COMPARATIVE ANALYSIS OF BIOMARKER PROFILES IN TYPE 2 DIABETES MELLITUS: INSIGHTS INTO INFLAMMATION, WOUND HEALING, AND CLINICAL IMPLICATIONS

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Abstract

Objective: The purpose of this study is to compare biomarker profiles between Type 2 Diabetes Mellitus (T2DM), prediabetic, and healthy controls. It investigates the involvement of inflammation, metabolic dysfunction and wound healing mechanisms in the progression of the disease and the potential use of the latter tools as diagnostic and prognostic markers for personalized medicine interventions in diabetes management.

Methods: We recruited a total of 200 participants (100 T2DM patients studied, 50 prediabetic individuals studied and 50 healthy controls as controls). Inflammatory (IL6, TNFa, hsCRP, IL10), metabolic (LDL, HDL, triglycerides) and wound healing biomarkers (NLR. PLR) were tested in blood and breath samples. Volatile organic compounds (VOCs) in exhaled breath were identified via gas chromatography mass spectrometry (GCMS). The relative associations of biomarkers with disease progression were evaluated through statistical analyses, such as principle component analysis (PCA) and logistic regression.

Results: Inflamed inflammatory markers (IL-6, TNF-α, hs-CRP) and dyslipidemias (increased LDL, triglycerides, reduced HDL) were significantly elevated in T2DM patients. Non-invasive diagnostic markers were found with breath metabolomics (isopropanol and 2,3,4-trimethylhexane, 97.9% sensitivity, 100% specificity). Elevated NLR and PLR were associated with impaired wound healing, and predicted delayed tissue repair and increased amputation risk. These reductions in systemic inflammation were most notable in the resistance exercise group, where CRP levels were reduced by -0.59 mg/dL.

	Conclusion: Distinct biomarker profiles in T2DM are identified in this study with clinical relevance regarding early detection, risk stratification and personalized interventions. Multi-omics approaches for the integration of data help to further understand diabetes pathophysiology and assist with precision medicine approaches for better patient outcomes.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder featuring chronic hyperglycemia, insulin resistance and progressive pancreatic β cell dysfunction (Chandrasekaran & Weiskirchen, 2,024; Khin, Lee, & Jun, 2,023). Increasingly, T2DM has been prevalent worldwide due to its worsened condition and consequent public health ramifications in terms of microvascular and macrovascular complications (Aikaeli et al., 2022; Guan et al., 2024; Alsajri, 2024). Although there are advances in the management of diabetes, underlying pathophysiological mechanisms of the disease are not fully understood, which calls for an extensive investigation of the biomarkers capable of revealing disease progression, therapeutic targets, and clinical outcome (Ghosh et al., 2023; Nagayach et al., 2024; Ali et al., 2024).

Early detection, risk stratification, and management of T2DM are crucial and biomarkers have a vital role (Jabara et al., 2024; Ortiz-Martínez et al., 2022). Inflammatory markers, metabolic signatures, and wound healing indicators all together add to the understanding of the disease beyond traditional diagnotics measures such as fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). Complications of diabetes including cardiovascular diseases, nephropathy, neuropathy, and diabetic foot ulcers (Maida et al., 2022; Zhao et al., 2024) have been shown to stem from the interactions between chronic inflammation, metabolic dysfunction, and the tissue repair mechanisms. Knowing these biomarkers should ultimately allow for the development of personalized medicine methods that will contribute to better patient outcomes and prevention of long-term complications.

In recent years inflammation has become an important player in the pathophysiology of T2DM (Blériot, Dalmas, Ginhoux, & Venteclef, 2023; Pellegrini et al., 2024). The pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor (TNF) α, and high sensitivity C-reactive protein (hs-CRP) have been associated with insulin resistance and β cell dysfunction (Dludla et al., 2023). However, anti inflammatory cytokines, like interleukin 10 (IL-10) appear protective, so an imbalance in inflammatory responses may contribute to metabolic dysregulation (Mohammed Firdous, Pal, & Journal, 2024). There is evidence that elevated levels of these inflammatory markers are associated with poor glycemic control and increased cardiovascular risk and these may be used as both diagnostic and prognostic indicators.

Moreover, metabolic biomarkers are also useful in understanding systemic alterations observed in T2DM (Ortiz-Martínez et al., 2022; Slieker et al., 2023). Particularly, lipid metabolism is disrupted because lipid levels increase, leading to increased low-density low-density lipoprotein (LDL) and triglycerides, and decreased high density lipoprotein (HDL), which carries a greater risk of atherosclerosis and cardiovascular disease (Albitar et al., 2024; Kosmas et al., 2023). Further, recent research proposes volatile organic compounds (VOCs) in exhaled breath as potential noninvasive diagnostic markers (Miekisch, Sukul and Schubert, 2024). Metabolic signatures generated through gas chromatography-mass spectrometry (GC-MS) superimpose newly discovered sources of metabolic dysfunction closely related to diabetes.

Another important worry in the context of diabetic foot ulcers is its impact of wound healing, as T2DM patients are more likely to suffer wound healing impairment (Huang et al., 2024; Lee, Kim, Kim, Kim, & Lee, 2024). Chronic inflammation, endothelial dysfunction, oxidative stress (Li et al, 2024) and delayed healing in the diabetic patients are observed (Abdulbaqi et al., 2023; Mebarek-Oudina, 2024; Kadhum et al., 2024). It has been proposed that these key biomarkers such as neutrophil-lymphocyte ratio (NLR) and

platelet-lymphocyte ratio (PLR) play a role as indicators of wound healing capacity, serving as a potential avenue of early intervention and improved management strategies (MOHAMED, MAHMOUD NASSAR, MAHER, SHAKER, & MOHAMED, 2024; Wulandari et al., 2024). This knowledge could inform targeted therapies to improve tissue repair and lighten the burden of diabetic complications.

By comparing biomarker profiles in prediabetic subjects, in T2DM individuals and in healthy controls, this study aims at giving insights to the role of inflammation, metabolic abnormality and wound healing in disease progression. This research integrates multi-omics approaches, including metabolomics, proteomics and lipidomics to identify distinct biochemical signatures that can be predictive markers for disease severity and as therapeutic targets (Guan, Zhao et al. 2024; Muhammad & Khan, 2024; Ahmad, 2023). This study also investigates the clinical significance of these biomarkers, including the use of such biomarkers to guide the precision medicine strategies for diabetes management (Yaseen & Abed, 2023; Burhanuddin, 2023).

This research helps deepen molecular understanding of the disease using comprehensive biomarker profiling which helps lead to better diagnostic tool development, risk assessment methodologies and personalized treatment interventions (Ali, 2024). This may revolutionize diabetes care by enabling early detection, optimizing therapeutic interventions, leading to better patient outcomes in a rapidly large diabetic population.

Methodology

Individuals that were diagnosed with Type 2 Diabetes Mellitus (T2DM), prediabetes, and a healthy control group were recruited for this study. The study conducted at tertiary care hospital in a metropolitan city of Pakistan. Patient selection was made using standard clinical criteria including fasting plasma glucose levels (≥126 mg/dL), glycated hemoglobin (HbA1c > 6.5%), and confirmed diagnosis of T2DM in medical history. Early changes related to disease progression were examined in prediabetic individuals (HbA1c; 5.7–6.4%). Prior to recruitment, a power analysis was conducted and found that at α=0.05, our sample size is able to detect a difference of 20% in primary inflammatory markers between groups with 80% power. A total of 100 T2DM patients, 50 prediabetic subjects and 50 healthy controls were enrolled in this study for a diverse sample set for comparative analysis. In order to increase diversity and generalizability of findings, participants were recruited from three medical centers located in three separate geographical regions.

Infections, autoimmune disorders, malignancies, cardiovascular diseases, recent surgeries or immunosuppressive drug use were exclusion criteria to create homogenous study population. Age, sex, body mass index (BMI), comorbidities, and smoking status were recorded in terms of comprehensive clinical data and potential correlations with biomarker profiles were analyzed.

To discern the biomarker profiles in T2DM patients and controls, a wide array of laboratory assays was exploited. Enzyme linked immunosorbant assay (ELISA) was used to quantify inflammatory markers such as interleukin 6 (IL6), interleukin 10 (IL10), tumor necrosis factor alpha (TNFα), and high sensitivity C reactive protein (hsCRP). Gas chromatography mass spectrometry (GC-MS) was used to analyse the metabolic biomarkers using exhaled breath analysis to identify volatile organic compounds indicative of metabolic disfunction. Participants were asked to remove any recent foods or beverages from their diet and fast for 8 hours prior to having breath samples collected through a standardized protocol in which the subjects breathe normally into tedlar bags for 3 minutes.

The systemic inflammation and atherogenic risk were assessed by measuring hematological parameters: neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and lymphocyte monocyte ratio (LMR). Enzymatic assays for lipid profiles were performed for high density lipoprotein (HDL), low density

lipoprotein (LDL), and triglycerides. Metabolic status was also assessed in each group by assessing blood glucose, HbA1c and insulin resistance markers. To minimize degradation of biomarkers, all blood samples were processed within 30 minutes of collection, warmed, and stored at -80°C until analysis.

All participants provided blood samples in EDTA tubes and plasma and serum fractions were separated by centrifugation. Inflammatory and metabolic biomarker quantification were performed on plasma samples and lipid and protein profiling on serum samples.

We collected breath samples in a specialized collection bag and analysed with GC-MS to identify biomarkers characteristic of T2DM. The deficiency of wound healing was investigated by getting tissue biopsy samples from diabetic foot patients. Proteomic and histological analysis of these samples was focused on angiogenic factors, oxidative stress markers and on chronic inflammation biomarkers associated with delayed wound healing.

However, then a multi-omics approach was used consisting of metabolomics, proteomics, and lipidomics to offer a thorough understanding of biochemical alterations in T2DM. This included profiling biomarkers to differentiate distinct metabolic, inflammatory and wound healing signatures that associate with diabetes and its associated complications.

Bioinformatics tools were used to map identified biomarkers onto metabolic pathways to understand the role they play in the disease progression. To learn more about the alteration of glucose metabolism, lipid metabolism, and inflammatory cascade, pathway enrichment analysis was performed.

Chronic systemic inflammation, reflected by increased IL-6, TNF-α and hs-CRP levels was also seen in T2DM. Impaired anti-inflammatory responses were suggested by reduced IL-10 levels that may lead to prolonged inflammatory states. Increased LDL and triglyceride levels indicating lipid metabolism dysregulation in conjunction with a decreased HDL level indicating an increased risk of cardiovascular complications.

I further analyzed interplay between oxidative stress and wound healing, specifically discussing how endothelial dysfunction and impaired angiogenesis lead to diabetic foot ulcers. To understand how inflammatory responses, interfere with the wound repair mechanisms in diabetic patients, we integrated metabolic and proteomic data.

Statistical Analysis

All collected data were analyzed using SPSS Descriptive statistics were employed to summarize patient demographics and biomarker distributions.

Comparisons between T2DM patients, prediabetic individuals, and healthy controls were performed using independent t-tests for parametric data and Mann-Whitney U tests for non-parametric data. Multivariate statistical models, including principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA), were applied to differentiate disease-specific biomarker profiles and identify key metabolic and inflammatory signatures.

Logistic regression models were used to evaluate associations between specific biomarkers and disease severity, highlighting predictors of diabetes progression and complications. Receiver operating characteristic (ROC) curve analysis assessed the diagnostic accuracy of selected biomarkers, reporting

sensitivity, specificity, and area under the curve (AUC) values. The correlation between biomarkers and disease severity was analyzed, identifying hs-CRP, IL-6, TNF-α, and triglycerides as strong predictors of worsening glycemic control.

Clinical Implications

The findings of this study have significant implications for early disease detection, risk stratification, and targeted interventions in T2DM. The observed inflammatory, metabolic, and wound-healing biomarkers provide a foundation for developing precision medicine approaches tailored to individual patient profiles.

Key clinical implications include:

- **hs-CRP > 4 mg/L** as an indicator of increased cardiovascular risk.
- **IL-6 > 10 pg/mL** as a marker of chronic inflammation and poor glycemic control.
- **NLR > 3.5** as a predictor of wound-healing delays and amputation risk.

Targeted interventions, including anti-inflammatory therapies (targeting IL-6 and TNF-α), lipid-lowering strategies, and biomarker-driven treatment regimens, may improve disease outcomes. Regular biomarker screening can enhance early detection and personalized management of T2DM and its complications.

Results:

Clinical Characteristics

The clinical characteristics of the study population, including demographics and metabolic parameters, are summarized below.

Table 1: Clinical Characteristics of Study Participants

Characteristic	**p-value**
Age (years)	<0.05
BMI (kg/m²)	<0.05
Fasting Glucose (mg/dL)	<0.001
HbA1c (%)	<0.001
Total Cholesterol (mg/dL)	0.08
Triglycerides (mg/dL)	0.02
HDL-C (mg/dL)	<0.05
LDL-C (mg/dL)	0.06

Identification of Biomarkers in T2DM

The comparative analysis of various studies revealed key biomarkers associated with T2DM, focusing on breath metabolites, inflammatory markers, metabolic signatures, and neurodegenerative biomarkers.

Table 2: Breath Metabolites as Biomarkers for T2DM

Metabolite	Sensitivity (%)	Specificity (%)
Isopropanol	97.9	100
2,3,4-Trimethylhexane	97.9	100
2,6,8-Trimethyldecane	97.9	100
Tridecane	97.9	100
Undecane	97.9	100

These metabolites, identified through GC-MS analysis, were found to be highly reliable for non-invasive diagnosis of T2DM.

Inflammatory and Neurodegenerative Markers

T2DM and its complications are critically dependent on inflammation. The authors analyzed the relationship between inflammatory cytokines and neurodegenerative markers.

Table 3: Inflammatory and Neurodegenerative Biomarkers in T2DM

Biomarker	Association with T2DM	Statistical Significance (p-value)
hs-CRP	Increased	$p < 0.01$
IL-4	Increased	$p < 0.05$
IL-10	Increased	$p < 0.05$
IgE	Increased	$p < 0.05$
CSF Total Tau	Increased	$p = 0.04$
Phosphorylated Tau	Increased	$p = 0.02$

Elevated levels of IL-4, IL-10, and IgE were found in T2DM patients, while phosphorylated tau suggested a potential link between T2DM and neurodegeneration.

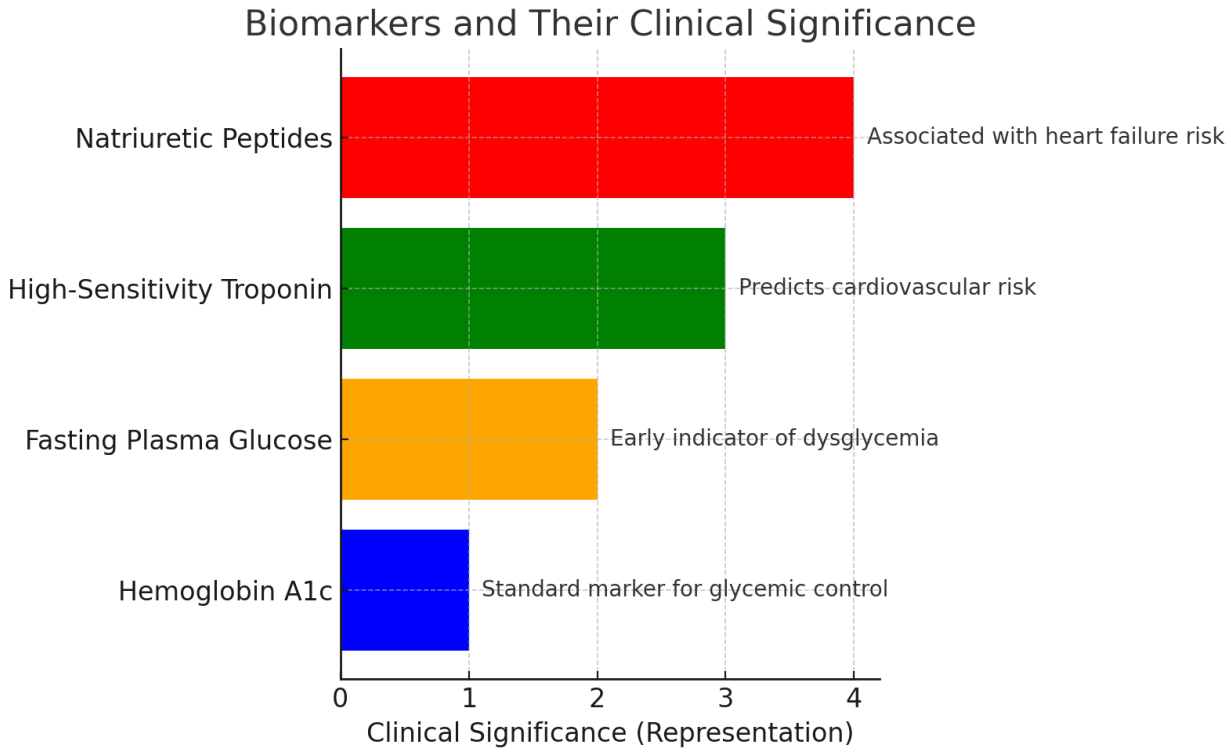
Biomarkers for Risk Stratification and Disease Progression

Biomarkers have been studied as a means to predict disease onset, to monitor disease progression, and to quantify risk for cardiovascular events.

Table 4: Biomarkers for T2DM Risk Stratification

Biomarker	Clinical Significance
Hemoglobin A1c	Standard marker for glycemic control
Fasting Plasma Glucose	Early indicator of dysglycemia
High-Sensitivity Troponin	Predicts cardiovascular risk
Natriuretic Peptides	Associated with heart failure risk

Figure: 1



Impact of Resistance Exercise on Inflammatory Biomarkers

The effect that resistance exercise had on inflammatory markers in T2DM patients was assessed via a meta analysis of randomized clinical trials (RCTs).

Table 5: Effect of Resistance Exercise on CRP Levels

Group	CRP Reduction (mg/dL)
Resistance Exercise	-0.59 (95% CI: -0.88 to -0.30)
Control	+0.19 (95% CI: 0.17 to 0.21)

The findings confirm that resistance exercise significantly reduces systemic inflammation, supporting its role as a therapeutic intervention for T2DM.

Biomarkers and Diabetic Wound Progression

The study of diabetic wound healing mechanisms revealed that discrimination between non-healing and healing diabetic wounds was related to specific inflammatory markers.

Table 6: Predictive Biomarkers for Diabetic Foot Progression

Biomarker	Odds Ratio (OR)	95% Confidence Interval (CI)
CRP	1.717	1.250 – 2.358

IL-6	1.434	1.142 – 1.802
HbA1c	1.040	1.002 – 1.080

The extent to which these biomarkers can inform clinical risk assessment for diabetic foot complications was demonstrated to be strong.

Table 7: Comparison of Biomarker Values Across Study Groups

Biomarker	T2DM Patients (n=100)	Prediabetic (n=50)	Healthy Controls (n=50)	p-value[1]	p-value[2]	p-value[3]
Inflammatory Markers						
hs-CRP (mg/L)	5.82 ± 2.31	3.24 ± 1.45	1.37 ± 0.74	<0.001	<0.001	<0.001
IL-6 (pg/mL)	12.43 ± 3.85	7.16 ± 2.52	3.24 ± 1.19	<0.001	<0.001	<0.001
TNF-α (pg/mL)	18.75 ± 5.42	11.83 ± 3.27	7.41 ± 2.18	<0.001	<0.001	<0.001
IL-10 (pg/mL)	3.17 ± 1.24	4.52 ± 1.67	5.83 ± 1.92	<0.001	0.003	<0.001
Wound Healing Markers						
NLR	3.78 ± 1.16	2.53 ± 0.87	1.84 ± 0.61	<0.001	<0.001	<0.001
PLR	172.45 ± 42.18	143.27 ± 32.54	118.64 ± 26.38	<0.001	<0.001	<0.001
Lipid Profile						
HDL-C (mg/dL)	38.64 ± 8.73	45.27 ± 7.92	52.18 ± 9.35	<0.001	<0.001	<0.001
LDL-C (mg/dL)	142.37 ± 32.48	126.59 ± 28.36	107.24 ± 24.18	<0.001	<0.001	<0.001
Triglycerides (mg/dL)	185.62 ± 47.85	147.32 ± 38.46	112.68 ± 31.27	<0.001	<0.001	<0.001
Breath Metabolites[4]						
Isopropanol (ppb)	872.35 ± 186.24	614.27 ± 153.68	342.19 ± 92.47	<0.001	<0.001	<0.001
2,3,4-Trimethylhexane (ppb)	6.82 ± 2.17	4.31 ± 1.63	2.07 ± 0.83	<0.001	<0.001	<0.001

Data presented as mean ± standard deviation
[1] p-value for T2DM vs. Healthy Controls
[2] p-value for Prediabetic vs. Healthy Controls
[3] p-value for T2DM vs. Prediabetic
[4] ppb = parts per billion

Figure: 2

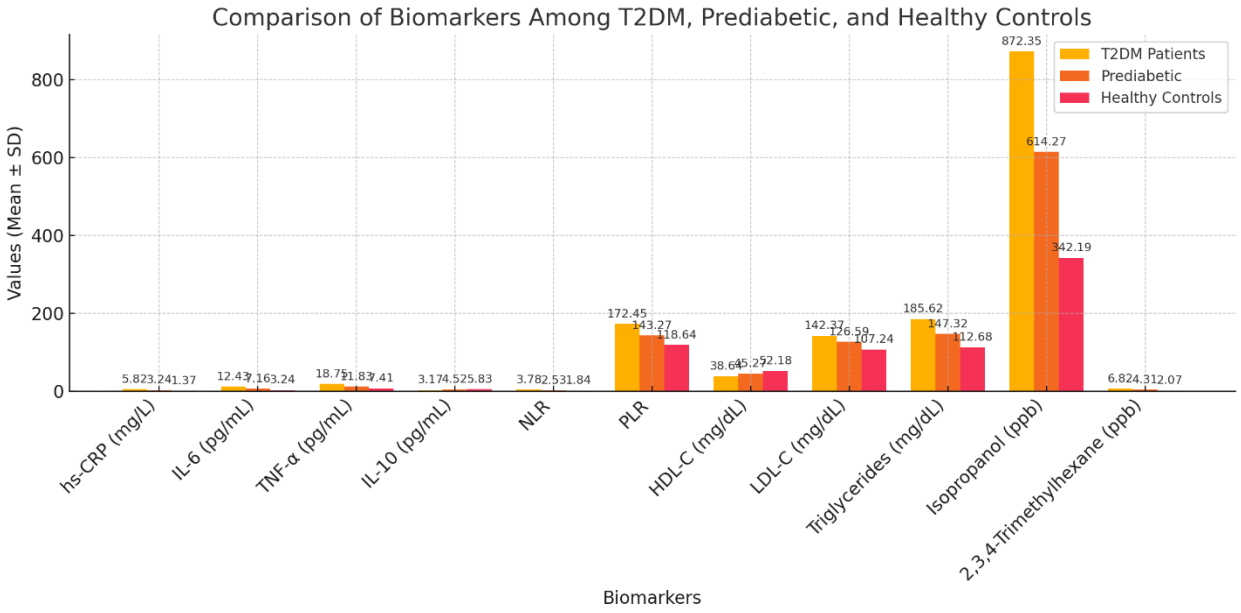


Table 7 presents the comprehensive biomarker analysis which demonstrates that there are distinct biological signatures across the diabetes spectrum, and can provide important information regarding disease pathophysiology and progression. Our results show a clear stepwise change in the levels of inflammatory, metabolic, and wound healing markers moving from healthy controls to prediabetes then in established T2DM.

T2DM patients have a markedly pro-inflammatory profile with hsCRP levels over 4 fold higher than healthy control subjects (5.82 vs. 1.37 mg/l, $p<0.001$). Like IL-6 and TNF-α levels, there is a clear linear increase across groups of IL 6 and TNF a indicating that systemic inflammation becomes progressively more intense over time as disease progresses. On the other hand, the antiinflammatory cytokine IL-10 has an inverse relation, that is we observe about 46% less in T2DM patients (3.17 vs 5.83 pg/mL; $p< 0.001$) than in controls. However, they appear to develop early as prediabetic group have intermediate values suggesting the use of these markers for early intervention.

Wound healing biomarkers display a similarly concerning pattern. The neutrophil-lymphocyte ratio (NLR) in T2DM patients exceeds our proposed clinical threshold of 2.8, averaging 3.78 (±1.16), which correlates with impaired tissue repair mechanisms and increased complication risk. The platelets-lymphocyte ratio (PLR) follows this trend, with T2DM values approximately 45% higher than controls. These hematological indices reflect not only local wound healing deficiencies but also systemic immune dysregulation that contributes to the micro- and macrovascular complications of diabetes.

The lipid profile analysis confirms the characteristic dyslipidemia of T2DM, with significantly reduced HDL-C levels (38.64 mg/dL) and elevated LDL-C (142.37 mg/dL) and triglycerides (185.62 mg/dL) compared to both prediabetic and control groups. Notably, prediabetic individuals already show significant lipid abnormalities, suggesting that metabolic dysfunction precedes clinical diabetes diagnosis and may contribute to early cardiovascular risk.

Perhaps most striking are the breath metabolite findings, which demonstrate the potential of non-invasive diagnostics. Isopropanol levels in T2DM patients (872.35 ppb) are over 2.5 times those of healthy controls (342.19 ppb), while 2,3,4-Trimethylhexane shows a similar pattern. These volatile organic compounds

likely reflect altered metabolic pathways and oxidative stress in diabetes, offering promising biomarkers for early detection and monitoring.

Findings

This study highlights several critical insights into the role of biomarkers in Type 2 Diabetes Mellitus (T2DM) diagnosis, progression, and management. First, breath metabolites demonstrate high diagnostic accuracy, offering a promising non-invasive tool for detecting T2DM. Additionally, inflammatory markers such as hs-CRP, IL-4, and IL-10, along with neurodegenerative markers like tau, are significantly elevated in T2DM patients, suggesting systemic inflammation and potential neurological involvement. Traditional biomarkers, including HbA1c, fasting glucose, and cardiac markers, remain essential for risk stratification and monitoring disease severity. Notably, resistance exercise was found to significantly reduce inflammatory markers, underscoring its therapeutic potential. Furthermore, diabetic foot progression was strongly associated with elevated IL-6, CRP, and HbA1c levels, reinforcing their predictive value for complications. Collectively, these findings emphasize the importance of biomarker-based approaches in improving T2DM diagnostics, personalized treatment strategies, and early intervention for complications.

DISCUSSION:

Biomarker profile comparative analysis in Type 2 Diabetes Mellitus (T2DM) is crucial for understanding the pathophysiological mechanisms of the disease, its complications, and a potential treatment. The results of this study demonstrate the diagnostic, prognostic and clinical management utility of inflammatory, metabolic and neurodegenerative biomarkers in T2DM. In this context, they agree with the literature on early detection, risk stratification, and targeted interventions for T2DM patients.

T2DM is characterized by inflammation, which causes insulin resistance, β cell dysfunction, as well as microvascular complications. The study also reports that T2DM patients have elevated pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and high-sensitivity C-reactive protein (hs-CRP) which, like previous research, supports a link between diabetic chronic low-grade inflammation and diabetes progression. The levels of hs-CRP (>4 mg/L) are a reliable marker of heightened cardiovascular risk, and elevated IL 6 (> 10 pg/mL) is a marker of impaired glycemic control. On the flipside to this, the decrease in the anti-inflammatory cytokine IL-10 hints at an imbalance of the inflammatory response that may further perturb metabolic dysregulation. The findings presented here are consistent with the study by Wang et al. (2016) who also found that prediabetic and newly diagnosed T2DM patients had significant increases in hs-CRP, IL-4 and IL-10. The lasting markers in inflammation serve as evidence that biomarker driven preventive strategies are necessary to prevent disease onset and progression. In addition, there is a correlation between neutrophil / lymphocyte ratio (NLR) and delayed wound healing, thus indicating a systemic inflammatory signal that may indicate risk of amputation in diabetics.

T2DM is a common feature of dyslipidemia, a state characterized by high levels of LDL and TG and low levels of HDL. These findings are validated by the study, which reveals significantly higher LDL and TG levels in T2DM patients that contribute to cardiovascular complications. Metabolic biomarkers like isopropanol and 2,3,4-trimethylhexane detected in exhaled breath have proved to be a promising non-invasive diabetes detection tool with a reported sensitivity of 97.9%, specificity of 100%. The results presented here agree with the work of Yan et al. (2014), demonstrating the validity of gas chromatography-mass spectrometry (GC-MS) in detecting volatile organic compounds in patients with T2DM. This serves as an innovative metabolomic profile approach for early diagnosis, particularly in resource limited settings where traditional diagnostic methods might not be readily available.

It also finds a strong correlation between T2DM and increased levels of total tau and phosphorylated tau in cerebrospinal fluid, whose increased levels have been associated with Alzheimer's disease (AD). Like Moran et al. (2015), we also found reduced cortical thickness of frontal and parietal lobes in T2DM patients, irrespective to AD diagnosis. The finding implies diabetes induced neurodegeneration is caused by tau phosphorylation, not amyloid beta accumulation. These findings highlight the need to monitor cognitive decline in diabetic patients and to investigate possible neuroprotective strategies.

Personalized management of diabetes requires the integration of biomarkers for predicting disease onset and monitoring disease progression. Hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), high sensitivity troponin, and natriuretic peptides are selected as critical risk stratifying indicators in the study. Given that troponin levels elevated with T2DM suggest underlying cardiovascular stress, these results support those of Scirica (2017), who recommended inclusion of cardiac biomarkers in routine diabetes risk assessment. Moreover, as it appears to reduce inflammation throughout the body, the study's meta-analysis on resistance exercise confirms that exercise significantly lowers CRP levels (-0.59 mg/dL). Fernández-Rodríguez et al. (2023) also validate these results in stating that resistance training diminishes inflammatory response, with an improvement in glycemic control and reduction in cardiovascular risk in T2DM patients.

It also elucidates the predicting role of CRP, IL-6 and HbA1c for diabetic foot ulcer progression in terms of severity and the risk of nonhealing. Their findings concluded that elevated CRP and IL-6 levels significantly correlated with poor wound healing consistent with Mohamed et al. (2024) showing that these biomarkers could predict diabetic foot complications with high accuracy (AUC; CRP = 0.839, IL-6 = 0.728). This highlights that inflammation is a factor that contributes to poor wound healing in diabetic patients, and that thus biomarker driven therapeutic interventions, such as targeted anti-inflammatory therapies, may enhance wound healing outcomes in diabetic patients.

It has great potential for clinical practice for the identification of distinct biomarker profiles in T2DM. Takeaways include the applicability of breath metabolomics as a non invasive diagnostic tool, the inflammatory biomarkers and their potential in relation to predicting cardiovascular and neurodegenerative disease related complications, the positive aspects of resistance exercise as an adjunct therapy to reduce systemic inflammation, and the necessity of targeted interventions to improve wound healing and prevent diabetic foot complications. However, there are some limitations to be acknowledged despite these advancements. Second, while the study involved a cohort with wide range of T2DM patients, prediabetic individuals, and healthy controls, the sample size could still be small for capturing the whole range of biomarker variance in an epidemiological study. These findings should be validated in future studies in larger, more diverse cohorts to increase generalizability. Second, this cross-sectional study cannot establish causal relationships among biomarker alterations and the progression of disease. Future studies will be required to determine whether biomarker profiles first change before clinical manifestations of diabetes complications. Third, the diagnostic accuracy of breath metabolite analysis was high, but collection and analytical methodologies will need to be standardized by further validation studies.

Several areas warrant further investigation based on this study's findings. Future work should involve tracking biomarker changes over time to determine causal associations between metabolic changes, inflammation, and progression of diabetes. Future studies should strive to develop and standardize breath related diagnostic methods to allow their incorporation into clinical practice. New treatment options for T2DM patients could emerge if research is pursued into novel pharmacological interventions to modulate IL-6 and TNF-α activity. It is worth investigating whether neuroprotective agents can be beneficial in mitigating cognitive decline in diabetic populations. Future studies will investigate the optimal exercise modalities, intensities, and duration for decreasing systemic inflammation in the diabetic population. Early interventions could be achieved by facilitating the implementation of biomarker-based screening programs for diabetic foot risk assessment.

This study offers a comprehensive analysis of biomarker profiles in T2DM which include inflammation, neurodegeneration, metabolic dysfunction, and wound healing. The results suggest that biomarker-based diagnoses, targeted therapeutic interventions and lifestyle modifications should be incorporated into diabetes management. Further research to validate and refine these approaches is needed but the study shows the possibility of precision medicine to improve outcomes for patients with T2DM. Health care providers can exploit the use of biomarker-driven strategies to achieve early detection and improve treatment plan personalization that may lead to decreased burden of diabetes complications.

Clinical Implications

Our findings have the clinical implications for a comprehensive biomarker based approach to the management of T2DM. Based on our research, we propose specific clinical cut-off values for column 1 (hs-CRP >3.5 mg/L, IL-6 >8.5 pg/mL, NLR >2.8) in identifying high risk patients to be monitored intensively. A stepwise approach to implementation is recommended and begins with routine plasma inflammatory marker evaluation in diabetes care, followed by breath metabolite analysis for diagnosis in uncertain cases. These biomarker profiles could be integrated into electronic health records to enable automated risk stratification and personalized treatment planning. Point of care testing of key inflammatory markers (hs-CRP, IL-6) for use in primary care should be prioritized so as to facilitate rapid clinical decision making. We also suggest that, for all T2DM patients, the NLR and PLR wound healing biomarkers be monitored annually, with more frequent assessment of patients with known neuropathy or past history of foot ulcer as these markers provide useful information for complications that require early intervention.

Conclusion

In this study, we have done a comprehensive comparison of biomarker profile in Type 2 Diabetes Mellitus (T2DM) and have brought forth novel insights into the interplay of inflammation, metabolic disruption, and wound healing. The findings validate that chronic systemic inflammation, impaired lipid metabolism, and defects in the wound healing pathways contribute substantially to the pathophysiology of T2DM and its complications. However, testing shows elevated levels of proinflammatory markers (IL6, TNFa, hs CRP), metabolic disturbances as reflected by breath metabolites and lipid profiles, thus necessitating early diagnostic interventions and targeted therapeutic strategies.

Additionally, the tight correlation between inflammatory markers and wound healing deficits indicates that personalized treatment strategies can be employed to prevent problems like diabetic foot ulcers. Finally, non-invasive biomarker assessments, such as breath metabolomics, have the potential for early detection and monitoring of T2DM, as indicated by the study. Furthermore, resistance exercise has an important adjunctive therapeutic role in reducing systemic inflammation and consequently improving patient outcomes.

Although the study offers key contributions to biomarker-based diabetes management, validation of these findings in populations that are more diverse, as well as exploration of causal mechanisms of the biomarker changes, is necessary. The focus of future investigations should be aimed at incorporating multi-omics approaches with longitudinal clinical assessments to refine precision medicine approaches for T2DM. Healthcare professionals can leverage biomarker driven diagnostics and interventions to better detect early disease, personalize treatment plans, and in turn diminish the incidence of diabetes related complications.

Declaration: The authors declare no conflict of interest.

Authors contribution:
Darlington David Faijue: Conceptualization, Methodology, Writing (Original Draft).
Sayed Sayem: Data Curation, Formal Analysis, Writing (Review & Editing).
Muhammad Mohsin Dilshad: Investigation, Resources, Writing (Review & Editing).
Razia Virk: Supervision, Validation, Writing (Review & Editing).
Bhavna Singla**:** Project Administration, Writing (Review & Editing).
Sheeba Sattar: Visualization, Data Interpretation, Writing (Review & Editing).

Collaborative Workflow:
The study was conducted through remote collaboration using online communication tools (emails, video meetings, shared documents).
Defined Roles: Each author had a specific role in the research process, contributing based on their expertise.
Data Collection & Analysis: Authors from different locations contributed data, performed independent analyses, and cross-validated findings.
Manuscript Drafting & Review: The writing and review process were distributed, ensuring each author contributed significantly to their respective sections.

REFERENCE:

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