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Review Article

Biochemistry Section

Retinol-binding Protein 4 and Diabetes Mellitus: A Review on Current Understanding and Clinical Importance

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ABSTRACT

The Retinol-binding Protein 4 (RBP4) has evolved as an important metabolic signal associated with insulin resistance and diabetes mellitus. Research shows that RBP4 increases early in metabolic stress and thus a potential marker for identifying individuals at risk for type 2 diabetes, gestational diabetes, and diabetic nephropathy. The present review highlights the RBP4's biological function, its relationship with different states of glucose intolerance, and its potential clinical utility. RBP4 regulates various metabolic pathways which include impairing Glucose Transporter 4 (GLUT4) translocation, enhancing hepatic glucose production and inducing inflammatory pathways. These molecular effect explain the elevated serum RBP4 level in insulin-resistant states and rises even before the changes in fasting glucose or HbA1c. In type 2 diabetes, elevated RBP4 level associates with insulin resistance, dyslipidaemia, and central obesity. During pregnancy, women with elevated RBP4 in the first trimester develop gestational diabetes later, indicating that metabolic changes begin even before routine screening may detect. In diabetic nephropathy, RBP4 reflects early tubular injury and may rise prior to the onset of microalbuminuria. Currently, RBP4 has been considered as a sensitive marker of early metabolic disturbance and renal stress. Prospective studies with larger cohorts and standardised assay can establish RBP4 as part of multimarker panels for predicting diabetes mellitus and monitoring high-risk pregnancy and early kidney and vascular damage. The present review brings into perspective the biological relevance of RBP4, summarises its clinical correlates, and addresses the key challenges that need to be resolved before this protein finds routine applications in diabetes mellitus management.

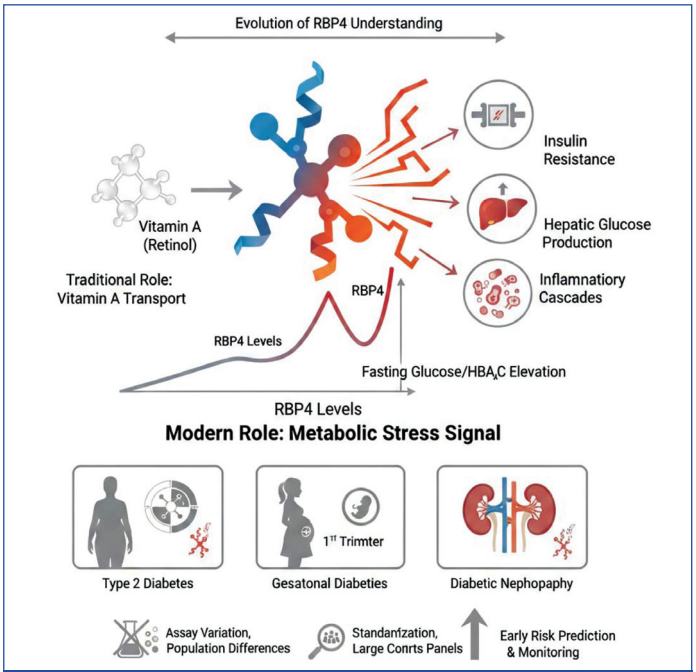
Keywords: Adipose tissue, Biomarkers, Gestational diabetes, Inflammation mediators, Insulin resistance

INTRODUCTION

During the last two decades, there has been much interest in Retinol-binding Protein 4 (RBP4) because research now shows that it is more than just a carrier for vitamin A. Earlier, RBP4 was mainly discussed in the context of the transport of retinol from the liver to peripheral tissues [1]. It formed a stable complex with Transthyretin (TTR), thereby preventing its excretion by the kidneys [2]. That was the basic physiological understanding for many years. But with the rise of metabolic research and more detailed work on adipokines, the role of RBP4 has expanded beyond the transport of retinol [Table/Fig-1]. It is nowadays viewed as a signalling molecule reflecting and contributing to metabolic stress, especially in insulin resistance states [3,4].

Diabetes mellitus is among the major global health concerns. Its prevalence continues to rise globally, especially in developing countries like India [5]. Insulin resistance is the main driving factor. It happens long before the appearances of abnormal blood glucose appear, and thus early biomarkers become important for such a long asymptomatic period. This is one of the major reasons that RBP4 has gained importance in recent years. In most studies, it is evident that RBP4 concentrations increase at an early stage and remain elevated in subjects with insulin resistance, obesity, fatty liver, and chronic low-grade inflammation [3].

The RBP4 has been associated with gestational diabetes mellitus and diabetic nephropathy. In Gestational Diabetes Mellitus (GDM), RBP4 appears to increase long before glucose intolerance becomes detectable [6]. Since GDM screening is normally conducted at 24-28 weeks, any biomarker that increases earlier may be helpful in identifying high-risk pregnancies during the first trimester. In diabetic nephropathy, RBP4 increases due to decreased reabsorption in the proximal tubules [7]. Tubular dysfunction often precedes glomerular damage [8]; hence, RBP4 may be one of the early markers of renal stress, even before microalbuminuria becomes detectable.



[Table/Fig-1]: RBP4: From retinol transporter to an emerging metabolic stress marker (Created in BioRender.com).

Although many studies suggest a strong association of RBP4 with metabolic disease, results across different populations are not always consistent. Assay variation is the main reason. Different Enzyme-Linked Immunosorbent Assay (ELISA) kits measure different forms of RBP4 (total RBP4, apo-RBP4, holo-RBP4), and many laboratories follow different sample handling practices. RBP4 levels also vary with BMI, renal function, vitamin A status, and inflammation [1]. As not all studies adjust for these factors, reported values are somewhat variable.

The review was written with the aim of providing an overall picture of RBP4 and its association with diabetes. RBP4 can act as a biomarker as it is involved in regulation of metabolic pathways, inflammation, retinol biology, and endocrine regulation. This makes it important to explore RBP4 that are involved in multiple pathways. This review discusses the current knowledge of RBP4 at the molecular level, its link with diabetes, and its potential clinical utility. It further discusses the limitations in knowledge and the area for future research.

Literature Search

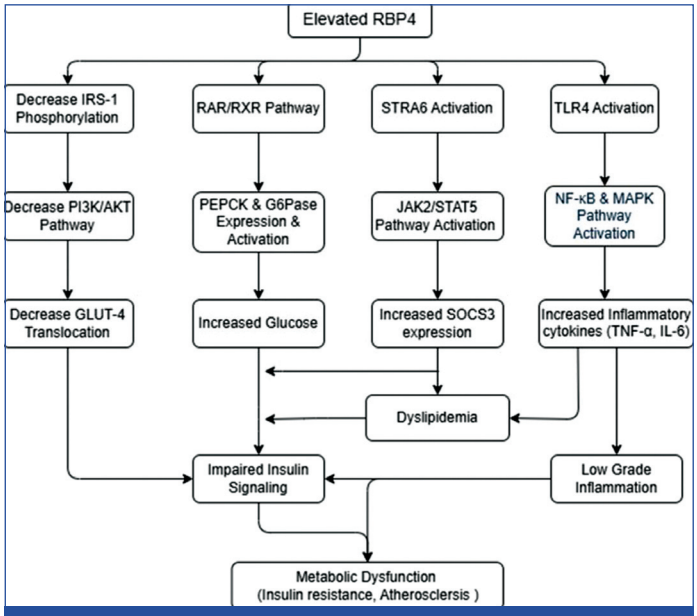
The present comprehensive literature search was conducted across PubMed, Scopus, and Google Scholar for studies published between January 2021 and December 2025. The review includes studies from 2021 onwards to highlight the recent evidence, developments, mechanistic insights, clinical updates and the understanding of RBP4-mediated metabolic signalling.

DISCUSSION

Physiology and Molecular Background of RBP4

The RBP4 is a 21-kDa protein that is primarily synthesised in the liver but whose circulating levels are significantly contributed to by adipose tissue [1,6]. Under physiological conditions, RBP4 transports retinol from the liver to tissues requiring vitamin A for vision, epithelial growth, and immune function [9].

The concentrations of RBP4 in healthy adults remain within a narrow range. They reflect a balance between hepatic production, the availability of retinol, kidney filtration, and the secretion from adipose tissue. However, this balance changes under metabolic stress. Insulin resistance reduces glucose uptake in adipose tissue because there is reduced expression of GLUT4 [10]. Stressed adipocytes as in obesity, secrete more RBP4 into the circulation, where it assumes the additional role of a signalling molecule instead of acting as a transport protein. RBP4, an adipokine through various signalling pathways such as activation of Stimulated by Retinoic Acid 6 (STRA6)/Toll-Like Receptor 4 (TLR4) pathways, can lead to insulin resistance, chronic inflammation and pancreatic beta cell dysfunction, which can cause type 2 diabetes. Elevated RBP4 also contributes to diabetic complications by promoting microvascular damage through oxidative stress and chronic inflammation, and macrovascular damage through vascular inflammation [3,11]. Rising RBP4 levels contribute to metabolic dysfunction through multiple pathways [Table/Fig-2]. Several studies explain how increased RBP4 contributes to metabolic dysfunction [Table/Fig-3] [4,6,7,11-13].



[Table/Fig-2]: Mechanism of increased RBP4 causing metabolic dysfunction.

Biological area	Mechanistic details	Relevance to diabetes
Skeletal muscle [4]	• Reduces GLUT4 translocation • Decreases insulin-stimulated glucose uptake	Contributes to peripheral insulin resistance
Adipose tissue [6]	• Secreted in higher amounts during adipocyte expansion • Downregulates GLUT4 expression • Increases free fatty acid release	Early insulin resistance; impaired glucose uptake; dyslipidaemia
Kidney (Proximal Tubule) [7]	• Filtered at glomerulus • Reabsorbed in tubules • Tubular injury reduces reabsorption	Early marker of diabetic nephropathy; elevated serum and urinary RBP4
Immune Cells (Macrophages) [11]	• Activates STRA6 → JAK2/STAT5 pathway • Increases SOCS3 expression • Stimulates TNF-α, IL-6 release	Chronic low-grade inflammation; worsens IR
Liver [12]	• Activates gluconeogenic enzymes (PEPCK, G6Pase (Glucose-6-Phosphatase) • Increases hepatic glucose output • Alters retinol metabolism	Fasting hyperglycaemia; elevated hepatic insulin resistance
Placenta (Pregnancy) [13]	• STRA6 expressed in trophoblasts • Influences placental cytokines	Higher RBP4 predicts GDM risk; early insulin resistance

[Table/Fig-3]: Key biological functions and mechanisms of RBP4 in diabetes mellitus [4,6,7,11-13].
GLUT4: Glucose transporter type 4; PEPCK: Phosphoenolpyruvate carboxykinase; G6Pase: Glucose-6-phosphatase; STRA6: Stimulated by retinoic acid 6; JAK2/STAT5: Janus kinase 2/signal transducer and activator of transcription 5; SOCS3: Suppressor of cytokine signaling 3; TNF-α: Tumour necrosis factor alpha; IL-6: Interleukin-6; TGs: Triglycerides; LDL: Low-density lipoprotein; IR: Insulin resistance; T2DM: Type 2 diabetes mellitus; GDM: Gestational diabetes mellitus

RBP4 in Type 2 Diabetes Mellitus

Type 2 diabetes is the result of combined insulin resistance and declining β-cell function. Of the many biochemical observations reported in T2DM, one of the most consistent is the elevation of circulating RBP4 [14].

A cross-sectional study by Jadhao AG et al., 2024 shows significant positive correlation between RBP4 levels and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) ($r=0.237$, $p<0.0001$), fasting insulin ($r=0.388$, $p<0.0001$), and fasting glucose ($r=0.216$, $p<0.0001$). The study also shows RBP4 levels were significantly higher in T2DM with essential hypertension compared to healthy controls (49.17±19.37 vs 26.86±14.26 mg/L, $p<0.0001$) [15]. Another study by Perumalsamy S et al., 2021 shows RBP4 as a predictor of IR with an OR=1.166 (95% CI: 1.009 – 3.042, p=0.030) on binary logistic regression analysis [16].

Link with Insulin Resistance

One of the most robust and reproducible observations represents the correlation of RBP4 with HOMA-IR. Elevated level of RBP4, an emerging adipokine, is linked to insulin resistance and vascular injury. RBP4 impairs insulin signalling by reducing IRS-1 phosphorylation and PI3K activity [4,17]. Studies have shown statistically significant correlation between RBP4 and HOMA-IR, with Chen T et al. showing $r>0.3$, $p<0.001$ [7] while Liu C et al., showing $r=0.205$, $p=0.028$ [18]. Higher RBP4 levels indicate reduced insulin sensitivity. Zhang K et al., highlight that RBP4 reduction correlates with improved insulin resistance and decreased HOMA-IR. Study also shows correlations with fasting glucose, fasting insulin, and markers of fatty liver [4]. Such patterns suggest that RBP4 reflects overall metabolic stress.

Mechanistic studies support these clinical data. Comprehensive analyses have shown that elevated RBP4 inhibits GLUT4 expression and translocation as well as activation of IRS-1 [3,16], which leads to increased hepatic gluconeogenesis via expression of Phosphoenolpyruvate Carboxykinase (PEPCK) [12]. Furthermore, RBP4 promotes chronic inflammation by binding to cell-surface receptors (STRA6/TLR4), upregulating the NLRP3 inflammasome pathway [4]. These actions resemble the earliest consequences of insulin resistance, providing one potential explanation for the early increase in RBP4 during metabolic disease.

Vascular Injury related to Insulin resistance: Insulin resistance causes vascular injury and contributes significantly to increasing the risk of development of cardiovascular disease during such metabolic dysregulation. Physiologically, insulin has a protective role on the vascular structure and function via activation of Insulin Receptor Substrate-Phosphoinositide 3-Kinase-Akt (IRS-PI3K-AKT) signalling pathway in endothelial cells which stimulates nitric oxide production causing vasodilation and inhibits inflammation, production of vascular adhesion molecules and thrombosis [18].

In insulin resistance, PI3K/AKT signalling pathway is impaired while the Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway remains active leading to production of vasoconstrictor and proatherogenic factors such as endothelin-1, Vascular Adhesion Molecules (VCAM-1, Intercellular Adhesion Molecule 1 (ICAM-1)), Plasminogen Activator Inhibitor-1 (PAI-1) while the production of nitric oxide is reduced. These promote inflammation, oxidative stress, adipokine dysregulation impair fibrinolysis, vascular smooth muscle proliferation and thrombosis [19]. Oxidative stress associated with insulin resistance further degrades Nitric Oxide (NO) which aggravates endothelial injury [20]. These alterations result in vascular endothelial dysfunction and structural modifications including arterial stiffness, increased intima-media thickness, and vascular calcification which are the early markers of subclinical vascular disease [21].

Subsequently, insulin resistance is strongly associated with both microvascular and macrovascular damage and significantly increases the risk of atherosclerosis, hypertension, and other cardiovascular complications [22]. Vascular functional abnormalities such as impaired endothelium-dependent vasodilation, reduced capillary recruitment, and altered microvascular perfusion limit the delivery of insulin and glucose to peripheral tissues and thus exacerbate metabolic dysfunction in insulin resistance [23].

Furthermore, the hyperinsulinaemia condition in insulin-resistant state contributes to vascular injury by the stimulation of sympathetic nervous system activity, enhancing sodium retention, and promoting vascular smooth muscle cell proliferation, thereby increasing the risk of hypertension and atherosclerosis [24].

Influence of Organ Function

RBP4 levels are influenced by several conditions through distinct mechanisms. Mild renal impairment reduces renal clearance and altered tubular handling, falsely elevating the RBP4 levels and requiring adjustments for baseline renal status when interpreting RBP4 as a metabolic biomarker [7]. Fatty liver disease increases RBP4 because the liver produces RBP4, and oxidative stress/inflammation associated with the disease, which may be driven by obesity or insulin resistance, upregulating hepatic RBP4 expression [25]. In obesity, adipocyte hypertrophy triggers an infiltration of inflammatory cells such as macrophages, leading to a low-grade inflammatory state that increases RBP4 expression and secretion [11,26]. RBP4 interacts dynamically with pancreatic architecture, beyond its effects on insulin sensitivity. Elevated RBP4 may contribute to pancreatic β-cell dysfunction; RBP4 activates Stimulated by Retinoic Acid 6 – Janus Kinase 2 – Signal Transducer and Activator of Transcription (STRA6-JAK2–STAT) signalling in β-cells, leading to impaired insulin secretion and β-cell dysfunction [27].

RBP4 and Gestational Diabetes Mellitus (GDM)

GDM develops when a pregnant woman cannot maintain normal glucose levels due to the natural increase in insulin resistance occurring during gestation. This physiological shift is caused mainly by placental hormones such as human placental lactogen, oestrogen, progesterone, and cortisol, which divert glucose toward the foetus while diminishing the mother's insulin response [28]. Individuals with underlying metabolic stress, excess weight, or a history of polycystic ovary syndrome are more likely to cross the threshold into GDM.

The RBP4 is one of the important factors since several studies indicate that its levels increase very early in pregnancy [6,29], even before standard screening tests for GDM are normally conducted. The usual glucose challenge test is performed late in the second trimester when most of the metabolic changes have already advanced. An early marker would enable healthcare providers to identify high-risk women much earlier. This may be helpful in lifestyle interventions which might prevent or decrease the severity of GDM [6,30].

Evidence of an Increase in Circulating RBP4 during Early Pregnancy

Many prospective studies have measured RBP4 in the first trimester and followed the women to delivery. Most studies showed a significantly higher RBP4 level in women who developed GDM later, when compared to those who remained normoglycaemic. A meta-analysis conducted by Leca BM et al., includes 32 studies involving 3,595 GDM and 4,544 controls across different gestation groups. They found positive Standardised Mean Differences (SMD) for all trimesters (first trimester: SMD=0.322, $p<0.001$; 24–28 weeks: SMD=0.628, $p<0.001$; >28 weeks: SMD=0.875, $p=0.006$). However, there was high statistical heterogeneity (I^2 values between 80% to 97%) in all trimesters. This heterogeneity is driven by differences in study populations like BMI, maternal age, ethnicity (e.g., East Asian vs. European), gestation time, along with diverse diagnostic criteria and RBP4 measurement methods [6]. This suggests that the metabolic disturbance leading to GDM begins much earlier than previously thought.

This consistent trend is reinforced by Wu P et al., confirmed elevated RBP4 levels in early pregnancy as a predictor of GDM risk, participants with the highest quartile having a 2.26-fold higher risk (95% CI: 1.34-3.81, $p<0.001$) compared to the lowest quartile [29]. Similarly, Javed K et al., observed significantly higher median serum RBP4 concentrations in females with GDM compared to healthy controls (37.3 ng/dL vs 33.2 ng/dL, $p=0.021$) [31]. This consistently shows moderate to strong associations between early-pregnancy RBP4 and glucose intolerance later in pregnancy.

The association of RBP4 with glucose intolerance remains significant after adjusting for Body Mass Index (BMI), age, parity, and fasting insulin [32]. This strengthens the concept that RBP4 has an independent role in the early pregnancy metabolism, not just a reflection of either obesity or inflammation.

Possible Biological Explanations for Rising RBP4 in GDM

There are several overlapping pathways that explain the rise in RBP4 during pregnancy:

1. **Increased metabolic load in early pregnancy:** In pregnancy, more glucose is needed for the growth of the foetus. This is met by reduced sensitivity to insulin. Elevated RBP4 compromises metabolic compensation and increases the risk of GDM [6].
2. **Placental contributions to inflammation:** The available literature suggests that RBP4 and its receptor STRA6 are expressed in the placenta, with their structural expression and staining patterns altering significantly in pregnancies complicated by GDM [13]. Therefore, RBP4 can influence placental immune signalling, leading to inflammation by inducing a localised cascade of proinflammatory molecules (such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6)), and thereby further reducing insulin sensitivity [11].
3. **Altered hepatic glucose production:** The liver is the central organ in pregnancy metabolism. The increased gluconeogenesis elicited by RBP4 may induce an early rise in

glucose load that becomes more obvious during the second trimester, suggesting progressive insulin resistance [29].

4. **Association with maternal adiposity:** Obesity raises circulating RBP4. Many women who develop GDM also have greater body fat, and thus the rise in RBP4 might reflect both increases in adipose secretion and impairment in insulin signalling [32].
5. **Vitamin A metabolism effect:** Vitamin A requirements are altered during pregnancy. Altered transport of retinol may influence RBP4 dynamics, although this is not yet fully understood [33].

RBP4 and Diabetic Nephropathy

Diabetic nephropathy is one of the serious long-term complications of diabetes. It develops slowly over years and involves both glomerular and tubular injury. However, microalbuminuria is only a standard early marker, and by the time microalbuminuria becomes present, there may already be significant renal damage [34]. For this reason, a biomarker that rises earlier and gives a clearer view of tubular health is needed. RBP4 is one of the most promising molecules in this category, since its renal handling makes it sensitive to tubular dysfunction [7]. Under normal conditions, RBP4 is freely filtered at the glomerulus. It is almost completely reabsorbed by proximal tubule cells; very little appears in the urine [35]. This suggests that kidney is one of the factors in the regulation of RBP4 levels. When the proximal tubules are intact, serum RBP4 is within a normal range. However, when tubular cells are injured, their reabsorption capacity for RBP4 decreases and results in higher levels in serum and urine.

Many studies have documented that in patients with diabetic nephropathy, the serum RBP4 is higher. Chen T et al., cross-sectional study showed that RBP4 alone have an Area Under the Curve (AUC) of 0.666, superior to other risk factors like creatinine, uric acid. Combining RBP4 with common risk factors, the accuracy of Chronic Kidney Disease (CKD) prediction improved (AUC from 0.801 to 0.810) [7]. A meta-analysis by Cao X et al., involving 29 studies identified RBP4 as a promising early diagnostic biomarker for diabetic nephropathy, with sensitivity of 0.78, specificity of 0.85 and Diagnostic Odds Ratio (DOR) of 13.76 (95% CI, 9.29-20.37) [36]. A review study by Ratajczyk K et al., noted that normoalbuminuric T2DM patients with endothelial dysfunction have significantly higher levels of urinary RBP4 (uRBP4) than T2DM subjects with normal endothelial function and healthy controls [35]. A large, well-designed clinical validation study is required to ultimately assess the diagnostic and clinical utility of RBP4 measurements in type 2 diabetic patients.

It tends to increase progressively:

- Normal albumin excretion → lowest RBP4
- Microalbuminuria → moderate increase
- Macroalbuminuria → highest levels

This stepwise increment indicates that RBP4 is correlated with the severity of nephropathy. In some studies, RBP4 showed a stronger association with renal dysfunction when compared to the traditional markers such as Albumin-to-Creatinine Ratio (ACR) alone [7].

Inflammation biomarkers: These findings further support the view that RBP4 may not be a passive result of glomerular damage but could be associated with renal pathology more generally. Chen T et al., have demonstrated a strong to moderate correlation (r>0.3) between RBP4 and indicators of renal function {serum creatinine, Blood Urea Nitrogen (BUN), ACR and Estimated Glomerular Filtration Rate (eGFR)}. The proximal renal tubules reabsorbed 99% of RBP4, making uRBP4 a highly sensitive marker of tubular dysfunction. The reduction of glomerular filtration rate and tubular reabsorption impairment can elevate RBP4 levels [7]. Cao X et al., through their analysis reported that AUC for RBP4 is 0.912 against 0.819 for ACR, indicating RBP4 as a strong predictor of renal function [36].

Urinary RBP4 as a Marker

Urinary RBP4 may be even more sensitive than serum RBP4. When tubular cells are damaged, the amount of RBP4 excreted in the urine rises dramatically, sometimes before changes in albumin or creatinine become apparent. A review by Ratajczyk K et al., highlight that uRBP4 excretion increases $>10^4$ fold during tubular damage and inflammation even before glomerular filtration marker like creatinine, microalbuminuria increases [35]. However, urinary measurements are dependent on urine concentration and hydration status, as well as appropriate normalisation methods such as uRBP4 to creatinine ratio adjustment to ensure accurate interpretation. Due to these problems, uRBP4 is not commonly used at this time. Widespread clinical translation is also hampered by profound multistudy heterogeneity. Differences in sample collection and processing, assay method, study population, statistical methods and concentration cut-offs impede the direct comparison of results. Without standardisation and harmonisation, uRBP4 cannot yet establish its clinical validity [35].

Role of Inflammation and Systemic Metabolic Stress

Kidney injury in diabetes mellitus is not always straightforwardly a result of hyperglycaemia. Inflammation contributes significantly to the damage of glomeruli and tubules, with RBP4 activating immune cells and promoting inflammatory responses via the Toll-like receptor/JNK pathway [7]. Thus, RBP4 may not only reflect kidney injury but also contribute to it.

Many studies demonstrate that high RBP4 correlates with TNF-α and IL-6 and may contribute to inflammation-associated renal damage in diabetic nephropathy [7,26,36].

Therefore, RBP4 may be part of a feedback loop through which inflammation raises RBP4 and high RBP4 further increases inflammation. Low inflammatory state associated with obesity or hyperglycaemia may induced the over-expression of RBP4 which in turn further promotes release of inflammatory cytokines like IL-6, TNF-alpha via the TLR4/c-Jun N-terminal Kinase (JNK)/NF-κB pathways, which exaggerate the condition [4,26].

Despite a recent surge in interest in studies involving RBP4, there are some current limitations in the analysis of this biomarker, which indicates a need for improved study design and a wider degree of standardisation.

CONCLUSION(S)

The RBP4 is implicated in metabolic alterations of diabetes mellitus across multiple tissues such as adipose tissue, skeletal muscle, the vascular system. RBP4 can serve as an early biomarker because its levels rise before other detectable markers become elevated, and it correlates with insulin resistance, dyslipidaemia, obesity, and chronic inflammation. RBP4 increases early in pregnant women who later develop GDM, even before routine screening can detect it, and it rises during early tubular dysfunction prior to the onset of microalbuminuria. This provides an opportunity for early detection, prevention and intervention. However, further clinical and prospective studies are needed to validate its clinical implications and establish its utility in routine practice.

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