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ADIPOSE TISSUE, TYPE 2 DIABETES, AND THE LIVER IN THE CARDIOVASCULAR-KIDNEY-METABOLIC FRAMEWORK: FROM CKM TO CRHM, CARDIAL-MS, AND MALCKS

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ABSTRACT

Cardiovascular-Kidney-Metabolic syndrome (CKM), introduced by the American Heart Association in 2023, provides an integrated staging framework for metabolic dysfunction, chronic kidney disease, and cardiovascular disease. In 2025-2026, three proposed extensions emerged: Cardiovascular-Renal-Hepatic-Metabolic syndrome (CRHM), Cardio-Renal-Diabetes-Liver-Metabolic Syndrome (CARDIAL-MS), and Metabolic associated Liver-Cardiovascular-Kidney syndrome (MALCKS). This narrative critical review uses CKM as the comparator and examines how these proposals reposition adipose tissue dysfunction, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease within a shared multiorgan network. Their main differences are conceptual: CRHM names the hepatic component explicitly, CARDIAL-MS foregrounds adiposopathy, ectopic fat, diabetes, and liver disease within a proposed staging system, and MALCKS starts from the MASLD-metabolic axis. None has yet demonstrated standardized operational definitions, incremental prognostic value, or an ability to improve treatment decisions beyond CKM. The 2026 CKM guideline now incorporates MASLD and liver fibrosis assessment, updating-but not closing-the benchmark against which these proposals should be evaluated. Their future value will depend on whether they identify measurable phenotypes that improve prediction, treatment selection, or coordinated care rather than merely expanding nomenclature.

Key words: CKM syndrome; CRHM; CARDIAL-MS; MALCKS; MASLD.

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1. Introduction

Obesity, T2D, CKD, and CVD are closely interconnected through multiple shared pathogenic mechanisms, particularly insulin resistance, adipose tissue dysfunction, metabolic inflammation, oxidative stress, and endothelial dysfunction. In 2023, the AHA proposed CKM, establishing an integrated framework in which the interactions among metabolic disorders, CKD, and CVD are approached as a continuous disease spectrum [1, 2].

Between early 2025 and early 2026, three proposed frameworks were published: CRHM, CARDIAL-MS, and MALCKS [3-6]. They share an emphasis on the liver and MASLD, T2D, adipose tissue dysfunction, and ectopic fat within a multiorgan pathogenic network. For brevity, this review uses the expression “post-CKM models” only as a chronological descriptor for these three publications; it is not a recognized taxonomic category, and the proposals have not been standardized as distinct clinical syndromes.

Building on CKM, this review examines the physiological and pathophysiological basis of CRHM, CARDIAL-MS, and MALCKS, focusing on how they reposition adipose tissue, T2D, and the liver. Its central question is whether this conceptual reorganization provides incremental value over current CKM by improving risk prediction, treatment selection, or multidisciplinary coordination, rather than simply redescribing an already recognized biological network.

This article is a narrative critical review rather than a systematic review. Targeted PubMed searches were updated through September 2026 using combinations of “cardiovascular-kidney-metabolic,” “cardiovascular-renal-hepatic-metabolic,” “CARDIAL-MS,” “metabolic associated liver-cardiovascular-kidney syndrome,” “MASLD,” “adipose tissue,” and “type 2 diabetes.” We considered peer-reviewed articles that explicitly proposed a named integrative framework related to CKM, together with major mechanistic reviews and clinical guidelines needed to compare biological plausibility and clinical utility. Reference lists of the identified framework papers were also screened. CRHM, CARDIAL-MS, and MALCKS were selected because they were the named peer-reviewed proposals meeting these criteria. This targeted approach supports conceptual synthesis but cannot exclude related formulations that use different terminology.

2. Physiological and pathophysiological basis of the cardiovascular-kidney-metabolic network

2.1 Adipose tissue: from energy storage to endocrine function

Adipose tissue is a metabolically active endocrine organ. During positive energy balance, adaptive expansion of subcutaneous adipose tissue buffers excess lipid and limits the exposure of organs not specialized for lipid storage to fatty acids and bioactive lipid intermediates [7, 8].

Through adipokines, cytokines, lipid mediators, and extracellular vesicles, adipose tissue communicates with the immune system, vascular endothelium, liver, pancreas, and heart. Adiponectin generally supports insulin sensitivity and fatty acid oxidation, whereas leptin contributes to central energy-balance signaling [7, 8].

When storage capacity and remodeling are inadequate, adipocyte hypertrophy, hypoxia, fibrosis, cellular stress, and immune-cell infiltration impair insulin action and adipokine secretion. Loss of insulin-mediated suppression of lipolysis increases circulating nonesterified fatty acids and favors ectopic lipid deposition in the liver, muscle, pancreas, myocardium, and periorgan depots [7-9].

Metabolic risk therefore depends not only on BMI or total fat mass but also on fat distribution, subcutaneous adipose expandability, and tissue dysfunction. This concept of adiposopathy provides the pathophysiological rationale for the prominence of adipose dysfunction and ectopic fat in CARDIAL-MS [5, 7].

2.2 Insulin resistance and the redistribution of energy substrate fluxes

Insulin coordinates postprandial substrate use by promoting glucose uptake and storage, suppressing endogenous glucose production, and restraining adipose lipolysis. Its tissue-specific actions make insulin resistance an interorgan disorder rather than a single uniform defect [10, 11].

In muscle, insulin resistance reduces postprandial glucose uptake; in adipose tissue, it increases fatty-acid and glycerol flux to the liver; and in the liver, it impairs suppression of glucose production. Hepatic de novo

lipogenesis may nevertheless remain active or increase, a pattern often termed selective hepatic insulin resistance [10, 11].

This coexistence of hepatic glucose production and lipogenesis cannot be reduced to a simple bifurcation of insulin signaling. Fatty-acid and glucose delivery, hyperinsulinemia, and other nutrient signals jointly disturb the coordination of hepatic substrate fluxes [11].

The resulting redistribution of energy substrates promotes ectopic fat and accumulation of lipid intermediates, including diacylglycerols and ceramides, which can further impair insulin signaling, mitochondrial function, and cellular stress responses. Insulin resistance thus links adipose tissue dysfunction to injury in the liver, pancreas, heart, and kidneys [9, 10, 12].

2.3 The endocrine pancreas and T2D: from beta-cell compensation to failure of metabolic regulation

When insulin sensitivity declines, pancreatic beta cells increase insulin secretion to preserve glucose homeostasis. This compensation may maintain near-normal glucose levels for a period despite established insulin resistance [12, 13].

T2D develops when beta-cell compensation no longer matches metabolic demand. Endoplasmic reticulum and mitochondrial stress, oxidative stress, islet inflammation, lipotoxicity, and chronic hyperglycemia contribute to progressive secretory dysfunction [13].

Once established, T2D amplifies multiorgan injury through hyperglycemia, dyslipidemia, advanced glycation, oxidative stress, and endothelial dysfunction affecting the vasculature, kidneys, liver, and myocardium [12, 13].

Separating “DIAbetes” from the metabolic component in CARDIAL-MS therefore has conceptual value. However, T2D is heterogeneous and does not invariably follow a fixed sequence from obesity to insulin resistance and beta-cell failure; it is better viewed as a major pathogenic node than an obligatory stage in linear progression [5, 12].

2.4 The liver: a central regulator of energy flux and the bidirectional role of MASLD

The liver integrates glucose and lipid flux through glycogen metabolism, gluconeogenesis, fatty-acid oxidation, triglyceride synthesis and export, ketogenesis, and lipoprotein production. Its response to nutritional and hormonal signals therefore influences multiple organs [11, 14].

In adipose dysfunction and insulin resistance, increased fatty-acid delivery, de novo lipogenesis, and imbalance among lipid synthesis, oxidation, and export promote hepatic triglyceride accumulation. Triglycerides may be relatively inert storage products, whereas diacylglycerols, ceramides, and related intermediates can disrupt insulin signaling and mitochondrial and stress-response pathways [11, 14].

MASLD, defined by hepatic steatosis plus at least one cardiometabolic risk factor, is not merely a passive consequence of obesity or T2D [15]. The liver can transmit its metabolic state through glucose and lipoprotein output and through hepatokines such as FGF21 and fetuin-A, linking hepatic dysfunction to adipose tissue, muscle, the pancreas, and the cardiovascular system [16, 17].

Progression toward steatohepatitis and fibrosis recruits Kupffer-cell activation, hepatocellular stress, and hepatic stellate-cell signaling, increasing systemic inflammatory and profibrotic influences. The liver is therefore both a target and a potential amplifier of metabolic dysfunction [14, 17].

This bidirectional role underpins CRHM and MALCKS. Its clinical relevance, however, depends on whether liver-specific characteristics-particularly fibrosis severity-add prognostic or therapeutic information beyond established CKM components [4, 6, 18].

2.5 The kidney: both a hemodynamic regulator and a metabolic organ

The kidney is both a hemodynamic regulator and a metabolic organ. Proximal tubules reabsorb filtered glucose through SGLT2 and SGLT1 and contribute to gluconeogenesis, particularly during fasting [19, 20].

Proximal tubular cells rely heavily on mitochondrial fatty-acid oxidation to meet transport-related energy demands. Reduced oxidation, increased lipid uptake, and lipid synthesis can produce energy deficiency, oxidative stress, and tubular injury that promote kidney fibrosis [21].

In T2D, increased proximal glucose-sodium reabsorption alters tubuloglomerular feedback and contributes to intraglomerular hypertension and early hyperfiltration. RAAS activation, oxidative stress, endothelial dysfunction, inflammation, and metabolic abnormalities then reinforce glomerular and tubulointerstitial injury [18, 19, 22].

With CKD progression, impaired volume regulation, RAAS and sympathetic activation, altered insulin and lipid metabolism, and uremic metabolites feed back on cardiovascular and metabolic function. This bidirectionality is central to CKM rather than a downstream complication alone [1, 2, 18].

2.6 The heart: energy metabolism, ectopic fat, and cardiovascular-kidney-metabolic feedback loops

The heart has high energy requirements and normally shifts among fatty acids, glucose, lactate, ketone bodies, and amino acids according to nutritional, hormonal, and oxygen conditions. Loss of this metabolic flexibility can contribute to myocardial dysfunction [23].

Obesity, insulin resistance, and T2D increase fatty-acid delivery, ectopic fat, lipid intermediates, oxidative stress, and microvascular dysfunction. Epicardial and pericardial adipose depots may additionally influence the myocardium through local paracrine signaling [8, 23, 24].

Heart failure adds hemodynamic and neurohumoral feedback: reduced output and venous congestion impair kidney function, whereas sympathetic and RAAS activation alter both circulation and metabolism. Declining kidney function then worsens volume overload, inflammation, and uremic toxicity [1, 2, 23].

2.7 Interorgan crosstalk: from individual disorders to a pathophysiological network

Obesity, T2D, MASLD, CKD, and CVD therefore form a network rather than a unidirectional sequence; each organ can receive and generate signals that modify the others [12].

The network is carried by substrate exchange, endocrine signals, metabolic inflammation, oxidative stress, and endothelial dysfunction. Disturbed glucose and lipid flux favors ectopic fat and mitochondrial stress, whereas insulin, glucagon, adipokines, and hepatokines transmit organ-specific changes throughout the system [8, 12, 17, 25].

The RAAS, sympathetic nervous system, and natriuretic peptides add a neurohumoral layer that simultaneously regulates hemodynamics, sodium balance, and metabolism. Disease progression reflects the strength and direction of these feedback loops as well as injury within individual organs [1, 2, 18].

From a systems-physiology perspective, adipose tissue represents energy-storage capacity; insulin resistance reflects failed coordination among insulin-sensitive tissues; beta cells provide endocrine compensation; the liver processes substrates and generates endocrine signals; the kidney links metabolism to hemodynamic control; and the heart couples energy use to circulatory feedback.

Against this shared biology, CKM, CRHM, CARDIAL-MS, and MALCKS mainly select different nodes for conceptual organization. CKM prioritizes cardiovascular-kidney-metabolic interactions; CRHM explicitly names the liver; CARDIAL-MS foregrounds adipose dysfunction, ectopic fat, T2D, and proposed progression; and MALCKS starts from the MASLD-metabolic axis. The clinically relevant question is whether any emphasis improves classification, prediction, or intervention [1, 3-6].

A RECIPROCAL MULTIORGAN NETWORK

Energy flux • endocrine signaling • hemodynamic feedback

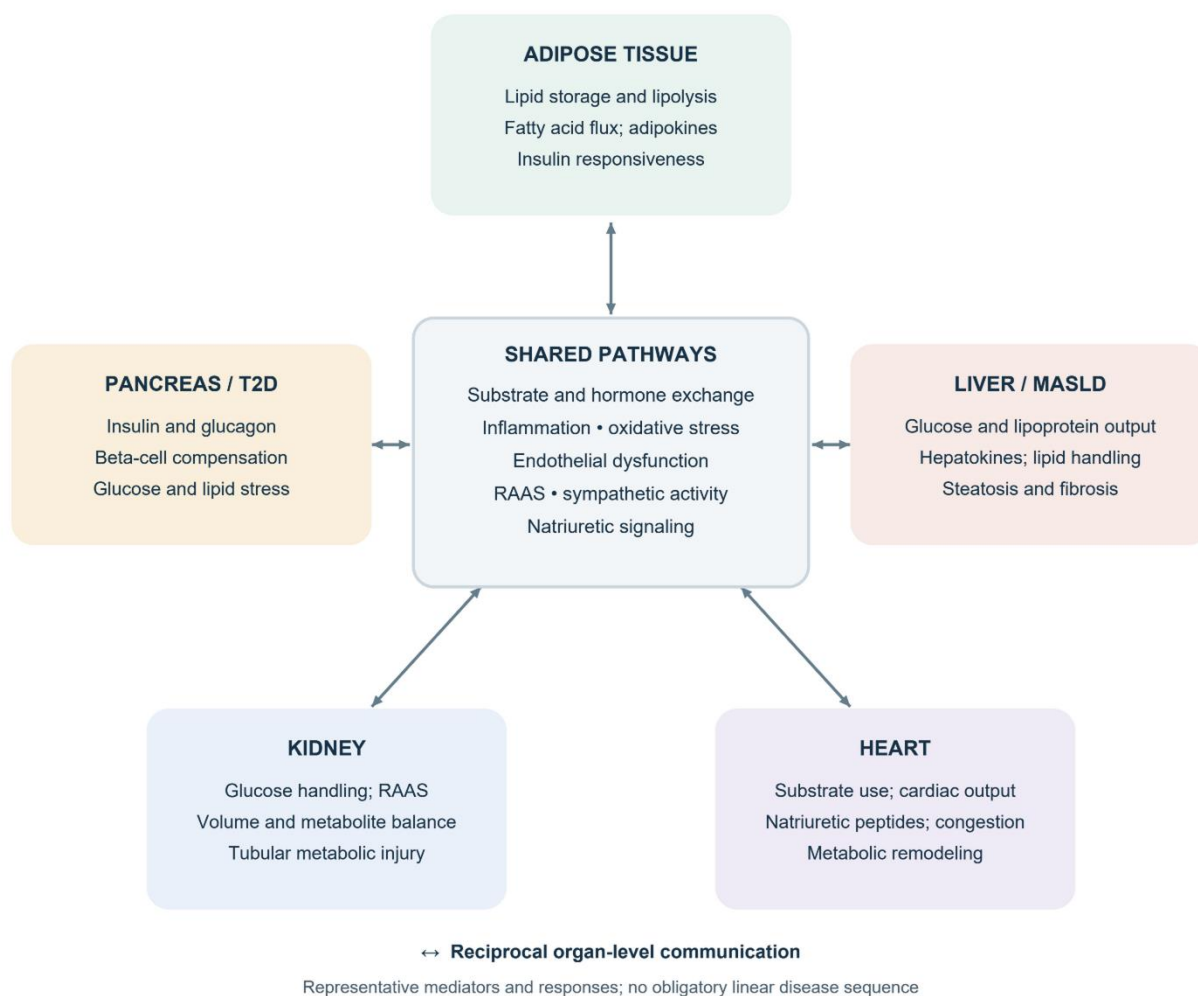


Figure 1. Interorgan physiological and pathophysiological network in CKM and post-CKM models. Adipose tissue, the liver, pancreas, kidneys, and heart exchange energy substrates and endocrine signals within a shared inflammatory, endothelial, and neurohumoral environment. Paired arrows indicate reciprocal organ-level interactions; their labels identify representative pathways and mediators, rather than implying that each mediator acts identically in both directions. Feedback through kidney and cardiac dysfunction can amplify metabolic injury. The network does not imply an obligatory sequence of disease progression or equal causal strength for all pathways. Original conceptual illustration synthesized from references [1, 2, 7-25].

3. Three post-CKM models: CRHM, CARDIAL-MS, and MALCKS

3.1 CRHM: making the hepatic component explicit within a multiorgan framework

CRHM appeared in an article by Theodorakis and Nikolaou published in January 2025 on integrated cardiovascular-renal-hepatic-metabolic management [3]. The authors subsequently presented it explicitly as an expanded framework in a February 2025 Biomolecules article [4]. February 2025 therefore marks the publication outlining the expanded framework, but should not be regarded as the first appearance of the term CRHM in the literature.

The organizing logic of CRHM is relatively straightforward: it makes the liver, primarily through MASLD, an explicit organ component alongside the heart and kidneys. The authors emphasize overlapping insulin resistance, metabolic inflammation, oxidative stress, dyslipidemia, and endothelial dysfunction across MASLD,

CVD, CKD, and metabolic disorders [3, 4]. Its intuitive structure and ease of communication in multidisciplinary care are key strengths of CRHM.

However, the limitations of CRHM also arise from this simplicity. Adipose tissue and T2D remain largely subsumed under the metabolic component; a dedicated staging system and operational criteria have not been standardized; and much of its proposed value rests on biological plausibility or integrated management strategies rather than evidence of superior predictive performance [3, 4]. CRHM should therefore be described as an organ-based expansion of the framework rather than an established clinical syndrome.

3.2 CARDIAL-MS: restructuring around a proposed pathogenic progression

Godoy-Matos and colleagues introduced CARDIAL-MS in 2025 as an expanded, unified pathophysiological model [5]. Unlike CRHM, CARDIAL-MS not only incorporates the liver but also names diabetes as a distinct component, while assigning prominent roles to adiposopathy, ectopic fat, and disrupted adipokine/hepatokine signaling.

The authors propose four stages of progression: (1) weight gain and adipose tissue dysfunction; (2) metabolic risk factors and risk markers; (3) cardiometabolic disease and CKD; and (4) advanced cardiovascular-renal-hepatic-metabolic disease [5]. This can be viewed as an attempt to restructure CKM along a pathophysiological axis, emphasizing adipose tissue health and ectopic fat as early intervention targets.

Nevertheless, the substantive differences from CKM require careful evaluation. CKM already places excess or dysfunctional adipose tissue at stage 1 and T2D at stage 2; the 2026 guideline further incorporates MASLD, liver fibrosis, and related treatment [1, 18]. The novelty of CARDIAL-MS therefore lies largely in its organization of priorities and interpretation of progression, rather than in the introduction of mechanisms entirely absent from CKM. Its four-stage system also remains a conceptual proposal, without evidence that it improves risk stratification or outcomes compared with CKM staging.

3.3 MALCKS: starting from the MASLD-metabolic axis

Bian and colleagues published MALCKS online in 2026 from an endocrine and metabolic perspective [6]. The authors regard MASLD as a hepatic manifestation of metabolic dysfunction and emphasize its associations with CVD, CKD, and endocrine and metabolic disorders. MALCKS can therefore be understood as a framework that uses the MASLD-metabolic axis as its conceptual starting point for linking cardiac and kidney injury.

Compared with CRHM and CARDIAL-MS, MALCKS reverses the organizing emphasis: rather than starting with a cardiovascular-kidney-metabolic framework and adding the liver, it starts with metabolic liver disease and extends to the cardiovascular and kidney systems. This approach aligns with endocrine and hepatology practice, where MASLD frequently coexists with obesity, insulin resistance, and T2D. However, a liver-centered approach should be understood as a conceptual emphasis, not as evidence that the liver is the dominant biological cause in every disease phenotype.

Notably, the MALCKS authors themselves acknowledge that formal acceptance as a clinical syndrome requires clear operational definitions, validation in adequately powered cohort studies, demonstration of distinct clinical value, and multidisciplinary consensus [6]. This distinction separates a biologically plausible model from a classification system that is ready for clinical practice.

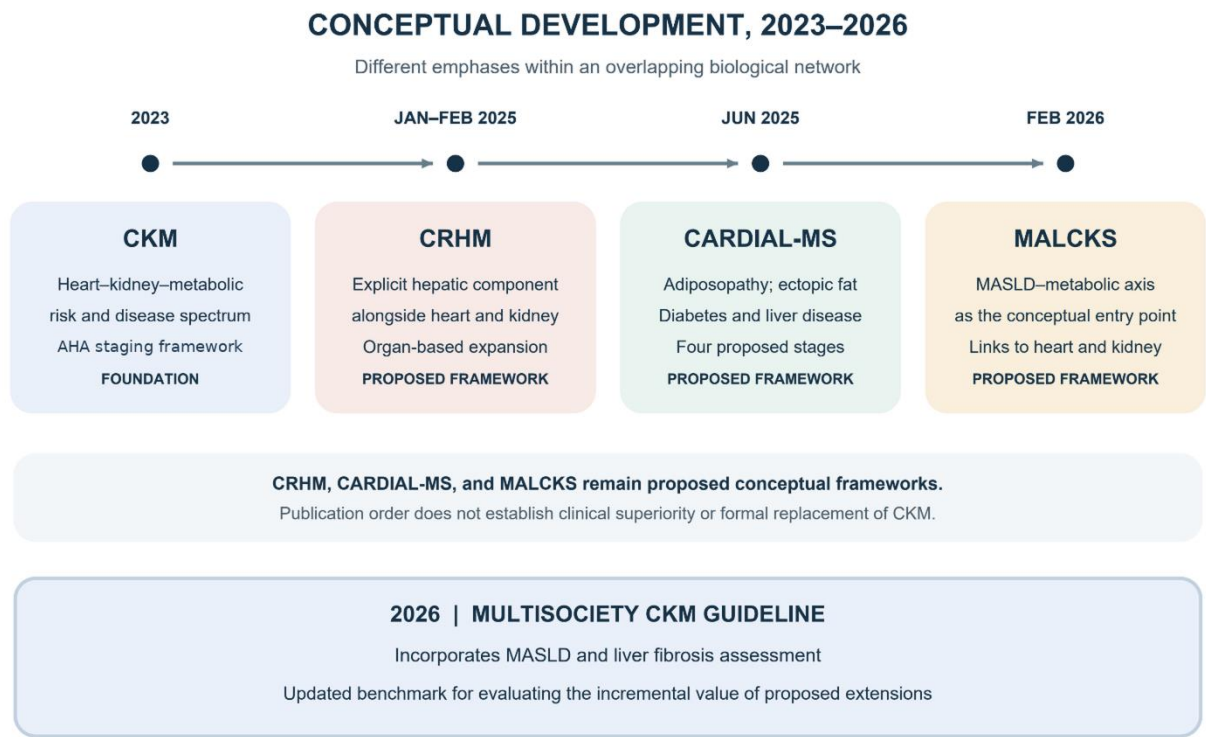


Figure 2. Conceptual development from CKM to CRHM, CARDIAL-MS, and MALCKS, 2023-2026. The timeline locates the initial CKM framework, the emergence of the three proposed extensions, and the subsequent multisociety CKM guideline. Each model emphasizes different components of an overlapping biological network. Arrows denote publication chronology and changing conceptual emphasis, not formal replacement, endorsement, or a validated hierarchy of syndromes. The 2026 CKM guideline, which incorporates MASLD and liver fibrosis assessment, provides an updated comparator for the proposed extensions. Original conceptual illustration synthesized from references [1, 3-6, 18].

Table 1. Comparison of CKM and the three post-CKM models

Feature	CKM	CRHM	CARDIAL-MS	MALCKS
Timing	2023; multisociety guideline in 2026	January-February 2025	June 2025	February 2026
Current status	AHA-proposed staging framework with multisociety clinical guidance	Proposed expanded framework	Proposed pathophysiological and staging framework	Proposed expansion from an endocrine perspective; not formally established as a clinical syndrome
Organizing logic	Cardiovascular-kidney-metabolic risk and disease spectrum	Makes the liver an explicit organ component	Emphasizes progression from adipose tissue dysfunction to metabolic risk and multiorgan disease	Starts from the MASLD-metabolic axis to connect heart and kidney disease
Adipose tissue	Excess dysfunctional adipose tissue at stage 1	or Primarily within the metabolic component	Adiposopathy and ectopic fat are central upstream features	Linked through metabolic dysfunction and MASLD

Feature	CKM	CRHM	CARDIAL-MS	MALCKS
T2D	Explicit component of stage 2	Within the metabolic component	Named separately	Endocrine-metabolic link
Liver/MASLD	Recognized; explicitly integrated in the 2026 guideline	Explicit hepatic component alongside the other organs	Key component of the multiorgan model	Conceptual starting point
Question requiring evidence	How can implementation and personalization be optimized?	Does the liver add independent value beyond CKM?	Does the new staging system improve prediction or treatment?	Does a MASLD-centered model add clinical value?

4. Comparison and synthesis: where do the models truly differ?

CRHM, CARDIAL-MS, and MALCKS overlap extensively in their biological foundations. All three recognize the same network of adipose tissue dysfunction, insulin resistance, ectopic fat, T2D, MASLD, CKD, and CVD. The principal linking mechanisms include metabolic inflammation, oxidative stress, endothelial dysfunction, dyslipidemia, and interorgan endocrine signaling [3-7, 10, 12, 14, 17]. Their greatest differences therefore concern conceptual emphasis and component prioritization, rather than three entirely distinct pathophysiologies.

CRHM can be viewed as an organ-based expansion that makes the liver an explicit component alongside the heart and kidneys. CARDIAL-MS expands the framework around a proposed pathogenic progression, organizing adipose tissue, ectopic fat, diabetes, and the liver into four stages. MALCKS expands from a hepatic-metabolic starting point, using MASLD as an entry point for linking metabolic dysfunction to cardiac and kidney injury. These differences may aid conceptualization and communication across specialties, but do not establish that the three terms represent distinct disease entities.

From a systems physiology perspective, a network of bidirectional interactions is more appropriate than a linear sequence. Adipose tissue dysfunction may increase fatty acid flux and promote ectopic fat deposition; the liver may develop MASLD and alter glucose, lipoprotein, and hepatokine production; insulin resistance and beta-cell dysfunction promote T2D; and CKD and CVD may feed back on metabolism through hemodynamic changes, the RAAS, sympathetic activation, inflammation, and oxidative stress [2, 10, 12, 17]. The relative prominence of each node differs among individuals, so a single causal sequence should not be assumed.

Within this approach, adipose tissue, T2D, and the liver are not three independent additions to CKM but pathogenic nodes operating at different levels within the same multiorgan network. Adipose tissue often represents an upstream source of disordered energy storage and distribution; T2D reflects failure of glucose regulation while amplifying injury; and the liver/MASLD is both a target of metabolic dysfunction and a systemic regulator. The heart and kidneys are both target organs and participants in feedback loops. This perspective explains how different groups can develop different nomenclatures from an overlapping biological foundation.

The key criterion is therefore not which model encompasses more organs, but which generates measurable incremental information. A new framework has practical value only if it identifies risk earlier, improves predictive performance, identifies groups likely to benefit from intervention, or simplifies multidisciplinary coordination without creating redundancy and terminological complexity.

Table 2. Mechanistic and clinical emphasis of the models

Component / mechanism	CKM	CRHM	CARDIAL-MS	MALCKS
Dominant organizing node	Integrated cardiovascular-kidney-metabolic risk	Explicit heart-kidney-liver network	Adiposopathy and ectopic fat as early drivers	MASLD-metabolic axis as the entry point
Primary interorgan emphasis	Hemodynamic, metabolic, and vascular feedback	Hepatic signaling within a multiorgan system	Adipokine-hepatokine signaling and progressive multiorgan injury	Liver-to-heart and liver-to-kidney links
Model progression	of AHA stages 0-4 with multisociety guidance	No standardized staging system	Four proposed stages	No standardized staging system
Potentially discriminating measurements	CKM stage, PREVENT risk, eGFR/UACR, metabolic markers	Liver steatosis and fibrosis measures added to CKM assessment	Adipose distribution, ectopic fat, diabetes, and liver phenotypes	Steatosis and fibrosis measures added to metabolic and cardiorenal risk
Current therapeutic implication	Stage-directed management supported by multisociety guidance	Integrated management proposed; no framework-specific algorithm	Earlier targeting of adiposity and ectopic fat proposed; no validated algorithm	MASLD assessment and multidisciplinary care proposed; no validated algorithm
Main validation gap	Implementation and personalization	Independent value of liver-specific information	Incremental prediction and treatment value of the proposed stages	Incremental value of a MASLD-centered classification
Risk of conceptual overlap	Reference framework	May relabel liver features already captured within CKM	May repackage CKM stages and existing risk factors	May double-count MASLD cardiometabolic criteria

5. Unresolved issues and research directions

The successive emergence of CRHM, CARDIAL-MS, and MALCKS reflects a real need to integrate the liver and MASLD more explicitly into the understanding of multiorgan metabolic disease. At the same time, it creates a risk of fragmented nomenclature, with multiple new terms describing the same biological foundation without demonstrating added value. Adding an organ to an acronym does not, by itself, establish a new syndrome.

At least four levels of evidence are needed for a post-CKM model to progress beyond a conceptual proposal. First, operational definitions and staging criteria must be applicable consistently across populations, specialties, and clinical settings. Second, the model must demonstrate incremental prognostic value over CKM staging, the Predicting Risk of CVD EVENTS (PREVENT) equations, estimated glomerular filtration rate (eGFR)/urine albumin-to-creatinine ratio (UACR), and current MASLD assessment tools. Evaluation should extend beyond statistical associations to discrimination, calibration, and clinical decision value. Third, classification under the new model must lead to meaningful changes in testing, monitoring intensity, or treatment selection. Fourth, evidence must show that implementation improves patient outcomes, care efficiency, or multidisciplinary coordination [6, 18].

Overlapping definitions present another challenge. T2D, obesity, hypertriglyceridemia, and hypertension are both CKM components and cardiometabolic risk factors used to define MASLD [14, 15, 18]. When MASLD is reintroduced as an independent component of the same system, the risk of double-counting the same underlying factors must be examined statistically and conceptually. New models must therefore demonstrate

that liver-specific information, such as the extent of hepatic steatosis, fibrosis, or hepatokine signals, contributes information independent of established metabolic factors.

Post-CKM models should also be compared with more than the 2023 version of CKM. CRHM, CARDIAL-MS, and MALCKS were developed before the 2026 CKM guideline and cannot be expected to have incorporated later guidance. From the current perspective, however, the guideline includes MASLD in CKM assessment, with first-line fibrosis risk assessment using the Fibrosis-4 index (FIB-4) and secondary assessment using vibration-controlled transient elastography (VCTE) or the Enhanced Liver Fibrosis (ELF) test when appropriate [18]. This integration partly narrows the gap the newer proposals sought to address and raises the threshold for demonstrating incremental value; it does not, by itself, establish that the proposals are redundant.

Therapeutic convergence further illustrates why nomenclature alone is insufficient. SGLT2 inhibitors, GLP-1 receptor agonists, and dual GIP/GLP-1 receptor agonists can target overlapping metabolic and cardiorenal pathways, while incretin-based therapies may also improve hepatic disease activity in selected patients [3, 14, 18]. Resmetirom is a liver-directed option for selected patients with noncirrhotic MASH and clinically significant fibrosis, but it should not be described as having established broad cardiovascular or kidney protection [14, 18]. These evidence bases are not interchangeable: improvement in hepatic surrogate or histological outcomes does not automatically imply fewer cardiovascular or kidney events. A new framework would add clinical value only if it improves treatment selection, sequencing, or monitoring beyond current organ-specific indications and CKM guidance.

Mechanistic research should prioritize quantifying adipose tissue function and ectopic fat; identifying biologically meaningful adipokine-hepatokine signatures; characterizing MASLD-CKD-CVD interactions over time; and determining whether hepatic or adipose markers improve prediction beyond CKM. Longitudinal studies and deep phenotyping will be particularly important for distinguishing causation, mediation, and co-occurrence, while avoiding causal inference from cross-sectional data.

For Vietnam, we propose a staged research agenda rather than immediate adoption of a new nomenclature. The first step is to characterize CKM burden using the current staging system and describe the co-occurrence of MASLD, T2D, and CKD. Subsequent studies should test whether FIB-4, liver stiffness, adipose distribution, or metabolic markers add prognostic information beyond CKM in Vietnamese populations. This proposal remains to be supported by prospective local validation.

6. Conclusions

The 2023 CKM framework provides the foundation for integrating cardiovascular, kidney, and metabolic disease. CRHM, CARDIAL-MS, and MALCKS subsequently emphasized different nodes within the same network: an explicit hepatic component, adiposopathy/ectopic fat and diabetes within a proposed staging system, or the MASLD-metabolic axis as an entry point. These are conceptual reorganizations, not yet validated clinical syndromes.

Pathophysiologically, the models converge on bidirectional interactions among adipose tissue, liver, pancreas, heart, and kidneys. Their scientific value should therefore be judged by whether the selected nodes can be measured and used to improve prediction or intervention, rather than by the breadth of their nomenclature.

At present, CRHM, CARDIAL-MS, and MALCKS have not demonstrated incremental clinical value over CKM as updated in 2026. Progress will require standardized definitions, external validation, improved discrimination and decision value, and evidence that classification changes treatment or patient outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-Assisted Technologies

Artificial intelligence (AI) tools were used to assist in the creation and design of figures and illustrations for this manuscript. All figures were reviewed and approved by the authors.

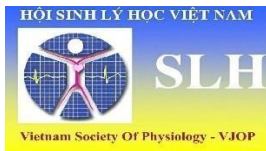
Author Contributions

Trong Nhan Le: Conceptualization, study design, literature collection and synthesis, data analysis, and manuscript drafting. Linh Ly Luong: Scientific supervision, contributions to study design, manuscript review, and editing. Duc Anh Tran Vu and Van Quy Nguyen: Assistance with literature collection and data synthesis, and contributions to manuscript revision. All authors read and approved the final manuscript.

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MÔ MỠ, ĐÁI THÁO ĐƯỜNG TYPE 2 VÀ GAN TRONG KHUNG BỆNH LÝ TIM MẠCH - THẬN - CHUYỂN HOÁ: TỪ CKM ĐẾN CRHM, CARDIAL-MS VÀ MALCKS

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TÓM TẮT

Hội chứng tim mạch-thận-chuyển hóa (CKM) do Hiệp hội Tim mạch Hoa Kỳ (AHA) đề xuất năm 2023 đã thiết lập khung tích hợp mô tả tương tác giữa rối loạn chuyển hóa, bệnh thận mạn (CKD) và bệnh tim mạch (CVD). Từ đầu năm 2025 đến đầu năm 2026, ba khung khái niệm mở rộng lần lượt xuất hiện: hội chứng tim mạch-thận-gan-chuyển hóa (CRHM), hội chứng tim-thận-đái tháo đường-gan-chuyển hóa (CARDIAL-MS) và hội chứng gan-tim mạch-thận liên quan chuyển hóa (MALCKS). Cả ba cùng phản ánh nhu cầu làm rõ vai trò của gan, rối loạn chức năng mô mỡ, mỡ lạc chỗ và đái tháo đường type 2 (T2D) trong bệnh lý đa cơ quan liên quan chuyển hóa. Lấy CKM làm nền tảng, bài tổng quan phân tích cơ sở sinh lý và sinh lý bệnh của ba mô hình hậu-CKM, tập trung vào rối loạn chức năng mô mỡ, đề kháng insulin, T2D, bệnh gan nhiễm mỡ liên quan rối loạn chuyển hóa (MASLD) và tương tác gan-tim-thận. CRHM chủ yếu làm rõ thành phần gan; CARDIAL-MS nhấn mạnh mô mỡ, mỡ lạc chỗ, đái tháo đường và MASLD trong một hệ thống phân giai đoạn; còn MALCKS lấy trục MASLD-chuyển hóa làm điểm khởi đầu để liên kết tổn thương tim và thận. Tuy nhiên, khác với CKM vốn đã có hệ thống phân giai đoạn và hướng dẫn liên hiệp hội, cả ba vẫn là khung đề xuất, chưa được kiểm chứng đầy đủ về định nghĩa vận hành, giá trị tiên lượng gia tăng hay khả năng thay đổi điều trị. Đặc biệt, hướng dẫn CKM năm 2026 đã tích hợp đánh giá MASLD và xơ hóa gan, làm thay đổi mốc so sánh cho các mô hình hậu-CKM. Do đó, giá trị của các thuật ngữ này phụ thuộc vào khả năng nhận diện kiểu hình sinh học có thể đo lường, dự đoán và can thiệp hiệu quả hơn CKM hiện hành, chứ không phải số cơ quan trong tên gọi.

Từ khóa: Hội chứng tim mạch-thận-chuyển hóa; CRHM; CARDIAL-MS; MALCKS; MASLD.