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Thrombospondin-1 as a Biomarker in Coronary Artery Disease: Pathophysiological Roles and Clinical Implications

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ABSTRACT

Background: Coronary artery disease (CAD) remains a dominant cause of morbidity and mortality globally, driven by complex mechanisms involving atherosclerosis, inflammation, and vascular remodeling. While advances in diagnostic modalities and therapeutics have improved patient outcomes, the need for sensitive, specific, and easily measurable biomarkers to assess disease severity and predict clinical outcomes persists. Thrombospondin-1 (TSP-1), a matricellular glycoprotein abundantly expressed in the cardiovascular system, has gained increasing attention for its multifaceted role in the pathogenesis of CAD. Acting at the intersection of extracellular matrix remodeling, platelet activation, vascular inflammation, and endothelial dysfunction, TSP-1 contributes to the initiation, progression, and destabilization of atherosclerotic plaques. This review aims to critically examine the role of TSP-1 as a biomarker in coronary artery disease, with a focus on its molecular structure, regulation, and pathophysiological actions within the coronary vasculature. We summarize current knowledge on the clinical associations between circulating TSP-1 levels and the extent or severity of CAD, as assessed by angiographic scoring systems and clinical outcomes. The review discusses the potential mechanisms linking elevated TSP-1 to plaque burden, coronary thrombosis, and adverse cardiovascular events, as well as its interaction with traditional risk factors such as diabetes, hypertension, and dyslipidemia. Furthermore, the review evaluates the strengths and limitations of using TSP-1 in clinical practice for risk stratification, prognosis, and guiding therapeutic interventions in CAD. The integration of TSP-1 with established and emerging biomarkers is explored in the context of enhancing the accuracy of disease assessment and improving personalized management strategies. **In conclusion,** TSP-1 emerges as a promising biomarker and mediator in the complex pathophysiology of coronary artery disease. Its measurement in serum or plasma holds potential to complement traditional diagnostic and prognostic tools, although further large-scale, prospective studies are needed to confirm its clinical utility and to address current analytical and biological challenges.

Keywords: *Thrombospondin-1, Coronary Artery Disease, Clinical Implications*

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Introduction

Coronary artery disease (CAD) stands as the leading cause of death and disability worldwide, reflecting the persistent global burden of atherosclerotic cardiovascular disease despite notable advances in medical and interventional therapies [1]. CAD is characterized by progressive atherosclerosis of the coronary arteries, resulting in impaired myocardial perfusion and a wide spectrum of clinical manifestations, from stable angina to acute coronary syndromes [2]. Early and accurate risk stratification remains central to improving patient outcomes, yet existing diagnostic and prognostic tools—while valuable—are not without limitations. Traditional risk factors, imaging modalities, and angiographic scores do not fully capture the underlying biological complexity or predict individual disease trajectories in CAD patients [3].

Recent research has shifted focus toward the identification of novel circulating biomarkers that mirror ongoing pathophysiological processes within the coronary vasculature. Thrombospondin-1 (TSP-1), a multifunctional matricellular glycoprotein, has emerged as a key regulator of cardiovascular homeostasis and disease. TSP-1 is actively involved in extracellular matrix (ECM) remodeling, platelet activation, inflammation, endothelial dysfunction, and angiogenesis—processes fundamental to the initiation, progression, and complication of atherosclerotic lesions [4,5]. Experimental and clinical studies have increasingly linked TSP-1 to the pathogenesis of coronary artery disease, highlighting its potential role in both structural vascular changes and acute thrombotic events [6].

Despite these insights, the precise clinical utility of TSP-1 as a biomarker in CAD remains underexplored. Conflicting evidence exists regarding its association with disease severity, plaque instability, and cardiovascular outcomes, while the interplay between TSP-1 and conventional risk factors or comorbidities requires further clarification [7]. Additionally, analytical variability in TSP-1 measurement and a lack of standardized reference ranges pose significant challenges to its routine application in clinical practice.

The aim of this review is to synthesize current evidence on the biological functions and clinical significance of TSP-1 in coronary artery disease. Specifically, we seek to elucidate the mechanistic pathways by which TSP-1 contributes to coronary atherogenesis, summarize the relationship between circulating TSP-1 levels and CAD severity, and critically evaluate its potential as a diagnostic and prognostic biomarker. By integrating recent advances in both basic science and clinical research, this review highlights existing knowledge gaps and outlines future directions for translational studies targeting TSP-1 in the context of coronary artery disease [8].

1. Thrombospondin-1: Structure and Biological Functions

Thrombospondin-1 (TSP-1) is a large, multifunctional glycoprotein belonging to the thrombospondin family, which comprises five structurally related members. TSP-1 is primarily produced by platelets, endothelial cells, vascular smooth muscle cells, and various immune cells in response to vascular

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injury, hypoxia, and inflammation. Its multi-domain structure enables it to interact with a wide range of extracellular matrix components, growth factors, cytokines, and cell surface receptors, orchestrating complex processes such as cell adhesion, migration, proliferation, and apoptosis. These interactions position TSP-1 as a key mediator at the interface of vascular homeostasis and pathological remodeling [1].

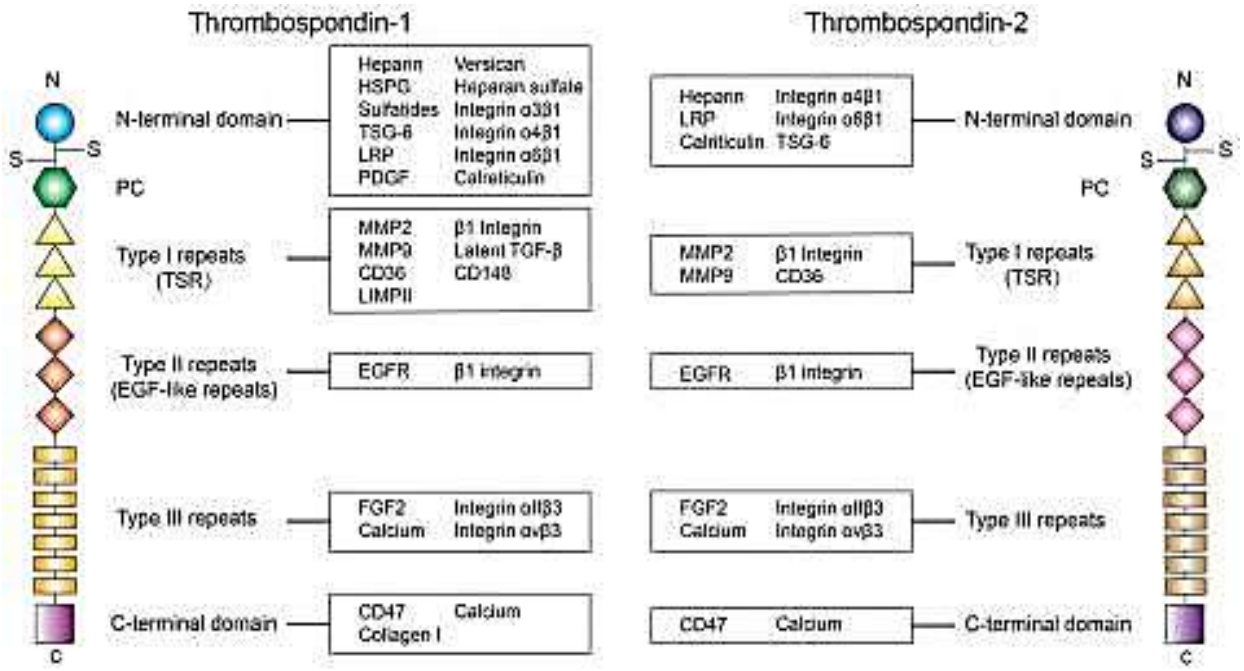

Figure (1) Structural diagrams of TSP-1 and TSP-2. Ligands demonstrated to interact with each domain are summarized in the boxes. At present, the understanding of the interaction of ligands of each domain in TSP-1 is more advanced compared with that of TSP-2, and numerous molecules that interact with TSP-2 remain to be identified. From the current results, a number of interacting molecules are shared between TSP-1 and TSP-2. However, certain particular ligands, including TGF-β, may only function when it interacts with TSP-1 instead of TSP-2 [1].

2. Regulation and Expression of TSP-1 in the Vasculature

TSP-1 expression is tightly regulated by diverse physiological and pathological stimuli, including cytokines, oxidative stress, hyperglycemia, and hypoxia. Transcriptional control involves several factors, such as transforming growth factor-beta (TGF-β), hypoxia-inducible factors (HIFs), and nuclear factor-kappa B (NF-κB). Notably, platelets serve as a major reservoir, rapidly releasing pre-formed TSP-1 upon activation, thereby amplifying its effects in acute vascular injury or thrombosis. The dynamic regulation of TSP-1 reflects its pivotal role in both acute and chronic phases of vascular disease [2,3].

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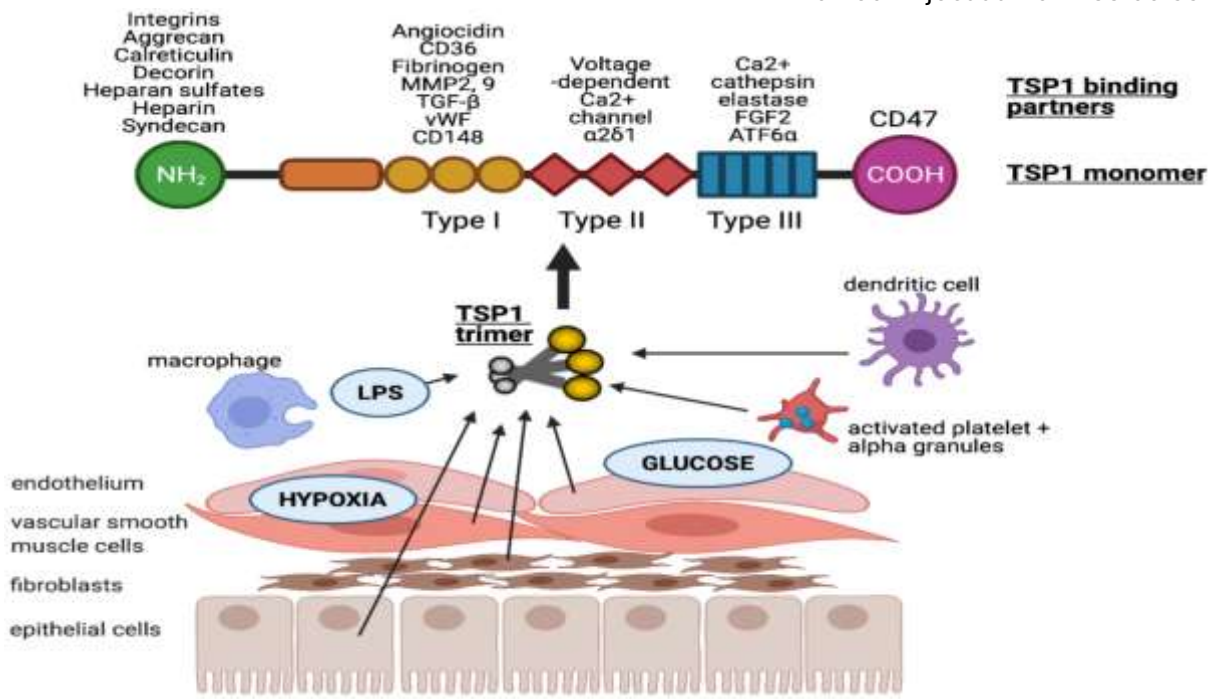

Figure (2) shows that TSP1 is produced by many nucleated cells, including antigen presenting cells (macrophages and dendritic cells) and parenchymal cells (endothelial, vascular smooth muscle and epithelial cells, as well as fibroblasts). TSP1 is up regulated in response to injurious stimuli such as low oxygen tension (hypoxia), hyperglycaemia and lipopolysaccharide (LPS). It is typically secreted in trimeric form which is required for activity. Each monomer consists of multiple binding domains capable of interacting with a wide variety of factors [2].

3. TSP-1 and Extracellular Matrix Remodeling in Atherogenesis

A hallmark of atherosclerosis is the disruption and remodeling of the extracellular matrix (ECM) within the arterial wall. TSP-1 facilitates ECM organization by binding to proteoglycans, integrins, and matrix metalloproteinases (MMPs), modulating the balance between matrix deposition and degradation. This action not only impacts the structural integrity of the vessel wall but also influences the migration and phenotypic modulation of vascular smooth muscle cells—key events in plaque development and progression [4,5].

4. Platelet Activation and Thrombosis: TSP-1 in Acute Coronary Syndromes

Platelet-derived TSP-1 plays a direct role in thrombus formation and stabilization at sites of plaque disruption or endothelial injury. By promoting platelet aggregation and activating integrin receptors, TSP-1 amplifies thrombotic responses central to the pathogenesis of acute coronary syndromes. Experimental data have shown increased local and systemic TSP-1 levels following myocardial infarction, with correlations to major adverse cardiovascular events and outcomes [6,7].

5. TSP-1 as a Modulator of Endothelial Function and Vascular Tone

TSP-1 modulates endothelial function by interacting with cell surface receptors such as CD36 and CD47. Through these pathways, it inhibits nitric oxide (NO) signaling, diminishes cyclic guanosine

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monophosphate (cGMP) levels, and suppresses the vasodilatory capacity of endothelial cells. The resultant endothelial dysfunction is a fundamental precursor to atherosclerotic lesion formation, fostering an environment conducive to inflammation, leukocyte adhesion, and vascular constriction [8,9].

6. Inflammation and Immune Regulation: TSP-1 in Coronary Plaques

Inflammation is a central driver of CAD, and TSP-1 is intimately involved in immune cell recruitment and activation within the atherosclerotic milieu. TSP-1 enhances the adhesion and transmigration of monocytes and other inflammatory cells through the endothelium, while also modulating cytokine signaling and matrix degradation. These actions facilitate plaque growth, destabilization, and potential rupture—the primary cause of acute myocardial infarction [10,11].

7. TSP-1 in Angiogenesis and Neovascularization of Atherosclerotic Lesions

While angiogenesis can aid tissue repair, excessive or aberrant neovascularization within atherosclerotic plaques contributes to intraplaque hemorrhage and instability. TSP-1 exhibits context-dependent anti-angiogenic properties by binding to and inhibiting vascular endothelial growth factor (VEGF) and other pro-angiogenic factors. In coronary lesions, high TSP-1 levels may limit compensatory neovascularization, thereby influencing plaque composition and vulnerability [12,13].

8. Clinical Evidence Linking TSP-1 to Coronary Artery Disease Severity

Numerous clinical studies have examined the association between circulating TSP-1 levels and the severity of coronary artery disease. Elevated serum or plasma TSP-1 has been correlated with higher Gensini and SYNTAX scores, increased plaque burden, and adverse cardiovascular outcomes. These relationships persist even after adjustment for conventional risk factors, supporting TSP-1's independent prognostic value in CAD populations [14,15].

9. TSP-1 and Plaque Instability: Insights from Acute Coronary Syndromes

Patients presenting with acute coronary syndromes, including ST-elevation myocardial infarction (STEMI) and unstable angina, frequently exhibit elevated TSP-1 levels during the acute phase. Declines in TSP-1 following successful revascularization have been linked to improved clinical outcomes, while persistently high levels may predict recurrent ischemic events. This suggests a dynamic relationship between TSP-1 release, plaque instability, and myocardial injury [16,17].

10. Interplay Between TSP-1, Diabetes, and Coronary Atherosclerosis

Diabetes mellitus is a well-established risk factor for CAD and is associated with enhanced expression of TSP-1 in the vascular wall. Hyperglycemia, oxidative stress, and chronic low-grade inflammation characteristic of diabetes upregulate TSP-1, further promoting endothelial dysfunction, vascular inflammation, and adverse remodeling. This interplay may partly explain the accelerated and more severe coronary atherosclerosis seen in diabetic patients [18,19].

11. Hypertension and TSP-1: Synergistic Effects on Vascular Damage

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Hypertension exacerbates atherosclerotic disease through mechanical stress and endothelial injury. Studies suggest that hypertensive patients with CAD exhibit higher TSP-1 levels compared to normotensive individuals, indicating a potential synergistic effect in accelerating vascular damage. TSP-1 may amplify hypertensive remodeling and fibrosis, compounding the risk of coronary events [20].

12. Dyslipidemia, Lipoproteins, and TSP-1 in Coronary Pathology

Dyslipidemia, particularly elevated LDL and triglycerides, is integral to coronary atherogenesis. TSP-1 interacts with modified lipoproteins and may facilitate their retention and uptake within the vascular intima, contributing to foam cell formation and plaque development. The connection between lipid abnormalities and TSP-1 underscores its multifactorial involvement in the progression of CAD [21].

13. Genetic Polymorphisms of TSP-1 and Susceptibility to CAD

Emerging evidence highlights the impact of genetic variants in the TSP-1 gene on individual susceptibility to myocardial infarction and coronary artery disease. Specific polymorphisms affecting TSP-1 expression or function have been linked to increased risk of acute coronary events, suggesting a heritable component to TSP-1-mediated vascular pathology [22,23].

14. TSP-1 as a Biomarker for Risk Stratification in CAD

As a circulating biomarker, TSP-1 offers promise for improving risk stratification beyond traditional measures. Its levels may reflect active vascular injury, ongoing inflammation, and plaque instability, complementing established scores such as Gensini or SYNTAX. The integration of TSP-1 measurement with conventional risk assessment could enhance the early identification of high-risk patients and guide personalized therapeutic strategies [24,25].

15. Analytical Considerations and Challenges in Measuring TSP-1

Despite its potential, several challenges limit the routine clinical use of TSP-1 as a biomarker. Pre-analytical variables, such as sample handling and platelet activation during blood collection, can significantly influence measured concentrations. Furthermore, a lack of standardized assays and reference ranges hampers comparability between studies. Addressing these methodological issues is essential for the future adoption of TSP-1 in clinical practice [26,27].

16. TSP-1 and Response to Revascularization Therapies

Interventional studies suggest that serum TSP-1 levels change in response to percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Declining TSP-1 following successful revascularization has been associated with better clinical outcomes and fewer recurrent events, indicating its potential as a dynamic marker for monitoring therapeutic efficacy in CAD patients [28].

17. Therapeutic Implications: Targeting TSP-1 Pathways in CAD

Given its central role in vascular pathology, TSP-1 and its signaling partners represent potential therapeutic targets in CAD. Strategies aimed at modulating TSP-1 expression or blocking its

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interaction with key receptors (such as CD36 or CD47) may attenuate inflammation, thrombosis, and adverse remodeling. Preclinical studies provide a rationale for developing TSP-1–targeted therapies, though translation into clinical practice remains in early stages [29,30].

18. Integration of TSP-1 with Multi-Biomarker Panels

No single biomarker is likely sufficient for comprehensive risk assessment in CAD. Combining TSP-1 with other established markers of inflammation, thrombosis, and endothelial dysfunction—such as CRP, fibrinogen, or interleukins—may improve diagnostic accuracy and prognostic value. Multi-marker strategies are increasingly favored in the era of personalized cardiovascular medicine [31,32].

19. Future Perspectives: TSP-1 in Precision Cardiovascular Medicine

The ongoing shift toward precision medicine in cardiology necessitates biomarkers that provide actionable insights into individual disease mechanisms and treatment response. TSP-1, with its broad mechanistic links to atherosclerosis, thrombosis, and inflammation, holds promise as part of an integrated precision approach. Further research is needed to clarify its role in diverse patient populations and to validate its predictive capacity in prospective, large-scale studies [33,34].

20. Conclusions and Research Directions

In summary, thrombospondin-1 represents a multifaceted biomarker and mechanistic player in the pathogenesis and progression of coronary artery disease. Its measurement offers a window into active vascular remodeling, plaque instability, and thrombotic risk. While significant challenges remain—including assay standardization, biological variability, and integration with clinical workflows—the potential of TSP-1 to improve CAD diagnosis, prognosis, and management is increasingly recognized. Continued translational and clinical research will be crucial to fully realize the value of TSP-1 in the landscape of cardiovascular disease [35].

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