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ORIGINAL PAPER

Determination of soluble tumor necrosis factor receptor II and secretory immunoglobulin A in saliva of patients with dementia

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Abstract

The prevalence of pain and dementia increases with age, affecting a significant percentage of the population due to aging. Both pathologies are connected through the inflammatory process, specifically through the tumor necrosis factor. The effect of this cytokine is mediated through the modulation of its TNFRI and TNFRII receptors, which are linked to the dementia process. In addition, immunoglobulins such as secretory immunoglobulin A (sIgA) have been recognized as one of the main biomarkers of pain in saliva. sTNFRII and sIgA levels were determined in saliva samples by ELISA from healthy people and patients with dementia in GDS stages 5–7. The concentrations of these markers were also correlated with the GDS stage and sex. We observed a significant decrease (*** $p \leq 0.001$) in the levels of sTNFRII (pg/mL) and a significant increase (** $p \leq 0.01$) in the levels of sIgA (ng/mL) in the saliva of patients with dementia compared to the healthy control group. We did not observe a correlation with the data of the biomarkers regarding the GDS stage and sex. The results obtained for sTNFRII are consistent with those obtained by other authors on brain tissue, who conclude that unopposed neuronal TNFRI signaling, when TNFRII is selectively downregulated, leads to a more severe course of AD pathogenesis. Regarding sIgA, the elevated values of sIgA may reflect the immune status of these patients. Therefore, these biomarkers can provide us with relevant information through a non-invasive method such as saliva analysis.

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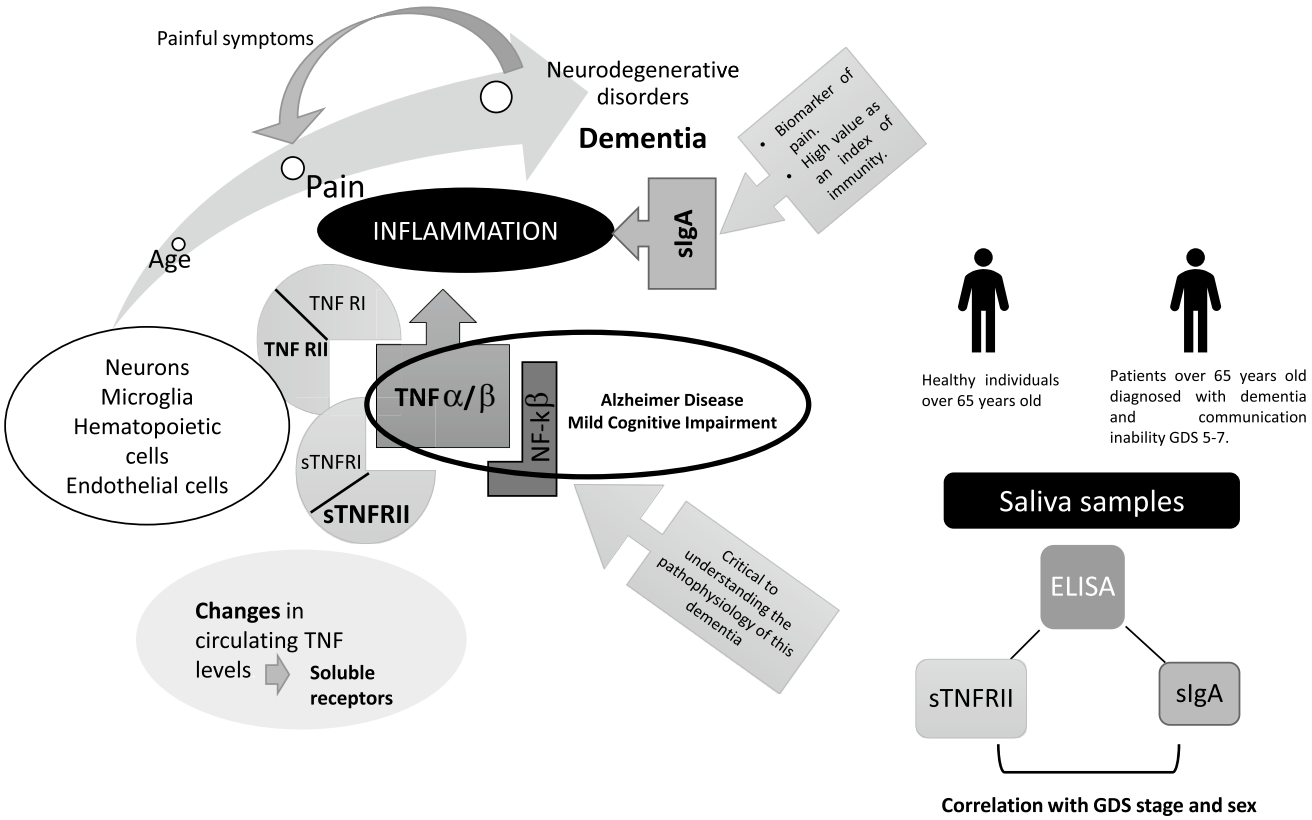
Graphical abstract



Keywords Dementia · Alzheimer disease · Pain · STNFRII · sIgA · Inflammation

Introduction

The origin of pain in neurodegenerative diseases is multifactorial, whether it is nociceptive or neuropathic, with both occurring in some cases. The prevalence of pain and dementia increases with age [17] In fact, around 38 to 75% of patients with Alzheimer's disease (AD), the most common form of dementia, show painful symptoms in addition to other clinical disorders [15, 16].

The activation of pain mechanisms is mediated by the modification of levels of inflammatory cytokines, chemokines, and microglial activation responsible for neuroinflammation [33]. One of the main cytokines affected in the inflammatory response is tumor necrosis factor (TNF), even in neurodegenerative diseases such as AD [19, 30, 41]. Tumor necrosis factor is part of a complex system for which two variants, called TNFα and TNFβ, have been described that exert their effects via binding to cell surface receptors, TNFRI and TNFRII. Both receptor types exhibit high affinity binding for both TNFα and TNFβ. The two receptor types are immunologically different, yet their extracellular domains exhibit similarities in the pattern of cysteine residue placements in four domains [18]. Soluble TNF receptors I and II (sTNFRI and sTNFRII) are released by proteolytic cleavage of the extracellular domains of these receptors where it binds to circulating TNF and functions to attenuate TNF-mediated inflammation [42, 46].

Soluble receptors for TNF are released in response to changes in circulating TNF levels and can stabilize the activity of TNF by gradually binding and releasing the cytokine, thereby regulating its bioavailability. Therefore, soluble TNF receptors are considered more reliable markers of TNF activity than TNF itself [3].

In this context, TNFα has been proposed to play a role in the pathophysiological process of AD through its signaling [5, 28, 41]. In this signaling process, it is important to consider the dynamics of TNF levels and its soluble receptors sTNFRI and sTNRII, and as these markers can inform about the levels and chronicity of the immune response in patients with frontotemporal dementia [48].

The signaling function of TNF occurs through the transmembrane receptors, which are expressed and regulated differently. TNFRI is constitutively expressed in most tissues, while the expression of TNFRII is induced and restricted to

specific cell populations, such as hematopoietic cells, microglia, neurons, and endothelial cells [4, 49]. In the signaling process mediated by TNF, the nuclear factor kappa β (NF-β) also participates. Both have been associated with AD and mild cognitive impairment [27, 31, 35, 49], suggesting a possible relationship with the neurodegenerative process. In fact, the temporal expression of TNF and NF-κβ in AD could be critical to understanding the pathophysiology of this dementia and improving the development of therapeutic strategies, both for the pathological process, [35, 39] and for addressing pain in these patients.

In this context, NF-κβ has been involved in regulating proinflammatory mediators implicated in pain [26, 50, 51]. Thus, TNFα and its soluble receptors [7, 25, 50] can directly influence pain or interact with other inflammatory mediators that are part of NF-κB-mediated pain processes [26, 29, 45].

Recently, secretory immunoglobulin A (sIgA) has been recognized as one of the main biomarkers of pain present in saliva [44], as it is released in response to pain and emotional stress. sIgA is considered an antibody present in various external secretions, such as saliva, tears, milk, and intestinal mucosa, with unique structural and functional characteristics that are not observed in other classes of antibodies [23, 34, 47]. Although the classical function of sIgA is considered to be the elimination of pathogens through immune exclusion, it also participates in specific immunity provoked by pathogens [12]. For this reason, it is considered one of the most relevant proteins present on the mucosal surface and has a high value as an index of immunity. However, it has also been shown that sIgA plays an important role in the inflammatory process, being involved in the proinflammatory activation of intestinal epithelial cells [20].

In this regard, results from our laboratory regarding the levels of sIgA in saliva in patients with dementia and communication incapacity showed a positive correlation with the data obtained from the pain assessment in advanced dementia (PAINAD) scale, which is an observational pain scale validated by our group. The PAINAD scale assesses pain in patients with advanced dementia based on five behavioral indicators: breathing, vocalization, facial expression, body language, and consolability. Additionally, we have observed a positive correlation between sIgA levels and sTNFRII levels in this group of patients, with pain prediction ranging between 97.3 and 96.2%, according to the PAINAD scale [9].

In this study, the levels of pain biomarkers sTNFRII and sIgA are described in healthy individuals over 65 years old as well as in patients over 65 years old diagnosed with dementia and communication inability, and their correlation with the GDS stage of the patients is analyzed, to understand the usefulness of these biomarkers in evaluating the development of the painful/inflammatory process throughout the pathological evolution of the disease during its moderate-advanced stage. Sex differences are also analyzed, as it is one of the main risk factors associated with dementia.

Materials and methods

Design

This study was a secondary analysis of data collected in a case-control study carried out in healthcare districts in Andalusian provinces, located in the south of Spain, through the Andalusian network of Primary Care centers and institutions dedicated to the care of patients with dementia**.**

Selection criteria and participants

The study involved 221 participants, divided into two groups: 96 cases and 125 controls. The control group consisted of individuals over 65 years of age with no diagnosis of cognitive impairment, while the experimental group consisted of patients with dementia and/or Alzheimer's disease. To be included in the study, patients had to meet the following criteria:

- Age of 65 years or older.
- Diagnosis of dementia or AD with a GDS score between 5 and 7.
- Diagnosis of probable or possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.
- Inability to communicate verbally.
- Receiving healthcare at the community level for at least 3 months due to a diagnosis of dementia.
- Having a relative or legal representative who could provide informed consent for the patient's participation in the study.

Patients with dementia were recruited consecutively by the interventional nurses among the subjects under their care in their healthcare institution. All patients meeting the inclusion criteria were included in the study. Furthermore, controls were recruited simultaneously from the surrounding environment of participants with dementia and/or in the area of influence of the recruitment healthcare centers. In this sense, controls were selected from individuals within the same age range as the participants with dementia who were willing to participate in the study.

Sample collection

The saliva samples were collected using the passive drool method, according to the method described by Golatowski et al.[24];

1. Subjects were not allowed to engage in physical exercise, eat, ingest any drinks (except for water), chew gum, brush their teeth, or consume caffeine for the 2 h prior to sample collection in the present study.
2. Five minutes before sample collection, the subjects were asked to rinse their mouth with clean water to reduce contamination of saliva with food debris. Before starting the sample collection, any saliva present in the mouth was to be swallowed.
3. The saliva accumulated in the mouth for 5 min was deposited in a collection tube, with a minimum volume of 1 mL required. If the 5 mL collection tube was filled before those 5 min, the corresponding amount of time elapsed was recorded.

The GDS was determined by the research team at sample collection or, if available and not older than 3 months, collected from the clinical record. Saliva samples were collected in a clinical setting under supervision, ensuring that the previously mentioned criteria were always met.

Determination of salivary biomarkers

After collection, the samples centrifuged at 3000 g for 15 min in the cold; the supernatant was stored at – 80 °C until used for subsequent assays to determine salivary biomarkers.

Human TNFRII/TNFRSF1B immunoassay

The samples were measured using a human TNFRII ELISA kit (R & D Systems, Minneapolis, MN, USA), following the manufacturer's instructions. The recombinant protein represents the non-glycosylated, N-terminal methionyl form of the natural human soluble Type II receptor for TNF. The sensitivity of detection ranged from 0.2 to 2.3 pg/mL. The mean minimum detectable dose (MDD) was 0.6 pg/mL.

Human sIgA immunoassay

sIgA levels were measured using the ELISA kit (Cloud-clone Corp), following the manufacturer instructions. The sensitivity of detection ranged from 0.14 to 100 ng/mL. The minimum detectable dose was typically less than 0.07 ng/mL. In addition, Bradford's method was the one used for the determination of total protein levels in saliva.

Statistics

Descriptive statistics were used to summarize the characteristics of the sample, and the results are presented as the mean ± standard error. The statistical tests used to evaluate differences in biomarker levels between two groups were one-way ANOVA followed by a Student–Newman–Keuls test. The ANOVA test was also used to assess the correlation between the levels of sTNFRII and sIgA with GDS. Finally, the Student's t test was used to examine the relationship between sTNFRII and sIgA levels with sex. The level of statistical significance was set at $p < 0.05$.

Ethics

This study was conducted in accordance with the principles set forth in the Belmont Report and the Helsinki Declaration (updated at the Seoul Assembly in 2008) for biomedical research. A Patient Information Sheet (PIS) was provided to all individuals included in this study. For the experimental group, it was given to family members or legal representatives of the candidates to provide them with information about the general aspects of the study. Written informed consent was obtained and voluntarily signed by the patient's relative or legal representative. All participants were allowed to withdraw consent to participate at any time during the process. Data confidentiality and subject anonymity were always guaranteed. In this sense, the study was approved by all participating centers and the Ethics Committee for Research of Andalusia (Acta nº 271, ref. 3672, approved on December 5, 2017).

Results

Out of the 173 subjects in the sample, 75 (43.35%) had dementia, while 98 (56.65%) did not. In terms of general sociodemographic characteristics, 40 (23.12%) were men and 133 (76.88%) were women, with a mean age of 79.13 years (SD=8.25). Table 1 provides a breakdown of this information by group.

In Fig. 1A, salivary levels of sTNFRII (pg/mL) are shown for healthy controls and patients with dementia and inability to communicate. The results indicate a significant decrease ($p \leq 0.001$) in sTNFRII levels among patients with dementia and inability to communicate compared to healthy controls.

In Fig. 1B, salivary levels of sIgA (ng/mL) are shown for healthy controls and patients with dementia and inability to communicate. The results indicate a significant increase ($p \leq 0.01$) in sIgA levels among patients with dementia and inability to communicate compared to healthy controls.

With regard to the correlation study conducted on the GDS, the observed values were 33.3395 (SD = 50.0174) for patients in stage GDS-5, 32.5312 (SD = 40.2673) for those in stage GDS-6, and 37.0946 (SD = 39.9548) for patients in stage GDS-7. Thus, the values of sTNFRII of patients with dementia and inability to communicate did not differ based on GDS ($p = 0.6344$).

Table 1 Socio-demographic characteristics of cases and controls

Dementia patients	
Sex %(*n*)	
Men	21.33 (16)
Women	78.67 (59)
Age (years)	
Mean (SD)	84.41 (7.44)
Maximum–minimum	95–65
Type of dementia % (*n*)	
Alzheimer's type dementia	74.67 (56)
Vascular dementia	10.67 (8)
Mixed dementia	14.66 (11)
Global impairment scale % (*n*)	
GDS-5	17.33 (13)
GDS-6	38.67 (29)
GDS-7	44 (33)
Healthy patients' controls	
Sex %(*n*)	
Men	24.49 (24)
Women	75.51 (74)
Age (years)	
Mean (SD)	75.08 (6.36)
Maximum–Minimum	94–65

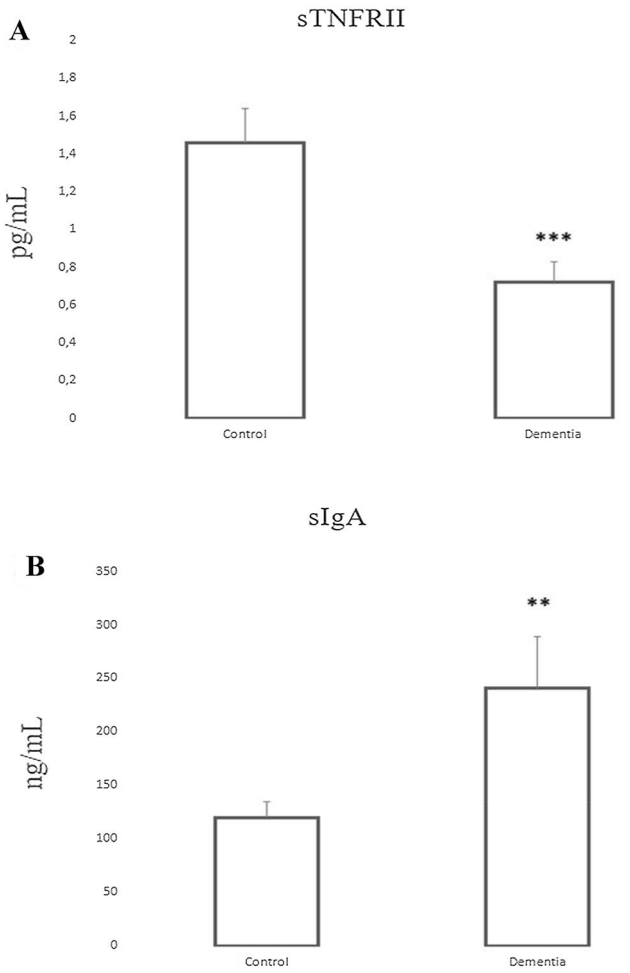


Fig. 1 Levels of sTNFRII (pg/mL) (A) and levels of sIgA (ng/mL) (B) in the saliva of patients with dementia and communication impairment compared to the healthy control group. Results are expressed as mean ± SEM. *** $p \leq 0.001$; ** $p \leq 0.01$

With respect to the data obtained for sIgA, for those patients in stage GDS-5, it was 11,021.9704 (SD = 11,988.0597); for patients with GDS-6, it was 22,861.2694 (SD = 42,242.0738); and for patients with GDS-7, it was 31,266.0656 (SD = 36,182.0136). Thus, its values in patients with dementia with inability to communicate do not differ based on GDS ($p = 0.1788$).

Finally, the data obtained regarding the correlation between the levels of sTNFRII and sIgA with sex in patients with dementia showed that there are no differences based on sex. For sTNFRII, the values in patients with dementia were, for men, 24.4706 (SD = 32.4135) and 38.2210 (SD = 43.2598) for women. For sIgA ($p = 0.5930$), the values were 20,811.2450 (SD = 22,013.6586) for men and 25,489.9435 (SD = 38,938.0765) for women. Therefore, the values in patients with dementia with the inability to communicate do not differ according to sex neither for sTNFRII nor for sIgA.

Discussion

The link between inflammation and pain is particularly relevant in patients with dementia. Cao et al. [10] describe that neuroinflammation resulting from microglial proinflammatory activation in brain areas that mediate the affective component of pain and cognition influences both chronic pain and the development of AD. This is because microglial proinflammatory activation promotes the release of proinflammatory molecules that include TNF-α, interleukin (IL)-1β, IL-6, and inducible nitric oxide synthase (iNOS), a process similar to that caused by a state of chronic pain, where proinflammatory microglia releases cytokines and chemokines associated with inflammation, such as IL-6, IL-1β, and TNF-α [6, 32].

In the present study, we have observed a significant decrease in the levels of sTNFRII, as well as a significant increase in the levels of salivary sIgA in individuals with dementia and communication impairment, compared to the control group, where 74.67% of the patients with dementia had a diagnosis of AD, 14.66% had a diagnosis of mixed dementia, and 10.67% had vascular dementia.

Pathophysiologically, AD, the most common diagnosis within dementia, is characterized as a neurodegenerative process characterized by the formation of ß-amyloid plaques,

loss of synapses, inflammation, and neuronal death. All of these circumstances lead to severe memory loss and cognitive impairment. Regarding the associated neuroinflammatory process, an increase in levels of proinflammatory cytokines has been reported, as we mentioned before. In fact, in brain tissue affected by AD, microglia co-localize intimately with ß-amyloid peptide plaques, where it acts as the main source of proinflammatory mediators [36].

In this context, TNF, a pleiotropic proinflammatory cytokine, increases as the deposition of ß-amyloid plaques increases, suggesting that TNF-α type levels reflect the pathological progression of AD [38]. In this sense, several groups have elucidated divergent signaling pathways for TNFRI and TNFRII in neurons. Hippocampal neuron survival is unaffected in culture in the absence of TNFRI, according to Yang et al. [52], but neurons lacking TNFRII are extremely sensitive to TNF at concentrations as low as 100 pmol/L. In the later stages of the disease in 3xTg-AD mice, persistent suppression of TNFRII selectively increases the amyloid charge and rises Tau hyperphosphorylation.

However, in terms of their levels of expression in human brain tissue, the levels of TNFRI protein increase, while the levels of TNFRII decrease in patients with AD compared to brain tissue from non-demented individuals. These results obtained by Cheng et al. [14] are consistent with those obtained in the present study regarding the significant decrease observed in salivary sTNFRII levels in patients with dementia, and with the information reported by Montgomery et al. [38], where they conclude that unopposed neuronal TNFRI signaling, when TNFRII is selectively downregulated, leads to a more severe course of AD pathogenesis. That is, low neuronal/brain levels of TNFRII are associated with worsening pathology. However, in the correlation study conducted between the GDS stage of the patients and the levels of salivary sTNFRII protein, we did not observe a positive correlation, nor did we observe a positive correlation with the sex variable, which was considered in this study, since female sex is an important risk factor for developing late-onset Alzheimer's disease [43]. The results obtained may be due to the small sample size for each GDS stage, and to the fact that both biomarkers associated with pain could be involved in specific pathophysiological events of advanced pathology, regardless of sex. It should also be noted that the previously described results were carried out on brain tissue, while our study used saliva samples.

The results related to the determination of salivary sTNFRII in the context of dementia, to our knowledge, are practically non-existent, although authors, such as Sobas et al. [44], have determined this receptor in saliva in the context of pain, which has allowed it to be established as a biomarker of pain [9]. In this sense, we must point out that the scientific literature describes saliva as a biological fluid that not only contains a high variety of useful metabolites as specific biomarkers for the early detection of various pathologies, but also contains exosomes of various cellular origin, including brain tissue. In fact, it has been suggested that exosomes play an important role in the pathogenesis and dissemination of inflammatory diseases, in addition to a recognized potential as biomarkers and/or therapeutic vehicles [8]. Indeed, reactive microglia releases exosomes that transport various proinflammatory cytokines such as IL-1β or the processing enzyme IL-1β caspase-1, which can induce and propagate inflammatory reactions throughout the brain. Even exosomes enriched in the L1CAM protein, implicated in the processing of the amyloid precursor peptide (APP), which plays a decisive role in the neuropathology of AD, have been described [11, 21, 22]. Another important fact to assess these results is the description, in the late 1990s, of the significant correlation between the levels detected in saliva of sTNFalphaRII and those obtained in plasma [40]. Thus, a positive correlation was shown between plasma levels of sTNFRII with gray matter atrophy involving temporal poles, precuneus, and cerebellum in patients with frontotemporal dementia [48].

Regarding sIgA and its relationship with dementia, our results show an increase that it is possible that reflects the immune status of these patients. Advanced stages of dementia often cause complications, such as immobility, swallowing disorders, and malnutrition, which significantly increase the risk of serious acute conditions that can cause death [1, 2]. The patients with dementia in our study were in moderate-to-advanced stages, where the mentioned circumstances could be present. Additionally, in this situation, they are more susceptible to respiratory conditions, with pneumonia being the most commonly identified immediate cause of death among older adults with AD or other dementias [1, 2]. Since most infectious agents enter the body through mucosal surfaces, sIgA is one of the first lines of defense against respiratory, intestinal, and urogenital infections, as well as against periodontal disease and tooth decay [37]. Recently, a cohort study described that patients with chronic periodontitis for at least 10 years had a higher risk of developing AD, but they also had a higher prevalence of hyperlipidemia, depression, traumatic brain injury, and comorbidities than patients without periodontitis [13], all factors also linked to the diagnosis of AD.

Previous data from our laboratory showed a positive correlation between salivary sTNFRII and sIgA levels and those obtained in the observational PAINAD scale, which would indicate that although both molecules are involved in the pain process in people with dementia and communication incapacity, they would also be involved in particular and specific inflammatory processes of Alzheimer's disease.

Conclusion

The determination of the sTNFRII and sIgA biomarkers in saliva in states of dementia is extremely relevant in our view due to two main aspects; first, because we have obtained results comparable to those obtained in brain tissue for sTNFRII in a fluid such as saliva; second, it allows us to assess its determination in early stages, which would allow us, together with other tools, to assess the progression of the Alzheimer's disease and even consider certain biomarkers, especially sTNFRII, as a potential complementary non-invasive tool for the diagnosis of dementia. However, we consider that additional studies including a larger number of samples and analysis in patient groups within a wider range of GDS are necessary.

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Author contributions Designed research/study: VC-H, MR-R, and MPC-G, performed research/study: VC-H, MR-R, and MPC-G, contributed important reagents: MJR-E and JMM-M, collected data and analyzed data: VC-H, JMM-M, and MPC-G; edited, wrote, and reviewed the article: VC-H, MR-R, JMM-M, MJR-E, and MPC-G. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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