Original Article

Serum and Saliva Biomolecules in Periodontitis Patients with and without Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD) and periodontitis are linked to a systemic pro-inflammatory state, potentially influencing the progression of one another. **Aims:** This study aims to evaluate serum and salivary IL-10, IL-18, and resistin levels between periodontitis patients with and without AD. **Materials and Methods:** Forty-three periodontitis patients with AD (mild or moderate), 40 without AD were included in the study. To determine the cognitive status Mini-Mental State-Examination (MMSE) test was used. Samples of blood and saliva were collected a day after measurement of periodontal parameters. ELISA method was used to analyze IL-10, IL-18, and resistin levels both in serum and saliva samples. **Results:** No difference was detected regarding clinical periodontal parameters across both groups ($P > 0.05$). The periodontitis patients with AD had elevated serum IL-18 levels compared to those without AD ($P < 0.05$). In the AD group, salivary resistin levels were higher in severe periodontitis patients than in moderate ones ($P < 0.01$). Furthermore, MMSE score was correlated negatively with serum levels of IL-18 ($P < 0.05$), and salivary levels of resistin positively with gingival index, bleeding on probing, and probing depth ($P < 0.05$). **Conclusion:** This study confirms the possible role of serum IL-18 in the inflammatory process of AD. Additionally, the present relationship between salivary resistin levels and the severity of periodontitis in AD patients needs further investigation to fully understand the implications.

Keywords: *Alzheimer's disease, interleukin-10, interleukin-18, periodontal disease, resistin*

Introduction

Dementia is a progressive neurodegenerative disorder characterized by a decline in cognitive functions such as learning, memory, orientation, language, and personality. Approximately 50–80% of all dementia cases are Alzheimer's disease (AD).[1] Worldwide, more than 50 million people suffer from AD or other dementias, and this number could reach 152 million by 2050.[2] The hallmark of AD is the accumulation of beta-amyloid protein in the brain, which forms plaques that interfere with the communication between nerve cells. Another key feature is the presence of tau protein tangles inside nerve cells.[3] One of the most determining factors in the prevalence and incidence of AD is age.[4] ApoE-ε4 allele increases disease risk and reduces the age of onset. By carrying at least one ApoE-ε4 allele, the risk of late-onset AD raises three times, but having the homozygous allele, the risk rises 12 times.[5]

Periodontitis is a destructive chronic inflammatory disease characterized by the formation of the periodontal pocket and alveolar bone loss.[6] Cytokines secreted against periodontopathogen bacteria in the microbial dental plaque are considered the primary cause of

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periodontal diseases and are associated with an increased systemic proinflammatory state.[7] Studies proposed a potential link between AD and periodontal disease, although the exact nature of this relationship is not yet fully understood. One theory is that chronic inflammation associated with periodontitis can trigger a systemic inflammatory response that can contribute to the development of AD by causing amyloid accumulation and tau[8,9] addition, bacteria associated with periodontitis may be able to travel from the mouth to the brain, potentially contributing to the development of AD by causing inflammation and/or producing toxic substances that can damage neurons.[10,11]

Macrophages serve as the primary producers of the anti-inflammatory cytokine IL-10, which is inversely correlated with inflammatory reactions and autoimmune disorders.[12] Elevated levels of IL-10 have been observed in the brains of individuals diagnosed with AD compared to those without the condition and exhibited a strong correlation with the clinical condition and imaging metrics that reflect the severity of AD.[13,14] This suggests that IL-10 might play a role in decreasing inflammation and could be considered a compensatory response during the development of the disease.[15] Although elevated serum levels of IL-10 have been documented in individuals with AD in comparison to those without the condition.[14] Other studies have indicated comparable serum levels of IL-10 in both individuals with AD and healthy controls.[16,17] Furthermore, it was suggested that IL-10 has regulatory effects on periodontal inflammation since previous studies found lower serum and saliva IL-10 levels in patients with periodontitis compared to control ones.[18,19]

Macrophages release the proinflammatory cytokine IL-18.[20] It has been shown that high amyloid accumulation is observed in neuroblastoma cells exposed to IL-18.[21] A study has shown that IL-18 levels are increased in the brains of individuals with AD.[22] These increased levels of IL-18 might be a consequence of the ongoing inflammatory response within the brain or could potentially contribute to the neuroinflammation observed in the disease. Moreover, elevated levels of IL-18 in the brain may lead to increased inflammation and damage to neurons, potentially exacerbating the progression of AD.[21,22] Similarly, in periodontitis, IL-18 has been implicated in the disease's progression and the associated inflammatory processes.[23-25] It has been shown to promote the differentiation and activation of osteoclasts, cells responsible for bone resorption in periodontitis.[26] Increased levels of IL-18 have been reported in gingival crevicular fluid, saliva, and serum.[23-25]

Resistin is a cysteine-rich peptide produced by adipocytes.[27] The primary cells of resistin expression associated with the proinflammatory state are macrophages.[28] It was found together with amyloid in cerebrospinal fluid in AD patients.[29] Both IL-18 and resistin levels in saliva or serum were found to be higher in periodontitis[24,30,31] or Alzheimer's patients compared to healthy controls.[32-34] However, to our knowledge, no information is currently available on periodontitis patients with AD regarding IL-10, IL-18, or resistin levels.

The study aimed to assess ApoE-ε4 allele carrying status and levels of serum and salivary IL-10, IL-18, and resistin in periodontitis patients with AD and to compare them with patients without AD.

Material and Methods

Ethics statement

The study protocol received approval from the Clinical Research Ethics Committee at Marmara University, Faculty of Medicine (#09.2017.317, date: 07.04.2017) and was in accordance with the Helsinki Declaration of 1975, as revised in 2013. Prior to the study, verbal and written information about the objective and content of the study was given to all patients participating in the study. Signed informed consent forms by the main caregiver for the AD patient were obtained.

Study design and population

A total of 83 subjects meeting the inclusion criteria were recruited for this study [Figure 1]. Firstly, 480 Alzheimer's patients with no other neurological disease from the Department of Neurology, Marmara University were screened for eligibility for the study. Forty-three mild-moderate stage AD[35] patients with no other systemic disease were included in the study. Among the 235 periodontitis patients without AD, who were referred to the Periodontology Department at Marmara University, 40 of them fulfilled the inclusion criteria.

The inclusion criteria were having mild-to-moderate stage AD [for AD patients], no systemic disease (for AD patients other than AD), having at least six teeth and moderate or severe periodontitis,[36] non-smoker, no use of anti-inflammatory and corticosteroid, within last six months no periodontal treatment and use of antibiotic. This study was carried out between May 2017 and April 2018.

Cognitive assessment

All subjects were examined by a neurologist (IM) at the Department of Neurology, Marmara University. Mini-Mental State-Examination (MMSE) test, accepts 24–30 points as normal and 18–23 points as mild-moderate stage,[35] and the clock drawing test[37] was used for the cognitive assessment of all patients. Additional blood tests (hemogram, biochemical profile,

etc.) and brain magnetic resonance and/or computed tomography techniques were carried out for the AD patients.

Periodontal examination

All patients went through full-mouth periodontal and radiographic examination by a single examiner (DÖ). Calibration of the intra-examiner was performed in five periodontitis patients out of this study. Probing depth (PD) and clinical attachment level (CAL) measurements were performed in double with a day apart, and the reliability of PD measurements was found to be 0.91 and CAL 0.89. Clinical periodontal parameters including plaque index (PI),[38] gingival index (GI),[39] bleeding on probing (BOP), PD, and CAL were recorded from six sites of each tooth, except for the third molars. A UNC15 probe (Hu-Friedy, Chicago) was used for measurements of the periodontal parameters. The periodontal disease severity was determined according to the criteria set by the Centers for Disease Control and Prevention-American Periodontology Academy.[36] All patients had moderate or severe periodontitis. Moreover, the main caregivers were interviewed to evaluate the medical and dental history of AD patients.

Blood and saliva sampling

One day after the periodontal measurements, collection of blood and unstimulated saliva samples were carried out in the morning following eight-hour fasting. Blood samples for DNA isolation were collected from the antecubital vein with vacuum tubes (BD Vacutainer- K2EDTA, USA) and stored at −20°C. Blood samples for biomolecule analyses were collected with vacuum tubes (BD Vacutainer-SST, USA), and then the serum was obtained from blood by centrifugation at a speed of 5000 rpm for ten minutes. After blood sampling, saliva samples were collected by funnel from patients sitting in a relaxed position and accumulating their saliva in their mouths. All serum and saliva samples were stored in sterile polypropylene tubes (Axygen Snaplock, USA) at −80°C until sent to Brain and Neurodegenerative Disorders Research Laboratories, Istanbul University Cerrahpaşa for biomolecule analyses.

DNA isolation and ApoE genotyping

DNA isolation from blood samples was performed by a QIAamp DNA Mini Kit (QIAGEN, Germany) with the guidance of the manufacturer's instructions. ApoE genotypes were determined by real-time polymerase chain reaction (RT-PCR) using a LightSnip assay as previously described.[40] LightMix® Kit ApoE-C112R-R158C (TibMolBiol, Germany) and LightCycler® 480 Instrument II (Roche Diagnostics, Germany) were used in RT-PCR. Melting curve analyses were used in genotyping.

ELISA assays

All serum and saliva samples were thawed for biochemical analysis. Saliva samples were centrifuged at 5000 rpm for ten minutes. Levels of IL-10, IL-18, and resistin were analyzed in duplicate from serum and saliva samples by ELISA method using Platinum ELISA kits (eBioscienceTM, Austria). All test procedures were conducted following the provided guidelines, and optical density was measured at 450 or 490 nm. The results were presented as the total amount (picogram) for all biomolecules. The levels of all tested biomolecules exceeded the detection limit in all serum and saliva samples.

Statistical analysis

The statistical evaluation was performed by SPSS version 25.0 (IBM, USA). All data were presented both as median (Min-Max) and mean ± standard deviation. Comparisons were carried out between periodontitis patients with and without AD and moderate or severe periodontitis patients with and without AD. The normality of distributions was determined by the Kolmogorov-Smirnov test. Since all parameters did not show normal distribution, the pairwise comparisons of quantitative data were carried out by the Mann–Whitney U test. The Chi-square test was used for the evaluation of categorical data. Correlations between clinical and biochemical parameters were carried out by the Spearman correlation test. The diagnostic ability of serum IL-18 in AD was determined using the receiver operating characteristic (ROC) curve and area under the curve (AUC). Multinominal logistic regression was performed to determine associations between AD and biomolecule levels. The P value < 0.05 was considered statistically significant.

Results

Demographic and clinical data

Age, sex, and education level were similar in both groups ($P > 0.05$) [Table 1]. The number of teeth and MMSE score were lower ($P < 0.05$) in periodontitis patients with AD than those without AD group. All clinical periodontal parameters and severity of periodontitis were similar in both groups ($P > 0.05$) [Table 1].

Genotyping and biochemical results

The ApoE-ε4 carrier rate in periodontitis patients with AD was found to be 34.9%. Periodontitis patients with AD had higher ApoE-ε4 allele carrier rates than those without AD ($P = 0.003$) [Table 2]. Serum IL-10 and resistin levels and salivary IL-10, IL-18, and resistin levels were similar in both groups ($P > 0.05$) [Table 2].

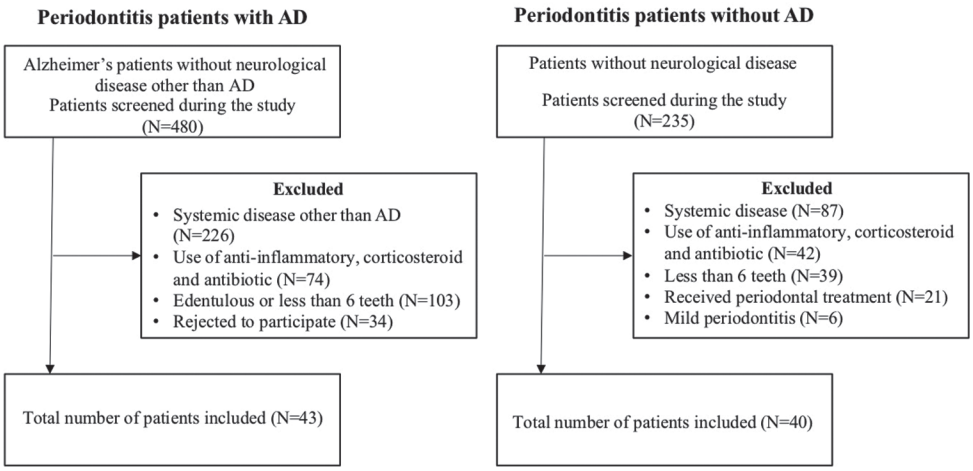

Figure 1: Flow chart of the study

Table 1: Comparisons of socio-demographic data, periodontal parameters and severity of periodontitis between groups

	Periodontitis patients		*P**	*P*†
	With AD (*n*=43)	Without AD (*n*=40)		
Age				
Median (Min-Max)	71 (52–87)	70 (53–86)	0.405	
Mean±SD	71.30±7.71	70.30±5.25		
Sex *n* (%)				
Female	21 (48.8)	20 (50)		0.916
Male	22 (51.2)	20 (50)		
Education Level *n* (%)				
Untutored	11 (25.5)	10 (25)		0.585
Primar/Middle School	26 (60.5)	21 (52.5)		
High School/University	6 (14)	9 (22.5)		
Teeth Number				
Median (Min-Max)	15 (6–27)	18 (6–27)	0.040	
Mean±SD	15.21±6.97	18.38±5.8		
PI				
Median (Min-Max)	1.53 (1.06–3.58)	1.39 (1–2.06)	0.173	
Mean SD	1.60±0.46	1.44±0.28		
GI				
Median (Min-Max)	1.41 (1.01–2.17)	1.42 (1–1.92)	0.771	
Mean±SD	1.40±0.25	1.42±0.25		
BOP (%)				
Median (Min-Max)	38.88 (0.30–82.61)	42.85 (2.78–91.67)	0.297	
Mean±SD	37.10±22.78	42.06±22.11		
PD (mm)				
Median (Min-Max)	3 (1.69–4.29)	3.03 (1.94–5.58)	0.489	
Mean±SD	2.94±0.63	3.09±0.71		
CAL (mm)				
Median (Min-Max)	4.09 (1.89–7.54)	3.74 (2.39–7.44)	0.978	
Mean±SD	4.14±1.37	4.11±1.12		
Severity of periodontitis *n* (%)				
Moderate	16 (37.2)	14 (35)		0.834
Severe	27 (62.8)	26 (65)		

*Mann–Whitney *U* test, †Chi-Square test, $P<0.05$. PI=Plaque index, GI=Gingival indeks, BOP=Bleeding on probing, PD=Probing depth, CAL=Clinical attachment loss, SD=Standard deviation, AD=Alzheimer's disease

Table 2: Comparison of ApoE-ε4 allele carrier status and biomolecule levels between groups

	Periodontitis patients		*P**	*P*†
	With AD *n*=43	Without AD *n*=40		
ApoE-ε4 N (%)				
ε4+	15 (34.9)	3 (7.5)	0.003	
ε4−	28 (65.1)	37 (92.5)		
Serum IL-10 (pg/mL)				
Median (Min-Max)	3.60 (0.90–9.90)	4 (0.90–156.40)		0.294
Mean±SD	3.83±1.9	8.69±24.3		
Saliva IL-10 (pg/mL)				
Median (Min-Max)	3.50 (1.40–25.10)	3.35 (1.20–60.20)		0.777
Mean±SD	5.18±5.05	6.89±10.85		
Serum IL-18 (pg/mL)				
Median (Min-Max)	151.40 (7.50–1242.50)	102.15 (7.50–775)		0.003
Mean±SD	207.71±220.84	141.21±156.37		
Saliva IL-18 (pg/mL)				
Median (Min-Max)	360 (51.25–4405)	321.25 (65–3645)		0.682
Mean±SD	640.73±782.55	624.11±788.69		
Serum resistin (pg/mL)				
Median (Min-Max)	4974 (2995–13201)	4628 (805–9555)		0.240
Mean±SD	5533.55±2020.16	4943.20±1964.98		
Saliva resistin (pg/mL)				
Median (Min-Max)	13768 (738–45240)	14832 (429–44106)		0.802
Mean±SD	16404.93±12187	17219.17±12692.89		

*Fisher's Exact test, †Mann–Whitney-*U* test, *P*<0.05, SD=Standard deviation, AD=Alzheimer's disease

Table 3: Intragroup comparisons of cytokine levels according to severity of periodontitis

	Periodontitis patients with AD (*n*=43) Median (Min-Max) Mean±SD		*P**	Periodontitis patients without AD (*n*=40) Median (Min-Max) Mean±SD		*P**
	Moderate *n*=16	Severe *n*=27		Moderate *n*=14	Severe *n*=26	
Serum IL-10	2.90 (1.20–9.10)	3.70 (0.90–9.90)	0.213	4.10 (0.90–156.40)	3.80 (2–22.1)	0.747
(pg/mL)	3.59±2.08	3.97±1.93		14.70±40.81	5.45±5	
Saliva IL-10	3.60 (1.80–21)	3.30 (1.40–25.10)	0.660	4.90 (1.30–18.10)	3.30 (1.20–60.20)	0.664
(pg/mL)	5.08±4.62	5.24±5.37		5.59±4.96	7.58±13.01	
Serum IL-18	169.65 (16.3–1242.5)	148.60 (7.50–756.30)	0.910	85 (7.50–437.10)	112.85 (8.60–775)	0.424
(pg/mL)	231.67±293.01	193.51±169.38		119.19±129.92	153.06±170.14	
Saliva IL-18	230 (85–1147.50)	402.5 (51.25–4405)	0.097	301.25 (91.30–1190)	358.75 (65–3645)	0.510
(pg/mL)	418.29±387.37	772.55±924.22		389.75±317.83	750.30±933.01	
Serum resistin	5197.5 (2995–9220)	4974 (3096–13201)	0.725	4242.5 (805–6290)	5262 (810–9555)	0.067
(pg/mL)	5640±1887.94	5470.48±2127.2		4111.57±1475.45	5391±2072.56	
Saliva resistin	7194 (738–34258)	19168 (3146–45240)	0.006	13545 (429–29490)	16303.5 (1532–44106)	0.220
(pg/mL)	10423.56±9446.23	19949.44±12384.62		13411±10155.99	19269.73±13608.89	

*Mann–Whitney *U* test, *P*<0.05. SD=Standard deviation, AD=Alzheimer's disease

However, serum IL-18 levels were higher in periodontitis patients with AD than those without AD (P = 0.003). Moreover, levels of salivary resistin were higher in severe periodontitis patients than moderate ones in the AD group (P = 0.006) [Table 3]. Serum IL-18 levels were negatively correlated with MMSE scores (r = −0.224, P = 0.042) but positively with serum resistin levels (r = 0.491, P = 0.00). Moreover, a positive correlation was detected between salivary IL-18 levels and PD (r = 0.260, P = 0.018). Furthermore, salivary resistin levels were positively correlated with GI, BOP, PD, and salivary IL-18 levels (r = 0.236, P = 0.031; r = 0.224, P = 0.042; r = 0.243, P = 0.027 and r = 0.368, P = 0.001, respectively), negatively with salivary IL-10 levels (r = −0.414, P = 0.00). Serum IL-18 was able to discriminate

Table 4: Logistic regression analysis for the association of biomolecule levels with AD

	Periodontitis patients with AD versus without AD	
	Unadjusted OR (95%, CI)	Adjusted OR (95%, CI) (Age, gender, periodontitis severity, and teeth number)
Serum IL-10 (pg/mL)	0.891 (0.757–1.049), 0.167	0.896 (0.753–1.067), 0.218
Saliva IL-10 (pg/mL)	0.974 (0.918–1.032), 0.371	0.968 (0.905–1.034), 0.333
Serum IL-18 (pg/mL)	1.004 (1.000–0.007), 0.039	1.004 (1.000–1.007), 0.043
Saliva IL-18 (pg/mL)	1.000 (0.999–1.001), 0.922	1.000 (1.000–1.001), 0.586
Serum resistin (pg/mL)	1.000 (1.000–1.000), 0.184	1.000 (1.000–1.000), 0.277
Saliva resistin (pg/mL)	1.000 (1.000–0.000), 0.763	1.000 (1.000–1.000), 0.814

95% CI=Confidence interval of 95%, OR=Odds ratio, $P<0.05$, AD=Alzheimer's disease

periodontitis patients with AD from those without AD and provided AUC = 0.69 (sensitivity = 63% and specificity = 62%). Both before and after adjusting for age, gender, periodontitis severity, and teeth number, significant associations were observed between AD and serum IL-18 levels ($P < 0.05$) [Table 4].

Discussion

A potential link between peripheral inflammation and AD was proposed, suggesting that chronic systemic inflammation exacerbates brain inflammation due to elevated pro-inflammatory mediators in the bloodstream. Given that periodontitis is a common peripheral immunoinflammatory condition, it has been suggested to significantly impact the progression of AD.[8,9] In light of these considerations, the current study focuses on investigating both the genetic risk factor ApoE-ε4 and the inflammatory response in patients with periodontitis, with and without AD.

Age, sex, and education level are the common risk factors for both AD[41] and periodontal disease.[42] In the present study, age, sex, and education level were found to be similar in both groups. In addition, no difference in periodontal parameters was detected between the two groups. In this way, the risk of bias between periodontitis patients with and without AD groups was greatly reduced.

Since the mean number of teeth in Turkish AD patients was reported as 5.07,[43] subjects with at least six teeth were included in the present study. Periodontitis patients with AD had a lower number of teeth than those without AD, which is in accordance with other studies.[44,45] It can be related to a decrease in oral care due to reduced motor functions, and radical extraction decisions preferred in the dental treatment history and the age onset of the AD.

Previous studies in the Turkish population showed that the ApoE-ε4 carrier rate was between 29.4% and 40.4% and higher in AD patients.[46,47] In the present study, the ApoE-ε4 carrier rate was found to be 34.9% and higher in periodontitis patients with AD, which is in accordance with previous studies.

The present study revealed that periodontitis patients with AD had elevated serum IL-18 levels compared to periodontitis patients without AD. Similarly, several studies revealed that levels of serum IL-18 were higher in AD patients compared to those without AD despite the lack of information about the periodontal status of the patients included.[32,34] Elevated levels of IL-18 in serum may indicate an intensified inflammatory response in both periodontitis and AD. This could suggest a potential link between the chronic inflammation associated with periodontitis and the inflammatory processes observed in AD. Limited studies comparing the serum IL-18 levels in periodontally healthy and periodontitis patients showed that the levels of serum IL-18 were either similar between groups[24] or not detectable.[23] Although periodontally healthy subjects were not included in the present study, due to previous studies, we may claim that higher serum IL-18 levels were related to the pathology of AD rather than periodontitis. A negative correlation between serum IL-18 levels and MMSE scores has supported this inference. Furthermore, serum IL-18 has a medium discriminative role in AD (AUC = 0.63). In serum samples, a positive correlation was observed between IL-18 and resistin levels. A similar correlation was found by Demirci *et al*.[34] in AD patients with no periodontal status information. A recent study showed that amyloid and resistin coexist in the cerebrospinal fluid of AD patients.[29] Moreover, levels of serum resistin were evaluated in limited studies, and higher levels of serum resistin were found in AD patients compared to systemically healthy ones.[33,34] In contrast, the present study showed similar serum resistin levels between the two groups. This may be due to the periodontal status. Since elevated serum resistin levels were detected in periodontitis patients compared to periodontally healthy ones,[30] we can speculate that the periodontitis patients already had high serum resistin levels so that the true impact of AD on serum resistin levels may be masked to reach the level of significance.

Studies on saliva resistin and IL-18 showed elevated levels in individuals with periodontitis compared to periodontally healthy ones.[24,25,31,48] However, no study

was performed on saliva resistin and IL-18 levels in periodontitis patients with AD. Although no significant difference was found regarding saliva resistin and IL-18 levels between the two groups in the present study, saliva resistin and IL-18 levels were positively associated with most of the clinical parameters, including PD. Since the mean PD was similar in both groups, this result could be expected. Moreover, we analyzed all biomolecules within each group according to the severity of the periodontitis, and only salivary resistin reached elevated levels in severe periodontitis compared to moderate levels in AD patients. Therefore, we think that the salivary resistin levels may be associated with the severity of periodontal inflammation in AD patients.

In the presence of periodontitis, the systemic proinflammatory state is triggered, and the serum TNF-α levels rise.[49] It is also known that the anti-inflammatory cytokine IL-10 inhibits TNF-α synthesis.[50] Previous studies found lower serum and saliva IL-10 levels in patients with periodontitis compared to healthy ones.[18,19] In the present study, Serum and saliva IL-10 levels were found to be similar in both groups. In accordance with the present findings, Bonotis *et al*. and Gezen-Ak *et al*.[16,17] also reported similar serum IL-10 levels between subjects with and without AD. It seems that IL-10 has no effect on AD in periodontitis subjects.

The limitation of this study is the lack of periodontally healthy groups, which is attributed to the rarity of subjects in this age group in the Turkish population, especially in AD. It should be noted that our results do not reflect all periodontitis severity levels. Nonetheless, a notable strength of the study lies in the well-matched clinical groups concerning age, sex, and severity of periodontitis.

Within the limits of the study, our findings indicate that higher serum levels of IL-18 are associated with AD in individuals with periodontitis. Additionally, elevated salivary levels of resistin may be linked to the severity of periodontitis in AD patients. Further studies involving periodontally healthy subjects have emerged to uncover the pathophysiological mechanisms underlying the impact of periodontitis on AD.

Informed consent

Written informed consent was obtained from all individual participants included in the study (signed by the main caregiver for the AD patient).

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Key messages

Our study is the first to investigate both together genetic risk factor ApoE-ε4, and the inflammatory response in serum and saliva of periodontitis patients with and without Alzheimer's disease. The findings presented in this manuscript can significantly contribute to the existing body of knowledge.

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Conflicts of interest

No conflicts of interest was declared by the authors.

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