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THE CLINICAL RELEVANCE OF INTERLEUKIN 6 & hs-CRP IN CARDIOVASCULAR DISEASES: A CASE STUDY.

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ABSTRACT

Background

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, necessitating the identification of reliable biomarkers for early detection and risk assessment. Among these, high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) have emerged as crucial inflammatory mediators linked to the pathogenesis and development of CVD. Pro-inflammatory cytokine IL-6 is essential in endothelial dysfunction, atherosclerosis, and plaque instability, while hs-CRP serves as a systemic marker of inflammation, correlating with vascular injury and adverse cardiac events. This study aims to assess the association of baseline IL-6, hs-CRP, and LDL-C levels with cardiovascular events over one year in patients undergoing intensive cardiovascular treatment.

Methods

This research consisted of 100 patients with cardiovascular disease (CVD) and 100 healthy controls. After obtaining consent, demographic data, medication history, and cardiovascular risk factors were recorded. Clinical parameters, including age, sex, height, body weight, and blood pressure, were also recorded. Patients with liver diseases, renal dysfunctions, thyroid disorders, HIV, and acute inflammatory conditions were excluded. Blood samples were obtained for biochemical examination after a 12-hour fast. IL-6 levels were quantified using an ELISA kit (Ray Biotech, Inc.), Serum hs-CRP was measured using photometric analysis (autoimmune), and lipid profiles were assessed using enzymatic and colorimetric techniques.

Results

Patients with CVD showed significantly raised levels of total cholesterol, LDL, VLDL, triglycerides, hs-CRP, and IL-6 ($p<0.0001$), while HDL levels were lower. Increased BMI, waist circumference, and blood pressure were also noted. These results reinforce the link between dyslipidemia, inflammation, and CVD, emphasizing their importance in disease progression and risk evaluation.

Conclusion

Elevated hs-CRP and IL-6 levels may help in the prediction of cardiovascular risks and further improve the stratification in suspected coronary artery disease (CAD) cases. Managing risk factors in high-risk patients and further research on IL-6's causal role are essential.

Keywords: *Cardiovascular Disease (CVD), Lipid Profile, High-Sensitivity C-Reactive Protein (hs-CRP), Interleukin-6 (IL-6).*
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INTRODUCTION

Over the past three decades, Interleukin-6 (IL-6) and C-reactive protein (CRP), two inflammatory biomarkers, have been identified as independent predictors of cardiovascular events, with predictive accuracy comparable to low-density lipoprotein cholesterol (LDL-C) [1-5]. High-sensitivity C-reactive protein (hs-CRP) has since become an established biomarker in North America for assessing inflammatory risk in primary prevention and residual inflammation following statin therapy in secondary prevention [6]. However, its clinical use remains limited in Europe.

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CRP, a downstream liver-synthesized acute-phase protein, is not likely to directly contribute to atherothrombosis. In contrast, IL-6, a key cytokine that regulates CRP production, plays a central role in the inflammatory pathway relation with vascular events [7,8]. Mendelian randomization studies have shown that genetic variations in the IL-6 signaling pathway are linked to lifelong alterations in hs-CRP levels and cardiovascular risk [9,10]. Furthermore, findings from the CANTOS study showed that lowering inflammation through anti-cytokine therapy is directly associated with a lower incidence of atherothrombotic events [11-13]. As a result, IL-6 has emerged as a crucial focus for upcoming treatments for cardiac conditions [14-17].

Recent evidence from the COLCOT trial suggests that colchicine-based anti-inflammatory treatment can help lower the incidence of vascular events. This is particularly relevant as colchicine may influence the NLRP3 inflammasome, a regulator of IL-6 and hs-CRP production [18]. From a diagnostic perspective, IL-6, being a key component of the inflammatory cascade, may provide a more accurate assessment of cardiovascular risk than hs-CRP. However, limited comparative research exists on the predictive value of IL-6, hs-CRP, and LDL-C, particularly in patients on statin therapy, which has both lipid-lowering and anti-inflammatory effects [19].

To address these gaps, a large-scale prospective study was conducted on 100 participants as part of the Cardiovascular Inflammation Reduction Trial (CIRT) [20]. The study analyzed baseline IL-6, hs-CRP, and LDL-C levels and tracked their association with cardiovascular events during a period of one year. The findings focus on importance for further research to better understand the evolving association among inflammation, lipid levels, and vascular risk in patients receiving intensive cardiovascular treatment.

MATERIALS AND METHODS:

Study design

This study was a case-control analysis conducted to evaluate the clinical significance of interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) in cardiovascular disease (CVD) participants.

Study setting

The study was conducted on the patients attending the outpatient department (OPD) of General Medicine, IGIMS, Patna. The Outpatient Department (OPD) of General Medicine at IGIMS, Patna, provides comprehensive medical care for patients with a wide range of acute and chronic illnesses. It serves as a primary point for diagnosis, treatment, and follow-up, catering to a diverse patient population. The blood samples were collected and processed in collaboration with the Department of Microbiology and Biochemistry, IGIMS, Patna.

Study Duration and Sample Size

The study included a total of 200 participants, comprising 100 patients diagnosed with cardiovascular disease and 100 age-matched, healthy individuals as controls. The study included 200 participants to ensure a balanced comparison between cardiovascular disease (CVD) patients and healthy controls, improving the reliability of the results. A sample size of 100 per group was chosen to achieve statistical power for detecting significant differences in inflammatory and lipid markers between the two groups. The research was carried out over one year (April 2022-March 2023).

Inclusion Criteria as Follows:

- Patients diagnosed with cardiovascular diseases.
- Individuals aged 18 years and above.
- Participants who provided informed consent.

Exclusion Criteria as Follows:

- Individuals with liver diseases, renal dysfunction, thyroid disorders, and HIV infection.
- Patients presenting with acute inflammatory conditions such as infections, trauma, or fever.

Study procedure

After obtaining informed consent, participants completed a structured questionnaire covering demographic details, cardiovascular risk factors, and medication history. Measurements, including age, sex, weight, height, and blood pressure, were recorded. Among the CVD patients, 82% had hypertension, and 56% had diabetes. Most were undergoing treatment with antihypertensive drugs, cholesterol-lowering medications, or glycemic control therapy at the time of the study.

Blood samples were taken following a 12-hour fast and were transported to the respective Departments. IL-6 was quantified using a commercially available ELISA Kit (Ray Biotech, Inc.), and serum hs-CRP was measured using photometric analysis (autoimmune) in the Department of Microbiology. Lipid profiles, including total cholesterol, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, were measured using enzymatic and colorimetric methods in the Department of Biochemistry.

Data collection

Data collection ensured comparability between CVD patients and healthy controls by using a standardized questionnaire to gather demographic and clinical data. Key variables such as age, sex, BMI, blood pressure, and medication history were recorded uniformly across both groups. Laboratory analyses followed identical protocols to minimize variability and ensure accurate comparisons of inflammatory and lipid biomarkers.

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Statistical Analysis

Data analysis was carried out employing XLSTAT 2014 software, considering a p-value of <0.001 as statistically significant. A one-way analysis of variance (ANOVA) was applied to evaluate repeated measures within the groups. For comparisons among two groups, a paired Student's t-test was used, with results presented as Mean ± SD.

Ethical clearance

Ethical clearance for this study was obtained by the Institutional Ethics Committee, Indira Gandhi Institute of Medical Sciences, Patna (vide letter no. 451/IEC/IGIMS/2022, dated 01.04.2022), and informed consent was obtained from all patients.

Bias

To minimize potential bias, the study used age-matched healthy controls and standardized laboratory procedures for biomarker analysis. Additionally, data collection was conducted using a structured questionnaire to ensure consistency and statistical adjustments were made to account for confounding factors.

RESULTS

The study included 200 participants, with a mean age of 54.6 ± 9.3 years for CVD patients and 45.9 ± 11.3 years for controls, showing a significant age difference (p<0.0001). Males constituted a higher proportion of the CVD group, while both groups were matched for socioeconomic status. BMI and waist circumference were significantly higher in CVD patients, indicating greater obesity-related risk factors. Most CVD patients had hypertension (82%) and diabetes (56%), reflecting common comorbidities in this population (Table 1).

Table 1: Anthropometric and biochemical parameters of study participants

Parameter	CVD (n=100)	Control (n=100)	p-value
Age (years)	54.6 ± 9.3	45.9 ± 11.3	<0.0001
BMI (Kg/m²)	26.7 ± 2.4	22.01 ± 2.7	
WC (cm)	93.0 ± 6.3	82.6 ± 6.6	
Systolic BP (mmHg)	136.7 ± 20.7	118.1 ± 2.8	
Diastolic BP (mmHg)	86.1 ± 7.8	79.0 ± 2.5	
Total Cholesterol (mmol/L)	5.3 ± 0.8	3.6 ± 0.4	
Triglycerides (mmol/L)	2.1 ± 0.4	1.23 ± 0.2	
HDL (mmol/L)	0.8 ± 0.1	1.2 ± 0.19	
LDL (mmol/L)	3.5 ± 0.9	1.8 ± 0.44	
VLDL (mmol/L)	0.9 ± 0.2	0.56 ± 0.07	
hs-CRP (mg/L)	3.3 ± 0.6	1.17 ± 0.25	
IL-6 (pg/mL)	5.6 ± 0.65	4.00 ± 0.65	

Lipid profile analysis revealed a marked increase in total cholesterol, very-low-density lipoprotein (VLDL) levels, low-density lipoprotein (LDL), and triglycerides, whereas high-density lipoprotein (HDL) levels were significantly lower (p<0.0001) in CVD patients compared to controls (Figure 1).

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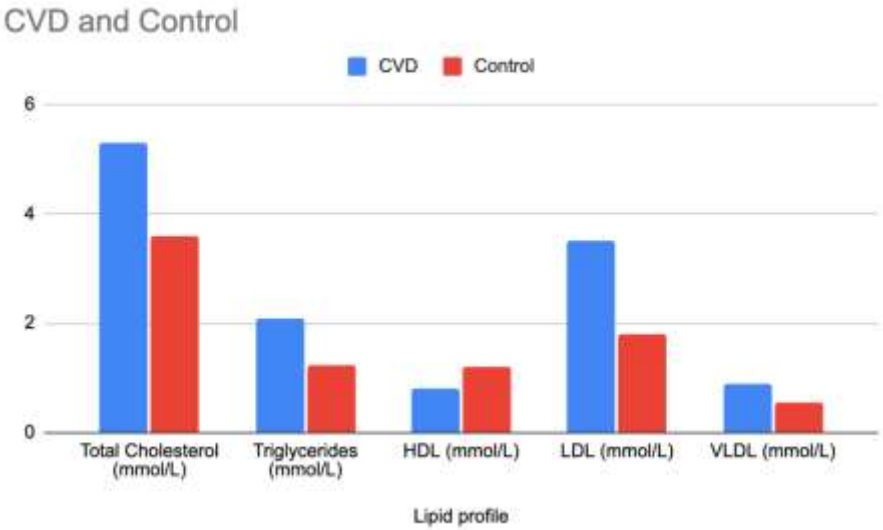

Figure 1: Comparison of lipid profile

Additionally, Interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP), two inflammatory biomarkers, were markedly increased ($p<0.0001$) in CVD patients compared to the baseline levels observed in the control group (Figure 2).

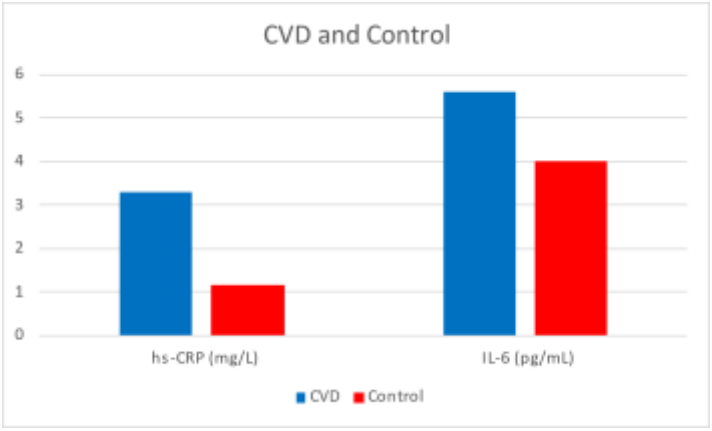

Figure 2: Comparison among CVD patients and controls

DISCUSSION

The present study demonstrated a significantly altered lipid profile in cardiovascular disease (CVD) patients compared to the control group ($p<0.0001$), characterized by elevated total cholesterol, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and triglycerides, with a concurrent reduction in high-density lipoprotein (HDL) levels. These lipid abnormalities indicate a heightened risk of atherosclerosis, as elevated LDL and triglyceride levels promote plaque formation and vascular inflammation, while reduced HDL impairs cholesterol clearance and endothelial function. This aligns with previous studies identifying dyslipidemia as a major risk factor for atherosclerotic cardiovascular disease (CVD) [21]. Elevated LDL, triglycerides, and total cholesterol levels have been strongly correlated with an increased risk of coronary heart disease, whereas HDL exerts a protective effect by facilitating reverse cholesterol transport and inhibiting oxidative stress [22,23]. The presence of hyperlipoproteinemia further underscores the importance of lipid regulation in preventing the progression of atherosclerosis and cardiovascular complications [24].

Our study also highlights the critical role of systemic inflammation in CVD pathogenesis, as evidenced by significantly elevated levels of high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) in CVD patients

compared to controls. IL-6, a pro-inflammatory cytokine, has been established as a key contributor to CVD, with increased serum levels correlating with a higher risk of cardiovascular death, stroke, and coronary artery disease [25,26]. Volpato et al. [27] and Maeda et al. [28] further reported that IL-6 levels serve as strong predictors of adverse cardiovascular outcomes, emphasizing its potential role as both a diagnostic and prognostic biomarker. Similarly, elevated CRP levels have been linked to myocardial infarction and unstable angina, reinforcing its value in cardiovascular risk stratification [29,30]. The strong association between inflammation and CVD suggests that chronic immune activation contributes to disease progression beyond traditional risk factors.

The mechanistic relationship between IL-6 elevation and CVD remains complex. IL-6 is synthesized by monocytes, endothelial cells, macrophages, and smooth muscle cells, particularly under ischemic and hypoxic conditions [31,32]. It promotes leukocyte activation and endothelial dysfunction, thereby exacerbating vascular inflammation and plaque instability [33]. Additionally, IL-6 is implicated in autonomic nervous system dysregulation, which further increases the risk of cardiovascular dysfunction [34]. Elevated hs-CRP levels, which are stimulated by IL-6, intensify the inflammatory response, contributing to enhanced monocyte recruitment, endothelial activation, and thrombus formation, thereby accelerating atherosclerosis and increasing the likelihood of cardiovascular events [35,36].

The anthropometric and biochemical characteristics of study participants provide additional evidence of metabolic and inflammatory dysregulation in CVD. CVD patients had significantly higher waist circumference, BMI, and blood pressure than controls, supporting previous findings that obesity and hypertension are major cardiovascular risk factors [37,38]. Excess adiposity contributes to insulin resistance, oxidative stress, and chronic inflammation, all of which promote endothelial dysfunction and atherogenesis. Hypertension, in particular, exacerbates vascular injury by increasing arterial stiffness and disrupting normal blood flow regulation, further accelerating cardiovascular damage [39].

The findings of this study underscore the importance of lipid abnormalities and systemic inflammation in CVD pathogenesis. Given that both dyslipidemia and inflammation contribute to cardiovascular events, integrated therapeutic strategies targeting lipid-lowering and anti-inflammatory pathways may be beneficial in CVD prevention and management. Statins, in addition to lowering LDL, exhibit anti-inflammatory effects by reducing CRP levels, making them a cornerstone in CVD treatment. Lifestyle interventions, including dietary modifications, physical activity, and weight management, remain essential in reducing cardiovascular risk. Future research should focus on elucidating the molecular mechanisms linking inflammatory cytokines and lipid metabolism to cardiovascular risk, which may aid in the development of innovative therapeutic strategies.

CONCLUSION

Elevated levels of these markers were strongly associated with dyslipidemia and adverse cardiovascular outcomes. The findings suggest that IL-6 and hs-CRP can serve as valuable indicators for cardiovascular risk assessment, aiding in the early detection and management of CVD. Targeting inflammation alongside traditional lipid-lowering therapies may provide a more comprehensive approach to reducing cardiovascular morbidity and mortality. Large-scale, multicenter studies are necessary to show the predictive accuracy and clinical applicability of these biomarkers in routine practice.

LIMITATIONS

This study offers important insights into the association between inflammatory biomarkers and cardiovascular disease; however, certain limitations should be considered. One key limitation is the relatively small sample size, which may limit the applicability of the findings to a larger population. Secondly, this was a case-control study, limiting the ability to show causality among elevated IL-6 and hs-CRP levels and CVD progression. Additionally, confounding factors such as diet, lifestyle, and genetic predisposition were not extensively controlled, potentially influencing the observed outcomes. Finally, the study relied on single-time-point biomarker measurements, which may not fully capture dynamic changes over time.

RECOMMENDATIONS

Future research should focus on prospective cohort studies to assess the temporal relationship among IL-6, hs-CRP, and cardiovascular events. Expanding the study population to include diverse ethnicities and risk profiles will enhance the generalizability of the findings. Evaluating additional markers alongside IL-6 and hs-CRP may give a more comprehensive risk assessment tool. Investigating the efficacy of anti-inflammatory therapies targeting IL-6 signaling in reducing cardiovascular risk can help determine potential therapeutic applications. Integrating biomarker-based risk stratification into clinical guidelines may improve individualized treatment strategies for high-risk patients.

GENERALIZABILITY

The generalizability of this study's findings may be influenced by the specific population characteristics, including demographic, genetic, and lifestyle factors, which may not be representative of broader populations. Since the study was conducted in a defined clinical setting, variations in healthcare access and treatment approaches in different regions could affect the applicability of the results.

Additionally, the relatively small sample size may limit extrapolation to larger, more diverse populations. Future studies with multi-center cohorts and diverse ethnic groups are needed to validate these findings across different populations. Despite these limitations, the study provides valuable insights into the interplay between lipid abnormalities, inflammation, and cardiovascular disease risk.

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SOURCE OF FUNDING
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CONFLICT OF INTEREST
No conflict of interest.

DATA AVAILABILITY
The data supporting the findings of this study are available from the corresponding author upon reasonable request.

LIST OF ABBREVIATIONS
CVD: Cardiovascular diseases
hs CRP: High-sensitivity C-reactive protein
IL-6: interleukin-6
CAD: coronary artery disease
LDL-C: low-density lipoprotein cholesterol
CIRT: Cardiovascular Inflammation Reduction Trial
OPD: Outpatient Department
VLDL: Very-Low-Density Lipoprotein
LDL: Low-Density Lipoprotein
HDL: high-density lipoprotein

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