Review

Statins Therapy, C-Reactive Protein (CRP) Levels and Type 2 Diabetes

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ABSTRACT **Purpose:** The effectiveness of therapy with hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, for reducing elevated C-reactive protein (CRP) levels and cardiovascular risk at patient with type 2 diabetes. Atherosclerotic plaque growth may be attenuated with therapy aimed at minimizing inflammation. CRP is considered to be a major inflammatory cytokine that functions as a non-specific defense mechanism in response to tissue injury or infection. Synthesized mainly in the liver, CRP activity is stimulated by other cytokines, especially interleukin (IL)-6, IL-1b, and tumor necrosis factor-a (TNF-a). CRP binds to a variety of molecules, particularly liposomes and lipoproteins, such as LDL and VLDL cholesterol, and is a powerful activator of the classic complement way. Accumulating evidence suggests that CRP, which is also found within macrophages of atherosclerotic plaques, is causally or mechanistically related to atherothrombosis. Inflammation plays an important role in the pathogenesis of type 2 diabetes. Because increased levels of CRP have been associated with arterial-wall inflammation, statins can prevent ischemia by both inhibiting deposition of lipids and decreasing inflammation. **Conclusions**: Inflammation underlies diabetes and may predict it. The role of lowering CRP in reducing the risk for and improving the prognosis of diabetes is undergoing assessment. The lowering of elevated CRP levels by statins may reduce the risk of cardiovascular events independently of the effect of statins on lipid levels. The results of ongoing clinical trials will continue to provide data on the additive value of testing levels of CRP and other inflammatory markers for cardiovascular risk assessment and should delineate the clinical utility of such testing in various disease states.

KEY WORDS *statins, C-reactive protein, diabetes type 2, cardiovascular risk*

Introduction

Despite advances in the detection of risk factors, cardiovascular events continues to affect many patients worldwide. The National Cholesterol Education Program (NCEP) developed guidelines for the treatment of high blood cholesterol in adult patients, known as the Adult Treatment Panel III (ATP III) Guidelines. The major emphasis of the ATP III Guidelines is the primary prevention of CHD in at-risk patients by lowering levels of low-density-lipoprotein (LDL) cholesterol.[1] While it is crucial to achieve lipid goals, it is important to realize that half of all acute myocardial infarctions (MI) occur in patients with normal lipid levels.[2,3] Considering that treatment of LDL cholesterol, high-density-lipoprotein (HDL) cholesterol, and triglycerides to goal levels only partially reduces CHD risk, the risk of CHD complications stemming from acute and chronic inflammatory processes must be quantified.

A growing database[12,13] reinforces the concept that inflammation also plays an important role in the pathogenesis of type 2 diabetes and links diabetes with concomitant conditions with inflammatory components.[14] Evidence exists for the prior linkage of euglycemic insulin resistance as a proinflammatory state that may have existed for years before the occurrence of type 2 diabetes.[15]

Atherosclerosis is a complex disease not solely dependent on the accumulation of lipids in vessel walls. Lipid deposition, along with macrophage infiltration and creation, promotes an inflammatory response marked by increased levels of C-reactive protein (CRP).[4] A nonrandomized cohort of patients with CHD showed that hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) decreased plasma levels of CRP.[5] This effect is primarily observed in patients with elevated CRP levels. Elevated levels of CRP have been shown to be a strong predictor of future cardiovascular events, perhaps even stronger than LDL cholesterol levels.[6]

Modest elevations of CRP can be found even in apparently healthy people.[7] A progressive rise in CRP can reflect augmented stages of vascular

inflammation, but the specific clinical conditions under which this occurs are incompletely understood.

Although LDL cholesterol remains a major risk component for cardiovascular disease, at least one-third of coronary events occur in individuals with LDL levels < 130 mg/dl,12 which is generally considered an average level in individuals without overt coronary artery disease. Evaluation of CRP levels under those clinical conditions may be very helpful in risk stratification. Reports that CRP levels are elevated during acute cardiovascular and cerebrovascular events suggest that CRP has value in predicting the subsequent occurrence of such events.[8,9]

Most of the benefit ascribed to statins derives from the reduction of cardiovascular mortality because of well-documented reductions in LDL cholesterol levels. Obtained data suggest that statins reduce inflammation and may affect CRP levels.[3,10] Considered a modifiable risk factor, CRP is an inflammatory marker that can indicate the presence of active vascular inflammation and atherosclerosis and may be decreased with statin therapy.[4] CRP levels have been shown to remain constant over long periods of time and exhibit no diurnal variation, suggesting that CRP may be a reliable predictor of cardiovascular risk.[6] This statin-mediated reduction of CRP levels is independent of the drug's lipid-lowering effects.[11] In addition, many clinical trials have explored the association of statin-induced reduction of CRP levels and whether this reduction decreases CHD endpoints, such as fatal and nonfatal MI.

The purpose of this review is to discuss clinical trials evaluating the effectiveness of statin therapy for reducing elevated CRP levels and associated cardiovascular events. A literature search was completed using MEDLINE (1999, 2007) and EMBASE using the following search terms: C-reactive protein, statin or HMG-CoA reductase inhibitors, diabetes type 2, cardiovascular events. References used in the primary literature were reviewed to identify additional articles.

Role of statins

Because of the high numbers of mortalities due to cardiovascular diseases, primary prevention is of the utmost importance.

The major aim of statin therapy has been to decrease lipid deposition in the arterial walls. Statins prevent the intracellular production of cholesterol in hepatocytes by blocking the rate-limiting step in cholesterol synthesis.[16,17] HMG-CoA reductase inhibitors upregulate receptors in the liver, which enhances the removal of LDL cholesterol from the plasma. It has been demonstrated that statins have an effect on markers of inflammation, including CRP, independent of their lipid-lowering effect.[17]

Atherosclerotic plaque growth may be attenuated with therapy aimed at minimizing inflammation.[11] Because increased levels of CRP have been associated with arterial-wall inflammation, the reduction in CRP levels may reduce the extent of endothelial-cell opsonization, macrophage recruitment, and blunting of nitric oxide release. Prevention of vasoconstriction by attenuating the proinflammatory process and preserving vasodilation may allow sufficient perfusion to prevent myocardial ischemia. Further research is needed to determine the extent to which CRP contributes to the inflammatory process. The use of statins may prevent ischemia by both inhibiting deposition of lipids and decreasing inflammation.[11] Several trials have been aimed at developing a correlation between statin-induced reductions in CRP and a subsequent decline in coronary events.[3,10]

CRP and diabetes type 2

It has been suggested that low grade inflammation may play a role in the development of type 2 diabetes.[12] Patients with type 2 diabetes had increased levels of hsCRP.[18,19] High hsCRP levels were found to be a independent predictor of risk for the development of type 2 diabetes.[20,22] In the Women's Health Study[14] and the West of Scotland Coronary Prevention Study (WOSCOPS),[23] patients with the highest levels of hsCRP were at a much higher risk of developing diabetes. Interleukin-6 was also found to be a predictor of who would develop type 2 diabetes and increasing levels of hsCRP and IL-6 were associated with insulin resistance.[14] Elevated levels of hsCRP and plasminogen-activator inhibitor (PAI) have been demonstrated to predict the incidence of type 2 diabetes in the IRAS.[12] Abdominal obesity and the subsequent secretion of pro-inflammatory cytokines and acute phase reactants may contribute to the relationship between chronic inflammation and type 2 diabetes. Adipocytes are 1 of many cells that secrete IL-6 and the amount of IL-6 produced by adipocytes is proportional to the amount of fat cell mass. Interleukin-6 is the main stimulus for hepatic CRP production, and adipocytes supply approximately 33% of systemic IL-6.[14] Therefore, increased cytokine production by adipocytes in obese people may be the stimulus for increased CRP production. In support of a connection between obesity and chronic

inflammation, IL-6 and hsCRP levels decreased in obese, post-menopausal women after 6 months of weight loss.[24] Increased glucose utilization and insulin sensitivity were also apparent in these women after the 6 months.

Much evidence exists that inflammatory mechanisms play a major role in the cascade of events that results in rupture of atherosclerotic plaque. Upregulation of receptors for advanced glycation end products has been associated with enhanced inflammatory reactions. Increased expression of these receptors has been found to be associated with impaired glycemic control and may be a contributory factor in the complex array of mechanisms that leads to accelerated atherosclerosis in patients with diabetes.[25]

In a national survey study, respondents with hemoglobin A1c (A1C) levels ≥ 9% had a significantly higher rate of elevated CRP than those with A1C levels < 7%. This suggests an association between diminished glycemic control and systemic inflammation in people with established diabetes.[26]

In a nested case-control study carried out as part of the Women's Health Study among initially nondiabetic participants who developed diabetes over the course of the study, median baseline levels of IL-6 and CRP were significantly higher among case than among control subjects (P<0.001), and increasing levels of both markers were associated with a higher risk of developing diabetes.[14] In this study, increased CRP levels predicted the new onset of diabetes even after adjustment for obesity, coronary risk factors, and fasting insulin levels.

Clinical Trials

Evaluation of recent clinical trials, including WOSCOPS, PRINCE, AFCAPS/ TexCAPS, MIRACL, CURVES, REVERSAL, and JUPITER, demonstrated the correlation of statin therapy with decreased levels of CRP. WOSCOPS found that patients with CRP values of >4.59 mg/L at baseline were at the highest risk of acute cardiovascular events.

The PRINCE trial evaluated the antiinflammatory effects of pravastatin and found a mean 16.9% reduction in CRP levels after 24 weeks of therapy.[27]

AFCAPS/TexCAPS researchers found that lovastatin provided a 14.8% reduction in the median levels of CRP ($p < 0.001$).[28]

The MIRACL study showed that atorvastatin reduced CRP levels by 83% ($p < 0.001$). Researchers in the CURVES study found a significant reduction in CRP levels with pravastatin, simvastatin, and atorvastatin compared with baseline ($p < 0.025$).[29]

Results of the REVERSAL study linked atorvastatin with a 36.4% decrease in CRP levels, while pravastatin was associated with a 5.2% decrease ($p < 0.0001$).[31]

JUPITER is ongoing and will determine whether long-term use of rosuvastatin can reduce the rate of coronary events. In addition, JUPITER investigators will evaluate the safety of long-term rosuvastatin use in terms of total mortality, mortality unrelated to cardiovascular events, and adverse events from therapy and to determine whether rosuvastatin reduces the frequency of type 2 diabetes mellitus.

At the end of the study, researchers hope to answer critical questions regarding treatment for patients without overt hyperlipidemia but with elevated risk for cardiovascular events, indicated by increased CRP levels. A strong positive finding from JUPITER would advocate the broader use of statins for cardiovascular and antiinflammatory benefits independent of lipid-lowering effects, risk reduction, even in patients who do not require the lipid-lowering effects of statins.[10]

Discussion

Strategies that target obesity and insulin resistance, when found to be effective, may ameliorate both endothelial dysfunction and low-grade inflammation and have the theoretical potential to decelerate or prevent the occurrence of type 2 diabetes and cardiovascular disease.[30] Pharmacological and lifestyle interventions may reduce both the risk for CHD and levels of CRP, if elevated. Results of recent studies also suggest a potential association between lower CRP levels and improved clinical outcomes with statin therapy.[31,32]

Approximately half of all coronary events occur in patients without overt hyperlipidemia.[3] Large proportions of first cardiovascular events have occurred in patients whose LDL cholesterol levels were below the current NCEP guidelines for intervention and treatment.[1,6] According to NCEP guidelines, patients without multiple risk factors should be treated if their LDL cholesterol concentration is over 160 mg/dL, while patients with multiple risk factors should receive treatment if their LDL cholesterol concentration is more than 130 mg/dL.[1] In patients who do not qualify for statin therapy based on these guidelines, other methods should be used to assess their cardiovascular risk. It is clear that the interactions of novel biological markers, such as CRP, and other known risk factors may contribute to the

occurrence of cardiovascular events. Screening for CRP levels in patients without traditional risk factors may identify a cohort of patients who would benefit from the antiinflammatory effects of statins.[6] Due to the high rate of cardiovascular disorders, many patients are prescribed statins to manage their lipid abnormalities. In addition to their lipid-lowering effects, statins reduce plasma levels of CRP, a soluble marker of inflammation.

The screening of patients with elevated CRP levels may identify patients who have an increased risk for cardiovascular events but would not ordinarily qualify for treatment with a statin under current guidelines. Statin treatment in patients with elevated CRP levels but normal to mildly elevated LDL cholesterol values is currently under investigation. The study population in JUPITER is unique because these patients are not otherwise indicated for lipid-lowering therapy because their LDL cholesterol levels are within normal limits.[1] In addition, the use of CRP levels as a predictor of cardiovascular events is not well defined for patients who already qualify for statin treatment because of elevated cholesterol levels. Further investigation is warranted to clarify the utility of routine CRP measurements and statin therapy in these patient populations.

Conclusions

Inflammation underlies diabetes and may predict it. The role of lowering CRP in reducing the risk for and improving the prognosis of diabetes is undergoing assessment.

The lowering of elevated CRP levels by statins may reduce the risk of cardiovascular events independently of the effect of statins on lipid levels.

The results of ongoing clinical trials will continue to provide data on the additive value of testing levels of CRP and other inflammatory markers for cardiovascular risk assessment and should delineate the clinical utility of such testing in various disease states.

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