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VALUE OF C-REACTIVE PROTEIN IN PATIENTS WITH CORONARY HEART DISEASE AND CONCOMITANT TYPE-2 DIABETES MELLITUS

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ABSTRACT:

Coronary heart disease (CHD) is one of the worldwide leading causes of death in patients with type 2 diabetes mellitus (T2DM). This situation may worsen in future since various uncontrollable risk factors mainly diabetes, smoking, obesity, hypercholesterolemia, hypertension etc have been enormously increasing and hence future consequences of CHD might be quite alarming. Vascular indices, circulating inflammatory biomarkers and insulin resistance have important prognostic value, and explain the multifactorial pathophysiological events of atherosclerosis in patients with T2DM. The T2DM is almost 90 % of all cases of diabetes. It is documented that atherosclerosis is not developed only by dyslipidemia, but also by inflammation via plaque complexity and instability, and a variety of other still unknown factors. However, C-reactive protein (CRP) and especially the high sensitivity CRP (hsCRP)- an acute phase protein of hepatic origin and the inflammatory biomarker or indicator of systemic inflammation/metaflammation is helpful in predicting inflammation and atherosclerosis. The hsCRP levels may serve as predictor in healthy people for a possibility of their cardiac complications in future and it is considered a marker for the degree of acute and chronic inflammation in CHD, other ischemic diseases, diabetes mellitus and various other disorders presenting inflammation. Despite the diagnostic, prognostic and efficacious role, CRP in average risk adults without symptoms is currently not recommended as a cardiovascular disease (CVD) screening test. Furthermore, the hsCRP test should not be considered alone and should be combined with elevated levels of cholesterol, low density lipoprotein-cholesterol (LDL-C), triglycerides, glucose level and other variables since beside diabetes, smoking, hypertension and a variety of other factors also increase the risk level of CVD. Statin and other therapeutic approaches have been found efficacious for improving vascular endothelial functions, plaque stability, inflammation and hence, reducing the hsCRP in patients with CHD, T2DM, coronary heart disease and other ischemic/ inflammatory/ atherosclerotic disorders. Hopefully the future considerations will help identifying common biomarkers for coronary heart disease and type-2 diabetes mellitus and will lead to better management of the patients with co-occurrence of coronary heart disease and type-2 diabetes mellitus.

KEYWORDS: *Coronary heart disease (CHD), type-2 diabetes mellitus (T2DM), high sensitivity C-reactive protein (hsCRP), atherosclerosis, inflammation, inflammatory biomarker, statin therapy*

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INTRODUCTION

Coronary heart disease (CHD) is one of the worldwide leading causes of death. The World Health Organization (WHO) reports show that 31% of deaths due to cardiovascular diseases across the globe.[1] This situation may worsen in future since various uncontrollable risk factors mainly diabetes, smoking, obesity, hypercholesterolemia, hypertension etc have been enormously increasing and hence future consequences of CHD might be quite alarming.[2,3] Coronary heart disease (CHD) or coronary artery disease (CAD) is characterized by either stenosis or occlusion of coronary arteries leading to myocardial ischemia or infarction respectively. Inspite of extensive studies in CHD, precise information for the exact cause and pathogenesis requires further studies to be carried out to relate the genetic factors with the clinical manifestations. Hereditary information of CHD along with genetic polymorphism studies, however, indicates the involvement of genetic architecture in the occurrence and progression of CHD. We and our associated research groups have studied the ischemic disorders in T2DM[4-7] pathophysiological perspectives of T2DM,[8] ischemic heart disease [2,9] and have reviewed various aspects of T2DM,[10] coronary heart disease[11] and therapeutic aspects.[12,13] These studies emphasize the role of inflammation in T2DM and CHD.

There are a variety of factors/ diseases co-occurring with coronary heart disease, e.g. diabetes mellitus (DM). Coronary Heart Disease (CHD) is a complication that may lead to death in patients with type 2 diabetes mellitus (T2DM). Vascular indices, circulating inflammatory biomarkers and insulin resistance have important prognostic value, and explain the multifactorial pathophysiological events of atherosclerosis in patients with T2DM.[14]The T2DM diabetes mellitus is almost 90 % of all cases of diabetes.

Adjustment of high sensitivity C-reactive protein (hsCRP), demographic factors and other variables help studying the concept of ideal CVH (cardiovascular health) and health of patients with diabetes mellitus.[15] Type 2 diabetes mellitus (T2DM) is mainly characterized by increased systemic inflammation. The present article provides a brief review of the role of hsCRP in patients with the co-occurrence of coronary heart disease and type-2 diabetes mellitus (T2DM).

CRP IN CORONARY HEART DISEASE:

Estimation of CRP is widely suggested for investigating the degree of inflammation and is considered as a marker of acute and chronic inflammation especially in CAD and other ischemic disorders,[16,17]though it has been revealed that hs-CRP is helpful in predicting ischemic heart disease (IHD) and other disorders in young and elder men and women, whereas hs-CRP levels may also serve as predictor in healthy people for a possibility of their cardiac complications in future. However, precise correlation of hsCRP levels with the severity of injury is not known.

The hsCRP and cardiovascular risks have been studied in detail and even small increase in the level of hsCRP in view of its high sensitivity serves as an indicator for predicting complications and diseased conditions especially related to Coronary heart disease(CHD).[18] The hsCRP elevates in patients with increasing severity in IHD.[11,19]However, controversial results for the role of hsCRP in cardiac ischemic disorders have also been obtained.[20] Membrane self-assembly studies reveal the subtle alterations clarifying these studies.[21]One report shows hs-CRP levels associated to CHD (coronary heart disease) but not to the severity of CHD though CRP was not associated to the levels of hsCRP in normal subjects and individuals with higher risk of ischemic disorders (Rashidinejad et al., 2013).[20] Male and female patients with ischemic heart disease indicated various inflammatory and behavioral mechanisms with even small associations of hsCRP and other markers.[22] Patients with SIHD (stable form of ischemic heart disease) under DAPT (dual-antiplatelet-therapy) showed increased hsCRP.[23] The hsCRP estimated in men showed increase in the development of venous thromboembolism (VTE) with a linear association.[24] Increased hsCRP were obtained though not related to IHD severity in patients of mean age 60.3 years.[25]

Furthermore, most of the studies related to

CRP in ischemic disorders were carried out in Europe and America and when compared it was found that levels of CRP were higher in Asians compared to European people. In view of this reason, we assessed the levels of hsCRPin female patients having ischemic stroke, epilepsy, post-stroke epilepsy and ischemic heart disease.[26] Our major aim was to have idea whether patients with ischemic disorders without obesity or over-weight status have high hsCRP levels. This information was also essential to verify that ischemic disorders and atherosclerosis may also occur due to dysfunction in inflammatory disorders manifesting change in the levels of inflammatory markers including hsCRP beside occurring due to dyslipidemia.We found inflammation as a major factor causing atherosclerotic conditions in neurovascular and cardiovascular disorders including coronary heart disease, ischemic stroke and post-stroke epilepsy.[26]

CRP IN TYPE-2 DIABETES MELLITUS:

The previously thought low systemic inflammation in patients with T2DM could not be confirmed that revealed an association of hsCRP measured by ELISA (enzyme-linked immunosorbent assay) method and diabetes classification. Elevated CRP has been found associated with high risk of T2DM and the systemic inflammation is one of the main factors manifesting T2DM characteristics,[27]and it was shown that increased circulating levels of CRP in acute phase are associated with T2DM.

The CRP and various other inflammatory markers associate with higher occurrence in T2DM and leads to cardiovascular disease (CVD).[28] Systemic inflammation, metabolic inflammation or metaflammation occurring in T2DM is usually chronic or low grade.[29] Furthermore, the elevated hsCRP plasma levels in postmenopausal women with T2DM were found associated with higher levels of specific plasma ceramides independent of other diabetes and cardiovascular related factors.[30]

The CRP that is a nonspecific systemic inflammatory marker and is an acute phase reactant is one of the important inflammatory biomarkers associated with obesity. Relationships between obesity and inflammation (by determining CRP and other inflammatory factors) in the incidence of T2DM showed elevated CRP and potential effect of targeted control of systemic inflammation on reducing the risk of T2DM development.[31]A recent study revealed improvement in hsCRP in obese T2DM patients under 6-months treatment with exenatide.[32]Effects of various training modes showed decreased levels of blood inflammatory factor CRP levels in patients with T2DM.[33]

The T2DM patients revealed higher inflammatory response to COVID-19 (Coronavirus disease-2019)with higher CRP levels.[34] Further studies may bring newer aspects of the role of hsCRP in CHD patients with diabetes and other medical disorders.

CRP IN CORONARY HEART DISEASE WITH TYPE-2 DIABETES MELLITUS

Controlling the risk factors of cardiovascular disorders in T2DM resultantly causes decrease in CVD. A recent report revealed inflammation involving CRP and other inflammatory factors as a common characteristic in T2DM and CHD.[35]Inflammatory markers including hsCRP have a significant role in the progression of CHD in T2DM.[36]Hence, elevated CRP levels may be considered a prognostic biomarker of CHD development in patients with T2DM.[37]

A study to examine the predictive value of baseline hsCRP for CHD and T2DM showed the involvement of hsCRP in both CHD and microvascular disorders in T2DM.[38] It was suggested that LVdys(left ventricular dyssynchrony)is an early marker of myocardial dysfunction in asymptomatic diabetic patients and hence, it is helpful to employLVdys and left ventricular mechanical reserve (LV-MR) where hs-CRP & left-atrial volume index values were found inversely correlating to LV-MR.[39]

A variety of factors including central obesity, insulin resistance, glycemic control, non-low density lipoprotein-cholesterol (non-LDL-C) etc in patients with T2D and LDL-C<70 mg/dL, are the possible contributors for RIR ('Residual-inflammatory risk' properly defined as the persistent concentrations of circulating hsCRP with even an optimal control of LDL-C representing an emerging factor as risk for the development of CVD in patients having high atherosclerosis risk).[40]

ROLE OF CRP INTREATMENT OF CHD PATIENTS WITH T2DM:

Patients with T2DM and CHD usually have abnormal vascular endothelial functions, increased inflammatory cells and abnormal insulin resistance beside a number of other abnormal alterations.[41]Patients with T2DM and CHD under the intense effect of multiple risk factors may lead rapidly even in quite early stage to severe disorders of heart, kidney, brain, liver and other vital organs but show reduced serum hsCRP in moderate or high-dose rosuvastatin subjects than those getting low dose rosuvastatin along with other

alterations.[42]Emerging approaches for investigating the biomarkers including plasma CRP for CHD and incident DM risk in statin treated patients help identifying the common biomarkers for CHD with/ without DM.[43]

It was quite valuable investigation that rosuvastatin therapy can decrease several blood factors including hsCRP in subjects with T2DM and CHD leading to improved vascular endothelial functions and decreased inflammation.[44] Study of the risk factors in CHD and T2DM provided information that a change in LDL-C had no relationship with the plaque compositions and hsCRP, and a remarkable change in hsCRP (but not LDL-C) associated with greater decrease in necrosis after one-year rosuvastatin therapy.[45]

Treatment of T2DM patients with CHD by using ezetimibe and combined with atorvastatin was safe and well tolerated, though the effect of combined use of atorvastatin and ezetimibe was found better than atorvastatin alone, for effectively reducing hsCRP, improving plaque stability and altering various other serum variables.[46] Effect of single parental dose of vitamin D on the control of glucose and inflammation in T2DM patients with CHD showed improved glycemic control but not the serum hsCRP- an indicator of inflammatory status.[47] Further studies are required to be carried out for CRP influencing approaches for better management of CHD patients with T2DM.

CONCLUSION:

Atherosclerosis is not developed only by dyslipidemia, but also by inflammation via plague complexity and instability, and a variety of other still unknown factors. However, CRP and especially the hsCRP- an acute phase protein of hepatic origin and the inflammatory biomarker or indicator of systemic inflammation/metaflammation is helpful in predicting atherosclerosis. The hsCRP levels may serve as predictor in healthy people for a possibility of their cardiac complications in future and it is considered a marker for the degree of acute and chronic inflammation in CHD, other ischemic diseases, diabetes mellitus and various other disorders presenting inflammation. It is recommended that persistent circulating levels of hsCRPwith even an optimal control of LDL-C represents an emerging risk factor for the development of CVD in patients having high risk of atherosclerosis.

Systemic inflammation or metaflammation is considered a major factor manifesting T2DM characteristics and associates with the increased circulating levels of CRP that may lead to CVD. It has been revealed that controlling the risk factors of CVDin T2DM in patients with diabetic ischemic heart disease resultantly causes decrease in CVD. In that perspective, adjustment of hsCRP, demographic factors and other variables help understanding the concept of ideal cardiovascular health and health of patients with diabetes mellitus. Despite the diagnostic, prognostic and efficacious role, CRP in average risk adults without symptoms is currently not recommended as a CVD screening test. Furthermore, the hsCRP test should not be considered alone and should be combined with elevated levels of cholesterol, LDL-C, triglycerides, glucose level and other variables since beside diabetes, smoking, hypertension and a variety of other factors also increase the risk level of CVD.

Inflammatory markers including hsCRP has a significant role in the progression of CHD in T2DM. Hence, elevated CRP levels may be considered a prognostic biomarker of CHD development in patients with T2DM. Statin and other therapeutic approaches have been found efficacious for improving vascular endothelial functions, plaque stability, inflammation and hence, reducing the hsCRP in patients with CHD, T2DM, diabetic coronary heart disease and other ischemic/ inflammatory/ atherosclerotic disorders. The emerging approaches for investigating the biomarkers including plasma/ serum CRP for CHD and incident DM risk in statin treated patients help identifying the common biomarkers for CHD with/ without DM.

Hopefully the future considerations will help identifying common biomarkers for coronary heart disease and type-2 diabetes mellitus and will lead to better management of the patients with co-occurrence of coronary heart disease and type-2 diabetes mellitus.

ABBREVIATIONS	
CAD	Coronary artery disease
CHD	Coronary heart disease
COVID-19	Coronavirus disease-2019
CRP	C-reactive protein
CVH	Cardiovascular health
CVD	Cardiovascular disease
CRT	Cardiac resynchronization therapy
DAPT	Dual-antiplatelet-therapy
DM	Diabetes mellitus
ELISA	Enzyme-linked immunosorbent assay
hsCRP	High sensitivity CRP
IHD	Ischemic heart disease
LDL-C	Low density lipoprotein-cholesterol
LVdys	Left ventricular dyssynchrony
LVMR or LV-MR	Left ventricular mechanical reserve
non-LDL-C	non- low-density lipoprotein-cholesterol
SIHD	Stable form of ischemic heart disease
T2DM	Type 2 diabetes mellitus
VTE	Venous thromboembolism
WHO	The World Health Organization

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