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Blood Plasma Coenzyme Q_{10} and P-Selectin Are Predictive Factors for Mild Cognitive Dysfunction in Elderly Women

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Abstract

Detection of the early phases of cognitive dysfunction is critical for identifying individuals at risk of neurodegeneration before irreversible damage occurs. High levels of coenzyme Q_{10} (CoQ_{10}) in plasma are associated with high cognitive and executive capacities. Plasma CoQ_{10} has been associated with the prevention of oxidative damage and maintenance of mitochondrial health in the endothelium. Maintenance of endothelial function is also an important factor in the prevention of neurodegeneration and dementia. Therefore, this study aimed to determine plasma markers of endothelial health that, in conjunction with CoQ_{10}, can effectively serve as predictors of cognitive dysfunction in a cohort of 45 elderly women (78.36 ± 8.41 years) from Seville, Spain. Utilizing a cross-sectional design, we assessed cognitive and executive capacities via the widely used MMSE-30 and FAB-E scales. Physiological health was evaluated through plasma biomarkers (including GDF-15, GFAP, BDNF, P-selectin, NfL, and p-Tau181) and the determination of CoQ_{10} levels. Furthermore, the study also analyzed exosome levels by measuring CD63 and their content in DNA and mtDNA. Our results indicate that low plasma CoQ_{10}, elevated P-selectin (P-sel), and reduced exosomal DNA content can serve as early warning signs of neurodegeneration, appearing before traditional markers like GFAP, NfL, or p-Tau^{181}. Our results indicate a link between CoQ_{10} levels, endothelial damage, and cognitive dysfunction risk.

Keywords: coenzyme Q_{10}; ubiquinone; ubiquinol; aging; antioxidant; cognitive dysfunction; endothelium

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1. Introduction

Cognitive decline is one of the most important causes of morbidity in elderly people [1]. Preventive strategies to delay the onset and progression of neurodegeneration are essential to significantly reduce the social and healthcare impact of neurodegenerative diseases on an increasingly aging population [2,3]. When symptoms are clear and biomarkers of neurodegeneration such as β-amyloid protein and phospho-Tau forms are already found in blood plasma, we can consider that the damage in neurons has already occurred and only palliative treatment can be provided. Probably this is the main reason because more than 99% of clinical trials based on β-amyloid accumulation have failed [4].

Knowledge of biomarkers of very early stages of cognitive deficiency can greatly improve therapeutic interventions able to delay the progression of the disease. Access to cerebrospinal fluid (CSF) is complex, excessively intrusive and has severe secondary effects, whereas peripheral blood offers a great number of possible biomarkers, although many of them are related to many other age-related diseases [5].

The combination of early detection strategies combining psychological determinations with low-intrusiveness and reduced-cost plasma biomarkers that announce the onset of cognitive decline is complex. This difficulty is largely attributable, in part, to the methodological and sampling heterogeneity of the studies, the intrinsic characteristics of individual biomarkers, technical variability in measurement methods, and their association with different stages of the disease [6]. Recently, Hampel et al. highlighted the importance of timely detection of biomarkers in blood in order to detect early events in Alzheimer's disease [7]. However, most of these biomarkers are based on proteins that have already started to accumulate in the central nervous system, and their detection in the bloodstream suggests that neuronal damage has already occurred, too late for preventive therapies [8]. In fact, blood tests are currently approved solely for patients exhibiting symptoms of Alzheimer's disease; however, these tests are not applicable to patients who are asymptomatic [9,10].

In previous studies, we have found that plasma levels of coenzyme Q_{10} (CoQ_{10}) and physical activity are associated with higher cognitive and executive capacity in elderly people [11,12]. Our results indicate that CoQ_{10} levels in plasma are more protective against cognitive dysfunction than physical activity [12]. High-quality education and improved diet, exercise, and social stimulation could help protect against symptoms of cognitive decline [13]. In agreement with our results, recently, the Rosenfeld group in Australia has demonstrated that short-term supplementation with ubiquinol, the reduced form of CoQ_{10}, can positively affect memory performance, probably by reducing oxidative stress [14].

To date, the effect of CoQ_{10} on cognitive capacity is not clear. A reduction in oxidative stress [14], an increase in blood flow [15], or improvement in mitochondrial activity in neurons have been proposed [16] as key factors affected by CoQ_{10} treatment in cognitive dysfunction. Blood–brain barrier (BBB) integrity is crucial for central nervous system homeostasis, tightly regulating the exchange of substances between blood and the brain and preventing the influx of potentially neurotoxic agents. In this context, inflammation, both systemic and central-nervous system-specific, disrupts BBB through the degradation of junctional proteins and immune cell infiltration, playing a key role in the pathogenesis of various neurological disorders, including the progression of neurodegenerative processes and cognitive impairment [17].

On the other hand, soluble P-selectin (P-sel) in plasma is stored in specialized secretory granules of endothelial cells [18], which can be released in high levels in endothelial damage [19]. In fact, high levels of P-sel have been proposed as predictors of adverse cardiovascular events [20] in patients with venous thrombosis [21].

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Plasma CoQ_{10} can directly interact with endothelial cells and protect them against oxidative stress, ferroptosis and mitochondrial dysfunction [22]. Further, it has been shown that in cardiovascular disease patients, CoQ_{10} supplementation reduces oxidative stress, decreases vascular stiffness, improves endothelial dysfunction, and increases NO levels for vasodilation [23]. Understanding the mechanisms underlying the protective effect of CoQ_{10} on the vascular endothelium, and particularly on BBB, could open the door to potential protective therapies against age-related neurodegeneration [24,25].

The aim of the present work was to determine which plasma markers associated with endothelial health and related to cognitive capacity and executive function are also linked to plasma CoQ_{10} levels and can be used as predictors of cognitive dysfunction together with the levels of plasma CoQ_{10}.

2. Materials and Methods

2.1. Participants

A cohort of 45 women volunteers aged 65–93 years (78.36 ± 8.41 years) from community centers of Seville, Spain, participated in the study, which was performed during 2021–2022. Participants showed common diseases associated with aging. The characteristics of the population are included in Table 1. In general, the population does not smoke, drinks alcohol moderately, and has a high BMI, and most of the participants received treatments mainly against hypertension, such as enalapril and valsartan, against inflammation, such as paracetamol or aspirin, as well as gut-protective compounds such as omeprazole. The exclusion criteria were a previous diagnosis of cognitive dysfunction and treatment with hypolipidemic compounds, including statins.

All participants were informed about the objective of the research and signed the informed consent to take part in the study. All procedures were approved by the Ethics Committee for Biomedical Research of the Andalusian Government (2355-N-19) and followed the guidelines of the International Conference of Good Clinical Practice in accordance with the 1975 Declaration of Helsinki guidelines.

Table 1. Sociodemographic characteristics of the population of study.

Parameter	Value
N	45
Age	78.36 ± 8.41
Smoking habits	
Never	78.7%
Before study	21.3%
During study	0.0%
Alcohol drinking habits	
Never	40.4%
Before study	2.5%
During study	51.1%
Pharmacological treatments	
Hypertension	42.0%
Diabetes	6.4%
Others	74.5%
Anatomical aspects	
Height	152.0 ± 6.6
Weight	73.1 ± 5.3
BMI	30.2 ± 4.5
Blood pressure	
Sistolic	134.8 ± 17.5

Diastolic	73.6 ± 9.0

2.2. Cognitive and Executive Capacity Determinations

The Mini-Mental State Examination (MMSE-30) [26] is a widely used screening test for cognitive dysfunction. It is composed of 30 items grouped into six categories: orientation, fixation, concentration and calculation, memory, language, and construction. The maximum score is 30 points. The cutoff point indicating the onset of cognitive dysfunction is 24. The reliability of the scale is high (α = 0.772).

The Frontal Assessment Battery (FAB-E) [27] is a screening test that measures executive function. This battery includes six cognitive tests: conceptualization, mental flexibility, programming, interference sensitivity, inhibitory control, and grasp control. Each test is scored from 0 to 3, with a maximum total score of 18 points; a higher score indicates higher executive function. The cutoff determining the presence of frontotemporal dementia (FTD) is 12. The reliability of the scale is high (α = 0.744).

2.3. Procedure

Data collection was carried out in the Community Centers attended by the older adults in three collection sessions spaced 1 week apart: the first session was dedicated to the collection of data on sociodemographic variables and health; the second session was dedicated to the evaluation of cognitive functioning; and the third session was dedicated to fasting blood collection. The data from the first two phases were collected by research personnel trained in the application of the different tests, and the blood samples were collected by a professional nurse.

2.4. Blood Collection and CoQ_{10} Determination

Blood was collected after overnight fasting (10 h) by venipuncture in Vacutainer tubes containing heparin or ethylenediaminetetraacetic acid (EDTA) as anticoagulants between 8 and 10 AM. The tubes were centrifuged at 3000× *g* at room temperature, and plasma was collected and transferred to several Eppendorf tubes to be stored at −80 °C until measurements were performed, as previously indicated [12,28].

Levels of CoQ_{10} in plasma were quantified using the protocol previously described [28]. One hundred pmol of CoQ_6 was used as an internal control to check recovery during the extraction. The CoQ_{10} content was determined as nmol/mL (μM).

2.5. Plasma Biomarkers Determinations

The analysis of metabolites in plasma was performed by an automated system in a professional clinical laboratory from whole blood samples obtained the same day as the extraction for plasma. The presence of plasmatic markers of neurodegeneration and endothelial function was determined in platelet-free human plasma using a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) following the commercial instructions of the respective manufacturers. The following specific ELISA kits were used: for human brain-derived neurotrophic factor (BDNF), Calbiotech/Biosensis (El Cajon, CA, USA) BEK-2211-1P-CE kit; for Human Glial Fibrillary Acidic Protein (GFAP), Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA) EEL079 kit; for human neurofilament light chain (NfL), Sandwich ELISA kit from Proteintech (Rosemont, IL, USA) KE00305; for P-selectin (P-sel), ELISA kit from Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA) BMS219-4; for Growth Differentiation Factor-15 (GDF-15), AssayGenie (Dublin, Ireland) ELISA kit HUFI00135; for p-Tau^{181}, the AssayGenie (Dublin, Ireland) ELISA kit HUFI03189; Syndecan 4 (SDC4) was determined by the AssayGenie (Dublin, Ireland) ELISA kit HUFI02840; and for Soluble Receptor for Advanced Glycation End-Products (sRAGE), the R&D systems (Madrid, Spain) Quiantiquine kit DRG00. Standard curves were generated

for each assay to calculate the concentration values of each marker, as indicated by the manufacturer.

2.6. Exosome Purification and Analysis

To isolate exosomes from human plasma, 200 µL of plasma was centrifuged at 2000× *g* for 30 min at 4 °C to remove debris. One hundred µL of the supernatant was mixed with 0.5 volumes of 1X PBS, then 0.2 volumes of total exosome precipitation reagent (Thermo Fisher Scientific, Waltham, MA, USA) were added to the sample. The solution was mixed until it had a cloudy appearance, incubated for 10 min, and centrifuged at 10,000× *g* for 5 min at room temperature. Finally, the pellet of exosomes was resuspended in 1X PBS for analysis.

The Wizard Genomic DNA Purification kit (Promega, Madison, WI, USA) was used to extract total exosome DNA. Firstly, 300 µL of Nuclei Lysis Solution, 33.3 µL Protein Precipitation Solution, and exosome suspension in 100 µL PBS were mixed. The mixture was centrifuged at 14,000× *g*, and the supernatant was transferred to a new tube containing 100 µL of isopropanol and centrifuged again at 14,000× *g* for 1 min to collect DNA. The supernatant was discarded, and 100 µL of ethanol was added to purify the DNA and centrifuged as before. The pellet was dried and finally rehydrated with 150 µL of DNA Rehydration Solution and incubated at 4 °C overnight. DNA concentrations were measured on a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) before storage at −20 °C.

To determine the number of copies of mitochondrial DNA (mtDNA) in isolated DNA, TaqMan qPCR was performed for each sample. We determined a nuclear gene, APP (Amyloid Precursor Protein) (probe: Hs02339796_cn, Applied Biosystems) (Thermo Fisher Scientific, Waltham, MA, USA), and a mitochondrial gene, COI (cytochrome oxidase 1) (probe: Hs02596864_g1, Applied Biosystems), in duplicate with a negative control using the Mix qPCR TaqMan® Gene Expression Master Mix (Applied Biosystems). The 20 µL qPCR system contained 10 µL Mix qPCR, 1 µL probe APP or COI, 5 µL DNase/RNase-Free ddH2O, and 4 µL DNA solution (5ng/µL). The qPCR program was run as follows: hold at 50 °C for 2 min (AmpErase® UNG Activation, Thermo Fisher, Waltham, MA, USA) and 95 °C for 10 min (AmpliTaq Gold® DNA Polymerase Activation, Thermo Fisher, Waltham, MA, USA), followed by 40 cycles of 95 ◦C for 15 s (Melt) and 60 °C for 60 s (Anneal/Extend) on a Mastercycler Gradient (Vaudaux-Eppendorf, Schönenbuch, Switzerland).

To determine the mtDNA copy number in relation to nuclear DNA, we used the following equations:

$$\Delta C_T = (nucDNA\ C_T - mtDNA\ C_T),$$

$$\text{mtDNA copy number} = 2^{\Delta C_T}$$

To determine the relative amount of exosomes in plasma, we used the specific marker CD63. We mixed 7 µL of human plasma, 1 µL of Dithiothreitol (DTT) 1M, and 2 µL of 5X Loading buffer (LB). A Bio-Dot® Microfiltration Apparatus (Bio-Rad, Hercules, CA, USA) was used to charge the nitrocellulose membrane, 3 µL per well. Then, the membrane was submerged in the Blocking buffer (5% *w*/*v* nonfat dry milk, 1X TBS, 0.5% Tween-20) for 1 h and washed three times with TTBS (1X TBS, 0.5% Tween-20) for 10 min each. After that, the membrane was incubated with the monoclonal antibody CD63 (Thermo Fisher Scientific, Waltham, MA, USA) at a 1:250 dilution overnight at 4 °C under agitation. The next day, the membrane was washed three times with TTBS for 10 min each and incubated with anti-mouse secondary antibody 1:1000 for 1 h. Consequently, the membrane was washed two times with TTBS for 10 min and two times with 1X TBS for 10 min. Finally,

the membrane was incubated with the Immobilon Crescendo Western HRP substrate (Merck-Millipore, Darmstadt, Germany) for 3 min, and the bands were visualized and quantified with ChemidocTM (Bio-Rad, Hercules, CA, USA).

2.7. Statistics

We compared the biochemical parameters, cognitive capacity and executive function of the participants. Pearson's correlation test was used to explore relationships between variables. For all analyses, relationships between variables were considered significantly different if the p value was less than 0.05 using 2-tailed tests. ROC curves and data were analyzed using GraphPad Prism 8.0.2 software.

3. Results

A total of 45 women participated in this study. The mean age of the participants was 78.36 ± 8.41. Their biochemical parameters are described in Table 2.

Table 2. Biochemical characteristics of plasma samples of the population of the study.

Parameter	Value
N	45
Age	78.36 ± 8.41
Glucose (mg/dL)	110.7 ± 29.27
Uric acid (mg/dL)	5.57 ± 1.74
Urea (mg/dL)	36.61 ± 13.68
Creatinine (mg/dL)	1.09 ± 0.23
Bilirrubin (mg/dL)	0.78 ± 0.19
GGT (U/L)	14.48 ± 15.37
GOT (U/L)	22.66 ± 5.97
GPT (U/L)	14.57 ± 4.84
Creatine kinase (CK) (U/L)	63.42 ± 29.71
Cholesterol (mg/dL)	196.0 ± 43.1
Chol HDL (mg/dL)	49.55 ± 12.78
Chol LDL (mg/dL)	126.5 ± 41.2
Chol VLDL (mg/dL)	19.97 ± 6.44
Chol no-HDL (mg/dL)	146.5 ± 42.0
Triglycerides (mg/dL)	99.86 ± 32.19
CoQ_{10} (nmol/mL)	0.806 ± 0.236
CoQ_{10}/Chol (nmol/mmol)	160.4 ± 42.9
CoQ_{10}/Chol HDL (nmol/mmol)	672.3 ± 289.4
CoQ_{10}/Chol LDL (nmol/mmol)	262.3 ± 90.0
CoQ_{10}/Chol VLDL (nmol/mmol)	1668 ± 624
CoQ_{10}/Chol no-HDL (nmol/mmol)	220.4 ± 65.6
CD64 (AU/7 µL plasma)	265.8 ± 244.8
Exosome DNA (ng/100 µL plasma)	1371 ± 780
Exosome mtDNA (copy number/100 µL plasma)	14,121 ± 82,702
GFAP (pg/mL)	302.6 ± 220.5
NfL (pg/mL)	15.25 ± 23.35
P-Tau^{181} (pg/mL)	76.04 ± 26.49
GDF-15 (pg/mL)	1176 ± 322
BDNF (pg/mL)	5559 ± 3929
SDC4 (ng/mL)	25.36 ± 7.20
sRAGE (pg/mL)	1126 ± 468
P-sel (ng/mL)	45.78 ± 27.69

The relationship between plasma parameters and cognitive capacity and executive function measured by the MMSE-30 and FAB-E tests respectively demonstrated a high and positive correlation with CoQ_{10} levels (r = 0.359, p = 0.011) and a high and negative correlation with soluble P-sel levels in plasma (r = −0.470, p = 0.007). Further, MMSE-30 score also showed a positive and significant relationship with the amount of DNA in exosomes (r = 0.377, p = 0.017). Interestingly, DNA amount also showed a similar correlation with CoQ_{10} levels in plasma (r= 388, p = 0.013) (Table 3).

None of the other parameters showed a significant relationship with MMSE-30 or FAB-E, although BDNF levels did show a near-significant negative correlation with MMSE-30 score (r = −0.277, p = 0.072). Altogether, these results indicate that high MMSE-30 and FAB-E scores are found in participants showing high CoQ_{10} and low P-sel plasma levels, with exosomes showing high DNA content and, in the case of MMSE-30, probably low levels of BDNF in plasma.

In the case of the relationships between other parameters, high mtDNA levels in exosomes strongly correlated with high SDC4 levels in plasma, probably indicating a positive relationship between mitochondrial damage and endothelial damage. On the other hand, BDNF levels in plasma positively correlated with SDC4 and negatively with sRAGE, depicting a complex relationship between BDNF and endothelial damage markers. Further, p-Tau^{181}, a known biomarker of neurodegeneration, showed a stronger positive relationship with BDNF and SDC4 and a negative relationship with sRAGE, probably indicating a synchronized shift in neurotrophic and inflammatory regulation during neurodegeneration (Table 3). Interestingly. GDF-15, a marker of mitochondrial dysfunction, showed a near-significant correlation with CoQ_{10} levels (r = 0.326, p = 0.074). This probably indicates that high levels of CoQ_{10} in plasma probably protect cells against mitochondrial dysfunction.

To further study the relationship of the parameters that showed some significant relationship with CoQ_{10} levels, we performed correlations of MMSE-30 and FAB-E scores together with DNA amount in exosomes, and GDF-15, BDNF, and P-sel levels in plasma with the amount of CoQ_{10} in relation to cholesterol levels. This correlation is interesting since CoQ_{10} is vehiculated in plasma, associated with lipoproteins and mainly with VLDL and LDL lipoproteins (Table 4). FAB-E total score correlated more strongly with CoQ_{10}/Chol, CoQ_{10}/Chol LDL, CoQ10/Chol VLDL, and CoQ_{10}/Chol non-HDL than MMSE-30, which only significantly correlated with CoQ_{10}/Chol and CoQ10/Chol VLDL. This agrees with our previous study that showed a higher correlation with executive function than with cognitive capacity [12].

Exosome DNA only correlated with total CoQ_{10} but not with any of the ratios of CoQ_{10} with cholesterol. The same occurs with BDNF, whose correlation with CoQ_{10} associated with cholesterol was worse than with total CoQ_{10}. On the other hand, GDF-15 showed a near-significant negative correlation with total CoQ_{10}, and this correlation was stronger and significant when correlated with CoQ_{10}/Chol, CoQ_{10}/Chol LDL, and CoQ_{10}/Chol non-HDL. In the case of P-sel, it was only moderately correlated with CoQ_{10}/Chol LDL and CoQ_{10}/Chol non-HDL (Table 4). These results can indicate that the uptake of lipoproteins charged with CoQ_{10} by endothelial cells and tissues is the factor that prevents mitochondrial dysfunction (as indicated by GDF-15) and endothelial damage or platelet activation (P-sel).

Table 3. Pearson's correlation between the different parameters determined in this study. Upper part: Pearson's r; lower part: significance. Significant correlations are indicated in orange ($p < 0.05$); light orange indicates correlations near significance ($p < 0.10$).

	CoQ_{10}	MMSE-30	FAB-E	CD64	DNA	mtDNA	GFAP	NfL	p-Tau_{181}	GDF-15	BDNF	SDC4	sRAGE	P-sel
CoQ_{10}		0.359	0.485	−0.122	0.388	−0.172	0.076	0.203	0.045	−0.326	−0.255	−0.041	−0.166	−0.233
MMSE-30	0.016		0.596	−0.176	0.374	0.101	−0.181	0.111	0.272	−0.153	−0.277	0.090	−0.083	−0.470
FAB-E	0.001	0.000		−0.248	0.135	0.074	−0.115	0.174	0.236	−0.101	−0.183	0.243	0.011	−0.415
CD64	0.460	0.285	0.128		−0.229	−0.124	−0.080	−0.031	−0.199	−0.048	0.101	−0.150	−0.095	−0.109
DNA	0.013	0.017	0.480	0.160		−0.221	0.110	0.108	0.053	−0.099	−0.291	−0.227	−0.021	−0.263
mtDNA	0.289	0.534	0.650	0.452	0.171		−0.003	−0.082	0.038	−0.093	0.048	0.544	0.066	0.040
GFAP	0.641	0.265	0.427	0.633	0.513	0.985		0.029	0.231	−0.044	0.306	0.127	−0.199	0.202
NfL	0.216	0.449	0.289	0.854	0.519	0.625	0.862		−0.002	−0.175	−0.207	−0.108	−0.232	−0.027
p-Tau_{181}	0.810	0.138	0.201	0.310	0.785	0.844	0.238	0.993		0.039	0.447	0.391	−0.475	−0.187
GDF-15	0.074	0.410	0.568	0.810	0.610	0.630	0.824	0.383	0.837		0.173	−0.169	0.185	0.090
BDNF	0.089	0.072	0.241	0.544	0.072	0.774	0.055	0.212	0.008	0.361		0.382	−0.371	0.303
SDC4	0.827	0.629	0.187	0.447	0.237	0.002	0.518	0.595	0.030	0.367	0.037		−0.224	−0.054
sRAGE	0.341	0.658	0.953	0.630	0.915	0.735	0.309	0.245	0.007	0.318	0.043	0.187		0.086
P-sel	0.266	0.007	0.008	0.559	0.154	0.830	0.275	0.881	0.394	0.682	0.098	0.807	0.694	

Table 4. Correlations between MMSE-30 and FAB-E scores, exosome DNA, GDF-15, BDNF, and P-sel in plasma with total CoQ_{10} and its relationship with cholesterol.

	MMSE-30		FAB-E		Exosome DNA (ng)		GDF-15 (pg/mL)		BDNF (pg/mL)		P-sel (ng/mL)	
Parameter	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
CoQ_{10} (nmol/L)	0.359	0.016	0.485	0.001	0.388	0.013	−0.236	0.074	−0.255	0.089	−0.233	0.266
CoQ_{10}/Chol (nmol/mmol)	0.308	0.039	0.425	0.004	0.265	0.098	−0.473	0.007	−0.215	0.167	−0.294	0.103
CoQ_{10}/Chol HDL (nmol/mmol)	0.191	0.208	0.260	0.084	0.421	0.070	−0.299	0.102	−0.229	0.140	0.020	0.915
CoQ_{10}/Chol LDL (nmol/mmol)	0.252	0.095	0.331	0.026	0.107	0.515	−0.400	0.026	−0.121	0.438	−0.362	0.042
CoQ_{10}/Chol VLDL (nmol/mmol)	0.283	0.050	0.327	0.029	0.113	0.489	−0.327	0.072	−0.116	0.458	−0.301	0.094
CoQ_{10}/Chol no-HDL (nmol/mmol)	0.271	0.071	0.384	0.009	0.089	0.584	−0.466	0.008	−0.138	0.374	−0.415	0.018

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Plasma biomarkers were also studied in relation to the different dimensions of the MMSE-30 (Table 5) and FAB-E (Table 6) tests. In the case of the MMSE-30 test, CoQ_{10} correlated with the total score and essentially with orientation and near attention tests, without correlating with the other dimensions. Language was the test that showed lower correlation. DNA amount in exosomes correlated mainly with language. P-sel strongly correlated with orientation and attention and did not show significant correlation with the other dimensions, probably indicating a different incidence of vascular damage on central nervous system physiology. Interestingly, the amount of exosomes determined by CD64 levels correlated with registration but with no other dimensions (Table 5).

In the case of the FAB-E test, CoQ_{10} positively correlated with lexical fluency, motor series, conflicting instructions, and Go-no-go sections, and P-sel negatively correlated with similarities, motor series, and Go-no-go sections. CD64 levels only significantly and negatively correlated with conflicting instructions and DNA levels in these exosomes, and negatively with prehension behavior. BDNF levels only showed a positive and significant correlation in the Go-no-go test.All these results indicate that plasma CoQ_{10} levels positively correlate with all the dimensions of the FAB-E test except prehension behavior, whereas P-sel shows a negative relationship in most of them (Table 6).

To check the predictive value of CoQ_{10}, P-sel and DNA amount in exosomes for cognitive dysfunction and executive capacity, we used ROC curves (Figure 1). The results indicate that participants showing scores below the cutoffs of the MMSE and FAB-B tests, namely, at "risk" of cognitive decline or executive dysfunction, show significantly lower levels of CoQ_{10} in plasma. In the case of DNA amount in exosomes, a significantly higher amount is associated with maintenance of cognitive capacity in the MMSE-30 test (Figure 1A). However, in the case of P-sel, participants at "risk" for both cognitive dysfunction and executive incapacity showed significantly higher levels in plasma in comparison with the "no-risk" group.

These relationships suggest that CoQ_{10} and P-sel levels possess significant predictive power as biomarkers for early cognitive dysfunction across both neuropsychological assessments. This was confirmed by the ROC curves for the MMSE-30 and FAB-E tests. Only DNA levels in exosomes can be considered predictive in MMSE-30 tests, suggesting that its utility as a biomarker may be limited to specific types of cognitive decline (Figure 1B).

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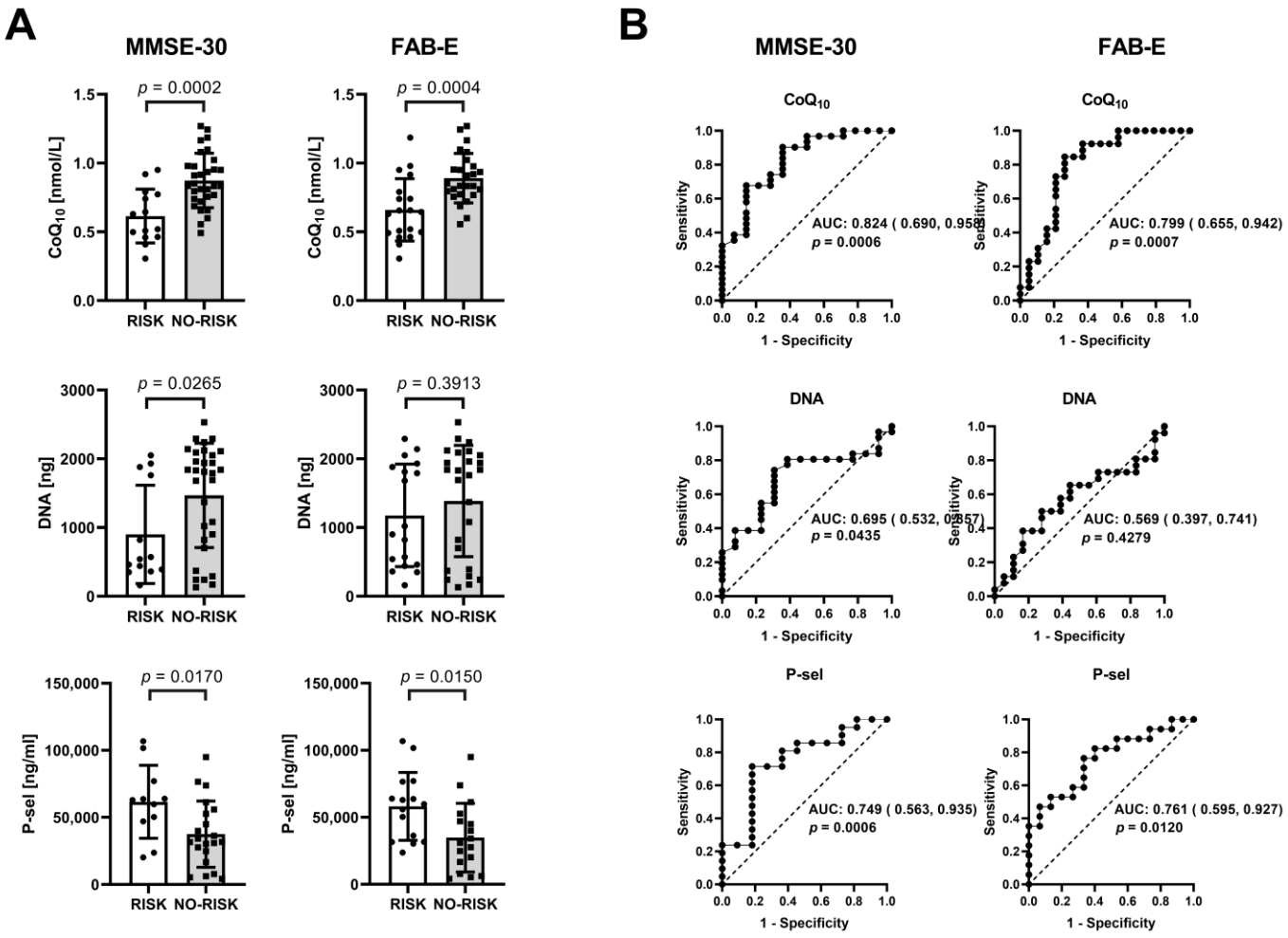


Figure 1. (**A**) Levels of CoQ_{10}, DNA in exosomes, and P-sel in reference to participants at risk or at no-risk of cognitive or executive dysfunction according to the cutoff score. Risk participants were considered below the indicated cutoff for cognitive dysfunction (score 24) for MMSE-30 and for frontotemporal dementia (score 12) for FAB-E. (**B**) ROC curves of CoQ_{10}, DNA in exosomes, and P-sel in cognitive and executive dysfunction. AUC and *p* are indicated in each figure.

Table 5. Relationship of plasma biomarkers with the total and different characteristics measured in the MMSE-30 test for cognitive dysfunction.

	TOTAL MMSE MAX 30		ORIENTATION MAX 10		REGISTRATION MAX 3		ATTENTION MAX 5		RECALL MAX 3		LANGUAGE MAX 9	
Biomarker	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
CoQ_{10}	0.359	0.016	0.326	0.029	0.224	0.139	0.282	0.067	0.248	0.101	0.084	0.581
CD64	−0.176	0.285	−0.039	0.814	−0.417	0.008	−0.181	0.276	−0.112	0.498	−0.120	0.460
DNA	0.374	0.017	0.241	0.135	−0.144	0.482	0.394	0.013	−0.059	0.718	0.535	0.000
mtDNA	0.101	0.534	0.064	0.694	0.028	0.866	0.100	0.554	0.198	0.222	−0.061	0.708
GFAP	−0.181	0.265	−0.120	0.461	0.075	0.647	−0.153	0.351	−0.318	0.046	0.037	0.820
NfL	0.111	0.499	0.165	0.316	−0.206	0.209	0.035	0.836	−0.079	0.633	0.197	0.230
p-Tau_{181}	0.272	0.138	0.261	0.157	0.132	0.479	0.442	0.016	−0.030	0.874	0.180	0.332
GDF-15	−0.153	0.410	−0.256	0.104	−0.057	0.761	−0.064	0.741	−0.132	0.478	−0.061	0.744
BDNF	−0.277	0.072	−0.287	0.062	−0.100	0.522	−0.196	0.220	−0.136	0.386	−0.161	0.301
SDC4	0.090	0.629	0.086	0.695	0.133	0.476	0.115	0.551	−0.021	0.910	−0.121	0.517
sRAGE	−0.083	0.658	−0.066	0.722	−0.028	0.883	−0.369	0.049	0.264	0.151	−0.075	0.687
P-sel	−0.470	0.007	−0.494	0.004	−0.113	0.538	−0.474	0.007	−0.160	0.387	−0.148	0.418

Table 6. Relationship of plasma biomarkers with the total and different characteristics measured in the FAB-E test for executive function. SIM: similarities; L FLU: lexical fluency; M SER: motor series; C INS: conflicting instructions; Go: Go-no-go; P BEH: prehension behavior.

	TOTAL FAB-E MAX 18		SIM MAX 3		L FLU MAX 3		M SER MAX 3		C INS MAX 3		GO MAX 3		P BEH MAX 3	
Biomarker	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
CoQ_{10}	0.485	0.001	0.236	0.118	0.348	0.019	0.346	0.020	0.478	0.001	0.477	0.001	−0.210	0.165
CD64	−0.248	0.128	−0.190	0.248	−0.234	0.151	−0.074	0.653	−0.353	0.028	−0.061	0.710	0.049	0.765
DNA	0.135	0.408	0.153	0.346	0.093	0.566	−0.025	0.880	0.286	0.093	0.206	0.201	−0.352	0.026
mtDNA	0.074	0.650	0.178	0.272	0.186	0.249	−0.187	0.247	0.104	0.524	−0.093	0.570	0.080	0.625
GFAP	−0.115	0.479	−0.076	0.641	0.033	0.840	−0.196	0.225	0.039	0.812	−0.032	0.847	−0.272	0.089
NfL	0.174	0.289	0.238	0.145	0.307	0.058	0.110	0.504	0.093	0.574	0.138	0.403	−0.329	0.041
p-Tau_{181}	0.236	0.201	0.223	0.229	0.318	0.081	0.177	0.341	0.088	0.639	−0.045	0.812	0.025	0.886
GDF-15	−0.101	0.588	−0.063	0.737	0.127	0.496	−0.309	0.091	−0.084	0.652	−0.167	0.370	0.141	0.448
BDNF	−0.183	0.241	−0.119	0.447	−0.085	0.590	−0.253	0.102	−0.072	0.649	0.303	0.048	−0.214	0.168
SDC4	0.243	0.187	0.220	0.233	0.138	0.460	0.171	0.357	0.071	0.705	0.020	0.915	0.257	0.162
sRAGE	0.011	0.953	−0.099	0.597	−0.232	0.210	−0.021	0.911	0.117	0.503	0.237	0.206	0.046	0.806
P-sel	−0.415	0.018	−0.378	0.033	0.119	0.516	−0.377	0.033	−0.223	0.220	−0.437	0.012	0.049	0.789

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4. Discussion

Our results indicate that high levels of CoQ_{10} in plasma, low levels of P-sel, and a high amount of DNA in exosomes from 100 μL of plasma are associated with better cognitive performance in elderly women. The relationship between CoQ_{10} in plasma and cognitive and executive capacities in elderly people has already been shown [11,13], and the positive effect of supplementation with the reduced form of CoQ_{10} has been recently proposed [14,15]. Here we propose that high levels of CoQ_{10} in plasma can prevent endothelial damage, reducing the possibility of neuroinflammation as a main factor in neurodegeneration [17]. Interestingly, plasma levels of CoQ_{10} were related to the amount of DNA in exosomes. In our study, the number of endosomes measured by the level of CD64 did not increase, nor was it associated with cognitive dysfunction. Thus, the amount of exosomes was not a factor, but the DNA content within them was. It has been proposed that exosomes contribute to the maintenance of cellular homeostasis by releasing damaged DNA from cells and preventing the activation of innate immune responses [29,30]. The release of exosomes loaded with DNA has been associated with cell survival rather than cell death [30]. Other authors have indicated that these exosomes correlated with the percent of cells in the G1 phase, indicating an active release of DNA via these extracellular vesicles [31]. Thus, high DNA in exosomes would indicate a higher capacity to release harmful DNA from tissues, including endothelium and a lower inflammatory response. In agreement with this, our results would indicate that high levels of CoQ_{10} in plasma would correlate with a healthier endothelium, including the blood–brain barrier, which maintains a higher capacity to release harmful DNA from cells.

In a rat model of Alzheimer's disease, exosomes obtained from adipose-derived stem cells, loaded with CoQ10, improved cognition and delayed memory deficiency [32].

The amount of DNA in exosomes also correlated with P-sel, but negatively (−0.408; $p = 0.007$), whereas, in the same cohort, the endothelial damage marker P-sel positively correlated with CK levels (0.403; $p = 0.001$), the risk of cardiovascular disease (0.309, $p = 0.044$) and negatively with CoQ_{10}/LDL (−0.295, $p = 0.05$). Elevated P-sel levels reflect enhanced platelet activation and promote a prothrombotic environment, while also contributing to inflammatory processes involved in atherosclerotic progression [33]. Thus, our results could indicate that high CoQ_{10} levels are associated with less endothelial dysfunction, as indicated by DNA release by exosomes and plasma P-sel levels [34].

To our knowledge, very few articles have related the levels of CoQ_{10} with P-sel. In a study performed with obese baboons, neither α-tocopherol nor CoQ_{10} supplementation significantly altered P-sel levels [35]. However, in humans, the combination of CoQ_{10} with selenium decreased the levels of P-sel in serum in elderly individuals [36]. A mitochondrial-targeted CoQ_{10}-related molecule, MitoQ, decreased expression of P-sel, platelet adhesion and spreading on a collagen surface and, at the same time, inhibited platelet aggregation induced by different inducers, including collagen and phorbol 12-myristate 13-acetate (PMA), indicating a role of mitochondrial ROS protection in the prevention of platelet induction [37]. In fact, supplementation with ubiquinol restores mitochondrial capacity in platelets affected by COVID-19, improving their activity [38].

P-sel positively correlated with BDNF (0.380; $p = 0.013$), probably indicating that greater endothelial damage permits a higher release of BDNF to the blood from the central nervous system. In agreement with this, high release of P-sel due to platelet activation has been associated with an increase in BDNF in plasma, although this increase has been considered a protective response against cognitive dysfunction [33]. On the other hand, plasma BDNF has been associated with age-related white matter atrophy but not with cognitive function in non-demented adults [39].

In our cohort, the near-significant negative correlation of BDNF with CoQ_{10} plasma levels points to a protective effect of CoQ_{10}. In agreement with the relationship of CoQ_{10}

and endothelial health, DNA in exosomes also strongly negatively correlated with BDNF levels (r = −0.426, p = 0.001), indicating a relationship between high CoQ_{10} levels, high release of DNA in exosomes, and low BDNF levels.

Another significant biomarker was GDF-15, considered a biomarker of mitochondrial dysfunction during aging [40]. Although no significant relationship was found between GDF-15 and MMSE-30 or FAB-E, we did find a near-significant negative relationship with total CoQ_{10} levels in plasma (r = −0.326, p = 0.074) and a strong significant and negative correlation with CoQ_{10}/Chol levels (r = −0.473, p = 0.007) and with CoQ_{10}/Chol non-HDL levels (r = −0.466, p = 0.008) indicating that high levels of CoQ_{10} in plasma lipoproteins prevent the release of GDF-15, probably by preventing mitochondrial dysfunction.

GDF-15 has recently been proposed as a proxy for epigenetic aging due to the strong positive correlation between GDF-15 and DNAm Grim AGE, DNAm Pheno Age, Hannyn and Zhang clocks, and frailty in elderly people [41,42]. It has also been linked to markers of impaired glycemic control, systemic inflammation, and physical decline, all of which are associated with aging [42]. In fact, GDF-15 is considered the most elevated circulating protein in aging [43,44] and age-related functional decline [42]. In agreement with our results, supplementation with CoQ_{10} and its incorporation into lipoproteins correlates with a reduction in GDF-15 and other cardiovascular disease biomarkers [45]. This indicates that high levels of CoQ10 in plasma are indicative of healthier mitochondrial function.

Our results also show a relationship between the levels of the marker of cognitive deterioration, p-Tau^{181}, with BDNF and SDC4 (positive) and with sRAGE (negative). SDC4 is a marker of endothelial inflammation, and its increase has been associated with systemic inflammation in pathological aging [46]. Interestingly, in our cohort, a strong positive and significant relationship was found between SDC4 and mtDNA in exosomes, probably indicating their relationship with mitochondrial dysfunction in the vascular endothelium.

On the other hand, sRAGE levels are considered protective against inflammation caused by AGEs. Further, sRAGE levels have been considered relevant biomarkers of cognitive impairment in patients suffering from alcohol disorders [47]. Its negative relationship with pTau^{181} levels indicates that lower protection can be associated with a higher release of neurodegenerative markers to the blood.

In general, our results indicate that in elderly women, high levels of CoQ_{10} may protect endothelial function by maintaining a higher release of damaged DNA through exosomes and preventing P-sel release. All these factors have demonstrated their predictive capacity for early cognitive dysfunction and a decrease in executive capacity as indicated by the ROC curves.

5. Limits

Our study was performed only on women older than 65 years. The lack of response from men to our call—only 16 men participated at the beginning of the study—did not permit us to compare the results between genders, and it forced us to discard the data for the men for the final analysis. However, we have seen some differences, and the literature has already shown some of them. In the case of NfL, its levels increase with age but more in men than in women [48]. In that study, only in men, NfL levels negatively correlated with normal walking speed (r = −0.460, p = 0.041) and grip strength (r = −0.535, p = 0.015), and positively with the chair stand test (r = 0.478, p = 0.033), indicating that the increase in NfL levels was accompanied by a decrease in physical capacity. However, the low number of male participants did not permit us to reach conclusions. We consider that differences between genders are important and must be considered for future analysis. Further studies are needed to determine if the protective effect of CoQ_{10} is similar in men and women.

Furthermore, the cohort used in the study has a high BMI that could be considered a bias, but in the Spanish women population, our mean BMI, 30.2 ± 4.5, falls into the BMI of women older than 65 years, 29.1, as was published by Gutierrez-Fisac in 2012 [49].

6. Conclusions

Finding molecular biomarkers able to indicate earlier phases of endothelial damage or inflammatory processes that can end in neurodegeneration is essential to design and prescribe preventive therapies to delay the onset of symptoms and the progression of cognitive dysfunction. Considering the positive relationship of CoQ_{10} with cognitive function and executive capacity [12,13] and its important role in the maintenance of endothelial function [23], we show here that low CoQ_{10} and high P-sel levels in plasma, together with low DNA content in exosomes, can be good markers of the risk of entering cognitive dysfunction prior to the appearance of typical markers such as amyloid protein, NfL, or p-Tau. We already know that lifestyle changes such as a healthier diet and more dynamic social and physical activities are more effective when adopted before the appearance of advanced symptoms [13]. These plasma factors can help to adapt preventive therapies to lifestyle in elderly women against cognitive dysfunction.

Our results agree with the recommendations of other authors that suggest that supplementation with ubiquinol, the reduced form of CoQ_{10}, can be recommended as a complement to conventional treatments for patients with mild cognitive impairment [14,50]. They suggested that reaching 2 or 2.2 μg/mL (approximately 2.3 to 2.5 μmol/L), more than double the mean level in the population, can be enough to protect against neurodegeneration. We propose here that an increase in CoQ_{10} in plasma would reduce endothelial damage, inflammatory processes, and the imbalance between protective and inflammatory factors, thereby impeding the onset or increase of neuroinflammatory processes in the central nervous system.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee for Biomedical Research of the Andalusian Government (protocol code 2355-N-19 approved 8 May 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: To protect clinical information from participants, in accordance with the rules approved by the Ethics Committee for Biomedical Research of the Andalusian Government, experimental data generated in this study are available from the corresponding author only upon reasonable request.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CoQ_{10}	Coenzyme Q_{10}
CSF	Cerebro-spinal fluid
FAB-E	Frontal Assessment Battery
FTD	Frontotemporal dementia
GDF-15	Growth Differentiation Factor-15
GFAP	Human Glial Fibrillary Acidic Protein
MMSE-30	Mini-Mental State Examination -30
NfL	Neurofilament light chain
P-sel	P-selectin
SDC4	Syndecan 4
sRAGE	Soluble Receptor for Advanced Glycation End-Products

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