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Evaluation of serum triosephosphate isomerase levels in rheumatoid arthritis patients on infliximab; a prospective case-control study on the Iraqi population

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by synovial inflammation and joint destruction. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor-alpha (TNF-α), has been widely used for the treatment of RA.

Objectives: This study aims to evaluate serum levels of triosephosphate isomerase (TPI), an enzyme involved in glycolysis, in RA patients undergoing infliximab therapy compared to healthy controls.

Patients and Methods: This prospective case-control study at AL-Yarmouk Teaching Hospital in Baghdad, Iraq, involved 65 RA patients undergoing infliximab therapy and 25 healthy controls, with ethical approval obtained from Mustansiriyah University. Data collection included demographic information and blood samples, where serum was isolated for TPI analysis using ELISA, while whole blood was retained for erythrocyte sedimentation rate (ESR) measurement. Disease activity was evaluated according to Clinical Disease Activity Index (CDAI) scores and ESR levels.

Results: Results from the study indicated that among 90 participants (84.4% female), 65 were diagnosed with RA and 25 were healthy controls. A statistically significant correlation was found between serum TPI levels and RA, with an odds ratio (OR) of 81.12; after adjusting for confounding variables, TPI remained an independent predictor of RA diagnosis (OR = 12.73), suggesting that higher TPI levels are significantly associated with the disease. Furthermore, TPI demonstrated high diagnostic sensitivity and specificity at 98.5% and 100%, respectively, with a significance level of $P < 0.05$, underscoring its potential utility as a biomarker for RA.

Conclusion: The results demonstrated a significant correlation between elevated TPI levels and RA, with TPI serving as an independent predictor of the disease. The findings, which include a high sensitivity of 98.5% and specificity of 100%, suggest that TPI could be a valuable biomarker for the early diagnosis and management of RA.

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Introduction

Rheumatoid arthritis (RA) is a systemic, destructive inflammatory disease. While it may not directly result in immediate mortality, this condition significantly impacts the daily lives of patients; it can lead to disability and reduced mobility (1). Polyarthritis and tenosynovitis are the primary clinical manifestations of the disease, commencing in the small joints and subsequently progressing to bigger ones. As the disease advances, it affects more organs (2). The disease often affects subjects between the ages of 40 and 70; however, it can also occur at a younger age. Globally, the prevalence rate of RA is approximately 1%, with females experiencing a higher incidence. However, in Babylon-Iraq, the prevalence of RA is approximately 3% (3,4). The exact RA etiology remains unclear, with studies suggesting that various environmental and genetic factors contribute to its development (5). During RA, low- oxygen levels (hypoxia) result in changes in the way cells produce energy, specifically by altering mitochondrial function and switching to the glycolytic pathway. This modification leads to the development of abnormal blood vessel growth (angiogenesis), cell invasion, and the production of abnormal tissue (pannus). The lack of oxygen causes angiogenesis, a notable characteristic of rheumatoid synovitis (6).

Triosephosphate isomerase (TPI) is a metabolic enzyme that regulates the flow of glycolysis and energy generation by converting dihydroxyacetone phosphate (DHAP) into D-glyceraldehyde 3-phosphate (G3P). TPI is one of the glycolytic enzymes implicated in the pathogenesis of RA. Additionally, TPI has been shown to possess functions beyond glycolysis, including potential roles in the nucleus related to cancer pathogenesis and chemotherapy resistance (7). Deficiency of

Key point

The results of this study have significant clinical implications for the diagnosis and management of rheumatoid arthritis. The identification of serum triosephosphate isomerase (TPI) as a strong independent predictor of rheumatoid arthritis, with high sensitivity and specificity, suggests that TPI could serve as a valuable biomarker for early diagnosis, allowing for timely intervention and treatment adjustments. This is particularly important in a clinical setting where early detection can significantly influence disease progression and patient outcomes. By incorporating TPI measurement into routine clinical practice, healthcare providers may enhance their ability to monitor disease activity and response to infliximab therapy, potentially leading to more personalized treatment strategies. Furthermore, the findings underscore the need for ongoing research into the role of TPI in rheumatoid arthritis (RA) pathophysiology, which could open new avenues for therapeutic targets and improve overall patient care in managing this complex autoimmune disorder.

TPI leads to an autosomal recessive disease that causes neuromuscular degeneration, anemia, and death in early childhood (8). Among several biological disease-modifying anti-rheumatoid drugs, infliximab is a chimeric (human and animal) monoclonal antibody that attaches to tumour necrosis factor-alpha (TNFα), thus inhibiting its biological activity. It is typically used in concomitant with methotrexate for patients with moderate to severe disease. It is administered via intravenous infusion every eight weeks at a dose of 3 or 10 mg/kg following the initial dose at weeks 0, 2, and 6 (9).

In RA, different clinical scores and blood tests are utilized to assess disease activity. The laboratory test erythrocyte sedimentation rate (ESR) serves as a marker for inflammation and disease activity, but it is not specific to RA. Additionally, the Clinical Disease Activity Index (CDAI) score, is commonly used to evaluate disease activity without relying on inflammatory markers (10).

Objectives

The objective of this study is to assess the serum level of TPI in patients with RA receiving infliximab therapy compared to healthy controls, to evaluate the potential relationship between TPI levels and disease activity. By utilizing a prospective case-control design at AL-Yarmouk Teaching Hospital in Baghdad, Iraq, the study aims to determine whether elevated TPI levels correlate with the diagnosis of RA disease. This research seeks to evaluate TPI as a potential biomarker for RA diagnosis and treatment monitoring, thereby contributing valuable insights into the management of RA within the Iraqi population.

Patients and Methods

Study design and participants

This prospective case-control study was conducted at AL-Yarmouk Teaching Hospital in Baghdad, Iraq, to evaluate the serum levels of TPI in RA patients undergoing infliximab therapy. The study comprised 65 RA patients and 25 healthy individual controls. Ethical approval for the study was obtained from the scientific committee at the College of Pharmacy, Mustansiriyah University, ensuring adherence to ethical standards in research involving human subjects.

Inclusion and exclusion criteria

The inclusion criteria for this study required participants to be diagnosed with RA, aged between 18 and 65 years, and receiving infliximab infusion therapy for a minimum duration of six months. Conversely, exclusion criteria encompassed RA patients who had been on infliximab therapy for less than six months, as well as individuals with chronic diseases such as diabetes, heart disease, liver or kidney disease, other autoimmune disorders, tumors, and pregnant women. Additionally, patients with incomplete data were excluded to maintain the integrity and reliability of the study findings, allowing for a focused examination of the relationship between infliximab therapy and serum TPI levels in the specified population.

Data collection

Data collection for this study commenced with obtaining written informed consent from all participants. Comprehensive data were gathered from each enrolled patient, including demographic information such as age, gender, body mass index, family history, smoking status, and disease duration. Approximately 5 ml of blood was drawn from both patients and healthy controls; specifically, 3 ml was placed in a sterile gel tube and allowed to stand for approximately one hour before being centrifuged at 3000 rpm for 15 minutes. The serum obtained was carefully isolated using a micropipette, transferred to labeled Eppendorf tubes, and subsequently frozen at -40 °C until a quantitative assay of TPI could be conducted using the sandwich enzyme-linked immunosorbent assay (ELISA) technique. Additionally, the remaining 2 mL of whole blood was retained in an ethylenediaminetetraacetic acid (EDTA) tube for immediate measurement of the ESR.

Assessment of clinical disease activity index

The CDAI is a rapid and straightforward tool for measuring disease activity in RA patients, derived from a simple summation of various clinical parameters. Specifically, the CDAI is calculated by adding the count of tender joints (ranging from 0 to 28) and swollen joints (also ranging from 0 to 28), alongside the patient's overall assessment of disease severity and the physician's evaluation of disease activity, both measured using a Visual Analogue Scale (VAS) that spans from 0 to 10. The resulting CDAI score provides a clear classification of disease activity (11). A score of ≤2.8 indicates remission, scores ≤10 reflect low disease activity, scores ≤22 denote moderate disease activity, and scores > 22 signify high disease activity. This structured approach allows clinicians to effectively monitor RA progression and treatment response, facilitating timely adjustments in therapeutic strategies (12).

Statistical analysis

Statistical analysis for this study was performed using the Statistical Package for Social Science (SPSS) version 27 (IBM Corp, USA) and GraphPad Prism version 10 (GraphPad Software, CA, USA) to assess the correlation between TPI levels and the diagnosis of RA. Chi-square tests were utilized to evaluate associations between qualitative variables, while independent T-tests were employed to compare quantitative variables across the two groups of RA patients and healthy controls. Additionally, both univariate and multivariate logistic regression analyses were conducted to further explore the relationship between TPI levels and RA diagnosis. To identify optimal cut-off points for TPI in predicting RA, receiver operating characteristic (ROC) analysis was performed, maximizing the sum of sensitivity and specificity through the calculation of the area under the curve (AUC). A significance level for all tests was set at $P < 0.05$.

Results

Results showed that out of 90 participants (84.4% female), 65 were RA patients and 25 healthy individuals. A significant majority of participants reported no smoking history and a notable portion lacked a family history of RA. In terms of disease activity, a considerable number of RA patients exhibited moderate clinical disease activity, while a smaller group was classified as having low or high activity. The age range of participants varied widely, and body mass index (BMI) values indicated a tendency towards overweight status among the group. Disease duration in RA patients was 8.35 years, reflecting a chronic condition, while biochemical markers showed a range indicative of varying inflammatory responses (Table 1).

The results indicated that the frequency distribution of participants' gender and smoking status did not reveal a statistically significant difference between the two groups of RA patients and healthy individuals; however, significant statistical differences were observed in terms of age, BMI, TPI (triose-phosphate isomerase), and ESR between the two groups (Table 2).

The univariate logistic regression analyses revealed a statistically significant correlation between TPI levels and RA, with an odds ratio (OR) of 81.12, indicating a strong association. When adjusting for confounding variables such as age, gender, BMI, cigarette smoking, and ESR in the multivariate regression analysis, TPI emerged as an independent predictor for the diagnosis of RA, yielding an OR of 12.73; this suggests that higher TPI levels are significantly associated with the likelihood of having RA even after accounting for other influencing factors (Table 3).

The ROC analysis indicated that TPI demonstrated a highly favorable diagnostic performance. It was characterized by an excellent AUC value, a minimal standard error, and a confidence interval supporting its reliability. The statistical significance of the findings was reinforced by a *P* value indicating robust evidence against the null hypothesis, alongside a determined cut-off value for TPI. Furthermore, the analysis highlighted TPI's exceptional sensitivity and perfect specificity, suggesting its potential as a highly effective biomarker for diagnosing RA (Figure 1 and Table 4).

The results indicated that the levels of TPI varied across different disease activity categories in RA patients, with distinct mean values observed for low, moderate, and high disease activity, suggesting a potential relationship between TPI levels and disease severity. Similarly, the ESR exhibited differing median values across these categories, reflecting variations in inflammatory activity associated

Table 1. Demographic characteristics and sonographic findings of the included mothers in the study

Variable	Sub-variable	Frequency	Percent
Gender	Male	14	15.6
	Female	76	84.4
Smoking	No	84	93.3
	Yes	6	6.7
Family history of RA in RA patients	No	71	78.9
	Yes	19	21.1
CDAI in RA patients	Low	10	15.4
	Moderate	33	50.8
	High	22	33.8
Group	RA patients	65	72.2
	Healthy individual	25	27.8

Variable	Mean	SD	Min	Max
Age (year)	44.94	11.60	20	63
BMI (kg/m²)	30.09	5.67	17.10	45.48
Disease duration in RA patients (year)	8.35	6.26	1	25
TPI (ng/mL)	9.48	2.35	5.95	17.24
ESR (mm/h)	39.92	28.90	4	124

RA, Rheumatoid arthritis; CDAI, Clinical Disease Activity Index; SD, Standard deviation; Min, Minimum; Max, Maximum; BMI, body mass index; TPI, Triose-phosphate Isomerase; ESR, Erythrocyte sedimentation rate.

Table 2. Frequency distribution of participants' characteristics between the two groups of healthy individuals and RA patients

Variable		Group				*P* value
		Healthy individual (n = 25)		RA patients (n = 65)		
		N	%	N	%	
Gender	Male (n = 14)	5	35.7	9	64.3	0.471*
	Female (n = 76)	20	26.3	56	73.7	
Smoking	No (n = 84)	25	29.8	59	70.2	0.116*
	Yes (n = 6)	0	0	6	100	
Variable		**Mean**	**SD**	**Mean**	**SD**	
Age (year)		35.08	9.30	48.73	10.10	<0.001**
BMI (kg/m²)		26.13	4.24	31.61	5.44	<0.001**
TPI (ng/mL)		6.59	0.41	10.58	1.76	<0.001**
ESR (mm/h)		12.72	8.94	44.96	28.56	<0.001**

RA; Rheumatoid arthritis, SD; Standard deviation, BMI; Body mass index, TPI; Triose-phosphate isomerase, ESR; erythrocyte sedimentation rate.
*Chi-square; **Independent t test.

Table 3. The correlation between TPI level and rheumatoid arthritis and its predictive power by using both univariate and multivariate logistic regression analysis

Variable		RA patients compared to healthy individuals			
		P value	OR	95% CI	
				Lower	Upper
Unadjusted	TPI (ng/mL)	0.002	81.12	5.21	12.61.49
Adjusted	TPI (ng/mL)	0.018	12.73	6.72	19.63

CI, Confidence interval; OR, Odds ratio; TPI, Triose-phosphate isomerase.

Table 4. Diagnostic value of TPI in the predicting of RA using ROC analysis

Biomarker	AUC	SE	95% CI	*P* value	Sensitivity	Specificity	Cut-off value
TPI (ng/mL)	0.998	0.002	0.9936 to 1.000	<0.001	98.5%	100%	> 7.979

TPI, Triosephosphate isomerase; ROC, Receiver operating characteristic; AUC: Area under the curve; SE, Standard error; CI: Confidence interval.

with each level of disease activity. These findings underscore the importance of TPI and ESR as biomarkers that may correlate with the clinical status of RA, providing insights into the underlying pathophysiology and aiding in the assessment of disease progression (Figure 2).

Discussion

The study revealed a notable association between serum TPI levels and RA diagnosis among a cohort of participants, with a significant correlation indicating that elevated TPI levels serve as an independent predictor of RA, even after controlling for confounding factors. The odds ratio for this association was substantial, demonstrating a strong link between increased TPI levels and the likelihood of RA diagnosis. Furthermore, TPI exhibited exceptional diagnostic performance, achieving high sensitivity and specificity rates, which underscores its potential role as a reliable biomarker for RA. The findings emphasize the importance of TPI in enhancing diagnostic accuracy for this condition, suggesting its utility in clinical settings for the early identification of RA. A recent study by Lei et al on a collagen-induced arthritis model and clinical samples found the TPI gene expression in RA patients was higher than in the general population (13). Additionally, a proteomic analysis study on human plasma conducted by Escal et al revealed differences in TPI expression levels between patients with active RA and those in remission after methotrexate treatment, suggesting a potential role of TPI as a blood marker for methotrexate resistance (14).

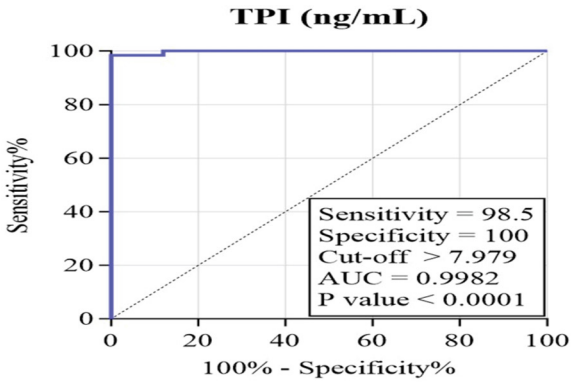

Figure 1. Diagnostic value of TPI in the predicting of RA using ROC analysis.

The ROC analysis was applied to demonstrate the diagnostic performance of TPI on RA patients. The data shows that TPI has an excellent ability to predict RA patients from healthy individuals with high sensitivity and specificity indicating it is a good biomarker to discriminate RA from normal individuals. Jean Escal et al observed that the mean AUC of patients with active RA was significantly lower compared to those with remission, with a ratio of 1.14 (14). Research conducted by Li et al found that TPI has

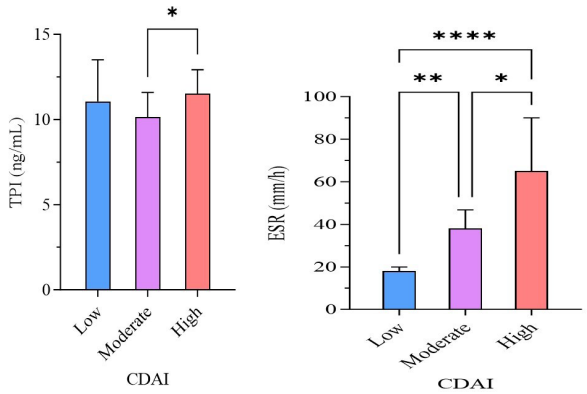

Figure 2. Comparative distribution of TPI and ESR levels according to different disease activity categories based on CDAI in RA patients.

a high discrimination ability between laryngeal squamous cell carcinoma (LSCC) and non-laryngeal squamous cell carcinoma (non-LSCC) tissue (15).

In RA, inflammatory parameters such as ESR and CRP, along with clinical scores including the CDAI and Disease Activity Score-28 joint count (DAS-28) are used to assess disease activity (10). In this study, the CDAI score was used to evaluate RA activity. Results showed that from 65 RA patients receiving infliximab, none were in remission, 10 had low disease activity, 33 had moderate activity, and 22 had severe disease activity. This could be due to patients receiving infliximab for extended periods, leading to a secondary loss of responsiveness. Additionally, there was a significant difference in mean TPI levels across CDAI scores, suggesting that TPI could serve as a marker for disease activity. Escal et al found a potential association between TPI levels and disease activity as measured by the DAS-28 score (14).

Furthermore, this study found a difference in ESR values according to disease activity. This indicates that ESR is a reliable marker for disease activity in RA patients. These results are consistent with those of Seringec Akkececi et al and Movahedi et al but contradict the findings of Mohammed et al and Gernert et al who suggested that ESR values did not significantly differ between the CDAI categories in RA patients (16-19). Studies on the correlation between TPI and ESR have been limited. However, there is an indirect explanation for this correlation. In RA, elevated ESR readings often indicate higher levels of inflammation. Immune cells, including macrophages and vascular endothelial cells, often shift their metabolism to glycolysis, a phenomenon referred to as the Warburg effect, to meet the greater need for energy requirements during rapid activation and proliferation. This change promotes the heightened activity of these cells, leading to an increase in glycolysis enzymes such as TPI (20).

The findings from this study provide significant insights into the relationship between serum TPI level and RA disease. The results indicate a strong correlation between elevated TPI levels and the presence of RA, suggesting that TPI could serve as a valuable biomarker for diagnosing this autoimmune condition. The analysis revealed that even after accounting for confounding factors, TPI remained an independent predictor of RA, highlighting its potential role in the disease's pathophysiology. The high diagnostic sensitivity and specificity observed for TPI further emphasize its reliability as a biomarker. Such performance characteristics suggest that TPI could not only assist in the early detection of RA but also enhance the accuracy of diagnosis, which is crucial for timely intervention and management of the disease. The statistical significance of these findings underscores the need for further exploration into the mechanisms by which TPI may influence or reflect RA activity.

In conclusion, this study advocates for the continued investigation of serum TPI levels in relation to RA. The potential of TPI as a diagnostic tool could lead to improved clinical outcomes through better identification and monitoring of RA. Future research should focus on validating these findings across broader populations and examining the biological implications of TPI in the context of RA, ultimately aiming to integrate this biomarker into routine clinical practice for enhanced patient care.

Conclusion

In conclusion, the results of this study highlight a significant association between elevated serum TPI levels and RA disease, with TPI identified as an independent predictor of the disease, evidenced by an odds ratio of 12.73 after adjusting for confounding factors. The high diagnostic sensitivity of 98.5% and specificity of 100% further underscore the potential of TPI as a reliable biomarker for RA, suggesting its utility in clinical practice for early diagnosis and effective management of the disease. These findings pave the way for further research into TPI's role in RA pathophysiology and its application in enhancing diagnostic accuracy and patient outcomes.

Limitations of the study

This study has several limitations that should be acknowledged. First, the relatively small sample size of 65 RA patients and 25 healthy controls may limit the generalizability of the findings to broader populations, particularly outside the Iraqi context. Second, the study's cross-sectional design restricts the ability to establish causal relationships between serum TPI level and RA, as it does not account for changes in TPI levels over time or in response to treatment. Additionally, while TPI was identified as a potential biomarker for RA, other confounding factors such as comorbidities, variations in disease duration, and treatment regimens were not fully controlled, which may influence TPI levels and disease activity. Furthermore, reliance on self-reported demographic information could introduce bias or inaccuracies in data collection. Lastly, the study primarily focused on a specific population undergoing infliximab therapy, which may not reflect the experiences of RA

patients receiving other treatments or those in different geographical regions. These limitations highlight the need for larger, multicenter studies to validate these findings and explore the role of TPI in diverse patient populations.

Authors' contribution

Conceptualization: Wassan Abdul Kareem Abbas, Mayssaa E. Abdalaha.
Data curation: Sana Dhia Khalil.
Formal analysis: Sana Dhia Khalil.
Investigation: Sana Dhia Khalil.
Methodology: Sana Dhia Khalil and Wassan Abdul Kareem Abbas.
Validation: Wassan Abdul Kareem Abbas.
Visualization: Wassan AbdulKareem Abbas, Mayssaa E. Abdalaha.
Resource: All authors.
Project administration: Sana Dhia Khalil.
Supervision: Wassan Abdul Kareem Abbas, Mayssaa E. Abdalaha.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Ethical issues

The research was conducted in accordance with the Declaration of Helsinki. The study was extracted from the MSc thesis of Sana Dhia Khalil at the Department of Clinical Laboratory Science at the College of Pharmacy, Mustansiriyah University (Thesis title: Evaluation of Serum Triosephosphate Isomerase and Col3-4 levels in RA patients on Methotrexate and Infliximab). This study was approved by the Ethic Research Committee of Pharmacy College (Approval No. 125 in 2024). Written informed consent was obtained from each participant. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Conflicts of interest

The authors declare no conflict of interest.

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