International Journal of Research in Medical Sciences
Syyeda A et al. Int J Res Med Sci. 2016 Aug;4(8):3336-3342
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20162290

Research Article

Acute phase reactants and lipid profile in acute chest pain presentations: a multimarker approach

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Received: 08 June 2016
Accepted: 01 July 2016

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ABSTRACT

Background: Cardiovascular diseases cause more deaths and disability and incur greater economic cost than any other illness in the world. Our objective is to study the biological activity and evaluate the diagnostic and prognostic values of acute phase reactants, high sensitivity C-reactive protein (hsCRP) and ferritin in association with traditional lipid profile, in screening subjects who developed chest pain due to cardiac event as indicated by a positive cardiac troponin I (cTnI) test.
Methods: In this hospital-based prospective study, a total of 150 cases (n=150), presented consecutively to the emergency department with symptoms of cardiac ischemia and tested positive for troponin I (enzyme-linked flourescent assay), were compared with an equal number of age and gender matched healthy controls (n=150) for hsCRP (immunoturbidimetric assay), ferritin (immunoturbidimetric assay) and lipid profile (enzymatic colorimetric assay).
Results: Median serum hsCRP levels were 2.12 mg/L)±1.79 mg/L) than controls (2.82±significantly elevated in cases (3.57 (p0.05) different between the two groups.
Conclusions: hsCRP and ferritin are independent novel predictors for cardiovascular risks and events. Lipid profile demonstrates low specificity in such cases.

Keywords: Acute phase reactants, hsCRP, Serum ferritin, Lipid profile, AMI

INTRODUCTION

Suspected myocardial infarction (MI) is a common reason for emergency hospital attendance and admission. The development and acceptance of biomarker measurement as part of the diagnostic strategies for patients presenting with chest pain and suspected Acute Myocardial Infarction (AMI) could be said to have reached maturity with the publication of the 1979 WHO criteria for AMI. Directly quoted from the WHO document: 3.1.1. Definite acute myocardial infarction. Definite acute myocardial infarction is diagnosed in the presence of unequivocal ECG changes and/or unequivocal enzyme changes; the history may be typical or atypical.[1] Assays for cardiac troponins I (cTnI) and T (cTnT) were developed in the late 1980s.[2,3] The measurement of cTnT and cTnI was truly a paradigm shift in the role of cardiac biomarker measurement in the diagnosis of patients presenting with chest pain. Further, elevated troponin levels were associated with significant risk of subsequent major adverse cardiac events. The clear diagnostic superiority of measurement of cTnT and cTnI led to reappraisal of the role of cardiac biomarkers in patients presenting with suspected coronary artery disease (CAD). Subsequent proposals produced by the International Federation of Clinical Chemistry (IFCC) culminated in the redefinition of MI in 2000, which placed cTnT and cTnI measurement central to diagnosis, followed by the subsequent Universal Definition, now in its third refinement.[4-6] Dyslipidemia has been since long known as a major risk factor for atherosclerosis, which may eventually manifest as CAD. Hyperlipidemia,

including hypertriglyceridemia, has been shown to be an independent risk factor for major cardiac events.[7,8] Randomised controlled trials have demonstrated that lipid-lowering therapy improves all-cause mortality and morbidity in patients with risk factors for and with established CAD. However, many patients still develop atherosclerotic complications despite being on lipid-lowering therapy and/or having target low lipid profiles.[9,10] We tested the hypothesis that the biomarker value of admission lipid profile has not been established in patients presenting with acute cardiac events. Atherosclerosis is a pathology characterized by low-grade vascular inflammation rather than mere accumulation of lipids. It is a multistep disease and chronic inflammation plays a role in its every stage from its onset, progression and finally to plaque rupture.[11] Many markers of inflammation appear during atherogenesis, which are used for risk prediction, particularly CRP and serum ferritin. CRP plays a proatherogenic role in the process of atherosclerosis by up regulating and stimulating the release of several cytokines and growth factors and by down regulating nitric oxide, a potent vasodilator.[12] It is a phylogenetically highly conserved plasma protein that participates in the systemic response to inflammation.[13] Iron, a dietary constituent, is a prooxidant and a high concentration of blood ferritin, which measures stored iron, is a potential risk factor for CAD. Free iron which acts as a catalyst for the production of free radicals has been implicated in lipid peroxidation and atherosclerosis leading to MI.[14] Results of various studies showed statistically significant association of high serum ferritin and AMI.[15,16] However, some authors did not find any significant association of high serum ferritin and AMI.[17] There is a plethora of articles reporting the relationship between serum ferritin and AMI but with conflicting and contradicting results. The main objective of our study was to compare the serum ferritin levels in association with hsCRP in cases and controls, in order to assess their relationship with AMI. Intriguing evidence suggests that lipid-lowering therapy reduces coronary events in past by muting the inflammatory aspects of pathogenesis of atherosclerosis.

METHODS

This study was carried out at Princess Esra Hospital, attached to Deccan College of Medical Sciences, Hyderabad, India, from March 2014 to October 2015, to know the association of acute phase reactants and lipid profile with AMI. It included 150 AMI patients (cases, n=150), aged between 30-50 years, consecutively admitted to the emergency department, with complaints of sudden onset chest pain for more than 30 minutes duration and tested positive for cTnI. Diagnosis of AMI was based on the American College of Cardiology and European Society of Cardiology guidelines.[5,6] Admission blood sample for inflammatory markers and lipid profile estimation was obtained before administration of any thrombolytic therapy. These patients were with first episode of chest pain, had no past history of such clinical symptoms and were not on any known medication for the same. An equal number of age and gender matched normal healthy individuals, tested cTnI negative, were taken up as controls (n=150). Fasting venous blood samples were drawn. Subjects with hypertension, diabetes mellitus, obesity, chronic inflammatory diseases, renal dysfunction, surgical procedure in three months duration, past history of AMI or cardiovascular diseases and patients on medication such as iron therapy, antioxidant supplements, anti-inflammatory, immunosuppressive or lipid-lowering drugs, were excluded from the study. As per the selection criteria in both groups, subjects were included in the study only after obtaining their informed consent. This study was approved by the Medical Ethics Committee of this institution. Biochemical analysis: Blood samples were drawn from ante cubital vein under aseptic conditions and centrifuged at 3000 rpm for 10 minutes and sera obtained for analysis. Troponin I was estimated (Enzyme-Linked Fluorescent Assay) using VIDAS auto analyzer (Biomerieux). The 99th percentile of troponin I in a normal population with this assay was established at 0.01 ng/mL. The measurement values of the VIDAS Troponin I Ultra (TNIU) kit range from 0.01 to 30 ng/mL. A value of more than 0.11ng/mL is considered to be significant. All troponin I values <0.01 ng/mL (detection limit) were taken as 0.009 ng/mL for the purpose of calculation. Fully automated analyzer cobas c311 by Roche/Hitachi was used for estimation of hsCRP, ferritin (immunoturbimetric assay, total cholesterol (TC) (CHOD-POD photometric assay), triglycerides (TG), high density lipoprotein cholesterol (HDL-c),low density lipoprotein cholesterol (LDL-c) (homogenous enzymatic colorimetric assay) and very low density lipoprotein cholesterol (VLDL-c =TG/5).[18-26] Statistical analysis: All the data so collected was duly recorded and compiled; results and observations drawn and statistically analyzed using SPSS software (version 22.0). Values were expressed as mean±standard deviation (SD) and unpaired Student's t test. All 'p' values were two-tailed with significance defined as $p<0.05$ at the level of 95% confidence limit.

RESULTS

The present study aimed at analysing the hsCRP levels in acute mi, its relationship with the conventional lipid profile and association of serum ferritin with mi in the Indian population.

Table 1 shows the baseline characteristics of the total 300 subjects studied. Mean age of 150 patients with AMI was 45.36±2.82 and the patient group was comprised of 87 males and 63 females, whereas, mean age of 150 healthy controls was 45.95±2.70 years and it comprised of 94 males and 56 females (both the groups have a same sex distribution ratio) (Figure 1). There were no significant ($p>0.05$) differences between AMI cases (n=150) and controls (n=150) in terms of age and gender.

Table 2 shows mean values and standard deviation (SD) of all parameters studied in both groups with test of statistical significance. Baseline serum levels of troponin i (5.87±9.28 vs. 0.009±0 ng/ml, p<0.0001) and inflammatory markers, hscrp (3.57±1.79 vs. 2.82±2.12 mg/l, p<0.001) and ferritin (2.57.35±76.34 vs. 242.81±40.60 µg/l, p<0.05) were significantly higher in AMI patients as compared to the controls (Figure 2).

Table 1: Baseline characteristics of study subjects (cases and controls) showing mean and standard deviation (mean±sd) for age and gender.

Parameters	Cases	Controls	't' value	'p' value
30-40 years	37.33±2.17 (n=18)	36.83±2.33 (n=23)	0.71	0.48
41-50 years	47.16±2.58 (n=132)	46.72±2.72 (n=127)	0.82	0.40
30-50 years	45.36±2.82 (n=150)	45.95±2.70 (n=150)	0.98	0.32
Males	58% (n=87)	63% (n=94)		
Females	42% (n=63)	37% (n=56)		

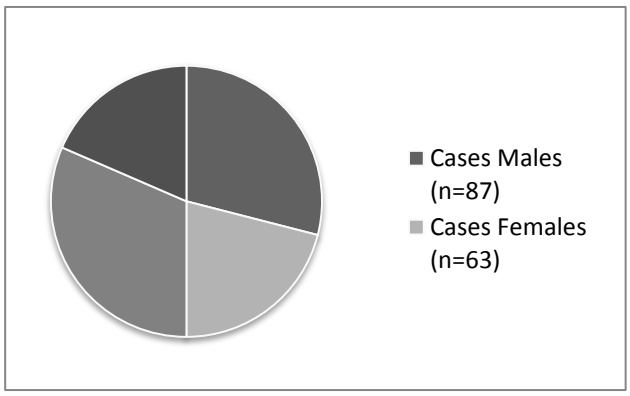

Figure 1: Graphical representation of gender distribution (%) of cases and controls.

The comparison on the basis of lipid profile demonstrated that there was not much significant difference between tc (223.41±52.08 vs. 214.56±80.73 mg/dl, p>0.05), tg (128.36±39.68 vs. 124.00±29.90 mg/dl, p>0.05), hdl-c (40.26±20.74 vs. 43.14±11.34 mg/dl, p>0.05), ldl-c (113.79±46.12 vs.105.55±30.39 mg/dl, p>0.05) and vldl-c (35.38±6.98 vs. 32.88±21.45 mg/dl, p>0.05) (figure 3). The mean serum values of tc of both the groups are in the borderline range (200-240 mg/dl), whereas tg values are within the desirable level of <150 mg/dl. Hdl-c and ldl-c values of both the groups fall within the optimal (40-59 mg/dl) and near optimal (100-130 mg/dl) ranges respectively.

Within the control group 42% (63/150) of the subjects demonstrated hsCRP levels between 1-3 mg/l, while 28% (42/150) demonstrated hsCRP levels between 3-10 mg/l, suggesting that the basal hsCRP level among the present study population was on the higher side.

Overall hsCRP levels were significantly elevated by three-fold (p=0.001) in the AMI patients at presentation. Serum ferritin concentration in the case control population ranged from 50 µg/l to 410 µg/l and averaged 230 µg/l. The distribution of serum ferritin for cases and controls indicated a shift towards higher concentration in patients with AMI.

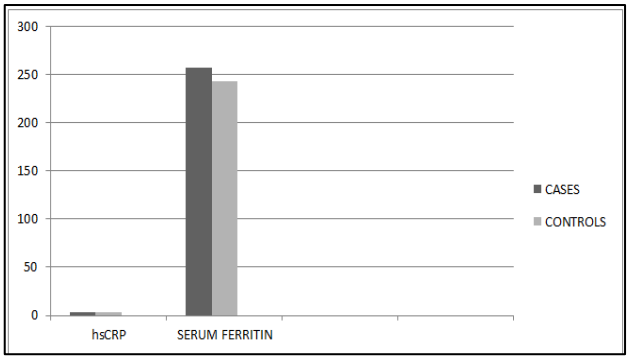

Figure 2: Graphical representation of mean serum baseline values of inflammatory markers in cases and controls.

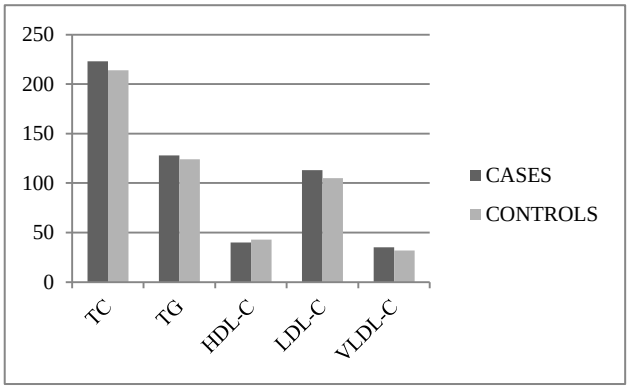

Figure 3: Graphical representation of serum baseline values of lipid profile parameters in cases and controls.

Table 2: Mean levels (mean±sd) of CTNI, inflammatory markers (hsCRP and ferritin) and lipid profile in baseline serum samples of AMI patients and controls.

Parameters	Cases (n=150)	Controls (n=150)	't' value	'p' value
cTnI (ng/mL)	5.87±9.28	0.009±0	7.7	<o.ooo1
hsCRP (mg/L)	3.57±1.79	2.82±2.12	3.3	0.001
Ferritin (µg/L)	257.35±76.34	242.81±40.60	2.0	0.04
TC (mg/dL)	223.41±52.08	214.56±80.73	1.1	0.26
TG (mg/dL)	128.36±39.68	124.0±29.90	1.0	0.28
HDL-c (mg/dL)	40.26±20.74	43.14±11.34	1.4	0.13
LDL-c (mg/dL)	113.79±46.12	105.55±30.39	1.8	0.06
VLCL-c (mg/dL)	35.38±6.98	32.88±21.45	1.3	0.17

DISCUSSION

Incidence of AMI is alarmingly increasing across the globe among all ages and both sexes with increasing morbidity and mortality. It remains the focus of intense research and management efforts, despite many recent scientific and clinical breakthroughs. In AMI, irreversible tissue injury occurs due to sustained ischemia and recent pivotal studies have shown that the innate immune system is activated sequentially mediating both injury and repair mechanisms.[27] Experimental studies have shown that short periods of ischemia followed by reperfusion elicit a cascade of pro inflammatory reactions that include production of oxygen-derived free radicals, activation of the complement system, adherence of the neutrophils to the coronary endothelium, leukocyte-mediated injury of the myocardial cells, and production of cytokines and acute phase proteins.[28] High sensitivity testing for CRP (hsCRP) has emerged as a convenient tool for detecting low-level systemic inflammation that portends a higher risk of developing atherothrombotic vascular disease in ostensibly healthy men and women and poor short- and long-term prognosis in patients after AMI.[29] American Heart Association guidelines risk stratifies people on the basis of the amount of CRP in blood.[30] Although the precise mechanistic links between inflammation and cardiovascular risk are not conclusively established, it is plausible the elevated levels of circulatory markers of inflammation reflect an intensification of focal inflammatory process that destabilize vulnerable plaques. In addition, growing evidence implicates CRP as a mediator, in addition to a marker, of atherothrombosis.[31] In the present study, the control group was screened very meticulously to be free of atherosclerosis and of any other organic disease. Inspite of that % of our study population of healthy individuals demonstrated elevated hsCRP levels. This maybe one of the reasons for increased risk of MI in our population. Prior studies have demonstrated deceased hsCRP levels in stable MI patients who had statins as an integral part of their standard medication. This is in accordance with Nissen et.al.[32] who observed that statins bring down CRP level and reduce the risk of CAD. In the last few decades there has been an ever increasing awareness regarding the factors responsible for atherogenesis and CAD. Identification of various inflammatory markers has opened up new horizons for different aspects of control and management of epidemic CAD. Sullivan postulated a link between tissue iron stores and the risk of ischemic heart disease (IHD), to explain the sex difference in IHD as early as in 1981.[33] Free iron as a catalyst for the production of free radicals has been implicated in lipid peroxidation and atherosclerosis leading to MI. There is strong evidence that oxidative free radicals have a role in the development of degenerative diseases including CAD. Oxidative stress leading to modification of LDL is a central paradigm of atherogenesis and plaque destabilization. The deposition of LDL into the sub-endothelial space creates a tendency for LDL to be exposed to oxidation.[34] Under conditions of high oxidant stress there is increased peroxidation of lipoprotein phospholipids, thereby increasing the LDL-uptake by macrophages with increased foam cell formation and atherosclerosis, initiating a potent inflammatory response in the process observed in the form of increased serum ferritin levels.[35] Our finding correlates with prior studies, where it was observed that patients with chest pain and positive cardiac enzyme test were found to have significantly elevated levels of serum ferritin when compared to healthy controls. This study indicates that serum ferritin indirectly enhances the role of LDL-cholesterol in the induction of cardiovascular diseases. This role is further enhanced by elevation of serum CRP accordingly. Elevations in acute phase reactants such as ferritin and CRP reflect the overall inflammatory burden, not just vascular foci of inflammation. Intriguing evidence suggests that lipid-lowering therapy reduces coronary events in part by muting the inflammatory aspects of the pathogenesis of athero sclerosis. Regular monitoring of serum ferritin levels may help in reduction of cardiovascular morbidity and mortality. MI is a complex and multifactorial process with atherosclerosis playing a major role in the underlying pathophysiology. Indeed clinical symptomatology in MI is frequently triggered by a thrombus formation on an eroded or ruptured atherosclerotic, lipid-rich plaque characterized by a thin fibrous cap.[29] Dyslipidemia preponderated among the

nine major risk factors (smoking, diabetes, hypertension, visceral obesity, psychosocial stress, sedentary life, low fruit and vegetable consumption and alcohol consumption) and alone accounted for more than 50% of population attributable risk. This analysis demonstrated that the mean values of TC, TG, HDL-C, LDL-C and VLDL were not significantly different ($p>0.05$) between the MI cases and healthy controls. To the best of our knowledge, this is the first study to report this observation in AMI patients. This finding initially appears to contradict the current thinking about lipids and outcome in patients with CAD. A series of changes in lipid metabolism occur during acute phase response. First time Biorck et al. reported that serum cholesterol levels decreased during MI.[36] There are several reports indicating that cholesterol reduction takes place in the initial phase of an acute cardiac event; thus plasma levels determined at this point should be interpreted with caution. This reduction may just be a consequence of the inflammatory response, or it may be related to an increase in cellular uptake of cholesterol for tissue repair and hormonal synthesis (Correia et al).[37] A previous report by Khan et al showed significantly decreased levels of TC in AMI patients.[38] In this study TG levels were found to be around the desirable level of 150 mg/dL. Hypertriglyceridemia has been a known risk factor for major cardiac events, even after controlling for cholesterol levels.[7,8] It is possible that patients who have MI inspite of a low TG level have other risk factors that are not readily modifiable. Thus, plaque rupture in the setting of a low TG level may signify more complex atherosclerotic disease in patients with a higher risk of long-term events.[39] Acute phase response alters not only the concentration of lipoproteins, but also the composition of the circulating LDL and HDL. During acute reaction, LDL synthesis is increased due to adrenergic-mediated adipocyte lipolysis. LDL particle size is smaller in patients with AMI as compared to non-MI patients. Despite that, LDL levels do not increase due to up-regulation of LDL receptor activity. In addition, LDL has the predisposition of oxidation exposure following AMI. Important functions of HDL include reverse transport of cholesterol and modulation of inflammation. Although HDL has anti-inflammatory effects in baseline conditions, it has pro-inflammatory effects during acute phase response. There is a decrease in levels of several plasma proteins included in HDL-mediated reverse transport of cholesterol and inhibition of lipid oxidation during inflammation.[34] The idea that there is an early modification in serum lipids and lipoproteins, brings the thought that their estimations are unreliable, as they undergo phasic changes post-MI. Therefore, it is difficult to find the patients' baseline lipid profile correctly. However, if we consider that the changes are minimal in the first 24 hours, it seems reasonable to evaluate the lipid profile in that period.[40] A fasting lipid profile should be obtained within 24hrs of the onset of any major cardiac event. Although the evidence that a multimarker approach can be valuable for comprehensive risk assessment is compelling, two major limitations must be recognized. Single sample was tested for troponin I, hsCRP, ferritin and lipid profiles. It is recommended that samples should be drawn serially at definite intervals in high risk patients and tested for the aforementioned parameters. In addition, there is a need for follow-up studies to evaluate the post-therapy effect on biochemical markers. Sample size may not be sufficient to draw major conclusions. Large prospective studies in Indian population are needed to support the results of present study.

Although the appropriate clinical responses to an elevated level of troponin in patients with suspected AMI is well established, to date we do not have a consistent base of evidence to attribute diagnostic importance to elevated levels of inflammatory markers in this setting. Nevertheless, there is a reason for optimism that appropriate therapeutic responses to different patterns of biomarker elevation in cardiovascular diseases will be defined.

The clinical application of cardiac biomarkers in acute cardiac events is no longer restricted to confirming the diagnosis of myocardial necrosis. Cardiac biomarkers provide a non-invasive and inexpensive means to assess the underlying causes and consequences of major cardiac events which may have potential risk of recurrence and maybe targets for specific therapeutic interventions. Proteomic and genomic strategies for novel marker discovery are likely to extend this approach. Moreover, as point-of-care technology continues to advance, each of these markers might be incorporated into a single cassette offering a rapidly and conveniently obtained multi marker profile to guide risk assessment and therapeutic decision-making thereby, improving substantially the outcomes in patients with cardiovascular diseases.

CONCLUSION

hsCRP and ferritin are independent novel predictors for cardiovascular risks and events. Lipid profile demonstrates low specificity in such cases.

ACKNOWLEDGEMENTS

Authors would like to thanks for the kind support from Deccan College of Medical Sciences for carrying out the work and Princess Esra Hospital for recruitment of patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Medical Ethics Committee of this institution

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Cite this article as: Syyeda A, Fatima J, Hyder AM. Acute phase reactants and lipid profile in acute chest pain presentations: a multimarker approach. Int J Res Med Sci 2016;4:3336-42.