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Evaluation of ERK-5 expression in type 2 diabetic patients following COVID-19 vaccination; a prospective case-control study

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is associated with increased risk and altered immunity to infections, yet little is known about how COVID-19 vaccination affects key signaling pathways in these patients. Extracellular signal-regulated kinase 5 (ERK-5) plays a vital role in vascular health and inflammation.

Objectives: This study aims to assess ERK5 levels in type 2 diabetic patients following COVID-19 vaccination, compared to non-diabetic controls.

Patients and Methods: This case-control study enrolled 90 male participants at Fallujah hospital in Al-Anbar province, Iraq, during February to October 2024, stratified into three groups; vaccinated T2DM patients, unvaccinated T2DM patients, and non-diabetic unvaccinated individuals. After obtaining written informed consent, demographic data (age) were collected through interviews. Blood samples from all participants were analyzed for blood sugar, HbA1c, key serum electrolytes (phosphorus, sodium, potassium and chloride), and ERK-5 biomarker levels. The primary outcome was the comparison of serum ERK-5 concentrations across groups to assess the impact of diabetes status and COVID-19 vaccination on ERK-5 expression.

Results: This study included 90 males, with 30 in each of three treatment groups. The comparative analysis indicated that unvaccinated T2DM patients showed significantly higher ERK-5 levels compared to both non-diabetic unvaccinated individuals and vaccinated T2DM groups. Vaccinated T2DM patients exhibited intermediate ERK-5 levels, significantly lower than unvaccinated diabetic counterparts but higher than non-diabetic unvaccinated. These findings indicated a pronounced elevation of ERK-5 in the context of T2DM, with COVID-19 vaccination status appearing to attenuate this increase.

Conclusion: Our study found a significant correlation between T2DM, COVID-19 vaccination, and ERK-5 expression, suggesting vaccination may modulate ERK-5 expression in T2DM. These results introduce ERK-5 as a potential T2DM biomarker and found that COVID-19 vaccination may influence ERK-5 signaling in diabetic patients.

Implication for health policy/practice/research/medical education:
In this case-control study, we found that elevated extracellular signal-regulated kinase 5 (ERK-5) levels were found in unvaccinated type 2 diabetes mellitus (T2DM) patients compared to non-diabetic controls, with vaccination in T2DM individuals resulting in decreased ERK-5 concentrations. This suggests that COVID-19 vaccination may help moderate ERK-5 pathway activity in patients with type 2 diabetes.

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Introduction

Type 2 diabetes mellitus (T2DM) represents a complex metabolic disorder characterized by defective insulin secretion from pancreatic β-cells and impaired insulin sensitivity in peripheral tissues, leading to chronic hyperglycemia and associated complications (1). Beyond its metabolic implications, T2DM is increasingly recognized as an inflammatory disease, with low-grade systemic inflammation serving as both a contributing factor and consequence of the disease process (2,3). This chronic inflammatory state is characterized by elevated concentrations of circulating cytokines, including

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Original

C-reactive protein, tumor necrosis factor (TNF)-α, and various interleukins, which interfere with insulin signaling pathways and perpetuate metabolic dysfunction (2,4). The inflammatory trajectory of T2DM involves multiple pathogenic mechanisms, including immune cell activation, accumulation of senescent cells, and alterations in adipose tissue, liver, pancreatic islets, and vascular endothelium, creating a self-perpetuating cycle of metabolic inflammation (5,6).

The immunocompromised status associated with diabetes mellitus has raised significant concerns regarding the effectiveness and safety of COVID-19 vaccination in this vulnerable population (7). Multiple studies have demonstrated that patients with T2DM exhibit impaired antibody responses to COVID-19 vaccines compared to healthy controls, with reduced immunogenicity observed across various vaccine platforms, including mRNA, vector-based, and inactivated vaccines (8-10). The diminished vaccine effectiveness in diabetic patients ranges from 24% to 96%, compared to 33% to 97% in the general population, with breakthrough infections occurring more frequently in vaccinated individuals with diabetes (9). Furthermore, patients with T2DM demonstrate increased susceptibility to severe adverse events following COVID-19 vaccination, including thrombotic complications such as cerebral venous sinus thrombosis, deep vein thrombosis, and pulmonary embolism (11). The duration of antibody protection is also compromised in diabetic patients, with significantly decreased anti-receptor-binding domain immunoglobulin G (IgG) titers and neutralizing antibody responses observed beyond six months post-vaccination (10).

Extracellular signal-regulated kinase 5 (ERK-5), a member of the mitogen-activated protein kinase family, plays a crucial role in cardiovascular development and endothelial cell integrity, with emerging evidence suggesting its involvement in diabetes-related inflammatory responses (12-15). In diabetic conditions, ERK-5 expression and activity are significantly altered, with glucose-induced downregulation of ERK-5 contributing to the pathogenesis of diabetic complications, including retinopathy and angiopathy (13,14). The ERK-5 signaling pathway demonstrates dual functionality in inflammatory processes, exhibiting both pro-inflammatory and anti-inflammatory properties depending on the cellular context and stimulus. In diabetic endothelial cells, reduced ERK-5 activity leads to increased expression of inflammatory mediators such as vascular endothelial growth factor (VEGF), endothelin-1, and fibronectin, while simultaneously decreasing protective factors like Kruppel-like factor 2 (KLF2) (12-14,16). Given the critical role of ERK-5 in regulating inflammatory responses and its documented alterations in diabetes, investigating the ERK-5 expression following COVID-19 vaccination in T2DM patients (17) may provide valuable insights into the differential immune responses and potential mechanisms underlying reduced vaccine efficacy in this population.

Objectives

The main objective of this study is to evaluate and compare ERK-5 levels among adult males with T2DM who have either received or not received COVID-19 vaccination, as well as among healthy, non-diabetic, unvaccinated controls. This investigation aims to assess the impact of COVID-19 vaccination on the ERK-5 signaling pathway in the context of T2DM.

Patients and Methods

Study design and participants

This prospective case-control study enrolled 90 male participants attending Fallujah hospital in Al-Anbar province, Iraq, from February to October 2024. Participants were divided into three groups; the first group comprised vaccinated against COVID-19 individuals with a history of T2DM; the second group included unvaccinated T2DM patients; and the third group consisted of non-diabetic and unvaccinated individuals.

Inclusion and exclusion criteria

Inclusion criteria

- Group 1: adult males with confirmed T2DM + completed 3-dose COVID-19 vaccination
- Group 2: adult males with confirmed T2DM + no COVID-19 vaccination
- Group 3: healthy males (no diabetes) + no COVID-19 vaccination

Exclusion criteria

- Diabetes subtypes: type 1, gestational, or secondary diabetes
- Comorbidities: severe cardiovascular, renal, or hepatic diseases affecting vascular biomarkers
- Medications: use of high-dose corticosteroids or drugs altering inflammatory/vascular pathways
- Acute conditions: active infections or inflammation at enrollment
- COVID-19 history: infection within 3 months before study
- Vaccination status; partial vaccination

Demographic data collection

Initially, all male participants provided written informed consent. Demographic information, focusing primarily on age, was gathered directly from each individual by interview.

Laboratory data collection

To assess laboratory data, blood samples were collected from every participant. These samples underwent comprehensive laboratory analysis, which included measurements of blood sugar, HbA1c (glycosylated hemoglobin), and key serum electrolytes, including

phosphorus, sodium, potassium, and chloride. Additionally, biomarker assessment was performed, specifically targeting ERK-5 levels in the blood samples.

Outcomes

The primary outcomes of this study are the measured serum ERK-5 levels in each participant group. Specifically, the study will compare ERK-5 concentrations between vaccinated T2DM patients, unvaccinated T2DM patients, and non-diabetic, unvaccinated controls, to identify significant differences that may reflect the influence of both diabetes status and COVID-19 vaccination on ERK-5 expression.

Data analysis

IBM SPSS (Statistical Package for Social Sciences) version 27 was used for the statistical analyses conducted in this study. To assess data normality, the Kolmogorov-Smirnov test was performed. The distribution of age and laboratory data among the three groups was assessed by analysis of variance (ANOVA). Differences in ERK-5 levels among non-diabetic, unvaccinated individuals, fully vaccinated T2DM patients, and unvaccinated T2DM patients were assessed using one-way ANOVA. For post hoc analysis, the least significant difference (LSD) post hoc test was used to identify specific group differences. A P value of less than 0.05 was deemed statistically significant.

Results

This study included 90 males, with 30 in each of three treatment groups. The results indicated that the frequency distribution of demographic characteristics and laboratory data across the three treatment groups, including people without vaccination, individuals with T2DM without vaccination, and fully vaccinated T2DM patients, showed different results. Significant differences were observed in glycosylated hemoglobin and blood sugar levels, with both variables demonstrating statistically significant variation among the groups, which was expected due to diabetes in some groups. In contrast, no statistically significant differences were detected in age, chloride, potassium, sodium, or phosphorus levels, indicating comparable distributions of these parameters across the cohorts (Table 1).

The comparative analysis of ERK-5 levels across the three treatment groups, including non-diabetic unvaccinated individuals, unvaccinated T2DM patients, and fully vaccinated T2DM patients, revealed statistically significant disparities in mean concentrations. Post hoc analysis demonstrated that unvaccinated T2DM patients exhibited markedly higher ERK-5 levels compared to both non-diabetic unvaccinated individuals and vaccinated T2DM cohorts, with all pairwise comparisons reaching statistical significance. Vaccinated T2DM patients showed intermediate ERK-5 levels, significantly lower than unvaccinated diabetic counterparts but higher than non-diabetic controls. These findings suggest a pronounced elevation of ERK-5 in the context of T2DM, with COVID-19 vaccination status appearing to attenuate this increase (Table 2 and Figure 1).

Discussion

This study identified a statistically significant correlation between T2DM, COVID-19 vaccination, and the expression levels of ERK-5, proposing that vaccination may modulate ERK-5 expression in individuals with T2DM. The findings position ERK-5 as a potential biomarker for diabetes progression, highlighting a novel interaction wherein COVID-19 vaccination could influence ERK-5-mediated signaling pathways in diabetic patients. The observed elevation of ERK-5 in unvaccinated individuals with T2DM aligns with prior investigations demonstrating dysregulated ERK-5 signaling in diabetic pathophysiology. For instance, studies have reported increased ERK-5 expression in endothelial cells under hyperglycemic conditions, where its downregulation exacerbates vascular dysfunction by promoting endothelin-1 (ET-1) and VEGF production (13,17). Similarly, in the studies by Wu et al (14) and Zhao et al (18), retinal tissues from diabetic rodents exhibited

Table 1. The frequency distribution of demographic characteristics and laboratory data among treatment groups

Variable	People without vaccination (n=30)	T2DM without vaccination (n=30)	Full-vaccinated T2DM (n=30)	*P* value*
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (year)	54.57 (11.95)	52.30 (10.84)	57.33 (9.01)	0.194
Glycosylated hemoglobin (%)	5.12 (0.31)	8.23 (2.20)	8.82 (1.56)	<0.001
BS (mg/dL)	99.86 (8.86)	174.30 (79.43)	208.20 (62.67)	<0.001
Chloride (mEq/L)	101.90 (17.40)	97.80 (17.40)	99.53 (13.89)	0.473
Potassium (mEq/L)	4.58 (0.87)	4.66 (0.68)	4.71 (0.65)	0.794
Sodium (mEq/L)	137.10 (15.15)	134.76 (12.14)	135.93 (11.60)	0.743
Phosphorus (mg/dL)	4.70 (1.25)	3.64 (0.59)	12.90 (5.10)	0.418

T2DM; Type-2 diabetes mellitus; HbA1c, Glycosylated hemoglobin; BS, Blood sugar; SD, standard deviation.
*ANOVA.

Table 2. Comparative analysis of ERK-5 among the three treatment groups

	Group		Mean (SD)	*P* value*
ERK-5 (ng/mL)	People without vaccination		0.96 (0.26)	
	T2DM without vaccination		3.16 (0.50)	<0.001
	Full-vaccinated T2DM		1.77 (0.54)	
	Groups		**Mean difference**	***P* value****
	People without vaccination	T2DM without vaccination	2.19	<0.001
		Full-vaccinated T2DM	0.81	<0.001
	T2DM without vaccination	Full-vaccinated T2DM	1.39	<0.001

T2DM, Type-2 diabetes mellitus; ERK-5, Extracellular signal-regulated kinase 5; SD, Standard deviation.
*One-way ANOVA, **Post hoc LSD.

reduced ERK-5 activation alongside elevated VEGF and fibronectin levels, suggesting a compensatory increase in total ERK-5 protein to counterbalance impaired signaling (14, 18). However, these findings contrast with reports of glucose-induced ERK-5 suppression in microvascular endothelial cells, where hyperglycemia diminished phospho-ERK-5 levels and disrupted KLF2-mediated vasoprotection (13). This discrepancy may stem from differences in tissue-specific ERK-5 dynamics, as systemic ERK-5 elevation in T2DM could reflect a maladaptive response to chronic inflammation, whereas localized reductions in activated ERK-5 contribute to microvascular complications (14,17). The intermediate ERK-5 levels in vaccinated T2DM patients mirror observations in diabetic models treated with ERK-5 modulators, such as mitogen-activated protein kinase 5 (MEK5) inhibitors, which attenuated pathological angiogenesis without fully restoring baseline ERK-5 activity (18,19).

The attenuation of ERK-5 elevation in vaccinated T2DM patients suggests COVID-19 vaccination may modulate inflammatory or metabolic pathways influencing ERK-5 expression. ERK-5 is intricately linked to oxidative stress and cytokine signaling, with its transcriptional activity regulated by nuclear factor erythroid 2-related factor 2 (NRF2) and peroxisome proliferator-activated receptors (20,21). Vaccination-induced immune activation could temper chronic inflammation in T2DM, thereby reducing ERK-5 upregulation driven by pro-inflammatory cytokines like interleukin-6 (IL-6) and TNF-α (22,23). Notably, IL-6 overexpression in T2DM exacerbates insulin resistance and adipose tissue inflammation, processes modulated by ERK-5's interaction with nuclear factor of activated T-cells 4 (24). The partial normalization of ERK-5 levels post-vaccination may reflect improved glycemic control or reduced oxidative stress, as ERK-5 activation is sensitive to hyperglycemia-induced small ubiquitin-like modifier (SUMO) and p90 ribosomal S6 kinase inhibition (25,26). Furthermore, ERK-5's role in maintaining endothelial integrity through KLF2 and endothelial nitric oxide synthase regulation (12,21) implies that vaccination might mitigate diabetes-associated vascular dysfunction by restoring ERK-5 homeostasis. However, the persistence of higher ERK-5 in vaccinated T2DM patients compared to non-diabetic controls underscores residual metabolic

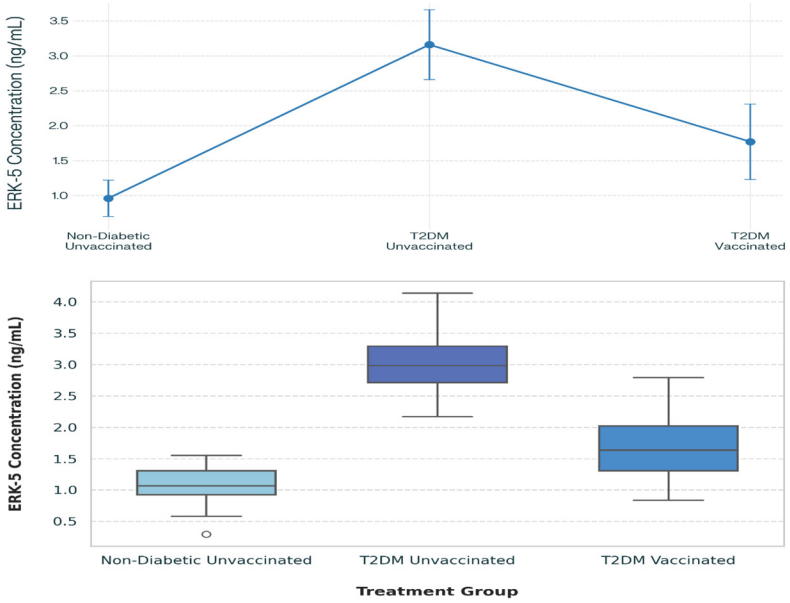

Figure 1. Comparison of ERK-5 between the three treatment groups. T2DM, Type-2 diabetes mellitus; ERK-5, Extracellular signal-regulated kinase 5.

dysregulation, potentially necessitating adjunct therapies targeting ERK-5 signaling.

Overall, these findings underscore ERK-5 as a pivotal mediator of diabetic vasculopathy, with its dysregulation reflecting a dual role in compensatory signaling and pathological inflammation. The intermediate ERK-5 levels in vaccinated T2DM patients suggest COVID-19 vaccination partially ameliorates diabetes-driven ERK-5 elevation, possibly through immunomodulatory effects on inflammatory pathways. This aligns with evidence that ERK-5 inactivation reduces VEGF-driven retinopathy and ET-1-mediated endothelial dysfunction (14,17), highlighting its therapeutic potential. However, the incomplete normalization of ERK-5 post-vaccination warrants further investigation into long-term metabolic outcomes and targeted interventions, such as MEK5 inhibitors or ERK-5 activators, to optimize vascular protection in T2DM (18,26). Future studies should delineate whether ERK-5 modulation directly enhances vaccine efficacy or mitigates diabetes-related complications, particularly in the context of hybrid immunity and emerging SARS-CoV-2 variants.

Conclusion

The findings from this study demonstrated a significant association between T2DM, COVID-19 vaccination status, and ERK-5 expression. The elevated ERK-5 levels observed in unvaccinated T2DM patients, which exceeded both non-diabetic controls and vaccinated diabetic cohorts, indicate a potential dysregulation of ERK-5 signaling pathways in uncontrolled metabolic disease. The intermediate ERK-5 concentrations in vaccinated T2DM patients, coupled with the statistically significant reduction compared to unvaccinated counterparts, suggest that COVID-19 vaccination may modulate ERK-5 expression, possibly through indirect immune or inflammatory mechanisms. These results highlight ERK-5 as a biomarker of interest in T2DM pathophysiology and imply that vaccination status could influence cellular signaling pathways in diabetic populations, warranting further investigation into the mechanistic links between metabolic health, immune interventions, and kinase regulation.

Limitations of the study

This study was conducted on a limited number of the patients and was a single-center study. We suggest larger multi-center investigations on these aspects of diabetic patients.

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Authors' contribution

Conceptualization: All authors.
Data curation: Jassim M. Abd Al-Hameed.
Formal analysis: Bushra H Ali.
Investigation: Jassim M. Abd Al-Hameed.
Methodology: Bushra H Ali.
Project Management: Jassim M. Abd Al-Hameed.
Resources: All authors.
Supervision: Bushra H Ali.
Validation: Bushra H Ali.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

The study was conducted under the guidelines of Declaration of Helsinki. Informed written consent was obtained from all participants. This study resulted from research by the Department of Chemistry, which is a part of a larger research project with ethical code 9224 registered on December 28, 2023, approved by the Ethics Committee of the College of Education for Pure Science (Ibn-Al-Haitham), University of Baghdad, Iraq. Some of this data has been published before, and this study presents separate data. Besides, the authors have thoroughly addressed ethical issues (including plagiarism, data fabrication, and double publication).

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Conflicts of interest

The authors declare no conflict of interest.

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