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REVIEW-1

C-REACTIVE PROTEIN AND STATINS

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ABSTRACT:

Atherosclerosis is now widely considered as a form of inflammatory disorder rather than merely a consequence of dyslipidemia. C-reactive protein (CRP) is an acute phase reactant, seen elevated in case of ongoing inflammation. Measuring both CRP and cholesterol provide a more accurate indication of risk than cholesterol estimation alone.

It is observed that lipid lowering drugs reduce the incidence of coronary events and stroke. This is mainly due to the pleiotropic action which is independent of their hypolipidemic action.

In this review article, recent developments regarding the role of statin therapy in prevention of adverse cardiovascular events is discussed succinctly.

A. *Background:*

The prevalence of cardiovascular disorders is increasing day by day. Atherosclerosis is the most prevalent cause of these diseases (Libby, 2002), producing obstruction for normal blood flow, commonly leading to the infarction of the tissues or organs distal to the obstruction (Anderson *et al*., 1998) For the last two and a half decades the understanding of the process of atherosclerosis has become much clearer (Libby, 2001).

Atherosclerosis is now widely considered as a form of inflammatory disorder. The association of inflammation and atherosclerosis can yield predictive and prognostic information of considerable clinical utility. In a variety of animal models of atherosclerosis, signs of inflammation occur together with incipient lipid accumulation in the arterial wall (Libby *et al*., 2002). For example, blood leukocytes, which are mediators of host defenses and inflammation, localize in the earliest lesions of atherosclerosis. This phenomenon is observed in humans as well.

B. *Association of C-Reactive Protein with Cardiovascular Disorders:*

C-reactive protein (CRP) is an acute phase reactant, seen elevated in case of ongoing inflammation. A strong association of elevated serum CRP has been observed with acute myocardial infarction (Yusuf *et al*., 2001; Albert *et al*., 2003; Koeing *et al*., 1999 and Morrow etal., 1998)), sudden coronary deaths and stroke (Burke *et al*., 2002 and LaMonte *et al*., 2002). In addition, it shows a positive correlation with the extent of coronary artery stenosis (Erren *et al*., 1999) Animal research (Barrett *et al*., 2002) has shown that serum CRP is positively correlated with myocardial infarct size. In patients of angina, whether stable or unstable, CRP has also associated to be an independent predictor of adverse cardiovascular events (Ikonomidis *et al*., 1999 and Ferreiros *et al*., 1999)).

Inflammation, systemic or local, triggers the production of pro-inflammatory cytokines, which can be used as markers for the inflammatory status of the individual (Libby *et al*., 1999). During inflammation expression of cell adhesion molecules (required for leukocyte response to the area of injury), production of chemokines, and LDL uptake by macrophages (leading to formation of foam cells) are enhanced by mediators like endothelin-1 (ET-1) and interleukin-6 (IL-6) (Verma *et al*., 2002). CRP, a member of the pentraxin family, consists of five identical

non-covalently linked subunits of 23,000 kDa md mass, the total molecular mass of CRP being 1 18,000kDa. Its serum concentration of <1 μg/ml can increase during the first 24-48 hours of inflammation or tissue necrosis by several thousand-fold (Burke *et al*., 2002 and Cermak *et al*., 1993). It stimulates the production of ET-1 and IL-6, thus facilitating pro-inflammatory state. Atherosclerotic plaque shows signs of local inflammation, like macrophage recruitment, foam cell formation, smooth muscle hyperplasia etc. (Verma *et al*., 2002).

Normally functioning vascular endothelium opposes thrombosis as well as atherosclerosis. CRP is also implicated in vascular endothelial dysfunction and in the progression of atherosclerosis (Venugopal *et al*., 2003). The normal endothelium does not support avid binding of white blood cells. However, early after the initiation of an atherogenic diet, patches of arterial endothelial cells begin to express on their surface selective adhesion molecules that bind to leukocytes. Vascular Cell Adhesion Molecule-1 (VCAM-1), an important adhesion molecule, binds particularly to those classes of leukocytes found in nascent atheroma, the monocytes and the T-lymphocytes (Libby *et al*., 2002), VCAM-1 rises before the leukocyte recruitment begins. Endothelial cells express VCAM-1 in response to cholesterol feeding (Libby *et al*., 2001). It is found that CRP also up-regulates adhesion molecule expression on vascular (Libby, 2002) endothelium.

CRP causes the opsonization of the native LDL which is then taken up by the macrophages. The macrophages ultimately convert into foam cells by accumulating large amount of lipids (Zwaka *et al*., 2001). So this process can happen without acetylation, oxidation, and enzymatic modification of LDL (Zwaka *et al*., 2001 and Torzewski *et al*., 1998). Thus, higher CRP levels can potentially make the atheroma more grumous and vulnerable to rupture. This could be a reason why some studies have shown an association between high serum CRP with higher rate as well as poorer prognosis of the coronary events (Burke *et al*., 2002; Libby *et al*., 1999; Verma *et al*., 2002; Ridker, 2001 and Sano *et al*., 2003).

CRP stimulates the production of ET-1 and IL-6, thus facilitating pro-thrombotic state. CRP is thus a mediator of atherosclerosis because it contributes to the substrate underlying the atherosclerotic plaque's formation as well as rupture ultimately leading to the coronary thrombosis (Verma *et al*., 2002).

In deciding whether a patient requires therapy to prevent an atherosclerosis-related heart attack or stroke, physicians usually rely heavily on measurements of cholesterol in the person's blood, thus missing many vulnerable individuals. Several studies suggest that measuring blood concentration of CRP could add useful information. It was recently reported that examining both CRP and cholesterol provide a more accurate indication of risk than cholesterol estimation alone. (Libby, 2002; Anderson *et al*., 1998; Burke *et al*.,2002; LaMonte *et al*., 2002 and Zwaka *et al*., 2001). The high sensitivity assay of CRP is well standardized, widely available, and reproducible that adds to the predictive value of traditional risk factors of cardiovascular disorders, including the lipoprotein profile (Libby, 2001).

A large number of studies suggest that elevated serum CRP is an independent risk factor for atherosclerotic vascular disease (Anderson *et al*., 1998; Koenig *et al*., 1999; Morrow *et al*., 1998; Burke *et al*., 2002 and Ridker *et al*., 1998). It is associated with two- to five-fold increased risk of coronary events (2, 10) as well as poor prognosis in acute coronary syndrome (Burke *et al*., 2002; Sano *et al*., 2003). Large prospective studies have shown strong, independent association of high serum levels of CRP with risk of MI, stroke, peripheral arterial disease and vascular death among individuals without known cardio-vascular disease (Sano *et al*., 2003). In addition, among the patients with acute

coronary ischemia, stable angina pectoris, and history of myocardial infarction, higher levels of the CRP have been associated with increased event rate (Libby and Ridker, 1999; Verma *et al*., 2002 and Ridker, 2001). It has also been seen that there is variation in plasma CRP levels by race (LaMonte *et al*., 2002). We reported in a study conducted recently (article accepted, in press: Journal of Pakistan Medical Association) in a Karachi-based population sample that serum CRP was significantly raised in subjects suffering from myocardial infarction as compared to otherwise healthy controls.

It is observed that lipid lowering drugs reduce the incidence of coronary events and stroke. This is mainly due to their pleiotropic action. In animals with experimental atherosclerosis, lowering plasma lipids reduces the number of inflammatory cells, including macrophages and various inflammatory mediators as well as the level of the collagenolytic enzymes such as metallo-proteinase-1 (Libby, 2001), all the factors inflicted in the progress of atherosclerosis.

C. *Role of Statins in Cardiovascular Disorders:*

Statins are effective hypolipidemic agents. The group consists of several agents for example atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. All these agents are inhibitors of an enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate-limiting enzyme in de-novo cholesterol synthesis in liver (Malloy and Kane, 2004).

Since dyslipidemia is an important factor governing the onset and progression of atherosclerosis-related cardiovascular diseases, statins are one of the widely prescribed drugs for primary and secondary prevention of cardiovascular events all over the world. Several large clinical trials of secondary prevention of coronary heart disease have shown that statins reduce the risk of death by about 30% (Anonymous, 1994; 1998).

A recently published meta-analysis (Law *et al*., 2003) concluded that statins can lower LDL cholesterol concentration by an average of 1.8 mmol/l which reduces the risk of ischemic heart disease events by about 60% and stroke by 17%. However, recent studies indicate that controlling dyslipidemia is just one aspect of the beneficial role of statins in prevention of cardiovascular disease.

There are other mechanisms also through which the statins may act and contribute to the overall benefit in prevention of cardiovascular diseases, such as stabilizing atherosclerotic plaques, improving endothelial dysfunction, controlling immune and inflammatory response, reducing free radical injury as well as thrombogenicity (Muniz-Junqueira *et al*., 2006; Martin-Ventura *et al*., 2005; Davignon, 2004; Delbosc *et al*., 2002; Albert *et al*., 2001 and Joukhadar *et al*., 2001).

Schillinger *et al*. (2004) conducted a study in which they examined the interrelationship between statin therapy, inflammation and cardiovascular outcomes in 515 patients with atherosclerotic arterial disease. As inflammatory markers they analyzed hs-CRP, SAA, serum fibrinogen, serum albumin and neutrophil count. They reported that statin therapy works best in patients having adverse levels of inflammatory markers. Since fibrinogen is a coagulation factor as well, a reduction in its levels may also decrease the prothrombotic state (Schillinger *et al*., 2004).

It is also reported that continuous statin therapy leads to regression of atherosclerotic plaques (Corti *et al*., 2002). In addition, statins help in plaque stabilization by reducing the production of matrix metalloproteinases by macrophages, which are involved in digestion of matrix proteins within the atheromatous plaque (Crisby *et al*., 2001). This effect reduces the chances of plaque rupture and subsequent thrombosis.

D. *Effect of Statin Therapy on Serum C-Reactive Protein:*

The role of inflammation in onset and progress of atherosclerosis is currently the focus of research. Elevated levels of

inflammatory markers such as acute phase reactants (serum CRP, serum amyloid A protein [SAA]) interleukin-6, and cell adhesion molecules have been associated with increased risk for adverse cardiovascular events. CRP levels, especially, appear to be among the most powerful predictors of adverse cardiovascular events. Statin therapy reduces inflammation and risk of cardiovascular events. The Cholesterol and Recurrent Events (CARE) trial has reported that subjects with elevated levels of CRP and SAA benefited more from statin therapy as compared to those with lower levels of these markers. The relative risk of a recurrent coronary event was significantly reduced in both groups, compared with placebo. At baseline, both subsets had nearly identical plasma lipid profile (Ridker *et al*., 1998). In addition, continuous statin therapy reduces serum CRP levels (Albert *et al*., 2001; Ridker *et al*., 2005 and Jialal *et al*., 2001) and increases survival (Ridker *et al*., 2005).

Jialal *et al*. (2001) reported in a crossover trial comparing the effect of pravastatin, simvastatin, and atorvastatin therapy on hs-CRP levels in patients with combined hyperlipidemia that at doses reported to have equivalent effects on LDL-cholesterol. Median hs-CRP levels were significantly reduced irrespective of reductions in LDL-cholesterol.

E. ***Anti-Inflammatory Role of Statins:***

Adhesion molecules and chemoattractants also play an important role in the inflammatory process in concert with acute phase reactants such as CRP and SAA by favoring adhesion and transmigration of leukocytes to the subendothelial tissues as part of the atherogenic process (Blake *et al*., 2001). Recently it was demonstrated that statins irrespective of their inhibitory effect on HMG-CoA reductase could have a selective and potent direct anti-inflammatory effect via blockade of beta2 integrin leukocyte function antigen-1 (LFA-1) (Weitz-Schmidt *et al*., 2001).

As described earlier, statins also reduce the production of matrix metalloproteinases by macrophages, thus limiting the inflammatory response (Corti *et al*., 2002).

F. ***Conclusion:***

Since statins reduce CRP as well as immune response, block novel targets in the activation of leukocytes, downregulate cell adhesion molecules and curtail free radical production, it becomes evident that statins' pleiotropic effect is not dependent upon cholesterol synthesis inhibition. Instead, it is a combination of both lipid-lowering and pleiotropic activity which is the key to success. That is why statins are emerging as important modality in prevention of adverse cardio-vascular events in the practice of modern medicine. In addition, it can also be inferred that while investigating cardiovascular risk, one should not omit the value of measuring inflammatory markers in serum.

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