Journal of Alzheimer's Disease 65 (2018) 577–587
DOI 10.3233/JAD-180184
IOS Press

Improvement of Main Cognitive Functions in Patients with Alzheimer's Disease after Treatment with Coconut Oil Enriched Mediterranean Diet: A Pilot Study

José Enrique de la Rubia Ortí[a,*], María Pilar García-Pardo[b,*], Eraci Drehmer[a], David Sancho Cantus[c], Mariano Julián Rochina[d], Maria Asunción Aguilar Calpe[e] and Iván Hu Yang[a]
[a]*Faculty of Nursing, Catholic University of Valencia, Valencia, Spain*
[b]*Pre-Departmental Unit of Medicine, Faculty of Health Sciences, Universitat Jaume I. Castelló de la Plana, Castelló, Spain*
[c]*Faculty of Psychology, Catholic University of Valencia, Valencia, Spain*
[d]*Faculty of Nursing and Podiatry, University of Valencia, Valencia, Spain*
[e]*Faculty of Psychology. University of Valencia, Valencia, Spain*

Accepted 2 July 2018

Abstract.
Background: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder (mainly in women), and new therapies are needed. In this way, ketone bodies are a direct source of cellular energy and can be obtained from coconut oil, postulating that coconut oil could be a new non-pharmacological alternative in AD patients.
Objective: The aim of this study is to detect changes in the main cognitive functions of patients with AD after following a coconut oil enriched Mediterranean diet, and to determine whether there are differences in function of stage or sex.
Methods: A prospective, longitudinal, qualitative, analytic, experimental study was carried out in 44 patients with AD, who were randomly divided into two homogenous groups of 22 patients each: an experimental group of patients who followed a coconut oil enriched Mediterranean diet for 21 days and a control group. In order to determine the cognitive changes after the intervention, we carried out the 7 Minute Screen, which analyses temporal orientation, visuospatial and visuoconstructive abilities, and semantic and episodic memory.
Results: After intervention with coconut oil, improvements in episodic, temporal orientation, and semantic memory were observed, and it seems that the positive effect is more evident in women with mild-moderate state, although other improvements in males and severe state were also shown.
Conclusions: The isocaloric coconut oil enriched Mediterranean diet seems to improve cognitive functions in patients with AD, with differences according to patient sex and degree of severity of the disease, although more studies in this line are needed.

Keywords: Alzheimer's disease, coconut oil, cognitive functions, ketone bodies, Mediterranean diet

*Correspondence to: María Pilar García Pardo, PhD, Postdoctoral Researcher, Pre-Departmental Unit of Medicine, Faculty of Health Sciences, Universitat Jaume I. Castelló de la Plana, Castellón, Spain. Tel.: +34 660588390; E-mail: m.pilar.garcia-pardo@uv.es and José Enrique de la Rubia Ortí, PhD, Associate Professor, Faculty of Nursing, Catholic University of Valencia, c/Espartero 7, 46007, Valencia, Spain. Tel.: + 34 669367704; E-mail: joseenrique.delarubi@ucv.es.

INTRODUCTION

Alzheimer's disease (AD) is the most common type of dementia (60%–70% of cases) and increases dramatically with age [1]. It is a progressive and irreversible brain disorder which slowly impairs memory and several other cognitive functions. The estimated survival of AD patients ranges from 3 to 9 years [2], with women being more commonly affected than men [3].

It is a disease that to date has no cure, although there are some drugs that can alleviate the symptoms, which are mainly acetylcholinesterase inhibitors (for example, rivastigmine, galantamine, and donepezil), indicated when the disease is between mild to moderately severe, and N-Methyl-D-Aspartate (NMDA) receptor antagonists (like memantine) that is indicated in moderate-severe cases [4]. However, drugs used for other disorders are also used in this type of dementia to treat associated symptoms, such as neuroleptics, antidepressants, and anxiolytics. In addition, many of the drugs currently used have a high number of side effects, greatly limiting the capabilities of the patient, so the search for more effective treatments remains a challenge.

Typically, AD has an insidious onset that becomes apparent initially with progressive loss of episodic memory, followed by gradual impairment of declarative and non-declarative memory [5]. Later, loss of other main cognitive functions, such as language, executive functions, attention span, and working memory, have also been observed [6] as well as alterations in temporal orientation [7], visuospatial ability [8], and visuoconstructive ability [9].

The etiology of AD is complex and heterogeneous, and multiple causes have been suggested, such as the absence of the neurotransmitter acetylcholine [10], genetic alterations [11–13], and the accumulation of amyloid plaques together with hyperphosphorylated tau protein in the brain. However, metabolic disorders, such as brain insulin resistance [14], which causes neuronal death due to lack of glucose, have also been mentioned as a cause of AD. This lack of glucose, which involves energy hypometabolism, begins to occur about a decade before the onset of the first signs of the disease. The explanation for this poor glucose utilization may be the early destruction of the noradrenergic brainstem nucleus, the *locus coeruleus*, which stimulates glucose metabolism, in astrocytes and possibly in other brain cells [15]. However, during that preclinical period, the metabolism of ketone bodies (a group of compounds produced from fat stored during periods of low glucose availability) does not decrease and they can provide an alternative to glucose for brain metabolism [16], constituting an extra source of energy. In addition, these ketone bodies, in adequate doses, also regulate glutamate release in the synaptic cleft. Glutamate is a neurotransmitter which is involved in most aspects of normal brain function, including learning. However, in AD patients, due to the severe alterations caused by the disease, its levels are high and lead to neuronal hyperexcitability and inflammation associated with an increase of calcium within the neuron, which produces neuronal death, decreasing synapsis. Therefore, ketone bodies would reduce such hyperexcitability and inflammation, thus improving the course of the illness [17]. This has been observed not only in mouse models of AD, in which the ability of ketone bodies to reverse pathological alterations at the brain level has been demonstrated, improving brain cognition [18], but also in humans diagnosed with AD [19].

In line with this, medium-chain triglycerides (MCTs) made up of medium-chain saturated fatty acids (MC-SFAs), such as linoleic acid, lauric acid, caprylic acid, etc., are metabolized quickly and efficiently [20, 21], giving rise to ketone bodies. Coconut oil is one of the foods that produces a higher number of these ketone bodies, because 90% of its saturated fats are medium-chain, of which approximately 45% is lauric acid, followed by palmitic acid, stearic acid, and myristic acid [22]. The effectiveness of coconut oil has already been proven in other neurological disorders, such as in epilepsy [23], in animal models of Parkinson's disease [24], and even in decreasing inflammation [25]. Regarding AD in particular, a potential role of coconut supplementation as a therapeutic option in the prevention and management of AD has been shown [26]. It seems that coconut supplementation increases the neuronal survival of cell cultures exposed to amyloid plaques [27], with an overall improvement in the cognitive performance of patients with AD after the administration [28], thus confirming its neuroprotective activity [29].

Therefore, it seems that the administration of an appropriate dosage of ketone bodies is a good alternative way of improving the course of AD, and especially of improving the main cognitive functions affected by this illness that affect the patient's daily life. Thus, the main objective of the present study is to test the efficacy of an isocaloric coconut oil enriched Mediterranean diet in improving cognitive functions, and to establish which of those functions

will improve more. At the same time, the secondary aim is to determine if there are differences in all these cognitive functions depending on patient sex and the severity of the illness (mild/moderate versus severe). This way, we will be able to better understand if all the cognitive functions depend, to the same extent, on the physiological alterations which are characteristic of AD and which lost functions are recovered more easily with the treatment described in the study.

According to the theoretical references showed here, our initial hypothesis is that patients who follow a coconut oil enriched Mediterranean diet experience an improvement in temporal orientation, visuospatial abilities, and semantic and episodic memory, with a difference in intensity. At the same time, an improvement on these variables will be dependent on patient sex and the severity of the disease.

MATERIAL AND METHODS

Design

A prospective, longitudinal, qualitative, analytic, and experimental design was used in the present study.

Participants

The inclusion criteria for the final sample in the study were the following: patients diagnosed with AD, institutionalized in the Alzheimer's Family Association of Valencia (AFAV), with ages ranging from 65 to 85 years old. The exclusion criteria were patients diagnosed with other types of degenerative cognitive disorder or with any type of verbal disability which prevented them from answering the test, patients with any metabolic chronic disease or treated with drugs which could alter the cognitive functions such as antidepressants, antipsychotics or hypnotic drugs.

The required sample size was determined on the basis of previous studies [28, 30]. After applying these inclusion and exclusion criteria to the 458 AFAV patients, a sample of 44 patients was obtained. These patients were randomly divided into two homogenous groups of 22 patients each: an experimental group of patients who followed a coconut oil enriched Mediterranean diet, and a control group of patients who followed a Mediterranean-style diet, with the same calorie intake as that of the experimental group, but without coconut oil.

To form these groups, and given that patients belonged to two strata according to their stage of the disease (severe or moderate/mild), and another two according to sex (male or female), a stratified random sampling technique was used, which consisted of the following: each patient, per stratum, was assigned an identification number at random. Subsequently, the sample was randomized using a balanced allocation methodology, in which each subject was assigned to a group with variable probability, depending on the subjects that were previously assigned to the groups. As a result, patients were randomly distributed between the experimental group and the control group.

Regarding gender, both groups had the same percentages of male and female patients (75% female and 25% male), which reflected the percentages of AD distribution according to gender [31]. As for the degree of impairment, both groups had the same percentage of patients in each stage of the illness. Before starting the study, all patients were classified by the institution neurologists using the Mini-Mental State Examination (MMSE) [32] with 36.37% having a mild/moderate level of cognitive impairment (scores ranging from 26 to 11 in the MMSE) and 63.63% having a severe level of cognitive impairment (scores ranging from 10 to 0 in the MMSE). The MMSE is a commonly used method to study cognitive impairment and to assess the outcome of patients with these symptoms through different questions and tasks that the patients are asked. The evaluation system consists in increasing the punctuation when the patient responds correctly, allowing us to assess different aspects like orientation, attention, concentration, memory or language [32]. In previous works, the test had shown good sensitivity and specificity levels, 0.87 and 0.82, respectively [33]. The institution psychologists gathered the information of the questionnaire.

The level of education was similar in all patients. All of them had higher education and a high socioeconomic level. All patients took similar doses of anticholinesterases and did not take any other type of medication over the 21 days of intervention.

Tools

Each participant was cognitively assessed by the same institutional blinded psychologist, before therapy (10 a.m. the day before the intervention, described in the following section) and after therapy

(10 a.m. the day after treatment), using the Seven Minute Screen composed of four tests.

The first test to be conducted was Benton's temporal orientation test, which consists of 5 questions (day of week, day of month, month, year, and hour). If the patient did not answer the first question correctly (day of week), they get 1 point for each day over or under the actual day, with a maximum error score of 3 points. If they did not answer the day of month correctly, they get 1 point for each day over or under the actual day, with a maximum error score of 15 points. If they did not answer the month correctly, they get 5 points for each month over or under the actual one, with a maximum error score of 30 points. If they did not answer the year correctly, they get 10 points for each year over or under the actual one, with a maximum error score of 10 points; and if they did not answer the hour correctly, they get 1 point for each 30 minutes of error with a maximum error score of 5 points. The obtained score is subtracted from 113 (total success), with 0 being the maximum error. So, the higher the score, the better the prognosis (from 0 to 113) [34].

Secondly, the Clock drawing test, which measures visuospatial and visuoconstructive abilities, was conducted. In this test, the investigator requests the patient to draw a watch face with all the hour numbers and draw the hands so that they point twenty to four. The score is 0–7 depending on the following criteria: 1) all the hours are present, 2) they are in the correct order, 3) in the correct position, 4) there are two hands, 5) the hour hand is closer to 4 than any other number, 6) the minutes hand is closer to the number 8, and 7) the hour hand is smaller than the minutes hand. Each of these 7 requests is scored 1 point. Higher scores indicate higher cognitive function (from 0 to 7) [34].

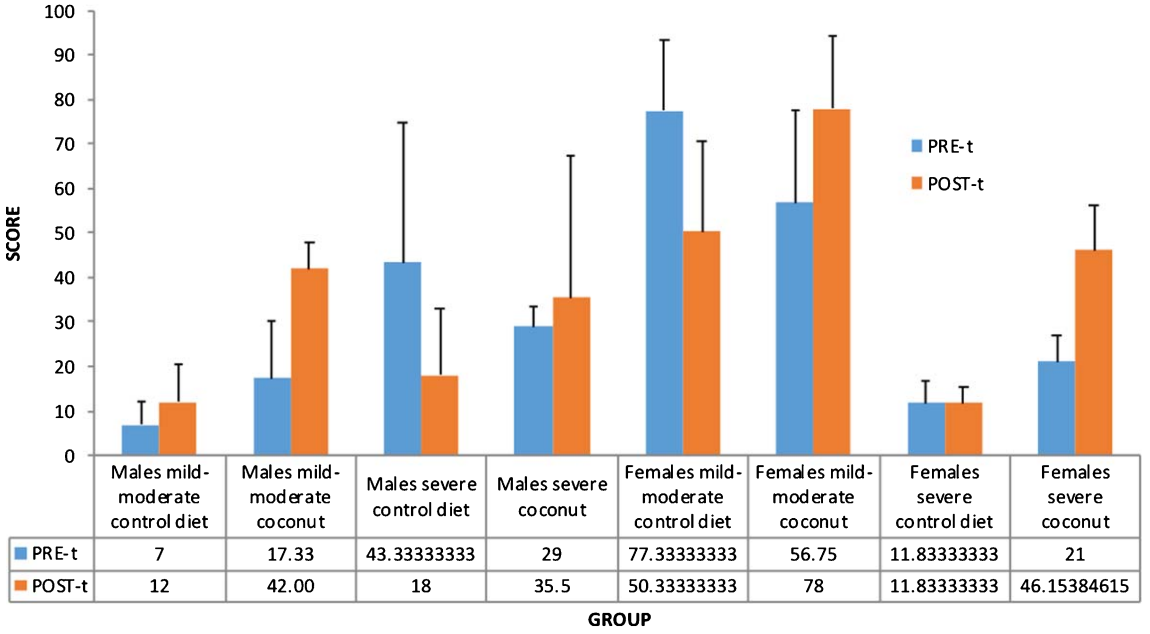
Thirdly, the Categorical Verbal Fluency test, which assesses semantic memory, was performed. In this test, the investigator tells the patient: "I'm going to tell you the name of a group or category and I want you to tell me as many words belonging to said category as fast as you can". Using an example, the investigator ensures that the patient understands the test. The maximum time is 60 s. The score is the number of words that the patient said with a maximum score of 20 words (from 0 to 20). However, any variation in number (singular versus plural) or grammatical gender (masculine versus feminine, in the case of Spanish) from a word, as well as repeated words, is not counted toward the score [34].

Finally, the episodic memory was evaluated with an adapted version of the Free and Cued Selective Reminding Test. In this case, 16 figures of different categories are presented to the patient. Following this, the patient gets 1 point for each remembered figure. If the patient does not remember the name of the figure, the investigator gives the patient a hint (such as the category of the figure) in order to evaluate the ability to use this type of information. The maximum score is 16 and the minimum, 0. Higher scores indicate higher cognitive function [34].

The Seven Minute screen has a sensitivity of 92.98%, a specificity of 93.5%, and a test-retest reliability of 93% [35].

Procedure

After assessing the patients for the first time with these four tests, the experimental group received 40 ml of coconut oil (20 ml during breakfast and 20 ml during lunch) since that dose has already proven to improve cognitive functions in AD patients [36, 15], for only 21 consecutive days, which is justified with the observed fact that cognitive improvement in AD patients becomes patent a few hours after coconut oil administration (it correlates with an immediate increase of ketone bodies in their blood) [36]. The doses were administered orally by the professional blinded workers of the center using a millimeter syringe. Both groups followed the same diet, i.e., an isocaloric Mediterranean diet associated with a decrease in cognitive impairment in AD patients [37–39]. This diet met the energy needs of the sample population and a ketogenic diet low in carbohydrates and proteins was not necessary to generate ketoacidosis, since it is possible to induce ketosis with MCT and without dietary modification [40]. In order to achieve this, 30 kcal/kg of body weight was administered after calculating the average baseline energy expenditure and the degree of physical activity of each individual (the minimum number of calories were 1,200 kcal/day, which could be increased to 2,000 kcal/day in the case of high energy consumption patients) [41]. The calorie intake was the same for all participants, taking into account that in the Mediterranean diet proteins account for 15% of the total energy intake, carbohydrates for 55% (with more slow-absorbing carbohydrates and less simple sugars [42]), and lipids for 30% of the total [43], so in the experimental group lipids were reduced to be completed up to 30% by coconut oil. This way, the daily lipid amount for all the study participants (for



	Males mild-moderate control diet	Males mild-moderate coconut	Males severe control diet	Males severe coconut	Females mild-moderate control diet	Females mild-moderate coconut	Females severe control diet	Females severe coconut
PRE-t	7	17.33	43.33333333	29	77.33333333	56.75	11.83333333	21
POST-t	12	42.00	18	35.5	50.33333333	78	11.83333333	46.15384615

Fig. 1. Effects of coconut on the temporal orientation. During the treatment, subjects were divided into the following treatment groups: Males Mild-Moderate Control Diet, Males Mild-Moderate Coconut, Males Severe Control Diet, Males Severe Coconut, Females Mild-Moderate Control Diet, Females Mild-Moderate Coconut, Females Severe Control Diet, and Females Severe Coconut. The bars represent the score obtained in the temporal orientation test before treatment (Pre-t, blue bars) and after treatment (Post-t, orange bars). The interaction of all the variables was not significant. However, the interaction "Time" x "Group" was significant, showing that the treatment induced improvements in all the groups regardless of State or Sex.

the control group and the intervention group) was the same.

Finally, in order to complete the diet, 20–30 g/day of soluble and insoluble fiber was administered to prevent and/or improve constipation, which is prevalent in older patients [42].

Ethical considerations

The present study was conducted with the approval of the Ethics Commission for Experimental Research with Humans of the University of Valencia (Process number HI433498684966), Spain, and fully complies with all the principles established in the Declaration of Helsinki (1975) and the Belmont Report (1983).

Statistical data processing

Through the SPPP statistical program, the data were analyzed with a mixed four-way ANOVA with a three between-subjects variables, "Treatment" with two levels (Control Diet, Coconut), "Sex" with two levels (Female, Male), "Stage" with two levels (Mild-Moderate, Severe), and a within-subjects variable "Time" with two levels (Pre-Treatment and Post-Treatment). All *Post-hoc* comparisons were performed with Bonferroni test.

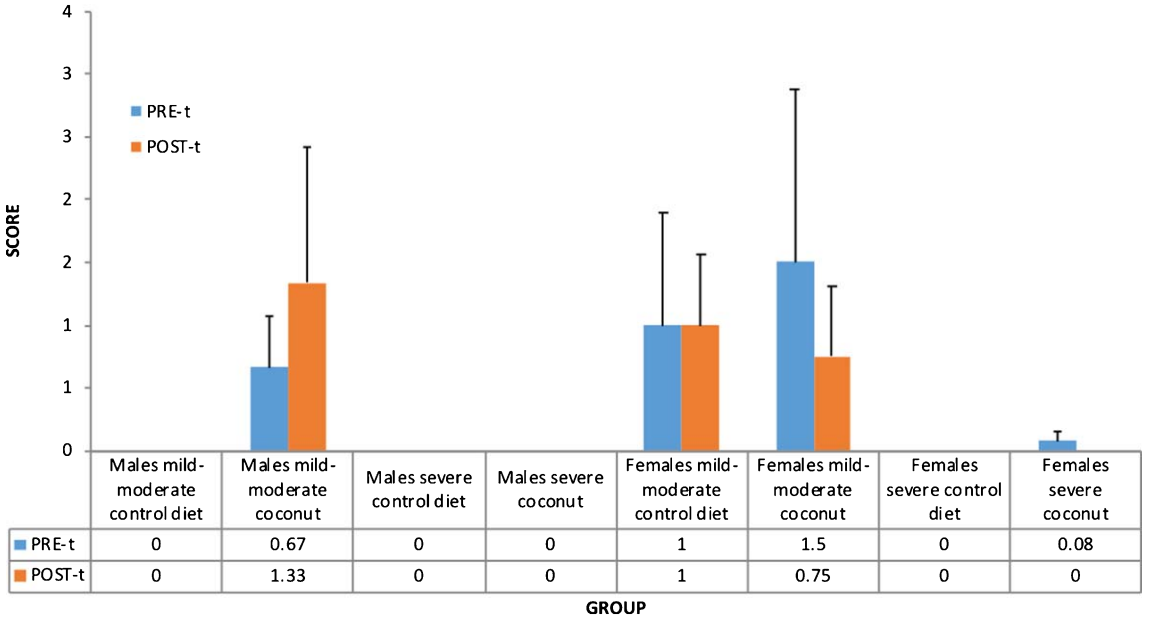
RESULTS

Effects of coconut diet on temporal orientation

Data about temporal orientation are shown in Fig. 1. Only the interaction "Time x Group" [$F(1,36) = 5{,}541$; $p < 0.05$; $\eta^2_p = 0.133$] and "Sex x State" [$F(1) = 8{,}799$; $p < 0.05$; $\eta^2_p = 0.196$] were significant. *Post-hoc* comparisons revealed that there are differences in mild moderate state between women and men and the experimental group that received coconut had more punctuation in Post-treatment that Pre-treatment ($p < 0.05$).

Effects of coconut diet on visuospatial memory

The ANOVA revealed that only the "State" [$F(1, 36) = 7{,}614$; $p < 0.01$; $\eta^2_p = 0.175$] was significant (See Fig. 2).



	Males mild-moderate control diet	Males mild-moderate coconut	Males severe control diet	Males severe coconut	Females mild-moderate control diet	Females mild-moderate coconut	Females severe control diet	Females severe coconut
PRE-t	0	0.67	0	0	1	1.5	0	0.08
POST-t	0	1.33	0	0	1	0.75	0	0

Fig. 2. Effects of coconut on the visuospatial memory. During the treatment, subjects were divided into the following treatment groups: Males Mild-Moderate Control Diet, Males Mild-Moderate Coconut, Males Severe Control Diet, Males Severe Coconut, Females Mild-Moderate Control Diet, Females Mild-Moderate Coconut, Females Severe Control Diet, and Females Severe Coconut. The bars represent the score obtained in the visuospatial memory test before treatment (Pre-t, blue bars) and after treatment (Post-t, orange bars).

Effects of coconut diet on semantic memory

The scores in episodic memory are shown in Fig. 3. The ANOVA showed that the variable "Time" [$F(1,36) = 4{,}564$; $p < 0.05$; $\eta^2_p = 0.113$] and the interaction "Time x Sex x Group x State" [$F(1,36) = 6{,}412$; $p < 0.05$; $\eta^2_p = 0.151$] were significant. *Post-hoc* comparisons revealed that after the treatment (Post-treatment) females with mild-moderate state in experimental group had high punctuations than before the treatment (Pre-treatment) and that males with severe state in experimental group showed high punctuations in Post-treatment than Pre-treatment.

Effects of coconut diet on episodic memory

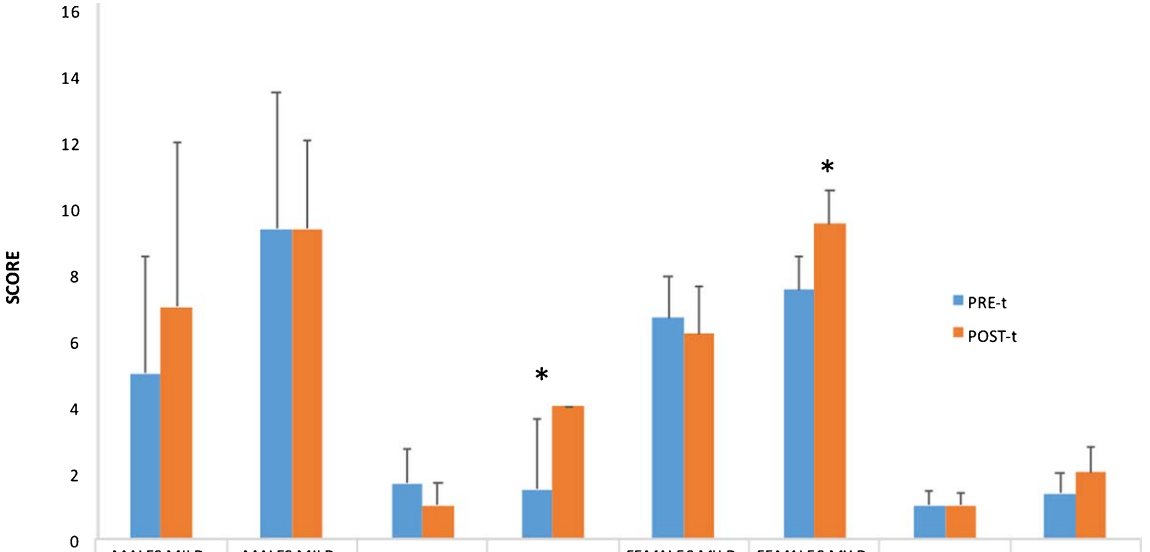
The scores in episodic memory are shows in Fig. 4. The ANOVA revealed a significant effects of the variable "Time" [$F(1,36) = 9{,}826$; $p < 0.05$; $\eta^2_p = 0.214$], "State" [$F(1,36) = 30{,}667$; $p < 0.001$; $\eta^2_p = 0.460$], and the interactions "Time x Sex" [$F(1,36) = 11{,}044$; $p < 0.05$; $\eta^2_p = 0.235$], "Time x State" [$F(1,36) = 9{,}146$; $p < 0.05$; $\eta^2_p = 0.203$], "Time x Sex x Group" [$F(1,36) = 5{,}279$; $p < 0.05$; $\eta^2_p = 0.128$], "Time x Sex x State" [$F(1,36) = 6{,}135$; $p < 0.05$; $\eta^2_p = 0.146$], "Time x Sex x Group x State" [$F(1,36) = 7{,}105$; $p < 0.05$; $\eta^2_p = 0.165$]. *Post-hoc* comparisons showed that in experimental group females and males with mild-moderate state have more punctuation in episodic memory in Post-treatment than in Pre-treatment ($p < 0.05$). However, in control group females with mild moderate state had worse punctuation in Post-treatment than in Pre-treatment ($p < 0.05$). On the other hand, in control group males with moderate state improve the punctuation in Post-treatment too ($p < 0.05$). No differences were observed in the severe state.

Brief descriptive results of the sample characteristics and the mean differences in each group (Pre-t versus Post-t scores) can be observed in Table 1.

DISCUSSION

This study has demonstrated that a coconut oil enriched Mediterranean diet improves cognitive functions. This type of therapy increases the execution results in temporal orientation, semantic memory, and episodic memory comparing pre and post treatment of experimental groups. In addition, our study demonstrates for the first time that the improvement in these cognitive functions is linked to the sex of the patient and the severity of the disease.

Our results coincide with the results of other studies in which other cognitive tests have been used to

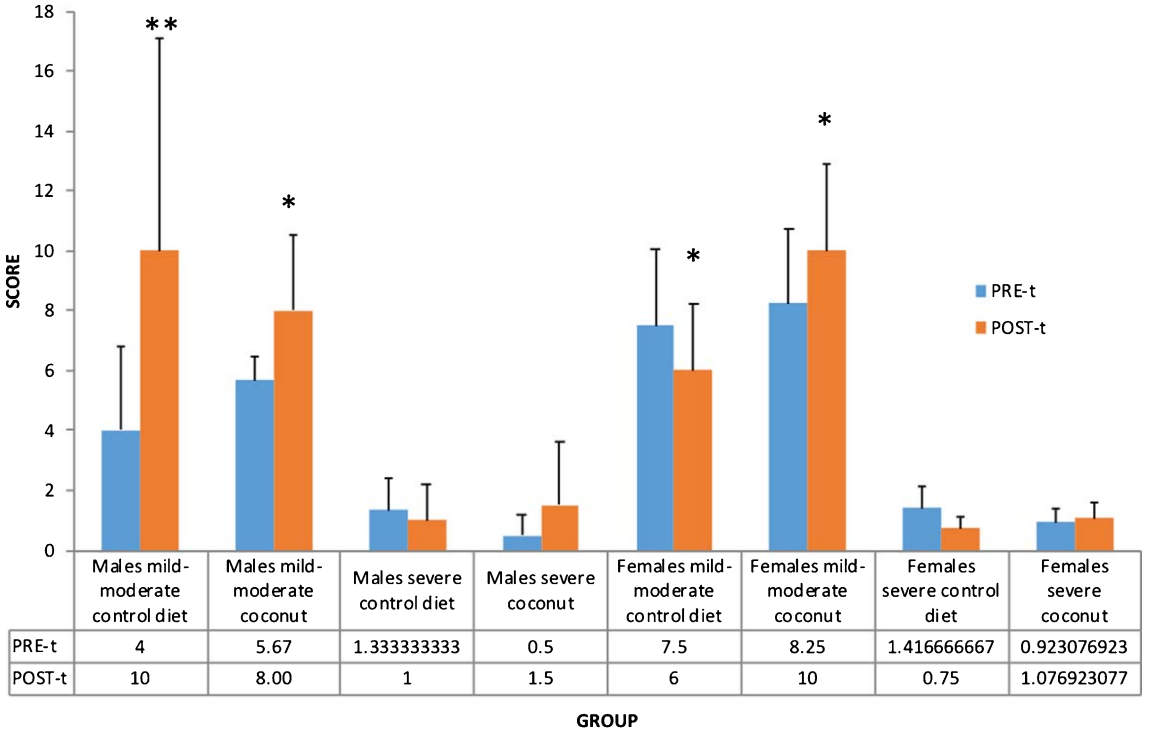


	MALES MILD-MODERATE CONTROL DIET	MALES MILD-MODERATE COCONUT	MALES SEVERE CONTROL DIET	MALES SEVERE COCONUT	FEMALES MILD-MODERATE CONTROL DIET	FEMALES MILD-MODERATE COCONUT	FEMALES SEVERE CONTROL DIET	FEMALES SEVERE COCONUT
PRE-t	5	9.33	1.666666667	1.5	6.666666667	7.5	1	1.38
POST-t	7	9.33	1	4	6.166666667	9.5	1	2

Fig. 3. Effects of coconut on the semantic memory. During the treatment, subjects were divided into the following treatment groups: Males Mild-Moderate Control Diet, Males Mild-Moderate Coconut, Males Severe Control Diet, Males Severe Coconut, Females Mild-Moderate Control Diet, Females Mild-Moderate Coconut, Females Severe Control Diet, and Females Severe Coconut. The bars represent the score obtained in the semantic memory test before treatment (Pre-t, blue bars) and after treatment (Post-t, orange bars). $^{*}p < 0.05$, a significant difference in the score in semantic memory in Pre-t versus Post-t.

report improvements after administering changes in the diet, initially in animals [44] and, later, in human beings [15, 36]. Taking a closer look at the changes observed in the group that received coconut oil, these changes seem to point to the fact that certain cognitive functions improved more than others as the brain energy source recovered, such as temporal orientation, semantic memory and episodic memory. This improvement coincides with other studies [40, 45] where an increase in the global memory of patients is already observed with small increments of hydroxybutyrate in blood. The improvement of the two types of memory could be explained by the decrease in insulin resistance due to the action of ketone bodies [15], since memory improvement has been observed after intranasal administration of insulin in AD patients, which increases glucose metabolism [46]. On the other hand, an improvement in temporary orientation has only been evidenced in a previous study in our laboratory where comparable doses of coconut oil were administered [30]. This fact could be explained because this function, like memory, depends on the hippocampus, so if it is recovered, it is expected that the other one will recover too [47]. Along these lines, visuospatial and visuoconstructive abilities, which do not improve after the intervention, depend on other brain areas, which in turn would explain the lack of recovery. Visuospatial abilities are supported by the caudal intraparietal sulcus [48] and parts of the inferior parietal lobule, including the angular gyrus and posterior supramarginal gyrus [49], while visuocontructional abilities are mediated by parts of the superior parietal lobule, including areas V6A and the medial intraparietal area [50]. It could be deduced that not all regions of the cerebral cortex recover to the same degree.

In addition, the present study shows differences regarding sex, since it seems that female patients recover more easily than male patients, which confirms our previous results, where a global cognitive improvement was shown in women [28]. These results could possibly be explained by hormonal differences in sex, but not only with respect to low estrogen levels or to the role played by gonadotropins in women (luteinizing hormone and follicle-stimulating hormone), which modulate susceptibility to AD and the progression of the disease [3], but also, and especially, by testosterone, whose levels of production are much lower in women with AD and cause them to have higher insulin resistance



	Males mild-moderate control diet	Males mild-moderate coconut	Males severe control diet	Males severe coconut	Females mild-moderate control diet	Females mild-moderate coconut	Females severe control diet	Females severe coconut
PRE-t	4	5.67	1.333333333	0.5	7.5	8.25	1.416666667	0.923076923
POST-t	10	8.00	1	1.5	6	10	0.75	1.076923077

Fig. 4. Effects of coconut on the episodic memory. During the treatment, subjects were divided into the following treatment groups: Males Mild-Moderate Control Diet, Males Mild-Moderate Coconut, Males Severe Control Diet, Males Severe Coconut, Females Mild-Moderate Control Diet, Females Mild-Moderate Coconut, Females Severe Control Diet, and Females Severe Coconut. The bars represent the score obtained in the episodic memory test before treatment (Pre-t, blue bars) and after treatment (Post-t, orange bars). $^{*}p < 0.05$, a significant difference in the score in episodic memory in Pre-t versus Post-t. $^{**}p < 0.01$, a significant difference in the score in episodic memory in Pre-t versus Post-t.

[51]. This could explain the better use of an alternative energy source in women, i.e., ketone bodies provided by coconut oil.

Regarding the degree of severity, as previously mentioned, differences were also found. For example, in episodic memory, only mild-moderate state showed improvement but in semantic memory both severe and mild-moderate state showed differences after the treatment. Maybe, the real effect of coconut oil on AD patients could be to inhibit the gene expression of an oxidative stress mediator enzyme which slows down aging in severely ill patients with more amyloid plaques at the brain level [52]. However, this theory contradicts recent findings on neuronal cultures exposed to amyloid plaques. These findings indicate that cells that have been in contact with these plaques recover less after treatment with coconut oil, and that there is greater neuronal survival in cells that have been exposed fewer hours to it [28]. Therefore, the improvement observed in the severely ill patients of the present study could be less due to the cessation of oxidation caused by an increase in amyloid plaques, and more due to the better metabolic recovery (greater neurogenesis) of the areas affected in severely ill patients in particular [52]. In fact, AD causes the degeneration of the dentate gyrus, made up of cells that sustain neurogenesis, whose recovery has been observed after the administration of dietary supplements based on MCTs [53].

In short, the results of the present study show improvements in episodic, temporal orientation, and semantic memory in AD patients after administering an isocaloric coconut oil enriched Mediterranean diet, with differences between women and states. This seems to corroborate the great neuroprotective ability of MCFA-based ketogenic diets observed in other neurodegenerative diseases and neurological disorders, such as epilepsy [23], Parkinson's disease [54], traumatic brain injuries in the young [55], and amyotrophic lateral sclerosis [56].

However, this study has some limitations: on the one hand, measures to check cognitive improvements have been made from cognitive tests. These cognitive analyses should be complemented by other types

Table 1
Brief descriptive results of the sample characteristics and the mean differences between groups

	Males mild-moderate control diet	Males mild-moderate coconut	Males severe control diet	Males severe coconut	Females mild-moderate control diet	Females mild-moderate coconut	Females severe control diet	Females severe coconut
Participants (n)	1	3	3	2	6	4	12	13
Middle age	84	80	75	76	80	77	82	78
Pre-Temporal orientation (Mean ± SEM)	7.00 ± 0.00	17.33 ± 18.14	43.33 ± 44.65	29.00 ± 4.24	77.33 ± 36.06	56.75 ± 36.29	11.83 ± 16.61	21.00 ± 20.06
Post-Temporal orientation (Mean ± SEM)	12.00 ± 0.00	42.00 ± 8.00	18.00 ± 20.95	35.50 ± 31.81	50.33 ± 44.97	78.00 ± 28.29	11.83 ± 12.40	46.15 ± 35.41
Pre-Visuospatial memory (Mean ± SEM)	0.00 ± 0.00	0.66 ± 0.57	0.00 ± 0.00	0.00 ± 0.00	1.00 ± 2.00	1.50 ± 2.38	0.00 ± 0.00	0.07 ± 0.27
Post-Visuospatial memory (Mean ± SEM)	0.00 ± 0.00	1.33 ± 1.52	0.00 ± 0.00	0.00 ± 0.00	1.00 ± 1.26	0.75 ± 0.95	0.00 ± 0.00	0.00 ± 0.00
Pre-Semantic memory (Mean ± SEM)	5.00 ± 0.00	9.33 ± 5.85	1.66 ± 1.52	1.50 ± 2.12	6.66 ± 2.73	7.50 ± 1.73	1.00 ± 1.41	1.38 ± 2.10
Post-Semantic memory (Mean ± SEM)	7.00 ± 0.00	9.33 ± 3.78	1.00 ± 1.00	4.00 ± 0.00*	6.16 ± 3.25	9.50 ± 1.73*	1.00 ± 1.27	2.00 ± 2.76
Pre-Episodic memory (Mean ± SEM)	4.00 ± 0.00	5.66 ± 1.15	1.33 ± 1.52	0.50 ± 0.707	7.50 ± 5.75	8.25 ± 4.27	1.416 ± 2.31	0.92 ± 1.65
Post-Semantic memory (Mean ± SEM)	10.00 ± 0.00**	8.00 ± 3.60*	1.00 ± 1.73	1.50 ± 2.12	6.00 ± 4.97*	10.00 ± 4.96*	0.75 ± 1.21	1.07 ± 1.70

*$p < 0.05$, a significant difference in the score memory in Pre-t versus Post-t. **$p < 0.01$, a significant difference in the score memory in Pre-t versus Post-t.

of biochemical measurements and/or imaging techniques. It is only a pilot study and more studies in this area with more size sample are needed to confirm the results. In fact, the small sample of each group is another limitation of this work. In addition, the interventions lasted 21 days; therefore, similar interventions could be carried out for longer periods of time with a larger sample to certify if cognitive improvements are maintained over time.

ACKNOWLEDGMENTS

The authors would like to thank the José Navarro Foundation for funding the present study, as well as all the patients, their legal guardians, and the Alzheimer's Family Association of Valencia who took part in this study.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/18-0184r3).

REFERENCES

[1] Bullain SS, Corrada MM (2013) Dementia in the oldest old. *Continuum* **19**, 457.

[2] Tom SE, Hubbard RA, Crane PK, Haneuse SJ, Bowen J, McCormick WC, McCurry S, Larson EB (2015) Characterization of dementia and Alzheimer's disease in an older population: Updated incidence and life expectancy with and without dementia. *Am J Public Health* **105**, 408-413.

[3] Webber KM, Casadesus G, Perry G, Atwood CS, Bowen R, Smith MA (2005) Gender differences in Alzheimer disease: The role of luteinizing hormone in disease pathogenesis. *Alzheimer Dis Assoc Disord* **19**, 95-99.

[4] Reyes-Figueroa JC, Rosich-Estragó M, Bordas-Buera E, Gaviria-Gómez AM, Vilella-Cuadrada E, Labad-Alquézar A (2010) Síntomas psicológicos y conductuales como factores de progresión a demencia tipo Alzheimer en el deterioro cognitivo leve. *Rev Neurol* **50**, 653-660.

[5] Schroeter ML, Stein T, Maslowski N, Neumann J (2009) Neural correlates of Alzheimer's disease and mild cognitive impairment: A systematic and quantitative meta-analysis involving 1351 patients. *Neuroimage* **47**, 1196-1206.

[6] Campos C, Rocha NB, Vieira RT, Rocha SA, Telles-Correia D, Paes F, Yuan T, Nardi AE, Arias-Carrión O, Machado S, Caixeta L (2016) Treatment of cognitive deficits in Alzheimer's disease: A psychopharmacological review. *Psychiatr Danub* **28**, 2-12.

[7] Marcos T, Salamero M, de Azpiazu P, Pujol J, Boget T, Peri JM, Lázaro ML (2000) Neuropsychological pattern of cognitive impairment in Alzheimer type dementia and vascular dementia. *Med Clin (Barc)* **114**, 566-570.

[8] Neitzel J, Ortner M, Haupt M, Redel P, Grimmer T, Yakushev I, Drzezga A, Bublak P, Preul C, Sorg C, Finke K (2016) Neuro-cognitive mechanisms of simultanagnosia in patients with posterior cortical atrophy. *Brain* **139**, 3267-3280.

[9] Förster S, Teipel S, Zach C, Rominger A, Cumming P, Fougere Cl, Yakushev I, Haslbeck M, Hampel H, Bartenstein P, Bürger K (2010) FDG-PET mapping the brain substrates of visuo-constructive processing in Alzheimer s disease. *J Psychiatr Res* **44**, 462-469.

[10] Shen ZX (2004) Brain cholinesterases: II. The molecular and cellular basis of Alzheimer's disease. *Med Hypotheses* **63**, 308-321.

[11] Lott IT, Head E (2005) Alzheimer disease and Down syndrome: Factors in pathogenesis. *Neurobiol Aging* **26**, 383-389.

[12] Nistor M, Don M, Parekh M, Sarsoza F, Goodus M, Lopez GE, Kawas C, Leverenz J, Doran E, Lott IT, Hill M, Head E, Hill M (2007) Alpha-and beta-secretase activity as a function of age and beta-amyloid in Down syndrome and normal brain. *Neurobiol Aging* **28**, 1493-1506.

[13] Polvikoski T, Sulkava R, Haltia M, Kainulainen K, Vuorio A, Verkkoniemi A, Niinistö L, Halonen P, Kontula K (1995) Apolipoprotein E, dementia, and cortical deposition of β-amyloid protein. *New Engl J Med* **333**, 1242-1248.

[14] Wood H (2017) Alzheimer disease: Is p-tau the missing link between insulin resistance and AD? *Nat Rev Neurol* **13**,706.

[15] Farah BA (2014) Effects of caprylic triglyceride on cognitive performance and cerebral glucose metabolism in mild Alzheimer's disease: A single-case observation. *Front Aging Neurosci* **16**, 1-4.

[16] Croteau E, Castellano CA, Fortier M, Bocti C, Fulop T, Paquet N, Cunnane SC (2017) A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Exp Gerontol* **107**, 18-26.

[17] Hertz L, Chen Y, Waagepetersen HS (2015) Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, β-amyloid toxicity, and astrocyte function. *J Neurochem* **134**, 7-20.

[18] Mamelak M (2017) Energy and the Alzheimer brain. *Neurosci Biobehav Rev* **75**, 297-313.

[19] Steele M, Stuchbury G, Münch G (2007) The molecular basis of the prevention of Alzheimer's disease through healthy nutrition. *Exp Gerontol* **42**, 28-36.

[20] Aas M (1971) Organ and subcellular distribution of fatty acid activating enzymes in the rat. *Biochim Biophys Acta* **231**, 32-47.

[21] Metges CC, Wolfram G (1991) Medium-and long-chain triglycerides labeled with 13C: A comparison of oxidation after oral or parenteral administration in humans. *J Nutr* **121**, 31-36.

[22] Bezar J, Bugaut M, Clement G (1971) Triclyceride composition of coconut oil. *J Am Oil Chem Soc* **48**, 134-139.

[23] Stafstrom CE, Rho JM (2012) Theketogenic diet as a treatment paradigm for diverse neurological disorders. *Front Pharmacol* **3**, 59.

[24] Cheng B, Yang X, An L, Gao B, Liu X, Liu S (2009) Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson's disease. *Brain Res* **1286**, 25-31.

[25] Ruskin DN, Kawamura M, Masino SA (2009) Reduced pain and inflammation in juvenile and adult rats fed a ketogenic diet. *PLoS One* **4**, e8349.

[26] Fernando WM, Martins IJ, Goozee KG, Brennan CS, Jayasena V, Martins RN (2015) The role of dietary coconut for the prevention and treatment of Alzheimer's disease: Potential mechanisms of action. *Br J Nutr* **114**, 1-14.

[27] Nafar F, Clarke JP, Mearow KM (2017) Coconut oil protects cortical neurons from amyloid beta toxicity by enhancing signaling of cell survival pathways. *Neurochem Int* **105**, 64-79.

[28] Hu Yang I, de la Rubia Ortí JE, Selvi Sabater P, Sancho Castillo S, Julián Rochina M, Manresa Ramón N, Montoya-Castilla I (2015) Aceite de coco: Tratamiento alternativo no farmacológico frente a la enfermedad de Alzheimer. *Nutr Hosp* **32**, 2822-2827.

[29] Maynard SD, Gelblum J (2013) Retrospective case studies of the efficacy of caprylic triglyceride in mild-to-moderate Alzheimer's disease. *Neuropsychiatr Dis Treat* **9**, 1629-1635.

[30] De la RubiaOrti JE, Sánchez Alvarez C, Selvi Sabater P, Bueno Cayo AM, Sancho Castillo S, Julián Rochina M, Hu Yang I (2017) How does coconut oil affect cognitive performance in alzheimer patients? *Nutr Hosp* **34**, 352-356.

[31] Carrillo-Alcalá ME, Bermejo-Pareja F (2008) Demencia en nonagenarios. Revisión sistemática de estudios poblacionales con datos de España. *Rev Neurol* **47**, 347-354.

[32] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[33] Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJ, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton GF, Neale BE, Watton ME, Cullum S (2016) Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. *Cochrane Database Syst Rev* **13**, CD011145.

[34] Sel ser Quijano T, Sánchez Sánchez F, García de Yébenes MJ, Otero Puime A, Zunzunegui MV, Múñoz DG (2004) Spanish version of the 7 Minute screening neurocognitive battery. Normative data of an elderly population sample over 70. *Neurología* **19**, 344-358.

[35] Solomon PR, Hirschoff A, Kelly B, Relin M, Brush M, DeVeaux RD, Pendlebury WW (1998) A 7 minute neurocognitive screening battery highly sensitive to Alzheimer's disease. *Arch. Neurol* **55**, 349-355.

[36] Reger MA, Henderson ST, Hale C, Cholerton B, Baker LD, Watson GS, Hyde K, Chapman D, Craft S (2004) Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. *Neurobiol Aging* **25**, 311-314.

[37] Plassman BL, Williams JW, Burke JR, Holsinger T, Benjamin S (2010) Systematic review: Factors associated with risk for and possible prevention of cognitive decline in later life. *Ann Intern Med* **153**, 182-193.

[38] Solfrizzi V, Panza F, Frisardi V, Seripa D, Logroscino G, Imbimbo BP, Pilotto A (2011) Diet and Alzheimer's disease risk factors or prevention: The current evidence. *Expert Rev Neurother* **11**, 677-708.

[39] Wyka J (2012) Nutritional factors in prevention of Alzheimer's disease. *Rocz Panstw Zakl Hig* **63**, 135-140.

[40] Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC (2009) Study of the ketogenic agent AC-1202 in mild to moderate Alzheimer's disease: A randomized, double-blind, placebo-control, multicenter trial. *Nutr Metab* **6**, 31.

[41] Carbajal A (2001) Ingestas recomendadas en personas de edad avanzada. *Alimentacion Nutr Salud* **8**, 100-114.

[42] Arbonés G, Carbajal A, Gonzalvo B, González-Gross M, Joyanes M, Marques-Lopes I, Martín ML, Martínez A, Montero P, Núñez C, Puigdueta I, Quer J, Rivero M, Roset MA, Sánchez-Muniz FJ, Vaquero MP (2003) Nutrition and dietary recommendations for the elderly" Public Health" Working Group of the Spanish Nutrition Society. *Nutr Hop* **18**, 109-137.

[43] Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J, Wilson RS (2003) Dietary fats and the risk of incident Alzheimer disease. *Arch Neurol* **60**, 194-200.

[44] Aso E, Semakova J, Joda L, Semak V, Halbaut L, Calpena A, Escolano C, Perales JC, Ferrer I (2013) Triheptanoin supplementation to ketogenic diet curbs cognitive impairment in APP/PS1 mice used as a model of familial Alzheimer's disease. *Curr Alzheimer Res* **10**, 290-297.

[45] Costantini LC, Barr LJ, Vogel JL, Henderson ST (2008) Hypometabolism as a therapeutic target in Alzheimer's disease. *BMC Neurosci* **9**(Suppl 2), S16.

[46] Hölscher C (2014) First clinical data of the neuroprotective effects of nasal insulin application in patients with Alzheimer's disease. *Alzheimers Dement* **10**, S33-S37.

[47] Squire LR (2009) The legacy of patient HM for neuroscience. *Neuron*, **61**, 6-9.

[48] Sakata H, Taira M, Kusunoki M, Murata A, Tanaka Y (1997) The TINS Lecture. The parietal association cortex in depth perception and visual control of hand action. *Trends Neurosci* **20**, 350-357.

[49] Tranel D, Vianna E, Manzel K, Damasio H, Grabowski T (2009) Neuroanatomical correlates of the Benton Facial Recognition Test and Judgment of Line Orientation Test. *J Clin Exp Neuropsychol* **31**, 219-233.

[50] Galletti C, Fattori P, Kutz DF, Battaglini PP (1997) Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. *Eur J Neurosci* **9**, 410-413.

[51] de la Rubia Orti JE, Julián Rochina M, García-Pardo MP (2018) Value of testosterone in saliva in the diagnosis of Alzheimer's disease. *Med Clin (Barc)*, doi: 10.1016/j.medcli.2018.03.006

[52] Jagua A, Ávila VÁ (2007) Insulina y enfermedad de Alzheimer: Una diabetes tipo 3? *Rev Fac Med* **55**, 66-70.

[53] Cao D, Kevala K, Kim J, Moon HS, Jun SB, Lovinger D, Kim HY (2009) Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J Neurochem* **111**, 510-521.

[54] Cheng B, Yang X, An L, Gao B, Liu X, Liu S (2009) Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson's disease. *Brain Res* **1286**, 25-31.

[55] Deng-Bryant Y, Prins ML, Hovda DA, Harris NG (2011) Ketogenic diet prevents alterations in brain metabolism in young but not adult rats after traumatic brain injury. *J Neurotrauma* **28**, 1813-1825.

[56] Zhao W, Varghese M, Vempati P, Dzhun A, Cheng A, Wang J, Lange D, Bilski A, Faravelli I, Pasinetti, GM (2012) Caprylic triglyceride as a novel therapeutic approach to effectively improve the performance and attenuate the symptoms due to the motor neuron loss in ALS disease. *PLoS One*, **7**, e49191.