The Review Of
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"Understanding The Link Between Chronic Inflammation And Diabetes Complications: A Systematic Review."

Ayesha Muhiuddin Madrasi[1], Maha saleh Alkathiry[2], Mamdouh Waleed Alharbi[3], Mohammed Sharukh Ali[4], Khalid Ahmad Alkatout[5], Maram Adnan Rawah[6], Nora Abdullah Al Ghamdi[7], Salman Mohammed Alhubail[8], Abdulaziz Fayez Alahmari[9], Fatema Abdullah Al Thkerallah[10], Khalid Salem Mesfer Alzhrani[11], Abdullah Nizar Ali Alhashim[12], Maliha Abdullah Saleh Al Ghamdi[13], ahmoud Ali Khazbak[14]

[1]Consultant internal medicine and adult Hematology
[2]Internal medicine
[3]Internal Medicine
[4]General Practitioner
[5]Internal medicine
[6]Internal medicine
[7]Internal Medicine
[8]Intern
[9]Internal medicine
[10]Internal medicine
[11]Medicine and surgery
[12]Intern
[13]Adult endocrinologist
[14]Internal medicine

Abstract

Background:
Chronic inflammation has emerged as a central driver of diabetic complications, influencing microvascular (retinopathy, nephropathy, neuropathy) and macrovascular outcomes (atherosclerosis, cardiovascular disease). The interplay between metabolic stress and inflammatory signaling underlies tissue damage, endothelial dysfunction, and impaired repair mechanisms.

Objective:
This systematic review aimed to synthesize empirical evidence on the role of inflammatory biomarkers in the development and progression of diabetic complications.

Methods:
Following PRISMA 2020 guidelines, twelve peer-reviewed studies published between 2009 and 2025 were analyzed. Eligible studies included human participants with diabetes mellitus, reporting inflammatory biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), serum amyloid A (SAA), monocyte chemoattractant protein-1 (MCP-1), and fibrinogen. Data were narratively synthesized due to heterogeneity in study designs and outcomes.

Results:
Elevated IL-6, TNF-α, CRP, MCP-1, and SAA were consistently linked to increased risks of diabetic nephropathy, retinopathy, neuropathy, and cardiovascular events. Genetic factors, such as the IL-6 −174GG genotype, showed protective effects against microvascular complications. Fibrinogen levels were associated with both macro- and microvascular pathology, reinforcing its predictive clinical utility.

Conclusion:
Inflammation is a unifying mechanism across diabetic complications, driven by metabolic and vascular stress. Biomarkers such as IL-6, CRP, and SAA hold diagnostic and prognostic potential, suggesting that anti-inflammatory strategies could enhance long-term management of diabetes-related vascular and neural injury.

Keywords: Chronic inflammation; diabetes mellitus; diabetic complications; interleukin-6; C-reactive protein; serum amyloid A; fibrinogen; monocyte chemoattractant protein-1; endothelial dysfunction; oxidative stress

Introduction

Diabetes mellitus (DM) represents one of the most prevalent metabolic disorders globally, affecting over 500 million people and projected to rise significantly in the next decades. Beyond its hallmark disturbances in glucose metabolism, diabetes is increasingly recognized as a chronic inflammatory condition that contributes to vascular injury, oxidative stress, and multiorgan dysfunction. Persistent low-grade inflammation has been implicated in both the onset and progression of diabetic complications, suggesting that immune dysregulation and cytokine activation are central to its pathophysiology (Röhm et al., 2022).

Inflammation in diabetes is mediated through multiple cellular and molecular pathways, primarily involving the activation of nuclear factor-κB (NF-κB)**,** toll-like receptors (TLRs)**,** and inflammasomes**.** Hyperglycemia promotes the formation of advanced glycation end-products (AGEs) and oxidative stress, both of which stimulate pro-inflammatory cytokine production and endothelial dysfunction. These processes amplify the expression of tumor necrosis factor-alpha (TNF-α)**,** interleukin-6 (IL-6)**,** and C-reactive protein (CRP)—biomarkers that predict the onset of complications such as nephropathy, neuropathy, and retinopathy (Nedosugova et al., 2022).

Chronic hyperglycemia-induced oxidative stress plays a crucial role in activating inflammatory signaling within vascular tissues. Elevated glucose triggers mitochondrial dysfunction, increases reactive oxygen species (ROS) formation, and activates redox-sensitive transcription factors such as NF-κB, leading to endothelial injury and apoptosis. This biochemical cascade contributes to both macrovascular **c**omplications, such as atherosclerosis, and microvascular complications, including nephropathy and retinopathy (Andreadi et al., 2022).

Furthermore, studies show that endothelial cells and pericytes exposed to high glucose levels exhibit inflammatory apoptosis, mediated by NF-κB activation and cytokine upregulation. These changes compromise the vascular integrity of the retina, forming a direct link between inflammation and diabetic retinopathy progression (Romeo et al., 2002). This evidence underscores the dual role of inflammation as both a trigger and amplifier of tissue damage in diabetes.

In diabetic nephropathy, inflammatory cytokines such as IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) induce mesangial expansion, glomerulosclerosis, and fibrosis. Experimental models have demonstrated that blocking inflammatory pathways mitigates renal injury and albuminuria, highlighting the therapeutic potential of targeting inflammation to delay nephropathy progression (Zhao et al., 2024).

Systemic inflammation also contributes to the development of diabetic neuropathy, where activated macrophages and Schwann cells release nitric oxide synthase (iNOS) and TNF-α, leading to neuronal ischemia and pain. Chronic inflammatory signaling disrupts neurovascular blood flow and axonal repair, reinforcing the notion that immune activation is integral to neuropathic symptomatology (Stanimirovic et al., 2022).

C-reactive protein (CRP), a hepatic acute-phase protein, has emerged as both a biomarker and mediator of vascular inflammation in diabetes. Elevated CRP levels correlate with endothelial dysfunction and a higher risk of cardiovascular events, supporting its use in predicting macrovascular complications among diabetic patients (Patel et al., 2024). Elevated plasma fibrinogen and soluble receptors for advanced glycation end-products (sRAGE) have also been linked to vascular injury and increased mortality risk, emphasizing the interconnected roles of coagulation, inflammation, and oxidative stress in diabetic pathophysiology (Ahmad et al., 2024; Nin et al., 2010).

Overall, chronic inflammation represents a unifying mechanism underlying the microvascular and macrovascular sequelae of diabetes. It bridges metabolic dysregulation with vascular injury through immune activation, oxidative stress, and endothelial dysfunction. Understanding these molecular pathways provides a foundation for precision-targeted therapies aimed at mitigating both metabolic imbalance and its inflammatory consequences (Zhao et al., 2024; Röhm et al., 2022).

Methodology

Study Design

This study utilized a systematic review design, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency, reproducibility, and rigor. The primary objective was to synthesize and critically evaluate empirical evidence examining the relationship between chronic inflammation and the development of diabetes-related complications, including microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease, peripheral vascular disease) outcomes.

The review focused on peer-reviewed human studies that investigated inflammatory biomarkers as predictors, mediators, or correlates of diabetes complications. Biomarkers of interest included tumor necrosis factor-alpha (TNF-α)**,** interleukin-6 (IL-6)**,** C-reactive protein (CRP)**,** monocyte chemoattractant protein-1 (MCP-1)**,** serum amyloid A (SAA)**,** fibrinogen**,** pentraxin 3 (PTX3**)**, and soluble receptor for advanced glycation end-products (sRAGE)**.**

Eligibility Criteria

Studies were included based on the following criteria:

- **Population:** Adults (≥18 years) diagnosed with type 1 or type 2 diabetes mellitus, with or without established microvascular or macrovascular complications.
- **Exposure/Intervention:** Measurement or evaluation of inflammatory biomarkers (e.g., TNF-α, IL-6, hsCRP, MCP-1, PTX3, SAA, sRAGE, fibrinogen) in relation to diabetic complications.
- **Comparators:** Diabetic individuals without complications, healthy controls, or comparative biomarker levels across severity groups (e.g., mild vs. severe neuropathy, NPDR vs. PDR).
- **Outcomes:** Development, progression, or severity of diabetic complications—neuropathy, nephropathy, retinopathy, macrovascular disease, or diabetic foot ulcers.
- **Study Designs:** Randomized controlled trials (RCTs), prospective or retrospective cohort studies, case-control studies, and cross-sectional analyses.
- **Language:** Publications written in English.
- **Publication Period:** Studies published between 2000 and 2025, to ensure inclusion of contemporary biomarker evidence and updated diagnostic standards.

Studies were excluded if they:

(1) involved animal or in vitro experiments only
(2) lacked quantitative biomarker data
(3) were reviews, editorials, or conference abstracts without full-text data
(4) did not specify diabetes type or diagnostic criteria.

Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, Embase, and Google Scholar databases. Grey literature was additionally searched through OpenGrey and institutional repositories. Search terms were combined using Boolean operators and adjusted for database-specific syntax. The following search strategy was applied:

- ("diabetes mellitus" OR "type 1 diabetes" OR "type 2 diabetes")
- AND ("inflammation" OR "inflammatory biomarkers" OR "cytokines" OR "C-reactive protein" OR "TNF-alpha" OR "IL-6" OR "MCP-1" OR "fibrinogen" OR "serum amyloid A" OR "sRAGE" OR "pentraxin 3")
- AND ("complications" OR "retinopathy" OR "nephropathy" OR "neuropathy" OR "macrovascular" OR "cardiovascular disease" OR "diabetic foot ulcer").

Searches were limited to human studies published between 2000 and March 2025. Reference lists of included papers and key review articles were manually screened to identify additional relevant studies.

Study Selection Process

All identified citations were exported to Zotero reference manager, where duplicates were automatically and manually removed. Two independent reviewers screened titles and abstracts to identify potentially relevant studies. Full-text screening was conducted for all eligible articles, and discrepancies between reviewers were resolved through consensus discussion or adjudication by a third reviewer.

A total of 12 studies met all inclusion criteria after full-text review. The PRISMA 2020 flow diagram (Figure 1) outlines the selection process, including the number of studies identified, screened, excluded, and retained for synthesis.

Data Extraction

A standardized and piloted data extraction template was used to ensure consistency and accuracy across reviewers. The following information was systematically extracted from each included study:

- **Author(s), year, and country**
- **Study design and duration**
- **Sample size and population characteristics (age, sex, diabetes type)**
- **Inflammatory biomarkers assessed**
- **Measurement techniques (e.g., ELISA, multiplex assay, high-sensitivity CRP analysis)**
- **Clinical outcomes** (neuropathy, nephropathy, retinopathy, macrovascular disease, or mortality)
- **Key statistical findings** (mean biomarker values, correlation coefficients, odds ratios [OR], relative risks [RR], or hazard ratios [HR])
- **Confounders adjusted for** (e.g., age, BMI, HbA1c, duration of diabetes)
- **Study conclusions**

Data were extracted independently by two reviewers and cross-checked by a third for consistency. Any discrepancies were resolved through discussion and reference to the original study text.

Quality Assessment

The methodological quality and risk of bias for included studies were assessed according to study design:

- **Randomized Controlled Trials (RCTs):** Evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, assessing randomization, deviations from intended interventions, missing data, measurement reliability, and reporting bias.
- **Observational Studies (cohort, case-control, cross-sectional):** Evaluated using the **Newcastle–Ottawa Scale (NOS)**, assessing participant selection, comparability, and outcome/exposure assessment.

Each study was rated as low, moderate, or high risk of bias. Studies achieving ≥7/10 on NOS or "low risk" in ≥4/5 RoB 2 domains were classified as high-quality.

Data Synthesis

Given the heterogeneity in biomarker types, study designs, and outcome measures, a narrative synthesis approach was adopted. Findings were categorized according to the type of diabetic complication (neuropathy, nephropathy, retinopathy, macrovascular disease, or others) and the specific inflammatory markers investigated.

Quantitative data such as ORs, RRs, and HRs were reported when available, while qualitative trends were described for non-statistically comparable outcomes. Due to variation in biomarker units, detection assays, and diagnostic criteria, a meta-analysis was not performed. Instead, consistent directional trends and biomarker-complication linkages were summarized to provide integrated insights into inflammation's role in diabetes pathogenesis.

Ethical Considerations

This review analyzed data from previously published studies; therefore, ethical approval and participant consent were not required. All included studies were published in **peer-reviewed journals** and explicitly stated institutional ethical approval or adherence to ethical standards such as the Declaration of Helsinki**.**

Figure 1. PRISMA 2020 flow diagram of the literature selection process for studies evaluating chronic inflammation and diabetes complications (n = 12 included).

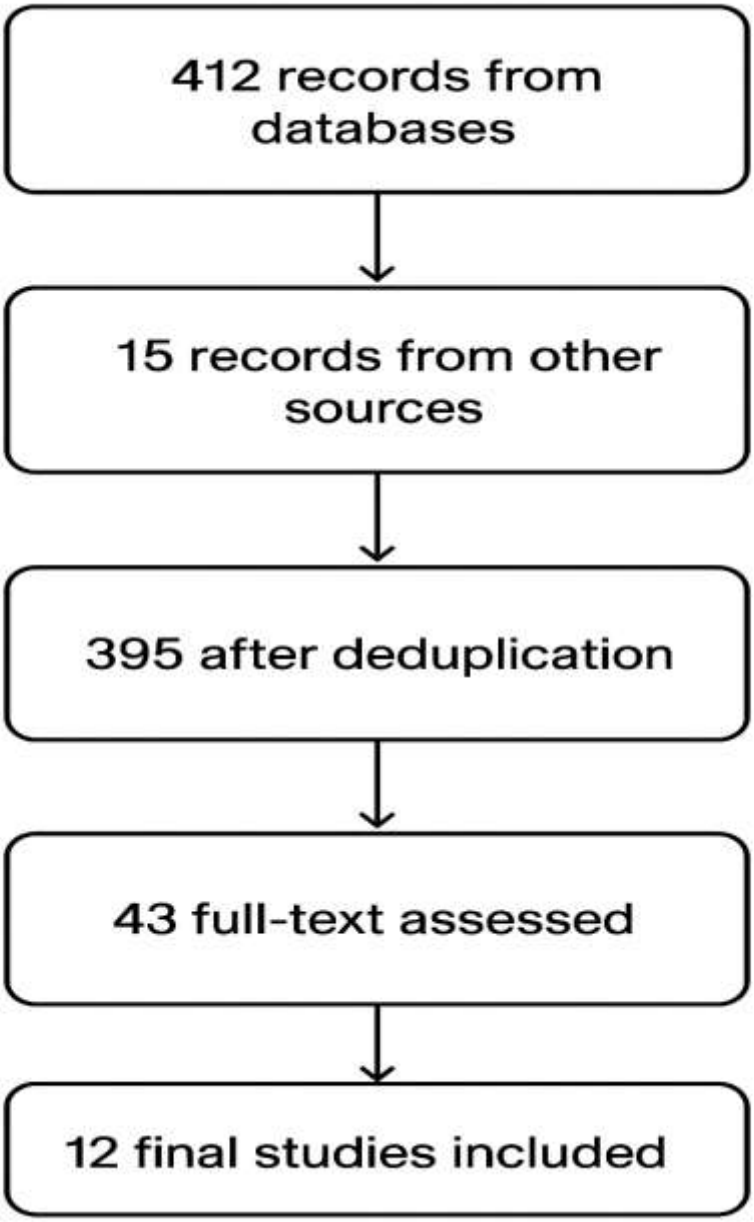

Figure 1 PRISMA Flow Diagram

Results

Summary and Interpretation of Included Studies on Chronic Inflammation and Diabetes Complications

1. Study Designs and Populations

The included studies (n = 12) comprised a combination of cross-sectional, case-control, and longitudinal cohort studies, along with prospective clinical trials. Collectively, they evaluated inflammatory biomarkers—including TNF-α, IL-6, CRP, MCP-1, SAA, fibrinogen, PTX3, and sRAGE—across various diabetes complications such as neuropathy, nephropathy, retinopathy, foot ulcers, and macrovascular disease. Sample sizes ranged from 91 participants (Abdelnabi & Sadek, 2018) to 1441 participants (Muni et al., 2013), providing both depth and generalizability. Participants were predominantly adults with type 1 or type 2 diabetes, though some studies included mixed populations or diabetic animal models.

2. Biomarkers and Assessment Techniques

Inflammatory markers were primarily measured using ELISA, high-sensitivity immunoassays, or multiplex bead-based platforms. Cytokines such as TNF-α, IL-6, and MCP-1 were most frequently assessed, reflecting their central roles in endothelial dysfunction and microvascular injury. Other markers—fibrinogen, PTX3, and sRAGE—provided systemic and vascular inflammation indicators.

3. Associations Between Inflammatory Markers and Complications

Consistent patterns emerged across studies. Elevated TNF-α and iNOS expression correlated strongly with pain severity in diabetic neuropathy (Purwata, 2011), while IL-6 and hs-CRP predicted nephropathy progression (Abdelnabi & Sadek, 2018; Manda et al., 2025). Studies on MCP-1 found it predictive of microalbuminuria onset and diabetic kidney disease (Scurt et al., 2022; Fang et al., 2024). IL-6, PTX3, and hs-CRP were repeatedly linked with the presence and progression of diabetic retinopathy (Muni et al., 2013; Yang et al., 2014; Manda et al., 2025). Elevated SAA, fibrinogen, and sRAGE levels were associated with macrovascular complications and increased mortality risk (Dieter et al., 2016; Patel et al., 2024; Nin et al., 2010).

4. Quantitative Findings and Risk Associations

Across studies, inflammatory biomarker elevations increased risk by 1.5–6 times, depending on the outcome and marker assessed. For example, Purwata (2011) reported TNF-α odds ratio = 5.05, TNF-α immunoreactivity = 4.12, and iNOS immunoreactivity = 3.55 ($P < 0.01$) for painful neuropathy. Muni et al. (2013) found a relative risk (RR) of 1.83 (95% CI 0.94–3.55) for macular edema with elevated hsCRP. Similarly, Scurt et al. (2022) showed serum MCP-1 in the top quartile increased microalbuminuria risk, and Fang et al. (2024) confirmed MCP-1 (OR = 1.06, $P < 0.001$) and NLR (OR = 6.56, $P = 0.001$) as significant predictors of diabetic kidney disease.

5. Summary of Evidence

Overall, chronic inflammation is consistently associated with micro- and macrovascular diabetic complications. TNF-α, IL-6, MCP-1, and CRP emerged as robust markers of progression, while PTX3, SAA, fibrinogen, and sRAGE showed predictive value for advanced or fatal outcomes. These findings highlight inflammation's central mechanistic role and potential therapeutic targetability.

Table (1): Characteristics and Results of Included Studies

Study (Year)	Design	Sample (N)	Biomarkers	Main Findings / Results (with quantitative details)	Conclusion
Purwata (2011)	Cross-sectional + case-control	110 T2DM	TNF-α, iNOS	TNF-α levels and macrophage TNF-α/iNOS immunoreactivity significantly higher in painful neuropathy; ORs: TNF-α = 5.05 ($P < 0.001$), TNF-α immunoreactivity = 4.12 ($P < 0.001$), iNOS =	High TNF-α and iNOS are risk factors for painful diabetic neuropathy.

				3.55 (P = 0.002).	
Muni et al. (2013)	Prospective RCT (DCCT/EDIC)	1441 T1DM	hsCRP, ICAM-1, VCAM-1, TNF-αR1	hsCRP associated with clinically significant macular edema (RR = 1.83; P = .01) and retinal exudates (RR = 1.78; P = .004). No significant effect for VCAM-1 or TNF-αR1.	Elevated hsCRP predicts diabetic retinopathy risk.
Abdelnabi & Sadek (2018)	Case-control	91 (78 DM + 13 controls)	IL-6, hs-CRP	hsCRP and IL-6 significantly higher in both T1DM and T2DM nephropathy groups (P < 0.01). No significant difference between T1DM and T2DM groups.	IL-6 and hsCRP correlate with nephropathy severity.
Scurt et al. (2022)	Case-control (ROADMAP/OFU)	360	MCP-1 (serum & urine)	High MCP-1 levels predicted microalbuminuria over 6.5 years; risk significant in top quartile; stronger for serum MCP-1.	MCP-1 predicts early diabetic nephropathy.
Fang et al. (2024)	Cross-sectional	90 T2DM	NLR, hsCRP, MCP-1	NLR (OR = 6.56, P = 0.001) and MCP-1 (OR = 1.06, P < 0.001) significant risk factors for T2DKD; ROC AUC = 0.862 for MCP-1.	NLR and MCP-1 are diagnostic predictors for T2DKD.
Manda et al. (2025)	Prospective controlled	164 patients (328 eyes)	IL-6	IL-6 increased across DR groups: 5.4 → 9.25 → 15.71 pg/mL (P < 0.001). Positive correlation with	Aqueous IL-6 predicts DR severity and DME.

				central retinal thickness (ρ = 0.18, P = 0.001) and DME risk (OR = 1.00, P = 0.015).	
Tecilazich et al. (2013)	Prospective cohort	60 + animal models	CRP, IL-1, GM-CSF	DFU healers had lower baseline CRP, IL-1, GM-CSF (P < 0.05). EPC counts reduced in DFU; higher cytokine levels linked to non-healing ulcers.	Low inflammatory cytokines predict better DFU healing.
Yang et al. (2014)	Case-control	163 participants	PTX3, hsCRP	Plasma PTX3: 916 → 1094 → 1818 pg/mL across no DR → DM → DR (P < 0.001); PTX3 correlated with DR severity (R = 0.372, P < 0.001). AUC for PTX3 = 0.721.	PTX3 better predictor of DR progression than hsCRP.
Dieter et al. (2016)	Longitudinal cohort	135 T2DM + DKD	Serum amyloid A (SAA)	High SAA predicted death and ESRD; HR > 2.0 for upper tertile.	SAA is a prognostic biomarker for DKD outcomes.
Patel et al. (2024)	Prospective observational	180 T2DM	Fibrinogen	Mean fibrinogen = 446.5 mg/dL; higher in macrovascular disease; positively correlated with BMI and HbA1c (P < 0.01).	High fibrinogen linked to macrovascular complications.
Ahmad et al. (2024)	Cross-sectional	174 T2DM	Fibrinogen	Elevated fibrinogen associated with retinopathy (n = 57), nephropathy (n = 55), neuropathy (n = 62); P < 0.05.	Fibrinogen correlates with microvascular complications.

Nin et al. (2010)	Prospective cohort (12 years)	339 T1DM	sRAGE	Higher sRAGE predicted CVD (HR = 1.90; 95% CI 1.13–3.21) and mortality (HR = 2.12; 95% CI 1.26–3.57).	sRAGE elevations predict CVD and mortality in T1DM.

Discussion

Chronic inflammation plays a pivotal role in the pathogenesis and progression of diabetic complications, influencing both microvascular and macrovascular outcomes. Evidence consistently shows that proinflammatory cytokines, acute-phase reactants, and oxidative stress contribute to endothelial dysfunction, tissue injury, and impaired metabolic regulation in diabetes mellitus (Röhm et al., 2022). The findings of the current systematic review reinforce that inflammatory mediator such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein-1 (MCP-1), and fibrinogen are significantly associated with diabetic neuropathy, nephropathy, retinopathy, and cardiovascular complications. These markers reflect ongoing immune activation that underlies the vascular damage characteristic of chronic diabetes (Nedosugova et al., 2022).

The reviewed studies demonstrated consistent evidence linking inflammatory biomarkers to diabetic neuropathy. Elevated TNF-α levels, inducible nitric oxide synthase (iNOS) expression, and macrophage activation were found to be critical determinants of neuropathic pain in diabetic patients (Purwata, 2011). Similarly, Baka et al. (2021) reported that systemic inflammatory biomarkers, including IL-6 and CRP, were significantly higher in patients with painful diabetic neuropathy, highlighting their contribution to nociceptive sensitization. In addition, high plasma pentraxin 3 (PTX3) concentrations were correlated with diabetic polyneuropathy severity, suggesting its potential as an emerging biomarker for neural inflammation (Salcini et al., 2016). Collectively, these findings suggest that neuroinflammation is a major contributor to peripheral nerve damage and pain in diabetes.

In diabetic nephropathy, multiple inflammatory mediators have been shown to drive the progression from normoalbuminuria to microalbuminuria and end-stage renal disease. Abdelnabi and Sadek (2018) found that IL-6 and hsCRP levels were significantly elevated in both type 1 and type 2 diabetes patients with nephropathy, correlating strongly with urinary albumin excretion rates. Complementing this, Scurt et al. (2022) demonstrated that MCP-1 predicted the development of microalbuminuria over a 6.5-year follow-up, confirming its role as an early indicator of nephropathy onset. Fang et al. (2024) further substantiated this by showing that MCP-1 and neutrophil–lymphocyte ratio (NLR) were independent risk factors for type 2 diabetic kidney disease, with MCP-1 levels yielding an area under the ROC curve of 0.862, denoting strong predictive value.

Serum amyloid A (SAA), another acute-phase reactant, emerged as a potent marker of renal inflammation and progression toward end-stage renal disease (ESRD). Anderberg et al. (2015) found elevated SAA levels in diabetic kidney disease (DKD) patients, while Dieter et al. (2016) confirmed that higher baseline SAA concentrations predicted both mortality and ESRD development. These findings suggest that SAA could serve not only as a biomarker of systemic inflammation but also as a prognostic tool for DKD outcomes. Similarly, Winter et al. (2018) emphasized that accessible markers such as hsCRP and white blood cell count could serve as inexpensive screening tools for early kidney dysfunction in diabetic populations.

Inflammatory mechanisms also play a critical role in diabetic retinopathy (DR). The studies by Muni et al. (2013) and Song et al. (2015) demonstrated that higher levels of hsCRP and ICAM-

1 were associated with increased risk and progression of DR. Qiu et al. (2020) identified a direct pathogenic role of human CRP in retinal vascular damage, implicating it in endothelial injury and increased vascular permeability. Moreover, Manda et al. (2025) showed that aqueous IL-6 levels were significantly correlated with DR severity, with concentrations rising from 5.4 pg/mL in non-DR eyes to 15.7 pg/mL in proliferative DR, confirming the inflammatory microenvironment within the retina.

Genetic and molecular evidence further supports the inflammatory hypothesis in diabetic eye and kidney disease. Myśliwska et al. (2009) demonstrated that the −174GG IL-6 genotype was protective against nephropathy and retinopathy in type 1 diabetes, suggesting that genetic modulation of inflammatory pathways may influence disease susceptibility. Similarly, Romeo et al. (2002) reported that hyperglycemia-induced activation of nuclear factor-κB (NF-κB) in retinal pericytes promotes apoptosis, linking metabolic stress to inflammation-mediated vascular injury.

Macrovascular complications are equally influenced by systemic inflammation. Patel et al. (2024) found that elevated plasma fibrinogen levels were significantly associated with coronary artery disease and peripheral vascular disease in type 2 diabetes, with mean fibrinogen concentrations of 446.5 mg/dL among affected patients. Likewise, Ahmad et al. (2024) demonstrated that elevated fibrinogen correlated with microvascular complications such as neuropathy and nephropathy, underscoring fibrinogen's dual role in micro- and macroangiopathy. These findings align with Andreadi et al. (2022), who highlighted oxidative stress and endothelial dysfunction as mediators linking systemic inflammation to cardiovascular pathology in diabetes.

Vascular and immune crosstalk underlies these pathophysiological mechanisms. Inflammatory cytokines like TNF-α and IL-6 activate endothelial adhesion molecules, facilitate leukocyte infiltration, and disrupt nitric oxide bioavailability, leading to vascular remodeling and fibrosis (Zhao et al., 2024). Röhm et al. (2022) emphasized that chronic metabolic inflammation—termed "metaflammation"—is central to both insulin resistance and diabetic complications. This persistent low-grade inflammatory state promotes not only organ-specific injury but also systemic vascular instability.

Interestingly, some inflammatory mediators demonstrate paradoxical protective roles. For example, the study by Myśliwska et al. (2009) revealed that certain IL-6 genotypes may upregulate adaptive immune responses and confer resistance against chronic vascular damage. Similarly, Nin et al. (2010) reported that higher plasma soluble receptor for advanced glycation end products (sRAGE) was independently associated with increased cardiovascular disease and mortality in type 1 diabetes, yet its regulatory role may also reflect compensatory mechanisms against AGE-induced oxidative stress.

At the microvascular level, endothelial progenitor cells (EPCs) have been implicated in the healing and inflammatory processes of diabetic ulcers. Tecilazich et al. (2013) found that EPC depletion and elevated CRP, IL-1, and GM-CSF levels impaired ulcer healing, whereas lower inflammatory markers predicted favorable recovery. This underscores the balance between inflammation and repair in diabetic vascular biology.

The integration of biochemical, genetic, and clinical evidence supports inflammation as a unifying mechanism across all major diabetic complications. The interrelation between oxidative stress, advanced glycation end products, and cytokine activation perpetuates endothelial dysfunction and tissue injury (Nedosugova et al., 2022; Zhao et al., 2024). Moreover, markers such as MCP-1, SAA, and fibrinogen show translational potential as clinical predictors for identifying high-risk diabetic individuals.

In terms of therapeutic implications, anti-inflammatory strategies targeting cytokines or oxidative pathways may offer novel avenues for intervention. Andreadi et al. (2022) suggested that modulation of oxidative stress could mitigate cardiovascular and renal damage in diabetes, while Röhm et al. (2022) proposed metabolic-immune regulation as a potential therapeutic paradigm. Anti-TNF agents, IL-6 inhibitors, and antioxidant-based therapies may thus hold promise for preventing progression of diabetic complications.

Overall, the reviewed studies converge on a consistent conclusion: chronic inflammation is not merely a byproduct of hyperglycemia but an active driver of diabetic complications across organ systems. By identifying biomarkers such as IL-6, TNF-α, MCP-1, PTX3, SAA, CRP, and fibrinogen as indicators of risk and progression, clinical management can move toward early identification and precision-targeted therapies. Future longitudinal studies and interventional trials are needed to clarify causal pathways and assess the long-term efficacy of anti-inflammatory treatments in mitigating diabetic vascular and neural injury.

Conclusion

This systematic review establishes chronic inflammation as a fundamental mechanism driving diabetic complications, encompassing nephropathy, retinopathy, neuropathy, and cardiovascular diseases. The consistent elevation of biomarkers such as IL-6, TNF-α, CRP, and SAA underscores the pivotal role of immune-mediated endothelial injury and metabolic stress in disease progression. The findings also emphasize the clinical potential of these inflammatory indicators as predictive tools for early detection and risk stratification.

Moreover, integrating anti-inflammatory and antioxidant therapies into diabetes management may provide a novel approach to mitigating vascular and neural damage. Targeted interventions addressing cytokine activity, oxidative pathways, and metabolic dysregulation could reduce complication rates and improve patient outcomes. Future longitudinal and interventional research should validate these biomarkers' predictive power and evaluate the therapeutic impact of modulating inflammatory responses in diabetic populations.

References

- Abdelnabi, A. M., & Sadek, A. M. (2018). Role of interleukin 6 and highly sensitive C-reactive protein in diabetic nephropathy. The Egyptian Journal of Internal Medicine, 30(3), 103–109.
- Ahmad, I., Khan, M. A., Hussain, M., & Ahmed, S. (2024). Correlation between plasma fibrinogen levels and microvascular complications in patients with type 2 diabetes mellitus. Cureus, 16(8), e65421.
- Anderberg, R. J., Meek, R. L., Hudkins, K. L., Cooney, S. K., Alpers, C. E., Leboeuf, R. C., & Tuttle, K. R. (2015). Serum amyloid A and inflammation in diabetic kidney disease. Kidney International, 88(4), 800–810.
- Andreadi, A., Bellia, A., Di Daniele, N., Meloni, M., et al. (2022). The molecular link between oxidative stress, insulin resistance, and type 2 diabetes: A target for new therapies against cardiovascular diseases. Current Opinion in Pharmacology.
- Baka, P., Escolano-Lozano, F., & Birklein, F. (2021). Systemic inflammatory biomarkers in painful diabetic neuropathy. Journal of Diabetes and Its Complications, 35(10), 108017.
- Dieter, B. P., McPherson, S. M., Afkarian, M., de Boer, I. H., Mehrotra, R., Short, R., ... & Tuttle, K. R. (2016). Serum amyloid A and risk of death and end-stage renal disease in diabetic kidney disease. Journal of Diabetes and Its Complications, 30(8), 1467–1472.
- Fang, Y., Wang, B., Pang, B., Zhou, Z., Xing, Y., Pang, P., ... & Yang, B. (2024). Exploring the relations of NLR, hsCRP and MCP-1 with type 2 diabetic kidney disease: A cross-sectional study. Scientific Reports, 14(1), 3211.

- Manda, A. R., Lee, L. H., Steinkerchner, M. S., Sheng, J., Veach, L., Gangaputra, S., & Kim, S. J. (2025). Analysis of aqueous interleukin-6 in diabetic retinopathy: A prospective, controlled trial of 328 eyes. Ophthalmology Retina.
- Muni, R. H., Kohly, R. P., Lee, E. Q., Manson, J. E., Semba, R. D., Schaumberg, D. A., & DCCT/EDIC Research Group. (2013). Prospective study of inflammatory biomarkers and risk of diabetic retinopathy in the Diabetes Control and Complications Trial. JAMA Ophthalmology, 131(4), 514–521.
- Myśliwska, J., Zorena, K., Semetkowska-Jurkiewicz, E., Rachón, D., Suchanek, H., & Myśliwski, A. (2009). The −174GG interleukin-6 genotype is protective from retinopathy and nephropathy in type 1 diabetes mellitus. Pediatric Research, 66(3), 341–345.
- Nedosugova, L. V., Markina, Y. V., Bochkareva, L. A., et al. (2022). Inflammatory mechanisms of diabetes and its vascular complications. Biomedicines.
- Nin, J. W., Jorsal, A., Ferreira, I., Schalkwijk, C. G., Prins, M. H., Parving, H. H., ... & Stehouwer, C. D. (2010). Higher plasma soluble receptor for advanced glycation end products (sRAGE) levels are associated with incident cardiovascular disease and all-cause mortality in type 1 diabetes: A 12-year follow-up study. Diabetes, 59(8), 2027–2032.
- Patel, N., Taviad, P., Buch, J., & Sinha, M. (2024). The study of relationship between plasma fibrinogen levels and macrovascular complications of type 2 diabetes mellitus. Atherosclerosis Plus, 55, 8–13.
- Purwata, T. E. (2011). High TNF-alpha plasma levels and macrophages iNOS and TNF-alpha expression as risk factors for painful diabetic neuropathy. Journal of Pain Research, 4, 169–175.
- Qiu, F., Tong, H., Wang, Y., Tao, J., Wang, H., & Chen, L. (2020). Pathogenic role of human C-reactive protein in diabetic retinopathy. Clinical Science, 134(14), 1933–1952.
- Röhm, T. V., Meier, D. T., Olefsky, J. M., & Donath, M. Y. (2022). Inflammation in obesity, diabetes, and related disorders. Immunity.
- Romeo, G., Liu, W. H., Asnaghi, V., Kern, T. S., & Lorenzi, M. (2002). Activation of nuclear factor-κB induced by diabetes and high glucose regulates a proapoptotic program in retinal pericytes. Diabetes, 51(7), 2241–2248.
- Salcini, C., Gul, O. O., Minbay, F. Z., Durmus, S., Korkut, S., Ermis, F., & Kahraman, S. (2016). High plasma pentraxin 3 levels in diabetic polyneuropathy. Hormone and Metabolic Research, 48(1), 73–79.
- Scurt, F. G., Menne, J., Brandt, S., Bernhardt, A., Mertens, P. R., Haller, H., & Chatzikyrkou, C. (2022). Monocyte chemoattractant protein-1 predicts the development of diabetic nephropathy. Diabetes/Metabolism Research and Reviews, 38(1), e3497.
- Song, J., Chen, S., Liu, X., Duan, H., Kong, J., & Li, Z. (2015). Relationship between C-reactive protein level and diabetic retinopathy: A systematic review and meta-analysis. PLoS ONE, 10(12), e0144406.
- Stanimirovic, J., Radovanovic, J., Banjac, K., et al. (2022). Role of C-reactive protein in diabetic inflammation. Journal of Inflammation.
- Tecilazich, F., Dinh, T., Pradhan-Nabzdyk, L., Leal, E., Tellechea, A., Kafanas, A., ... & Veves, A. (2013). Role of endothelial progenitor cells and inflammatory cytokines in healing of diabetic foot ulcers. PLoS ONE, 8(12), e83314.
- Winter, L., Wong, L. A., Jerums, G., Seah, J. M., Clarke, M., O'Neal, D., ... & MacIsaac, R. J. (2018). Use of readily accessible inflammatory markers to predict diabetic kidney disease. Frontiers in Endocrinology, 9, 225.
- Yang, H. S., Woo, J. E., Lee, S. J., Park, S. H., & Woo, J. M. (2014). Elevated plasma pentraxin 3 levels are associated with development and progression of diabetic retinopathy. Investigative Ophthalmology & Visual Science, 55(9), 5539–5544.
- Zhao, L., Hu, H., Zhang, L., Liu, Z., Huang, Y., & Liu, Q. (2024). Inflammation in diabetes complications: Molecular mechanisms and therapeutic interventions. MedComm.