Serum hs-CRP Levels Do Not Correlate With Carotid Intima-Media Thickness in Knee Osteoarthritis

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Abstract- Knee osteoarthritis (KOA) is prevalent morbidity which is associated with increased cardiovascular (CV) mortality. Any means to add to the risk stratification strategies especially prior to the total arthroplasty operations is of great applicability in terms of patient safety and cost reduction. We investigated the correlation between serum high sensitivity C-reactive protein (hs-CRP) levels, as a measure of CV risk, and common carotid intima-media thickness (IMT), as the cursor of underlying atherosclerosis. In a cross-sectional study, serum hs-CRP levels and common carotid IMT were determined in 68 patients with KOA. The mean serum hs-CRP level was 1.85±1.98 mg/L, and the mean carotid IMT was 0.67±0.16 centimeters with a Pearson's R=0.016 (*P*=0.898). Using linear regression models, no correlation was found between hs-CRP and IMT. Findings indicate the poor ability of hs-CRP to predict underlying atherosclerosis in patients with KOA. Although hs-CRP has been shown to be a powerful prognostic tool in general and is associated with increased mortality in patients with KOA, its applicability to predict the atherosclerosis risk especially prior to operation is limited. Further investigation to find the best cost-effective non-invasive indicator of CV risk in patients with KOA is mandatory.

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Introduction

Knee osteoarthritis (KOA) is prevalent morbidity accompanied by aging such that more than 50% of people over 60 years suffers from it (1). Observational studies reported that metabolic syndrome risk factors are accumulated among patients with KOA, and this can explain why they are at higher risk of death compared with the general population (1,2). The observed excess mortality is particularly pronounced for cardiovascular-associated mortality and severity of KOA disability is reported to be associated with serious cardiovascular disease (CVD) events after controlling for multiple confounders (2,3).

Consistently, large-scale studies have suggested an independent association of atherosclerosis with KOA (4), which can be attributed to the physical inactivity, obesity and prevalent CVD risk factors among them. Hence, determination of CVD risk seems mandatory in every patient with KOA particularly those scheduled for total knee arthroplasty (TKA). Being increasingly utilized as a therapeutic option, TKA is mainly preserved for those with advance disability (5,6). Although there are reports that long-term risk of CVD is increased after TKA, some researchers believe that primary elective TKA has potential cardioprotective benefits and even have reported reduced hazard ratios for CVD events (7,8). For cardiologists dealing with these patients, patients' inability to perform exercise stress testing impose diagnostic dilemma in that functional capacity can't be determined and a diagnosis of subclinical ischemic heart disease (IHD) demands other more expensive non-invasive or invasive procedures. Apparently, any means to provide more

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accurate risk estimates in clinically low-risk patients would obviate the need for invasive or potentially harmful diagnostic tests and facilitates a more precise risk stratification prior to TKA.

Cardiovascular risk assessment tools in general population as well as in a handful of disease states has been implemented for years using the conventional CVD risk factors as the main pillars (9). With the mentioned role of conventional risk factors of CVD in development and progression of KOA (10), a worse score among KOA patients is expected. Contemporary risk calculators however have incorporated newer markers to yield in better risk estimates among which high sensitivity C-reactive protein (hs-CRP) is the most widely accepted (9). With the well-documented ties between inflammation and atherosclerosis, hs-CRP has best served as an indicator of the overall inflammatory state of the body in apparently healthy individuals as well as those suffering from CVDs (9,11). Although KOA is primarily believed to be the consequence of mechanical stress on the knee, when it is developed is often associated with local inflammation, synovitis, and cartilage loss (12). While well-operated cohort studies have revealed that higher CRP concentrations were associated with both prevalent and incident KOA (13), configuring the association of hs-CRP with underlying atherosclerosis presence or progress among these patients, will provide useful information for risk prediction.

Common carotid artery intima-media thickness (IMT) has been used to define subclinical atherosclerosis though its accuracy as a predictive tool has been critically questioned. Still, as a vascular measure related to the atherosclerosis pathophysiology, IMT serves to estimate the degree of atherosclerosis progression in the vascular bed (14). In an attempt to find the best non-invasive tool to add to the clinical risk profile estimates of patients with KOA, we aimed to evaluate the association of carotid IMT as a cursor for atherosclerosis with hs-CRP levels in these patients.

Materials and Methods

Institutional review board of Fasa University of Medical Sciences (FUMS) and the regional ethics council for biomedical research at FUMS reviewed and approved the study.

We identified 68 patients with KOA who were candidates for TKA upon the diagnosis of a single experienced orthopedist. Patients were selected consecutively from a dedicated osteoarthritis clinic at Fasa university hospital after reviewing their clinical history, symptoms and signs and both knee radiographs. Categorization of patients regarding the severity of KOA was done using Kallgren-Lawrence (KL) grading scale and those scoring ≥2 were selected for further evaluations. Those with a history of rheumatologic disorders, myocardial infarction, heart failure, and active infectious or inflammatory diseases were excluded. A battery of laboratory tests including complete blood cell counts, fasting blood sugar, serum total cholesterol, high and low-density lipoprotein cholesterol, and triglycerides levels were measured. By means of the nephelometric method, serum hs-CRP levels were determined. An experienced radiologist/sonographer performed common carotid artery sonography and identified the IMT bilaterally. The higher value was used as the patient's IMT in the analysis.

Statistical analyses were done using SPSS software version 16. Means and standard deviations are reported for continuous variables and percentages for categorical ones. Pearson's correlation coefficient was calculated assuming a 5% type 1 error. Independent sample t-test was used for between-group comparisons.

Results

Sixty-eight patients with a mean age of 58.04±7.35 (range: 41-72) years old were studied. They were 53 (77.9%) women and 15 (22.1%) men. Table 1 summarizes their risk factor profile and anthropometric measurements. The prevalence of diabetes, hyperlipidemia, cigarette smoking, hypertension and ischemic heart disease among the study participants were 17.6, 50, 5.9, 44.1, and 25 percent respectively. Regarding the overall serum hs-CRP levels, with a mean of 1.85±1.98 mg/L, they fell into the category of intermediate risk. The mean carotid IMT was 0.67±0.16 centimeters with a Pearson's R=0.016 (P=0.898). Correlation coefficients of carotid IMT with other cardiovascular risk factors are shown in table 2. A significant correlation was observed for age (R=0.252, P=0.038), HDL cholesterol level (R=-0.269, P=0.27) and TG (R=0.314, P=0.009). Table-2 also shows the correlation coefficients for serum hs-CRP with the study parameters, showing that body mass index (R=0.446, P=0.0001) and waist circumference (R=0.314, P=0.009) exhibit the most significant correlations.

Linear regression models were applied to adjust for the confounding effects of CV risk factors; however, assuming a P<0.2 as the significance level of the model, we found no significant correlation between carotid IMT

and serum hs-CRP levels as well as the age, HDL cholesterol level, and TG. Finally dividing patients into those with and without a CV related outcomes and risk factors, we found no association between carotid IMT and the events. Results for this analysis are presented in table 3.

Table 1. Risk factor profile of patients

	Mean±standard deviation	Range
Fasting blood sugar (mg/dl)	83±25.2	45-204
Total cholesterol (mg/dl)	167.76±37.3	98-282
LDL cholesterol (mg/dl)	129.37±49.49	24-229
HDL cholesterol (mg/dl)	54.49±14.38	23-97
TG (mg/dl)	141.09±52.54	48-229
Weight (kg)	74.4±13.01	40-136
Height (cm)	158.6±7.96	143-195
Body mass index (kg/m^2)	29.52±4.36	17.78-41.33
Waist circumference (cm) in men	91.86±7.09	79-105
Waist circumference (cm) in women	93.13±11.06	66-124

FBS: fasting blood sugar, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride

Table 2. Pearson's R for study parameters and carotid IMT and serum hs-CRP

	Pearson's R (*P*)	
	IMT	**hs-CRP**
Fasting blood sugar	0.192 (0.118)	0.006 (0.960)
Total cholesterol	0.025 (0.838)	-0.038 (0.756)
LDL cholesterol	0.233 (0.056)	-0.041 (0.742)
HDL cholesterol	-.0269 (0.027)	-0.096 (0.435)
TG	0.314 (0.009)	-0.119 (0.332)
Weight	0.019 (0.878)	0.322 (0.006)
Height	0.212 (0.082)	-0.045 (0.713)
Body mass index	-0.112 (0.362)	0.446 (0.0001)
Waist circumference	0.056 (0.647)	0.314 (0.009)
hs-CRP	-0.016 (0.898)	1
Carotid IMT	1	-0.016 (0.898)

FBS: fasting blood sugar, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: triglyceride, IMT: intima-media thickness, hs-CRP: high sensitivity C-reactive protein

Table 3. Linear regression model constant and beta values for study parameters

Model	t	Standardized coefficient	Unstandardized coefficient		Significance
		Beta	**Standard error**	**Beta**	
Constant	-0.390	0.102	0.514	-.0201	0.698
Sex	0.737	0.173	0.053	0.039	0.464
Age	1.307	0.166		0.004	0.196
Height	1.383	0.173	0.003	0.004	0.186
FBS	0.817	0.101	0.001	0.001	0.417
TG	1.229	0.245	0.001	0.001	0.242
LDL	-0.150	-0.029	0.001	-9.230	0.882
HDL	-0.769	-0.104	0.002	-0.001	0.445
hs-CRP	0.033	0.004	0.010	0.000	0.974

Discussion

In a cross-sectional study, we didn't find any correlations between carotid IMT and serum hs-CRP levels in a patient population with KOA. While CV risk stratification has become a challenging dilemma for physicians dealing with these patients before such demanding procedures like TKA, any means toward a more accurate and reproducible risk estimate would be of great benefit in terms of patient safety and minimizing costly diagnostic tests. To the best of our knowledge, this is the first study focusing on this topic and as the most readily available non-invasive option previously proved to be of great applicability for CV

risk estimation, hs-CRP, failed to be promising in KOA patients according to our results.

Although the common carotid artery IMT is not a perfect indicator of the underlying atherosclerosis process, it is one the inexpensive imaging options to delineate the vascular integrity besides the modifications in vessel wall secondary to atherosclerosis. In a low-risk patient category for whom an understanding of the probability of the occurrence of hard cardiac events are of paramount importance, like the mentioned scenario of KOA patients scheduled for TKA, carotid IMT gives the facility of apprehending the patient's atherosclerosis status quo (14,15). Furthermore, regarding the study question in this research that asked whether hs-CRP correlated with carotid IMT as a harbinger of significant atherosclerosis in patients with KOA, a negative answer proposes two premises: first, it most probably indicates a lack of prognostic significance of hs-CRP in patients with KOA; and second, since the carotid IMT in the low-risk setting of stable asymptomatic patients with the low probability of advances atherosclerosis does not necessarily anticipate CV events, serum hs-CRP would actually retain its prognostic significance but not correlates with carotid IMT. Whichever the explanation turns out to be, still the quandary persists especially in developing countries where the financial burden of the unnecessary diagnostic tests for the health system is huge.

Besides the vindicated importance of hs-CRP as a prognostic tool in diverse clinical settings, the other rationale behind this study's choice for hs-CRP as a risk indicators was a report by Sowers *et al*., where they showed that higher CRP concentrations were associated with both prevalent and incident KOA in longitudinal cohort study with 2.5 years follow up (13). Though this report has not been reproduced yet, dating back several decades ago, conventional risk factors have well-supporting evidence of being associated with KOA. Lawrence reported an association of diastolic blood pressure with KOA in women (16); Hart *et al*., made suggestions of an association between blood sugar, hypercholesterolemia and hypertension and development of KOA (17); and Yoshimura *et al*., documented the accumulation of metabolic syndrome components in such patients (1). Follow up re-evaluations of KOA in the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study have also revealed that conventional CV risk factors are even associated with radiographic KOA progression, which logically implies at the high probability of ischemic heart disease presence in those with long-standing or severe KOA (10). This all well explains why cardiologists look obsessively for subclinical CV disease among KOA patients who are scheduled for TKA and justifies the logic behind this study's research question which ultimately looked for a non-invasive, inexpensive tool to add to the patients' prognostications.

We propose that serum hs-CRP applicability for further risk stratification of patients with KOA beyond the conventional risk factors is limited. This is consistent with the consensus statements about serum hs-CRP prognostic values in low-risk asymptomatic individuals where large-scale clinical observations have raised serious dubiousness. Serum hs-CRP levels in this context are best viewed as an adjunct to serum lipid profile where target LDL cholesterol levels are achieved, and physicians usually continue statins to reach a hs-CRP level below 1 mg/L (18). Participants of this study were relatively young, with an age range of 41-72-year-old and below the expected CV risk factors prevalence. None of them has sedentary lifestyle, and the rate of cigarette smoking was low as well. This all put them in the low CV risk category and may also explain the observed lack of association between serum hs-CRP and carotid IMT amongst them.

Furthermore, KOA is considered a local chronic inflammatory condition which hardly is contributed to a general inflammatory response. Although there are studies that strongly suggested a decreased vascular responsiveness in animal models of KOA, they have focused on the local sequelae of such endothelial dysfunction and vasculature disruption on the progression of KOA (19). The vascular responses beyond the affected knee have not been studied yet, and it may be interesting to know the alterations of endothelial function in patients with KOA in whom multiple CV risk factors are accumulated, and they mostly are physically inactive. Strategies to decrease modifiable risk factors become increasingly important then, especially when reports like Jungmann's *et al*., has indicated the role of them even in further cartilage loss and KOA progression (20).

Our study, cross-sectional in design, was not aimed at finding out the effects of hs-CRP, carotid IMT and conventional CV risk factors on KOA consequences, however, in a small clinical setting, we believe some pertinent issues in the daily practice with KOA have been raised concisely. Recruiting more patients with higher risk profiles in longitudinal studies will best answer these questions. Herein, we investigated whether hs-CRP levels could signify underlying atherosclerosis

process to find out patients with uncovered IHD. This would potentially be of great clinical importance knowing that hs-CRP in KOA patients with a handful of modifiable CV risk factors couldn't contribute to the physicians' judgment of underlying IHD presence. Rather the contemporary perception that subclinical IHD exists in patients with KOA would best be addressed preoperatively by means of coronary imaging modalities or perfusion scintigraphy. This is primarily important in developing countries with limited health system resources, and as a result, any attempt to distinguish less expensive tests to a better risk calculation with enough precision would benefit most.

In conclusion, serum hs-CRP levels didn't correlate with carotid IMT in patients with KOA which may either reflect its limited applicability as a risk estimator or the trivial significance of carotid IMT as the atherosclerosis indicant. Future studies are suggested to clearly answer these questions that whether KOA is accompanied by a generalized endothelial dysfunction or not; and what are the determinants of the increased mortality of patients with KOA and the decreased CV mortality after TKA?

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