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Original Article

The effect of chronic periodontitis on serum levels of tumor necrosis factor-alpha in Alzheimer disease

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ABSTRACT

Background: Despite the outbreak in dental science, oral and dental complications in Alzheimer are of the unsolved problems. It is assumed that tumor necrosis factor-α, which is a key factor in Alzheimer, has a relation with periodontal complications in patients with Alzheimer disease. The present study evaluated the effect of chronic periodontitis on serum levels of tumor necrosis factor-α in Alzheimer disease.

Materials and Methods: This case-control study was performed on 80 patients with Alzheimer disease seeking medical care at Nour Hospital, Isfahan, Iran. Eighty patients with Alzheimer disease between 40 and 70 years old attended this study. Forty had chronic periodontitis (case group), and 40 patients had healthy periodontium (control group). Blood sample was taken, and serum levels of tumor necrosis factor-α were measured by means of an ELISA Reader device. Independent T-Test was used to analyze data, and $P < 0.05$ was considered significant.

Results: The mean of tumor necrosis factor-α was 749.1 ng/μL in case group and 286.8 ng/μL in control group. Independent t-test showed that the mean of tumor necrosis factor-α in patients with Alzheimer and periodontitis was approximately three folds higher than the patients only with Alzheimer, and this difference was statistically significant ($P < 0.001$).

Conclusion: According to the results of this study, it seems that there is a difference between serum levels of tumor necrosis factor-α in patient with Alzheimer and chronic periodontitis and patients with Alzheimer disease and healthy periodontium. Tumor necrosis factor-α level in serum may act as a diagnostic marker of periodontal disease in patients with Alzheimer disease

Key Words: Alzheimer disease, chronic periodontitis, tumor necrosis factor-alpha

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INTRODUCTION

Alzheimer disease is a neurodegenerative disease characterized by impairment of cognition and severe memory loss. Its etiology is still unknown, but its pathophysiology is revealed. Neuro-inflammation has been discussed as its main pathophysiology. It includes the extensive production of pro-inflammatory molecules.[1]

One of these pro-inflammatory molecules is tumor necrosis factor-α, which is a neurotoxic and master regulator of pro-atherogenic phenotypic changes.[1,2] It is also related to endothelial dysfunction and apoptosis.[2] Tumor necrosis factor-α is elevated in Alzheimer disease and colonizes in amyloid plaques of human brain and also animal models.[1,3] It is shown that tumor necrosis factor-α expression increases in Alzheimer disease-affected mice preceding the development of amyloid plaques and pathological features, leading to neuronal death.[1,4]

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It has been suspected that tumor necrosis factor-α is involved in the pathogenesis of Alzheimer disease for a long time.[5-9] According to clinical evidences, it is accepted that tumor necrosis factor-α plays a main role in Alzheimer disease.[5-22]

On the other hand, cytokines play an important role in the immune response to periodontal disease.[2,3] Tumor necrosis factor-α is one of the cytokines that is elevated in a dose-dependent manner in response to stimulations from periodonto-pathogens such as *Porphyromonas gingivalis*, *Peptostreptococcus micros*, and *Aggregatibacter actinomycetemcomitans*.[23] Tumor necrosis factor-α along with Interleukin-1α play an important role in the initiation, regulation, and perpetuation of innate immune response in the periodontium, which results in inflammation and bone destruction.[2-4]

According to the available data, no study has been performed to evaluate the effect of chronic periodontitis on the serum level of tumor necrosis factor-α in Alzheimer disease.

MATERIALS AND METHODS

This case-control experiment was performed on 80 patients with Alzheimer disease, seeking medical care in Neurology Department of Nour hospital in Isfahan, Iran. They were between 40 and 70 years old. Forty patients had Alzheimer along with chronic periodontitis and served as case group. Another 40 patients only had Alzheimer disease, and their periodontium was healthy and served as control group. Patients with any other systemic disease, malignancies, blood disorders, smokers, alcoholic, drug abusers, and patients with less than 20 teeth were excluded from the study. Also, patients who had used any widespread antibiotics in the last six months prior to study and patients who had received dental treatment or underwent scaling and root planning were excluded. Chronic periodontitis diagnosis was established by clinical examination and attachment loss evaluation by means of a periodontal probe at the above-mentioned hospital.

Patients were informed about the settings of the study, and a written agreement was signed by each of the patients. This study was approved by the institutional Ethics Committee. 2.5 cc of intravenous blood was taken from each patient by means of a 5 cc syringe. Blood samples were transferred to sterile test tubes without any coagulant agent and were left in room temperature for one hour to coagulate, so the serum was separated and could be used for the process of measurement of the levels of tumor necrosis factor-α. All of the test tubes were labeled and transferred to the laboratory in a special flask filled with dry ice and with 2-6ºC temperature. In the laboratory, test tubes were centrifuged for ten minutes in 4ºC, and serum was extracted. A human tumor necrosis factor-α ELISA Kit (ANOGEN, Ontario, Canada) was used. Data were analyzed by independent T-test, and $P < 0.05$ was considered significant.

RESULTS

The mean of tumor necrosis factor-α was 749.1 ng/μL in case group and 286.8 ng/μL in control group. Independent t-test showed that the mean of tumor necrosis factor-α in patients with Alzheimer and periodontitis was approximately three folds higher than the patients only with Alzheimer, and this difference was statistically significant ($P < 0.001$) [Figure 1].

Receiver Operating Characteristic (ROC) curve revealed that tumor necrosis factor-α has predictability values for diagnosis of periodontitis [Figure 2]. The integral of the curve, which was calculated at 0.992, showed that tumor necrosis factor-α has a good diagnostic value to diagnose chronic periodontitis. According to this curve, the cut-off point for tumor necrosis factor-α was 410 ng/μL and sensitivity of tumor necrosis factor-α was 97.5% while its specificity was 95%.

DISCUSSION

Tumor necrosis factor-α is of special interest in the treatment of Alzheimer disease. This pro-inflammatory cytokine is released in response to lipopolysaccharide and other bacterial byproducts.[2,5] Elevation of its

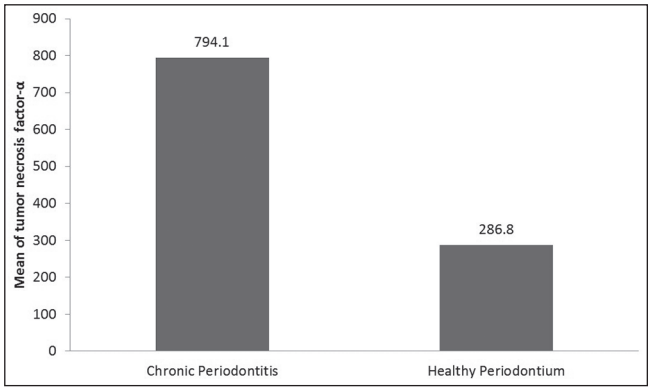

Figure 1: The mean of tumor necrosis factor-α in patients with Alzheimer and periodontitis and healthy periodontium

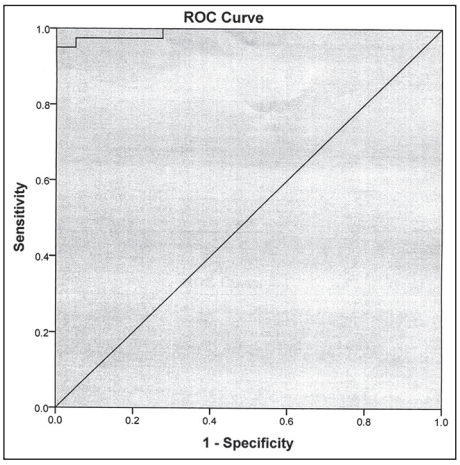

Figure 2: Receiver operating characteristic (ROC) curve

levels in serum induces the production of C-reactive protein, which results in the expression of adhesion molecules on endothelial cells. This process allows the diapedesis of neutrophils and induces Interleukin-1 activation, which finally results in activation of collagenase and destruction of cartilage, which is seen in rheumatoid arthritis.[23] Elevation in the levels of tumor necrosis factor-α also increases the production of prostaglandin E_2 and matrix-metalloproteinases. Matrix-metalloproteinases stimulate osteoclasts and results in bone destruction, which is the prominent pathogenesis of periodontal diseases.[5,6,22]

It is been shown that treatment with anti-inflammatory systemic drugs that decrease the levels of tumor necrosis factor-α diminishes the signs and symptoms of Alzheimer disease and sometimes results in complete abolishment of the disease.[1,5] Kamer *et al*.[24] also showed a relation between periodonto-pathogen bacteria and inflammatory mediators stimulated by periodontitis disease and Alzheimer disease.

Earlier studies had shown the relation between Alzheimer disease and tumor necrosis factor-α.[7,25-29] Although Cacabelos *et al*.[30] did not found any relations between levels of tumor necrosis factor-α and Alzheimer disease, they declared that the result of their study may be because of differences of age, sex, race, and the pattern of study.

Other studies that had investigated the effect of inflammatory mediators and their relationship with periodontitis had used gingival crevicular fluid; but, in this study, serum levels of tumor necrosis factor-α were investigated, because it is assumed that there is more direct relation between serum levels of tumor necrosis factor-α and Alzheimer than gingival crevicular fluid levels.

In this study, the mean of serum levels of tumor necrosis factor-α in patients with Alzheimer and periodontitis was significantly higher than patients with Alzheimer disease and a healthy periodontium ($P < 0.001$) and when patients with Alzheimer disease had chronic periodontitis, their serum levels of tumor necrosis factor-α were three folds higher than patients with Alzheimer disease and healthy periodontium.

It was also shown that serum level of tumor necrosis factor-α can act as a diagnostic marker for periodontal disease in Alzheimer disease with high percentage of sensitivity and specificity. In previous studies, it was shown that the levels of tumor necrosis factor-α in gingival crevicular fluid act as a diagnostic marker for periodontal disease, and the results of the present study is similar to previous studies.[31,32]

According to the results of the present study, it is suggested that patients with Alzheimer disease and chronic periodontitis and their caretakers should be taught about the importance of dental health and its effect on the status of Alzheimer disease. Patients also need to be provided with well-scheduled dental health maintenance. It must be noted that this study also did not exclude the effect of financial status and status of caretaking in patients with Alzheimer disease.

CONCLUSION

According to the results of this study, the mean of tumor necrosis factor-α level in serum was three folds higher in patients with Alzheimer disease and chronic periodontitis in comparison to patients with Alzheimer disease and a healthy periodontium. Also, tumor necrosis factor-α may act as a diagnostic marker with high sensitivity and specificity for periodontal disease in patients with Alzheimer disease. Further case-controlled clinical studies are needed to confirm the findings of the current investigation.

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