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Original Article

Comparison of Salivary Levels of Adenosine Deaminase and Interleukin-10 in COVID-19 Vaccine Recipients and Non-Vaccinated Individuals

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Abstract

Introduction: Global efforts to combat COVID-19 have led to the rapid development and widespread administration of various vaccines, including AstraZeneca. While vaccination remains a pivotal strategy for controlling the virus's spread, it is crucial to explore its potential immunomodulatory effects on salivary biomarkers. Adenosine deaminase (ADA) and interleukin-10 (IL-10), both implicated in immune responses, serve as vital indicators of the host's immune status. ADA is a marker related to purine metabolism and cellular immune activity, while IL-10 is a regulatory cytokine involved in limiting inflammatory responses. Therefore, this study aimed to compare the salivary levels of ADA and IL-10 between COVID-19–vaccinated and unvaccinated individuals.

Methods: Overall, 41 individuals with a history of at least two doses of the AstraZeneca vaccine and 41 unvaccinated individuals were included in this case-control study. Non-stimulated saliva samples were collected in sterile test tubes. Then, IL-10 levels in the saliva were measured by the enzyme-linked immunosorbent assay, and the total amount of ADA in the saliva was calculated using specific ADA kits. Finally, data were analyzed by SPSS 28 using ANCOVA test ($P=0.05$).

Results: The average ADA level was higher in COVID-19 vaccine recipients (20.26 ± 3.20) than in unvaccinated individuals (18.37 ± 2.12). Moreover, the average IL-10 level was higher in the vaccinated group (31.05 ± 8.32) compared to the unvaccinated group (21.12 ± 9.50).

Conclusion: AstraZeneca vaccination could alter the immune system's homeostasis compared to unvaccinated individuals. Our findings confirmed that COVID-19 vaccination significantly increases salivary IL-10 and ADA levels in vaccine recipients.

Keywords: COVID-19, Vaccination, Astrazeneca, Interleukin-10, Adenosine deaminase

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Introduction

Coronavirus disease 2019 (COVID-19) was first reported in 2019 in Wuhan, China. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and quickly spread worldwide. Infection with this virus is primarily associated with respiratory issues, and common transmission modes include respiratory droplets and direct contact. (1-3) The COVID-19 pandemic has caused widespread casualties, especially in densely populated areas. (4) Vaccination programs have been widely implemented using various reputable brands, and the disease is relatively controlled globally. However, vaccination does not necessarily prevent all vaccinated individuals from contracting COVID-19, particularly several months post-vaccination. This issue raises questions about the effectiveness of the existing vaccines against COVID-19 and its variants. (5) Additionally, numerous side effects related to COVID-19 vaccines have been reported recently. (6, 7) Adverse immune reactions following vaccination are not unique to SARS-CoV-2 vaccines; some previous studies have shown that vaccines for human papillomavirus, hepatitis B, and influenza may trigger or exacerbate autoimmune diseases through molecular mimicry mechanisms. (8-10) Adenosine

deaminase (ADA) is a crucial immune regulatory enzyme that is involved in the maturation and maintenance of the immune system. (11) ADA catalyzes the deamination of adenosine, which normally suppresses the immune system in order to prevent excessive inflammatory responses. (12, 13) Therefore, abnormal ADA activity can lead to altered adenosine levels, thereby disrupting immune homeostasis. Considering that immune homeostasis imbalance is a hallmark of autoimmune diseases, a correlation between abnormal ADA activity and autoimmune conditions is plausible. (14, 15) Salivary ADA levels significantly correlate with blood levels; thus, increased salivary ADA reflects elevated systemic ADA activity. (16) Likewise, interleukin-10 (IL-10) is a pleiotropic cytokine known for its potent anti-inflammatory and immunosuppressive effects. (17) During infection, IL-10 inhibits the host immune response to pathogens and microbiota, reducing tissue damage and immunopathology. (18) Emerging evidence also suggests that IL-10 plays a critical role in the onset and progression of autoimmune diseases. (19) Moreover, salivary IL-10 levels correlate with serum levels and can be used as an alternative biomarker. (20) Saliva is a promising sample for disease diagnosis and early detection due to its non-invasive nature compared to serum analysis. (21) ADA was described as a marker related to purine metabolism and cellular immune activity, while IL-10 was characterized as a regulatory cytokine that is involved in limiting inflammatory responses. Given the limited evidence regarding the impact of coronavirus vaccines on immune system regulation, further studies are warranted. Accordingly, this study seeks to investigate immune suppression status in vaccinated and unvaccinated individuals by examining the salivary levels of two immunosuppressive markers, namely, ADA and IL-10

Materials and Methods

This case-control study was conducted at the School of Dentistry, Qom University of Medical Sciences. The inclusion criterion included individuals aged 18 or older who had received at least two doses of the AstraZeneca vaccine, with a minimum interval of 3 months between doses (the vaccinated group). On the other hand, the exclusion criteria were a history of autoimmune or systemic diseases prior to vaccination, use of steroids or immunomodulatory drugs, vaccination with any other vaccine within the previous two years, a history of severe COVID-19 infection in either group, or an active COVID-19 infection, a common cold, or influenza at the time of sample collection. Participants were selected based on these criteria, resulting in 41 vaccinated and 41 unvaccinated individuals. Then, demographic data, vaccination history, systemic diseases (especially autoimmune), and autoimmune symptoms (e.g., morning joint stiffness, swelling, pain, and myalgia) were recorded.

Non-stimulated saliva samples were collected between 8 AM and 11 AM, with participants refraining from consuming any food or liquids for at least two hours prior to sampling. The spitting method was employed for sample collection. Then, all samples were thawed at 4°C and centrifuged at 10,000 rpm for 10 minutes. During centrifugation, saliva was passed through aerosol barrier pipette tips in order to remove particles and contaminants. Next, 1 mm of the extracted saliva was used for analysis, while the remaining samples were stored at -80°C. The concentration of IL-10 in the saliva was measured using the Karmania Pars Gen enzyme-linked immunosorbent assay kit. In brief, specific antibodies labeled with an enzyme were added to a plate coated with the antigen. After the addition of the substrate/chromophore, the enzyme catalyzed the reaction, and the color change was estimated at a wavelength of 450 nm. Furthermore, total ADA activity in the saliva was determined using an automated spectrophotometric method with the ADA Assay Kit (Biorex Fars Company). This kit employs an enzymatic reaction in which the adenosine substrate is converted to inosine and free ammonia. Subsequently, ammonia, in the presence of alpha-ketoglutarate and nicotinamide adenine dinucleotide phosphate, is converted to glutamate and nicotinamide adenine dinucleotide. The decrease in absorbance, measured at 340 nm, is proportional to the ADA activity in the sample.

Statistical Analysis

Frequencies and percentages, as well as means and standard deviations were employed to describe qualitative and quantitative data, respectively. In addition, the assumptions of statistical tests were assessed prior to data analysis according to the study objectives. Further, the Shapiro-Wilk test and Levene's test were utilized to evaluate normality and the homogeneity of variances, respectively. If the assumptions for quantitative variables were satisfied, the independent t-test, analysis of covariance with Tukey's post-hoc test for pairwise comparisons, and Pearson correlation were employed for assessment. When assumptions were not met, non-parametric alternatives, such as the Mann-Whitney test, Kruskal-Wallis test, and Spearman correlation, were applied for analysis. In addition, linear regression analysis was conducted to adjust for potential confounding variables. Ultimately, data were analyzed using SPSS (version 28), and a *P*-value of less than 0.05 was considered statistically significant.

Results

In the present study, 82 participants were equally included in the case (25 women and 16 men) and control (22 women and 19 men) groups. No significant difference was found between the two groups regarding gender distribution ($P=0.503$). The mean age of participants in the case and control groups was 23.97 ± 2.13 and 29.93 ± 9.20 years, respectively. Additionally, the age difference between the two groups was statistically significant ($P<0.001$). This difference in age could potentially act as a confounding factor affecting the study results. Therefore, covariance analysis was performed to adjust for the effect of age. Further, the mean ADA levels demonstrated a

statistically significant difference between the two groups ($P=0.004$), with higher mean ADA levels observed in the COVID-19–vaccinated group (Table 1). The results of the covariance analysis are presented in Table 2. Similarly, the mean IL-10 levels significantly differed between the two groups ($P<0.001$), with higher average levels found in the vaccinated group (Table 3). Covariance analysis results are provided in Table 4. Regarding vaccination status, 53.7%, 43.9%, and 2.4% of individuals had received two, three, and four doses of the AstraZeneca vaccine, respectively. Based on the results (Table 4, a significant and positive correlation was observed between IL-10 levels and the number of vaccine doses received ($P=0.028$). Thus, IL-10 levels increased with the number of vaccine doses.

Discussion

The AstraZeneca vaccine (ChAdOx1 nCoV-19) was developed by the University of Oxford in collaboration with the pharmaceutical company AstraZeneca. Following successful clinical trials in the UK, Brazil, and South Africa, this vaccine received emergency use authorization, including approval from the World Health Organization, and has been widely distributed, particularly in low-income to middle-income countries, such as Iran (22, 23). Moreover, this vaccine has been among the most widely used COVID-19 vaccines in these regions. The present study evaluated the salivary levels of ADA and IL-10 in individuals who had received at least two doses of the AstraZeneca vaccine compared to unvaccinated individuals. The results revealed that salivary ADA levels were significantly higher in vaccinated individuals than unvaccinated ones. Similarly, salivary IL-10 levels were substantially elevated in the vaccinated group. In addition, there was a positive and relatively weak correlation between the number of vaccine doses received and the salivary IL-10 level, indicating that an increase in the number of doses of the AstraZeneca vaccine is associated with increased salivary IL-10 levels.

To the best of our knowledge, no study has yet compared the salivary levels of IL-10 and ADA in recipients of the COVID-19 vaccine with non-vaccinated individuals. However, one study compared immune responses before and after influenza vaccination in 67 adults, demonstrating an increase in intracellular IL-6 production in classical and inflammatory monocytes in response to influenza vaccination. Furthermore, at each time point after vaccination, the level of IL-10 was significantly related to the level of intracellular IL-6. Thus, the anti-inflammatory cytokine IL-10 levels in the monocytes of these individuals remarkably increased after vaccination. (24) Moreover, in some studies, a considerable increase in the levels of other types of cytokines, known for their roles in autoimmune diseases, has been reported following the administration of various viral vaccines. For example, the serum levels of interferon-gamma increased in response to influenza vaccines and human cytomegalovirus infection. (25) Interferon-gamma is recognized as a crucial mediator for anti-tumor immunity, stimulating the innate immune response and enhancing the activity of macrophages. (26) This cytokine also plays a fundamental role in inflammation and autoimmune diseases. (27) Further, an increase in tumor necrosis factor-alpha (TNF-α) has been found following COVID-19 and hepatitis B vaccination. (28-30) TNF-α, initially recognized as a factor contributing to tumor necrosis, has recently been revealed to have other significant functions, serving as a pathological component in autoimmune diseases. It should be noted that excessive signaling of this factor is associated with chronic inflammation and can ultimately lead to the development of pathological consequences, such as autoimmune diseases. (31) ADA is an enzyme that catalyzes the conversion of toxic adenosine molecules

Table 1. Demographic Characteristics of All Participants

Characteristics		Vaccinated Group (n=41)	Unvaccinated Group (n=41)	*P*-Value
Female/male		25/16	22/19	0.50
Age, years, mean±SD		23.97±2.13	29.93±9.20	<0.001
Number of vaccine doses		2 (N/%) 22/53.7%		
		3 18/43.9%		
		4 1/2.4%		
Autoimmune disease after vaccination	Yes (N/%)	0/0		
	No (N/%)	41/100%		
Xerostomia sensation	Yes (N/%)	1/4.2%	3/7.3%	
	No (N/%)	40/97.6%	38/92.7%	

Table 2. The Mean ADA and Interleukin-10 Levels (pg/mL) in COVID-19 Vaccine Recipients (Case) and Unvaccinated Individuals (Control)

Group	ADA (U/L) Mean±SD	*P*-Value*	Interleukin-10 (pg/mL) Mean±SD	*P*-Value*
Case	20.26±3.20	0.004	31.05±8.32	0.001
Control	18.37±2.12		21.12±9.50	

Note. SD: Standard deviation; ADA: Adenosine deaminase; *ANCOVA: Analysis of covariance.

Table 3. Comparison of ADA and Interleukin-10 Levels in Covid-19 Vaccine Recipients (Case) and Unvaccinated Individuals (Control) With Age Adjustment

Group	ADA (U/L) Mean Square	*P*-Value*	Interleukin-10 (pg/mL) Mean±SD	*P*-Value*
Age	0.25	0.856	17.91	0.638
Group (case/control)	64.01	0.004	1824.32	0.001
Error	7.48		80.49	

Note. SD: Standard deviation; ADA: Adenosine deaminase; *ANCOVA: Analysis of covariance.

Table 4. Relationship Between the Level of Interleukin-10 in COVID-19 Vaccine Recipients and the Number of Vaccine Doses Received

	Interleukin-10 (pg/mL)
The number of vaccine doses	R=0.34
	P=0.028

Spearman's correlation

and deoxyadenosine into inosine and deoxyinosine, respectively. This enzyme is present in most tissues, especially those with lymphoid origins. Additionally, the growth and differentiation of T lymphocytes in the thymus depend on this enzyme. (32) In lymphoid tissues, ADA is involved in the maturation of single-nucleated cells from monocytes to macrophages and in the differentiation of B and T lymphocytes. (33) Therefore, the level of this enzymatic activity in the serum reflects cellular immunity. Furthermore, it is a biomarker for chronic inflammation and situations where T lymphocyte levels are elevated in circulation. (34, 35) It has been demonstrated that the serum levels of ADA increase in many clinical conditions, including infections, inflammation, immune disorders, and malignancies. (36-38) Our findings indicated that vaccination may influence the immune system homeostasis by increasing the levels of ADA As previously mentioned, the abnormal activity of this enzyme leads to an abnormal concentration of adenosine, which negatively affects the immune system's homeostasis. Likewise, immune system imbalance is considered a triggering factor for the onset or exacerbation of autoimmune diseases. Accordingly, our results strengthen the possibility of a connection between vaccination and the occurrence or exacerbation of autoimmune diseases.

IL-10 is a key immunosuppressive and anti-inflammatory agent. Similarly, IL-10 is an inactivating factor for macrophages and has inhibitory effects on neutrophils. Some infectious agents induce the synthesis of IL-10 or encode their own IL-10 homologs, consequently suppressing the host's immune response. (39) In addition, initial research on COVID-19 has reported that pro-inflammatory cytokines, such as IL-1, IL-6, TNF-α, and even IL-10 (which is presumed to be an anti-inflammatory molecule), are released by activated mast cells. The release of these cytokines may contribute to the worsening of the inflammatory status and pathogenesis. (40, 41) In the present study, the salivary levels of IL-10 in vaccinated individuals were significantly higher than in non-vaccinated individuals. de Melo Batista Dos Santos et al, comparing the levels of various salivary cytokines in COVID-19 patients with healthy individuals, demonstrated that the IL-10 levels in individuals with COVID-19 were higher than in healthy individuals, (42) indicating that the production of IL-10 increases to control the inflammation caused by SARS-CoV-2 infection and is crucial. However, as mentioned earlier, the elevation of serum IL-10 levels has also been observed in autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. (19) This issue may suggest that the increase in IL-10 as an anti-inflammatory factor in vaccinated individuals not infected with COVID-19 can potentially lead to the suppression of inflammatory pathways and the immune system in these individuals.

Therefore, the higher levels of IL-10 and ADA in individuals who have received the AstraZeneca vaccine may indicate a potential impact of this vaccine on the balance of the immune system, probably playing a role in the development of autoimmune diseases. This observation can explain the mechanisms underlying immune-related disorders reported in some recipients of the COVID-19 vaccine.

Age difference between the vaccinated and unvaccinated groups may act as a potential residual confounding factor despite adjustment using ANCOVA and can influence of age-related immune variability on salivary ADA and IL-10 levels.

However, this limited study may not be sufficient to draw definitive conclusions. Accordingly, further studies with larger sample sizes and more diverse populations are needed to gain a comprehensive understanding of the relationship between salivary IL-10 and ADA levels and COVID-19 vaccination.

Limitations

As with all studies, the current research had some limitations. First, the sample size was small, and the participants might not represent a diverse population. Additionally, the study's cross-sectional design provided only a snapshot of data at a single point in time, limiting the ability to establish causation or observe changes over a longer period. Thus, longitudinal studies are required to capture temporal relationships and assess the persistence of the observed effects. In accordance with significant age differences between the vaccinated and unvaccinated groups, study findings should be interpreted with caution. Moreover, the study may not have accounted for all potential confounding factors that could affect the relationship between vaccination and immune markers. Other variables, such as pre-existing health conditions, medication use, and lifestyle factors, might have influenced the results. In addition, it is noteworthy that prior asymptomatic or mild COVID-19 infection may influence salivary cytokine levels. Finally, since this study focused specifically on the AstraZeneca vaccine, generalizing the findings to other COVID-19 vaccines may be difficult. Different vaccines may elicit distinct immunological responses and have various mechanisms of action. Hence, future researchers should conduct a comparative analysis between the indigenous vaccine and the Pfizer vaccine.

Conclusion

Our study demonstrated a statistically significant increase in salivary IL-10 and ADA levels among individuals who received the AstraZeneca COVID-19 vaccine compared to those who were unvaccinated, suggesting that vaccination may influence immune system activity and potentially alter immunological homeostasis.

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Competing Interests

All authors declare that they have no conflict of interests.

Ethical Approval

The study was approved by the Ethics Committee of Qom University of Medical Sciences, Qom, Iran (approval No. IR.MUQ.REC.1402.123)

Consent to Participate

Informed consent was obtained from all patients prior to their enrollment in the study.

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