

Retinol-Binding Protein-4 and Cardiovascular Disease Risk in Type 2 Diabetes: A Review Article

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Abstract

Type 2 diabetes mellitus (T2DM) is a major metabolic disorder characterized by insulin resistance, progressive β -cell dysfunction, chronic hyperglycemia, and a high burden of cardiovascular disease (CVD). Increasing evidence indicates that adipose tissue is an endocrine organ whose secretory products, or adipokines, participate in the metabolic and vascular abnormalities linking obesity and T2DM to cardiovascular complications. Retinol-binding protein 4 (RBP4) is a 21-kDa lipocalin traditionally recognized as the principal circulating carrier of retinol, but it is now also regarded as an adipokine with potential metabolic and cardiovascular actions. This review summarizes the biological characteristics of RBP4 and critically examines its relationships with obesity, visceral adiposity, insulin resistance, dyslipidemia, vascular inflammation, endothelial dysfunction, atherosclerosis, hypertension, coronary artery disease, heart failure, and diabetic cardiomyopathy. Mechanistically, RBP4 may influence glucose homeostasis through retinol-dependent pathways involving retinoic acid signaling and hepatic gluconeogenesis, while retinol-independent pathways may involve STRA6-related signaling, macrophage activation, Toll-like receptor pathways, JNK/NF- κ B signaling, and inflammatory cytokine production. RBP4 has also been associated with atherogenic lipid profiles, macrophage foam-cell formation, oxidative stress, vascular smooth-muscle responses, impaired nitric-oxide signaling, and myocardial inflammatory injury. Human studies generally support associations between higher circulating RBP4 and cardiometabolic risk, although results are heterogeneous and may be influenced by adiposity distribution, renal function, metabolic status, assay methodology, and population characteristics. Therefore, RBP4 represents a biologically plausible and potentially useful biomarker of cardiometabolic risk, but its independent predictive value and therapeutic relevance require further prospective and mechanistic investigation.

Keywords: retinol-binding protein 4 (RBP4); type 2 diabetes mellitus (T2DM); cardiovascular disease (CVD); atherosclerosis; endothelial dysfunction.

Introduction

T2DM has become one of the most important chronic diseases worldwide, driven by the interaction of genetic susceptibility, obesity, sedentary behavior, dietary factors, aging, and environmental exposures. Its pathophysiology involves insulin resistance, impaired β -cell compensation, abnormal hepatic glucose production, altered lipid metabolism, and chronic low-grade inflammation [1-3]. The clinical importance of T2DM extends beyond hyperglycemia because persistent metabolic disturbance promotes microvascular and macrovascular complications, with CVD representing a major determinant of morbidity and mortality (Fig 1) [4].

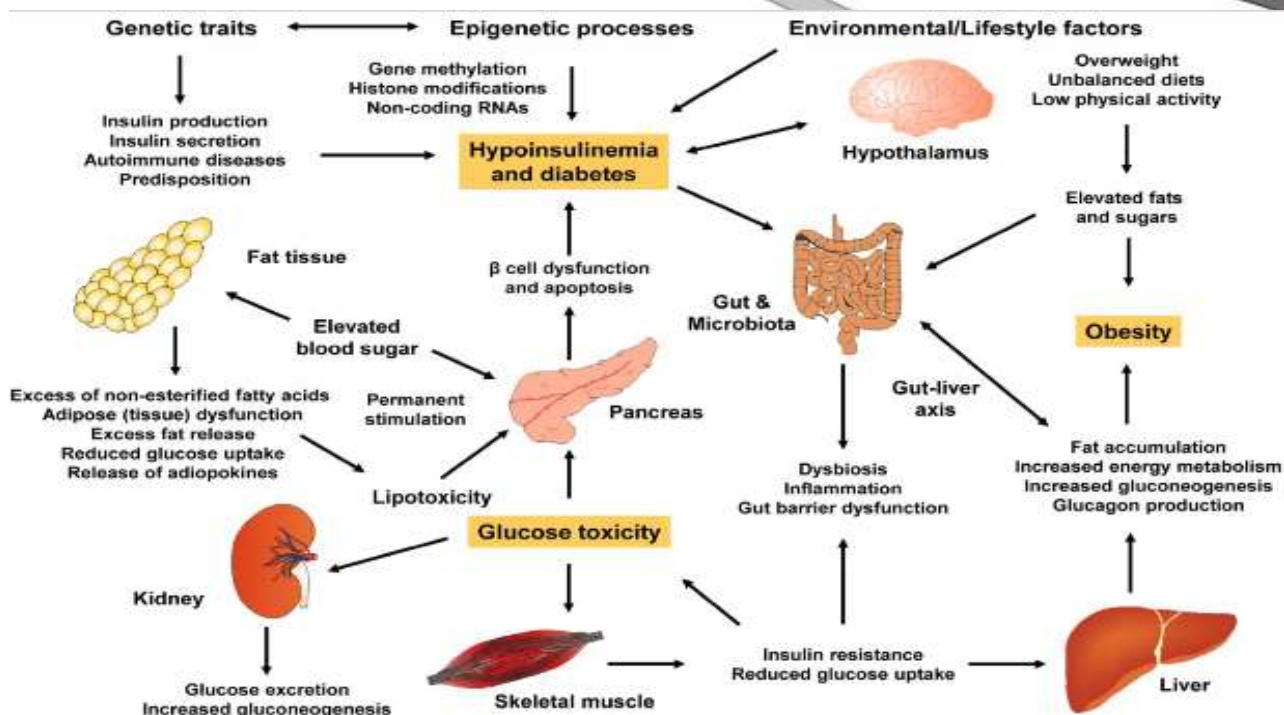


Figure (1): Multifactorial pathophysiology of type 2 DM [4].

The growing recognition of adipose tissue as an endocrine organ has changed the understanding of T2DM and its cardiovascular complications. Adipocytes and other cells within adipose tissue release numerous adipokines that regulate energy metabolism, insulin sensitivity, inflammation, vascular function, and inter-organ communication [5]. Visceral adipose tissue is particularly relevant because its expansion is associated with adipose inflammation, altered free-fatty-acid flux, ectopic lipid deposition, and an adverse cardiometabolic phenotype.

RBP4 occupies a distinctive position within this framework. It is a circulating retinol transporter predominantly produced by the liver and, to a clinically relevant extent, by adipose tissue. Beyond vitamin A transport, experimental and clinical evidence has implicated RBP4 in insulin resistance, dyslipidemia, inflammation, vascular dysfunction, and cardiovascular disease [6, 7]. The present review therefore focuses on the biological and clinical pathway linking RBP4 to T2DM and cardiovascular risk, with particular attention to mechanisms that could explain its potential value as a biomarker.

Type 2 Diabetes Mellitus and Cardiovascular Risk

T2DM develops through progressive interaction between insulin resistance and β -cell dysfunction. Early insulin resistance is often compensated by increased insulin secretion; with disease progression, β -cell compensation becomes inadequate and chronic hyperglycemia develops. Skeletal muscle, liver, and adipose tissue are the principal sites of insulin resistance, with impaired muscle glucose uptake, excessive hepatic glucose production, and increased adipose lipolysis contributing to the metabolic phenotype [1, 2].

Obesity, especially central and visceral adiposity, intensifies these abnormalities. Enlarged adipocytes, immune-cell infiltration, altered adipokine secretion, increased free fatty acids, and ectopic lipid deposition create an inflammatory and metabolically unfavorable environment. These changes can worsen insulin signaling and promote dyslipidemia, hypertension, endothelial dysfunction, and atherosclerosis. Thus, the relationship between obesity, T2DM, and CVD is not simply explained by excess body mass but by qualitative dysfunction of adipose tissue and its secretory activity (Fig 2) [5, 8].

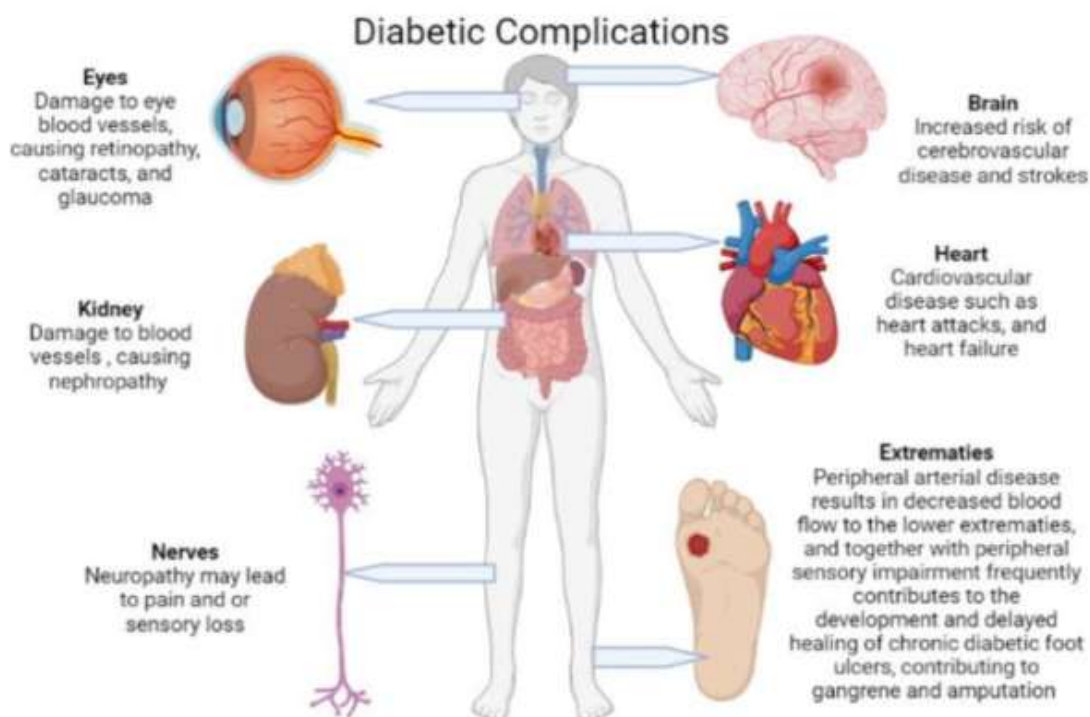


Figure (2): Diabetic complications [5].

Diabetes accelerates atherosclerotic cardiovascular disease through multiple interacting mechanisms. Hyperglycemia promotes oxidative stress, advanced glycation, protein kinase C activation, inflammatory signaling, and endothelial injury, while insulin resistance and dyslipidemia increase the availability of atherogenic lipoproteins and free fatty acids. Consequently, diabetic patients have increased risks of coronary artery disease, myocardial infarction, stroke, peripheral arterial disease, and heart failure. This complex pathophysiology provides a rationale for investigating circulating biomarkers that integrate metabolic and vascular risk rather than reflecting glycemia alone [4].

Adipose Tissue as an Endocrine Interface

Adipose tissue is composed not only of mature adipocytes but also preadipocytes, endothelial cells, fibroblasts, and immune cells. Collectively, these cells release adipokines, cytokines, chemokines, and metabolites that participate in autocrine, paracrine, and endocrine signaling. Adipose tissue therefore functions as an inter-organ communication hub linking nutritional status to the liver, skeletal muscle, pancreas, cardiovascular system, and central nervous system [5]. In metabolically healthy adipose tissue, storage and endocrine functions remain relatively balanced. In obesity, particularly visceral obesity, adipocyte hypertrophy and tissue hypoxia promote inflammatory-cell recruitment and abnormal adipokine secretion. The resulting increase in free-fatty-acid delivery and inflammatory signaling can impair insulin action and promote hepatic steatosis, dyslipidemia, and vascular injury. RBP4 is one of the adipokines proposed to participate in this process, although circulating concentrations do not consistently correlate with BMI alone. This suggests that adipose distribution, tissue dysfunction, hepatic metabolism, or other biological determinants may be more important than total fat mass [9, 10].

RBP4: Structure, Sources, and Physiological Function

RBP4 is a member of the lipocalin family and is approximately 21 kDa in molecular mass. It is encoded by the RBP4 gene on chromosome 10 and has a characteristic lipocalin fold that permits binding of small hydrophobic molecules. Its classical physiological function is the transport of retinol (vitamin A) from hepatic stores to extrahepatic tissues [6, 7]. Retinol is predominantly stored in the liver. In the circulation, RBP4 binds retinol and forms a complex with transthyretin (TTR), which increases molecular stability and reduces renal filtration. At target tissues, retinol delivery involves the membrane receptor stimulated by retinoic acid 6 (STRA6) and downstream intracellular pathways. Retinoids subsequently influence gene transcription through retinoic acid receptors and retinoid X receptors, providing a mechanistic link between vitamin A metabolism and metabolic regulation [7].

Although hepatocytes represent the principal source of circulating RBP4, adipose tissue is an important additional source, particularly in the setting of adipose dysfunction. RBP4 expression has also been detected in other tissues, supporting the concept that its circulating concentration reflects more than a single organ process. This distinction is important when interpreting RBP4 as a biomarker because serum concentration may be influenced by hepatic function, adiposity distribution, renal handling, metabolic state, and inflammatory signaling (Fig 3) [9, 10].

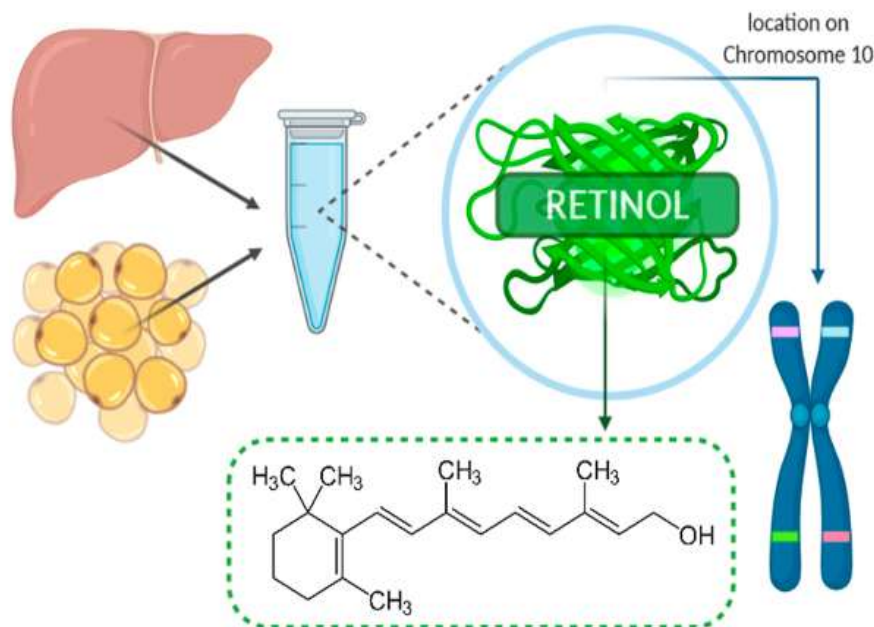


Figure (3): Retinol-binding protein 4 (RBP4) [7].

RBP4 and Type 2 Diabetes Mellitus

Association with Insulin Resistance

Elevated RBP4 has been associated with insulin resistance in multiple experimental and clinical studies. The relationship is biologically plausible because RBP4 can influence hepatic glucose production, skeletal-muscle insulin signaling, adipose lipolysis, and inflammation. In humans, circulating RBP4 has been related to impaired glucose disposal and altered suppression of lipolysis, while experimental work has demonstrated direct effects on metabolic signaling [10, 11].

One important pathway is hepatic. RBP4-related retinoid signaling may increase expression of phosphoenolpyruvate carboxykinase (PEPCK), a key gluconeogenic enzyme, thereby favoring hepatic glucose production and reducing the ability of insulin to suppress endogenous glucose output [12]. A second pathway involves skeletal muscle, where RBP4-associated signaling can interfere with insulin receptor substrate-1 and phosphatidylinositol-3-kinase signaling, potentially impairing glucose uptake. Together, these mechanisms provide a link between altered retinol transport and systemic insulin resistance [10].

RBP4 may also promote insulin resistance through adipose-tissue inflammation. Experimental studies indicate that RBP4 can activate antigen-presenting cells and macrophages, resulting in production of inflammatory mediators that interfere with insulin signaling and enhance lipolysis. Increased free-fatty-acid release can further stimulate hepatic glucose production and reduce peripheral glucose utilization, creating a self-reinforcing cycle of insulin resistance and metabolic inflammation (Fig 4) [11].

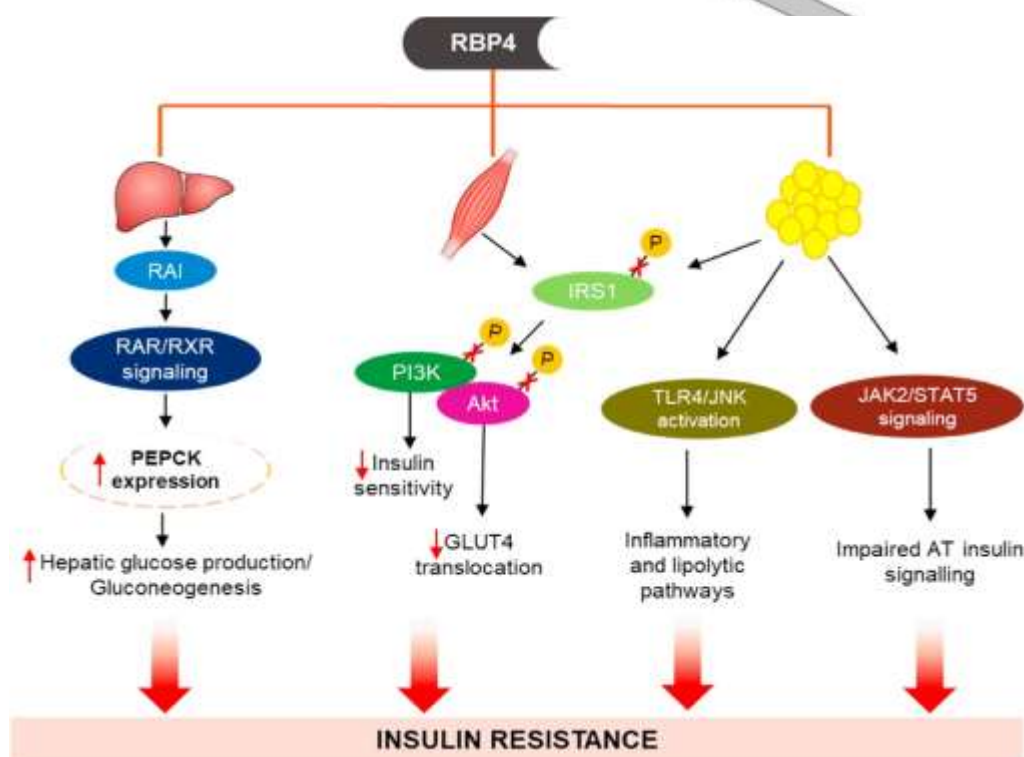


Figure (4): Potential effects of RBP4 on different tissues contributing to the pathogenesis of insulin resistance through retinol-dependent mechanisms [11].

Retinol-Dependent and Retinol-Independent Signaling

The metabolic effects of RBP4 are not necessarily dependent on retinol transport alone. Retinol-dependent mechanisms involve altered retinoid availability and retinoic-acid signaling, with effects on hepatic gluconeogenesis and lipid metabolism. In contrast, retinol-independent mechanisms include direct or indirect activation of immune and inflammatory pathways. RBP4 can activate antigen-presenting cells and promote cytokine production, while interaction with Toll-like receptor pathways can amplify innate immune signaling and inflammasome activation [13, 14].

This dual mechanism is clinically relevant because it explains why RBP4 may remain associated with metabolic disease even when conventional measures of adiposity do not fully account for the association. It also suggests that RBP4 may represent both a marker of adipose dysfunction and a mediator of metabolic inflammation rather than merely a passive consequence of obesity [15].

RBP4 and Pancreatic β -Cell Function

Emerging evidence suggests that the relationship between RBP4 and T2DM may extend beyond insulin resistance to pancreatic β -cell biology. Recent evidence has linked RBP4 with β -cell mass and function, although the underlying pathways remain incompletely defined [16]. This possibility is important because progressive β -cell dysfunction is a defining feature of T2DM and could provide an additional route through which RBP4 contributes to disease development. However, current evidence is less established than the association between RBP4 and insulin resistance, and further mechanistic studies are needed.

RBP4, Obesity, and Visceral Adiposity

RBP4 concentrations frequently increase in obesity, but the association is not uniform. Some studies demonstrate higher RBP4 in obese individuals, whereas others report weak or absent relationships with BMI or total fat mass. This apparent inconsistency may be explained by differences in fat distribution. Visceral adipose tissue is metabolically more active and more strongly associated with insulin resistance and cardiovascular risk than subcutaneous fat. RBP4 expression from dysfunctional adipose tissue may therefore be more closely related to visceral adiposity than to total body weight [9, 10].

RBP4 may consequently act as a molecular link between visceral adiposity and cardiometabolic disease. Increased visceral fat is accompanied by enhanced lipolysis, higher free-fatty-acid flux to the liver, adipose inflammation, and

ectopic lipid accumulation. RBP4-associated changes could reinforce these processes, contributing to hepatic insulin resistance and an atherogenic metabolic profile [17].

RBP4 and Dyslipidemia

Dyslipidemia is a major pathway connecting metabolic disease to atherosclerosis. Several studies have reported positive relationships between circulating RBP4 and triglycerides, while associations with LDL cholesterol, HDL cholesterol, total cholesterol, and lipoprotein subclasses have also been described. In particular, RBP4 has been related to large VLDL and small LDL particles, which are metabolically and atherogenically relevant lipoprotein phenotypes [18, 19].

Experimental and clinical observations suggest that RBP4 may influence lipid handling indirectly through insulin resistance and adipose lipolysis and, potentially, through effects on hepatic lipid metabolism. RBP4 has also been associated with hepatic steatosis, supporting a broader relationship between RBP4, ectopic lipid deposition, and cardiometabolic dysfunction [10, 20]. Nevertheless, lipid associations are not completely consistent across populations, emphasizing the need to interpret RBP4 in the context of the wider metabolic phenotype.

RBP4 and Cardiovascular Disease

Inflammation and Endothelial Dysfunction

Atherosclerosis is increasingly understood as a chronic inflammatory disease in which endothelial activation, lipid accumulation, immune-cell recruitment, and vascular remodeling interact. RBP4 may participate in this process by promoting inflammatory signaling in macrophages and endothelial cells. Experimental studies have linked RBP4 with inflammatory cytokines and adhesion molecules, including TNF- α , IL-1 β , IL-6, MCP-1, ICAM-1, VCAM-1, and E-selectin [6, 21].

Endothelial dysfunction is an early event in atherogenesis and is characterized by impaired nitric-oxide bioavailability, abnormal vascular reactivity, oxidative stress, and increased expression of adhesion molecules. Experimental evidence suggests that RBP4 can interfere with endothelial nitric-oxide signaling and may promote vascular oxidative and inflammatory responses. These mechanisms provide a plausible pathway from increased circulating RBP4 to impaired vascular function before overt cardiovascular disease becomes clinically apparent [6, 22].

Oxidative Stress and Vascular Injury

Oxidative stress provides another potential link between RBP4 and CVD. Excess reactive oxygen species can reduce nitric-oxide availability, activate inflammatory transcription pathways, promote endothelial dysfunction, and facilitate oxidation of atherogenic lipoproteins. RBP4 has been associated with mitochondrial dysfunction and oxidative vascular injury in experimental models. In parallel, RBP4-related inflammatory activation may amplify reactive oxygen species production, creating a feed-forward loop of metabolic and vascular injury [6].

Macrophage Foam Cells and Atherosclerosis

Macrophage foam-cell formation is central to plaque development. RBP4-dependent cholesterol uptake has been shown experimentally to promote macrophage foam-cell formation and accelerate atherosclerotic processes. This pathway is particularly relevant because it links an adipose-derived metabolic signal directly to arterial lipid accumulation [21]. RBP4 may therefore influence atherosclerosis through both indirect metabolic mechanisms—such as insulin resistance and dyslipidemia—and more direct vascular mechanisms involving macrophage lipid handling [23].

Carotid Intima-Media Thickness and Subclinical Atherosclerosis

Carotid intima-media thickness (CIMT) is a non-invasive marker of structural arterial remodeling and subclinical atherosclerosis. In patients with T2DM, higher circulating RBP4 has been associated with increased CIMT, supporting the possibility that RBP4 reflects early vascular injury before clinical cardiovascular events occur [24]. This observation is important for biomarker research because a useful marker may identify vascular risk at an earlier stage than conventional clinical endpoints.

Coronary Artery Disease

Clinical studies have reported associations between circulating RBP4 and the presence or severity of coronary artery disease (CAD). Lambadiari et al. [25] found that serum RBP4 levels were associated with the presence and severity of CAD, while other studies have reported associations with coronary risk factors and atherosclerotic burden. These

findings are consistent with the proposed effects of RBP4 on insulin resistance, dyslipidemia, inflammation, endothelial dysfunction, and foam-cell formation.

However, the evidence is not uniformly positive. Some population studies have not demonstrated an independent association between RBP4 and incident ischemic cardiovascular outcomes after accounting for conventional risk factors. This heterogeneity is important: an association between RBP4 and CVD does not automatically establish causality or prove that RBP4 adds predictive information beyond established clinical risk factors. Differences in population characteristics, renal function, obesity, diabetes duration, medications, and laboratory assays may contribute to discordant findings.

Hypertension and Arterial Stiffness

RBP4 has also been linked to blood-pressure regulation. Experimental evidence suggests effects on vascular nitric-oxide signaling, while clinical studies have reported associations between circulating RBP4 and blood pressure. RBP4 has additionally been associated with arterial stiffness in selected populations [22, 26]. These observations support the concept that RBP4 may influence vascular function beyond atherosclerotic plaque formation.

Heart Failure and Diabetic Cardiomyopathy

Cardiac involvement in diabetes includes ischemic heart disease, heart failure, and diabetic cardiomyopathy. Diabetic cardiomyopathy is characterized by structural and functional myocardial abnormalities that cannot be explained solely by coronary artery disease or hypertension. Insulin resistance, oxidative stress, mitochondrial dysfunction, altered substrate utilization, microvascular disease, and chronic inflammation all contribute to myocardial injury.

RBP4 may participate in these processes. Experimental work has linked RBP4 to TLR4/MyD88 signaling and cardiomyocyte hypertrophy, while clinical studies have reported higher RBP4 in cardiovascular conditions including heart failure and diabetic cardiomyopathy [27, 28]. In elderly patients with chronic heart failure, circulating RBP4 has also shown potential prognostic value for cardiovascular events [29]. These findings are promising but should be interpreted cautiously because heart failure itself can alter metabolic and renal physiology, potentially affecting circulating RBP4.

Integrated Pathophysiological Model

The available evidence supports an integrated model in which adipose-tissue dysfunction, rather than isolated hyperglycemia, provides the central context for RBP4 elevation. Visceral adiposity and metabolic inflammation may increase RBP4 production or circulating concentrations. Higher RBP4 may then contribute to hepatic insulin resistance, impaired skeletal-muscle glucose disposal, adipose lipolysis, and inflammatory activation. The resulting increase in free fatty acids and cytokine signaling can worsen insulin resistance and promote dyslipidemia [30].

At the vascular level, RBP4-associated inflammation, oxidative stress, endothelial dysfunction, impaired nitric-oxide signaling, and macrophage cholesterol uptake may accelerate atherogenesis. At the cardiac level, inflammatory and TLR-dependent pathways may contribute to myocardial remodeling and dysfunction. The overall pathway can therefore be conceptualized as: visceral adipose dysfunction → increased/altered RBP4 signaling → insulin resistance and inflammatory activation → dyslipidemia and endothelial injury → atherosclerosis and myocardial dysfunction. This framework explains why RBP4 is potentially relevant to both metabolic disease and cardiovascular risk [6, 7].

Table 1. Major biological pathways linking RBP4 with cardiometabolic disease

Pathway	Proposed effect of RBP4	Potential clinical consequence
Hepatic retinoid signaling	Increased retinoid-regulated gluconeogenic activity and impaired insulin suppression of hepatic glucose output	Hyperglycemia and hepatic insulin resistance
Skeletal-muscle signaling	Interference with IRS-1/PI3K-related insulin signaling	Reduced peripheral glucose disposal
Adipose inflammation	Macrophage/immune activation and inflammatory cytokine release	Insulin resistance and increased lipolysis
Lipid metabolism	Association with triglycerides, VLDL/small LDL phenotypes and ectopic lipid accumulation	Atherogenic dyslipidemia
Endothelial signaling	Oxidative stress, inflammatory	Endothelial dysfunction and

	activation and impaired nitric-oxide signaling	hypertension
Macrophage cholesterol uptake	Enhanced foam-cell formation	Atherosclerotic plaque development
Cardiac inflammatory signaling	TLR4/MyD88-related and other inflammatory pathways	Cardiomyocyte hypertrophy/remodeling and heart failure risk

Clinical Significance of RBP4 as a Biomarker

RBP4 has several characteristics that make it attractive as a candidate biomarker: it is measurable in blood, biologically linked to metabolic and vascular pathways, and associated in several studies with obesity-related metabolic dysfunction, insulin resistance, atherosclerosis, CAD, heart failure, and diabetic cardiovascular phenotypes. Associations with CIMT and cardiovascular events further suggest potential value for risk stratification [24, 29].

Nevertheless, several issues limit immediate clinical implementation. First, RBP4 concentrations are influenced by multiple biological determinants, including adiposity distribution, hepatic metabolism, renal handling, retinol status, and inflammation. Second, assays differ in analytical characteristics and may detect different molecular forms or complexes. Third, observational associations do not establish whether RBP4 is causally responsible for cardiovascular disease or simply reflects underlying metabolic dysfunction. Fourth, evidence for incremental predictive value beyond established risk factors remains insufficiently consistent.

Accordingly, RBP4 should currently be regarded as a promising research biomarker rather than a replacement for established cardiovascular risk assessment. Its greatest potential may lie in multimarker strategies that integrate RBP4 with glycemic indices, lipid profiles, blood pressure, adiposity measures, renal function, inflammatory markers, and imaging measures of subclinical atherosclerosis.

Therapeutic and Translational Perspectives

If RBP4 is confirmed to have a causal role in cardiometabolic disease, it could represent a therapeutic target in addition to a biomarker. Preclinical studies have investigated non-retinoid RBP4 antagonists and have demonstrated effects on metabolic phenotypes, providing proof of concept for pharmacological modulation [31]. However, RBP4 has an established physiological role in vitamin A transport, and indiscriminate inhibition could potentially disturb retinoid homeostasis. Therapeutic strategies would therefore need to separate pathological signaling from essential retinoid transport.

From a clinical perspective, interventions that reduce visceral adiposity, improve insulin sensitivity, correct dyslipidemia, and suppress chronic metabolic inflammation may also modify RBP4 concentrations. Whether a reduction in RBP4 independently translates into fewer cardiovascular events remains unknown. Prospective intervention studies are therefore required before RBP4-directed treatment can be considered clinically relevant.

Current Evidence Gaps and Future Research

Several gaps remain. Large prospective cohorts are needed to determine whether RBP4 independently predicts incident myocardial infarction, stroke, heart failure, and cardiovascular mortality after comprehensive adjustment for established risk factors. Studies should also clarify whether the association differs according to sex, age, obesity phenotype, diabetes duration, renal function, retinol status, and medication use.

Standardization of RBP4 measurement is another priority. Harmonized assays and clearly defined reference ranges would improve comparison across studies. Mechanistic studies should distinguish retinol-dependent from retinol-independent signaling and identify which molecular forms of RBP4 are most biologically active. Finally, intervention studies should determine whether changing RBP4 itself modifies cardiovascular outcomes or whether it is primarily a marker of broader adipose and metabolic dysfunction.

Conclusion

RBP4 has evolved from being viewed primarily as a retinol transport protein to being recognized as a potentially important adipokine at the interface of metabolism, inflammation, and vascular biology. The literature reviewed in the present thesis supports a biologically plausible association between elevated RBP4 and insulin resistance, visceral adiposity, dyslipidemia, endothelial dysfunction, atherosclerosis, coronary artery disease, and selected cardiac complications. Mechanistically, RBP4 may act through both retinol-dependent pathways affecting glucose and lipid metabolism and retinol-independent inflammatory pathways involving immune-cell activation, TLR signaling, oxidative stress, and vascular injury.

Despite these promising findings, the clinical significance of RBP4 remains incompletely established because associations are heterogeneous and may be confounded by adiposity, renal function, metabolic status, and other cardiovascular risk factors. RBP4 therefore represents a promising candidate biomarker and possible therapeutic target, but not yet a stand-alone clinical tool. Future standardized, prospective, and mechanistic studies should determine whether RBP4 adds meaningful predictive value beyond conventional risk factors and whether modifying RBP4-related pathways can reduce cardiovascular complications in patients with T2DM.

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