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REVIEW

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CARDIAL-MS (CArdio-Renal-DIAbetes-Liver-Metabolic Syndrome): a new proposition for an integrated multisystem metabolic disease

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Abstract

Background Metabolic Syndrome—a constellation of insulin resistance, cardiovascular risk factors as hyperglycemia, hypertension, and dyslipidemia, and systemic metabolic dysfunction—may be driven by dysregulation of adipose tissue, which manifests as adiposopathy (pathogenic adipose tissue expansion or maldistribution), ectopic fat deposition (in the liver, muscle, pancreas, and cardiorenal systems), and altered secretion of adipokines/hepatokines. Weight gain, obesity, and/or unfavorable fat distribution create a scenario wherein the type, size, location, secretions, or even scarcity of adipocytes drive pathophysiological mechanisms leading to hepatic steatosis and steatohepatitis, type 2 diabetes, and heart and kidney disease. While recent frameworks, such as cardiovascular-kidney-metabolic syndrome, emphasize holistic staging, the central role of metabolic dysfunction-associated steatotic liver disease (MASLD) in multisystem morbidity remains underrecognized.

Main text This narrative review synthesizes evidence linking MASLD and diabetes to cardiovascular and kidney diseases through shared pathways of adiposopathy, ectopic lipid accumulation, and dysregulated adipokine/hepatokine signaling. We propose CARDIAL-MS (CArdio-Renal-DIAbetes-Liver-Metabolic Syndrome), an expanded pathophysiological model that unifies these interactions into four progressive stages: (1) weight gain and dysfunctional adipose tissue; (2) metabolic risk factors and markers of risk; (3) cardiometabolic diseases and chronic kidney disease; and (4) advanced cardio-renal-liver-metabolic disease. By integrating MASLD as a pivotal component, CARDIAL-MS reframes metabolic syndrome as a continuum of interconnected organ injuries rather than isolated risk factors.

Conclusion CARDIAL-MS provides a staging model to identify patients at critical transition points—from reversible metabolic disturbances to irreversible organ damage. This model emphasizes early interventions targeting adipose tissue health and ectopic fat deposition to mitigate the progression of metabolic cardiorenal diseases. By recognizing

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the syndromic nature of these conditions, CARDIAL-MS offers clinicians an actionable paradigm for risk stratification, timely diagnosis, and personalized prevention strategies.

Keywords Obesity, Adiposopathy, Ectopic fat, Metabolic dysfunction-associated steatotic liver disease, Type 2 diabetes, Cardiovascular disease, Chronic kidney disease

Introduction

It is well established that cardiometabolic and renal diseases (CMRDs) have a complex pathophysiology involving multiple cardiometabolic risk factors (CMRFs) and interconnected systems. Recognizing the interrelationship between several conditions such as obesity, type 2 diabetes (T2D), and metabolic syndrome (MS), and the subsequent risk of cardiovascular (CV) and renal outcomes, the American Heart Association (AHA) introduced the concept of Cardiovascular-Kidney-Metabolic (CKM) syndrome in a 2023 scientific statement [1]. Although the AHA has considered the liver involvement in CKM syndrome, noting that metabolic dysfunction-associated steatotic liver disease (MASLD) "further amplifies systemic inflammation and insulin resistance (IR)," [1] we speculate that this major metabolic organ is a determinant for the development of T2D and CMRDs [2, 3]. Thus, aiming to expand the pathophysiological bases that lead to increased CV and renal risk, we propose a new concept: the CArdio-Renal-DIAbetes-Liver-Metabolic Syndrome (CARDIAL-MS).

The CARDIAL-MS considers that (i) adiposopathy (excess adipose tissue or unfavorable fat distribution), (ii) ectopic fat deposition (in liver, muscle, pancreas, pericardial/epicardial adipose tissues, and perirenal adipose tissues), and (iii) adipo/hepatokines are pivotal elements for the increased morbidity and mortality related to CMRDs. This narrative review proposes the CARDIAL-MS, an expanded and unifying pathophysiological model that delineates the interplay of key mechanisms driving CMRDs—the world's primary cause of death.

Adiposopathy: the trigger for the development of the CARDIAL-MS

Obesity (body mass index [BMI] ≥ 30 kg/m²) and its related conditions are established as a public health epidemic. Between 1980 and 2014, the prevalence of obesity doubled in 73 countries, reaching approximately 603.7 million adults [4]. In 2021, 1.00 billion (95% uncertainty interval [UI] 0.989–1.01) men and 1.11 billion (1.10–1.12) women were classified as overweight (BMI of 25–29.9 kg/m²) or obese [5]. Following current trends, overweight and obesity combined (i.e., BMI ≥ 25 kg/m²) are projected to affect nearly 3 billion adults (about 50% of the world's adult population) by 2030 [6].

Kim et al. [7] published the first umbrella review and meta-analysis that included observational and Mendelian randomization (MR) studies evaluating the association between adiposity and CV diseases (CVD). Utilizing data from 501 cohorts, 12 systematic reviews, 53 meta-analyses, and 12 MR studies, involving 30 million individuals, the authors confirmed an association and a causal relationship between high adiposity and CV outcomes [7]. BMI was directly related to coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), all-cause stroke, hemorrhagic stroke, ischemic stroke, hypertension, aortic valve stenosis, pulmonary embolism, and venous thromboembolism. All these outcomes, except stroke, were causally related to adiposity, as MR studies showed. A dose-response relationship has been demonstrated between BMI and CV outcomes, and the evaluation of central adiposity, assessed by waist circumference (WC) and waist-to-hip ratio (WHR), corroborated these findings [7].

Nonetheless, not all metabolic conditions typically associated with excess adiposity are present in individuals with obesity, and those with BMI-based normal weight are not exempt from adiposity-related complications and disorders [8, 9]. The distribution of body fat and ectopic fat accumulation may provide insights into this paradox [9]. The two primary fat storage sites in humans are subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). However, VAT is not an appropriate site for fat storage, as it is pathophysiological linked to IR and MS [9, 10]. In recent years, strong evidence has been accumulated defining VAT, measured by magnetic resonance imaging (MRI) or computed tomography, as an independent risk factor for T2D and cardiometabolic morbidity and mortality [11].

SAT is the most appropriate local for fat storage due to its expandability and plasticity [12], and the gluteofemoral adipose tissue (G-FAT) is generally considered to be metabolically protective [8, 9, 13, 14]. Indeed, Agrawal et al. [14] have recently confirmed, through a deep learning model that analyzed body MRI data from 40,032 individuals in the UK Biobank, that: (i) VAT is associated with an increased risk of T2D and CAD; (ii) G-FAT is linked to a reduced risk; and (iii) abdominal SAT (Ab-SAT) is mainly neutral, all adjusted for BMI [14]. Therefore, a scarcity of G-FAT leads to diminished storage capacity, which has been etiologically and genetically associated with IR and CMRDs [9, 15, 16]. Although VAT is metabolically important, among the SAT compartments, G-FAT is of utmost significance for metabolic health [2, 8, 9, 13].

Lotta et al. [15] evidenced that specific risk *loci* (e.g., *loci* near or within *L3MBTL3*, *DNAH10*, and *CCDC92*) influence adipose gene expression, resulting in impaired adipogenesis, reduced peripheral fat depots, and, ultimately, increased risk of CMRDs. In parallel with the genetic predisposition for unfavorable distribution of body fat, increased availability, accessibility, and affordability of energy-dense foods and reduced opportunities for physical activity that have followed urbanization and other changes in the built environment have been considered as potential environmental drivers to weight gain [4]. When the expansion capacity of the SAT is reached, there is a compromise in fat storage in this location, which favors visceral and ectopic deposition in tissues unsuitable for accumulating fat, such as the liver, muscle, pancreas, heart, and kidneys [9]. Thus, VAT itself may be regarded as an ectopic fat depot. Similarly, dysfunctional insulin-resistant adipose tissue may favor ectopic fat deposition by releasing free fatty acids (FFA) [17–20]. Thus, SAT plays a significant role in the availability of circulating FFA, which are ultimately directed to ectopic sites [17]. This process is outlined in Fig. 1 [2, 8–10, 12, 13, 17–20].

Schleh et al. [20] conducted an elegant and comprehensive study demonstrating, through clamp technique, abdominal MRI, and biopsies of Ab-SAT and muscle, that the suppression of insulin-mediated fatty acid ratio of appearance was associated with insulin-mediated glucose uptake ($r = 0.51$; $p < 0.01$) and was negatively correlated with liver fat (r = -0.36; $p < 0.01$) and VAT (r = -0.42; $p < 0.01$) [20].

Once ectopic fat deposition occurs, disruption of metabolic homeostasis is triggered, which includes dysregulated adipokine/hepatokine signaling, inflammation,

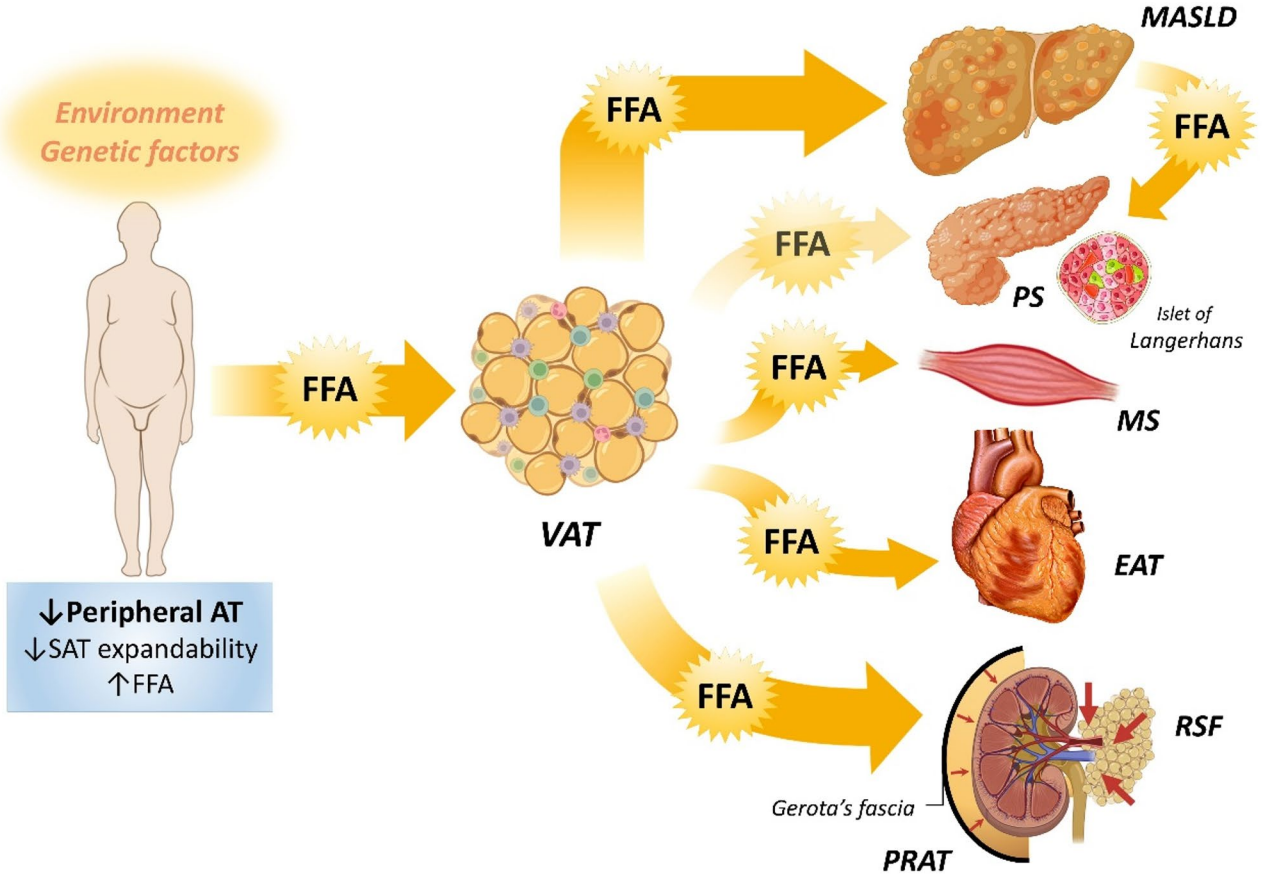

Fig. 1 Weight gain, fat distribution, and dysfunctional insulin-resistant AT. Free fatty acids (FFA) are stored as triglycerides in adipose tissue, and these triglycerides can be broken down to release FFA into the blood. When the expansion capacity of subcutaneous adipose tissue is exceeded, FFA are increasingly mobilized, leading to visceral and ectopic fat deposition. Gluteofemoral adipose tissue plays a protective metabolic role by sequestering excess FFAs and triglycerides. Visceral adipose tissue (VAT), due to its ectopic nature and proximity to vital organs, further contributes to systemic metabolic dysfunction. Concurrently, insulin resistance and impaired lipid storage in adipose tissue exacerbate lipolysis, amplifying FFA release into circulation. VAT, owing to its heightened insulin resistance and metabolic dysfunction, serves as a major source of FFA for the liver and systemic distribution. Excess FFA can overwhelm organs such as the pancreas, skeletal muscle, heart, and kidneys, promoting ectopic lipid accumulation and associated pathologies. For details, refer to the main text. AT: adipose tissue; EAT: epicardial adipose tissue; FFA: free fatty acids; MASLD: metabolic dysfunction-associated steatotic liver disease; MS, muscular steatosis; PRAT: perirenal adipose tissue; PS: pancreatic steatosis; RSF: renal sinus fat; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue. This image features content from BioRender

increased IR and impaired insulin secretion, endothelial dysfunction, tissue injury, and fibrosis, i.e., pathological processes that will lead to T2D, MASLD, and cardiorenal diseases [2, 8–10, 12, 13, 17–20].

Ectopic fat depots: disrupting metabolic homeostasis in the CARDIAL-MS

Steatotic liver disease

Liver fat or steatotic liver disease (SLD) is the most common hepatic disease, affecting more than 30% of people worldwide [21]. Due to its frequent association with IR, obesity, and T2D, the acronym "MASLD" was proposed as the most appropriate nomenclature, as well as "MASH" (metabolic dysfunction-associated steatohepatitis), when steatohepatitis is histologically characterized [22]. The SLD associated with at least one of the five CMRFs defines MASLD and is considered the manifestation of MS in the liver. These CMRFs are: (i) BMI ≥ 25 kg/m² or WC > 90 cm (men)/>80 cm (women) or ethnicity adjusted equivalent; (ii) prediabetes or T2D; (iii) blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment; (iv) plasma triglycerides ≥ 150 mg/dl or lipid lowering treatment; (v) plasma high-density lipoprotein (HDL)-cholesterol ≤ 40 mg/dl (men) and ≤ 50 mg/dl (women) or lipid lowering treatment [22]. In consonance with several scientific societies, the Brazilian Diabetes Society [23] and other Brazilian societies [24] also adopted the terms SLD, MASLD, and MASH.

Given MASLD's metabolic pathophysiology, its association with T2D, several CMRFs, and CMRDs is unsurprising [2, 25, 26]. Furthermore, there is growing evidence of a potential causal relationship between MASLD and CVD. A meta-analysis of 36 prospective cohort studies, involving more than 5.8 million middle-aged individuals, revealed that MASLD was associated with an increased risk of both fatal and non-fatal CV outcomes (pooled random effects hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.31–1.61) over a median follow-up of 6.5 years [27]. Interestingly, this finding was independent of age, sex, measures of adiposity, T2D, and other common CMRFs. Additionally, the risk of CVD increased with more advanced liver disease, particularly at higher fibrosis stages (pooled random effects HR 2.50, 95% CI 1.68–3.72) [27].

Regarding mortality, MASLD is associated with both liver-specific and non-specific deaths. However, CV mortality frequently contributes to severe outcomes. According to data from 13,099 patients with MASLD, matched with up to 10 controls from the general population, MASLD was linked to higher all-cause mortality (HR 1.85, 95% CI 1.74–1.96) [28]. The highest estimated 15-year cumulative incidence of death was attributed to cancer (non-hepatocellular carcinoma) and CV disease (7.3% and 7.2%, respectively) [28].

A burning question in the complex relationship between MASLD and CVD is whether there is a causal relationship or just an epidemiological and pathophysiological association. Considering that MR studies use genetic variants as instrumental variables to estimate causal effects, these studies may help to infer causality between MASLD and CVD [29, 30]. Miao et al. [29] identified 94 independent ($R^2 < 0.2$) MASLD genome-wide association study (GWAS) loci, of which 90 have not been identified before. Using a polygenic risk scoring model, the authors found a significant causal effect of MASLD on CAD [29]. Ren et al. [30] performed a two-sample MR analysis, and after exclusion of genetic variants implicated in impaired very low-density lipoprotein (VLDL) secretion, concluded for a robust association between genetically predicted elevated serum alanine aminotransferase (ALT), imaging-based, and biopsy-confirmed MASLD and CAD.

Finally, previous studies of the common genetic variants associated with MASLD strongly suggest that plasma lipids are responsible for their differential effects on CVD risk [31]. The associations of single-nucleotide polymorphisms (SNPs) that affect fatty acid flux and *de novo* lipogenesis with lipid-increasing effect (e.g., GCKR) may contribute to higher CAD risk. In contrast, those carriers of genetic variants predisposing to MASLD through impaired VLDL secretion (i.e., MTTP, PNPLA3, and TM6SF2) simultaneously reduce plasma lipids, resulting in a more cardioprotective phenotype [31]. Accordingly, Ahmed et al. [32], recognizing the complexity of MASLD pathophysiology and the limitations of some previous MR studies, conducted a genome-wide survey based on the UK Biobank MRI study. They identified 13 genetic variants associated with increased liver fat content, most of which had been previously described. Genetic variants linked to enhanced *de novo* lipogenesis revealed that liver fat-increasing alleles were associated with a higher risk of myocardial infarction and CAD (i.e., TRIB1, GCKR, ADH1B, and CDHR4). In contrast, variants associated with impaired hepatic triglyceride export indicated a reduced risk of CAD and myocardial infarction but an elevated risk of T2D (i.e., PNPLA3, TMS6SF2, APOE, and SUGP1) [32].

These findings suggest that MASLD is not only epidemiologically associated with CVD but also causally linked to it, despite genetic heterogeneity. Nonetheless, genetically increased liver fat content raises the risk of T2D, cirrhosis, hepatocellular carcinoma, and intrahepatic bile duct and gallbladder cancers, demonstrating a dose-dependent relationship, regardless of the mechanism.

MALSD as a cause of CVD: mediating factors

The increased influx of FFA into the liver results from adiposopathy and IR, i.e., the increased release of FFA

from adipose tissue and reduced uptake in skeletal muscle. These factors reinforce/exacerbate the insulin signaling dysregulation, in a vicious circle that stimulates hepatic *de novo* lipogenesis, further promoting hepatic lipid accumulation [33]. The long-lasting exposure to high levels of FFA and *de novo* lipogenesis leads to the hepatic accumulation of lipotoxic lipid species, inducing mitochondrial dysfunction, impaired autophagy, oxidative stress, inflammasome activation, hepatocyte injury, and apoptosis. Subsequent wound healing responses marked by stellate cell activation drive collagen deposition, progressive fibrosis, and eventual end-organ failure [27, 33].

Meanwhile, MASLD and VAT result in atherogenic dyslipidemia and hypertriglyceridemia through 2 mechanisms: (i) increased hepatic secretion of large, triglyceride-rich VLDL cholesterol molecules and (ii) impaired clearance of triglyceride-rich lipoproteins (TRL) associated with increased levels of apolipoprotein C-III (ApoC-III), resulting in a longer time in the circulation (before undergoing hydrolysis by lipoprotein lipase [LPL]) [34, 35] (Fig. 2). The increased secretion and impaired clearance of TRL result in long exposure in the vessels, giving them a greater chance of crossing the vascular endothelium and being deposited in the form of plaques, triggering the inflammatory process that characteristically accompanies atherosclerosis [35, 36]. The interplay of these diverse mechanisms (the presence of MASLD and the ectopic adiposopathy), in the context of subclinical inflammation and atherogenic dyslipidemia, promotes a metabolic phenotype with a high risk for vulnerable coronary plaque angiographic features such as napkin-ring signs, positive arterial remodeling, high-grade stenosis, triple vessel disease, and total occlusions [34, 37, 38].

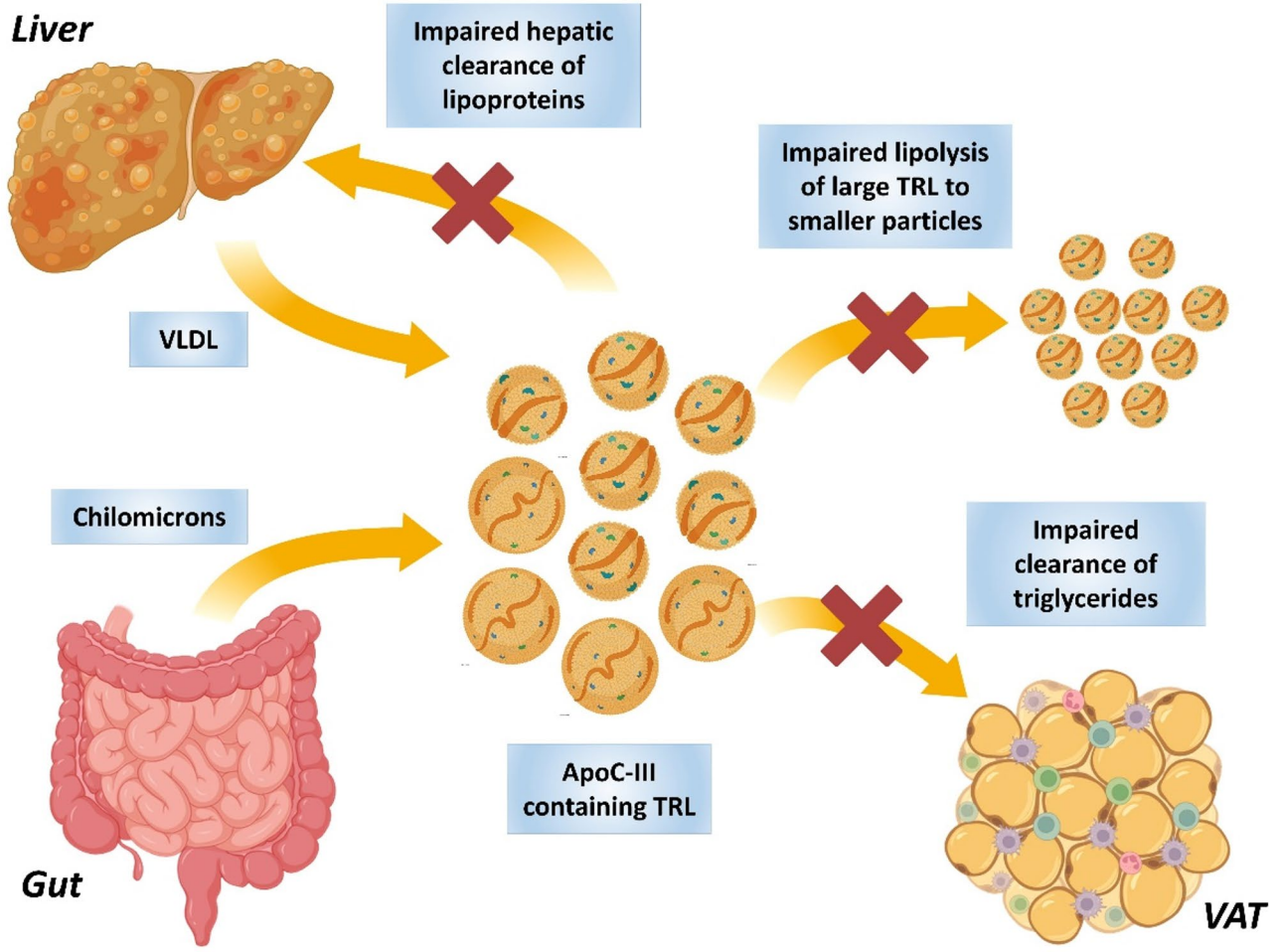

Fig. 2 Hypertriglyceridemia is associated with abdominal obesity and liver steatosis. ApoC-III: apolipoprotein C-III; TRL: triglyceride-rich lipoproteins; VAT: visceral adipose tissue; VLDL: very low-density lipoprotein. This image features content from BioRender.
Adapted from Björnson E et al. [35].

The role of hepatocytes in the induction of inflammation and IR in adipose tissue

Inflammation of VAT in obesity is a well-recognized pathological process. However, the source of this inflammation remains under investigation, and a hepatic-derived circulating factor (a hepatokine) may be involved [39]. For instance, Ghorpade et al. [40] highlighted the clinically evident interaction between the liver and VAT in metabolic diseases, demonstrating that obesity in mice stimulates hepatocytes to synthesize and secrete dipeptidyl peptidase 4 (DPP4), which interacts with plasma factor Xa to promote inflammation of adipose tissue macrophages and IR. They showed that soluble DPP4 activates the caveolin-1 pathway in adipose tissue macrophages. Alongside the activation of the protease-activated receptor two pathway by factor Xa, both pathways synergistically stimulate the extracellular signal-regulated protein kinases 1 and 2 and the nuclear factor kappa B, which are distal inflammatory signaling molecules. Silencing DPP4 expression in hepatocytes suppressed VAT and IR inflammation, while pharmacological inhibition of DPP4 did not [40]. These findings suggest that the liver, through hepatokines, may initiate inflammation and IR in adipose tissue, potentially leading to obesity-related CMRDs.

The gut-liver-adipose axis in the CARDIAL-MS

The gut-liver-adipose axis connects human microbiota to MASLD and adiposopathy. The gut microbiota is recognized as an "invisible organ" interconnected with various other tissues. The liver is the primary source of blood drainage from the gut, maintaining a continuous connection to microbiota health. Additionally, the liver connects back to the intestine through the biliary tract [41].

It is well known that intestinal products, such as host and/or microbial metabolites and microbial-associated molecular patterns, are transported to the liver and can modulate liver function [42]. Some researchers advocate for an intricate interplay among the gut microbiota, the intestine, and adipose tissue that influences liver action on insulin [43]. In a comprehensive multiomics, multitissue, cross-cohort integrative approach that encompasses transcriptomics of the intestine, liver, and adipose tissue (both visceral and subcutaneous), while incorporating plasma metabolomics, lipidomics, and metagenomics, along with a hyperinsulinaemic-euglycaemic clamp, fasting glucose measurements, and glycated hemoglobin (HbA1c), Castells-Nobau et al. [43] presented a series of intriguing results. Several genera and species from the *Proteobacteria phylum* were consistently negatively associated with insulin sensitivity. Transcriptomic analysis of the jejunum, ileum, and colon revealed T-cell-related signatures positively linked to insulin sensitivity [43].

A multiomics and multitissue integration connects *Proteobacteria* with jejunal deoxycholic acid and jejunal and VAT genes involved in actin cytoskeleton, insulin, and T-cell signaling. Fasting glucose was consistently associated with interferon-induced genes and antiviral responses in the intestine and VAT. Evidence suggests an interaction between serum bile acids and CVD within the biliary tree. Recently, Kipp et al. [44] described that urobilin is frequently elevated in the urine of individuals with CVD. This is just one example of how this new pathophysiological axis links the liver to MS and CVD, and it is as intriguing as it is uncertain [44]. They position the liver as the protagonist, further reinforcing the concept of CARDIAL-MS, human microbiota, MASLD, and adiposopathy.

May the liver drive T2D?

The global prevalence of MASLD in T2D is rising. A pooled global prevalence of MASLD in individuals with T2D has reached 65.33% (95% CI 62.35–68.2), ranging from 53.1% in Africa to 80.6% in Eastern Europe [45].

The relationship between the liver and T2D has been recognized for over a century [46]. Indeed, as early as 1906, a possible origin of T2D in liver cirrhosis was suggested, and the term "hepatogenous diabetes" was proposed (reviewed by Kumar R [46]). Nonetheless, the strongest association between MS and T2D has been with MASLD.

Observational studies have shown that a modest elevation of ALT, aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT) is associated with an increased risk of subsequently developing T2D. Several meta-analyses have confirmed the association of MASLD with the incidence of T2D [47–49]. Ballestri et al. [47] conducted a systematic review and meta-analysis involving 117,020 patients across 20 studies, followed for a median of 5 years (3–14.7 years). MASLD was linked to an increased risk of incident T2D; using ALT, AST, and GGT as the diagnostic criterion for MASLD, the relative risks were 1.97 (95% CI 1.80–2.15), 1.58 (95% CI 1.43–1.74), and 1.86 (95% CI 1.71–2.03), respectively [47]. The presence of steatosis, as evaluated by ultrasonography, conferred a relative risk of 1.86 (95% CI 1.76–1.95) [47].

An updated meta-analysis comprising 33 studies and including 501,022 individuals, among whom there were 27,953 cases of incident T2D over a median of 5 years (IQR: 4.0–19 years), demonstrated a higher risk among patients with MASLD compared to those without ($n = 26$ studies; random effects HR 2.19, 95% CI 1.93–2.48; I^2 91.2%) [48]. Interestingly, the risk was even greater among individuals with advanced liver disease and markedly across the severity of liver fibrosis (5 studies; random-effects HR 3.42, 95% CI 2.29–5.11; I^2 44.6%) [48].

To investigate the longitudinal outcomes associated with MASLD, a comprehensive systematic review and meta-analyses evaluated 129 studies involving thousands of participants [49]. The incidences of T2D (HR 2.56, 95% CI 2.10–3.13, $p < 0.01$), prediabetes (HR 1.69, 95% CI 1.22–2.35, $p < 0.01$), and MS (HR 2.57, 95% CI 1.13–5.85, $p < 0.02$) were higher in people with MASLD than in those without. Furthermore, in a subgroup of patients with advanced liver disease, the incidence of T2D was even more pronounced (HR 3.60, 95% CI 2.10–6.18, $p < 0.01$). The same pattern was observed in those with less severe MASLD when compared to non-MASLD (HR 1.63, 95% CI 1.00–2.45, $p < 0.02$) [49]. Taken together, there appears to be a dose-response relationship between the incidence of T2D and the presence and severity of MASLD.

Conversely, the presence of T2D results in more severe MASLD. In a study involving 713 Duke NAFLD clinical database patients, each 1% increase in HbA1c recorded 1 year before liver biopsy was associated with an odds ratio (OR) of 1.15 (95% CI 1.01–1.31) for increased fibrosis stage [50]. T2D is also an important risk factor for complications related to cirrhosis. In a retrospective Japanese study involving patients with MASLD, the presence of T2D was associated to a high risk for developing hepatocellular carcinoma (HR 3.21, 95% CI 1.09–9.50, $p < 0.05$) [51].

Despite the consistent pathophysiologic and epidemiologic relationship between MASLD and T2D, most evidence comes from observational studies, limiting the conclusion about the existence of a causal relationship. Therefore, some researchers have utilized MR to infer a probable causal effect of liver function biomarkers or liver fat [52, 53]. De Silva et al. [52] analyzed data from up to 64,094 T2D cases and 607,012 control subjects in a MR study, using genetic variants associated with liver parameters (ALT, AST, alkaline phosphatase [ALP], and GGT) and with T2D or fasting insulin, to evaluate a possible bidirectional effect. Genetically predicted higher levels of circulating ALT and AST were associated with an increased risk of T2D. Higher genetic predisposition to fasting insulin, but not T2D, correlated with increased circulating ALT [52]. These findings support MASLD as a cause of T2D, or IR resulting in MASLD, which in turn increases the risk of T2D. Moreover, these findings also support the Twin-Cycle hypothesis [52]. This will be discussed in detail later.

Martin et al. [53] utilized genetic variants associated with liver and pancreatic volume and fat content from MRI scans of UK Biobank participants. After conducting several sensitivity analyses, they concluded that hepatic fat (OR 1.27, 95% CI 1.08–1.49) and lower pancreatic volume are causal factors in the higher risk of T2D. In turn, higher pancreatic volume was associated with 24% reduction in risk per 1 standard deviation (OR 0.76, 95% CI 0.62–0.94) [53]. Despite these findings, the researchers were unable to identify a genetic association between pancreatic fat and the risk of T2D.

Hepatokines: liver-derived proteins linked to CMRDs

The liver produces and releases approximately thirteen proteins associated with metabolic disturbances. At least six of these may be particularly significant for CARDIAL-MS: fetuin-A, fibroblast growth factor 21 (FGF-21), sex hormone binding globulin (SHBG), angiopoietin-like 3 (ANGPTL3), selenoprotein P, and DPP4 [40, 54]. Among this group, only SHBG and FGF-21 are reduced in SLD. Most hepatokines are associated with IR, inflammation, β-cell dysfunction, and cardiometabolic risk regardless of the presence or absence of obesity (reviewed by Stefan [54]).

Associations with incident T2D have been reported for fetuin-A (also known as alpha 2-Heremans-Schmid), a hepatokine predominantly synthesized by the liver. Fetuin-A plays a crucial role in essential pathophysiological processes, such as insulin receptor signaling, adipocyte dysfunction, inflammation, liver fibrosis, lipid toxicity, triacylglycerol production, macrophage phenotype modification, promotion of angiogenesis, β-cell damage, apoptosis, and Toll-like receptor 4 (TLR4) activation, which are vital for liver integrity and function [54–56]. Fetuin-A levels are elevated in MASLD and linked to MS and its components. Interestingly, it seems to precede the onset of MS. Furthermore, several observational studies have established its correlation with the risk of T2D (meta-analyzed by Guo et al. [57]).

Despite findings from mechanistic, preclinical, observational studies, and meta-analyses suggesting a clear causal connection with fetuin-A and T2D, MR studies remain controversial [58, 59]. Using data from the EPIC-InterAct case-cohort study, based on 12,403 subjects with newly diagnosed T2D, Kröger et al. [58] could not identify a strong association between a genetic score involving SNPs in the fetuin-A-encoding AHSG gene and incident T2D. However, a subsequent MR study, which featured a larger number of participants, with longer follow-up, and employed newly identified genetic variants associated with fetuin-A, found that increased levels of genetically predicted fetuin-A correlate with an elevated risk of T2D (OR 1.21, 95% CI 1.13–1.30, $p < 0.01$) [59]. Moreover, its genetically predicted higher levels were connected to a higher risk of CAD in individuals with T2D, but not in those without (p for interaction = 0,03) [59].

Since individuals with MASLD predominantly die from CVD, potential links between CVD and hepatokines have been investigated. Given its pleiotropic metabolic and inflammatory effects, fetuin-A is considered a likely

mediator (as summarized by Dogru [55]). Among the 12 observational studies conducted, 7 reported associations with various CV manifestations [55].

Pancreatic steatosis

Pancreatic steatosis (PS) is a general term to describe the accumulation of fat in the pancreas, ranging from fatty infiltration of the gland to the development of inflammation and fibrosis [60]. Fat storage in the pancreas can be due to adipocyte infiltration (the most common situation) or the intracellular accumulation of fat droplets [61]. Although fatty infiltration can be reversed, irreversible fatty infiltration may also occur due to acinar cell death, a condition known as pancreatic liposubstitution [61].

PS was first described in the medical literature by Ogilvie in 1933 [62]. In the 1980s, an autopsy study showed that fat replacement of more than 25% of the pancreas was associated with an increased risk of generalized atherosclerosis and T2D, drawing attention to the fact that PS was not a harmless finding [63].

Pooling data on PS from eleven studies (12,675 individuals) yielded the prevalence of 33% (95% CI 24–41%) [64]. Weight gain, prediabetes or T2D, MS, MASLD, advancing age, and alcohol consumption are some of the main factors that affect the accumulation of pancreatic fat [60, 61]. The presence of one or more MS components was associated with a 37% increase in the prevalence of PS [65]. Other factors, including male sex, low birth weight, and monogenic diseases, may also be involved in PS. Notably among these monogenic conditions is maturity-onset diabetes of the young type 8 (MODY 8), a specific form of diabetes associated with severe pancreatic lipomatosis since childhood [61].

Although adipocyte infiltration of the exocrine pancreas is the most common degenerative change in the gland, lipid infiltration can also occur in the endocrine pancreas. The involvement of the islets of Langerhans by fat increases with advancing age and the development of T2D [61]. Moreover, utilizing MRI, our group evidenced increased pancreatic fat content in 11 female patients with type 2 partial familial lipodystrophy vs. 8 healthy matched controls, and it was inversely related to β-cell function, measured by the disposition index (DI) [16].

Roy Taylor et al. [66, 67] elaborated a hypothesis associating liver and pancreatic steatosis with T2D genesis (the Twin Cycle hypothesis). According to this hypothesis, increased hepatic triglyceride production would lead to fat accumulation in the pancreas, resulting in β-cell dysfunction (lipotoxicity), impaired insulin secretion, and increased blood glucose levels; consequently, these changes lead to a self-reinforcing cycle. In subsequent years, the Twin Cycle hypothesis was tested through a series of elegant studies (reviewed by Taylor [67–69]); recovery of β-cell function was demonstrated following dietary caloric restriction, an achievement that was temporally coincident with rapid reductions in liver fat and a more protracted decrease in PS [67–69]. Despite all this evidence, not all studies have demonstrated an association between MASLD and PS, indicating the existence of an alternative pathway of fatty acid deposition in the pancreas independent of hepatic triglyceride production and potentially derived from a direct flow of FFA from adipose tissue [60].

In a systematic review, meta-analysis, and meta-regression, PS was associated with an increased risk of T2D (RR 2.08, 95% CI 1.44–3.00, $p = 0.0001$) and MS (RR 2.37, 95% CI 2.07–2.71, $p < 0.0001$) [63]. A longitudinal study also found that lean individuals with PS were more likely to develop T2D than those without PS after a 6-year follow-up [60]. However, the presence of PS was not a risk factor for T2D in individuals with obesity, suggesting that different T2D phenotypes may have distinct associations with PS [60].

Interestingly, the metabolic context determines the role of pancreatic fat in the function of β-cells. PS does not appear to compromise insulin secretion per se. In experimental models, pancreatic adipocytes modulate this secretion by releasing FFA, which can increase insulin secretion via FFA receptor 1 (FFAR1, also called GPR40) in β-cells [70]. However, increased PS is associated with impaired insulin secretion under some metabolic circumstances, such as prediabetes. Genetic variants that mediate IR, but not insulin secretion capacity, appear responsible for this interaction [60].

In summary, insulin secretion seems to be impaired by the PS only in individuals genetically predisposed to T2D. It is thought that the mechanism involved is the paracrine action of metabolites or substances such as cytokines, chemokines, and adipokines secreted by pancreatic adipocytes. Furthermore, prolonged exposure of β-cells to long-chain saturated fatty acids promote intracellular changes, including ceramide production, oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, and activation of protein kinases. These factors can compromise insulin secretion and glucose homeostasis, contributing to the onset of T2D [60].

Cardiovascular steatosis

As discussed, hypertrophic triglyceride-rich adipocytes experience cellular stress, contributing to inflammation and IR in adipose tissue. At the same time, the activation of Toll-like receptors (TLRs) and the secretion of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), further impair insulin sensitivity. This cascade enhances lipolysis, increasing the release of FFA into circulation, accumulating in ectopic tissues, worsening local IR and

inflammation. Additionally, abnormalities in intracellular fatty acid metabolism—potentially linked to IR and hyperinsulinemia—synergistically promote intracellular fatty acid accumulation, fostering a pro-inflammatory *milieu* [71].

In the CV system, cardiomyocytes, epicardial adipose tissue, and endothelial cells are key targets for inter-tissue FFA transfer. Endothelial cells (ECs) take up circulating FFA via albumin and TRL, including chylomicrons (CMs) and VLDL [72]. LPL facilitates FFA release from these lipoproteins, enabling their uptake through multiple pathways. Once inside ECs, FFA are primarily converted into triglycerides via enzymatic processes involving diacylglycerol O-acyltransferase (DGAT). ECs also possess the machinery to form and metabolize intracellular lipid droplets (LDs), which serve as buffers against lipotoxicity and reservoirs for FFA, supplying both ECs and adjacent parenchymal cells [73]. The mobilization of FFA from triglycerides within LDs is initiated by adipose triglyceride lipase (ATGL), and its dysregulation, either through excessive lipid intake or ATGL deficiency, leads to LD accumulation. This, in turn, promotes endothelial dysfunction through mechanisms such as reduced endothelial nitric oxide synthase (eNOS) expression due to decreased eNOS messenger ribonucleic acid (mRNA) stability, increased endoplasmic reticulum (ER) stress, and endothelial inflammation. These pathological changes contribute to atherosclerosis progression and heighten vascular tone, ultimately predisposing to arterial hypertension [74, 75]. In a serial study of human heart transplant recipients, intracellular lipid accumulation in cardiomyocytes—specifically triacylglycerol and ceramide—was inversely associated with homeostasis model assessment of insulin resistance (HOMA-IR) values, suggesting a link between lipid deposition and IR [76]. Moreover, myocardial triacylglycerol and ceramide accumulation in the transplanted hearts was further associated with both early diastolic and systolic dysfunction, independent of BMI, at 12 months after transplantation [76].

Increased lipid droplet accumulation in the myocardium is also observed in patients and animal models of diabetes and obesity, reflecting impaired fatty acid homeostasis and lipotoxicity. In obesity-related HF with preserved ejection fraction (HFpEF), lipid droplet accumulation exceeds that seen in hypertensive HFpEF, highlighting a distinct metabolic pathology where lipotoxicity plays a more prominent role than hypertrophy and pressure overload [77]. Diabetes can independently contribute to this myocardial pathology, and in HFpEF, T2D is highly prevalent alongside obesity. However, BMI, rather than diabetes status, demonstrates a stronger association and emerges as the primary predictor of this histopathology [77]. Indeed, obesity, more than cardiac hemodynamics or diabetes, is strongly linked to ultrastructural abnormalities, including fibrosis, sarcomere disruption, increased lysosomal/phagosomal activity, and mitochondrial structure alterations.

Epicardial adipose tissue (EAT) is a unique fat depot between the myocardium and the visceral epicardium. Composed primarily of adipocytes, EAT also contains nerve cells, inflammatory cells (mainly macrophages and mast cells), stromal cells, vascular cells, and immune cells. While classified as white adipose tissue, it retains brown and beige fat-like properties and expresses a distinct transcriptome compared to other visceral and subcutaneous fat depots [78–80]. EAT distribution is region-specific, with distinct transcriptomic and proteomic profiles depending on location. EAT surrounding the left atrium differs from that infiltrating the coronary arteries, influencing adjacent cardiac structures differently [79].

No muscle fascia separates EAT from the myocardium, leading to a shared microcirculation. It plays a dual role: exerting cardioprotective effects through its thermogenic, brown fat-like function while promoting cardiac dysfunction via paracrine and vasocrine secretion of pro-inflammatory and profibrotic cytokines. The thermogenic function of EAT declines from childhood to adulthood but continues to provide energy and heat to the heart [81]. However, in pathological conditions such as CAD, T2D, HF, and AF, EAT shifts towards a pro-atherogenic and pro-arrhythmogenic phenotype. This transition is further worsened in advanced cardiac disease and aging, with a concomitant increase in profibrotic and pro-apoptotic gene expression.

Coronary EAT exhibits dense inflammatory infiltration in CAD, dominated by pro-inflammatory M1 macrophages [82]. It secretes cytokines (monocyte chemoattractant protein-1 [MCP-1], IL-6, TNF-α) and adipokines (chemerin, intelectin-1/omentin-1, resistin, and serglycin) into the coronary lumen, amplifying systemic and local coronary atherosclerotic plaque inflammation. EAT is also implicated in AF, influencing its development and recurrence post-ablation [83]. Increased EAT volume or thickness is associated with atrial conduction abnormalities, including prolonged P-wave duration, interatrial conduction block, and extended P–R interval [84]. This interaction likely involves genetic and neural factors, inflammation, fibrosis, fatty infiltration, and atrial structural and electrical remodeling. Importantly, the association between cardiac fat and AF appears partially or entirely independent of obesity.

In HF, EAT contributes to pathogenesis via inflammation, fibrosis, autonomic dysregulation, and mechanical effects of fibrotic fat deposits [85]. Its secretome plays a key role in HF, particularly with HFpEF [86]. The association between EAT thickness or volume and HFrEF

remains controversial, with studies reporting increased and, more frequently, decreased EAT volume compared to healthy individuals [87, 88]. Consequently, EAT volume assessment in HFrEF lacks clinical usefulness in guiding management decisions.

Perirenal adipose tissue, renal sinus fat, and chronic kidney disease

The reciprocal interplay between obesity, MS, MASLD, T2D, and CVD has been extensively explored. It is well established that the kidneys are susceptible to various disorders linked to these conditions. These disorders range from direct effects, such as obesity-related glomerulopathy [89], to secondary complications arising from obesity-driven systemic diseases, including T2D and hypertension [90]. The epidemiology and pathophysiology of classical diabetic nephropathy are well characterized and will not be further discussed here. However, the causal pathways linking obesity, MASLD, and MS to kidney damage remain an active and evolving area of research.

Recent large-scale studies have demonstrated robust associations between obesity and chronic kidney disease (CKD), independent of diabetes and hypertension. For instance, in a cohort of 1,405,016 adults from English primary care records, the risk of developing advanced CKD increased in a log-linear fashion with rising BMI, from overweight to obesity to severe obesity, regardless of the presence of T2D, hypertension, or CVD [91]. Similarly, using advanced MR techniques in a dataset of 337,422 individuals of European ancestry from the UK Biobank, in combination with GWAS of human adiposity traits, Xu et al. [92] demonstrated significant causal effects of genetic traits related to BMI, WC, and obesity on a composite measure of renal function, referred to as the kidney health index. Notably, T2D and blood pressure accounted for only 26–34% of the causal association between BMI/WC and the kidney health index, suggesting that most of the obesity's impact on kidney health occurs independently of these comorbidities. Interestingly, another large-scale MR study revealed a strong association between obesity and renal dysfunction but found no significant association with albuminuria in the absence of T2D [93]. This finding suggests the presence of distinct and complex pathways of kidney injury within the broader framework of metabolic-mediated kidney damage.

As mentioned above, MASLD is increasingly recognized as a systemic metabolic disorder extending beyond hepatic pathology. Several large-scale meta-analyses have reinforced the epidemiological link between MASLD and kidney disease [94–97].

A key question regarding the association between MASLD and CKD is whether this relationship results from shared metabolic and inflammatory pathways or whether a direct pathophysiological connection also exists, potentially contributing to CV complications [98]. In fact, CKD markedly increases the risk of CVD through a multifactorial pathophysiological process involving hemodynamic, neurohormonal, metabolic, and inflammatory pathways. Traditional risk factors such as hypertension, diabetes, dyslipidemia, and obesity are highly prevalent in CKD and accelerate atherosclerosis [99]. Additionally, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system contributes to left ventricular hypertrophy and heart failure [100]. Metabolic disturbances, including uremic toxin accumulation and calcium-phosphate imbalance, further promote vascular calcification and myocardial fibrosis [100]. In addition, CKD also induces endothelial dysfunction and chronic inflammation, which create a prothrombotic and proatherogenic environment [101, 102]. Coronary microvascular dysfunction and impaired nitric oxide bioavailability contribute to myocardial ischemia, even in the absence of epicardial coronary disease [103]. Finally, using clinical, laboratory, and baseline proteomic data from the EQUAL Study, three proteins—receptor protein-tyrosine phosphatase sigma, FCN2, and IGFBP6—were identified as being associated with estimated glomerular filtration rate (eGFR) decline in two independent cohorts of older adults with advanced CKD [104]. These findings suggest a potential link between elevated expression of proteins related to fibrosis and the complement cascade and progressive kidney function loss. Collectively, these interrelated mechanisms explain the heightened CVD burden in CKD and are well-documented in contemporary research.

Nevertheless, as one of the core tenets of epidemiology states, establishing causality from these observations is inherently challenging due to overlapping traditional risk factors for MASLD and CKD.

The hypothesis of a direct causal link between hepatic fat infiltration and CKD is relatively recent, and accumulating clinical and mechanistic evidence supports its plausibility. Several putative factors have been implicated, including genetic predisposition, intestinal dysbiosis, liver-driven IR, low-grade inflammation, prothrombotic states, hyperuricemia, reduced adiponectin production, activation of the renin-angiotensin system, impaired antioxidant defenses, nephrotoxicity of liver-derived metabolites, and the secretion of harmful hepatokines [105–108]. One interesting and relatively recent development is that the accumulation of renal fat deposits may contribute to renal damage mediated by obesity and MASLD. Perirenal adipose tissue (PRAT) and renal sinus fat (RSF) are compartments of VAT surrounding the kidneys. PRAT is the only adipose tissue enclosed by a tough fibrous membrane; therefore, excessive adiposity

in this non-distensible compartment can encapsulate and compress the kidneys (the Renal Tamponade hypothesis) [109]. The kidney is surrounded by an adherent renal capsule, a serosal layer composed of collagen and elastin that encloses most of the renal parenchyma but is discontinuous at the hilum, where vessels, nerves, and the renal pelvis pass through. At the hilum, PRAT extends inward to form RSF, which intersperses with and surrounds these structures, as well as the distal portions of the papillae. RSF can be seen as a unique variety of VAT and a particular type of perivascular adipose tissue, being vascularized, innervated, endowed with lymphatic drainage, and possessing a functional adrenergic system [110, 111].

Excess RSF can infiltrate and compress the renal papillae at the hilum and its main vessels, exerting mechanical and endocrine/paracrine effects that may contribute to renal injury [109, 112]. Mechanistically, RSF compression of the kidney may increase intrarenal pressure, impair renal perfusion, activate the renin-angiotensin system, increase sodium reabsorption, impair glomerular filtration, and enhance susceptibility to ischemic injury [113, 114]. Additionally, RSF is metabolically active and responds to systemic cues through direct lipotoxicity, local and systemic adipocytokines, hepatokines, oxidative stress, and endothelial dysfunction, which can further exacerbate renal damage [26].

Recent findings highlight PRAT inflammation as an emerging and independent CMRF [114]. This could explain, at least in part, why patients with early stages of CKD have a high risk of CV events. PRAT contains a mixture of brown and white adipocytes, which usually display an immunoregulatory phenotype in response to inflammation but may switch to an inflammatory phenotype characterized by increased secretion of pro-inflammatory cytokines (TNF-α, IL-6, MCP-1) and reduced production of protective adipokines such as adiponectin [114, 115]. This inflammatory shift may lead to endothelial dysfunction, fibrosis, and tubular injury, linking PRAT dysfunction to CKD progression.

Figure 3 details the proposed complex pathophysiology of CARDIAL-MS, which includes adiposopathy, ectopic lipid accumulation, and dysregulated adipokine/hepatokine signaling, leading to T2D, MASLD, and cardiorenal diseases

Adult-onset diabetes phenotypes and ectopic fat

Some studies have introduced a new concept for subphenotyping adult-onset diabetes, both clinically and genetically, beyond a binary classification of type 1 diabetes (T1D) and T2D [116, 117]. By subclassifying individuals with adult-onset diabetes into six distinct clusters, Ahlqvist et al. [116] observed that a sub-phenotype exhibiting greater IR was linked to an increased risk of developing CKD. Furthermore, Wagner et al. [118] identified six clusters of individuals at elevated risk for developing T2D in the Tübingen Family Study and Tübingen Lifestyle Program (TUEF/TULIP) and replicated their findings in the Whitehall II study cohort. Among these clusters, two subgroups were marked by elevated VAT and MASLD or VAT and RSF (clusters 5 and 6, respectively). The latter subgroups faced heightened risks for CKD and mortality, although with a distinct risk for imminent diabetes [118]. As discussed above, these studies add to the discussion of the interconnection of T2D and ectopic fat deposition in liver and surrounding kidneys.

CARDIAL-MS stages

Identifying patients at risk of developing downstream metabolic complications could streamline early detection. Figure 4 outlines the four stages of CARDIAL-MS, with anthropometric cut-offs defined as follows: WHR ≥ 0.95 (men)/≥0.85 (women), fat mass ratio [(the ratio between truncal and lower limbs fat evaluated by DXA); (FMR) ≥ 1.7 (men)/≥1.2 (women)], and waist-to-height ratio > 0.5 (both sexes) [119–122]. Beyond anthropometrics, CMRFs align with the International Diabetes Federation MS criteria [123]. We strongly recommend incorporating fasting and/or 1-hour post-load glucose tests to assess impaired glucose tolerance and T2D detection [124, 125].

Imaging methods for evaluating ectopic fat sites

The most used imaging methods for hepatic and pancreatic fat include ultrasound, computed tomography, and MRI [126–128]. However, because CKD has a distinct origin and pathophysiology, MRI has proven to be more informative. It is important to note that the biomarkers most frequently used in clinical practice (eGFR and albuminuria) only appear when the disease is already established and/or advanced, providing limited information about pathophysiology or early detection. Therefore, new methods of functional MRI have become increasingly effective and valuable.

MRI can estimate in vivo renal volume, glomerular perfusion rate, glomerular sclerosis rate, function, metabolism, perfusion, oxygenation, and detect microstructural changes and fibrosis at early stages without requiring contrast media [127, 128]. Examples of these new techniques include T1 and T2-weighted mapping, phase-contrast MRI, BOLD (blood oxygenation level-dependent) MRI, diffusion MRI, and Arterial Spin Labeling (ASL-MR). Finally, multiparametric MRI, which incorporates several of these techniques, may become the gold standard in studying kidneys and kidney diseases [127].

Final considerations

Following the AHA's publication of the CKM syndrome [1], we propose a more comprehensive definition to

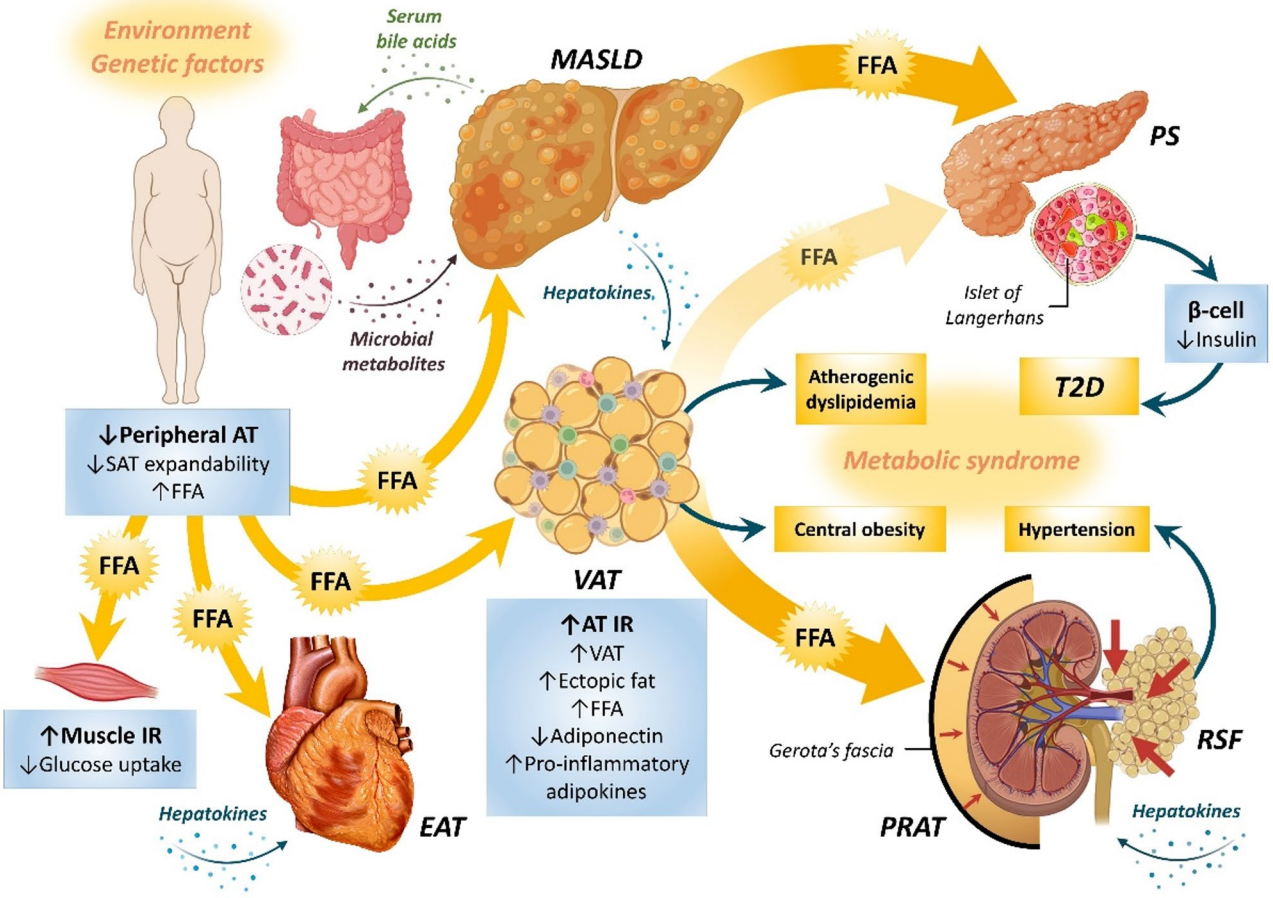

Fig. 3 Proposed pathophysiology of Cardio-Renal-Diabetes and Liver-Metabolic Syndrome (CARDIAL-MS). For details, refer to the main text. AT: adipose tissue; EAT: epicardial adipose tissue; FFA: free fatty acids; IR, insulin resistance; MASLD: metabolic dysfunction-associated steatotic liver disease; MS, muscular steatosis; PRAT: perirenal adipose tissue; PS: pancreatic steatosis; RSF: renal sinus fat; SAT: subcutaneous adipose tissue; T2D, type 2 diabetes; VAT: visceral adipose tissue. This image features content from BioRender

capture the frequent clustering of MS, CV, kidney, and liver diseases, prediabetes, and T2D. This led us to introduce a new model: CARDIAL-MS.

While preparing this proposal and review, Theodorakis & Nikolaou [129] independently suggested incorporating MASLD into their expanded framework, the Cardiovascular-Renal-Hepatic-Metabolic (CRHM) syndrome. Given that T2D is a well-established CMRF and is likely causally linked to MASLD, we argue that CARDIAL-MS aligns with their perspective while offering a more inclusive definition.

Conclusions

The acronym CKM was introduced to describe the final pathway of CV and renal complications from metabolic diseases [1]. While it is crucial to acknowledge the complex health issues stemming from these metabolic disorders, related to energy supply and accumulation, for developing guidelines for investigating and treating diseases associated with high morbidity and mortality, the acronym is limited by its focus on downstream events. The occurrences within the CKM model transpire well after the triggering factors emerge, indicating that preventive and therapeutic interventions would likely be much more effective at an earlier stage. Ultimately, recognizing CARDIAL-MS as a novel pathophysiological framework for MS and its distinct stages could enable earlier diagnosis and timely preventive interventions for CMRDs, addressing our foremost global health challenge.

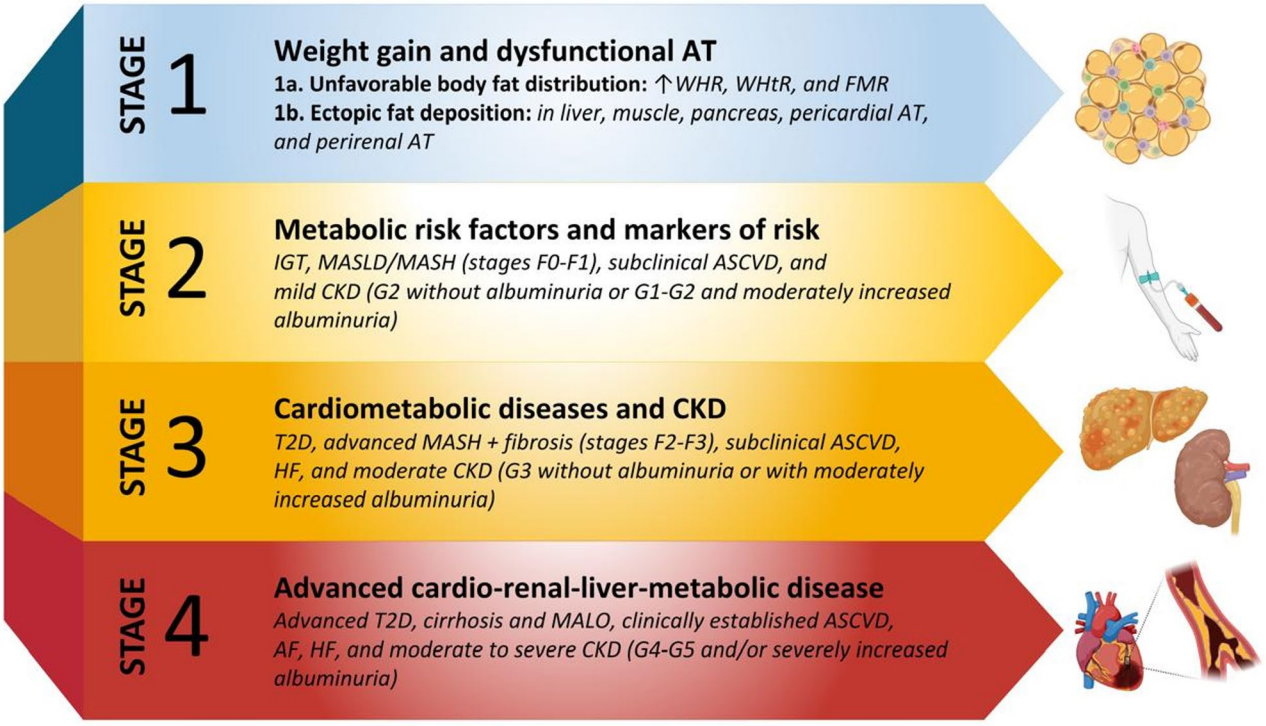

Fig. 4 Stages of CARDIAL-MS. AF: atrial fibrillation; ASCVD: atherosclerotic cardiovascular disease; AT: adipose tissue; CARDIAL-MS: cardio-renal-diabetes-liver-metabolic syndrome; CKD: chronic kidney disease; FMR: fat mass ratio (the ratio between truncal and lower limbs fat evaluated by DXA); HF: heart failure; IGT: impaired glucose tolerance; MALO: major adverse liver outcomes; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; T2D: type 2 diabetes; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. This image features content from BioRender

Abbreviations

Ab-SAT	abdominal SAT
AF	atrial fibrillation
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANGPTL3	angiopoietin-like 3
ApoC-III	apolipoprotein C-III
ASCVD	atherosclerotic cardiovascular disease
ASL-MRI	arterial spin labeling magnetic resonance imaging
AST	aspartate aminotransferase
AT	adipose tissue
ATGL	adipose triglyceride lipase
BMI	body mass index
BOLD	blood oxygenation level-dependent
CAD	coronary artery disease
CARDIAL-MS	cardio-renal-diabetes-liver-metabolic syndrome
CI	confidence interval
CKD	chronic kidney disease
CKM syndrome	Cardiovascular-Kidney-Metabolic syndrome
CM	chylomicron
CMRDs	cardiometabolic and renal diseases
CMRFs	cardiometabolic risk factors
CRHM syndrome	Cardiovascular-Renal-Hepatic-Metabolic syndrome
CV	cardiovascular
CVD	cardiovascular disease
DGAT	diacylglycerol O-acyltransferase
DI	disposition index
DPP4	dipeptidyl peptidase 4
EAT	epicardial adipose tissue
EC	endothelial cell
eGFR	estimated glomerular filtration rate
eNOS	endothelial nitric oxide synthase
ER	endoplasmic reticulum
FFAR1	free fatty acid receptor 1
FFA	free fatty acids
FGF-21	fibroblast growth factor 21
FMR	fat-to-muscle ratio
G-FAT	gluteofemoral adipose tissue
GGT	gamma-glutamyltransferase
GWAS	genome-wide association study
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HOMA-IR	homeostasis model assessment of insulin resistance
HR	hazard ratio
IGT	impaired glucose tolerance
IL-6	interleukin-6
IR	insulin resistance
LDs	lipid droplets
LPL	lipoprotein lipase
MALO	major adverse liver outcomes
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
MCP-1	monocyte chemoattractant protein-1
MODY 8	maturity-onset diabetes of the young type 8
MR	Mendelian randomization
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	metabolic syndrome
OR	odds ratio
PRAT	perirenal adipose tissue
PS	pancreatic steatosis
RR	relative risk
RSF	renal sinus fat

SAT	subcutaneous adipose tissue
SHBG	sex hormone binding globulin
SLD	steatotic liver disease
SNPs	single nucleotide polymorphisms
T1D	type 1 diabetes
T2D	type 2 diabetes
TLR4	Toll-like receptor 4
TLRs	Toll-like receptors
TNF-α	tumor necrosis factor alpha
TRL	triglyceride-rich lipoproteins
TUEF/TULIP	Tübingen Family Study and Tübingen Lifestyle Program
UI	uncertainty interval
VAT	visceral adipose tissue
VLDL	very low-density lipoprotein
WC	waist circumference
WHR	waist-to-hip ratio
WHtR	waist-to-height ratio

Author contributions
AFG-M drafted, formatted, and revised the manuscript; CMV drafted, formatted, and revised the manuscript; WSSJ drafted, formatted, organized figures, and revised the manuscript; JMA-N drafted, formatted, and revised the manuscript; ACS drafted and revised the manuscript; JHRS drafted and revised the manuscript. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All the authors approved this study for publication.

Competing interests
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