Research Article

A Novel Multi-Biomarker Approach For The Diagnosis Of Type 2 Diabetes Mellitus: Combined Evaluation Of Beta Trace Protein, Beta-2 Microglobulin, And Trefoil Factor-3

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder associated with persistent hyperglycemia, chronic inflammation, endothelial dysfunction, and progressive renal impairment. Early identification of biomarkers reflecting these pathological changes is essential for improving diagnosis and preventing diabetes-related complications. **Aim:** This study aimed to evaluate the diagnostic value of Beta Trace Protein (BTP), Beta-2 Microglobulin (β2M), and Trefoil Factor 3 (TFF3) as potential biomarkers for Type 2 Diabetes Mellitus using receiver operating characteristic (ROC) curve analysis. **Methodology:** A case-control study was conducted on 120 participants recruited from hospitals affiliated with the Baghdad Health Directorate/Al-Karkh between January and June 2025. The study included 90 patients diagnosed with T2DM and 30 age- and sex-matched healthy controls. Serum concentrations of BTP, β2M, and TFF3 were measured and compared between groups. Diagnostic performance was evaluated using ROC curve analysis, including the area under the curve (AUC), sensitivity, specificity, and optimal cut-off values. **Results:** Serum levels of BTP, β2M, and TFF3 were significantly higher in patients with Type 2 Diabetes Mellitus (T2DM) than in healthy controls (1072 ± 281.3 vs. 683.6 ± 153.5 µg/dL for BTP, 21.42 ± 3.672 vs. 8.142 ± 1.814 µg/mL for β2M, and 42.59 ± 16.81 vs. 16.86 ± 4.631 ng/mL for TFF3; $P < 0.0001$ for all comparisons). ROC curve analysis demonstrated excellent diagnostic performance for all three biomarkers. β2M showed the highest diagnostic accuracy (AUC = 0.9959), with 98.89% sensitivity and 100% specificity at a cut-off value >11.66 µg/mL. TFF3 also demonstrated excellent performance (AUC = 0.9578) with 90% sensitivity and 90% specificity, whereas BTP showed good diagnostic accuracy (AUC = 0.8844), with 82% sensitivity and 90% specificity. These findings indicate that β2M is the most accurate biomarker among those evaluated, while the combined assessment of BTP, β2M, and TFF3 may further enhance the early diagnosis of T2DM and improve the identification of patients at increased risk of renal and vascular complications. **Conclusion:** BTP, β2M, and TFF3 are promising biomarkers for the diagnosis of T2DM, as demonstrated by ROC curve analysis. Among them, β2M exhibited the highest diagnostic performance. Combined assessment of these biomarkers may improve the early detection of diabetes and facilitate the identification of patients at increased risk of renal and vascular complications.

Keywords: Type 2 Diabetes Mellitus; Beta Trace Protein (BTP); Beta-2 Microglobulin; Trefoil Factor 3 (TFF3); Biomarkers; ROC Curve Analysis; Diagnostic Accuracy; Renal Dysfunction.

Introduction:

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic disorder and a major public health issue, marked by chronic hyperglycemia due to insulin resistance and pancreatic β-cell dysfunction. Over 530 million adults have diabetes, with T2DM comprising 90–95% of cases. Contributing factors include aging, obesity, sedentary lifestyles, and unhealthy diets. Persistent hyperglycemia leads to severe complications such as diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease, and chronic kidney disease, negatively impacting quality of life and increasing healthcare costs. Thus, identifying reliable biomarkers for early diagnosis and disease monitoring is crucial in diabetes research [(1).] Recent advancements in diagnosing Type 2 Diabetes Mellitus (T2DM) highlight limitations in traditional methods like fasting blood glucose (FBG) and glycated hemoglobin (HbA1c). These tests can be influenced by factors such as anemia and ethnic differences and often miss early metabolic issues. They also provide limited insights into related complications like inflammation and renal injury. Consequently, research in molecular medicine is focusing on circulating biomarkers to improve diagnostic accuracy, enable early detection, and predict complications, with multi-biomarker strategies showing promise over single-marker assessments [(2)]

Diabetes mellitus is recognized as a chronic inflammatory disorder characterized by immune activation, oxidative stress, and metabolic dysregulation. Hyperglycemia leads to increased reactive oxygen species (ROS) production, activates inflammatory pathways like NF-κB, and promotes pro-inflammatory cytokines, contributing to insulin resistance and β-cell damage. Chronic inflammation exacerbates vascular injury and

promotes diabetic complications, making inflammatory biomarkers crucial for diagnosis and prognosis in T2DM. Advances in proteomic technologies have enabled the identification of circulating proteins related to glucose metabolism, β-cell dysfunction, and vascular damage, paving the way for biomarker-driven diagnosis and precision medicine [7–3].

Beta Trace Protein (BTP), or lipocalin-type prostaglandin D synthase, is an emerging renal biomarker that indicates glomerular filtration more reliably than serum creatinine, as it is less affected by muscle mass, age, or sex. Its clinical significance is particularly pertinent in diabetic nephropathy, a common complication of T2DM, as it can detect early renal function declines before changes in estimated glomerular filtration rate (eGFR). Elevated BTP levels correlate with impaired kidney function, heightened cardiovascular risk, and increased mortality, establishing it as a valuable tool for assessing renal filtration and identifying diabetic patients at risk for adverse health outcomes [4].

Beta-2 Microglobulin (B2M) is a significant biomarker associated with immune activation, inflammation, and renal function. Elevated B2M levels are linked to diabetic nephropathy, chronic kidney disease, systemic inflammation, and cardiovascular issues in Type 2 Diabetes Mellitus (T2DM) patients. A meta-analysis indicates that higher B2M concentrations predict diabetic nephropathy progression, highlighting its role as a sensitive biomarker for renal injury and disease progression. Monitoring B2M may offer valuable insights beyond traditional biochemical markers in T2DM, which often involves chronic inflammation and early renal impairment [2].

Material and Method

Sample Collection and Storage:
A total of 120 participants aged between 25 and 50 years were enrolled in this case-control study. Participants were recruited from hospitals affiliated with the Baghdad Health Directorate/Al-Karkh between January 2025 and June 2025. The study group consisted of 90 patients diagnosed with type 2 diabetes mellitus (T2DM) who had no known history of kidney dysfunction, while the control group included 30 apparently healthy individuals matched for age and sex.

Assay procedure of (beta trace protein):
Serum Beta Trace Protein (BTP) concentrations were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. All reagents, standards, and serum samples were brought to room temperature before use. Briefly, 50 µL of standards or 40 µL of serum samples were added to the appropriate wells, followed by 10 µL of anti-BTP antibody and 50 µL of streptavidin-horseradish peroxidase (HRP) conjugate. After gentle mixing, the plate was incubated at 37°C for 60 minutes, washed five times with wash buffer to remove unbound materials, and then incubated with substrate solutions A and B for 10 minutes at 37°C in the dark. The reaction was terminated by adding stop solution, resulting in a color change from blue to yellow, and the optical density was measured at 450 nm using a microplate reader. The assay is based on the sandwich ELISA principle, in which BTP present in the samples binds to immobilized capture antibodies and is subsequently detected by a biotinylated anti-BTP antibody and streptavidin-HRP conjugate. The intensity of the color produced is directly proportional to the concentration of BTP in the sample and was quantified by comparison with the standard calibration curve [5].

Assay Principle of (Beta-2 macroglobulin):
Serum Beta-2 Microglobulin (B2M) concentrations were determined using a competitive enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. All reagents, standards, and serum samples were brought to room temperature before the assay. Briefly, 50 µL of diluted standards or serum samples were added to the appropriate wells, followed by 50 µL of biotinylated antigen. After incubation at 37°C for 60 minutes, the wells were washed five times to remove unbound materials. Subsequently, 50 µL of avidin-horseradish peroxidase (HRP) conjugate was added, and the plate was incubated again at 37°C for 60 minutes, followed by a second washing step. Then, 50 µL each of substrate solutions A and B were added, and the plate was incubated for 10 minutes at 37°C in the dark. The enzymatic reaction was terminated by adding 50 µL of stop solution, resulting in a color change from blue to yellow. The optical density (OD) was measured

immediately at 450 nm using a microplate reader. This assay is based on the competitive ELISA principle, in which endogenous B2M in the sample competes with biotinylated B2M antigen for binding to the immobilized capture antibody. Consequently, the color intensity is inversely proportional to the concentration of B2M in the sample, and the final concentration was calculated by comparing the sample absorbance values with the standard calibration curve [6].

Assay procedure of (Trefoil factor 3):
Serum Trefoil Factor 3 (TFF3) concentrations were measured using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. All reagents, standards, and serum samples were brought to room temperature before the assay. Briefly, 50 µL of standard or 40 µL of serum sample was added to the appropriate wells, followed by 10 µL of biotinylated anti-TFF3 antibody and 50 µL of streptavidin-horseradish peroxidase (HRP) conjugate. After gentle mixing, the plate was sealed and incubated at 37°C for 60 minutes. The wells were then washed five times with wash buffer to remove unbound materials, after which 50 µL each of substrate solutions A and B were added. The plate was incubated for 10 minutes at 37°C in the dark, and the reaction was terminated by adding 50 µL of stop solution, resulting in a color change from blue to yellow. The optical density (OD) was measured immediately at 450 nm using a microplate reader. This assay is based on the sandwich ELISA principle, in which TFF3 present in the sample binds to immobilized anti-TFF3 capture antibodies, followed by detection with a biotinylated anti-TFF3 antibody and streptavidin-HRP conjugate. The intensity of the color produced is directly proportional to the concentration of TFF3 in the sample and was quantified using a standard calibration curve [7].
The study was approved by the Scientific Research ethics committee (Tikrit University), approval letter code MIDTUH142 on 28 August 2026.

Statistical analysis
Statistical methods Statistical study was performed through Statistical Package for Social Sciences (GraphPad Prism software (10.5.1) and Microsoft Excel Worksheet. Results and examples from the present study were obtained for the same purpose. P-value significance at level (P≤0.001) Value, 95% Confidence Interval. Receiver operating characteristic (ROC) curve was used to assess the diagnostic accuracy of the BTP, Beta 2microglobuline and TF3.

Result
The gender distribution did not differ significantly between the Type 2 Diabetes Mellitus and healthy control groups (χ^2 = 0.281, P = 0.596). Females constituted 54.44% of patients and 60.00% of controls, while males represented 45.56% and 40.00%, respectively. These findings indicate comparable gender distribution, minimizing potential gender-related confounding effects. As shown in figure (1).

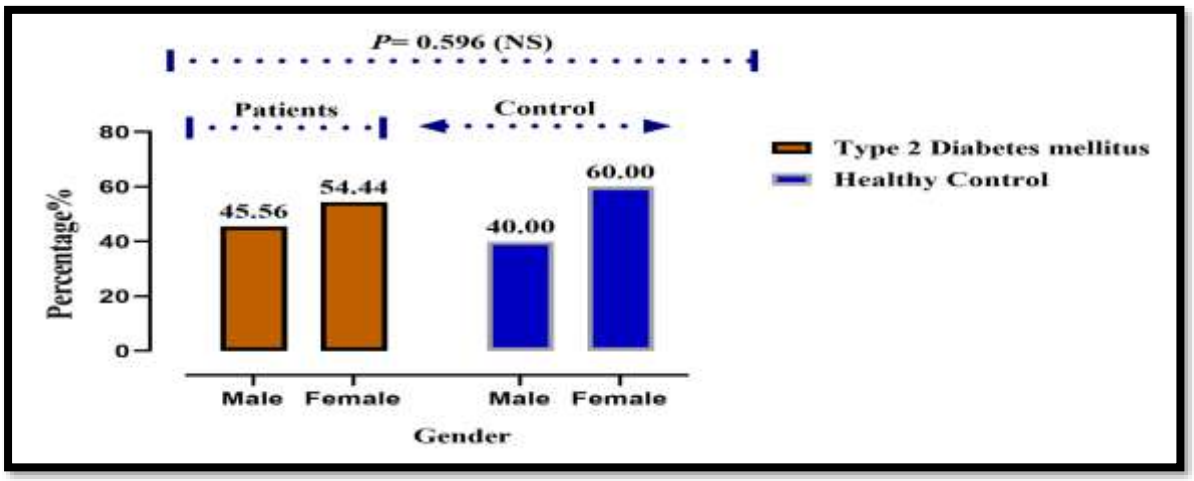

Figure 1: Gender Distribution Type 2 Diabetes mellitus (DM) Patients and Healthy Control Group

Levels of HbA1c (%) of Type 2 Diabetes mellitus patients compared with Healthy Controls
Figure (2) compares HbA1c levels between Type 2 DM patients and healthy controls. HbA1c is much higher in patients: 8.577 ± 1.645% vs 4.750 ± 0.3472% in controls. With P < 0.0001**, the difference is highly significant.

This confirms poor glycemic control in diabetic patient's vs normal levels in controls, which is expected for a Type 2 Diabetes diagnosis.

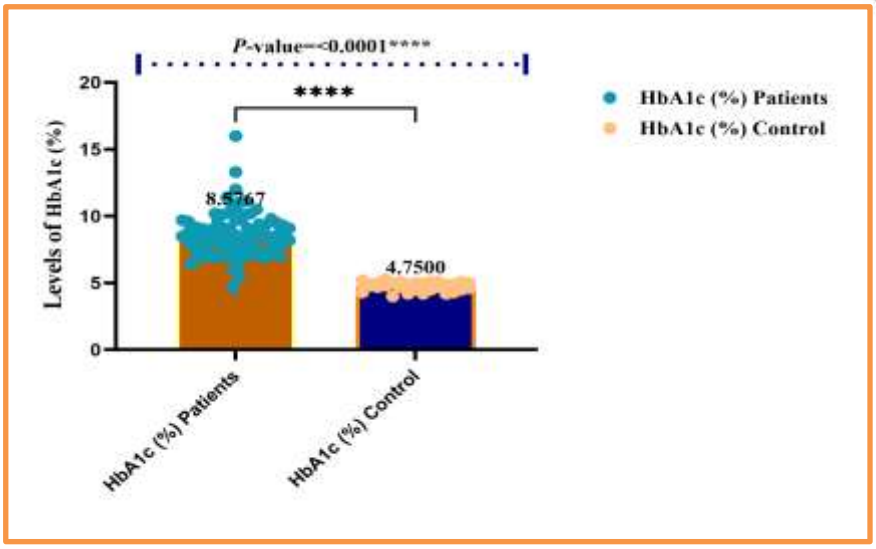

Figure 2: Levels of HbA1c (%) of Type 2 Diabetes mellitus patients compared with Healthy Controls.

Levels of BTP, Beta-2 Microglobulin and TF3 of type 2 diabetes mellitus (T2DM) patients compared with Healthy Control.

The study compares serum levels of Beta Trace Protein (BTP), Beta-2 Microglobulin (β2M), and Tissue Factor 3 (TF3) between Type 2 Diabetes Mellitus (T2DM) patients and healthy controls. Results show significant elevations in all three biomarkers in T2DM patients ($P < 0.0001$). The mean BTP level in T2DM patients was 1072 ± 281.3, indicating impaired renal function. β2M levels were 21.42 ± 3.672 in diabetics versus 8.142 ± 1.814 in controls, suggesting reduced renal clearance and chronic inflammation. TF3 levels were also higher in diabetics (42.59 ± 16.81) compared to controls (16.86 ± 4.631), indicating coagulation and endothelial dysfunction. The findings underscore the roles of BTP, β2M, and TF3 as potential biomarkers for renal dysfunction, inflammation, and thrombotic risk associated with T2DM, highlighting their utility in early detection of diabetes-related complications. As shown in table (1)

Table (1): Serum Levels of BTP, Beta 2microglobuline and TF3 of Type 2 Diabetes mellitus patients compared with Healthy Control.

Parameter (n=120)	Type 2 Diabetes mellitus (Mean± SD)	Healthy control (Mean± SD)	P-value
BTP (µg/dl)	1072 ± 281.3	683.6 ± 153.5	**<0.0001**** Highly significant**
Beta 2microglobuline(ug/ml)	21.42± 3.672	8.142± 1.814	**<0.0001**** Highly significant**
TF3 (ng/mL)	42.59± 16.81	16.86 ± 4.631	**<0.0001**** Highly significant**

Receiver Operating Characteristic (ROC) Curve Analysis of BTP, Beta-2 Microglobulin, and TF3 in Type 2 Diabetes Mellitus

The ROC curve analysis indicates that Beta Trace Protein (BTP), Beta-2 Microglobulin (β2M), and Tissue Factor 3 (TF3) are effective in distinguishing Type 2 Diabetes Mellitus (T2DM) from healthy controls, all showing significant diagnostic performance ($P < 0.0001$). β2M had the highest accuracy with an AUC of 0.9959, followed

by TF3 (AUC = 0.9578) and BTP (AUC = 0.8844). AUC values above 0.90 indicate strong discriminatory ability, affirming β2M and TF3 as excellent biomarkers for T2DM, with BTP also demonstrating strong diagnostic potential. These results are detailed in Table (2) and Figures (3), (4), and (5).

Table (2): Diagnostic sensitivity and specificity of BTP, Beta 2microglobuline and TF3 and selected parameters in patients with Type 2 Diabetes mellitus.

Type 2 Diabetes mellitus	BTP (µg/dl)	Beta 2microglobuline(ug/(ml)	TF3 (ng/mL)
AUC	0.8844	0.9959	0.9578
Cut-off value	> 807.6	> 11.66	> 23.17
95% confidence interval	0.8204 to 0.9485	0.9875 to 1.000	0.9245 to 0.9910
Asymptotic significance	<0.0001****	<0.0001****	<0.0001****
Sensitivity	82.00%	98.89 %	90.00%
Specificity	90.00%	100.0 %	90.00%

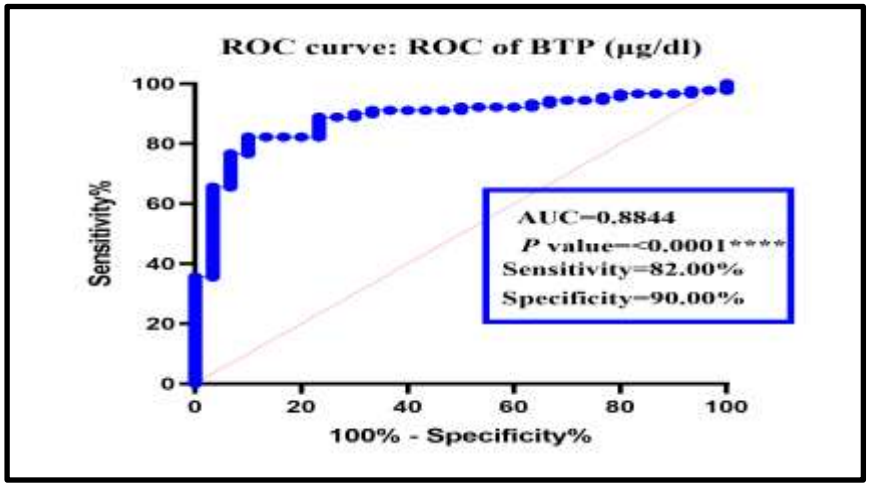

Figure (3): Diagnostic sensitivity and specificity of BTP (µg/dl) and selected parameters in patients with Type 2 Diabetes mellitus.

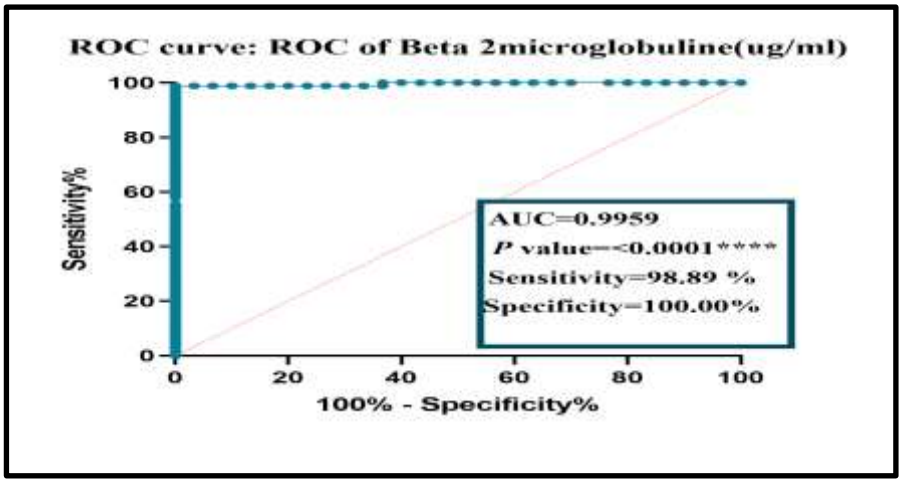

Figure (4): Diagnostic sensitivity and specificity of Beta 2microglobuline(ug/ml) and selected parameters in patients with Type 2 Diabetes mellitus.

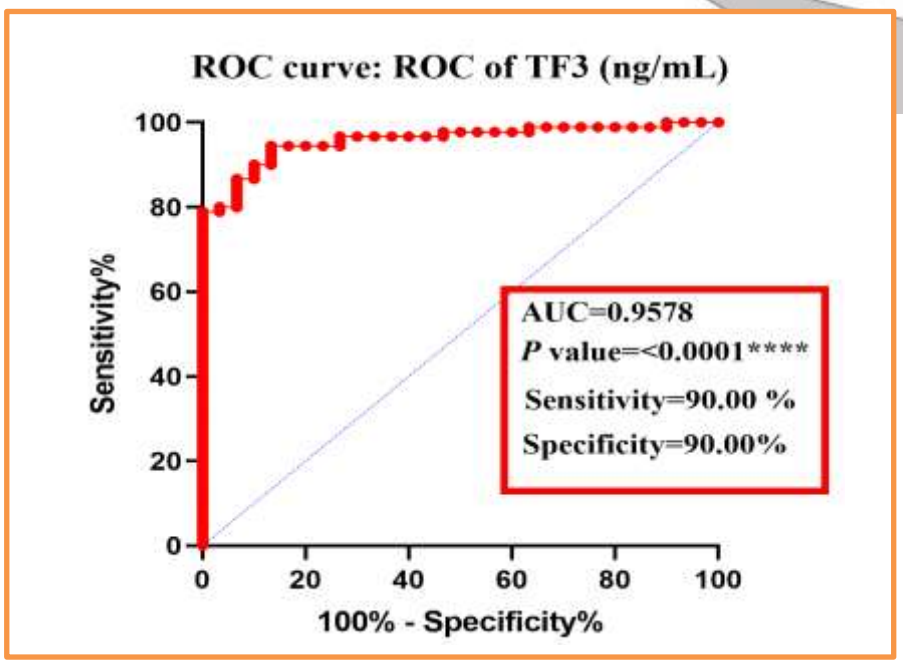

Figure (5): Diagnostic sensitivity and specificity of TF3 (ng/mL) and selected parameters in patients with Type 2 Diabetes mellitus

Discussion

The non-significant association between gender and T2DM observed in this study supports the concept that gender alone is not an independent determinant of diabetes prevalence without considering additional metabolic, genetic, and lifestyle factors [8]. This highly significant difference suggests that BTP may serve as a sensitive biomarker of renal dysfunction in patients with T2DM. BTP, also known as lipocalin-type prostaglandin D synthase, is a low-molecular-weight protein that is freely filtered by the glomeruli and is less influenced by muscle mass than serum creatinine. Consequently, elevated circulating BTP concentrations may reflect subtle reductions in glomerular filtration rate (GFR) and early kidney impairment before conventional renal markers become markedly abnormal [9].

In diabetic patients, increased serum BTP is plausible due to chronic hyperglycemia leading to oxidative stress, inflammation, and renal microvasculature damage, which impairs glomerular filtration. This results in higher levels of filtration biomarkers like BTP. Recent studies highlight the importance of novel protein biomarkers for early identification of diabetic kidney disease, crucial for recognizing renal injury before advanced chronic kidney disease develops, as diabetic nephropathy is a major contributor to end-stage kidney disease globally [10].

The study emphasizes the clinical potential of BTP as a biomarker for monitoring renal function in patients with T2DM. When used alongside serum creatinine, blood urea, eGFR, and urinary albumin excretion, BTP may enhance early detection of diabetic kidney disease and enable timely interventions. Elevated BTP levels suggest its value in identifying and monitoring diabetic renal complications, potentially improving risk stratification and long-term outcomes in diabetic patients [11].

This substantial elevation suggests that β2-MG is closely associated with the pathophysiological changes accompanying T2DM, particularly early renal dysfunction and chronic systemic inflammation. β2-MG is a low-molecular-weight protein that is freely filtered by the glomeruli and almost completely reabsorbed by the proximal renal tubules. Therefore, increased serum β2-MG concentrations may indicate impaired glomerular filtration or tubular dysfunction, making it a sensitive biomarker for the early detection of diabetic kidney disease[12].

The elevated β2-MG levels observed in the present study can be explained by persistent hyperglycemia, which induces oxidative stress, inflammatory cytokine production, endothelial dysfunction, and progressive microvascular injury within the kidneys. These pathological processes impair renal filtration and tubular reabsorption, resulting in the accumulation of β2-MG in the circulation. Recent studies have shown that elevated

serum β2-MG is not only associated with diabetic nephropathy but is also independently related to cardiovascular complications, including left ventricular hypertrophy, indicating that this biomarker reflects both renal and systemic vascular damage in patients with T2DM [13].

The findings of the current study agree with recent evidence identifying β2-MG as a promising biomarker for predicting diabetic complications and disease progression. Systematic reviews have reported that increased serum and urinary β2-MG concentrations are associated with diabetic nephropathy, retinopathy, and progression to chronic kidney disease. Consequently, measuring β2-MG together with conventional renal biomarkers such as serum creatinine, blood urea, estimated glomerular filtration rate (eGFR), and urinary albumin excretion may improve the early identification of renal impairment in patients with T2DM. Early recognition of elevated β2-MG levels may facilitate timely therapeutic interventions aimed at slowing the progression of diabetic kidney disease and reducing long-term cardiovascular and renal complications [14].

The large standard deviation observed in the diabetic group indicates considerable inter-individual variability, which may reflect differences in disease duration, glycemic control, inflammatory status, or the presence of diabetic complications. TFF3 is a peptide involved in epithelial protection, mucosal repair, and tissue regeneration. Recent evidence suggests that TFF3 also participates in metabolic and inflammatory pathways associated with T2DM, making it a promising biomarker for disease progression and tissue injury [15].

The higher serum TFF3 concentrations in diabetic patients may indicate a compensatory mechanism responding to damage and inflammation caused by chronic hyperglycemia. This condition leads to oxidative stress and inflammatory pathways that harm vascular and epithelial tissues. Studies suggest that TFF3 may enhance immune responses through Th17 cell activation and increased inflammatory cytokines like IL-17A, linking it to both tissue repair and inflammation in T2DM. This may clarify the elevated TFF3 levels found in the current study [16].

The variability in TFF3 concentrations indicates that serum TFF3 concentrations may reflect the severity of diabetes and complications such as diabetic nephropathy and chronic inflammation. Systematic reviews suggest no single biomarker adequately represents the complexity of T2DM, highlighting the benefit of combining TFF3 with traditional indicators like HbA1c and eGFR for improved risk assessment and early detection of complications. Elevated TFF3 levels support its potential as a novel biomarker for monitoring disease activity and identifying at-risk patients [17].

Among the evaluated markers for diabetes, β2M exhibited the highest sensitivity (98.89%) and specificity (100%) at a cut-off of >11.66 µg/mL, indicating excellent classification of diabetic and non-diabetic individuals. This performance is linked to β2M's association with chronic inflammation, immune activation, and renal function decline typical of T2DM. TF3 also showed strong diagnostic capability with 90% sensitivity and specificity at a cut-off of >23.17 ng/mL. BTP supported its role as an indicator of early renal dysfunction with 82% sensitivity and 90% specificity at a cut-off of >807.6 µg/dL. The findings reinforce those multimarket strategies enhance the detection and prediction of diabetes and its complications by reflecting various pathological mechanisms [18].

Overall, the findings suggest that β2M is the most effective diagnostic biomarker for identifying T2DM, with TF3 and BTP also showing excellent discriminatory ability. High AUC values, narrow confidence intervals, and significant P-values confirm their reliability for clinical use. Each biomarker reflects different aspects of T2DM pathophysiology: β2M indicates immune activation and renal dysfunction, TF3 highlights endothelial injury and prothrombotic states, and BTP signifies glomerular filtration impairment. Utilizing these biomarkers together may improve early diagnosis and risk assessment for diabetes-related complications, aligning with recent reviews advocating for multi-biomarker integration over single markers [15,19].

Conclusion

The present study showed that the serum levels of Beta Trace Protein (BTP), Beta-2 Microglobulin (β2M) and Trefoil Factor 3 (TFF3) were significantly increased in patients with Type 2 Diabetes Mellitus compared to healthy controls. ROC curve analysis confirmed good to excellent diagnostic performance of all the three biomarkers, with β2M showing the highest sensitivity, specificity and overall diagnostic accuracy. These results suggest that BTP, β2M and TFF3 represent different pathologic processes such as renal dysfunction, immune activation, inflammation and endothelial injury . Thus, combined assessment of these biomarkers may improve early diagnosis, risk stratification and clinical management of patients with Type 2 Diabetes Mellitus.

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