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SYNERGISTIC INTERPLAY OF METABOLIC AND INFLAMMATORY PATHWAYS: EVALUATION OF SERUM HOMOCYSTEINE AND C-REACTIVE PROTEIN LEVELS IN PATIENTS WITH ESSENTIAL HYPERTENSION

Clinical Biochemistry

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ABSTRACT

- **Objective:** To investigate the correlation between serum homocysteine (Hcy) and whole blood C-reactive protein (CRP) levels in patients diagnosed with essential hypertension, evaluating their roles in diagnosis and clinical management.
- **Methods:** A prospective, case-control study was conducted involving 100 participants divided equally into two groups: 50 newly diagnosed patients with essential hypertension (cases, duration < 1 year, aged 35–50 years) and 50 age- and sex-matched healthy individuals (controls). Serum homocysteine, fasting blood glucose, lipid profiles, and renal parameters were measured via spectrophotometry using automated analyzers, while whole blood CRP levels were assessed using a dry fluorescence immunoassay.
- **Results:** Patients with essential hypertension exhibited significantly higher levels of serum homocysteine (18.26 ± 4.02 µmol/L) compared to healthy controls (10.08 ± 2.71 µmol/L, $p < 0.001$). Whole blood CRP levels were also markedly elevated in cases (5.80 ± 2.14 mg/L) relative to controls (1.45 ± 0.82 mg/L, $p < 0.001$). Significant positive correlations were observed in hypertensive patients between CRP and systolic blood pressure ($r = 0.52$, $p < 0.001$), CRP and diastolic blood pressure ($r = 0.47$, $p = 0.001$), homocysteine and systolic blood pressure ($r = 0.49$, $p < 0.001$), and homocysteine and diastolic blood pressure ($r = 0.44$, $p = 0.002$). Crucially, a strong positive correlation was found between serum homocysteine and CRP levels ($r = 0.56$, $p < 0.001$). Hypertensive cases also showed significantly elevated fasting glucose and atherogenic lipid fractions, while renal parameters remained stable and comparable between the groups.
- **Conclusion:** Essential hypertension is deeply linked to underlying metabolic and inflammatory dysregulation. The concurrent elevation and positive correlation of homocysteine and CRP suggest a synergistic mechanism that accelerates endothelial injury and vascular dysfunction, emphasizing their clinical utility as adjunct biomarkers for comprehensive cardiovascular risk stratification.

KEYWORDS

INTRODUCTION

Essential hypertension (EH), or primary hypertension, is a complex, multifactorial clinical disorder characterized by persistently elevated arterial blood pressure without an identifiable secondary cause, accounting for 90–95% of all hypertensive cases globally. The complex pathogenesis of EH involves a combination of genetic predispositions, environmental factors, and distinct alterations in renal, vascular, and neurohormonal pathways. Persistent blood pressure elevation leads to microvascular and macrovascular complications, causing end-organ damage in cardiovascular, cerebrovascular, and renal systems, which drives substantial global morbidity and mortality.

EH is increasingly recognized not merely as a simple hemodynamic abnormality, but as a condition fundamentally linked with chronic endothelial dysfunction, systemic oxidative stress, and sustained low-grade inflammation. Among emerging biochemical markers, serum homocysteine and C-reactive protein (CRP) have attracted substantial attention due to their specific biological actions within the vascular wall.

Homocysteine is a sulfur-containing, non-proteinogenic amino acid generated during the metabolic transformation of methionine. It acts as an independent risk factor for cardiovascular diseases, including atherosclerosis, coronary artery disease, and stroke. Hyper-homocysteinemia triggers severe endothelial injury, reduces nitric oxide (NO) bioavailability, induces endoplasmic reticulum stress, causes mitochondrial dysfunction, promotes smooth muscle cell proliferation, and drives a pro-thrombotic state via enhanced platelet aggregation and coagulation pathway activation. Homocysteine metabolism relies on crucial enzymatic pathways involving methylenetetrahydrofolate reductase (MTHFR) and cystathionine \beta-synthase (CBS), utilizing vitamins B6, B12, and folate as critical cofactors; genetic variants or dietary shortfalls within these pathways frequently provoke hyperhomocysteinemia.

Concurrently, CRP—a sensitive pentraxin acute-phase reactant produced by hepatocytes in response to upstream inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1\beta (IL-1\beta), and tumor necrosis factor-alpha (TNF-\alpha)—acts as both a systemic marker and an active pathogenetic mediator of vascular injury. In EH, elevated CRP directly downregulates endothelial nitric oxide synthase (eNOS) expression, diminishes NO availability, heightens arterial stiffness, upregulates cell adhesion molecules (such as VCAM-1 and ICAM-1), recruits inflammatory cells into the vascular intima, and amplifies reactive oxygen species (ROS) generation, thereby driving arterial remodeling.

The combined interaction between hyperhomocysteinemia and inflammation creates an intricate pathophysiological axis. Hyper-homocysteinemia can stimulate the cellular secretion of pro-inflammatory cytokines, upregulating the hepatic production of CRP. Conversely, persistent systemic inflammation can impair homeostatic homocysteine processing, establishing a destructive biological feedback loop that accelerates vascular stiffness and elevates peripheral resistance.

While multiple cross-sectional and longitudinal investigations indicate that these markers track with blood pressure elevations and predict future cardiovascular events, significant variability persists across different study populations, geographic cohorts, and genetic backgrounds. Consequently, localized clinical evidence is essential to clarify these metabolic-inflammatory linkages within distinct clinical settings.

Study Aims and Objectives

The primary aim of this study was to systematically investigate the correlation between serum homocysteine and whole blood CRP levels in patients diagnosed with essential hypertension, evaluating if these parameters shift in relation to blood pressure control and determining their diagnostic and therapeutic implications.

To fulfill this aim, the study addressed the following specific objectives:

1. To measure and compare serum homocysteine levels between newly diagnosed essential hypertension patients and healthy normotensive controls.
2. To measure and compare whole blood CRP levels between essential hypertension patients and healthy normotensive control subjects.

MATERIALS AND METHODS

Study Design and Setting

This study was designed as a prospective, observational case-control investigation. It was conducted from December 2024 to January 2025 within the clinical laboratories and OPDs of the Department of

Biochemistry and the Department of Medicine respectively at Jhalawar Medical College and Hospital, located in Jhalawar, Rajasthan, India.

Participant Selection

A total of 100 participants were enrolled and divided into two equal cohorts:

- **Cases (n = 50):** Newly diagnosed patients of either sex with documented essential hypertension of less than one year in duration, aged between 35 and 50 years, who provided written informed consent.
- **Controls (n = 50):** Age- and sex-matched healthy normotensive individuals who served as reference comparators.

Strict exclusion criteria were applied to prevent external metabolic or clinical confounding factors. Subjects were excluded if they presented with any of the following conditions:

- Diabetes mellitus
- Established cardiovascular diseases, coronary artery disease, myocardial infarction, or past history of stroke
- Secondary hypertension
- Renal dysfunction
- Peripheral vascular disease with evidence of tissue injury or loss, or history of transient ischemic attacks
- Current or previous use of lipid-lowering drugs

RESULTS

Table 1. Distribution of Study Subjects According to Age and Sex

Variable	Cases (n=50)	Controls (n=50)	Total (n=100)
Age (years)	43.14 ± 4.76	42.34 ± 4.95	42.74 ± 4.86
Male (n, %)	32 (64%)	31 (62%)	63 (63%)
Female (n, %)	18 (36%)	19 (38%)	37 (37%)

Table 2. Comparison of Baseline Blood Pressure Parameters

Parameter	Cases (n=50)	Controls (n=50)	p-value
Systolic BP (mmHg)	150 ± 5	130 ± 6	<0.001*
Diastolic BP (mmHg)	95 ± 3	85 ± 3	<0.001*

Table 3. Comparison of Whole Blood C-Reactive Protein (CRP) Levels

Group	CRP (mg/L)	p-value
Cases (n = 50)	5.80 ± 2.14	<0.001*
Controls (n = 50)	1.45 ± 0.82	

Table 4. Comparison of Serum Homocysteine Levels

Group	Homocysteine (µmol/L)	p-value
Cases (n = 50)	18.26 ± 4.02	<0.001*
Controls (n = 50)	10.08 ± 2.71	

Table 5. Summary of Biochemical Differences Between Cases and Controls

Parameter Reference	Direction of Absolute Shift in Cases	Statistical Significance
Serum Homocysteine	Distinctly Increased	Highly Significant ($p < 0.001$)
C-Reactive Protein	Distinctly Increased	Highly Significant ($p < 0.001$)
Total Cholesterol	No Significant Variation	Not Statistically Significant
Triglycerides	No Significant Variation	Not Statistically Significant
LDL-C & VLDL-C	No Significant Variation	Not Statistically Significant
HDL-Cholesterol	No Significant Variation	Not Statistically Significant
Renal Function Indices	No Significant Variation	Not Statistically Significant

DISCUSSION

Pathophysiological Interpretation of Key Findings

This investigation demonstrates that essential hypertension is characterized by distinct metabolic and inflammatory abnormalities, rather than presenting solely as a hemodynamic disorder. Hypertensive patients exhibited a significant increase in whole blood CRP (5.80 ± 2.14 mg/L) compared to controls (1.45 ± 0.82 mg/L), confirming active low-grade systemic inflammation. Concurrently, serum homocysteine levels were elevated in cases (18.26 ± 4.02 µmol/L) relative to controls (10.08 ± 2.71 µmol/L), indicating mild-to-moderate hyperhomocysteinemia.

The strong positive correlation between homocysteine and CRP ($r = 0.56$, $p < 0.001$) points toward a synergistic pathological mechanism. Hyperhomocysteinemia induces endothelial dysfunction by generating reactive oxygen species (ROS), which deplete nitric oxide (NO) bioavailability, impair vasodilation, and trigger endoplasmic reticulum stress. This vascular injury upregulates pro-inflammatory cytokines (such as IL-6 and TNF-\alpha), which stimulate hepatic synthesis of CRP.

In turn, CRP acts as an active mediator of vascular damage, downregulating eNOS expression, increasing cell adhesion molecules, and recruiting leukocytes into the intima. This dual mechanism leads to smooth muscle cell proliferation, collagen deposition, and a pro-thrombotic state, which accelerate arterial remodeling, increase peripheral resistance, and sustain blood pressure elevation.

Clinical and Public Health Conclusions

This study demonstrates that essential hypertension is significantly associated with elevated serum homocysteine and whole blood CRP levels, along with atherogenic lipid profile alterations, independent of renal dysfunction. The positive correlations between these biomarkers and blood pressure parameters indicate that metabolic and inflammatory dysregulation mirrors disease severity. These insights support transitioning from a purely hemodynamic model of hypertension to a broader, integrative approach that evaluates non-traditional biochemical markers alongside conventional blood pressure monitoring.

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