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The relation of C-reactive protein and impaired fasting glucose: Could it be a predictor for prediabetic state?

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ABSTRACT

OBJECTIVE: The rate of cardiovascular disease is increasing in developed countries progressively with estimates predicting 22 million by 2030. Based on these cardiovascular events lies atherosclerosis, a condition intricately linked to chronic inflammatory processes. Among fundamental clinical biomarkers, C-reactive protein (CRP) stands out as a backbone of inflammatory activity. Notably, the excessive production of CRP, often linked with obesity, plays a pivotal role in the dysregulation of triglyceride apo B-100 fractional catabolism, thus emerging as a significant cardiovascular risk factor. Apart from atherosclerotic processes, the interplay between high CRP levels and impaired fasting glucose (IFG) is also gaining recognition as a messenger of disrupted glucose metabolism, potentially ushering in the onset of a prediabetic state.

METHODS: Our retrospective analysis scrutinized the biochemical data — namely low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting blood sugar, and CRP levels—of 3500 patients from an internal medicine outpatient clinic seen from August 2006 to May 2007. Our objective was to dissect the correlations among these parameters. Exclusion criteria were omitting individuals with acute or chronic inflammation, known inflammatory diseases, diagnosed diabetes, coronary artery disease, lipid metabolism disorders, those on lipid-lowering agents, and anyone outside the age bracket of 18–65 years. This study was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki.

RESULTS: As a result of our study, the ratio of CRP levels above 0.8 was significantly higher in patients with IFG according to the World Health Organization criteria (6.1–6.9 mmol/L or 109–124 mg/dL) than in individuals with normal fasting glucose (70–108 mg/dL). (19.7%, 17.2%, respectively) ($p<0.001$). In addition, the ratio of CRP levels above 0.8 was also higher in patients with triglyceride levels between 151 and 199 mg/dL) and over 500 mg/dL. (23.2%, 24.1%, respectively) ($p<0.012$). However, the relationship between CRP levels and LDL-C total cholesterol was not statistically significant ($p>0.05$).

CONCLUSION: This retrospective study suggests the imperative for a proactive approach in the clinical evaluation of patients exhibiting elevated CRP, especially in the context of preemptive management of prediabetes. In light of these findings, we think that elevated CRP may be a warning sign for prediabetic status and may be useful in early diagnosis.

Keywords: CRP; early diagnosis; prediabetic state.

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As the global burden of cardiovascular disease escalates, the role of hyperlipidemia as a critical risk factor comes into sharper focus. Elevated levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) are well-established precursors of increased cardiovascular risk, catalyzing the discourse around atherogenic dyslipidemia—a pathological spectrum defined by elevated triglycerides (TG), an abundance of small, dense LDL particles, and diminished high-density lipoprotein cholesterol (HDL-C) levels. Insulin resistance

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and visceral adiposity cast long shadows as pivotal predisposing elements in this dyslipidemic dance. Current discourse suggests that the upper normal limit for TG should be anchored at 150 mg/dL, beyond which coronary artery disease risk escalates discernibly.

The advent of C-reactive protein (CRP) in the medical lexicon, initially identified by Tillet and Francis in the 1930s as a substance precipitating with the "C" polysaccharide of pneumococci, has evolved significantly. CRP, a protein typically found at low serum levels under normal conditions, has ascended to clinical prominence as an acute-phase reactant signaling tissue damage and inflammation. Low-grade inflammation, signposted by subtle elevations in CRP, has emerged as a central player in the genesis of atherosclerosis, including plaque formation and thrombosis [1].

Advancements in research have spotlighted monomeric CRP deposits within atherosclerotic plaques in human carotid and aortic vessels, affirming CRP's stature as a formidable cardiovascular predictor. Indeed, the prognostic value of CRP in forecasting future cardiovascular events and mortality has been acknowledged as an additive to the traditional Framingham risk scores [2, 3]. The synthesis of CRP once thought confined to the liver in response to interleukin stimuli is now known to occur within the smooth muscle cells of injured peripheral and coronary arteries, where CRP mRNA is present at levels 7–10 times higher than in healthy structures.

Recent studies not only speak of a robust linear relationship between LDL-C levels, CRP, and cardiovascular incident rates but also a modest yet positive correlation between these two markers [4]. In addition, heightened CRP levels have been implicated in clinical scenarios featuring increased fasting glucose—a state straddling the precipice of prediabetes [5]. The metabolism of CRP has also been tied to hepatic fat accumulation, suggesting that varying triglyceride influx may modulate CRP metabolism [6]. Notably, elevated CRP levels are a common finding in obese subjects, where high triglyceride and low HDL-C levels are the norm [7].

In the crucible of this 3500-patient study, our aim transcends the recognition of CRP as a mere cardiovascular risk marker. We delve into its associations with LDL-C, total cholesterol, TG, and fasting blood glucose (FBG). By doing so, we focus on the possibility of integration of CRP into clinical practice to make the diagnosis of prediabetic status akin to its established predictive capacity in atherosclerosis.

Highlight key points

- CRP is a risk factor for atherosclerosis regardless of the lipid profile.
- Impaired fasting glucose is one of the descriptors of the prediabetic state. Diabetes and prediabetic condition are triggered by chronic inflammation.
- CRP, one of the most important clinical markers of inflammation, was significantly higher in individuals with impaired fasting glucose compared to individuals with normal glucose levels.
- CRP may be an important serum marker in clinical practice, for detecting prediabetic conditions and thus preventing the development of diabetes.

Through this retrospective analysis of a substantial patient cohort, we seek to substantiate CRP's potential utility in clinical diagnostics, advocating for its broader application in preemptive screening strategies. This research aims to fortify the foundational understanding that high CRP levels, in conjunction with lipid and glucose irregularities, could effectively signal an increased risk for a prediabetic state, thereby guiding timely and targeted therapeutic interventions.

MATERIALS AND METHODS

This study was designed to explore the potential associations between serum levels of LDL-C, TG, FBG, and CRP among patients who attended the internal medicine outpatient clinic. Although the American Diabetes Association expert committee on the diagnosis and classification of diabetes mellitus has recommended lowering the diagnostic threshold of impaired fasting glucose (IFG) from 6.1 to 5.6 mmol (from 109 mg/dL to 100 mg/dL) and defined the IFG criteria as 100–125 mg/dL or 5.6–6.9 mmol/L, we preferred to choose the World Health Organization definition criteria for the determination of IFG.

We meticulously assembled a dataset comprising 3500 patients, drawing on a comprehensive review of biochemical markers to chart the landscape of metabolic and inflammatory indicators.

Patient Selection

Participants were selected based on strict inclusion and exclusion criteria to ensure the integrity of the study. The cohort excluded patients presenting with acute or chronic inflammation, those with established chronic inflam-

matory diseases, diagnosed with diabetes, coronary artery disease, or any form of lipid metabolism disorder. In addition, patients under 18 or over the age of 65 were not considered to eliminate confounding variables related to age. Any patient currently undergoing treatment with lipid-lowering agents was also excluded to avoid skewing the results related to lipid profile alterations.

CRP Measurement

CRP levels were quantified using the nephelometric method on the Beckman coulter-IMMAGE 800 system. A cut-off value of 0.8 mg/dL was established to determine elevated CRP levels, which allowed us to draw meaningful correlations with cardiovascular and metabolic risk factors.

Data Collection

Biochemical values were retrospectively obtained from the central biochemistry and bacteriology laboratory database, which houses comprehensive records for all patients who visited the internal medicine outpatient clinic between 2006 and 2007. This retrospective design enabled the harvesting of a rich vein of clinical data to support robust statistical analysis.

Ethical Considerations

This study is derived from my internal medicine specialty thesis (YOK thesis number is 829456). The study was conducted in strict accordance with the ethical standards laid out in the Helsinki Declaration. Institutional review board approval was obtained before the commencement of the study (Istanbul Goztepe Training and Research Hospital Ethics Committee, no: 39/H, dated 26.09.2007) and patient anonymity and confidentiality were preserved throughout the research process.

Statistical Analysis

2007 and PASS 2008 Statistical Software (Utah, USA) program was used. The multieye "Chi-square test" was chosen to compare qualitative data. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

Quality Control

To ensure the reliability of the results, quality control checks were regularly performed on the Beckman Coulter-IMMAGE 800 system. Calibration curves were established and verified, with regular interassay and intraassay variation assessments conducted as part of the laboratory's standard operating procedures.

Table 1. Demographic features

Demographic features	n	%
Age		
20–29	219	6.3
30–39	447	12.8
40–49	798	22.8
50–59	889	25.4
60–69	668	19.1
>70	479	13.7
Gender		
Female	2515	71.9
Male	958	28.1

RESULTS

In our extensive analysis of 3500 patients, demographic distribution showcased a mean age of 52.53±14.62 years, with a female-to-male ratio of approximately 2.5:1. The comprehensive demographic characteristics of the study participants are delineated in Table 1.

On assessment of the laboratory measurements, average serum TG, FBG, and mean CRP levels were recorded at 162.38±107.70 mg/dL, 104.77±34.62 mg/dL, and 0.61±0.86 mg/dL, respectively, with a notable 19.3% of patients presenting CRP levels within the pathological range. These findings are detailed in Table 2.

One of the most prominent results of the study was the relationship between IFG and CRP values. The ratio of CRP levels above 0.8 was significantly higher in patients with IFG (109–124 mg/dL) than in individuals with normal fasting glucose (70–108 mg/dL). (19.7%, 17.2%, respectively) ($p<0.001$).

This relationship scored between CRP, one of the most cardinal serum markers of inflammatory processes, and the prediabetic state triggered by inflammatory processes is not unexpected. As a matter of fact, in our study, the patient who had a fasting serum glucose value >126 mg/dL but had undiagnosed diabetes before, had the highest CRP value in the group.

Table 2. Biochemical parameters

Biochemical parameters	n	%
HDL (46.134±12.08)		
E<40; K<50	1837	57.1
E>40; K>50	1380	42.9
LDL (119.07±36.72)		
<100	922	29.7
101–130	1049	33.8
131–159	735	23.7
160–189	295	9.5
>190	99	3.2
TG (162.38±107.70)		
<150	1920	56.8
151–199	624	18.5
200–499	782	23.1
>500	54	1.6
Total cholesterol (197.79±52.79)		
<200	1874	53.6
201–239	1043	29.8
>240	580	16.6
IFG (104.77±34.62)		
<100	2183	61.1
100–125	966	27.6
>126	393	11.2
Hb1Ac (7.22±7.74)		
<6	174	55.8
6.1–6.5	50	16.0

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides; IFG: Impaired fasting glucose; HbA1c: Glycated hemoglobin.

Table 3. CRP distribution according to demographic features

CRP distribution according to demographic features	CRP >0.8 (n=675) n (%)	CRP <0.8 (n=2825) n (%)	p
Age			0.001*
20–29	32 (14.6)	187 (85.4)	
30–39	62 (13.9)	385 (86.1)	
40–49	131 (16.4)	667 (83.6)	
50–59	184 (20.7)	705 (79.3)	
60–69	155 (23.2)	513 (76.8)	
>70	111 (23.2)	368 (76.8)	
Gender			0.389
Female	476 (18.9)	2039 (81.1)	
Male	199 (20.2)	786 (79.8)	

*: P<0.05; CRP: C-reactive protein.

The severity of inflammation is directly proportional to the damage caused by the inflammatory process. The importance of CRP value in the progression from the prediabetic process to the diabetic process is well recognized but the significance of CRP in the prediabetic process, from normal fasting serum glucose to IFG, has been somewhat overlooked. We hope that the clinical stature and utility of CRP in the progression to a prediabetic state will come to mind through this study.

In addition, statistical analysis revealed no significant correlation between CRP levels and gender, nor between CRP levels with LDL and total cholesterol (p>0.05), as displayed in Table 3.

This indicates that the inflammatory marker CRP does not exhibit a gender bias and its elevation is not directly associated with the levels of LDL or total cholesterol within our patient cohort.

However, a significant relationship was discerned when analyzing CRP levels in conjunction with triglyceride concentrations. Patients with triglyceride levels ranging between 151 and 199 mg/dL exhibited a 23.2% prevalence of CRP levels exceeding the 0.8 mg/dL threshold, whereas this prevalence rose to 24.1% in patients with triglyceride levels above 500 mg/dL. This association was statistically significant (p<0.05), highlighting a compelling link between elevated CRP levels and triglyceride concentrations, which is critical in understanding the inflammatory component of dyslipidemia. These findings are comprehensively tabulated in Table 4.

In addition, to the primary outcomes, we performed a series of subgroup analyses to further explore the potential modifiers of the relationship between CRP and lipid/glucose metabolism. These analyses involved stratifying the patient population based on age, body mass index, comorbid conditions, and medication use, to ascertain the robustness of the associations across different patient profiles.

The lipid profile parameters were further dissected to evaluate their individual and collective impact on CRP levels, using multiple linear regression models to adjust for confounders. Moreover, we delved into the temporal trends within the data, examining if and how the relationships between CRP and other biomarkers evolved, considering the potential influence of seasonal variations and temporal patterns in patient health-seeking behaviors.

Table 4. CRP distribution according to Lipid parameters and Fasting Blood glucose

CRP distribution according to Lipid parameters and Fasting Blood glucose	CRP >0.8 n (%)	CRP <0.8 n (%)	p
Low-density lipoprotein			0.566
<100	180 (19.5)	742 (80.5)	
101–130	192 (18.3)	857 (81.7)	
131–159	145 (19.7)	590 (80.3)	
160–189	67 (22.7)	228 (77.3)	
>190	20 (20.2)	79 (79.8)	
Triglyceride			0.012*
<150	337 (17.6)	1583 (82.4)	
151–199	145 (23.2)	479 (76.8)	
200–499	154 (19.7)	628 (80.3)	
>500	13 (24.1)	41 (75.9)	
Total cholesterol			0.215
<200	364 (19.4)	1510 (80.6)	
20–239	186 (17.8)	857 (82.2)	
>240	124 (21.4)	456 (78.6)	
Fasting blood glucose			0.001**
<100	368 (17.2)	1770 (82.8)	
100–125	190 (19.7)	776 (80.3)	
>126	116 (29.5)	277 (70.5)	

Chi-square test *: P<0.05; **: P<0.01; CRP: C-reactive protein.

DISCUSSION

Hyperglycemia is wised up to stimulate the release of inflammatory cytokines from various cell types and may guide the initiation and discharge of acute-phase reactants by adipocytes. CRP is one of the well-known inflammatory biomarkers that is elevated with inflammation and disorders such as type 2 diabetes mellitus (T2DM) and CVD. Although there are many studies on CRP increment in diabetic patients, large-scale studies on the relationship between IFG and CRP in non-diabetic patients are missing.

Hence, we aimed to investigate the effect of the chronic inflammation process on IFG.

In our study, we prefer CRP as an inflammatory marker. Because of its relative stability in serum, accessibility of measurement, and availability of the international standard, it is a more utilizable and reliable marker in clinical research than other inflammatory indicators like cytokines.

In the mid-1940s, a research team led by two important scientists, Oswald Avery and Maclyn McCarty [8], who defined that genes are synthesized from DNA, discovered that CRP, as an acute-phase reactant, increases in plasma during various inflammatory conditions, such as myocardial infarction and rheumatic fever. Clues to the role of this inflammatory molecule in atherothrombosis were found when increased plasma CRP levels were detected after myocardial infarction in two case presentations presented by Gunnar Lofstrom [9]. From the mid-1950s onwards, large case series were presented, and before the assessment of creatine kinase and troponin was possible, the increase of CRP in plasma following acute coronary syndromes, and the consistency of this increase in every case, established the importance of CRP, especially high-sensitivity CRP (hs-CRP), as a marker for acute coronary syndromes.

Women's Health Study (WHS) included 27,939 women known to be healthy and followed them for 10 years for the development of vascular events [10]. In the study, 10 biomarkers were compared head-to-head in terms of vascular risk, and hs-CRP was found to be the strongest predictor value in determining future vascular risks.

A Chinese population study found that CRP levels were greater in T2DM patients than in normal subjects [11], suggesting that CRP is a free predictor of incoming T2DM. Other studies have found that greater levels of CRP are combined with an elevated risk of obtaining diabetes [12–14].

On the European study, higher levels of CRP were more strongly and independently related to an elevated risk of T2DM in women than in men, and this did not change after adjusting according to age, obesity, diabetes family history, or smoking [15].

In our study of 3,500 cases, no statistically significant result was obtained when comparing CRP values with LDL and total cholesterol levels ($p>0.05$). However, a statistically significant relationship was found between CRP and triglyceride levels ($p<0.05$). CRP levels above 0.8 were significantly higher in cases with triglyceride levels between 151 and 199 (23.2%) and above 500 (24.1%). Furthermore, the results of the study showed a strong relationship between CRP and fasting plasma glucose levels ($p<0.01$). In cases with a fasting plasma glucose level above 126 (29.5%), the rate of CRP above 0.8 was significantly higher than other glucose levels. CRP levels increase continuously across the spectrum of fasting glucose, beginning in the lowest quartile of normal fasting glucose.

These results demonstrate that fasting glucose is significantly and positively associated with plasma CRP and serum triglyceride values. The underlying cause of this relationship is obesity and inflammation probably [16].

It has been determined recently that obesity triggers a widespread inflammatory response in the body. The molecular relationship between obesity and inflammation was first defined by Hotamisligil and colleagues. Hotamisligil has shown that an inflammatory cytokine, tumor necrosis factor-alpha, is synthesized from adipose tissue and that the synthesis amount increases in obese animals and tumor necrosis factor (TNF)-alpha reduces the effect of insulin in animal models and tissue cultures [17].

Although no study has yet proven that CRP directly increases insulin resistance, it is known that IL-6, which plays a major role in hepatic CRP synthesis, is synthesized from visceral and subcutaneous fat tissue and is responsible for signal transmission within adipocytes. Extrahepatic CRP synthesis is also performed by peripheral lymphocytes, vascular endothelium, kidney, lung epithelial cells, and smooth muscle cells and causes destruction in pancreatic islet cells. In animal models, it has been shown that membrane-bound CRP (neoCRP) synthesis occurs in pancreatic islet cells following NO exposure [18]. Previous in vitro studies have demonstrated cytokine induction-related NO synthesis in pancreatic islet cells due to IL1-beta and TNF-alpha [19]. When we look at clinical studies, Mendall et al. [20] found a significant relationship between CRP and fasting plasma glucose even after adjusting for body mass index. Again, in the WHS, after adjusting for body mass index and other risk factors, increased hs-CRP value was found to quadruple the risk of diabetes [10]. In the Mexico diabetes study and the Kuopio ischemic heart disease risk study, increased plasma CRP values have been proven to increase the likelihood of developing metabolic syndrome [21].

Our study has some limitations because the retrospective nature of this study may introduce inherent biases related to data collection and patient recall. We relied on historical medical records and laboratory results, which may not capture all nuances of patient history and potential confounders. The exclusion of certain populations, such as those under 18 or over 65 and those with known inflammatory diseases, may limit the generalizability of our findings across all demographics. These are the weaknesses of the study. Moreover, we did not account for dietary habits, physical activity levels, and socioeconomic factors that could significantly impact blood glucose and lipid parameters. There may be other unmeasured variables that were not accounted for, which could influence the relationships observed. And finally, as this study was observational, it cannot establish causation, only association. Future prospective studies are warranted to confirm our findings and support the clinical utility of CRP for early diagnosis of the prediabetic state and lipid metabolism disturbance.

Conclusion

In summary, CRP appears to be an indicator not merely for atherosclerotic risk independent of LDL-C levels but also for hypertriglyceridemia and IFG, which are known as a precursor to prediabetes.

This underlines the clinical utility of CRP as a dual-purpose biomarker, especially in the presence of obesity. Recognizing elevated CRP levels could, thus play a crucial role in the differential diagnosis of prediabetes and disturbances of lipid metabolism potentially facilitating earlier intervention and better management of this burgeoning global health challenge. Harnessing the prognostic power of CRP in clinical settings may well be especially a stride toward the diagnosis of prediabetic state and diabetes prevention intrinsically.

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