Role of high-sensitivity C-reactive protein measurements in HIV patients

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Abstract

As we herald into the 21st century, the quality of life and the repertoire of highly active antiretroviral therapy (HAART) have considerably improved. However, considerable work is still needed to educate the population about primary and secondary prevention modalities. Moreover, regular monitoring of immune response with patients on HAART with conventional biomarkers is still a problem in low resource settings which needs to be addressed. We aim to review high-sensitivity C-reactive protein as a potential biomarker in this regard.

Key words: Determinants of age of menopause, ethnicity and menopause, menopause, smoking and menopause

INTRODUCTION

Over the past two decades with the advent of highly active antiretroviral therapy (HAART), there is a substantial increase in the life span of HIV patients. Hence, the focus has now shifted to managing long-term complication of HIV infection and improving the quality of life of HIV patients, especially in developed nations. On the other hand, in developing nations, the ever-growing incidence of HIV infection has placed a huge burden on their frail economy, so there is a growing need for simplifying HIV treatment protocols and for having cheaper alternatives for monitoring disease activity.

High-sensitivity C-reactive protein (hsCRP) has been touted as a potential solution for both these problems. First, hsCRP is considered to be a potential biomarker for predicting long-term disease progression and cardiovascular disease (CVD) risk, which is one of the major long-term complications in HIV patients. Second, it is also considered to

be a marker for predicting mortality and as a tool for routine monitoring of disease activity with a potential to replace traditional costlier measures such as CD4 count and HIV RNA load. This review highlights the results of some promising studies conducted till now in this regard.

C-REACTIVE PROTEIN – AN INFLAMMATORY BIOMARKER

CRP was first identified by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide of pneumococcus (hence the name).[1] Later, it was found to be an acute phase reactant with a pentameric structure that remains stable for a sufficiently long time, allowing measurements of 1000s of stored serum samples.[2] Most CRP is produced from liver apart from vascular endothelium in response to interleukin-6 produced from macrophages and adipocytes.[3,4] Traditional CRP

assays have been available for decades, but these assays are not sensitive at a lower concentration of CRP. However, with the advent of newer hsCRP assays such as ELISA, immunoturbidimetric assay, and laser nephelometry, it is now possible to detect low range differences in CRP levels and has thus become the main focus of research in vascular inflammation.

HIGH-SENSITIVITY C-REACTIVE PROTEIN-MARKER OF HIV DISEASE PROGRESSION

Immune activation has been demonstrated to be a significant contributor to HIV disease progression in multiple studies.[5-8] It was observed that this immune activation was associated with increased levels of bacterial components in blood, which was hypothesized to be due to increased microbial translocation from the gastrointestinal tract of patients and this microbial translocation was hypothesized to contribute for HIV disease progression.[9,10] Naturally, CRP being an acute phase reactant should increase in patients with HIV disease progression if it is associated with microbial translocation and immune activation as hypothesized in these studies.[3,11-13] This theory was tested by Andrew *et al.* in Rakai, Uganda[14] in a longitudinal study, where study population was divided into three population – long-term nonprogressor (i.e., CD4 >600 cells/μl at >7 years after seroconversion), standard progressors (i.e., death >5 but <9 years after seroconversion), and rapid progressors (i.e., death within 4 years after seroconversion). The results of this study concluded that there is a significant association of immune activation as measured by hsCRP levels with HIV disease progression. However, there was no association of CRP levels with markers of microbial translocation (namely lipopolysaccharide [LPS], endotoxin antibody, LPS-binding protein, and soluble CD14) thus disproving the hypothesis that microbial translocation is responsible for immune activation associated with HIV disease progression.

HIGH-SENSITIVITY C-REACTIVE PROTEIN- PREDICTOR OF HIV-RELATED OUTCOMES

Higher CRP concentrations have been associated with lower CD4 counts and higher HIV viral RNA load among HIV-infected individuals.[11] Results from studies evaluating serum CRP as a predictor of HIV-related mortality yielded mixed results in resource-rich settings. Some studies have reported significant associations between increased CRP concentration and faster progression to AIDS and greater risk of mortality but did not use clinically established CRP cutoff concentration.[11,13,15] Some studies found that a clinically elevated CRP concentration was associated with significantly reduced mortality risk.[16]

Drain *et al.* studied CRP levels as a marker of maternal disease progression and child mortality in HIV-infected mothers from Tanzania.[17] They found out that high CRP concentration was better than either low CD4 count <200/μl and high viral load ≥50,000 copies/ml for predicting maternal disease progression to AIDS. While CRP was not better than CD4 count or viral load in predicting maternal mortality outcomes, they remained a very strong and almost comparable predictor. These findings could be supported by the fact that the HIV patients are prone to opportunistic infection (mostly bacterial). More the infection, higher will be their CRP level (as it is an acute phase reactant) and higher is their chances of progression to AIDS. The exception to this argument is that when the CD4 count is very low (<50), it was found that the ability to mount a CRP response to pneumocystis pneumonia infection is substantially small,[18] while there is a significant risk of death despite low levels of CRP. The second finding that supports the results of this study is that HIV infection is regarded as a generalized inflammatory state that leads to depletion of vitamins and minerals. Deficiencies of vitamins and minerals have been found to be associated with disease progression and mortality among HIV-positive patients.[19-21] Moreover, high CRP levels were found to be associated with depleted stores of vitamins and minerals among HIV-positive[19,22] and HIV-negative[23-26] adults. This indirectly supports the finding that high CRP was associated with greater risk of disease progression and mortality.

In addition, Drain *et al.* also found that high maternal CRP was a better marker than viral load in predicting child mortality <2 years of age independent of maternal anthropometric measurements, CD4 count, viral RNA load, and breastfeeding status at the time of CRP measurement. This finding was supported by the fact that high maternal CRP may be a marker or cause of disease progression in mother, leading to deficient transfer of passive immunity, and nutrients to the child making them prone for infection and subsequent higher risk of mortality.[27,28] Poor caring practice due to maternal morbidity or death is also a plausible social explanation for poor child outcomes.

HIGH-SENSITIVITY C-REACTIVE PROTEIN AS A CARDIOVASCULAR DISEASE RISK PREDICTOR IN HIV PATIENTS

HIV-infected patients are at higher risk of CVD than uninfected general population.[29,30] This is believed to be due to modification of traditional CVD risk factors[31] and pathogenic pathways of atherosclerosis and CVD[29,32-36] by HIV infection and cART (combination ART). A study by De Luca *et al.* found a significant association between elevated hsCRP and CVD risk in HIV-positive patients receiving cART. There was 8-fold increase in CVD risk in patients with CRP levels >3.3 mg/L than those with <0.9 mg/L. A key finding of this study was that the effect of CRP on CVD risk was independent of traditional risk factors (like deranged lipid profile) and potential confounders (such as BMI, renal function, and use of statins). There was a strong but crude association of this marker with short-term CVD risk, but it was found to be a useful marker to predict the medium to long-term risk of experiencing CVD events. This study also identified 3.3 mg/L as a potential threshold associated with significant risk of CVD in HIV-infected patients.[37] However, in disagreement with these findings, Ford *et al.* showed no association between hsCRP and CVD events in treated HIV patients.[38] While hsCRP was found to be elevated in patients with low risk of CVD events in a study by Boger *et al.*[39]

CHANGE IN HIGH-SENSITIVITY C-REACTIVE PROTEIN LEVELS WITH ASSISTED REPRODUCTIVE TECHNOLOGIES

Several studies have suggested a positive association between assisted reproductive technologies (ART) and CVD risk.[29,40,41] Theoretically hsCRP being a marker of CVD risk should increase with ART. On the contrary, there is also evidence that ART may improve endothelial function and protect against atherosclerosis thereby reducing CVD risk.[42,43] Considering these associations, the impact of ARV therapy on CRP levels is of significant interest. In the ACTG 5056s study, with the introduction of indinavir CRP levels remained stable or decreased slightly over an average of 42 months.[44] A similar slight decline was seen in the HEAT study over 96 weeks following initiation of lopinavir/ritonavir.[45] Both these findings were noted only in men. In a study by Shikuma *et al.*, a durably suppressive therapy with efavirenz did not improve hsCRP levels over a 96 week period but was associated with significantly increased levels of CRP in women and slight statistically nonsignificant increase in men. This study also showed that randomization to abacavir had no significant effect on changes in CRP levels.[46]

C-REACTIVE PROTEIN LEVELS IN HIV/HEPATITIS C VIRUS COINFECTION

Both HIV and hepatitis C virus (HCV) being a chronic infection, activates immune system and results in proinflammatory state.[47-51] CRP being a marker of immune activation should increase in both the infection. However, very few studies are available in this regard. Reingold *et al.* reported that HIV/HCV coinfection was associated with a 50% lower adjusted CRP levels when compared with HIV-monoinfected men and women. It was proposed that HCV infection decreases CRP production from the liver.[52] This concept is supported by *in vitro* studies of expression of HCV proteins in cultured hepatocytes, which causes inhibition of secretion of other liver proteins like apoB-100.[53]

COST-EFFECTIVENESS AND FEASIBILITY OF HIGH-SENSITIVITY C-REACTIVE PROTEIN ASSAY

hsCRP assays include ELISA, immunoturbidimetric assay, and laser nephelometry methods. Apart from the laser nephelometry method, the other two assays are cheaper and easy to perform, with nearly same sensitivity as laser nephelometry. In the Indian market, cd4 estimation costs around 1000 Rs. per sample, while hsCRP estimation costs around 300 Rs. per sample. As shown in the study by Drain *et al.*, internationally cd4 count and HIV viral load estimation cost approximately US$10 and US$40, respectively, while hsCRP by immunoturbidimetry method costs around US$2 per sample. Thus, it is approximately one-fifth the cost of a CD4 cell count and one-twentieth the cost of an HIV viral load.[17]

Regarding feasibility, HIV diagnosis is initially made by ELISA method. hsCRP measurement can be made using the same method, thus requiring the same equipment and workforce. Immunoturbidimetry employs the same technique as that of commonly used latex agglutination method.[54,55]

CONCLUSION

From the studies conducted till date it can be safely concluded that hsCRP is an excellent predictor of CVD risk in HIV patients. The importance of evaluating, preventing, and managing CVD in patients with HIV is recognized in guidelines for the use of antiretroviral agents in HIV-infected

adults.[56] Because hsCRP is cheap to measure and easily available, it may become a clinically useful tool to monitor CVD risk in HIV-positive patients. However, additional studies are required to analyze the influence of the addition of this marker to the cardiovascular risk scores before implementing routine measurement of hsCRP.

In a large international study, the baseline levels of CRP were independently associated with CVD events, including myocardial infarction, stroke, coronary revascularization, congestive heart failure, CVD death, and peripheral artery disease.[57] Hence, we propose that hsCRP should be measured in all HIV patients at greatest risk of cardiovascular morbidity and at least 6 monthly thereafter or at least as frequent as CD4 counts to monitor patients CVD risk profile.

hsCRP in HIV-infected patients is associated with traditional cardiovascular risk factors, principally in HAART-treated patients. hsCRP levels are not associated with CD4 cell counts and HIV-viral load and may constitute a marker for cardiovascular risk related to HIV infection and HAART;[58] therefore the additional cost of doing a hsCRP assay in all newly detected patients would be justifiable.

For a marker of risk to be valid, it must have:
1. A plausible biological mechanism
2. Applicability to both genders
3. Ability to enhance our current risk estimation
4. Applicability to populations in various geographic localities.

In case of hsCRP, not only all these criteria are met but the risk factor can also be modified.[2]

hsCRP is also a reliable marker of disease progression and a cheaper alternative for routine disease monitoring and predicting HIV-related outcomes, especially in a resource-poor setting. Further studies are required to understand the changes in hsCRP levels after HAART therapy and in HIV/HCV coinfection as the currently available data are either contradictory or insufficient.

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There are no conflicts of interest.

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5 MCQS

1. CRP was first identified as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide of :

    a.   Staphylococcus
    b.   Pneumococcus
    c.   Pseudomonas
    d.   E.coli

2. Most CRP is produced from liver apart from vascular endothelium produced from macrophages and adipocytes in response to :

    a.   interleukin-1
    b.   interleukin-3
    c.   interleukin-5
    d.   interleukin-6

3. hsCRP assays include:

    a.   ELISA
    b.   immunoturbidimetric assay
    c.   laser nephelometry
    d.   all of the above

4. A study by De Luca et al. identified serum hsCRP levels of __ as a potential threshold associated with significant risk of CVD in HIV-infected patients :

    a.   1.3 mg/L
    b.   2.3 mg/L
    c.   3.3 mg/L
    d.   4.3 mg/L

5. hsCRP may be preferred as a CVD risk biomarker over CD4 count and HIV RNA levels in HIV patients because:

    a.   hsCRP is cheap to measure and easily available
    b.   hsCRP is also a reliable marker of disease progression
    c.   baseline levels of CRP are independently associated with CVD events
    d.   all of the above

Answer key

1-b	2-d	3-d	4-c	5-d