vitamin C deficiency may lead to cognitive dysfunction, as suggested by results reported both by animal models and population surveys [11, 12]. Of particular interest in the present paper are the effects of vitamin C on age-related neuronal degeneration. According to one theory, ageing is the result of a lifetime accumulation of free radical attacks on the body's cells and macromolecules [13]. In the brain of an ageing individual, the degeneration of neurons is correlated with elevated oxidative stress, either through loss of electrons from the respiratory chain, an inflammatory reaction or peroxide generation from amyloid-beta [14, 15].

The primary purpose of the current study was to test the hypothesis that vitamin C would improve the Mini-Mental State Examination (MMSE) total score and/or either of its domains (orientation, delayed recall, working memory, language and visual construction).

Materials and Methods

Patients

In order to measure the influence of vitamin C on MMSE total scores and its domains, our experimental design consisted of two comparisons of four groups of patients with Cognitive Impairment, across four timelines. Firstly, we compared 25 patients who received no treatment with 25 patients who received only vitamin C treatment. Secondly, we compared 25 patients who received normal dementia treatment with 25 patients who received dementia treatment supplemented with vitamin C administration.

Regarding the demographics of our groups, we can mention that the subjects of this study (100 patients) consisted of 71 patients with mixed dementia, 22 with mild to moderate cognitive impairment and 7 patients with dementia and Alzheimer's disease. The average age was 65.8 years. The sex ration was rather equilibrated, with 59 males and 41 females. The same goes with the socio-demographic background, which consisted of 57 patients from urban areas and 43 from rural areas.

We measured MMSE scores at baseline and after 2, 6 and 12 months of treatment. For both of our comparisons, we used ANOVA for repeated measures in SPSS. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the "Grigore T. Popa" University of Medicine and Pharmacy (Iași, Romania) on July 11, 2016, protocol code 15239.

Vitamin C administration

Vitamin C 1000 mg - 1 capsule *per* day in the morning, half an hour before breakfast with a glass of water for two months.

Cognitive Assessment Procedure

Every participant in the study completed the MMSE before baseline, after two months, after six months and after 12 months. The MMSE is an 11-item assessment of cognitive function that measures seven cognitive domains: 1. Orientation to time (range 0 - 5), 2. Orientation to place (range 0 - 5), 3. Three-word registration (range 0 - 3), 4. Delayed recall of the three words (range 0 - 3), 5. Working memory (range 0 - 5), 6. Language involving the understanding of a three-step command, naming, repetition and writing (range 0 - 8), 7. Visual construction involving the reproduction of two intersecting pentagons (range 0 - 1). The MMSE is divided into two sections, the first of which requires vocal responses only and covers orientation, memory and attention; the maximum score is 21. The second part tests the ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt figure; the maximum score is nine. Because of the reading and writing involved in Part II, patients with severely impaired vision may have some extra difficulty that can usually be eased by large writing and allowed for in the scoring (16).

It takes around seven minutes to administer MMSE to an individual with dementia and about five minutes to an individual with normal cognition. The scores can range from 1 to 30, with the conventional cut-off

set at 24. Lower than 24 scores indicate some sort of cognitive impairment, even though other cut-off points have been proposed. There is a wide range of severity in the disorder that individuals with dementia have, and this will influence the diagnostic ability of a diagnostic test such as the MMSE. However, a score of 20 to 24 suggests mild dementia, 13 to 20 suggests moderate dementia, and less than 12 indicates severe dementia [16].

Results and Discussion

Dementia treatment versus dementia treatment plus vitamin C

MMSE score

A 4 (Time) x 2 (Treatment) mixed-model ANOVA revealed that there was a significant main effect of time on the MMSE total score of the patients ($F(3, 144) = 3.407$, $p = 0.019$ and $\eta p2 = 0.066$), showing an increase in the total score of MMSE from baseline (mean = 15.94) to 2 months (mean = 16.90), 6 months (mean = 16.88) and 12 months (mean = 17.10). However, there was no significant main effect of type of treatment on MMSE total scores overall ($F(1, 48) = 1.89$, $p = 0.281$ and $\eta p2 = 0.024$), with the dementia treatment group obtaining a mean of 15.80 in the MMSE total score, while the dementia plus vitamin C group obtained a MMSE total score mean of 16.08. Furthermore, there was a significant interaction between the type of treatment and time in terms of MMSE total scores ($F(3, 144) = 7.794$, $p < 0.001$ and $\eta p2 = 0.140$). Descriptive statistics showed an increase in the total MMSE score for the dementia treatment plus vitamin C group from an average of 16.08 at baseline to 17.80 after 2 months, 18.68 after 6 months and a mean of 18.64 after 12 months. In contrast, the dementia-only group's MMSE total score showed no significant improvement from 15.80 at baseline to 16.00 after 2 months, decreasing to an average of 15.08 after six months and to a mean of 15.36 after 12 months (Figure 1).

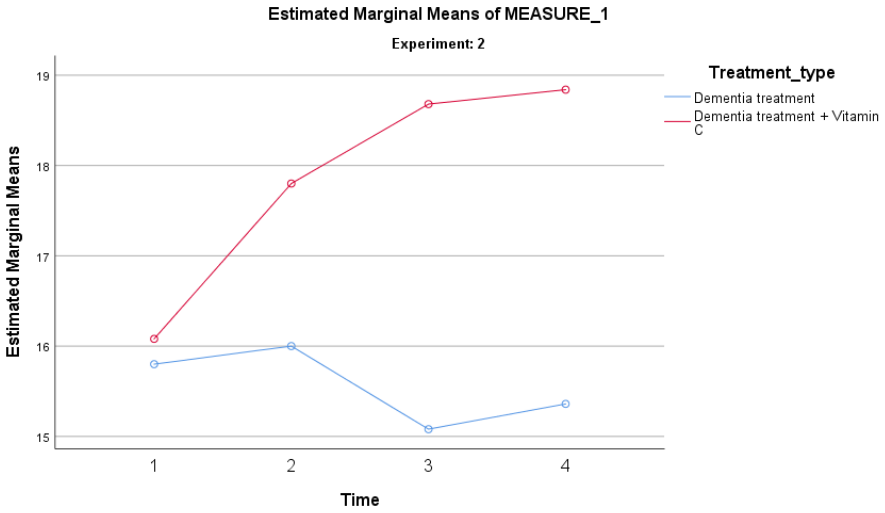

Figure 1.
Total score of MMSE for the two experimental groups (dementia treatment compared to dementia treatment plus vitamin C) across the 4 timelines (baseline, after 2 months, after 6 months and after 12 months)

Recall

A 4 (Time) x 2 (Treatment) mixed-model ANOVA revealed that there was a significant main effect of time on the recall score of the patients ($F(3, 144) = 3.781$, $p = 0.012$ and $\eta p2 = 0.068$), showing an increase in the recall score from baseline (mean = 0.74) to 2 months (mean = 0.98), 6 months (mean = 1.12) and 12 months (mean = 1.20). In addition, there was a significant main effect of type of treatment on recall scores overall ($F(1, 48) = 4.518$, $p = 0.039$ and $\eta p2 = 0.141$), with the dementia treatment group obtaining a mean of 0.72 in recall items and the dementia plus vitamin C group obtained a recall score mean of 0.76. Furthermore, there was a significant interaction between the type of treatment and time in terms of recall scores ($F(3, 144) = 2.145$, $p = 0.047$ and $\eta p2 = 0.236$). Descriptive statistics showed an increase in the recall score for the dementia treatment plus vitamin C group from an average of 0.76 at baseline to 1.20 after 2 months, 1.44 after 6 months and a mean of 1.56 after 12 months. In contrast, the dementia-only group's recall score showed no significant improvement from 0.72 at baseline to 0.76 after 2 months, increasing non-significantly to an average of 0.80 after six months and to a mean of 0.84 after 12 months (Figure 2).

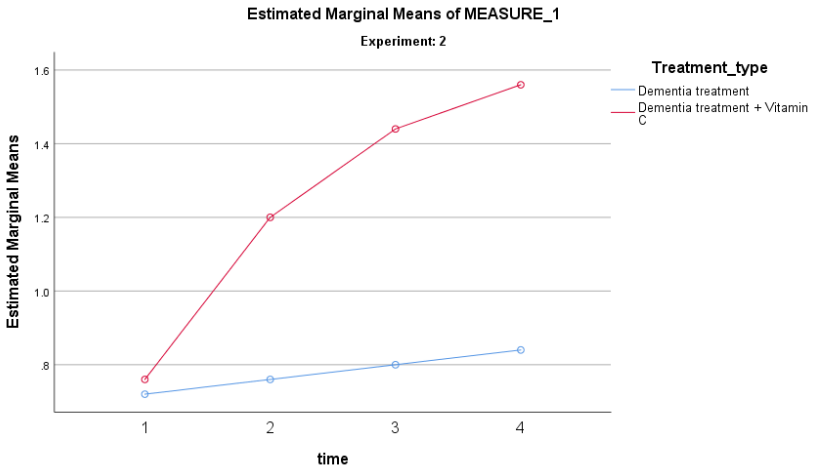

Figure 2.
Score of recall items for the two experimental groups (dementia treatment compared to dementia treatment plus vitamin C) across the 4 timelines (baseline, after 2 months, after 6 months and after 12 months)

No treatment versus vitamin C only
MMSE
A 4 (Time) x 2 (Treatment) mixed-model ANOVA revealed that there was no significant main effect of the time on the MMSE total score of the patients ($F(3, 144) = 0.192$, $p = 0.901$ and $\eta p2 = 0.004$), showing a non-significant increase in the total score of MMSE from baseline (mean = 21.76) to 2 months (mean = 21.54), 6 months (mean = 21.52) and 12 months (mean = 21.82). In addition, there was also no significant main effect of type of treatment on MMSE total scores overall ($F(1, 48) = 2.671$, $p = 0.109$ and $\eta p2 = 0.053$), the no treatment group obtained a mean of 21.72 in the MMSE total score, while the vitamin C group obtained a mean of 21.8 in the MMSE total score. However, there was a significant interaction between the type of treatment and time in terms of MMSE total scores ($F(3, 144) = 2.437$, $p = 0.049$ and $\eta p2 = 0.048$). Descriptive statistics showed an increase in the total MMSE score for the vitamin C group from an average of 21.80 at baseline to 22.36 after 2 months, to 22.80 after 6 months and a mean of 23.32 after 12 months. In contrast, the no treatment group's the MMSE total score showed a decrease from a MMSE total score of 21.72 at baseline to 20.72 after 2 months, decreasing furthermore, to an average of 20.04 after six months and to a mean of 20.32 after 12 months (Figure 3).

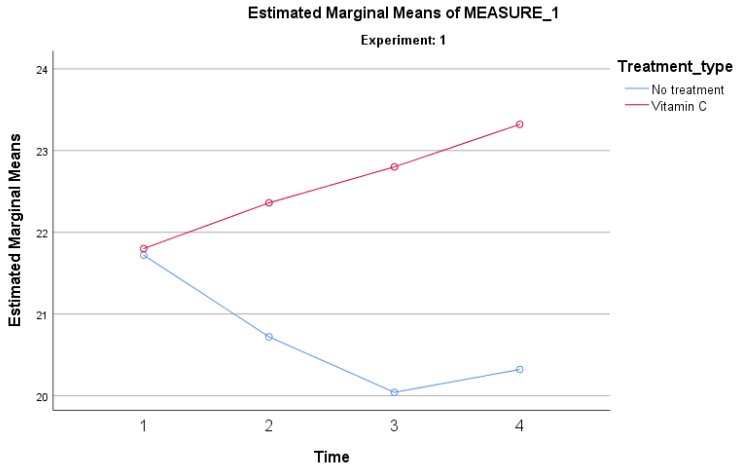

Figure 3.
Total score of MMSE for the two experimental groups (vitamin C compared to no treatment across the 4 timelines (baseline, after 2 months, after 6 months and after 12 months)

Recall
A 4 (Time) x 2 (Treatment) mixed-model ANOVA revealed that there was no significant main effect of time on the recall score of the patients ($F(3, 144) = 0.301$, $p = 0.825$ and $\eta p2 = 0.006$), showing a non-significant variance in the recall score from baseline (mean = 0.90) to 2 months (mean = 0.90), 6 months (mean = 0.84) and 12 months (mean = 0.96). However,

there was a significant main effect of type of treatment on recall scores overall ($F(1, 48) = 4.604$, $p = 0.037$ and $\eta p2 = 0.088$), the no treatment group obtaining a mean of 0.88 in recall items and the vitamin C group obtained a recall score mean of 0.92. Furthermore, there was a significant interaction between the type of treatment and time in terms of recall scores ($F(3, 144) = 3.092$, $p = 0.029$ and $\eta p2 = 0.061$). Descriptive statistics showed an increase in the recall score for the vitamin C group from an average of 0.92 at baseline to 1.00 after 2 months, to 1.12 after 6 months and to a mean of 1.32 after 12 months. In contrast, the no treatment group's recall score showed a small decrease from 0.82 at baseline to 0.80 after 2 months, decreasing to an average of 0.56 after six months and to a mean of 0.60 after 12 months (Figure 4).

Furthermore, our statistical analysis showed no other significant effect of vitamin C administration on any other domain of MMSE (Table I).

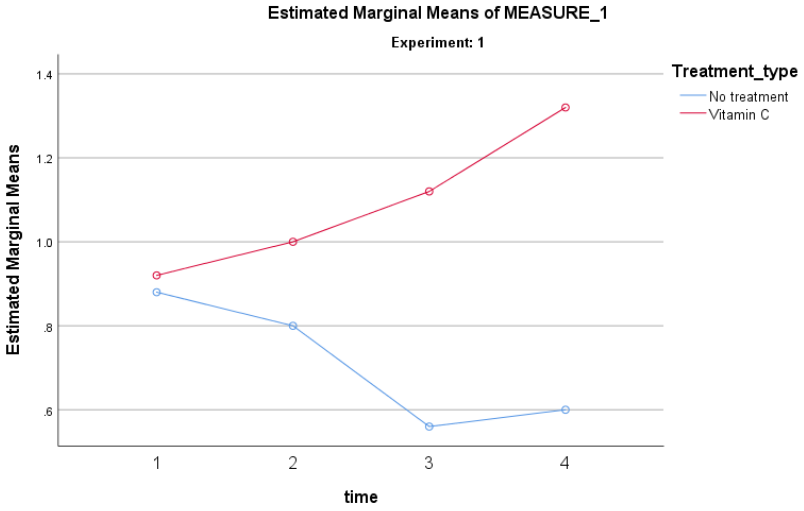

Figure 4.
The score of the recall items for the two experimental groups (no treatment compared to vitamin C only) across the 4 timelines (baseline, after 2 months, after 6 months and after 12 months)

Table I
P values for the total score and all the sub domains of MMSE [1]

Variable	No treatment *vs.* vitamin C treatment	Dementia treatment *vs.* dementia treatment + vit. C
MMSE total score	p = 0.049	p = 0.001
Orientation to time	p = 0.126	p = 0.886
Orientation to place	p = 0.221	p = 0.196
Three-word registration	p = 0.751	p = 0.687
Delayed recall	p = 0.029	p = 0.047
Working memory	p = 0.520	p = 0.106
Language	p = 0.065	p = 0.719
Visual-construction	p = 0.674	p = 0.564

[1] P significant if ≤ 0.05.

In our study, vitamin C administration significantly improved the score that patients obtained on the recall domain of the MMSE ($p = 0.029$). After 12 months of treatment with vitamin C only, patients improved their mean score on the recall domain from 0.92 to 1.32, in comparison to the group of patients that received no treatment and decreased their mean recall score from 0.88 to 0.60 (Figure 4). Furthermore, the same significant improvement in the recall domain of MMSE was observed in our second comparison ($p < 0.001$), when patients who received vitamin C as a supplement in addition to the dementia treatment improved their recall mean score from 0.76 to 1.56, compared to patients who received the dementia treatment only and presented a non-significant small increase score from 0.72 to 0.84 (Figure 2).

In addition, the vitamin C administration for 12 months in comparison to no treatment also significantly improved the total score of the MMSE ($p = 0.029$). The improvement was from a mean total MMSE score of 21.80 to a mean score of 23.32 for the vitamin C treatment group in comparison to a decline observed in the no treatment group from 21.72 to 20.32 (Figure 3). Furthermore, the vitamin C intervention also made a significant impact on the total score of the MMSE as an addition to the dementia treatment ($p = 0.049$). An improvement in the MMSE total score can be observed in the group of patients who

received vitamin C in addition to dementia treatment (from a mean total score of 16.08 to 18.84) in comparison with dementia treatment only (a decrease from a mean total score of 15.80 to 15.36). These differences between the two groups are statistically significant (Figure 1). Moreover, no other significant effect of vitamin C administration was observed for any other domain of MMSE (Table I).

This failure of vitamin C to improve any other domain measured by MMSE aside from the recall items might be explained by the fact that memory and other cognitive domains measured by MMSE are connected, but can also be dissociated, both anatomically and functionally, from one another. The delayed memory function, which is reflected by the MMSE word recall item, has been connected to three neuroanatomic areas of the brain (and the pathways that link these regions). These three areas are: the medial temporal lobe (represented by the hippocampus and the entorhinal cortex [17, 18]), the thalamus (dorsomedial and the anterior nuclei [19]), and lastly, the basal forebrain, which supplies the hippocampus with necessary cholinergic neurons [20]. Inefficiencies in these neuroanatomical areas and cognitive domains might be decreased by vitamin C administration. Indeed, memory and executive domains are also considered critical areas for maintaining a high quality of life in the geriatric population [21]. Older individuals as well as those with certain dementias, such as Alzheimer's disease, experience integrity decline within these neuroanatomical regions [22].

In addition, at least for healthy individuals, the quantity of the two-electron oxidation product of ascorbate DHA shows only a minimal percent of the total vitamin C pool. This is due to efficient intracellular recycling of ascorbate and is largely considered to be negligible in overall homeostasis [23]. Furthermore, vitamin C shows complex non-linear pharmacokinetics along with different tissue distributions [24]. For example, during chronic states of severe deficiency, the brain is able to preferentially retain vitamin C at the expense of other tissues to uphold concentrations 100 times higher than the kidney and liver, which are rapidly depleted [25].

Another possible explanation for our non-significant results is related to vitamin C transport in brain tissue. More precisely, vitamin C is distributed in the body under close homeostatic control by tissue-specific sodium-dependent vitamin C co-transporters (SVCT 1 and 2). SVCT1 and SCCT2 are actively transferring vitamin C in exchange for sodium [26]. This process results in a saturable plasma concentration (70 μM in humans [27]), a level that can only be elevated *via* parenteral vitamin C administration. The vitamin C intervention in our sample of patients consisted of one capsule of 1000 mg vitamin C *per* day taken with a glass of water. Therefore, the method of administration might play an important role in maximising the benefits of vitamin C interventions on human cognition.

Regarding the results available in the literature, in animal models, the administration of 60 - 120 mg/kg of vitamin C intraperitoneally to seven-month-old Swiss mice for three to eight days has been proven to attenuate decreased performance in the passive avoidance test and the elevated plus maze. These results suggest that vitamin C may play an important role in age-related cognitive decline [28].

Furthermore, given that human studies show that menopause is correlated with some significant decline in cognition [29], other animal models have tried to discover if vitamin C may attenuate the effect of ageing on cognition in this population. Therefore, in ovariectomized rat models of human menopause, the administration of vitamin C and vitamin E prevented cognitive deficits, thus connecting antioxidant status to the normal functioning of the cognitive processes [30]. It is important to mention, that findings from animal models should be interpreted with caution, as the results may not translate to humans. In this regard, an animal model of ageing guinea pigs subjected to long-term, non-scorbutic vitamin C deficiency (100 mg vit C/kg feed) presented results that showed no significant effect of age on biochemical markers in the brain. The authors of this study concluded that the age-related decrease in vitamin C status measured in several other species is not connected to ageing *per se*, but rather to maturation [31].

In humans, in a geriatric sample of 137 individuals with an age range of 66 - 90 years, plasma concentrations of vitamin C have been found to be positively associated with cognitive performance. Furthermore, the vitamin C level in the blood was significantly decreased in individuals who were suffering from various forms of dementia [32]. Similar results were reported by a prospective cohort study on 921 individuals older than 65 years [33]. The findings of this investigation showed that individuals with the lowest vitamin C levels also presented the poorest cognitive function. Interestingly, this finding persisted when the statistical analysis was corrected for age, mental health, social class or other nutritional variables [33]. On the same note, in another study with a sample of women aged 70 - 79 years, long-term treatment with vitamin C and vitamin E was found to significantly correlate with increased cognitive performance. In addition, in the same research, an increased duration of supplementing with vitamin C and vitamin E showed a trend towards increasing cognitive performance [32]. A similar positive influence of vitamin C on cognitive performance was found by Masaki *et al*. [34]. The reported results of these authors demonstrated that vitamin C supplementation is correlated with an increase in overall cognitive performance. Moreover, the statistical analysis revealed that vitamin C supplementation has a protective effect on vascular dementia and mixed/other dementia.

However, not every study available in the literature has found an effect of vitamin C supplementation on age-related dementia [35].

The possible positive effect of vitamin C on cognitive performance has also been broadly studied with regards to Alzheimer's disease [36]. Though the aetiology of Alzheimer's disease has not been completely elucidated, reactive oxygen species (ROS) and oxidative stress have been associated with AD progression [37]. As individuals who suffer from AD have been reported to have lower levels of plasma vitamin C, research regarding the role of antioxidants such as vitamin C in AD origination and development has been conducted [38].

In animal models of AD, mice who received vitamin C supplementation have presented decreased cognitive dysfunction compared to control animals [39]. Furthermore, in research that used APP/PSEN1 mice, high doses of vitamin C administration (125 mg/kg) significantly increased cognitive performance in both the Y-maze and the Morris Water Maze. However, the results from the same study showed no significant effect of vitamin C administration on either amyloid load, acetylcholine esterase (AChE) or oxidative stress markers. Moreover, vitamin C has also been reported to have a memory-enhancing effect in other research on age-dependent cognitive decline in animal models [28, 40].

In another study that used six-months-old APP/PSEN1 mice that received only dietary vitamin C or in combination with high or low vitamin E, results showed decreased levels of various markers of lipid oxidation, such as F4-neuroprostanes and MDA, in supplemented mice compared to controls [41]. The low vitamin C and vitamin E supplementation attenuated deficits in spatial memory deficits and improved performance in the water maze. Interestingly, the mice that received high doses of vitamin C and vitamin E presented decreased spatial memory compared to controls [41]. Likewise, another study on six-month-old AβPP mice that received vitamin C supplementation in their drinking water for six months reported a significant effect of vitamin C on cognitive function [42].

Therefore, the available data supports the idea that vitamin C decreases cognitive decline in animal models, while the exact mechanisms are yet to be discovered. Different hypotheses have been proposed: the first one suggests a role for vitamin C in the intricate regulation of cholinergic neurotransmission, given that studies of vitamin C administration on mice during amnesia induced by scopolamine have shown induction of AChE in the medial forebrain [43]. The second hypothesis speculates that vitamin C acts through the involvement of BH4:BH2 in the metabolism of monoamine neurotransmitters, DA, norepinephrine and serotonin, given that vitamin C maintains a decreased biopterin status and therefore regulates the levels of neurotransmitters, known to be decreased in the memory impairments reported by AD patients [44].

In humans, in a study on 32 individuals with mild to moderate AD, with a mean age of 71 ± 7 years, vitamin C plasma levels were investigated in relation to cognitive decline [12]. A low level of vitamin C was found to be a predictor of cognitive decline. Furthermore, each unit increase in the vitamin C plasma level was correlated with 1.1 units less point loss on the MMSE score and 2.7 units less loss on the cognitive section of the Alzheimer's Disease Assessment Scale [12]. Moreover, several other investigations have found that supplementation with vitamin C reduces the risk of AD [45]. However, not every study has found a significant effect. For example, Gray *et al*. [46] designed a study with 2969 participants, older than 65 years, who were followed for a mean of 5.5 years and found no significant effect of vitamin C on a decreased incidence of AD or dementia. In contrast, Engelhart *et al.* [45] reported results that demonstrated a lowered risk of AD following vitamin C supplementation in 5395 participants older than 55 years, followed for approximately seven years. A possible explanation for the inconsistent findings in human studies may be found in the considerable variation in plasma vitamin C status and vitamin C supplementation between studies. Since ROS is thought to play an important part in AD progression, it can be hypothesized that a constant high vitamin C level acts in a preventive manner, while vitamin C supplementation cannot be considered a treatment *per se* for clinical AD. Therefore, inconsistent supplementing may not present the same benefits as regular intake of adequate doses of vitamin C. The literature shows that degenerative diseases, such as dementia, Alzheimer's and Parkinson's, are strongly associated with "inflamm-ageing" [47]. Recent studies [48, 49] show that the administration of vitamin C (a natural antioxidant) in combination with nitric oxide donors seems to prevent inflammation, dementia and the decline of memory and learning. Dementia generally affects the elderly, who frequently have disabling associated diseases such as osteoporosis. The literature reports that vitamin C influences bone strength and is essential for promoting osteoblast differentiation [50]. For this reason, recent studies have investigated the effects of the combined administration of vitamin C and bisphosphonates in anti-osteoporotic treatment [50, 51]. Therefore, the beneficial effect of vitamin C on bone strength could also positively influence cognitive processes. In addition, vitamin C appears to be involved in bleeding of various causes [52], which raises serious medical problems, particularly in elderly patients. The literature indicates that in haemophilic subjects, there is a significantly lower plasma level of ascorbic acid. Although it is easy to fix, vitamin C deficiency left untreated has severe consequences and can even be

fatal. Due to its multiple physiological implications, vitamin C levels must be monitored [53, 54].

Of course, these aspects could also be correlated with some of the previous work describing treatment adherence [55] in various disorders [56].

Still, in order to prove the possible preventive effect of vitamin C supplementation on AD development, further well-designed investigations with an adequate sample size are required [57].

Conclusions

Our study supports the idea that vitamin C might help in the prevention of cognitive decline by mainly improving memory function following both ageing-associated alteration and neurodegenerative disorders.

Conflict of interest

There is no conflict of interest to disclose.

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