**Statins, Inflammation, and Sepsis**

**Hypothesis**

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Sepsis and septic shock are complex inflammatory syndromes. Multiple cellular activation processes are involved, and many humoral cascades are triggered. Statins have anti-inflammatory properties. Our preliminary observations indicate that patients receiving therapy with statins may have a lower incidence of severe sepsis. We hypothesize that statins have a strong protective effect against sepsis by virtue of diverse anti-inflammatory effects that are independent of their lipid-lowering ability.

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**Key words:** anti-inflammatory; apoptosis; nitric oxide; sepsis; statins

**Abbreviations:**

- CD = cluster of differentiation
- cNOS = constitutive nitric oxide synthase
- CRP = C-reactive protein
- ecNOS = endothelial constitutive nitric oxide synthase
- IL = interleukin
- iNOS = inducible nitric oxide synthase
- LDL = low-density lipoprotein
- LFA = leukocyte function antigen
- LPS = lipopolysaccharide
- TNF = tumor necrosis factor

Sepsis and septic shock are now the 13th most common causes of death in the United States. It is estimated that there are approximately 400,000 to 500,000 sepsis episodes each year in the United States alone and that only 55 to 65% of these patients will survive. Even though there are many confounding variables related to definitions and methodology, it seems that these numbers continue to rise.

It is now generally accepted that sepsis syndrome reflects the delicate balance between the extensive triggering of defense mechanisms (by invading microorganisms) and both the direct and indirect effects of these microorganisms and their products. In fact, the apparent outcome of this extremely complex proinflammatory and anti-inflammatory sequence of events is often referred to as *systemic inflammatory response syndrome.*

Our preliminary observations indicate that patients receiving therapy with statins may have a lower incidence of severe sepsis. For example, approximately 18% of patients who are admitted to the Department of Medicine in our institution are treated with statins. In contrast, only 3% of those admitted to the medical ICU with severe sepsis were treated with statins. Moreover, a recent retrospective study suggested an association between statin therapy and a reduction in mortality in patients with bacteremia. In this retrospective review of 388 bacteremic infections due to aerobic Gram-negative bacilli and *Staphylococcus aureus,* significant reductions in both the overall mortality rate (6% vs 28%, respectively; p = 0.002) and the attributable mortality rate (3% vs 20%, respectively; p = 0.01) were found. This reduction in mortality persisted in a multivariate analysis (odds ratio, 7.6; 95% confidence interval, 1.01 to 57.5).

In complex situations such as sepsis or septic shock, multiple cellular activation processes are involved and many humoral cascades are triggered, so that merely blocking a single component may be insufficient to arrest the inflammatory process. Therefore, any intervention affecting this complex syndrome should be able to do so by modifying several arms of the inflammatory cascade. We propose that statins have a strong protective effect.
against sepsis by virtue of diverse anti-inflammatory properties that are independent of their lipid-lowering ability.

**Endothelial Dysfunction and Apoptosis**

Sepsis affects virtually all body organs and cells. Endothelial cells create a lining layer that is in close and intimate contact with blood. In their intact form, they play an important role in the control of vascular tone, permeability, blood flow, coagulation, thrombolysis, inflammation, tissue repair, and growth (i.e., in maintaining homeostasis). However, once triggered they become activated, participating in the inflammatory process by generating a wide variety of mediators. If the inflammatory stimulus persists, they may become dysfunctional, eventually leading to apoptosis (i.e., programmed cell death).

The exact mechanisms that are responsible for signal transduction of endothelial proapoptotic and antiapoptotic stimuli are poorly understood. The available data seem to support the notion that the local balance between proapoptotic and antiapoptotic stimuli decides the survival of each cell. A wide variety of mediators may participate in endothelial activation or may contribute to their dysfunction and death. A study in children with meningococcal sepsis found a marked reduction in the expression of thrombomodulin and endothelial protein C receptor on the endothelium dermal vessels, reflecting the presence of sepsis-induced endothelial dysfunction. Lipopolysaccharide (LPS), tumor necrosis factor (TNF), and cecal ligation all have been shown to cause endothelial apoptosis in vivo. Extracellular adenosine triphosphate, angiotensin II, interleukin (IL)-1, ischemia/reperfusion, and transforming growth factor-β all have been implicated in sepsis-induced endothelial apoptosis. Statins also increase constitutive nitric oxide synthase (cNOS) activity, which has an antiapoptotic effect. It is generally held today that endothelial activation, dysfunction, and apoptosis play a crucial role in the pathogenesis of sepsis and its most dreaded sequela, multiorgan dysfunction syndrome.

**Pathogen-Associated Molecular Pattern Recognition**

The recognition of the microbial products of phagocytic leukocytes and other immune cells is the molecular basis of the beginning of the sepsis syndrome. This recognition process is accomplished by a variety of receptors that recognize conserved motifs on pathogens. These motifs are called **pathogen-associated molecular patterns**. Toll-like receptors, which are a transmembranal group of receptors that are found on a variety of immune cells, are important in such pattern recognition and in the initial mediation of the inflammatory response. Their extracellular domain may directly bind certain ligands such as LPS. Lovastatin reduces the surface expression of the cluster of differentiation (CD) 11b on monocytes and thus reduces their adhesiveness to the vascular endothelium. It was found that statins also influence the inflammatory response by directly inhibiting the main β2-integrin leukocyte function antigen (LFA)-1 (also known as αLβ2 or CD11a/CD18). LFA-1 is a heterodimeric glycoprotein that is constitutively expressed on the surface of leukocytes in an inactive state. It is involved in lymphocyte recirculation and leukocyte extravasations to sites of inflammation. The integrin is also important for effective T-cell activation by antigen-presenting cells. This study showed that several statins block the LFA-1-intercellular adhesion molecule-1 interaction. In addition, the inhibition of LFA-1 resulted in decreased lymphocyte adhesion to intercellular adhesion molecule-1 and impaired T-cell costimulation. It appears that statins are able to enhance anti-inflammatory processes. Furthermore, statins that do not block the function of the αLβ2 integrin can have clinically significant anti-inflammatory effects. In addition, statins deplete isoprenoids, which are important nonsterol cholesterol precursors. These precursors are essential for the farnesylation and geranaylation (a prenylation reaction yielding a covalent bond) of membranal G proteins. G proteins, in turn, play a pivotal role in signal transduction pathways that regulate cellular signaling, migration, and proliferation. Thus, statins may interfere with this receptor ligand interaction, blunting the first step in the activation of the cellular cascade.

**Acute-Phase Response**

The acute-phase response includes a wide variety of mediators, such as C-reactive protein (CRP), IL-6, and many others, and is known to have diverse effects. Metabolic pathways and coagulation are also affected by the acute-phase response. These acute-phase proteins have an important role, which has not yet been elucidated completely, in the body’s response to infection and injury. On the other hand, statins significantly decrease CRP production. The implications of such a reduction are not completely clear. Septic shock is a consequence of a maladaptive deregulated immune response. It follows that the attenuation of this exaggerated response, as reflected by the acute-phase reactants, could contribute to the restoration of homeostasis. By analogy, in a case-
control analysis from the Physicians’ Health Study, higher CRP levels predicted future cardiovascular events in healthy middle-aged men, and aspirin reduced events more in those persons with higher, rather than lower, levels of this inflammatory marker. In a more recent retrospective analysis of data from the Air Force/Texas Coronary Atherosclerosis Prevention Study, lovastatin therapy prevented the occurrence of coronary events in participants with high-normal CRP values whose baseline levels of low-density lipoprotein (LDL) cholesterol were <149.1 mg/dL. However, in participants whose levels of both CRP and LDL were below the median levels of the population, statin therapy did not significantly reduce the risk of coronary events. These findings implicate inflammation, reflected by elevated CRP levels, as an important contributor to atherosclerosis. We suggest a similar mechanism whereby statin therapy may create a nonfavorable milieu for the development of systemic inflammatory response by virtue of its ability to blunt the acute-phase response.

Nitric Oxide

Nitric oxide is physiologically produced by endothelial eNOS (ecNOS). It is not only an important regulator of vasomotor tone and blood flow, but is also an inhibitor of leukocyte and platelet adhesion as well as a modulator of coagulation activation. Sepsis is associated with a rapid decrease in ecNOS function and a delayed increase in inducible NOS (iNOS) expression. Nitric oxide production is increased as a result of the increased expression of iNOS, contributing to the hypotension and resistance to vasopressor drugs that occur in patients with vasodilatory shock. The mechanisms that are responsible for this overexpression are still under investigation, but several cytokines, such as IL-6, TNF, and others, are known to induce this increased synthesis. The use of nitric oxide synthase inhibitors restores the response to vasoconstrictors and improves BP in septic patients, but it has several harmful effects, such as increased organ injury. In fact, a phase 3 trial was prematurely terminated because of increased mortality. Moreover, chronic ecNOS overexpression in the endothelium of mice resulted in resistance to LPS-induced hypotension, lung injury, and death. Statins increase ecNOS activity. Using a model of human saphenous endothelial cells that were treated with oxidized LDL in the presence of simvastatin and lovastatin, it was shown that both up-regulated ecNOS expression by 3.8-fold. These effects on ecNOS expression correlated with changes in ecNOS activity. In a different study, 19 hyperlipidemic subjects were treated for 1 month with atorvastatin or placebo. These investigators demonstrated that intraplatelet ecNOS increased on average by approximately 1.7-fold without affecting iNOS expression. A more recent investigation demonstrated that pretreatment with statins in native endothelial cells in situ decreased TNF-α plus interferon-γ-stimulated iNOS expression. Indeed, it has been shown by several investigators that statins up-regulate the expression and function of ecNOS, independently of cholesterol levels. We suggest a theoretical role for statins in the balance between ecNOS underexpression and iNOS overexpression that favors hemodynamic stability and attenuates the vasoplegia that is so characteristic of sepsis-induced vasodilatation.

Summary

The exact mechanism of the anti-inflammatory effect exhibited by statins is unclear. As stated...
earlier, the depletion of cholesterol in the membranes of inflammatory cells or the reduced isoprenylation of signaling proteins in those membranes are primary possibilities.7,29 We propose several sites where statins could exert their anti-inflammatory, immune-modulating, and endothelium-protecting effects (Fig 1).

1. Ligand receptor interaction is a crucial first step in the sepsis cascade. Statins could interfere with this presentation process and its downstream consequences.

2. Infection elicits the acute-phase response, which, in turn, triggers inflammation and the perturbation of the coagulation system. Statins could attenuate the acute-phase response and its immediate consequences.

3. Statins could have an important protective effect on the delicate sequence of endothelial activation, dysfunction, and apoptosis. This sequence correlates with worsening severity of illness and organ dysfunction.

4. Statins could contribute to a favorable balance between cNOS and iNOS such that vasodilatation is diminished and hemodynamic stability and vasopressor response are restored.

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