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Article

Evaluation of Inflammatory Biomarkers in the Diagnosis of Type 2 Diabetes Mellitus Complications

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Abstract: Type 2 diabetes mellitus (T2DM) is also becoming known as a chronic metabolic and inflammatory disease and where low-grade inflammation is persistent, it is a primary cause of insulin resistance, endothelial malfunction, and tissue damage. An expanding numbers of inflammatory biomarkers such as hs-CRP, IL-6, TNF-a, and hematological indicators like NLR, PLR, and SII give valuable information about the presence inflammatory conditions in the patients with T2DM. These biomarkers have demonstrated close correlation with the manifestation and progression of the significant diabetic complications, especially the nephropathy, retinopathy, neuropathy, and cardiovascular disease. They are clinically useful in the sense that they can assist in the process of early detection, improve the process of risk stratification and complement the conventional metabolic indicators like fasting glucose and HbA1c. Nevertheless, inflammatory biomarkers do not live up to the promise because they have low specificity, variability by non-diabetic disease, and no universally accepted reference cutoffs. Hence, although they are not to be used as substitute diagnostic means, the use of these biomarkers in a standard clinical examination can enhance the early detection of individuals at a high risk and help to prevent and treat the long-term complications of T2DM.

Keywords: Type 2 Diabetes Mellitus (T2DM), Inflammatory Biomarkers, Insulin Resistance, Diabetic Complications, Risk Stratification.

Introduction

Diabetes mellitus type 2 (T2DM) is one of the major global health issues that is exemplified by chronic metabolic dysfunction and vascular complications progression (1). An increasing body of evidence suggests that T2DM is closely related to low-grade inflammation that is long-term and is at the core of the insulin resistance and metabolic imbalance (2). Hyperglycemia induces oxidative stress and NF- -gB and JNK as inflammatory pathways that result in elevated cytokine release IL-6 and TNF-a (3). Biomarkers of inflammation such as high-sensitivity C-reactive protein (hs-CRP), IL-6, TNF-alpha, and hematologic factors such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have become relevant as disease severity and early predictors of complication in T2DM (4). Since these markers are closely correlated with systemic vascular inflammation, elevated levels of the

same are associated with increased risk of diabetic nephropathy, retinopathy, neuropathy and macrovascular disease (5). Since most inflammatory biomarkers are cheap, easy to measure and viewed as commonly available in the normal clinical setting, they serve as a valuable aid in the early detection of individuals at high risk and could be used to supplement glycemic biomarkers like HbA1c (6). Therefore, the clinical management of people with T2DM may be enhanced by measuring and assessing inflammatory biomarkers, which will enhance risk assessment (7).

Pathophysiology of Inflammation in Type 2 Diabetes Mellitus

The pathology of type 2 diabetes mellitus includes chronic low-grade inflammation as one of its basic elements and it directly leads to the emergence of insulin resistance. Obesity leads to dysfunctional adipose tissue that facilitates the infiltration of macrophages and secretion of inflammatory cytokines, including TNF- alpha and IL- 6, which disrupts insulin signals and glucose uptake (8). The hyperglycemia also enhances inflammation increasing oxidative stress, the activation of such pathways as the NF-kappaB and JNK, which leads to persistent release of cytokines and aggravates vascular dysfunction (9). These mechanisms decrease the supply of nitric oxide, enhance endothelial permeability and uptick the expression of adhesive molecules such as ICAM-1 and VCAM-1, which facilitate microvascular and macrovascular damage. Increased oxidative stress is also caused by free fatty acids and mitochondrial dysfunction, and this process makes a self-sustaining cycle of metabolic and inflammatory damage (10). Collectively, these pathways depict how metabolic derangements, immune response, and vascular damage interact to propagate the complications of T2DM in favor of the clinical applicability of inflammatory biomarkers as predictors of disease progression (11).

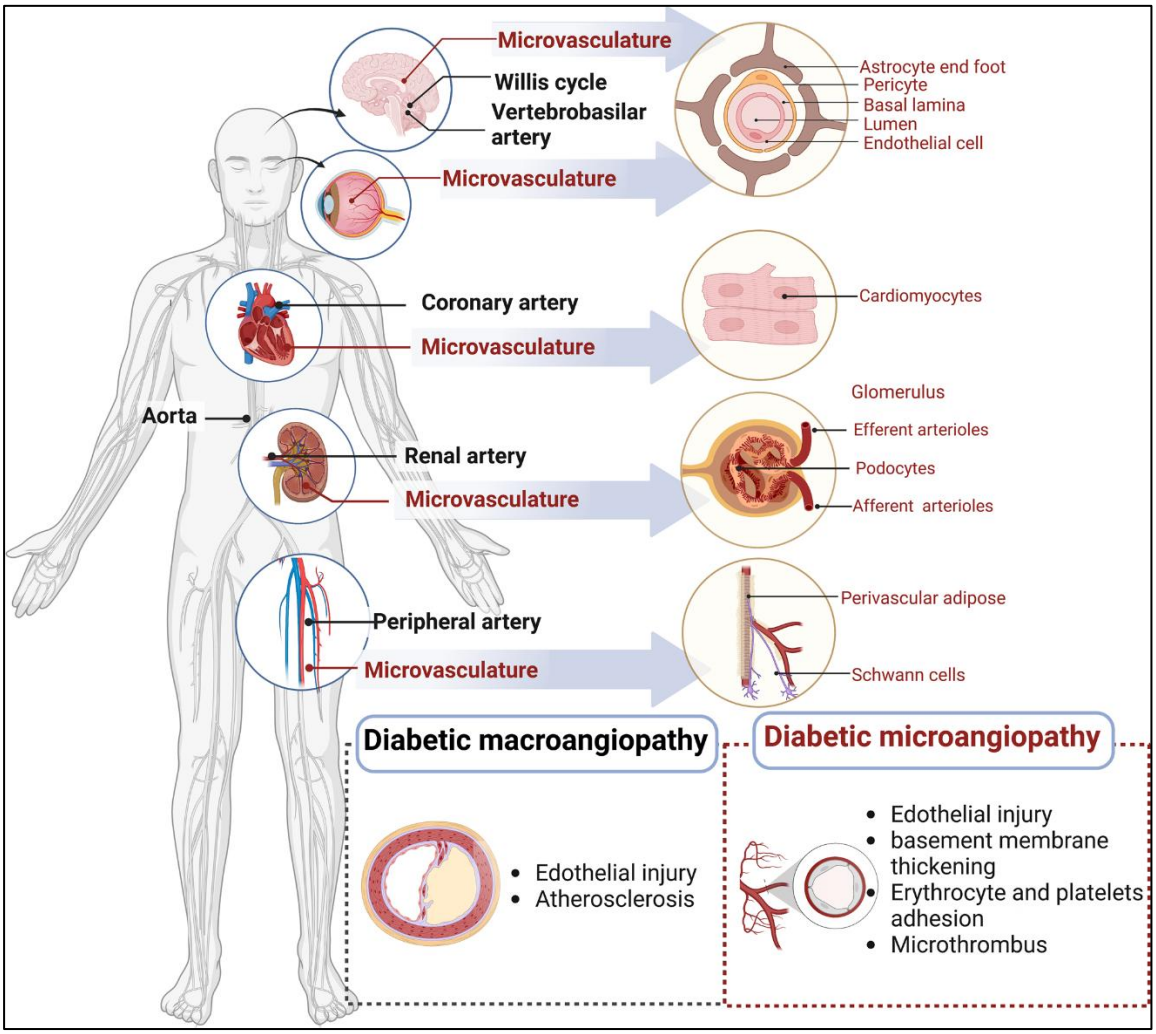

Figure 1. Overview of vascular targets affected in type 2 diabetes, illustrating the distribution of macrovascular and microvascular involvement and key structural components contributing to diabetic angiopathy.

Major Inflammatory Biomarkers in Type 2 Diabetes Mellitus

Inflammatory biomarkers represent essential indicators of metabolic stress, immune activation, and vascular injury in patients with type 2 diabetes mellitus . These biomarkers help characterize the degree of systemic inflammation and may offer useful insights into the risk of developing microvascular and macrovascular complications (12).

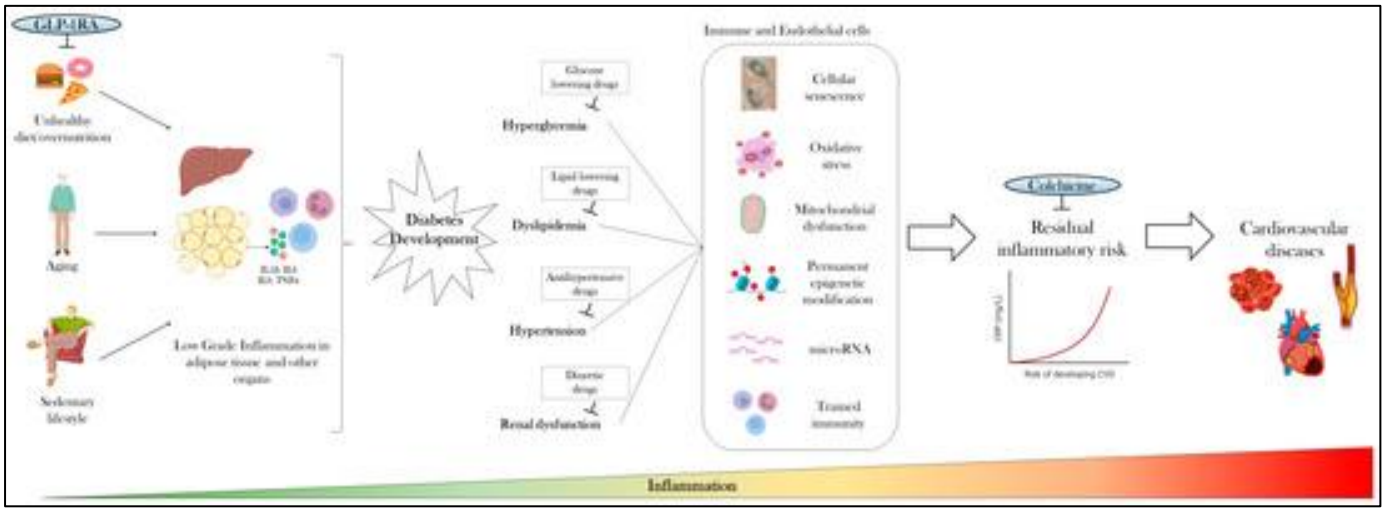

Figure 2. Inflammatory and metabolic pathways contributing to the development of type 2 diabetes and its cardiovascular complications.

The following groups represent the most widely studied inflammatory markers in T2DM:

1. High-Sensitivity C-Reactive Protein (hs-CRP)

hs-CRP is one of the most consistent markers of low-grade inflammation in T2DM and is strongly associated with insulin resistance, endothelial dysfunction, and cardiovascular risk . Elevated hs-CRP levels correlate with poor glycemic control and higher likelihood of diabetic nephropathy and retinopathy (13).

2. Interleukin-6 (IL-6)

IL-6 plays a dual metabolic and inflammatory role by promoting hepatic glucose production and stimulating acute-phase responses. Increased IL-6 concentrations are observed in both early metabolic dysregulation and advanced diabetic complications, reflecting persistent inflammatory activation (14).

3. Tumor Necrosis Factor-Alpha (TNF-α)

TNF-α interferes with insulin receptor signaling and enhances lipolysis, contributing to worsening hyperglycemia and adipose inflammation. Higher TNF-α levels have been linked to insulin resistance severity and increased risk of vascular injury in T2DM (15).

4. CBC-Derived Inflammatory Indices (NLR, PLR, MLR, SII)

Complete blood count–based indices are increasingly used due to their simplicity and affordability.

- **NLR (Neutrophil-to-Lymphocyte Ratio)** reflects systemic inflammation and correlates with nephropathy and retinopathy risk.
- **PLR (Platelet-to-Lymphocyte Ratio)** indicates thrombogenic inflammatory activity.
- **SII (Systemic Immune-Inflammation Index)** integrates neutrophils, lymphocytes, and platelets and has been proposed as a predictor of microvascular complications (16).

5. CRP/Albumin Ratio (CAR)

CAR is a combination of an inflammatory (CRP) and nutritional/vascular stability (albumin) marker, which gives a better indicator of inflammatory stress. High CAR comes with more serious diabetic complications, especially retinopathy (17).

6. Endothelial and Vascular Inflammation Markers (VEGF-A, ICAM-1, VCAM-1)

Endothelial activation (VEGF-A, ICAM-1, and VCAM-1) is an indicator of vascular injury and remodelling. Their increase adds to the microangiopathy, particularly, diabetic retinopathy and nephropathy (17).

7. Oxidative Stress–Related Markers (MDA, 8-OHdG)

Oxidative stress markers indicate cellular and DNA damage associated with chronic hyperglycemia and inflammation. Elevated MDA and 8-OHdG levels have been found in patients with poor glycemic control and advanced complications (18).

Table: Classification of Inflammatory Biomarkers in Type 2 Diabetes Mellitus (T2DM).

Category	Biomarkers Included	Sample Type	Primary Clinical Significance
1. Acute-Phase Proteins	hs-CRP, CRP, CRP/Albumin Ratio (CAR)	Serum	Indicators of low-grade systemic inflammation associated with early and advanced diabetic complications
2. Pro-Inflammatory Cytokines	IL-6, TNF-α, IL-1β	Serum (ELISA)	Directly involved in insulin resistance, vascular inflammation, and progression of diabetic complications
3. CBC-Derived Inflammatory Indices	NLR, PLR, MLR, SII	Whole blood (CBC)	Low-cost, accessible markers linked to both microvascular and macrovascular complications
4. Endothelial Dysfunction Markers	ICAM-1, VCAM-1, E-Selectin	Serum	Reflect endothelial injury and help predict vascular complications
5. Angiogenic and Vascular Growth Factors	VEGF-A, VEGF-C	Serum / Plasma	Strongly associated with diabetic retinopathy and pathological vascular changes
6. Oxidative Stress Markers	MDA, 8-OHdG, ROS indicators	Serum / Urine	Reflect oxidative damage and cellular injury caused by chronic hyperglycemia
7. Adipokines and Metabolic Inflammation Markers	Leptin, Adiponectin, Resistin	Serum	Associated with adipose tissue inflammation and insulin resistance
8. Emerging and Novel Biomarkers	GDF-15, Pentraxin-3, MCP-1	Serum	Potential early predictors of vascular injury and diabetic complications

Inflammatory Biomarkers and Diabetic Complications

Inflammatory biomarkers play a central role in predicting and understanding the pathogenesis of microvascular and macrovascular complications in type 2 diabetes mellitus. Persistent elevation of cytokines, acute-phase proteins, and blood-derived inflammatory indices reflects ongoing vascular injury, endothelial dysfunction, and oxidative stress key drivers of diabetic angiopathy. The following sections summarize the main complications associated with inflammatory marker alterations (19).

1. Diabetic Nephropathy (DN)

Diabetic nephropathy bears a close relationship with chronic inflammation, hs-CRP, IL-6, TNF-alpha, NLR, and CAR biomarkers are regularly raised in diabetic patients with microalbuminuria and deteriorating renal functioning. These are markers that are associated with glomerular damage, mesangial stretch, and intrarenal inflammatory pathway activation. Higher NLR and SII values have been rolled toward accelerated worsening to reduced eGFR, indicating that haematological ratios can be used to help to stratify risks early (20).

2. Diabetic Retinopathy (DR)

Inflammation plays an important role in microvascular damage of the retina and high NLR, PLR, SII, hs-CRP and VEGF-A have been associated with the existence and degree of DR. VEGF-A is a prominent crucial factor in retinal neovascularization, and vascular leakage, so it is an important predictor of proliferative retinopathy. CBC-based measures are easy to use and readily accessible measures of patients at increased risk of early retinal pathology (21).

3. Diabetic Neuropathy

Inflammatory responses are usually high in cases of peripheral nerve damage in T2DM. Nerve ischemia, demyelination and the chronic pain syndromes have been found to correlate with biomarkers like IL-6 and TNF-alpha. Continuous inflammation facilitates vascular insufficiency in vasa nervorum and oxidative damage of Schwann cells, which hastens the development of neuropathy (22).

4. Macrovascular Complications (CVD, PAD)

Macrovascular disease, including coronary artery disease (CAD) and peripheral arterial disease (PAD), is strongly influenced by chronic inflammation and atherosclerotic progression. High levels of hs-CRP and SII are linked to higher levels of arterial stiffness, dysfunction of endothelia and instability of the plaque. The roles of TNF-a and IL-6 in the stimulation of the vascular smooth muscle and lipid deposition enhance cardiovascular risks in T2DM patients (23).

5. Clinical Implications

Combined, these results depict that inflammatory biomarkers either serum cytokines or CBC-derived indices are useful indicators of microvascular and macrovascular diabetic complications. Despite being not standalone diagnostic methods, their application in combination with the conventional metabolic markers boosts the early diagnosis, risk evaluation, and clinical surveillance (24).

Clinical Importance and Limitations of Inflammatory Biomarkers

The inflammatory biomarkers have gained significant relevance in the progression of diabetes mellitus type 2 interventions since they offer useful details concerning the current metabolic stress, vascular endothelial injury, and inflammation of the vessels. These markers, together with the conventional ones (HbA1c and fasting glucose), can be used to detect patients that are more vulnerable to microvascular and macrovascular complications (25). The CBC-derived measures including NLR, PLR, and SII have a practical benefit since it is low-cost, common, and highly correlated with early diabetic issues. Inflammatory biomarkers are limited in a number of ways despite their utility. Several markers are not very specific and can be affected by infections, obesity and smoking, as well as medications, lowering their validity as single-party inferences. Cytokines like IL-6 and TNF-alpha demand special laboratory methods and their cutoff values are not fixed and hence cannot be regularly used in clinical practice (26).

Table 2. Advantages and Limitations of Key Inflammatory Biomarkers in T2DM (Short Version).

Biomarker	Advantages	Limitations
hs-CRP	Low-cost; widely available; reflects systemic inflammation	Non-specific; influenced by infection and obesity
IL-6	Directly linked to insulin resistance and metabolic inflammation	Requires ELISA; variable levels
TNF-α	Key mediator of adipose inflammation	High cost; affected by acute illness
NLR	Simple; derived from routine CBC	Non-specific; altered by infections
PLR	Reflects platelet activation and inflammation	Affected by hematologic disorders
SII	Combines three immune components; strong inflammatory indicator	No standard cut-off; variable
CAR	Integrates inflammation and nutritional status	Influenced by low albumin/liver disease
VEGF-A	Relevant for diabetic retinopathy and angiogenesis	Not routinely available; costly

ICAM-1 / VCAM-1	Early markers of endothelial injury	Limited sensitivity when used alone
MDA	Indicates oxidative stress	Non-specific; diet-related variability
8-OHdG	Sensitive marker of DNA oxidative damage	High analytical cost

Conclusion

Inflammatory biomarkers are useful in elucidating the complicated interaction between metabolic dysfunction, immune response, and vascular harm in type 2 diabetes mellitus. Their height is indicative of the persistent low-grade inflammation that causes insulin resistance and motivates the development of major diabetic complications, such as nephropathy, retinopathy, neuropathy, and cardiovascular disease. Even when these biomarkers give good information on disease progression and patient risk, they are supportive and not conclusive diagnostic markers. Their highest clinical utility comes about when they are combined with conventional metabolic parameters and general patient condition. The incorporation of inflammatory biomarkers in routine evaluation can have a positive impact in the identification of disease in its initial stages, the choice of monitoring protocols and the prevention of chronic diabetic complications.

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