Original Article

Serum retinol binding protein 4 in individuals with essential hypertension and type 2 diabetes: A cross-sectional study

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Abstract

Background: Cardiometabolic disorders, notably primary hypertension and type 2 diabetes, present substantial global health challenges. The intricate interplay between metabolic and cardiovascular pathways has prompted extensive research into molecular mechanisms linking these conditions. The adipokine Retinol Binding Protein 4 (RBP4), initially recognized for retinol transport, has emerged as a potential biomarker in the network of metabolic and cardiovascular dysfunction. Recent studies implicate RBP4 in insulin resistance and its complications, including hypertension. This study explores RBP4 dynamics in patients with primary hypertension and type 2 diabetes, aiming to contribute valuable insights into diagnostic and therapeutic advancements in managing these interconnected disorders. **Methods:** This cross-sectional study, conducted over 2 years in a tertiary healthcare centre of North India, aimed to investigate the serum concentration of Retinol Binding Protein 4 (RBP4) in 119 participants diagnosed with primary hypertension and type 2 diabetes. Ethical guidelines were strictly followed, and comprehensive clinical assessments, including blood pressure measurements, were performed. RBP4 levels were quantified using an ELISA kit, alongside markers of insulin resistance. Statistical analyses, involving t-tests and correlation assessments, sought to unravel potential associations between RBP4, insulin resistance, and blood pressure parameters using SPSS 20.0. **Results:** The study comprised 61 healthy control (HC) participants and 58 individuals diagnosed with both essential hypertension and type 2 diabetes (EH+T2D). EH+T2D participants were on average older (45.71 ± 9.29 years vs. 40.34 ± 9.47 years, $P = 0.002$). Dyslipidemia prevalence was markedly higher in EH+T2D (72.4% vs. 11.4%, $P < 0.0001$), accompanied by disrupted lipid profiles. Serum RBP4 concentration was significantly elevated in EH+T2D (49.17 ± 19.37 mg/L, $P < 0.0001$), suggesting its potential role in the shared pathophysiology of primary hypertension and type 2 diabetes. Pearson's correlation analysis revealed associations between RBP4 levels, metabolic, and cardiovascular parameters, underscoring its potential as a link between these conditions. **Conclusion:** Elevated serum RBP4 levels suggest its potential as a novel biomarker in the shared pathophysiology of primary hypertension and type 2 diabetes. The correlation analysis highlights the intricate interplay between metabolic, lipid, and cardiovascular parameters, emphasizing the need for holistic interventions.

Keywords: Blood pressure, diabetes, hypertension, insulin resistance, retinol binding protein

Introduction

Cardiometabolic disorders, such as primary hypertension and type 2 diabetes, pose significant global health challenges, contributing to the growing burden of non-communicable diseases.[1,2] The intricate interplay between metabolic and

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cardiovascular pathways has spurred extensive research aimed at unraveling the underlying molecular mechanisms that link these conditions.[3,4] In this context, the focus on adipokines, particularly Retinol Binding Protein 4 (RBP4), has gained prominence due to its emerging role as a potential biomarker and mediator in the intricate network of metabolic and cardiovascular dysfunction.[4]

RBP4, primarily secreted by adipocytes and the liver, was initially recognized for its involvement in retinol transport.[5] However, recent studies have implicated RBP4 in the pathophysiology of insulin resistance and its associated complications, including hypertension. The intricate crosstalk between adipose tissue, insulin signaling, and vascular function has led to the hypothesis that dysregulation of RBP4 may serve as a pivotal link between metabolic and cardiovascular disturbances.[6,7]

Patients with primary hypertension often exhibit insulin resistance, emphasizing the interconnectedness of these conditions.[8] Exploring the role of RBP4 in such individuals could provide valuable insights into the intricate mechanisms that contribute to the co-occurrence of hypertension and type 2 diabetes.[9,10] Understanding the dynamics of RBP4 in this context may pave the way for novel diagnostic and therapeutic strategies, offering a targeted approach to managing these closely intertwined disorders.[11,12]

This study aimed to comprehensively evaluate the serum concentration of RBP4 in patients diagnosed with primary hypertension and type 2 diabetes. Understanding the role of RBP4 in the context of cardiometabolic health is of particular relevance to primary care physicians as it may offer insights into the early identification, risk stratification, and management of individuals at risk of developing these conditions.

Materials and Methods

Study design

This comparative cross-sectional study was conducted among individuals diagnosed with primary hypertension and type 2 diabetes, in a tertiary healthcare centre of North India for a period of 2 years (December 2021 to November 2022). The study adhered to the ethical guidelines outlined in the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) [Approval number: MC/2021/12/78]. All participants provided informed consent before their inclusion in the study.

Participants

A total of 119 participants (61 controls and 58 cases) were recruited. Inclusion criteria for cases encompassed individuals aged 18 years or more diagnosed with both primary hypertension and type 2 diabetes. Controls included otherwise healthy individual accompanying the patient. Exclusion criteria included individuals with secondary hypertension, other significant comorbidities, and those currently undergoing treatment regimens that could influence RBP4 levels.

Clinical assessments

Comprehensive clinical assessments were conducted for each participant, including medical history, physical examinations (including height, weight, waist circumference), and laboratory tests (including lipid profile). Blood pressure measurements were obtained using standardised protocols, and individuals were classified as having primary hypertension based on established guidelines (JNC-8). Diagnosis of type 2 diabetes was confirmed through fasting blood glucose levels (using a standard glucose oxidase method), and glycated hemoglobin (HbA1c) measurements.

Serum RBP4 concentration

Fasting venous blood samples were collected from participants and processed to obtain serum. Serum RBP4 concentrations were quantified using RBP4 ELISA kit (Phoenix, USA), ensuring accuracy and reproducibility (intra- and inter-assay coefficients of variation of 5.22% and 11.29%, respectively). Quality control measures were implemented throughout the assay process to minimize variability.

Insulin resistance markers

In addition to RBP4, markers of insulin resistance, including fasting insulin levels using an enzyme-linked immunosorbent assay (ELISA) (normal range: 3 to 25 mU/L), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) where the cut-off point for diagnosis of IR was taken as 2.77, and C-peptide using chemilumiscence (normal range: 0.81 to 3.85 ng/mL), were measured. These markers were selected to provide a comprehensive assessment of insulin sensitivity and metabolic status.

Statistical analysis

Statistical analyses were performed using SPSS 20.0, and data were expressed as mean ± standard deviation (SD) for continuous variables and as percentages for categorical variables. Comparisons between groups were conducted using Student's t-tests for continuous variables and Chi-square tests for categorical variables. Correlation analyses, including Pearson correlation coefficients, were employed to examine associations between serum RBP4 concentration, insulin resistance markers, and blood pressure parameters.

Ethical considerations

This study was conducted in accordance with ethical principles, and written informed consent was obtained from all participants. The confidentiality of participant information was strictly maintained, and data were anonymised during analysis and reporting.

Results

The study included a total of 61 participants in the healthy control (HC) group and 58 participants in the group diagnosed

with both essential hypertension and type 2 diabetes (EH+T2D). The EH+T2D group, on average, was older (45.71 ± 9.29 years vs. 40.34 ± 9.47 years, $P = 0.002$). While gender distribution showed no significant difference, BMI and waist circumference were markedly higher in the EH+T2D group (BMI: 27.42 ± 2.76 kg/m² vs. 21.71 ± 2.65 kg/m², $P < 0.0001$; waist circumference: 95.35 ± 7.18 cm vs. 84.54 ± 4.14 cm, $P < 0.0001$), indicating central adiposity. Blood pressure parameters further distinguished the groups, with the EH+T2D group exhibiting significantly higher systolic (152.33 ± 12.25 mmHg vs. 111.22 ± 7.56 mmHg, $P < 0.0001$) and diastolic (95.47 ± 8.52 mmHg vs. 76.83 ± 7.34 mmHg, $P < 0.0001$) blood pressures [Table 1].

EH+T2D individuals (N = 58) displayed significant metabolic dysregulation compared to the HC group (N = 61). Elevated fasting plasma glucose (206.48 ± 32.33 mg/dL), hemoglobin A1c (8.41 ± 0.53%), and insulin resistance markers (fasting serum insulin: 8.76 ± 4.11 mU/L, C-peptide: 3.67 ± 0.38 ng/mL, HOMA-IR: 4.37 ± 0.52) indicated severe hyperglycemia and pronounced insulin resistance. Dyslipidemia prevalence was substantially higher in EH+T2D (72.4% vs. 11.4%, $P < 0.0001$), accompanied by disrupted lipid profiles, including elevated total cholesterol (214.27 ± 30.18 mg/dL) and LDL-C (122.36 ± 28.85 mg/dL) and reduced HDL-C (46.59 ± 16.44 mg/dL). Serum RBP4 concentration was markedly higher in EH+T2D (49.17 ± 19.37 mg/L, $P < 0.0001$), suggesting its potential role in the shared pathophysiology of primary hypertension and type 2 diabetes [Table 2].

The correlation analysis of serum Retinol Binding Protein 4 (RBP4) levels with various laboratory and baseline variables is summarized in Table 3. Serum RBP4 levels showed a significant positive correlation with fasting plasma glucose ($r = 0.216$, $p < 0.0001$), hemoglobin A1c ($r = 0.187$, $p < 0.0001$), fasting serum insulin ($r = 0.388$, $p < 0.0001$), C-peptide ($r = 0.244$, $p < 0.0001$), total cholesterol ($r = 0.212$, $p < 0.0001$), triglycerides ($r = 0.238$, $p < 0.0001$), low-density lipoprotein cholesterol (LDL-C) ($r = 0.162$, $p < 0.0001$), and the homeostasis model assessment of insulin resistance (HOMA-IR) ($r = 0.237$, $p < 0.0001$). Additionally, RBP4 levels correlated positively with systolic blood pressure ($r = 0.233$, $p < 0.0001$), diastolic blood pressure ($r = 0.101$, $p = 0.034$), BMI ($r = 0.137$, $p < 0.0001$), and waist circumference ($r = 0.181$, $p < 0.0001$). Conversely, a significant negative correlation was observed with high-density lipoprotein cholesterol (HDL-C) ($r = -0.128$, $p = 0.002$). No significant correlation was found between serum RBP4 levels and age ($r = 0.004$, $p = 0.899$). These findings indicate that elevated RBP4 levels are associated with multiple markers of metabolic dysfunction and cardiovascular risk factors. [Table 3].

Table 1: Comparison of baseline characteristics among the two groups

Characteristic	HC group (*n*=61)	EH+T2D group (*n*=58)	*P*
Age (years)	40.34±9.47	45.71±9.29	0.002
Gender			
Female	26 (42.6%)	24 (41.4%)	0.018
Male	35 (57.4%)	34 (58.6%)	
BMI (kg/m²)	21.71±2.65	27.42±2.76	<0.0001
Waist Circumference (cm)	84.54±4.14	95.35±7.18	<0.0001
Blood Pressure (mmHg)			
Systolic BP	111.22±7.56	152.33±12.25	<0.0001
Diastolic BP	76.83±7.34	95.47±8.52	<0.0001

Table 2: Comparison of laboratory parameters among the two groups

Laboratory Parameter	HC group (*n*=61)	EH+T2D group (*n*=58)	*P*
Fasting Plasma Glucose (mg/dL)	98.38±13.53	206.48±32.33	<0.0001
Hemoglobin A1c (%)	5.72±0.52	8.41±0.53	<0.0001
Fasting Serum Insulin (mU/L)	6.32±3.65	8.76±4.11	0.0008
C-peptide (ng/mL)	1.38±0.42	3.67±0.38	<0.0001
Total Cholesterol (mg/dL)	158.72±25.85	214.27±30.18	<0.0001
HDL-C (mg/dL)	55.56±19.36	46.59±16.44	<0.007
Triglycerides (mg/dL)	108.84±56.41	192.38±64.62	0.550
LDL-C (mg/dL)	101.56±22.47	122.36±28.85	<0.0001
HOMA-IR	2.18±0.15	4.37±0.52	0.002
Dyslipidemia	7 (11.4%)	42 (72.4%)	<0.0001
Serum RBP4 (mg/L)	26.86±14.26	49.17±19.37	<0.0001

Table 3: Correlation between serum RBP4 (mg/L) levels and laboratory and baseline variables

Variables	*r*	Statistical significance
Fasting Plasma Glucose (mg/dL)	0.216	<0.0001
Hemoglobin A1c (%)	0.187	<0.0001
Fasting Serum Insulin (mU/L)	0.388	<0.0001
C-peptide (ng/mL)	0.244	<0.0001
Total Cholesterol (mg/dL)	0.212	<0.0001
HDL-C (mg/dL)	-0.128	0.002
Triglycerides (mg/dL)	0.238	<0.0001
LDL-C (mg/dL)	0.162	<0.0001
HOMA-IR	0.237	<0.0001
Systolic BP	0.233	<0.0001
Diastolic BP	0.101	0.034
Age	0.004	0.899
BMI	0.137	<0.0001
Waist circumference	0.181	<0.0001

Discussion

The comprehensive assessment of individuals with both primary hypertension and type 2 diabetes (EH+T2D) in comparison to a HC group reveals crucial insights into the complex interplay of metabolic and cardiovascular factors in this high-risk population. The demographic and anthropometric disparities observed, including older age, higher BMI, and increased waist circumference in the EH+T2D group, emphasise the distinct clinical profile associated with the coexistence of these conditions. The elevated blood pressure parameters further underscore the severity of cardiovascular involvement in EH+T2D individuals.

Metabolic dysregulation in the EH+T2D group is strikingly evident, with markedly elevated fasting plasma glucose, hemoglobin A1c, and insulin resistance markers. The high prevalence of dyslipidemia, characterized by disrupted lipid profiles, including elevated total cholesterol and LDL-C and reduced HDL-C, aligns with previous findings by Yoshida *et al.*, Christou *et al.*, Graham *et al.*, Klöting *et al.*, Jia *et al.*, Ingelsson *et al.*, Usui *et al.*, Ng *et al.*, and Mallat *et al.*, indicating a heightened cardiovascular risk in individuals with primary hypertension and type 2 diabetes.[10,13-20]

The significant elevation in serum RBP4 levels in the EH+T2D group suggests a potential role for RBP4 in the shared pathophysiology of these metabolic and cardiovascular conditions. This finding opens avenues for further investigation into the mechanistic underpinnings of RBP4 and its implications as a potential biomarker or therapeutic target.[21-24]

Correlation analysis unveils intricate relationships between various parameters within the EH+T2D cohort. Positive correlations between glucose-related markers (fasting plasma glucose, hemoglobin A1c) and insulin resistance indicators (fasting serum insulin, C-peptide) highlight the intricate relationship between hyperglycemia and insulin dysregulation; it was also observed in the studies by Fan *et al.*, Li *et al.*, Yang *et al.*, Kwanbunjan *et al.*, Pandey *et al.*, Mahfouz *et al.*, and Zhang *et al.*[1,7,25-29] Dyslipidemia is further underscored by positive correlations in total cholesterol, triglycerides, and LDL-C, coupled with a negative correlation with HDL-C. The positive associations between HOMA-IR, blood pressure parameters, and anthropometric measures emphasise the interconnected nature of insulin resistance, cardiovascular risk, and central adiposity and also correlate with the studies by Li *et al.* and Zhang *et al.*[25,29]

While age exhibits minimal correlation with the studied variables, indicating that age may not be a major contributor to the observed associations, the overarching findings emphasise the need for a comprehensive approach to managing individuals with primary hypertension and type 2 diabetes.[30,31] Future research should delve into elucidating the specific mechanisms linking RBP4 with the observed metabolic and cardiovascular disturbances, offering potential avenues for targeted interventions in this high-risk population.[32]

Elevated serum RBP4 levels observed in individuals with both essential hypertension and type 2 diabetes suggest its potential utility as a biomarker for identifying high-risk patients in primary care settings. Understanding the intricate relationship between RBP4, metabolic factors, and cardiovascular parameters provides primary care providers with valuable insights into the underlying mechanisms of these conditions, enabling more targeted and personalised management strategies.

Limitations

The study has certain limitations that warrant consideration. The single-centre setting in North India may introduce regional biases, and findings may not be universally applicable. Additionally, the exclusion criteria based on ongoing treatment regimens influencing RBP4 levels may inadvertently exclude individuals with relevant medical histories, potentially impacting the comprehensiveness of the study cohort. The absence of specific details about participant demographics, socio-economic factors, or lifestyle variables may limit the contextual understanding of the findings. Future research endeavours could address these limitations to enhance the robustness and applicability of the study outcomes.

Conclusion

In summary, individuals with both EH+T2D exhibit distinctive clinical features, including an older age, central adiposity, and elevated blood pressure. The pronounced metabolic dysregulation, marked by severe hyperglycemia and disrupted lipid profiles, underscores the compounded cardiometabolic risks in this population. Elevated serum RBP4 levels suggest its potential as a novel biomarker in the shared pathophysiology of primary hypertension and type 2 diabetes. The correlation analysis highlights the intricate interplay between metabolic, lipid, and cardiovascular parameters, emphasising the need for holistic interventions. These findings contribute valuable insights for targeted therapeutic approaches in managing the complex comorbidity of EH+T2D, paving the way for further research to validate and refine these observations.

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Conflicts of interest

There are no conflicts of interest.

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