Long Non-coding RNA MALAT1 as a Novel Diagnostic Biomarker of Coronary Artery Disease in Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract

Background: Coronary artery disease (CAD) remains a major cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM). The coexistence of T2DM accelerates atherosclerosis and vascular inflammation through hyperglycemia-induced oxidative stress, endothelial dysfunction, and lipid abnormalities. However, early diagnosis of CAD in diabetic patients remains clinically challenging, as current biomarkers lack adequate sensitivity and specificity for subclinical disease. Recent studies have highlighted the regulatory role of long non-coding RNAs (lncRNAs) in cardiovascular and metabolic disorders, suggesting their potential as novel molecular biomarkers.

Aim:

This review aims to comprehensively evaluate the diagnostic significance of the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA in coronary artery disease among patients with type 2 diabetes mellitus. It explores its molecular mechanisms, interaction with key metabolic and inflammatory pathways, and potential application in early disease detection.

Conclusion:

MALAT1 plays an essential role in glucose metabolism, endothelial function, and vascular homeostasis. Elevated circulating levels of MALAT1 have been observed in diabetic patients with coronary artery disease, correlating with inflammatory cytokines and endothelial injury markers. Its modulation influences the expression of vascular adhesion molecules, oxidative stress mediators, and apoptosis-related genes, implicating it in atherogenesis and vascular remodeling. Given these findings, MALAT1 represents a promising non-invasive diagnostic biomarker and potential therapeutic target for diabetic cardiovascular complications. Further large-scale studies integrating MALAT1 expression profiling with clinical parameters could enhance precision diagnostics and risk stratification in T2DM-associated CAD.

Keywords: *Long Non-coding RNA MALAT1 , Coronary Artery Disease, Type 2 Diabetes Mellitus*

Introduction

Coronary artery disease (CAD) is the leading cause of death globally, and its incidence is significantly higher among individuals with type 2 diabetes mellitus (T2DM). The diabetic milieu fosters endothelial dysfunction, chronic inflammation, and lipid derangements, accelerating atherosclerotic plaque formation. Despite advances in imaging and serological biomarkers, early detection of CAD in diabetic patients remains difficult due to overlapping metabolic changes and subclinical disease manifestations [1]. Long non-coding RNAs (lncRNAs) have recently emerged as crucial regulators of gene expression, modulating diverse cellular processes such as inflammation, apoptosis, and metabolism. Among them, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has gained significant attention for its involvement in cardiovascular and metabolic diseases [2].

The current review aims to provide a comprehensive synthesis of the molecular and clinical evidence supporting MALAT1 as a novel diagnostic biomarker for CAD in T2DM. The discussion encompasses

pathophysiological mechanisms, diagnostic implications, and potential clinical translation. Importantly, this review highlights gaps in existing research and proposes directions for future studies to validate MALAT1's clinical utility [3].

2. Pathophysiology of Coronary Artery Disease in Type 2 Diabetes Mellitus

The interplay between insulin resistance, hyperglycemia, and dyslipidemia forms the cornerstone of diabetic vascular pathology. Persistent hyperglycemia promotes advanced glycation end-products (AGEs), leading to endothelial damage and activation of inflammatory cascades. Additionally, oxidative stress resulting from excessive reactive oxygen species (ROS) exacerbates vascular injury by impairing nitric oxide (NO) bioavailability [4]. The resulting endothelial dysfunction facilitates low-density lipoprotein (LDL) infiltration, macrophage activation, and foam cell formation—key events in atherogenesis. Furthermore, T2DM enhances vascular smooth muscle cell proliferation and extracellular matrix deposition, contributing to plaque instability and thrombosis [5]. These mechanisms collectively underscore the necessity for early molecular biomarkers that can identify CAD risk before clinical onset [6].

3. Role of Non-coding RNAs in Cardiovascular Diseases

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), regulate gene expression post-transcriptionally, influencing cellular growth, differentiation, and apoptosis. In cardiovascular pathology, dysregulated ncRNA expression has been implicated in myocardial infarction, heart failure, and atherosclerosis [7]. LncRNAs act as molecular sponges, scaffolds, and epigenetic modulators, interacting with transcription factors and chromatin modifiers. Studies have identified numerous lncRNAs—such as ANRIL, H19, and MIAT—associated with CAD pathogenesis [8]. MALAT1, a nuclear-retained transcript exceeding 8000 nucleotides, is particularly noteworthy for its regulatory roles in vascular biology and glucose homeostasis [9].

4. Overview of MALAT1: Structure, Function, and Biological Roles

MALAT1 is a highly conserved lncRNA located on chromosome 11q13.1, originally identified in lung cancer but later found to be ubiquitously expressed in endothelial and smooth muscle cells. Functionally, MALAT1 modulates alternative splicing, transcriptional regulation, and epigenetic modification through interactions with serine/arginine-rich (SR) splicing factors and Polycomb repressive complex 2 (PRC2) [10]. In cardiovascular tissues, MALAT1 influences endothelial cell proliferation, migration, and angiogenesis. It also serves as a competing endogenous RNA (ceRNA), binding microRNAs such as miR-145 and miR-22, thereby modulating target gene expression implicated in vascular homeostasis [11].

5. MALAT1 in Glucose Metabolism and Insulin Resistance

Recent data suggest that MALAT1 is upregulated in patients with T2DM and correlates with insulin resistance indices. Experimental models demonstrate that MALAT1 suppresses insulin signaling by modulating SIRT1 and FOXO1 pathways, leading to impaired glucose uptake and enhanced gluconeogenesis [12]. Moreover, MALAT1 interacts with inflammatory mediators such as NF-κB, promoting cytokine release and insulin receptor substrate-1 (IRS-1) inhibition [13]. These findings indicate that MALAT1 not only reflects metabolic dysregulation but also actively contributes to diabetic vascular injury, rendering it a potential integrative biomarker linking metabolic and cardiovascular pathology [14].

6. MALAT1 and Endothelial Dysfunction in Atherogenesis

Endothelial dysfunction is a hallmark of atherogenesis and one of the earliest vascular abnormalities in type 2 diabetes mellitus (T2DM). MALAT1 has emerged as a pivotal regulator of endothelial homeostasis through its influence on nitric oxide (NO) production, oxidative stress response, and

vascular inflammation. Upregulation of MALAT1 in diabetic conditions impairs endothelial nitric oxide synthase (eNOS) activation, resulting in diminished NO bioavailability and vasodilatory capacity [15]. Experimental silencing of MALAT1 in human umbilical vein endothelial cells (HUVECs) restores eNOS phosphorylation and attenuates oxidative damage, suggesting a protective effect against hyperglycemia-induced injury [16]. Moreover, MALAT1 promotes the expression of adhesion molecules such as ICAM-1 and VCAM-1 via activation of the NF-κB signaling pathway, facilitating monocyte recruitment and vascular inflammation [17]. These molecular interactions indicate that MALAT1 contributes directly to endothelial dysfunction and plaque initiation in diabetic vasculature, underscoring its role as a mechanistic link between hyperglycemia and atherosclerosis [18].

7. Molecular Mechanisms Linking MALAT1 to Coronary Artery Disease

The molecular interplay between MALAT1 and coronary artery disease (CAD) involves complex regulation of inflammatory, oxidative, and apoptotic pathways. MALAT1 modulates endothelial and smooth muscle cell behavior through interactions with microRNAs and transcription factors critical in atherogenesis. For instance, MALAT1 acts as a competing endogenous RNA for miR-22 and miR-145, both of which regulate smooth muscle differentiation and proliferation [19]. Its overexpression enhances proliferation and migration of vascular smooth muscle cells (VSMCs), contributing to neointima formation and plaque progression [20]. Additionally, MALAT1 activates the NLRP3 inflammasome and downstream cytokine release, exacerbating vascular inflammation and endothelial apoptosis [21]. Experimental inhibition of MALAT1 in murine models of atherosclerosis has been shown to reduce lesion size, lipid deposition, and macrophage infiltration, highlighting its direct contribution to vascular pathology [22]. Collectively, these findings support a mechanistic framework in which MALAT1 drives CAD development through modulation of vascular inflammation, smooth muscle proliferation, and endothelial dysfunction in diabetic settings [23].

8. MALAT1 as a Diagnostic Biomarker: Expression Patterns and Circulating Levels

Circulating levels of MALAT1 have gained recognition as a promising non-invasive biomarker for the early detection of coronary artery disease (CAD), particularly in patients with type 2 diabetes mellitus (T2DM). Several clinical studies have demonstrated significantly elevated plasma MALAT1 expression in diabetic patients with angiographically confirmed CAD compared to diabetic individuals without CAD and healthy controls [24]. Quantitative PCR analyses from peripheral blood mononuclear cells (PBMCs) and serum samples reveal that MALAT1 levels correlate positively with inflammatory mediators such as TNF-α, IL-6, and high-sensitivity C-reactive protein (hs-CRP), suggesting a link between MALAT1 and systemic vascular inflammation [25]. Furthermore, MALAT1 expression has been associated with markers of endothelial injury, including soluble ICAM-1 and endothelin-1, reinforcing its role in endothelial dysfunction and atherogenesis [26]. Receiver operating characteristic (ROC) curve analyses indicate that MALAT1 offers superior diagnostic accuracy over conventional biomarkers such as troponin and BNP in identifying subclinical CAD among diabetic populations [27]. These findings collectively underscore the potential of circulating MALAT1 as a sensitive and specific diagnostic indicator of CAD in T2DM, with potential integration into molecular diagnostic algorithms [28].

9. Clinical Studies Evaluating MALAT1 in CAD and T2DM

Human studies increasingly support circulating and cellular MALAT1 as a diagnostic indicator of coronary disease in diabetic cohorts. In a 2025 cross-sectional study of patients with type 2 diabetes mellitus (T2DM), those with coexisting coronary heart disease (CHD) showed significantly higher peripheral blood MALAT1 expression than T2DM controls, and combining MALAT1 with omentin-1 improved diagnostic performance (AUC ≈0.77; sensitivity ~67%, specificity ~75%) for CHD detection in T2DM [29]. Earlier work in coronary populations demonstrated elevated serum MALAT1 with meaningful discrimination for in-stent restenosis (ROC >0.80) and independent associations with

inflammatory markers (hs-CRP) and natriuretic peptides, implying pathophysiologic linkage to vascular injury [30]. Genetic studies complement expression findings: MALAT1 rs3200401 and other variants associated with CAD risk, severity (Gensini score), and adverse outcomes after myocardial infarction, suggesting that both genotype and transcript abundance may stratify risk [31–33]. Beyond diabetes, MALAT1 measured in PBMCs or plasma has shown diagnostic relevance in acute coronary syndromes (including AMI), supporting its broader cardiovascular signal that likely extends to the diabetic CAD phenotype [34,35]. Collectively, current clinical evidence indicates that MALAT1—alone or in multi-analyte panels—offers noninvasive diagnostic value for CAD among patients with T2DM, though larger, multi-center studies with standardized assays are needed to refine thresholds and validate incremental utility over established biomarkers. [29–35]

10. Comparison of MALAT1 with Other lncRNA Biomarkers in CAD

When benchmarked against other CAD-linked lncRNAs, MALAT1 shows a distinctive profile that may favor its diagnostic use in T2DM. **ANRIL (CDKN2B-AS1)** is strongly associated with 9p21 risk and plaque biology, yet its circulating levels show variable diagnostic performance across cohorts, partly due to complex splice isoforms and ethnic heterogeneity [36]. **MIAT** correlates with myocardial injury and adverse remodeling, but several studies suggest stronger prognostic than diagnostic value, and glucose dysregulation can blunt its specificity in diabetics [37]. **H19** and **NEAT1** are robust inflammatory responders; however, both are pleiotropic across metabolic organs, raising concerns for off-target signals in obesity and fatty liver common in T2DM [38]. **SENCR** appears vasculoprotective and downregulated in atherosclerosis, but low abundance complicates routine qPCR detection [39]. Mitochondria-derived signatures such as **LIPCAR** capture post-MI remodeling risk more than stable CAD detection, limiting screening utility [40]. In contrast, MALAT1 is abundant, stable in plasma and extracellular vesicles, inducible by hyperglycemia and endothelial stress, and repeatedly elevated in CAD—including in diabetic subsets—yielding reproducible ROC performance and additive value when combined with inflammatory proteins or cardiometabolic scores [41]. These features position MALAT1 as a pragmatic anchor biomarker within multi-lncRNA or multi-omic panels tailored to CAD in T2DM. [36–41]

11. Diagnostic and Prognostic Value of MALAT1 in Diabetic Populations

The diagnostic and prognostic performance of MALAT1 in diabetic cohorts has become an emerging focus of translational cardiovascular research. Elevated circulating MALAT1 levels have been consistently observed in T2DM patients with coronary artery disease (CAD), correlating not only with the presence of CAD but also with its angiographic severity as measured by the Gensini and SYNTAX scores [42]. In longitudinal analyses, higher baseline MALAT1 expression predicted adverse cardiovascular outcomes, including myocardial infarction and revascularization events, suggesting a role in risk stratification [43]. Furthermore, combining MALAT1 with traditional biomarkers such as HbA1c, hs-CRP, and NT-proBNP improves diagnostic precision and outcome prediction in diabetic patients [44]. MALAT1's stability in plasma and exosomes enhances its clinical feasibility, as exosomal MALAT1 mirrors intracellular signaling changes in vascular and inflammatory cells [45]. Notably, post-intervention analyses show a decline in MALAT1 expression following intensive glycemic control or statin therapy, indicating potential responsiveness to metabolic and anti-inflammatory treatment [46]. These findings support MALAT1 not only as a diagnostic marker but also as a dynamic prognostic indicator reflecting therapeutic modulation and vascular risk evolution in T2DM-associated CAD [47].

12. Therapeutic Modulation of MALAT1: Current Evidence and Future Potential

Therapeutic targeting of MALAT1 is biologically plausible and supported by preclinical studies employing antisense oligonucleotides (ASOs/GapmeRs), siRNA, and CRISPR interference to suppress MALAT1, resulting in reduced endothelial inflammation, attenuation of VSMC proliferation, and smaller atherosclerotic lesions in vivo. Pharmacologic modifiers of upstream pathways—AMPK

activators (e.g., metformin), statins, and anti-inflammatory agents—appear to indirectly downregulate MALAT1 by dampening NF-κB signaling, oxidative stress, and cytokine release, aligning molecular change with improved vascular phenotypes in diabetic models. Advanced delivery platforms, including lipid nanoparticles and engineered extracellular vesicles, can enhance nuclease resistance and vascular tropism of oligonucleotide therapeutics, though immunostimulation and off-target hybridization remain key hurdles requiring careful sequence chemistry and rigorous pharmacovigilance. Translational progress will depend on establishing dose–exposure–response relationships, tissue-specific target engagement (e.g., endothelium vs. circulating cells), and composite pharmacodynamic readouts that couple MALAT1 knockdown with changes in validated inflammatory and endothelial biomarkers. Ultimately, integrating MALAT1-directed therapies with standard cardiometabolic care (statins, SGLT2 inhibitors, GLP-1 receptor agonists) could provide additive benefit by simultaneously correcting hemodynamic, metabolic, and transcriptomic derangements characteristic of T2DM-associated CAD, but this awaits early-phase clinical trials with hard vascular endpoints. [48–54]

13. Limitations and Challenges in MALAT1 Research

Despite substantial progress, several methodological and translational challenges limit the clinical deployment of MALAT1 as a biomarker or therapeutic target in type 2 diabetes mellitus (T2DM)–associated coronary artery disease (CAD). First, **heterogeneity in study design and sample types** (whole blood, plasma, PBMCs, or exosomes) leads to variability in reported MALAT1 expression and diagnostic accuracy [55]. Differences in normalization methods and reference genes further complicate inter-study comparability. Second, **the influence of comorbidities and pharmacologic agents**—such as statins, metformin, and anti-inflammatory drugs—on MALAT1 expression remains incompletely understood, posing confounding effects in observational studies [56]. Third, **the temporal dynamics** of MALAT1 in disease progression are unclear; whether elevated MALAT1 is a cause or consequence of vascular injury requires longitudinal validation [57]. Additionally, small sample sizes and single-center recruitment in many studies limit statistical power and generalizability. From a technical standpoint, lack of **standardized RNA extraction and quantification protocols** hinders clinical translation, as preanalytical factors such as hemolysis and sample storage can alter RNA yield [58]. Finally, the **pleiotropic nature of MALAT1**—involved in oncogenesis, fibrosis, and immune regulation—raises concerns about tissue specificity and off-target effects in therapeutic targeting [59]. Addressing these challenges through multicenter trials, standardized assays, and mechanistic exploration will be essential to confirm MALAT1's reliability as a diagnostic and prognostic biomarker for CAD in T2DM [60].

14. Emerging Technologies for lncRNA Detection in Clinical Practice

Translating MALAT1 into a clinically actionable biomarker depends on robust, scalable assays that withstand pre-analytical variability and yield precise quantification at low copy numbers. Digital PCR (ddPCR) improves absolute quantification over RT-qPCR, minimizing reference-gene dependency and enabling tighter limits of detection for plasma and exosomal MALAT1 [61]. Targeted RNA-seq and capture-based panels allow multiplexed lncRNA profiling with unique molecular identifiers to correct amplification bias, while nanopore single-molecule sequencing provides isoform-level resolution and real-time analysis suited to rapid triage workflows [62]. Standardized extracellular vesicle isolation—combining size-exclusion chromatography with immunoaffinity capture—enhances signal-to-noise for vesicular MALAT1, and synthetic spike-ins plus hemolysis indices improve normalization and quality control [63]. Point-of-care microfluidic cartridges integrating on-chip lysis, magnetic bead purification, and ddPCR can compress turnaround times to <60 minutes, and CRISPR–Cas13 collateral-cleavage assays (SHERLOCK/CARMEN) or RT-LAMP readouts on lateral-flow strips offer low-infrastructure alternatives for screening [64]. Label-free electrochemical and plasmonic biosensors—graphene FETs, nanostructured gold, and photonic crystals—have achieved picomolar detection of lncRNAs in serum, opening avenues for bedside monitoring and home sampling [65]. To enable multi-site trials, adherence to MIQE/REMARK-style reporting, external RNA controls consortium (ERCC) spike-ins, and ring-trial proficiency testing must be mandated, alongside automation-friendly SOPs and cloud pipelines that

harmonize batch effects for MALAT1 across platforms [66–68].

15. Integration of MALAT1 Biomarkers into Predictive Models for CAD in T2DM

Embedding MALAT1 into risk stratification requires rigorous model development and validation beyond univariable associations. Pragmatically, MALAT1 can be incorporated as a continuous covariate alongside age, sex, diabetes duration, HbA1c, eGFR, lipids, blood pressure, hs-CRP, and medication use, with evaluation of **incremental discrimination** (ΔC-statistic), **reclassification** (categorical/continuous NRI, IDI), and **calibration** (calibration slope, Brier score) against established scores (e.g., pooled cohort equations, UKPDS, ADVANCE) [69]. Penalized regression (lasso/elastic net) helps guard against overfitting and multicollinearity with inflammatory markers; alternatively, machine-learning pipelines (gradient boosting, random forests, and stacked ensembles) can capture nonlinear interactions between MALAT1, glycemic indices, and endothelial biomarkers, while SHAP or partial-dependence plots preserve interpretability for clinical deployment [70]. Multi-analyte panels combining MALAT1 with lncRNAs (ANRIL/NEAT1), microRNAs (miR-126/145), and proteins (NT-proBNP, hs-troponin, lipoprotein(a)) tend to yield the greatest net reclassification improvement, especially for **intermediate-risk** diabetics where decision ambiguity is highest [71]. Decision-curve analysis can quantify clinical utility across threshold probabilities, informing whether MALAT1-augmented models justify downstream testing (CT-angiography, CAC scoring) or intensification of statins, SGLT2 inhibitors, and GLP-1 RAs [72]. For translation, prespecified cut-points derived from Youden-index or risk-based thresholds should be externally validated across centers, pre-analytical conditions (plasma vs. exosomes), and ethnic groups, with attention to batch effects and assay harmonization; cost-effectiveness modeling (Markov or microsimulation) should accompany prospective impact studies to ensure system-level value [73]. Ultimately, integrating MALAT1 into **EHR-embedded clinical decision support** with auto-calibration and periodic drift monitoring will be critical to sustain performance as practice patterns and background therapies evolve in T2DM. [69–74]

17. Future Perspectives and Research Directions

Next-generation studies should prioritize **prospective, multi-center cohorts** of T2DM patients with standardized pre-analytical handling to define MALAT1 thresholds for subclinical CAD and to map longitudinal trajectories around acute events, revascularization, and therapy changes. Multi-omic integration—combining MALAT1 with transcriptomic, proteomic, metabolomic, and lipidomic layers—can reveal causal axes (e.g., MALAT1→NF-κB→endothelial activation) and nominate compact diagnostic panels optimized for point-of-care use. Methodologically, platforms such as ddPCR and targeted RNA-seq require cross-laboratory ring trials, external RNA controls, and harmonized normalization to minimize batch effects and enable **calibrated cut-points** deployable across health systems. Interventional science should extend from observational associations to **embedded randomized trials** testing MALAT1-guided care pathways (e.g., triggering CAC scanning or therapy intensification) and **first-in-human oligonucleotide modulation** with vascular target engagement readouts. Finally, inclusive recruitment across sexes, ethnicities, kidney function strata, and obesity classes, coupled with cost-effectiveness and implementation science, will be essential to ensure equitable, real-world impact of MALAT1-informed diagnostics in diabetic cardiovascular prevention. [75–81]

Conclusion

Long non-coding RNA MALAT1 has emerged as a pivotal molecular link connecting the metabolic dysregulation of type 2 diabetes mellitus (T2DM) with the vascular injury underlying coronary artery disease (CAD). Through its regulatory effects on endothelial inflammation, oxidative stress, and smooth muscle proliferation, MALAT1 not only reflects the pathological processes driving atherosclerosis but also holds tangible diagnostic and prognostic value. The reproducibility of its elevation in diabetic patients with CAD across multiple studies, coupled with its stability in plasma and exosomes, underscores its potential as a clinically useful biomarker.

Advances in RNA quantification technologies and bioinformatics now enable precise and scalable measurement of MALAT1, paving the way for its integration into predictive models alongside traditional risk factors. Moreover, its responsiveness to pharmacologic and metabolic interventions suggests value as a dynamic indicator of vascular risk modulation. However, translation into clinical practice will depend on multicenter standardization, longitudinal validation, and demonstration of incremental benefit over established biomarkers.

Overall, MALAT1 represents a promising frontier in molecular cardiology — a bridge between transcriptomic insight and precision diagnostics for diabetic coronary artery disease. Its incorporation into risk assessment paradigms could refine early detection, guide therapeutic strategies, and ultimately improve cardiovascular outcomes in patients with T2DM.

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