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Research Article

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Assessment of TNF-alpha Levels in Pre-Diabetic Patients for Predicting Type 2 Diabetes

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ABSTRACT

Background: Type 2 Diabetes is a prevalent chronic disease with significant health implications, and early identification of individuals at high risk is crucial for effective prevention and management strategies. This study assesses Tumour Necrosis Factor-alpha levels in patients with pre-diabetes and determines its effectiveness as a predictive biomarker for the development of Type 2 Diabetes Mellitus (T2DM).

Methods: This cross-sectional study was conducted at the Department of Medicine, Mardan Medical Complex Teaching Hospital, Khyber Pakhtunkhwa, Pakistan. Patient were divided into three groups: control, pre-diabetic, and diabetic, based on their glycemic status. The Kruskal-Wallis One-Way Analysis of Variance (ANOVA) was used to compare Control, Pre-Diabetes, Diabetic, and all study variables, including TNF. TNF's ability to predict pre-diabetics and diabetics was assessed utilizing receiver operating characteristic (ROC) curve analysis and area under the curve calculation.

Results: This study included a total of 270 patients. The pre-diabetic patients demonstrated significantly elevated levels of TNF-α (46.62±18.76 pg/mL), which were much higher than the control group (13.15±3.55 pg/mL). The increase in TNF-α levels was also correlated with other characteristics connected to diabetes, including body mass index (BMI), HBA1c levels, insulin resistance, and lipid profile parameters. The AUC values for the pre-diabetic and diabetic groups were higher, with the pre-diabetic group having a slightly higher AUC of 0.84 than the diabetic group's AUC of 0.81.

Conclusion: Increased TNF-alpha levels in pre-diabetics indicate an elevated inflammatory response, potentially crucial in the progression from insulin resistance to overt diabetes.

Key-words: TNF-alpha, Immune cells, Prognostic marker, Pre-diabetes, type 2 diabetes

INTRODUCTION

Type 2 Diabetes (T2D) is a primary worldwide health concern that affects a large number of people worldwide and results in significant morbidity and mortality [1]. This condition is characterized by insulin resistance and insufficient insulin production, leading to chronically elevated blood sugar levels.

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Early detection and intervention are essential in preventing or delaying the onset of T2D [2]. There is a growing emphasis on identifying biomarkers that can reliably predict the probability of acquiring T2D among people who are in the pre-diabetic phase.

Tumor Necrosis Factor-alpha (TNF-alpha) is a biomarker that contributes to the pathogenesis of insulin resistance and T2D by facilitating the process of inflammation. Elevated levels of TNF-alpha have been linked to the impairment of insulin signaling pathways, leading to the development of insulin resistance, a defining trait of T2D [3]. Studies have shown that TNF-alpha plays a role in both the progression and the initiation of diabetes, suggesting its potential as a predictive marker [4].

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Pre-diabetes is a critical phase for intervention since it indicates a state where blood glucose levels are increased but not yet at the threshold to be classified as diabetes [5]. Individuals with pre-diabetes possess an elevated probability of developing T2D, making this population crucial for research studies focused on disease prevention [6]. Identifying biomarkers, such as TNF-alpha, in individuals with pre-diabetes could provide valuable insights for adopting timely intervention strategies.

There has been a lack of studies investigating the role of several biomarkers in T2D, specifically the precise importance of TNF-alpha in diabetes [7]. Nevertheless, our understanding of predicting the progression from pre-diabetes to T2D remains inadequate. Recent study data suggests a correlation between elevated levels of TNF-alpha and an increased susceptibility to developing T2D. Nevertheless, the findings are still inconclusive [8]. Insufficient data exists on the prognostic importance of TNF-alpha levels in individuals in the pre-diabeticphase. This study aims to analyze the levels of TNF-alpha in individuals with pre-diabetes and assess its viability as a predictive biomarker for the development of T2D. This research aims to improve the early detection and preventive strategies for T2D, which can potentially influence both clinical practices and public health policies.

MATERIALS AND METHODS

Place of the study- This analytical cross-sectional study was conducted at the Department of Medicine, Mardan Medical Complex Teaching Hospital in Khyber Pakhtunkhwa, Pakistan, from June 2023 to November 2023.

Selection criteria of Subject- Patient data was collected via a convenience sampling method and categorized into three groups: Control (non-diabetic), Pre-Diabetic, and Type 2 Diabetic. The American Diabetes Association (ADA) guidelines provided the diagnostic framework for diabetes mellitus, utilizing Fasting Plasma Glucose (FPG) and Hemoglobin A1c (HbA1c) results. Pre-diabetes was identified with FPG levels ranging from 100–125 mg/dl (5.6–6.9 mmol/l) and HbA1c between 5.7–6.4%. Diagnosis of diabetes was confirmed with FPG levels exceeding 126 mg/dl (7.0 mmol/l) or HbA1c levels at or above 6.5% [9].

Inclusion Criteria- Inclusion criteria for the study encompassed patients from the Type 2 Diabetes, Pre-Diabetic, and Control groups.

Exclusion Criteria- Exclusion criteria included patients with comorbidities other than diabetes, those under 18 years, incomplete laboratory or evaluation data, and presence of smoking or snuffing history.

Data collection- Demographic details, economic status, family diabetes history, diabetic medication type, Body Mass Index (BMI), and diabetes duration were collected through interviews and standardized questionnaires. Five millilitres of random and fasting blood samples were obtained from each patient for blood tests. TNF alpha and insulin levels were measured using a commercially available ELISA kit. To mitigate potential confounders, Roche Cobas e411 and c111 analyzers performed additional laboratory tests, including HbA1c, fasting and random blood glucose levels, postprandial glucose, lipid profiles (Cholesterol, triglycerides, high-density and low-density lipoproteins), C-reactive protein, creatinine, and blood urea. Hematological parameters like hemoglobin, platelet count, total leukocyte count, and differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) were assessed using a Sysmex XN-330 hematological analyzer. Biomarkers such as the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were calculated using the formula "HOMA-IR =fasting insulin (µU/ml) × fasting glucose (mg/dl)/405."[10]

Non-High-Density Lipoprotein (NHDL) is computed as "Cholesterol - NHDL", and Very Low-Density Lipoprotein (VLDL) as "Triglycerides ÷ 5."

Statistical Analysis- Continuous variables were summarized as mean and standard deviations, while categorical variables were reported as frequencies and percentages. To examine differences among the group's control, pre-diabetes, diabetic, and across all study variables, including tumor necrosis factor-alpha, the Kruskal-Wallis One-Way Analysis of Variance (ANOVA) was employed. The relationship between TNF and all studied variables was evaluated utilizing Pearson's correlation coefficient, represented as Standardized Coefficients. Simple linear regression analysis was conducted to investigate the associations between TNF levels, patient groups, and other variables while

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controlling for potential covariates. The discriminatory ability of TNF to predict Pre-Diabetic and diabetic patients was evaluated using receiver operating characteristic (ROC) curve analysis and calculating the area under the curve (AUC). A $p<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (version 27.0).

Ethical Approval- Patients were included in this study following approval from the Institutional Review Boards with Reference No 472/ BKMC, Dated 04/06/2023, of Mardan Medical Complex and Bacha Khan Medical College Pakistan. Participants provided explicit consent after being fully informed about the study and could choose whether to participate or withdraw at any time.

RESULTS

In this study of 270 patients across the Control, Pre-Diabetic, and Diabetic groups, we found noteworthy differences. Age varied, with pre-diabetic patients being slightly older (Mean±SD: 49.47±8.50) compared to Control (47.63±9.28) and Diabetic (48.46±8.93) groups. Family history of diabetes was consistent across the groups (Control: 46.66%, Pre-Diabetic: 53.33%, Diabetic: 52.22%). Economic status showed no significant differences. Notably, the type of diabetic drug use differed significantly (Oral: Diabetic 56.66%, Insulin: Diabetic 43.34%), and Diabetic patients had a duration of 12.41±3.01 years. The most striking finding was the substantial BMI disparity (Control: 20.45±1.44, Pre-Diabetic: 22.65±2.60, Diabetic: 42.60±5.15), emphasizing BMI's role in distinguishing these groups and suggesting its importance in the transition from pre-diabetes to Diabetes (Table 1).

Table 1: Distribution of demographic characteristics based on patient groups

Characteristics	All patients	Control	Pre-Diabetic	Diabetic	p-value
Total Patients	270(100)	90(33.33)	90(33.33)	90(33.33)	***
Age	48.52±8.91	47.63±9.28	49.47±8.50	48.46±8.93	0.00
Gender					
Male	156(57.77)	58(64.44)	47(52.22)	51(56.66)	0.24
Female	114(42.23)	32(35.56)	43(47.78)	39(43.34)	
Family history of diabetes					
Yes	137(50.74)	42(46.66)	48(53.33)	47(52.22)	0.63
No	133(49.25)	48(53.34)	42(46.67)	43(47.78)	
Type of diabetic drug used					
None	180(66.66)	0(0.00)	0(0.00)	0(0.00)	0.00
Oral	51(18.88)	0(0.00)	0(0.00)	51(56.66)	
Insulin	39(14.44)	0(0.00)	0(0.00)	39(43.34)	
Economic Status					
Lower	96(35.55)	29(32.22)	30(33.33)	37(41.11)	0.43
Middle	95(35.18)	37(41.11)	29(32.22)	29(32.22)	
Upper	79(29.25)	24(26.66)	29(32.22)	24(26.66)	
Diabetes duration	12.41±3.01	0(0.00)	0(0.00)	12.41±3.01	**
BMI	28.57±10.55	20.45±1.44	22.65±2.60	42.60±5.15	0.00

Data is presented as frequency and percentage or as mean and standard deviation; BMI: Body mass index
*p-value with *** represent the characteristic is either present in all study population or none.*
*** There are fewer than two groups for dependent variable Duration of diabetes. No statistics are computed. P-value<0.05 is statically significant*

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Assessing biomarkers in control, pre-diabetic, and diabetic groups, significant differences were observed, particularly in TNF-alpha (TNF-α) levels. Pre-diabetic individuals exhibited elevated TNF-α levels (46.62±18.76 pg/mL), markedly higher than in the control group (13.15±3.55 pg/mL), suggesting its potential as a predictive marker for the progression to type 2 diabetes. Other biomarkers, including HBA1c, insulin, various glucose levels, and lipid profiles (cholesterol, triglycerides, HDL, non-HDL, LDL, VLDL), also showed significant variations, with diabetic patients typically presenting higher values. Interestingly, C-reactive protein (CRP) levels did not significantly differ among the groups (Table 2).

Table 2: Distribution of all biomarkers based on patient groups.

Characteristics	All patients	Control	Pre-Diabetic	Diabetic	p-value
TNF-α	34.81±19.78	13.15±3.55	46.62±18.76	44.65±10.25	0.00
HBA1c	7.37±2.66	5.09±0.12	6.04±0.21	10.98±1.05	0.00
Insulin	20.53±12.9	7.50±0.90	16.61±2.62	37.47±4.74	0.00
RBG	178.36±69.80	108.06±12.55	169.20±17.72	257.83±52.78	0.00
FBG	117.72±30.78	86.35±3.96	111.37±7.56	155.45±17.79	0.00
Homa.IR	6.85±5.70	1.60±0.20	4.55±0.74	14.40±2.63	0.00
PPG	164.01±51.32	117.63±8.48	145.07±14.43	229.33±28.79	0.00
Urine glucose	91(33.70)	0(0.00)	44(48.88)	47(52.22)	0.00
Cholesterol	158.36±49.89	112.56±12.70	140.71±23.83	221.80±16.96	0.00
Triglycerides	249.79±88.83	146.81±9.74	251.44±16.70	351.08±48.84	0.00
HDL	44.18±4.85	48.56±2.98	45.07±1.83	38.90±3.23	0.00
Non-HDL	114.16±53.68	63.99±12.69	95.59±23.96	182.89±17.45	0.00
LDL	94.74±42.68	57.08±3.87	81.47±14.03	145.68±32.54	0.00
VLDL	49.95±17.76	29.37±1.94	50.28±3.34	70.21±9.76	0.00
CRP	4.52±1.39	4.61±1.47	4.47±1.26	4.48±1.43	0.73
Hemoglobin	13.09±1.15	13.64±0.93	13.62±1.03	12.01±0.57	0.00
TLC	8589±1490	7465±1109	8515±1038	9786±1291	0.00
Neutrophils	5325±923	4628±687	5279±643	6067±801	0.00
Lymphocytes	2490±423	2164±321	2469±301	2838±374	0.00
Eosinophils	171±29	149±22	170±20	195±25	0.00
Monocytes	429±74	373±55	425±51	489±64	0.00
Basophils	121±20	105±11	129±24	148±31	0.00
Platelets	267.2±19.17	277.3±49.58	269.8±49.84	254.6±45.77	0.007
Creatinine	1.12±0.35	0.88±0.058	0.91±0.059	1.57±0.27	0.00
Blood Urea	43.62±27.76	26.02±3.55	25.91±3.35	78.94±20.35	0.00

Data is presented as frequency and percentage or as mean and standard deviation
TNF-α: Tumor Necrosis Factor alpha, RBG: Random blood glucose, FBG: Fasting blood glucose, PPG: Postprandial Glucose, HDL: High density lipid, Non-HDL:Non- High density lipid, LDL:Low density lipid, VLDL: Very Low density lipid, CRP: C-Reactive Protein, TLC: Total leukocyte count, p-value<0.05 is statically significant.

The Simple Linear Regression Analysis revealed key factors significantly associated with Tumor Necrosis Factor alpha (TNF-α) levels. Notably, patient groups (control, pre-diabetic, diabetic) demonstrated a strong positive correlation with TNF-α, underscoring its predictive value. Metabolic factors such as BMI, HBA1c, insulin, various glucose measurements (RBG, FBG, PPG, Homa.IR), and lipid profiles (including cholesterol, triglycerides, and HDL) also showed significant positive associations. Conversely, urine glucose and hemoglobin were negatively associated with TNF-α levels. Blood cell counts (like TLC, neutrophils, lymphocytes) and renal function markers (creatinine, blood urea) were positively correlated with TNF-α levels. In contrast, gender, age, family history, and economic status did not exhibit a significant association (Table 3).

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Table 3: Simple linear regression analysis of factors associated with tumor necrosis factor alpha

Model	Unstandardized Coefficients		Standardized Coefficients	t-value	p-value
	Beta	Std. Error	Beta		
Gender	2.678	2.437	0.067	1.099	.273
Age	-0.01	0.13	-0.007	-0.11	0.90
Family history	-0.42	2.41	-0.01	-0.17	0.86
Patient groups	15.75	1.12	0.75	14.04	0.00
BMI	0.72	0.10	0.51	6.84	0.00
Type of drug	9.4	1.53	0.53	6.16	0.00
Economic status	-0.07	1.50	-0.00	-0.04	0.963
HBA1c	3.30	0.40	0.54	8.12	0.00
Insulin	0.77	0.08	0.63	9.56	0.00
RBG	0.151	0.01	0.61	10.32	0.00
FBG	0.35	0.03	0.58	10.57	0.00
Homa.IR	1.61	0.18	0.59	8.62	0.00
PPG	0.17	0.02	0.49	8.49	0.00
Urine glucose	15.69	2.36	0.47	6.63	0.00
Cholesterol	0.19	0.02	0.53	8.99	0.00
Triglycerides	0.13	0.01	0.69	12.41	0.00
HDL	-1.95	0.21	-0.51	-8.93	0.00
Non-HDL	0.18	0.02	0.49	9.22	0.00
LDL	0.20	0.02	0.52	8.28	0.00
VLDL	0.67	0.05	0.63	12.41	0.00
CRP	-0.56	0.86	-0.040	-0.65	0.51
Hemoglobin	-4.58	1.00	-0.26	-4.55	0.00
TLC	0.006	0.00	0.49	8.04	0.00
Neutrophils	0.009	0.00	0.44	8.04	0.00
Lymphocytes	0.02	0.00	0.48	8.04	0.00
Eosinophils	0.29	0.03	0.44	8.04	0.00
Monocytes	0.11	0.01	0.45	8.04	0.00
Basophils	0.29	0.03	0.46	8.04	0.00
Platelets	-2.05	0.00	-0.05	-0.83	0.40
Creatinine	17.78	3.18	0.42	5.58	0.00
Blood Urea	0.20	0.04	0.38	5.03	0.00

Dependent Variable: Tumor Necrosis Factor alpha
TNF-α: Tumor Necrosis Factor alpha, RBG: Random blood glucose, FBG: Fasting blood glucose, PPG: Postprandial Glucose, HDL: High density lipid, Non-HDL: Non- High-density lipid, LDL: Low density lipid, VLDL: Very Low-density lipid, CRP: C-Reactive Protein, TLC: Total leukocyte count. p-value <0.05 is statically significant.

The AUC values for the pre-diabetic and diabetic groups are relatively high, with the pre-diabetic group having a slightly higher AUC of 0.84 than the diabetic group's AUC of 0.81 (Fig. 1).

Graphical analysis underscored significant differences in mean TNF-α levels between different groups, with notable variability in TNF-α levels among the pre-diabetes group, indicated by larger error bars (Fig. 2).

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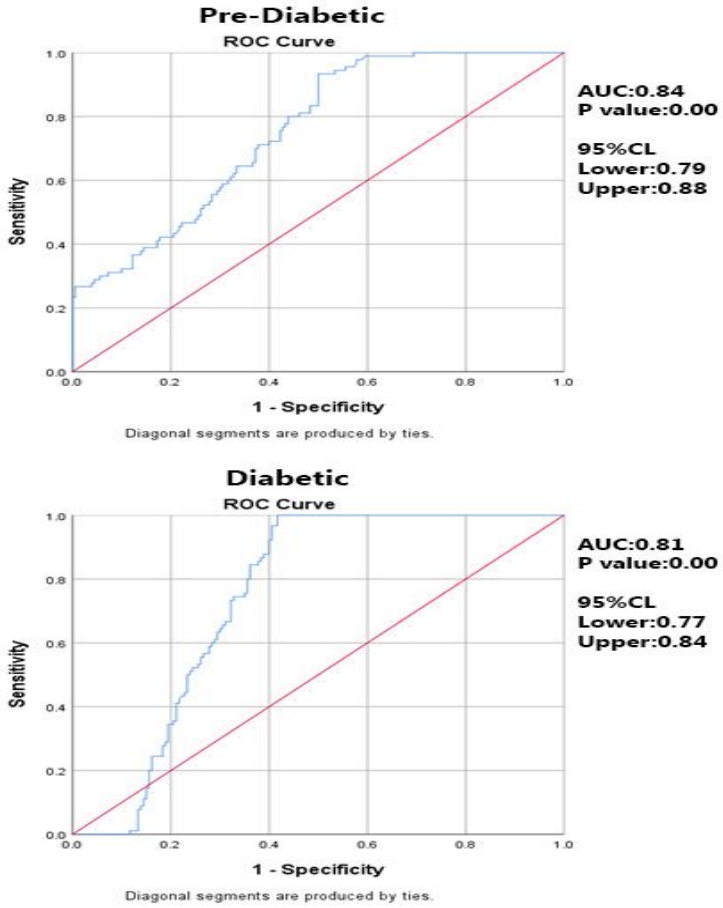

Fig. 1: Receiver operator characteristic curve analysis of tumor necrosis factor alpha

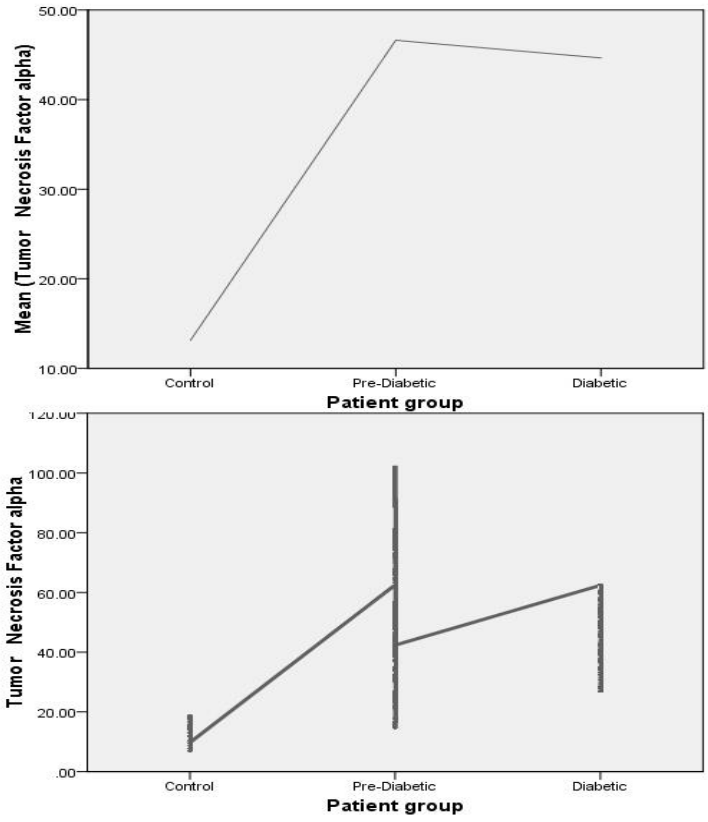

Fig. 2: Comparison of Mean and individual TNF-alpha Levels Between Different Groups

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DISCUSSION

This study's objective was to evaluate TNF-alpha levels in patients with pre-diabetes as a prognostic indicator for the development of Type 2 Diabetes Mellitus (T2DM). The results of our study showed that Patients with pre-diabetes had increased levels of TNF-alpha, which were considerably greater compared to the control group.

An important finding in this study is the substantial difference in BMI among the different groups. Individuals who were pre-diabetes had a BMI (22.65±2.60) that was between the BMI of the control group (20.45±1.44) and the diabetic group (42.60±5.15). The significant difference in BMI highlights the crucial role of BMI in differentiating patients with pre-diabetes from those with diabetes. These findings are consistent with Ng *et al.* [11]. who emphasizes the significant correlation between BMI and the likelihood of type 2 diabetes. The results of our study revealed a strong association between BMI and TNF-alpha levels, which aligns with the findings of Papatheodorou *et al*. [12], who also observed a connection between obesity, TNF-alpha levels, and T2DM. The presence of a family history of diabetes was uniform throughout all the groups, suggesting that genetic susceptibility alone may not be an adequate indicator for the development of diabetes. This finding highlights the complex and varied causes of diabetes and indicates that environmental and lifestyle factors may have a greater impact on the transition from pre-diabetes to diabetes.

The evaluation of biomarkers in our study showed noteworthy differences among the Patient groups, with a specific emphasis on TNF-alpha (TNF-α) levels. Pre-diabetic individuals demonstrated significantly elevated levels of TNF-α (46.62±18.76 pg/mL), which were much greater than those observed in the control group (13.15±3.55 pg/mL). A recent study by Navarro *et al.* [13] emphasized the significance of TNF-α in the development of diabetes, particularly its potential as a prognostic indicator for the advancement to type 2 diabetes. Additional biomarkers, such as HBA1c, insulin, and different glucose levels, also demonstrated substantial variations, with diabetes Patients typically displaying elevated values. A study has highlighted the significance of these indicators in evaluating the likelihood and advancement of diabetes. Higher levels of HBA1c have been associated with inadequate control of blood sugar levels and a greater likelihood of experiencing problems related to diabetes [14]. Notably, there were no significant differences in C-reactive protein (CRP) levels between the groups in our study. This suggests although inflammation is involved in diabetes, CRP may not be a reliable indicator for early identification. This indicates the necessity for a more extensive array of biomarkers to evaluate the inflammatory aspect of the risk of diabetes.

A novel finding in our study that has not been examined in the existing body of literature, the Simple Linear Regression Analysis revealed several parameters strongly linked to TNF-α levels. The classification of patient groups has emerged as a robust predictor, indicating the potential of TNF-α as a biomarker for differentiating between control, pre-diabetic, and diabetic individuals. Recent studies have emphasized the significance of TNF-α in insulin resistance and its potential as a target for treatment in diabetes management, and our findings were comparable [15].

Biomarkers associated with metabolisms, such as HBA1c, insulin, and different glucose measures, showed strong positive relationships with TNF-α levels in Simple Linear Regression Analysis. A study by Alzamil [16] has provided additional clarity on the complex connection between these metabolic variables and TNF-α, highlighting their significance in the advancement of diabetes. The levels of TNF-α were significantly associated with lipid profiles, specifically cholesterol, triglycerides, and HDL. Another study has emphasized the influence of dyslipidemia on inflammation and insulin resistance in individuals with diabetes [17]. The interaction between lipid metabolism and inflammation highlights the intricate nature of diabetes development.

Our study revealed a strong inverse correlation between hemoglobin and urine glucose levels and TNF-α levels. This finding implies a regulatory system that involves the production of red blood cells and the presence of inflammation, as well as the excretion of glucose and inflammation. However, additional research is required to clarify these pathways. The levels of TNF-α were shown to have favorable relationships with blood cell counts, specifically TLC, neutrophils, and lymphocytes. This indicates that inflammatory processes have a significant impact on hematological parameters. A study by Mzimela *et al.* [18] has investigated the complex interrelationships between inflammation and blood cell counts in individuals with diabetes. Levels of renal

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function Parameters, such as creatinine and blood urea, showed a positive correlation with TNF-α levels. A recent study has provided insight into the influence of renal function on inflammation and the course of diabetes, highlighting the need to consider kidney health in diabetes management [19].

Another novel finding in our study is the examination of AUC values. Our study showed that the pre-diabetic and diabetic groups had relatively high values. The pre-diabetic group had a slightly higher AUC of 0.84 than the diabetic group's AUC of 0.81. The AUC findings indicate that TNF-alpha levels possess strong discriminatory ability and clinical usefulness in identifying persons who are at risk of acquiring diabetes. Our study emphasized the potential of TNF-alpha levels as a promising biomarker for forecasting the transition from pre-diabetes to type 2 diabetes.

The conclusions of the current study have several limitations. First, our study employed a cross-sectional design, which only provides a snapshot of the data at a specific point in time. This limits our ability to establish causal relationships or track changes over time. Longitudinal studies would be beneficial in understanding the dynamics of TNF and their association with pre-diabetes and type 2 diabetes. Second, the limited sample size and our study's single-centre nature may reduce the generalizability of our findings. To address this issue, future studies should aim to include larger sample sizes and involve multiple centers to validate our results. Third, we did not evaluate patients with comorbidities other than type 2 diabetes in our study. Future studies should investigate the impact of different comorbidities TNF levels in pre-diabetes and type 2 diabetes patients, as we hypothesize that these patients may have higher TNF levels. Fourth, most of our patients were elderly. This introduces a potential bias as advanced age is known to be an independent risk factor for the increased levels of TNF. The findings from our study may not accurately represent the experiences and symptoms of younger individuals with diabetes. Therefore, the generalizability of our results to younger age groups may be limited. Future studies should aim to include a more diverse range of age groups to obtain a comprehensive understanding of the symptoms and complications associated with diabetes across different populations.

CONCLUSIONS

The increase in TNF-alpha levels in patients with pre-diabetes indicates an elevated inflammatory response, which may play a crucial role in the progression from insulin resistance to overt diabetes. The study's results suggest that TNF-alpha serves as a signal of inflammation and a possible early sign of metabolic conditions that can contribute to developing type 2 diabetes. This conclusion presents opportunities for developing early intervention measures. Through the identification of patients exhibiting increased levels of TNF-alpha, healthcare practitioners can more precisely focus on implementing preventative interventions, which could potentially result in the delaying or even prevention of the development of type 2 diabetes.

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CONTRIBUTION OF AUTHORS

Research concept-Murad Ali, Ashraf, Imran Ali Zaidi
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Critical review- Murad Ali, Ashraf, Imran Ali Zaidi
Article editing- Murad Ali, Ashraf, Imran Ali Zaidi
Final approval-Murad Ali, Imran Ali Zaidi

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