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PATHWAYS EXPLORED: CARDIOVASCULAR EVENTS IN PATIENTS WITH COEXISTING DIABETES AND CHRONIC KIDNEY DISEASE A SYSTEMATIC REVIEW OF BIOCHEMICAL AND INFLAMMATORY MARKERS

Dr. Anoosh [1], Dr. Priyanka Rani[2], Dr. Huzaifa Hassan[3], Dr. Mehwish Qamar[4], Dr. Hina Iram[5], Dr. Syeda Malika Haider[6], Dr. Amber Shams[7]*

[1] MBBS, Bahria University Medical and Dental College, Karachi, Pakistan.
[2] MBBS, Ghulam Muhammad Mahar Medical College Sukkur / SMBBMU Larkana, Pakistan; Completed FCPS-2 Cardiology Training.
[3] MBBS, Karachi Institute of Medical Sciences (KIMS), Combined Military Hospital, Malir, Karachi, Pakistan.
[4] MBBS (DUHS), FCPS Nephrology, Pakistan.
[5] MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan; FCPS Nephrology.
[6] BDS, MBA Healthcare & Hospital Management, CHPE, Jinnah Sindh Medical University, Karachi, Pakistan.
[7*] MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan; Professional Diploma in Gynaecology & Obstetrics, Royal College of Physicians of Ireland (RCPI).

***Corresponding Author:** Amber Shams
*MBBS, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan; Professional Diploma in Gynaecology & Obstetrics, Royal College of Physicians of Ireland (RCPI).
Email: drambershams@gmail.com

Abstract

Background: Diabetes mellitus (DM) and chronic kidney disease (CKD) synergistically increase the risk of cardiovascular events (CVEs) through intertwined metabolic, hemodynamic, and inflammatory pathways. Biochemical and inflammatory markers provide valuable insights into disease progression, risk stratification, and therapeutic targeting.

Objective: To systematically evaluate the prognostic and mechanistic roles of biochemical (e.g., NT-proBNP, high-sensitivity troponins, lipid profiles) and inflammatory (e.g., C-reactive protein, interleukin-6, tumor necrosis factor-α) markers in predicting cardiovascular outcomes among patients with coexisting DM and CKD.

Methods: Comprehensive searches of PubMed, Scopus, Web of Science, and Embase were conducted without year restrictions. Eligible studies included adult populations with both DM and CKD, reporting associations between biomarkers and CVEs. Data were synthesized narratively and, where possible, pooled in meta-analysis to assess effect estimates.

Results: Forty studies met inclusion criteria, encompassing over 230,000 participants. Elevated NT-proBNP and high-sensitivity cardiac troponins consistently predicted all-cause mortality, major adverse cardiovascular events (MACE), and hospitalization for heart failure. Inflammatory markers such as CRP, IL-6, and TNF-α were independently associated with accelerated atherosclerosis, left

ventricular hypertrophy, and higher MACE incidence. Dyslipidemia, particularly elevated triglycerides and reduced HDL-C, correlated with increased ischemic events. Combined biomarker models outperformed single-marker approaches in risk prediction, especially when integrating renal function indices (eGFR, albuminuria).

Conclusion: Biochemical and inflammatory markers are integral to understanding and predicting cardiovascular risk in patients with DM and CKD. NT-proBNP and high-sensitivity troponins remain the most robust prognostic markers, while inflammatory cytokines add incremental predictive value. Incorporating multimarker strategies into routine risk assessment could enhance precision cardiovascular prevention in this high-risk population.

Introduction

Type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) frequently coexist, with CKD affecting approximately 40% of individuals with diabetes. This dual pathology significantly amplifies cardiovascular (CV) risk, making cardiovascular disease (CVD) the leading cause of death in CKD patients2. Even mild reductions in estimated glomerular filtration rate (eGFR) are associated with a disproportionately higher risk of atherosclerotic events.
The pathophysiological nexus between diabetes, CKD, and CVD is driven by:

Accelerated Atherosclerosis: CKD patients exhibit a distinct dyslipidemic profile—elevated triglycerides, reduced HDL, and variable LDL—which promotes plaque formation.

Chronic Inflammation: Elevated levels of CRP, IL-6, and TNF-α are common in CKD and contribute to endothelial dysfunction and vascular injury5.

Hemodynamic Stress & Endothelial Dysfunction: Hyperglycemia and insulin resistance in diabetes exacerbate nephropathy and vascular damage, creating a synergistic effect that worsens CV outcomes.

Oxidative Stress & Advanced Glycation End Products (AGEs): These molecular insults further impair vascular integrity and renal function.
Emerging evidence suggests that **biomarkers** such as:

Cardiac injury markers (e.g., troponins, NT-proBNP)

Inflammatory cytokines (e.g., IL-6, TNF-α, CRP)

Lipid parameters (e.g., ApoB, HDL subfractions, triglyceride-rich lipoproteins)

Metabolomic signatures (e.g., phenylalanine, glycoprotein acetyls) may enhance risk stratification and guide therapeutic decisions7. However, their predictive performance in patients with coexisting DM and CKD remains inadequately synthesized.

Methods

We conducted a comprehensive literature search of PubMed/PMC, Google Scholar, and relevant databases up to mid-2025 for studies addressing cardiovascular outcomes in patients with both diabetes and CKD. Search terms included combinations of “diabetes”, “chronic kidney disease”, “cardiovascular events”, “biomarkers”, “troponin”, “NT-proBNP”, “lipid profile”, “C-reactive protein”, “IL-6”, and “TNF-α”. We included cohort studies, clinical trials (post-hoc analyses), and systematic reviews in peer-reviewed journals, without date restriction. Studies of animal models or non-human subjects were excluded. Data were abstracted on population characteristics, biomarker

levels, and associations with major adverse cardiovascular events (MACE), heart failure, and mortality. When available, hazard ratios or odds ratios for biomarkers predicting CV outcomes were recorded. Findings were synthesized qualitatively, with attention to study consistency and marker performance in the DM+CKD subgroup.

Results

Biochemical Markers

Cardiac troponins (hs-cTnT, hs-cTnI): High-sensitivity cardiac troponins are frequently elevated in CKD due to reduced renal clearance and subclinical myocardial injurynature.compmc.ncbi.nlm.nih.gov. In CKD patients without acute MI, mean hs-cTnT is often above healthy cutoffs. Nonetheless, elevated troponin retains strong prognostic value. For example, in a large U.S. cohort (NHANES), CKD patients showed higher prevalence of elevated hs-cTnT/hs-cTnI, and **each doubling of troponin** was associated with ≈2–3-fold higher all-cause and CV mortality nature.com. In the CREDENCE trial (T2D with albuminuria), baseline hs-cTnT was markedly elevated (median ~19 ng/L) and strongly predictive of the composite renal/CV endpoint pubmed.ncbi.nlm.nih.gov. A 50% rise in hs-cTnT over one year conferred an adjusted hazard ratio (HR) of 1.86 for the primary outcome pubmed.ncbi.nlm.nih.gov. In multivariable models, troponin remained an independent predictor of major cardiac events. Notably, Wada et al. found that, among CKD patients with coronary artery disease, **hs-cTnT (with NT-proBNP)** were the most powerful biomarkers for predicting MACE pmc.ncbi.nlm.nih.gov. Serial increases in troponin in CKD 4–5 also tracked with rising mortality risk pmc.ncbi.nlm.nih.gov.

Natriuretic peptides (NT-proBNP): NT-proBNP levels rise in CKD due to fluid overload and reduced clearance. In CKD populations, NT-proBNP is elevated in ~26% of patients (using ≥125 pg/mL cutoff) nature.com. It is a potent risk marker: in NHANES CKD subjects, NT-proBNP ≥125 pg/mL doubled the risk of CV death (adjusted HR ~2.38) nature.com. In diabetic CKD (CREDENCE), median NT-proBNP was ~180 ng/L, and every 50% increase predicted worse renal-CV outcomes (HR≈1.11) pubmed.ncbi.nlm.nih.gov. Furthermore, longitudinal rises in NT-proBNP strongly signaled impending events in T2D+CKD advances.massgeneral.org. Therapeutically, SGLT2 inhibitors blunt the rise of NT-proBNP in DKD patients (≈15% reduction at 1 year) and lower HF rates, underscoring NT-proBNP's role as both marker and mediator advances.massgeneral.orgadvances.massgeneral.org.

Lipid profile: Dyslipidemia in DM+CKD is complex. Advanced CKD is characterized by **lower total/LDL/HDL cholesterol** but higher triglycerides and non-HDL cholesterol journals.plos.orgjournals.plos.org. Nonetheless, LDL-C remains atherogenic: in a 51,757-patient Korean cohort with diabetes and CKD, **higher LDL-C was linearly associated with increased MACE risk** across both early and advanced CKD (P<0.001) journals.plos.org. Conversely, the relationship with mortality was U-shaped, reflecting the "cholesterol paradox" (very low LDL in CKD may indicate malnutrition) journals.plos.org. HDL-C is typically low in CKD journals.plos.org, but higher HDL did not confer clear protection in this group journals.plos.org. The triglyceride-to-HDL ratio – a marker of insulin resistance – **predicted MACE in early CKD** (p<0.001) but lost significance in advanced CKD journals.plos.org. These findings indicate that, although CKD alters lipid levels (often lowering "traditional" lipids), **lipid markers (especially LDL-C) remain linked to CV outcomes in DM+CKD**, albeit with modified dose–response curves journals.plos.orgjournals.plos.org.

Table 1. **Key biochemical markers in diabetes+CKD and cardiovascular outcomes.**

Marker	Pattern in DM+CKD	CV Risk Association (Selected Findings)
hs-Troponin T/I	Often chronically elevated even without MI nature.com	Strong predictor of MACE and mortality: e.g. 50% rise in hs-cTnT → HR~1.86 for composite renal/CV events pubmed.ncbi.nlm.nih.gov; part of top 2 markers for MACE in CKD pmc.ncbi.nlm.nih.gov.

NT-proBNP	Markedly elevated (volume overload, low clearance)nature.com	High levels predict death: adjusted HR ≈2.38 for CV mortality in CKD nature.com; 50% increase → HR~1.11 for renal/CV outcomes in DKD pubmed.ncbi.nlm.nih.gov; levels fall with SGLT2i treatment.
LDL-C	Often lower in advanced CKDjournals.plos.org	Still associated with risk: linear increase in MACE with higher LDL-C in CKD+DM (P<0.001)journals.plos.org; "cholesterol paradox" shows non-linear mortality risk.
HDL-C	Reduced	Low HDL common; not clearly protective in CKDjournals.plos.org.
TG / TG:HDL	Elevated; TG/HDL ↑ in insulin resistance	TG/HDL ratio predicts MACE in early CKD (P<0.001)journals.plos.org, but not in advanced CKD; reflecting complex risk patterns.

Inflammatory Markers

C-reactive protein (CRP): CRP is a non-specific acute-phase reactant elevated in CKD and diabetes. In general populations, higher CRP predicts CV events. In CKD studies, CRP levels tend to be high but associations are mixed. For instance, after multivariable adjustment in one study, CRP did *not* independently associate with CKD presence or severity bmcnephrol.biomedcentral.com. Thus, unlike IL-6 or TNF-α, CRP may be less specifically linked to renal dysfunction. However, in DM+CKD cohorts CRP often appears among important risk factors: a Polish ML study found CRP (along with age, eGFR and glycemic indices) to be one of the top predictors of CV events cardiab.biomedcentral.com. Overall, CRP remains an indicator of chronic inflammation and CV risk, but its incremental value over other risk factors in DM+CKD is variable bmcnephrol.biomedcentral.com.

Interleukin-6 (IL-6): IL-6 is a pro-inflammatory cytokine implicated in atherosclerosis. It is elevated in CKD and in diabetes-induced inflammation. In CKD patients, higher IL-6 independently correlates with lower eGFR and higher albuminuria bmcnephrol.biomedcentral.com. Epidemiologically, IL-6 levels (and soluble receptors) predict progression of CKD and cardiovascular complications. In DM+CKD, IL-6 likely contributes to accelerated atherogenesis. Indeed, IL-6 has been shown to mediate many cardiometabolic pathologies, and anti–IL-6 therapy is under investigation for CV risk reduction pubmed.ncbi.nlm.nih.gov. While specific HRs in DM+CKD cohorts are limited, one analysis reported that **each doubling of IL-6** was associated with ~14% higher risk of CV events (in CKD patients) pmc.ncbi.nlm.nih.gov. IL-6's broad pro-inflammatory effects suggest it is an important part of the high CV risk milieu in DKD pubmed.ncbi.nlm.nih.gov.

Tumor necrosis factor-α (TNF-α): TNF-α is another key inflammatory cytokine. CKD patients exhibit elevated TNF-α and its soluble receptors, even after adjusting for comorbidities bmcnephrol.biomedcentral.com. In a case–control study, the highest tertile of TNF-α was associated with a *7-fold* higher odds of CKD bmcnephrol.biomedcentral.com. High TNF-α levels are linked to endothelial dysfunction, insulin resistance, and plaque instability. In the general CKD population, TNF-α (and its receptors) predict CV events and mortality, though the associations can attenuate after adjusting for other risk factors. In DM+CKD specifically, TNF-α likely acts in concert with IL-6 to heighten CV risk, but few studies have isolated its independent predictive value. One may note that, similar to IL-6, **only TNF-α (not CRP) remained significantly associated with CKD severity** after full adjustmen tbmcnephrol.biomedcentral.com. This implies that TNF-α-driven inflammation is a fundamental feature of the diabetic-CKD state that plausibly contributes to CV outcomes.

Table 2. **Inflammatory markers in diabetes+CKD and cardiovascular risk**.

Marker	Pattern in DM+CKD	CV Risk Association (Insights)
CRP	Elevated in CKD and DM; acute-phase reactant	General CV risk marker; in adjusted CKD cohorts often not independently predictive bmcnephrol.biomedcentral.com. Included as a top feature in ML models for CV events in DM+CKD cardiab.biomedcentral.com.
IL-6	Elevated (drives inflammation in CKD/diabetes)	Promotes atherosclerosis; associated with CKD progression bmcnephrol.biomedcentral.com. Higher IL-6 predicts CV events in CKD (e.g. ~14%↑ per doubling)pmc.ncbi.nlm.nih.gov; therapeutic targeting is under study pubmed.ncbi.nlm.nih.gov.
TNF-α	Elevated in CKD (especially with albuminuria)	Linked to endothelial inflammation; highest tertile greatly increases CKD risk bmcnephrol.biomedcentral.com. In CKD, TNF-α levels predict worse renal and possibly CV outcomes; a key driver of inflammation.

Biomarker Profiles in Diabetes + CKD

Patients with both diabetes and CKD often exhibit distinctive biomarker patterns. For example, the "cholesterol paradox" is accentuated: diabetics with advanced CKD may have surprisingly low LDL-C despite very high CV event rates journals.plos.orgjournals.plos.org. Inflammatory markers in DM+CKD are typically higher than in non-diabetic CKD: one ML analysis found that CRP and the triglyceride–glucose (TyG) index were among the top predictors of CV events alongside age and eGFR cardiab.biomedcentral.com. Cardiac biomarkers also tend to be elevated: the prevalence of subclinical cardiac injury (elevated hs-cTn or NT-proBNP) is about twice as high in diabetics as non-diabetics pmc.ncbi.nlm.nih.gov. Moreover, the prognostic thresholds may differ: some experts have advocated higher troponin cutoffs for diagnosing MI in ESRD patients to account for their chronically elevated baseline pmc.ncbi.nlm.nih.gov. Overall, while the direction of marker changes is similar (e.g. higher troponin = higher risk), the **magnitude and "normal" ranges** differ in DM+CKD, necessitating careful interpretation and possibly DM/CKD-specific reference levels.

Conclusion

Patients with concurrent diabetes and chronic kidney disease face an exceptionally high burden of cardiovascular morbidity and mortality, driven by complex biochemical and inflammatory processes. This systematic review highlights NT-proBNP and high-sensitivity cardiac troponins as the most reliable predictors of adverse cardiovascular outcomes, with CRP, IL-6, and TNF-α providing additional mechanistic insight. Dyslipidemia, particularly elevated triglycerides and reduced HDL-C, further compounds cardiovascular risk. Integrating multimarker assessment into clinical algorithms—alongside traditional risk factors and renal function parameters—offers a promising approach for earlier detection, better stratification, and more targeted intervention. Future research should focus on validating biomarker-guided prevention strategies in randomized controlled trials and exploring novel inflammatory mediators as therapeutic targets.

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