LITERATURE REVIEW OPEN ACCESS

Immunometabolic Inflammation in the Cardiovascular-Kidney-Metabolic Continuum

Nur Shanti Retno Pembayun[1*], Hafshah Yasmina Abidah[1], Rizki Maulidya Putri[2]

[1]Medical Education Program, Faculty of Medicine, Universitas Negeri Surabaya, Surabaya, Indonesia
[2]Medical Profession Program, Faculty of Medicine, Universitas Negeri Surabaya, Surabaya, Indonesia
**Corresponding author: nurpembayun@unesa.ac.id*

Abstract

Cardiovascular, kidney, and metabolic disorders are traditionally classified as separate diseases, yet their biological trajectories are tightly coupled. Adiposity, insulin resistance, dyslipidaemia, endothelial dysfunction, chronic kidney disease, and heart failure frequently coexist because they are sustained by shared immunometabolic disturbances rather than by isolated organ failure. This narrative review examines inflammation as an organizing mechanism within the cardiovascular-kidney-metabolic (CKM) continuum. It integrates evidence on adipose-tissue immune remodelling, NLRP3 inflammasome activation, endothelial injury, maladaptive myelopoiesis, clonal haematopoiesis, renal innate immunity, and disturbed resolution pathways. In metabolically stressed tissues, nutrient excess and cellular damage alter macrophage, neutrophil, lymphocyte, endothelial, and parenchymal-cell metabolism. These changes amplify interleukin-1, interleukin-6, tumour-necrosis-factor, reactive-oxygen-species, and extracellular-trap signalling, thereby linking insulin resistance to vascular inflammation, glomerular injury, myocardial fibrosis, and heart failure. The review also evaluates circulating inflammatory indices and emerging tissue-informed biomarkers, emphasizing that association does not automatically establish clinical utility. Sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists demonstrate that therapies developed for metabolic control can improve cardiorenal outcomes, but their anti-inflammatory actions remain only one component of multifactorial benefit. Direct cytokine or inflammasome inhibition is biologically attractive but must be balanced against infection risk, patient heterogeneity, and uncertainty regarding the optimal stage for intervention. A clinically useful CKM framework should therefore combine organ staging with mechanistic phenotyping, longitudinal biomarker validation, and equitable prevention. Understanding when inflammation is causal, compensatory, or merely reflective of tissue injury is essential for translating immunometabolism into precision treatment and advancing Sustainable Development Goal 3.

Keywords: cardiovascular-kidney-metabolic syndrome; immunometabolism; inflammation; NLRP3 inflammasome; insulin resistance; chronic kidney disease; atherosclerosis

1. Introduction

The cardiovascular-kidney-metabolic continuum describes a dynamic network in which excess or dysfunctional adiposity, impaired glucose regulation, chronic kidney disease, and cardiovascular disease emerge through overlapping pathways. The American Heart Association CKM framework spans stage 0 (no CKM risk factors), stage 1 (excess or dysfunctional adiposity), stage 2 (metabolic risk factors or chronic kidney disease), stage 3 (subclinical cardiovascular disease in CKM), and stage 4 (clinical cardiovascular disease in CKM) [1-3,37]. The framework is clinically useful because risk develops before infarction, stroke, heart failure, or kidney failure. Epidemiological associations between inflammatory indices and CKM stage suggest accompanying immune activation, although cross-sectional markers cannot determine whether inflammation is a driver, mediator, consequence, or confounder [2,4].

Inflammation in CKM disease is neither a uniform elevation of C-reactive protein nor a simple extension of classical autoimmunity. It is a context-dependent response to nutrient overload, mitochondrial stress, hypoxia, cell death, altered lipids, uraemic toxins, and microbial products. These stimuli change how immune and structural cells generate and use energy. Immunometabolism is therefore important not only because activated leukocytes require glucose or fatty acids, but because metabolic intermediates control chromatin, cytokine production, redox balance, and cell fate. The resulting networks can persist after the initiating exposure has diminished and can transmit injury between adipose tissue, liver, vasculature, kidney, bone marrow, and myocardium [5-8].

This review critically examines immunometabolic inflammation as a unifying—but not exclusive—mechanism of CKM progression. The purpose is to identify where evidence supports causality, where it remains associative, and how mechanistic insight might improve biomarker development and therapy. The argument is deliberately cautious: CKM disease is heterogeneous, inflammation can be protective during repair, and suppression of a single pathway cannot substitute for control of blood pressure, atherogenic lipoproteins, glycaemia, smoking, diet, physical inactivity, or social determinants.

Table 1. Immunometabolic mechanisms across the CKM continuum (synthesized from references 7-22, 24, 28-36).

Domain	Mechanistic process	Translational implication
Adipose tissue	Macrophage remodelling, hypoxia, senescence, and inflammasome activation	Prioritize weight reduction and distinguish active inflammation from fixed fibrosis
Vasculature	Lipoprotein retention, endothelial activation, failed efferocytosis, and IL-1/IL-6 signalling	Combine lipid lowering with phenotype-specific inflammatory assessment
Kidney	Innate sensing, NETs, tubular injury, endothelial dysfunction, and fibrogenesis	Align immune intervention with stage and residual viable tissue
Bone marrow	Maladaptive myelopoiesis and clonal haematopoiesis	Potential precision-risk marker; intervention evidence remains incomplete
Therapeutics	SGLT2 and GLP-1 pathways modify haemodynamic, metabolic, redox, and immune signals	Benefits are systems-level and should not be reduced to one anti-inflammatory effect

Abbreviations: CKM, cardiovascular-kidney-metabolic; IL, interleukin; NETs, neutrophil extracellular traps; SGLT2, sodium-glucose cotransporter-2; GLP-1, glucagon-like peptide-1.

2. Narrative Review Approach

This focused narrative review integrates human observational studies, experimental models, mechanistic investigations, translational studies, randomized clinical trials, and major state-of-the-art reviews addressing CKM staging, adipose inflammation, atherosclerosis, diabetic kidney disease, clonal haematopoiesis, and the immunometabolic actions of contemporary therapies. Priority was given to evidence linking a molecular pathway with an organ phenotype or clinical outcome. Because the review was not prospectively registered, did not use duplicate systematic screening, and did not perform quantitative synthesis, it should be interpreted as a critical mechanistic narrative rather than a complete estimate of effect size.

[AUTHOR VERIFICATION REQUIRED: insert the databases actually searched, final search date, full search strings, language limits, eligibility criteria, and study-selection process. Delete any method element that was not performed.]

3. From Metabolic Stress to Interorgan Disease

CKM progression can be understood as repeated communication between metabolically stressed tissues. Adipocyte hypertrophy increases lipolysis and the release of free fatty acids, while inadequate adipose expandability promotes ectopic lipid deposition in liver, skeletal muscle, pancreas, myocardium, and kidney. Lipotoxic species, especially ceramides and oxidized lipids, disturb insulin signalling and organelle function. Endoplasmic-reticulum stress and mitochondrial dysfunction generate danger signals that activate resident macrophages and recruit circulating myeloid cells. At the same time, hyperglycaemia promotes advanced glycation, oxidative stress, endothelial activation, and persistent changes in myeloid progenitors. The consequence is a feedback loop in which metabolic dysfunction produces inflammation and inflammation further impairs metabolic flexibility [6-10].

The organs involved do not contribute symmetrically. The kidney regulates volume, electrolytes, neurohormonal activation, toxin clearance, and glucose homeostasis; loss of kidney function therefore magnifies vascular and myocardial stress. The heart and vasculature determine perfusion and venous pressure, influencing renal filtration and congestion. Adipose tissue functions as an endocrine and immune organ, while the liver integrates lipid, glucose, complement, and acute-phase responses. Bone marrow adapts leukocyte production to systemic signals. A CKM model becomes biologically meaningful when it recognizes these reciprocal relationships rather than treating comorbidity as the coincidental accumulation of diagnoses [1,3,11].

4. Adipose-Tissue Immune Remodelling and Insulin Resistance

Healthy adipose tissue contains immune populations that support extracellular-matrix turnover, vascular homeostasis, and insulin sensitivity. With chronic energy excess, adipocytes enlarge, local oxygen tension falls, and cell death increases. Macrophages accumulate around damaged adipocytes and adopt

heterogeneous states that cannot be fully represented by the binary M1/M2 nomenclature. Their lipid handling, lysosomal function, and mitochondrial activity determine whether they buffer excess lipid or propagate inflammatory injury. Studies in humans and experimental systems link macrophage abundance and phenotype with impaired insulin sensitivity, while molecular perturbations of macrophage lipid transport or proteostasis can alter systemic metabolism [7-10].

The NLRP3 inflammasome provides one bridge between nutrient stress and cytokine maturation. Saturated lipids, cholesterol crystals, mitochondrial reactive oxygen species, ion flux, and damaged organelles can facilitate inflammasome activation, caspase-1 activity, and release of interleukin-1β and interleukin-18. Experimental interruption of this axis improves insulin sensitivity in several diet-induced models, supporting a causal role [10]. Nevertheless, inflammasome activation is stimulus-, cell-, and tissue-specific. Clinical obesity encompasses different fat distributions, degrees of fibrosis, genetic backgrounds, diets, and medications; the presence of elevated circulating cytokines does not prove that adipose NLRP3 is the dominant therapeutic target in every patient.

Other immune and stromal populations refine the response. Dendritic cells influence T-cell recruitment, regulatory T-cell loss may weaken immune restraint, and senescent adipocyte progenitors secrete inflammatory mediators that impair tissue plasticity. Experimental clearance of senescent cells can alleviate obesity-related metabolic dysfunction, but senolytic translation requires careful evaluation of target specificity and long-term tissue effects [12-14]. Fibro-inflammatory remodelling is especially important because an adipose depot that cannot safely expand diverts lipid toward organs vulnerable to lipotoxic injury. Thus, adipose inflammation should be interpreted as both an immune process and a failure of tissue adaptation.

5. Vascular and Myocardial Inflammation

Atherosclerosis illustrates how metabolism and immunity converge. Retained apolipoprotein-B-containing particles become modified in the arterial intima, activating endothelial cells and recruiting monocytes. Macrophage lipid uptake, defective efferocytosis, cell death, smooth-muscle-cell phenotypic change, and failed resolution drive lesion progression [15-18]. Randomized trials provide direct evidence that inflammation can be therapeutically causal in selected patients: IL-1 beta inhibition with canakinumab reduced recurrent cardiovascular events after myocardial infarction, while low-dose colchicine reduced events after recent myocardial infarction and in chronic coronary disease [38-40]. These benefits do not eliminate residual lipid or thrombotic risk, and infection and other adverse effects remain clinically important.

Metabolic inflammation also contributes to heart failure. In obesity and diabetes, coronary microvascular dysfunction, oxidative stress, altered substrate utilization, endothelial activation, and interstitial fibrosis can promote myocardial stiffness even without a large infarction. Kidney dysfunction adds uraemic toxins, anaemia, mineral abnormalities, volume overload, and neurohormonal activation. Macrophage inflammasome signalling has been implicated in adverse ventricular remodelling in experimental models, but heart-failure phenotypes are mechanistically diverse [19]. An inflammatory biomarker that identifies one subgroup may be uninformative in another; a reduced ejection fraction after myocardial infarction and an obesity-associated preserved-ejection-fraction phenotype cannot be assumed to share the same dominant immune circuit.

Resolution biology is a useful corrective to the idea that inflammation should simply be eliminated. Successful repair requires clearance of dead cells, restoration of endothelial integrity, and transition of macrophages toward reparative functions. Specialized pro-resolving mediators and efficient efferocytosis can terminate inflammation without broad immunosuppression [16]. Therapeutic strategies that promote resolution may therefore preserve host defence more effectively than indiscriminate cytokine blockade, but robust clinical biomarkers of defective resolution are still lacking.

6. Renal Innate Immunity as an Amplifier of Systemic Risk

Diabetic and hypertensive kidney injury exposes tubular epithelial cells, podocytes, endothelial cells, and resident immune cells to hyperfiltration, mechanical stress, hypoxia, glucose, fatty acids, and damaged proteins. Pattern-recognition receptors, complement pathways, inflammasomes, and chemokine networks recruit monocytes and neutrophils. Innate immune activation can drive endothelial dysfunction, tubular injury, and fibrosis, while reduced filtration permits accumulation of pro-inflammatory metabolites. The kidney is consequently both a target of systemic immunometabolic stress and an amplifier of cardiovascular risk [16,21,22].

Neutrophil extracellular traps illustrate this bidirectionality. Although extracellular traps evolved to contain pathogens, excessive or poorly cleared traps expose histones, proteases, and DNA that injure endothelium and activate inflammasomes. Experimental evidence links trap formation to glomerular endothelial dysfunction in diabetic kidney disease [21]. C-reactive protein may also participate in renal injury rather than merely report it, as experimental work connects CRP with Smad3-dependent NLRP3 activation [22]. These

findings are mechanistically provocative, but clinical translation requires confirmation that target inhibition improves kidney outcomes without compromising antimicrobial defence.

Fibrosis is the common endpoint of many chronic kidney insults. Macrophages and damaged tubular cells release transforming-growth-factor-β and other mediators that activate fibroblasts and extracellular-matrix deposition. Once nephron loss becomes extensive, haemodynamic and structural forces can sustain progression even if inflammation is reduced. This stage dependence is critical: an immune intervention that is effective during active injury may have limited impact after advanced scarring. CKM trials should therefore align mechanism, biomarker, and disease stage rather than enrolling heterogeneous chronic kidney disease solely on the basis of estimated filtration rate.

7. Bone-Marrow Reprogramming and Clonal Haematopoiesis

Systemic metabolic stress can alter haematopoietic stem and progenitor cells, increasing myelopoiesis and generating monocytes with heightened inflammatory potential. This creates a biological memory through which transient hyperglycaemia, Western dietary exposure, or obesity may have prolonged vascular consequences. Clonal haematopoiesis of indeterminate potential (CHIP), conventionally defined by a somatic driver mutation with a variant-allele fraction of at least 2% in the absence of overt haematological malignancy, adds a genetically defined layer. TET2-deficient clones accelerate atherosclerosis in experimental systems through enhanced inflammasome and interleukin-1 signalling [20,24].

CHIP should not be treated as a deterministic diagnosis. Clone size, driver gene, age, cancer history, kidney function, smoking, and background cardiovascular risk influence its meaning. Obesity-related inflammation may facilitate clonal expansion, suggesting a two-way interaction rather than a simple linear pathway [28]. Screening asymptomatic populations is not yet equivalent to having an evidence-based intervention. Its immediate value is conceptual: cardiovascular risk can originate in bone marrow, and somatic evolution can connect ageing, inflammation, cancer, and CKM disease.

8. Biomarkers and Mechanistic Phenotyping

Inflammatory biomarkers range from high-sensitivity C-reactive protein and blood-cell ratios to cytokines, soluble receptors, lipid mediators, extracellular vesicles, proteomic panels, and cell-specific epigenetic signatures. Association with CKM stage or mortality is only an initial requirement [2,4]. A clinically useful biomarker must demonstrate analytical validity, intra- and inter-laboratory reproducibility, calibrated risk estimates, discrimination beyond established variables, and preferably improved reclassification or decision-curve net benefit. Most importantly, biomarker-guided action should improve outcomes at an acceptable cost.

Single measurements are vulnerable to acute infection, adiposity, medication, circadian variation, and platform effects. Longitudinal trajectories may better distinguish chronic activation from transient responses. Tissue-informed markers and multi-omic models can connect blood signals with interorgan biology, but high dimensionality increases overfitting. Validation should therefore prespecify thresholds, assess calibration and clinical utility, compare against simpler models, and test transportability across ancestry, geography, sex, age, kidney function, and socioeconomic context.

9. Therapeutic Interruption of the Inflammatory Continuum

The most effective CKM therapies frequently act on several pathways. Sodium-glucose cotransporter-2 inhibitors reduce heart-failure and kidney events in populations with and without diabetes. Proposed mechanisms include restoration of tubuloglomerular feedback, natriuresis, reduced intraglomerular pressure, improved cellular energetics, altered ketone handling, mitigation of oxidative stress, and reduced macrophage activation [29-33]. Experimental dapagliflozin can attenuate macrophage-mediated inflammation independently of SGLT2 expression [29], but this does not prove that anti-inflammatory activity accounts for clinical benefit. The strength of SGLT2 inhibition is precisely its systems-level action.

Glucagon-like peptide-1 receptor agonists reduce weight and improve glycaemia, with cardiovascular benefit in high-risk patients. Beyond weight loss, they may improve endothelial function, lipid handling, oxidative stress, and inflammatory signalling [34-36]. A randomized study combining exercise with a GLP-1 receptor agonist underscores the importance of integrated rather than drug-only management [34]. Nevertheless, receptor distribution, indirect metabolic effects, and differences among molecules complicate attribution of benefit to a single anti-inflammatory mechanism.

Direct targeting of interleukin-1, interleukin-6, NLRP3, neutrophil traps, or clonal-haematopoiesis-associated pathways may benefit selected patients, but broad implementation would be premature. Infection risk, treatment duration, cost, vaccine response, and the possibility that inflammation reflects irreversible tissue damage must be considered. A rational strategy is to combine aggressive control of causal metabolic

and haemodynamic exposures with pathway-specific treatment only when a validated biomarker identifies active, modifiable inflammation.

10. Critical Gaps and Research Priorities

Several limitations recur across both the field and this review. Mouse models reproduce selected mechanisms but not the full heterogeneity of human CKM disease; inflammatory measurements are often cross-sectional and obtained after medication has begun; and cardiovascular, kidney, and metabolic trials use different endpoints while rarely characterizing tissue biology. Women, older adults with multimorbidity, lower-income populations, and diverse ancestry groups remain under-represented. For this narrative synthesis specifically, the absence of a prospectively registered protocol, duplicate systematic screening, formal risk-of-bias assessment, and quantitative meta-analysis introduces selection and interpretation bias.

Future studies should recruit across CKM stages, collect repeated biospecimens, integrate immune and metabolic phenotypes, and prespecify analyses that distinguish prediction from causal mediation. Pragmatic trials should test whether mechanism-guided treatment improves outcomes beyond guideline-based multidomain care. Prevention must remain central. Food environments, air pollution, chronic stress, inadequate sleep, limited access to physical activity, and fragmented care shape both metabolism and inflammation. Addressing these determinants is essential to SDG 3 and is likely to produce broader benefit than any single immunomodulator.

11. Critical Synthesis and Implementation

11.1 Distinguishing causal inflammation from inflammatory burden

A persistent problem in CKM research is the tendency to infer causality from correlated biomarkers. C-reactive protein, neutrophil-to-lymphocyte ratios, and composite inflammatory indices often rise with adiposity, kidney dysfunction, smoking, infection, and socioeconomic adversity. They may summarize disease burden without identifying the pathway that should be inhibited. Mendelian approaches, randomized anti-inflammatory trials, mediation analyses, and target-engagement studies can strengthen causal inference, but each has limitations. Genetic instruments may represent lifelong subtle exposure rather than pharmacological inhibition, while biomarker mediation is sensitive to measurement error and treatment-induced confounding. The most persuasive evidence combines experimental perturbation, temporality, dose response, tissue concordance, and improved clinical outcome.

11.2 Phenotype-specific combinations

Future CKM treatment will probably involve combinations rather than one universal anti-inflammatory drug. A patient with visceral adiposity, albuminuric kidney disease, high apolipoprotein B, and heart failure may benefit from weight-reducing therapy, renin-angiotensin-system blockade, SGLT2 inhibition, lipid lowering, and blood-pressure control before direct immunomodulation is considered. Another patient with clonal haematopoiesis and recurrent events despite optimal risk-factor treatment may represent a more specific inflammatory phenotype. Trials should test treatment-by-biomarker interaction and should avoid using biomarker positivity as a substitute for biological validation.

11.3 Clinical implementation across disciplines

CKM care challenges conventional service boundaries. Primary care, endocrinology, nephrology, cardiology, nutrition, and laboratory medicine may each detect different parts of the same continuum. Shared care pathways should specify screening for albuminuria, kidney function, blood pressure, adiposity, glucose regulation, and atherogenic lipoproteins. Inflammatory testing should be added only when it changes management. Integrating such pathways into routine care is likely to prevent more events than deploying complex immune panels without access to basic risk-factor treatment.

11.4 Avoiding biological reductionism

An immunometabolic framework is valuable only if it expands rather than narrows explanation. Chronic stress, sleep disruption, pollution, infection, food insecurity, and discrimination can influence neuroendocrine and immune pathways, but describing these exposures solely as inflammation risks erasing their social origin. Molecular research should connect biological mechanisms with modifiable upstream conditions. This approach preserves scientific depth while ensuring that precision medicine does not become detached from public-health prevention.

11.5 Ageing and sex as biological modifiers

Ageing changes immune-cell composition, mitochondrial function, senescence, clonal haematopoiesis, kidney reserve, and body-fat distribution. Sex hormones and reproductive history influence adipose deposition, endothelial biology, and inflammatory responses. These modifiers may change both biomarker

ranges and treatment effects. Studies that adjust statistically for age and sex without testing interaction can miss mechanistically distinct trajectories. CKM phenotyping should therefore evaluate life-course exposure, menopause, frailty, and competing infection risk when considering immune-directed prevention.

12. Conclusion

Immunometabolic inflammation helps explain connections among dysfunctional adiposity, insulin resistance, atherosclerosis, kidney injury, and heart failure across CKM stages 0-4. NLRP3 signalling, maladaptive myelopoiesis, endothelial injury, extracellular traps, and clonal haematopoiesis are credible components, and randomized cardiovascular trials show that selected inflammatory pathways can be causally modifiable. Nevertheless, inflammation is heterogeneous, stage dependent, and intertwined with haemodynamic, lipid, glycaemic, behavioural, and social exposures. Clinical translation should prioritize validated phenotypes that change management, retain multidomain risk-factor control as the foundation of care, and reserve immune-directed therapy for populations in whom benefit, safety, and stage-specific action are demonstrated.

Declarations

Author contributions: Nur Shanti Retno Pembayun conceptualized the review, defined its scope, performed the literature search and evidence synthesis, and prepared the original draft. Hafshah Yasmina Abidah contributed to the immunological interpretation, critical appraisal of the evidence, and manuscript revision. Rizki Maulidya Putri contributed to the clinical interpretation of the cardiovascular-kidney-metabolic continuum, critical appraisal, and manuscript revision. All authors read and approved the final manuscript.

Funding: This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest: The authors declare that they have no conflicts of interest relevant to the content of this article.

Acknowledgements: The authors thank the Faculty of Medicine, Universitas Negeri Surabaya, for academic and institutional support during the preparation of this manuscript.

References

1. Sebastian SA, Padda I, Johal G. Cardiovascular-Kidney-Metabolic (CKM) syndrome: A state-of-the-art review. Curr Probl Cardiol. 2024;49(2):102344. doi:10.1016/j.cpcardiol.2023.102344.
2. Gao C, Gao S, Zhao R, Shen P, Zhu X, Yang Y, et al. Association between systemic immune-inflammation index and cardiovascular-kidney-metabolic syndrome. Sci Rep. 2024;14(1):19151. doi:10.1038/s41598-024-69819-0.
3. Kittelson KS, Junior AG, Fillmore N, da Silva Gomes R. Cardiovascular-kidney-metabolic syndrome - An integrative review. Prog Cardiovasc Dis. 2024;87:26-36. doi:10.1016/j.pcad.2024.10.012.
4. Xu Z, Yang S, Tan Y, Zhang Q, Wang H, Tao J, et al. Inflammation in cardiovascular-kidney-metabolic syndrome: key roles and underlying mechanisms-a comprehensive review. Mol Cell Biochem. 2025;480(12):6039-6075. doi:10.1007/s11010-025-05379-9.
5. Carvalho LRRA, Shimari M, Boeder AM, Zhuge Z, Cai M, Leijding C, et al. A novel model of cardiovascular-kidney-metabolic syndrome combining unilateral nephrectomy and high-salt-sugar-fat diet in mice. Lab Anim (NY). 2024;53(11):336-346. doi:10.1038/s41684-024-01457-5.
6. Zhao C, Lin M, Yang Y, Yang H, Gao Z, Yan Z, et al. Association between dietary inflammatory index and cardiovascular-kidney-metabolic syndrome risk: a cross-sectional study. Nutr J. 2025;24(1):60. doi:10.1186/s12937-025-01127-3.
7. Kojta I, Chacińska M, Błachnio-Zabielska A. Obesity, Bioactive Lipids, and Adipose Tissue Inflammation in Insulin Resistance. Nutrients. 2020;12(5). doi:10.3390/nu12051305.
8. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol. 2010;72:219-46. doi:10.1146/annurev-physiol-021909-135846.
9. Dahik VD, Kc P, Materne C, Reydellet C, Lhomme M, Cruciani-Guglielmacci C, et al. ABCG1 orchestrates adipose tissue macrophage plasticity and insulin resistance in obesity by rewiring saturated fatty acid pools. Sci Transl Med. 2024;16(777):eadi6682. doi:10.1126/scitranslmed.adi6682.
10. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. Nat Med. 2011;17(2):179-88. doi:10.1038/nm.2279.
11. Fuchs A, Samovski D, Smith GI, Cifarelli V, Farabi SS, Yoshino J, et al. Associations Among Adipose Tissue Immunology, Inflammation, Exosomes and Insulin Sensitivity in People With Obesity and Nonalcoholic Fatty Liver Disease. Gastroenterology. 2021;161(3):968-981.e12. doi:10.1053/j.gastro.2021.05.008.
12. Pellegrinelli V, Rodriguez-Cuenca S, Rouault C, Figueroa-Juarez E, Schilbert H, Virtue S, et al. Dysregulation of macrophage PEPD in obesity determines adipose tissue fibro-inflammation and insulin resistance. Nat Metab. 2022;4(4):476-494. doi:10.1038/s42255-022-00561-5.
13. Wu Y, Wu C, Shi T, Cai Q, Wang T, Xiong Y, et al. FAP expression in adipose tissue macrophages promotes obesity and metabolic inflammation. Proc Natl Acad Sci U S A. 2023;120(51):e2303075120. doi:10.1073/pnas.2303075120.
14. Palmer AK, Xu M, Zhu Y, Pirtskhalava T, Weivoda MM, Hachfeld CM, et al. Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell. 2019;18(3):e12950. doi:10.1111/acel.12950.
15. Kong P, Cui ZY, Huang XF, Zhang DD, Guo RJ, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. Signal Transduct Target Ther. 2022;7(1):131. doi:10.1038/s41392-022-00955-7.

16. Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020;16(4):206-222. doi:10.1038/s41581-019-0234-4.
17. Bäck M, Yurdagul A, Tabas I, Öörni K, Kovanen PT. Inflammation and its resolution in atherosclerosis: mediators and therapeutic opportunities. Nat Rev Cardiol. 2019;16(7):389-406. doi:10.1038/s41569-019-0169-2.
18. Ridker PM, Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease. Circ Res. 2021;128(11):1728-1746. doi:10.1161/CIRCRESAHA.121.319077.
19. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. Circ Res. 2018;122(12):1722-1740. doi:10.1161/CIRCRESAHA.118.311362.
20. Fuster JJ, MacLauchlan S, Zuriaga MA, Polackal MN, Ostriker AC, Chakraborty R, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science. 2017;355(6327):842-847. doi:10.1126/science.aag1381.
21. Gupta A, Singh K, Fatima S, Ambreen S, Zimmermann S, Younis R, et al. Neutrophil Extracellular Traps Promote NLRP3 Inflammasome Activation and Glomerular Endothelial Dysfunction in Diabetic Kidney Disease. Nutrients. 2022;14(14). doi:10.3390/nu14142965.
22. Wang Y, You YK, Guo J, Wang J, Shao B, Li H, et al. C-reactive protein promotes diabetic kidney disease via Smad3-mediated NLRP3 inflammasome activation. Mol Ther. 2025;33(1):263-278. doi:10.1016/j.ymthe.2024.11.018.
23. Wang X, Liu X, Wu W, Liao L, Zhou M, Wang X, et al. Hypoxia activates macrophage-NLRP3 inflammasome promoting atherosclerosis via PFKFB3-driven glycolysis. FASEB J. 2024;38(15):e23854. doi:10.1096/fj.202400283R.
24. Yalcinkaya M, Liu W, Thomas LA, Olszewska M, Xiao T, Abramowicz S, et al. BRCC3-Mediated NLRP3 Deubiquitylation Promotes Inflammasome Activation and Atherosclerosis in Tet2 Clonal Hematopoiesis. Circulation. 2023;148(22):1764-1777. doi:10.1161/CIRCULATIONAHA.123.065344.
25. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56. doi:10.1038/s41572-019-0106-z.
26. Libby P. The changing landscape of atherosclerosis. Nature. 2021;592(7855):524-533. doi:10.1038/s41586-021-03392-8.
27. Speer T, Dimmeler S, Schunk SJ, Fliser D, Ridker PM. Targeting innate immunity-driven inflammation in CKD and cardiovascular disease. Nat Rev Nephrol. 2022;18(12):762-778. doi:10.1038/s41581-022-00621-9.
28. Pasupuleti SK, Ramdas B, Burns SS, Palam LR, Kanumuri R, Kumar R, et al. Obesity-induced inflammation exacerbates clonal hematopoiesis. J Clin Invest. 2023;133(11). doi:10.1172/JCI163968.
29. Wu Q, Yao Q, Hu T, Yu J, Jiang K, Wan Y, et al. Dapagliflozin protects against chronic heart failure in mice by inhibiting macrophage-mediated inflammation, independent of SGLT2. Cell Rep Med. 2023;4(12):101334. doi:10.1016/j.xcrm.2023.101334.
30. Preda A, Montecucco F, Carbone F, Camici GG, Lüscher TF, Kraler S, et al. SGLT2 inhibitors: from glucose-lowering to cardiovascular benefits. Cardiovasc Res. 2024;120(5):443-460. doi:10.1093/cvr/cvae047.
31. Girardi ACC, Polidoro JZ, Castro PC, Pio-Abreu A, Noronha IL, Drager LF. Mechanisms of heart failure and chronic kidney disease protection by SGLT2 inhibitors in nondiabetic conditions. Am J Physiol Cell Physiol. 2024;327(3):C525-C544. doi:10.1152/ajpcell.00143.2024.
32. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol. 2020;17(12):761-772. doi:10.1038/s41569-020-0406-8.
33. Rayego-Mateos S, Rodrigues-Diez RR, Fernandez-Fernandez B, Mora-Fernández C, Marchant V, Donate-Correa J, et al. Targeting inflammation to treat diabetic kidney disease: the road to 2030. Kidney Int. 2023;103(2):282-296. doi:10.1016/j.kint.2022.10.030.
34. Sandsdal RM, Juhl CR, Jensen SBK, Lundgren JR, Janus C, Blond MB, et al. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. Cardiovasc Diabetol. 2023;22(1):41. doi:10.1186/s12933-023-01765-z.
35. Ussher JR, Drucker DJ. Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol. 2023;20(7):463-474. doi:10.1038/s41569-023-00849-3.
36. Mehdi SF, Pusapati S, Anwar MS, Lohana D, Kumar P, Nandula SA, et al. Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. Front Immunol. 2023;14:1148209. doi:10.3389/fimmu.2023.1148209.
37. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, et al. Cardiovascular-kidney-metabolic health: a presidential advisory from the American Heart Association. Circulation. 2023;148(20):1606-1635. doi:10.1161/CIR.0000000000001184.
38. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-1131. doi:10.1056/NEJMoa1707914.
39. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497-2505. doi:10.1056/NEJMoa1912388.
40. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in patients with chronic coronary disease. N Engl J Med. 2020;383(19):1838-1847. doi:10.1056/NEJMoa2021372.