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Beyond cholesterol: Exploring serum ferritin's and high-sensitivity C-reactive protein role in cardiovascular risk

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ABSTRACT

Background: Iron, a pivotal element in the oxidation of low-density lipoprotein (LDL) cholesterol, exerts influence on inflammatory responses and exhibits a positive association with coronary heart disease. Elevated levels of the inflammatory marker, C-reactive protein (CRP), serve as a predictive risk factor for subsequent cardiac events. **Aims and Objectives:** This study explores the interplay between cardiovascular disease risk factors and serum ferritin concerning CRP. **Materials and Methods:** A cohort of 750 subjects (375 males and 375 females) was subjected to analysis. Elevated levels were defined as CRP >3.0 mg/L, serum ferritin >200 ng/mL, total cholesterol >200 mg/dL, and LDL-cholesterol >160 mg/dL. HDL cholesterol levels below 40 mg/dL were categorized as low. **Results:** Within the low LDL-cholesterol group, no discernible correlation was observed between serum ferritin and high-sensitivity CRP (hsCRP) (odds ratio [OR] of 54.95, 95% confidence interval [CI] = 0.81–3.48, P<0.148). Conversely, a correlation was identified in the elevated LDL-cholesterol group (OR of 10.98, 95% CI = 1.12–111.22, P<0.05). Furthermore, the introduction of an interaction term in the assessment of the correlation between elevated hsCRP and LDL-cholesterol reaffirmed a robust correlation between hsCRP and serum ferritin (P<0.005). **Conclusion:** The oxidation of LDL-cholesterol by serum ferritin emerges as a potential contributor to inflammatory reactions and heightened hsCRP levels. Prospective studies are warranted to investigate whether interventions targeting the reduction of serum ferritin and CRP levels, through medical interventions and lifestyle modifications, could prove efficacious in preventing cardiovascular diseases.

Key words: Ferritin; C-reactive protein; CVS; Low-density lipoprotein cholesterol; Risk factors

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INTRODUCTION

In the intricate symphony of cardiovascular health, the role of iron transcends its mere biochemical significance, assuming a central position in the intricate dance of low-density lipoprotein (LDL) cholesterol. This elemental participant, indispensable for metabolic processes, weaves a narrative that extends into the realms of inflammation, intricately interwoven with coronary heart disease – a formidable adversary in the panorama of human health. Several investigations have proposed a correlation between anomalous iron storage and the initiation of atherosclerotic coronary artery disease (CAD).[1-5] A subset of studies has disclosed a remarkable 3-4-fold surge in the prevalence of cardiovascular disease among those with elevated serum iron levels compared to counterparts with diminished serum iron levels.[6] Moreover, serum ferritin has been pinpointed as a correlate with cardiovascular disease and cardiovascular mortality,[7] giving rise to the conceptual framework recognized as the "iron hypothesis."[3] The rationale behind this hypothesis lies in iron's capacity to donate electrons, thereby facilitating the generation of reactive oxygen species, notably the hydroxyl radical (OH^-), through the Fenton reaction involving hydrogen peroxide (H_2O_2). The accumulation of excess iron in tissues may catalyze the production of highly reactive oxygen free

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radicals, including the hydroxyl radical, singlet oxygen, or H_2O_2, instigating the oxidation of LDL – a pivotal trigger for the development of atherosclerotic CAD.[8]

Amidst this complexity, the ascendance of C-reactive protein (CRP) as a prognostic sentinel is noteworthy, with elevated CRP levels serving as an ominous harbinger, predicting the occurrence of future cardiac events. A recent study underscored an association between ferritin and CRP.[9] Chronic inflammatory processes have been implicated in fostering the progression of atherosclerosis and instigating cardiovascular diseases. The escalation of a key inflammatory marker, CRP, emerges as a risk factor for future cardiac events, even in ostensibly healthy individuals.[10,11] CRP has also exhibited associations with various cardiovascular risk factors, encompassing age, total cholesterol levels, triglycerides (TG), blood glucose levels, systolic blood pressure, and insulin resistance.[12,13] However, existing data, particularly in apparently healthy Asians, remain insufficient to establish a correlation between CRP and oxidative stress and serum ferritin.[6,14,15]

In the pursuit of unraveling the multifaceted dynamics within the cardiovascular landscape, our study embarks upon a meticulous exploration, guided by a cohort of 750 South Indian subjects thoughtfully balanced between genders. Within this diverse canvas, we scrupulously define thresholds for elevated CRP, serum ferritin, and lipid parameters, aiming to scrutinize the interplay between cardiovascular disease risk factors and the often-overlooked protagonist – serum ferritin. Through elucidating these intricate associations, we aspire to contribute meaningful insights into the nuanced interplay between iron metabolism, inflammation, and cardiovascular risk in a population hitherto underrepresented in existing literature.

Aims

The current study aims to understand how serum ferritin and hsCRP are connected to heart health.

Objectives

1) To investigate the intricate correlation between serum ferritin and hsCRP within the domain of cardiovascular risk factors. 2) To quantify the strength of observed relationships, offering insights with clinical implications and potential strategies for prevention.

MATERIALS AND METHODS

Study population

The study cohort was meticulously selected from individuals undergoing health screening at the Government General Hospital affiliated with Rangaraya Medical College, Kakinada, Andhra Pradesh, spanning from January 2023 to November 2023. A total of 750 subjects (375 males and 375 females) were included, all of whom had their serum ferritin levels measured. Exclusion criteria comprised individuals taking statins, antihypertensive agents, or antidiabetic agents, as well as those with acute or chronic inflammatory diseases, thyroid disorders, or any suspicion of malignancies. Written informed consent was obtained from all participants. Hypertension was defined as systolic blood pressure exceeding 140 mmHg or diastolic blood pressure surpassing 90 mmHg. Diabetes was ascribed to individuals with a blood glucose level exceeding 125 mg/dL following a 12-h fast.

Physical parameters, including height, weight, and systolic and diastolic blood pressure, were meticulously measured for each subject. Following confirmation of a fasting duration exceeding 12 h, serum total cholesterol, TG, serum high-density lipoprotein (HDL) cholesterol, and serum LDL cholesterol concentrations were determined. Automated measurements were obtained for height and weight, whereas serum lipid concentrations were assessed using a Beckman Coulter Autoanalyzer, AU 480. In accordance with adult treatment panel recommendations, serum HDL-cholesterol levels below 40 mg/dL were classified as low.[16] To gauge *in vivo* iron concentrations, serum ferritin levels were assessed using a Beckman Access 2.0, with levels exceeding 200 ng/mL considered elevated. High-sensitivity CRP (hsCRP) levels, quantified to 0.175 mg/L using the Beckman Coulter Autoanalyzer, AU 480, were deemed elevated if surpassing 3.0 mg/L, following American Heart Association guidelines.[17]

Ethical considerations

This study prioritizes ethical standards by securing informed consent, safeguarding participant privacy, and ensuring data security. Participants, comprising 750 South Indian subjects, underwent meticulous scrutiny, defining thresholds for elevated cardiovascular risk factors. Rigorous adherence to ethical guidelines, scientific integrity, and transparency in reporting aims to contribute meaningful insights into the complex interplay between iron metabolism, inflammation, and cardiovascular risk in an underrepresented population

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 26, IBM Corp. Released 2019). Continuous variable data were expressed as means ± standard deviations. Due to the skewed distribution of hsCRP levels, natural log transformation was employed for the correlation analysis between hsCRP and other variables, utilizing Pearson's correlation coefficient (Table 1). Age- and gender-adjusted odds ratios (OR) between ferritin and lipids were computed concerning elevated hsCRP levels (Table 2). To further

Table 1: Relationship (R-value) between log CRP and the CVS risk factors

Variable	Total		Male		Female	
	R	P	R	P	R	P
Age	0.189	<0.001	0.125	0.005	0.300	<0.001
BMI (kg/m^2)	0.245	<0.001	0.178	<0.001	0.288	<0.001
Serum ferritin (ng/mL)	0.213	<0.001	0.147	0.001	0.211	0.005
Total cholesterol (mg/dL)	0.008	0.05	0.07	0.186	0.110	0.058
HDL cholesterol (mg/dL)	−0.229	<0.001	−0.211	<0.001	−0.207	<0.001
LDL cholesterol (mg/dL)	0.092	0.022	0.061	0.223	0.097	0.088
Triglyceride (mg/dL)	0.188	<0.001	0.123	0.004	0.256	<0.001

BMI: Body mass index, HDL: High-density lipoprotein

Table 2: The age- and gender-adjusted probability of experiencing elevated hsCRP in relation to ferritin and TG levels

Variable	Elevated hsCRP	
	OR	95% CI
Low LDC group (LDL ≤ 160 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.88	1.04 − 4.56
High LDL group (LDL > 160 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	11.85	1.87 − 56.78
High HDL group (HDL ≥ 40 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.59	1.15 − 3.98
Low HDL group (HDL < 40 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.44	0.31 − 7.78

hsCRP > 3.0 mg/mL. CI: Confidence interval, HDL: High-density lipoprotein

Table 3: The likelihood of elevated hsCRP, adjusted for age, gender, non-smoker status, diabetes, BMI, and hypertension, in accordance with ferritin and TG levels

Variable	Elevated hsCRP	
	OR	95% CI
Low LDC group (LDL≤160 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.57	0.78–4.18
High LDL group (LDL>160 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	10.96	1.09–106.95
High HDL group (HDL≥40 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.56	0.83–5.32
Low HDL group (HDL<40 mg/dL) Ferritin: Elevated (>200 ng/mL)/not elevated	1.63	0.21–10.44

hsCRP>3.0 mg/mL. BMI: Body mass index, CI: Confidence interval, HDL: High-density lipoprotein

explore the association between serum iron, serum lipids, and elevated hsCRP levels, multiple logistic regression analyses were performed, accounting for potential confounders such as age, gender, smoking, body mass index (BMI), hypertension, and diabetes (Table 3). In addition, logistic regression incorporated an interaction term (LDL-cholesterol X serum ferritin) to evaluate the correlation between increased hsCRP, ferritin, and LDL-cholesterol. If the interaction term yielded a P<0.05, the analysis was reiterated with only LDL-cholesterol X serum ferritin as the independent variable. A significance level of P<0.05 was applied for statistical interpretation.

RESULTS

Clinical characteristics of the study population

The average age of the entire study cohort stood at 47.6±10.5 years, with nearly half of the subjects reaching the age milestone of 50 years. The gender distribution manifested as a ratio of 1 male-to-1 female. A scant 7.95% of the subjects exhibited a BMI exceeding 30, whereas 8.05% had diabetes, and 22.45% were smokers. The mean BMI registered at 23.35±3.6 kg/m^2, and 12.1% of the subjects were identified with hypertension. Serum biomarker profiles indicated mean total cholesterol of 237.21±25.4 mg/dL, mean HDL-cholesterol of 58.1±10.35 mg/dL, mean LDL-cholesterol of 138.47±22.65 mg/dL, mean hsCRP of 1.28±1.89 mg/dL, and mean serum ferritin of 114.75±53.95 ng/mL (Table 4). Elevated hsCRP levels were observed in 12.9% of the subjects, whereas 11.75% exhibited elevated serum ferritin levels, 8.55% had low HDL-cholesterol levels, and 13.42% displayed elevated LDL-cholesterol levels (Figures 1 and 2; Table 5).

Correlation of log CRP and other cardiovascular risk factors

The logarithmically transformed CRP (log hsRP) exhibited a statistically significant positive correlation with age, body mass index, total cholesterol, TG, and serum ferritin, while demonstrating an inverse relationship with HDL-cholesterol (Table 1).

Association of hsCRP and serum ferritin with lipid levels

After meticulous adjustments for age and gender, a significant association emerged between serum ferritin and hsCRP levels in subjects with low LDL-cholesterol (OR=1.88, 95% CI=1.04 −4.56, P<0.05). In the high

Table 4: Demographic characteristics of the study participants

Variable	Total (n=700) (%)	Male (n=375) (%)	Female (n=375) (%)
Age (years)	47.6±10.5	45.8±10.7	49.4±10.3
20–29	2.35	2.2	2.5
30–39	26.06	28.35	23.78
40–49	32.85	36.8	28.9
50–64	37.68	38.9	36.46
≥65	1.06	1.07	1.05
Body mass index (kg/m^2)	23.35±3.6	23.9±2.5	22.8±4.7
<30	92.05	91.3	92.8
≥30	7.95	8.7	7.2
Diabetes (%)	8.05	8.5	7.6
Hypertension (%)	12.1	12.45	11.75
Current smoker (%)	22.45	39.7	5.2
Total cholesterol (mg/dL)	237.21±25.4	247.65±22.7	226.78±28.27
HDL cholesterol (mg/dL)	58.1±10.35	56.7±10.8	59.5±9.9
LDL cholesterol (mg/dL)	138.47±22.65	137.7±25.8	139.25±19.5
Triglyceride (mg/dL)	136.12±67.75	154.3±72.1	117.94±63.4
hsCRP (mg/dL)	1.28±1.89	1.29±1.95	1.28±1.83
Serum ferritin (ng/mL)	114.75±53.95	168.2±73.3	61.3±34.9

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, hsCRP: High-sensitivity CRP

Table 5: Distributions of total cholesterol, HDL, LDL, hsCRP, and serum ferritin

Variable	Total (%)	Male (%)	Female (%)
Total cholesterol			
Normal	34.3	35.7	32.9
Elevated	55.2	64.3	46.1
HDL cholesterol			
Low	8.55	9.3	7.8
Normal	92.5	90.7	92.2
LDL cholesterol			
Normal	86.58	78.6	94.56
Elevated	13.42	21.4	5.44
hsCRP			
Normal	87.1	84.6	89.6
Elevated	12.9	15.4	10.4
Serum ferritin			
Normal	88.25	84.4	92.1
Elevated	11.75	15.6	7.9

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, hsCRP: High-sensitivity CRP

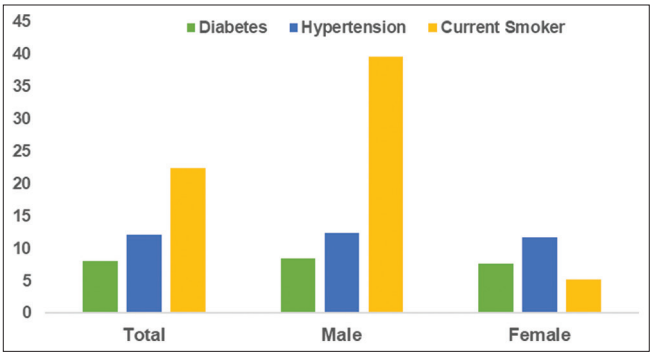

Figure 1: Distribution of CVS risk factors-diabetes, hypertension, smoking in male and female

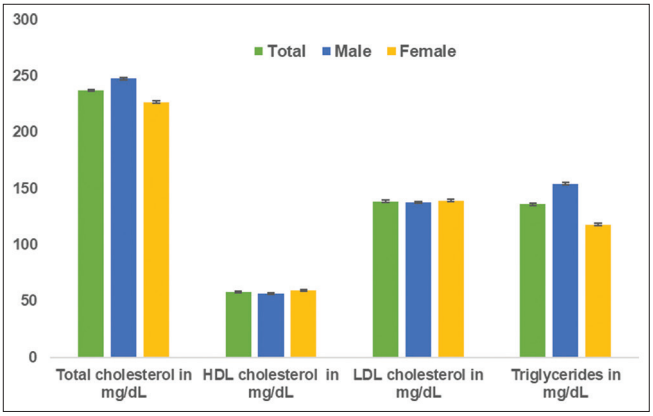

Figure 2: Confounders of CVS in male and females

LDL-cholesterol group, this correlation intensified compared to the low LDL-cholesterol group (OR=11.85, 95% CI=1.87 −56.78, P<0.008). A notable correlation was discerned between hsCRP and serum ferritin in the high HDL-cholesterol group (OR=1.59, 95% CI=1.15−3.98, P<0.05), whereas no such correlation was observed in the low HDL-cholesterol group (OR=1.44, 95% CI=0.31−7.78, P<0.5) (Table 2). Even after adjusting for potential confounders such as age, gender, smoking, diabetes, body mass index, and hypertension, the association between serum ferritin and hsCRP remained insignificant in the low LDL-cholesterol group (OR=1.57, 95% CI=0.78−4.18, P<0.1). However, in the high LDL-cholesterol group, elevated serum ferritin was associated with heightened hsCRP levels (OR=10.96, 95% CI=1.09−106.95, P<0.03). Notably, no correlation was observed between serum hsCRP and serum ferritin levels in the high HDL-cholesterol group (OR=1.56, 95% CI=0.83−5.32, P<0.1) or the low HDL-cholesterol group (OR=1.63, 95% CI=0.21–10.44, P<0.5) (Table 3). Logistic regression analysis, incorporating the interaction term (LDL-cholesterol X serum ferritin), validated a significant correlation between hsCRP and serum ferritin

when LDL-cholesterol levels were elevated (P<0.005).

DISCUSSION

Inflammatory processes are widely recognized for their pivotal role in initiating and hastening atherosclerosis. Numerous studies have highlighted the association between the inflammatory marker CRP and the heightened risk of cardiovascular disease.[10-13,18] Both CRP and serum ferritin serve as acute phase reactants, rising during episodes of inflammation or infection. Salonen's research[6] emphasized that elevated serum ferritin levels contribute to the accelerated oxidation of LDL-cholesterol, a phenomenon known to induce inflammation within blood vessels, thereby fostering the progression of atherosclerosis. Patients exhibiting serum ferritin concentrations exceeding 200 ng/mL faced a 2.2-fold higher risk of myocardial infarction compared to those with levels below 200 ng/mL. Nafari et al., underscored the significant role of LDL-cholesterol in cardiovascular disease induction through the indirect impact of serum ferritin. Notably, serum LDL-cholesterol levels exhibit a modest correlation with CRP, even after accounting for other cardiovascular risk factors. Simultaneous elevation of both CRP and LDL-cholesterol proves to be a superior indicator of cardiovascular risk compared to the elevation of either marker in isolation.[19]

Furthermore, Mainous et al. reported a positive correlation between elevated serum CRP concentrations and serum ferritin levels (OR=1.30, 95% confidence interval [CI]=1.10–1.55). In subjects with elevated levels of both ferritin and LDL-cholesterol, the correlation between serum CRP and serum ferritin concentrations strengthened (OR=1.88, 95% CI=1.19–2.94). Interestingly, HDL-cholesterol has also been implicated in contributing to the correlation between serum CRP and serum ferritin concentrations.[20]

Our findings affirm that both LDL-cholesterol and serum ferritin exhibit correlations with CRP, thereby inciting an inflammatory reaction indicative of cardiovascular disease risk. Furthermore, the introduction of an interaction term among subjects with elevated LDL-cholesterol reveals an intensified correlation between hsCRP and serum ferritin. This outcome suggests the potential role of ferritin in instigating an inflammatory reaction through the oxidation of LDL-cholesterol, consequently elevating CRP concentrations.

Contrastingly, the Atherosclerosis Risk in Communities (ARIC) study[21] failed to identify a correlation between serum ferritin and the early atherosclerosis marker, along with no association between serum ferritin and LDL oxidation parameters. However, caution is warranted in interpreting these results due to certain limitations. The method used to measure the lag phase to LDL oxidation lacked standardization, the sample size was relatively small, and precise classification based on smoking habits was not conducted, with most subjects exhibiting normal ferritin concentrations. In our study, adjustments for various cardiovascular factors, including smoking, revealed a correlation between hsCRP and serum ferritin in the elevated LDL group.

While acknowledging our study's limitations, such as serum ferritin being an acute phase reactant and not an accurate measure of total body iron stores, the absence of markers for increased oxidative stress or oxidized LDL-cholesterol measurement, and the cross-sectional nature of the study with self-selected subjects, we contend that our inclusion of a sizable population and the exclusion of subjects affected by other conditions bolster the reliability of our findings. In conclusion, elevated serum ferritin aligns with heightened hsCRP levels, particularly in the elevated LDL group, underscoring the potential inflammatory role of ferritin. Subsequent experimental studies are imperative to validate the relationship between ferritin and CRP and to ascertain whether medical intervention and lifestyle modifications aimed at decreasing ferritin and CRP levels confer benefits in reducing cardiovascular disease.

Limitations of the study

The serum ferritin as an acute phase reactant introduces uncertainty about its precision in reflecting total body iron stores, affecting its specificity as an indicator of iron-related inflammatory processes. Additionally, the cross-sectional design limits the establishment of causal relationships, calling for longitudinal investigations to better understand the dynamic nature of observed associations over time.

CONCLUSION

Our study underscores the pivotal role of inflammatory processes in atherosclerosis, highlighting the association between CRP and serum ferritin in cardiovascular disease risk. Elevated serum ferritin contributes to LDL-cholesterol oxidation, fostering inflammation and atherosclerosis. Correlations between LDL-cholesterol, serum ferritin, and CRP emphasize cardiovascular risk. Notably, a heightened correlation between hsCRP and serum ferritin is evident in subjects with elevated LDL-cholesterol. Despite differing study results, our findings support the potential inflammatory role of ferritin, particularly in the context of elevated LDL levels. Future studies are crucial to validate these relationships and explore interventions targeting ferritin and CRP for reducing cardiovascular disease risk.

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Author's contributions:
JN- As the corresponding author, played a pivotal role in study conception, design, and oversight; **VMG-** Contributed significantly to data collection, analysis, and interpretation; **PG-** Provided expertise in statistical analysis and contributed to result interpretation. All authors critically reviewed and approved the final manuscript, ensuring its scientific rigor and ethical standards; **JN-** Coordinated collaborative efforts, synthesizing the diverse contributions into a cohesive study exploring the intricate dynamics of cardiovascular risk factors.

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