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Reliability of High Sensitivity C-Reactive Protein As A Biomarker For Cardiovascular Disease In General Population

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Abstract:
Background: *The role of low grade general inflammation as proved by elevated high sensitivity C-reactive protein (hsCRP) levels within the pathological process of coronary-artery {disease} vascular disease has been intensely investigated through experimental studies and clinical trials within the past 20 years. On the premise of proof that has accumulated, hsCRP activity has been integrated into the Reynolds risk rating system to predict vessel risk. The JUPITER trial well-tried the good thing about statins in vessel risk reduction in patients with low grades of general inflammation and 'normal' steroid alcohol levels. However, substantial proof has been generated from western studies.*
Methodology: We intend to, therefore, conduct a scoping review for studies done in India with a read to spot the conspicuousgaps and build additional recommendations. Most Indian studies had tiny sample sizes and short term follow ups. there have been no giant population primarily based prospective studies wherever patients were followed up for long periods of your time for major vessel finish points.
Results: An analysis of the hsCRP level from the management arms of case-control studies derived a mean hsCRP price of one.88 mg/l, that is beyond the western population wherever values < one mg/l area unit classified as low vessel risk.
Conclusion: additional giant prospective cohort studies with long run follow ups area unit essential before we are able to build additional recommendations to integrate hsCRP into risk prediction models for upset bar.
Keywords: *Cardiovascular disease,hsCRP, atherosclerosis,Inflammation, myocardial infarction*

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I. Introduction

The role of inflammation within the pathologic process of coronary artery disease has been firmly established within the past 20 years. varied studies, each empiric (nested case management associate degreed prospective cohort) and irregular controlled trials (RCTs) have shown an association of pro-inflammatory biomarkers with incident cardiovascular disease, metabolic syndrome, arteria illness (CAD), acute coronary syndrome (ACS), peripheral artery illness, stroke and perennial coronary and neural structure events [1],[2],[3],[4] . or so twenty five massive empiric studies revealed since the Nineties have established high sensitivity CRP (hsCRP), a biomarker of inflammation, as associate degree freelance predictor for CAD. A meta-analysis of those empiric studies showed that individuals within the prime score for hsCRP levels had associate degree odds quantitative relation (OR) of one.5 compared with those within the lowest score for major vas events, once adjusting for established risk factors [5] . except for empiric studies, many RCTs evaluating statins like statin drug or Lipitor analysis and Infection Therapy- lysis in MI twenty two (PROVE-IT TIMI-22) [6] , cholesterin and perennial Events (CARE) [7] , The statin drug Inflammation/CRP analysis (PRINCE) [8] , Aggrastat- to- Zocor (A to Z) [9] associate degreed Justification for the utilization of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [10] indicate that vas edges area unit a lot of apparent once general inflammation (as proved by hsCRP reduction) is reduced additionally to intensive LDL cholesterin (LDL-C) lowering. The A to Z trial [9] incontestible that the simplest clinical outcomes occurred once the hsCRP levels were down below two mg/l additionally to LDL-C lowering to < seventy mg/dl. associate

degree imbalance between pro- and anti inflammatory factors contributes to the coronary-artery disease method. Inflammatory processes have a bearing on the integrity of the fibrous cap in coronary-artery disease plaque. Pro-inflammatory processes involving innate and accommodative immune mechanisms weaken the fibrous cap, inflicting a predisposition towards its rupture [2]. Interferon-γ (IFN-γ) detailed by activated T cells suppresses scleroprotein production by sleek muscles cells of the blood vessel wall. this can be in addition to increased scleroprotein degradation within the fibrous cap mediate by the matrix metalloproteinase enzymes (MMP-1, MMP-8, MMP-13) synthesized by activated macrophages. These processes enhance the crumbliness of the fibrous cap [11] .

The working party recommends conducting 2 hsCRP assays period of time apart in an exceedingly fast or a non-fasting state in an exceedingly metabolically stable patient with no obvious signs of infection or inflammation that would confound results.

Although hsCRP has for the most part been the central focus, different inflammatory markers like tumor gangrene issue (TNF)-α, lymphokine (IL)-6, IL-7 additionally the} matrix metalloproteinases have also been related to the coronary-artery disease method [2]. many factors, however, build hsCRP a gorgeous biomarker for vas risk prediction.

Reliability ofhsCRPas a marker of inflammation?Does it play a causative role?

A debated disceptation during this area has been whether or not hsCRP contributes to the hardening of the arteries method or is simply a marker of inflammation. The hsCRP has been noted to own opsonizing properties, increasing the achievement of monocytes into adipose tissue plaque and conjointly causation epithelium disfunction by suppressing basal and induced gas unleash. The hsCRP in and of itself has conjointly been found to extend the expression of vascular epithelium protease inhibitor-1 (PAI-1) and different adhesion molecules and alter low-density lipoprotein uptake by macrophages [11] . However, interventions that directly inhibit hsCRP would have to be compelled to be evaluated before once and for all establishing hsCRP as a right away contributor to the hardening of the arteries method. botanist organisation studies have hinted at a causative relationship between hsCRP genotypes and hardening of the arteries CVD, tho' stronger proof of relation is needed [16] .

JUPITER - a primary bar trial [10] wanted to judge the utility of a lipid-lowering medicine in reducing major adverse vessel events in patients with traditional to low steroid alcohol levels (LDL-C <130 mg/dl) however with high hsCRP levels (>2 mg/l). a complete of seventeen,802 apparently healthy men and girls were randomised to receive either rosuvastatin twenty mg or placebo. The trial was stopped untimely at intervals a median follow up period of one.9 yr, as rosuvastatin made a major reduction within the pre-specified primary composite finish purpose of infarct, stroke, vessel death, blood vessel revascularization and unstable angina. Rosuvastatin was shown to cut back LDL-C levels by fifty per cent and hsCRP levels by thirty seven per cent. The overarching question that this trial posed was whether or not the helpful effects on vessel finish points were thanks to macromolecule lowering alone, suppression of inflammation alone (as incontestible by hsCRP reduction), or a mixture of each mechanisms. JUPITER didn't address the question of whether or not selective suppression of the inflammatory method might conjointly deliver the goods helpful effects. the continued Canakinumab anti-inflammatory drug occlusion Outcomes Study (CANTOS) trial [17] tries to supply higher clarity on the queries raised by the JUPITER trial.

What does CANTOS imply for?

The CANTOS (ClinicalTrials.gov Identifier NCT01327846) trial addresses this controversy; it evaluates if selective inhibition of IL-1β with canakinumab can cut back vessel death, non-fatal pathology|myocardial infarct|MI|infarct|infarction} and stroke in stable post-myocardial infarction patients at high risk for continual events as proved by blood serum hsCRP>2 mg/l. part two trials with canakinumab have shown that upstream inhibition of IL-1β resulted in dose dependent fifty per cent reductions in downstream biomarkers, CRP and IL-6 levels, while not lowering macromolecule levels or blood pressures[18] . The results of the trial area unit expected in 2018.

The large numbers of Western studies that have evaluated the link between hsCRP and disorder, prompted a scoping review of the studies conducted in Bharat linking the inflammatory hypothesis generally and hsCRP especially, with metabolic syndrome and CVD. The objectives of this text area unit to review the studies linking the inflammatory hypothesis with diabetes, metabolic syndrome and coronary artery disease within the South Asian/Indian population, to spot gaps conspicuous and to form recommendations for any add this vital space within the Indian context.

The studies enclosed

Of the twenty four studies [Table 1], twelve (50%) were case-control studies, six (25%) were cohort studies and 6 (25%) were cross-sectional studies. Of the six cohort studies, four (66.6%) were comparative studies performed in a very nested cohort of patients, one (16.6%) was a retrospective and one (16.6%) was a prospective cohort study. Eight (33.3%) studies evaluated the utility of hsCRP as a predictor for diabetes, nine (37.5%) evaluated hsCRP levels in patients with metabolic syndrome together with polygenic disorder, six (25%) studies related hsCRP levels with abdominal adiposeness and body mass index. Ten (41.6%) studies reportable the utility of hsCRP as a predictor of CAD and 2 (8.3%) studies as vessel malady. solely 5 (20.8%) of the twenty four studies have massive sample sizes (n > 1000) of that just one was a prospective study and 3 were case-control studies. None of the studies evaluated parameters like sensitivity, specificity, positive and negative prognostic values of hsCRP in vessel risk prediction.

S. no.	Author	Design	n	Outcome	Control hsCRP value (mg/l)
1.	Asegaonkar *et al*[19] (2011)	Case-control	120	hsCRP levels correlate with T2DM	0.9
2.	Bhagwat *et al*[20] (2012)	Cross-sectional	101	hsCRP increased in diabetes, diabetes with hypertension & MI	1.22
3.	Chowta *et al*[21] (2012)	Cross-sectional	40	hsCRP levels higher in patients with CVD than no CVD	3.83
4.	Dambal *et al*[22] (2013)	Cross-sectional	30	hsCRP higher in patients with T2DM with acute MI than acute MI without type 2 diabetes	7.19
5.	Ghodke *et al*[23] (2012)	Case-control	200	hsCRP may be an indicator of CAD	Unreported
6.	Garg *et al*[24] (2012)	Case-control	74	hsCRP and other inflammatory markers associated with BMI, per cent body fat, HOMA-IR and other components of metabolic syndrome	2.09
7.	Gokulakrishnan *et al*[25] (2008)	Comparisons in a nested cohort	450	hsCRP associated with glucose intolerance and carotid IMT	N/A
8.	Gokulakrishnan *et al*[26] (2009)	Nested cohort	865	hsCRP and leucocyte count correlates with metabolic syndrome and other CV risk factors	1.35
9.	Goswami *et al*[27] (2011)	Case-control	200	hsCRP is an independent predictor of CAD	0.3
10.	Guruprasad *et al*[28] (2012)	Case-control	442	hsCRP associated with increasing severity of CAD	0.35
11.	Jaiswal *et al*[29] (2012)	Case-control	1726	hsCRP independently associated with IFG & IGT	1.64
12.	Jeemon *et al*[30] (2011)	Comparisons in a nested cohort	600	BMI and abdominal adiposity can be surrogates for elevated hsCRP levels	N/A
13.	Mahadik *et al*[31] (2008)	Retrospective cohort	267	hsCRP correlates with central obesity and is a predictor	3.06
14.	Mahajan *et al*[32] (2009)	Cross-sectional	2520	hsCRP independent predictor of type 2 diabetes mellitus	1.22
15.	Mahajan *et al*[33] (2012)	Cross-sectional	9517	hsCRP independently predicts the risk of metabolic syndrome, apart from obesity and insulin resistance	1.49
16.	Mahajan *et al*[34] (2009)	Case-control study	140	hsCRP in addition to MMP-9 & TIMP-1 is associated with increased CAD severity	1.68
17.	Misra *et al*[35] (2012)	Case-control	71	hsCRP is an independent predictor of diabetes and metabolic syndrome	0.44
18.	Mohan *et al*[36] (2005)	Comparisons in a nested cohort	150	hsCRP is an independent predictor of CAD in diabetic patients and correlates with increasing body fat	0.99
19.	Nyandak *et al*[37] (2007)	Cross-sectional	73	hsCRP associated with increasing severity of angiographic lesions	2.28
20.	Rajeshwar *et al*[38] (2012)	Case-control	1156	hsCRP and NO levels predict the occurrence of ischaemic stroke	N/A
21.	Rao *et al*[39] (2010)	Prospective cohort	1021	hsCRP is an independent predictor of a repeat coronary event	2.81
22.	Roopkala *et al*[40] (2012)	Case-control	75	hsCRP associated with increased risk of diabetic nephropathy	2.75
23.	Shalia *et al*[41] (2012)	Case-control	200	-717 A/G genotype does not influence hsCRP level; hsCRP level correlates with BMI and triglycerides	Mean N/A; 76% participants had hsCRP range of 1 – 10 mg/l
24.	Thakur *et al*[42] (2011)	Case-control	200	hsCRP concentration elevated in CHD subjects	0.93

ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment-estimated insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MMP-9, matrix metalloproteinase enzyme; NO, nitric oxide; T2DM, type 2 diabetes mellitus; TNF-α, tumour necrosis factor-α. Superscript numerals denote reference numbers

Implications of the Indian studies so far

he hsCRP was found to be an independent predictor of numerous finish points starting from fatness, kind two DM, metabolic syndrome, inflated arteria intima-media thickness, stable CAD, initial acute coronary event, and repeated CVD events. The larger studies have principally evaluated the association of hsCRP and risk factors for CVD, DM and aldohexose intolerance. Mahajan et al[32] , in a very study of two,520 subjects, reported hsCRP to be AN freelance predictor of kind two DM (OR, 1.66; 95% CI, 1.21 - 2.28, p0 =0.002). In another study, a cross-sectional survey of nine,517 subjects [32] , the authors once more found AN association between hsCRP levels and metabolic syndrome, fatness and internal secretion resistance (OR, 1.65; 95% CI, 1.41 - 1.92).

Jaiswal et al[29] in a very case-control study of one,726 subjects, reported hsCRP to be severally related to impaired abstinence aldohexose (IFG) and impaired aldohexose tolerance (IGT) (OR, 2.60; 95% CI, 1.56 - 5.34). Studies with clinical CVD events enclosed a case-control study by Rajeshwar et al[38] (1,156 subjects; hsCRP levels predict ischemic stroke),

Goswami et al[27] (200 subjects; hsCRP is AN freelance predictor of CAD) ANd Guruprasad et al[28] (442 subjects; hsCRP levels square measure related to an increasing severity of CAD). A prospective cohort study by Rao et al[39] with one,021 subjects, of whom 772 had established CAD and therefore the rest were controls, found that hsCRP was AN freelance predictor of repeat coronary events. The revealed studies from Asian country have therefore reported AN association between hsCRP and metabolic syndrome, IGT, DM, CAD, and stroke. These studies used completely different styles and ways of estimating hsCRP and every now and then used whimsical cut-off levels. A majority of those studies had little sample sizes and were case-control, cross-sectional or retrospective cohort studies. It is, therefore, insufferable to outline traditional values and cut-off levels as identifiers of risk specifically for the Indian population from these studies. this is often notably necessary as current proof points to elevated basal levels of hsCRP even within the traditional management cluster patients. If one should outline a particular worth and vary as traditional for Indian subjects and cut-off values for estimation of risk for CVD, knowledge from massive high-quality studies square measure required to allow the development of a receiver in operation characteristic (ROC) curve.

To achieve this, it's necessary to initiate massive prospective cohort studies with standardization of diagnostic tests across sites and adequate follow of participants for vessel outcomes to derive risk cut-off values within the Indian population. Such studies are required to estimate the role of hsCRP versus alternative risk factors like lipids to justify the advice and/or of routine mensuration of hsCRP in estimating the danger for CVD in Indian patients.

II. Conclusion

Multiple little Indian studies using variable styles have found AN association between hsCRP and arterial blood vessel malady, DM and therefore the metabolic syndrome. the traditional or basal values of hsCRP square measure probably higher within the Indian population. Larger prospective cohort studies using standardized hsCRP mensuration assays with adequate follow up length square measure needed to derive risk cut-off values for CVD within the Indian population.

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