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Extended Abstract
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Heart Congress 2019: It?s time to focus on decreasing cardiovascular mortality in NAFLD population: potential use of statins and PCSK9 inhibitors - Issues with Management - Tarek Ajam - Saint Louis University Saint Louis, MO, USA

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Introduction

Nonalcoholic fatty liver disease (NAFLD), considered the most common liver disorder in Western countries, is estimated to affect approximately one-quarter of the general population. The prevalence of NAFLD matches the increasing rates of type 2 diabetes mellitus and obesity worldwide. In addition, there are up to 95% of obese persons and 75% of diabetics likely to have NAFLD. NAFLD is a slowly progressive disease which covers a spectrum of hepatic pathologies, ranging from simple steatosis, variable grades of fibrosis, and nonalcoholic steatohepatitis (NASH). Lipid accumulation is the major hallmark with fatty infiltrates affecting more than 5% of hepatocytes.

Pathogenesis

There is some significant association between NAFLD and cardiovascular disease (CVD) as multiple studies have reported increased adverse cardiovascular events at NAFLD patients compared with the general population. A recent metaanalysis with 27 cross-sectional studies demonstrated that NAFLD was associated with markers of subclinical atherosclerosis, such as increased carotid artery intimal-medial thickness, impaired flow-mediated vasodilation, or increased coronary artery calcification. In a prospective study, the 14-year risk of mortality from cardiovascular causes was twofold in patients with biopsy-proven NAFLD where the primary cause of death was CVD rather than liver disease.

Currently, the understanding of the pathophysiological pathways linking NAFLD to CVD remains elusive. Although mechanisms such as oxidative stress, abdominal obesity and insulin resistance have been considered. The liver is central to regulation of systemic inflammation and is acted upon numerous inflammatory factors. There is an evidence that suggests in NAFLD exacerbates hepatic and peripheral insulin resistance predisposing subjects to atherogenic dyslipidemia while releasing pro-inflammatory, vasoactive, and thrombogenic factors that instigate the development of CVD. NAFLD patients have more systemic inflammation and have higher risk of thrombosis than that of the general population as evidenced by higher levels of oxidative stress and inflammation. Several studies have demonstrated increased coronary atherosclerotic plaque burden in the presence of NAFLD.

A known marker of adverse cardiovascular outcomes, Creactive protein, is significantly elevated in NAFLD patients compared to non-NAFLD group. C-reactive protein is a predictor of cardiovascular events in several studies. The severity of NAFLD is a direct predictor of worsening inflammatory and insulin resistance. A second known marker of adverse cardiovascular outcomes is gammaglutamyltransferase (GGT) level. GGT has a role in oxidative stress and is expressed in atherosclerotic plaques. Several studies have shown an association between GGT levels and cardiovascular mortality including a meta-analysis of relationship of GGT and adverse cardiovascular events such as myocardial infarction.

Excessive free fatty acid supply leads to cardiac lipotoxicity by triggering intracellular lipid accumulation and consuming cardiomyocyte oxidative capacity. This results in increased oxidative stress and subsequent cardiomyocyte dysfunction and apoptosis. Adverse alterations in fatty acid, glucose, and lipoprotein metabolism seen in NAFLD leads to the progression of insulin resistance and overall dysfunctional metabolic state.

NAFLD has been found to affect carotid artery disease and incidence at cerebrovascular accidents via direct effects of plainsmen activator inhibitor-1 (PAI-1). PAI-1 is produced by hepatic tissue and when fatty infiltration is present, less PAI-1 is produced creating a pro-thrombotic state and higher prevalence of cerebral vascular accidents secondary to carotid atherosclerotic

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plaques and luminal narrowing. One study showed significant association between NAFLD and carotid intima-media thickness with an estimated 13% increase in carotid intima-media thickness for NAFLD cases compared with controls.

Statins

Due to the association between NAFLD and CVD, lipidlowering agents, such as statins, may be beneficial because of their ability to significantly reduce atherogenesis and inflammation. The benefit of statins in primary and secondary prevention of cardiovascular disease is well described. However, adverse effects of statin therapy, such as myalgias and transaminitis, create an obstacle for health care providers when attempting adequate cholesterol control.

The current guidelines for cholesterol management in patients with an ASCVD risk score of less than 7.5% would recommend against initiating statin therapy. However, because of the known risk with NAFLD, not previously considered in current guidelines, statin therapy would likely prove beneficial.

The use of statin medications has been accompanied by concern for hepatotoxicity. The primary mechanism of action for statin therapy is to inhibit the central pathway of 3- hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They also initiate activation of Sterol Regulatory Element Binding Proteins (SREBPs) which subsequently increase the number of hepatic LDL receptors and serum lipid degradation. In addition, peroxisome proliferator-activated receptor gamma (PPARγ) within macrophages are activated via cycloxygenase 2-mediated reaction which promote fatty acid oxidation reducing the triglyceride supply for VLDL synthesis.

Recent studies have not demonstrated an increase in serum aminotransferase level with use of statins. A meta-analysis of 49,275 patients with hyperlipidemia and NAFLD treated with statins with baseline elevated liver enzymes demonstrated no significant changes in liver biochemistry on statins.

Patients with NAFLD have approximately a two-fold increased risk of cardiovascular mortality compared with age-matched general population. With increased cardiovascular risk associated with NAFLD as a result of pro-atherogenic and proinflammatory states, it should be clear that an antiatherosclerotic and pleiotropic agent would be of great benefit in reducing cardiovascular risk.

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as a novel class of medications for dramatic lowering of cholesterol levels. LDL receptors (LDLR) which are present on the liver and other cell membranes bind to and reduce serum LDL particles. PCSK9 enhances the degradation of liver LDLRs resulting in LDL accumulation. With PCSK9 blockade, more LDLRs on the surface of the cells become available which results in significant lowering of serum LDL levels. Individuals with loss-of-function mutations in PCSK9 have reduced levels of LDL cholesterol and therefore have been found to be protected from coronary heart disease. PCSK9 deficiency confers resistance to liver steatosis, but its effect on LDLR is independent of this function.

At this time, the estimated cost-effectiveness of PCSK9 inhibitors outweigh the benefits and reducing the price remains the primary goal to improving the value of this therapy. However, a recent randomized, double-blinded, placebocontrolled trial demonstrated when Evolocumab, a monoclonal antibody that inhibits PCSK9, was added to statin therapy, it lowered LDL cholesterol levels by 59%, and it significantly reduced the risk of cardiovascular events with a 15% reduction in the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke. Current guidelines recommend PCSK9 inhibitors for patients who may not tolerate statins and for familial hypercholesterolemia. The outcome of ongoing large scale cardiovascular endpoint trials testing PCSK9 inhibitors over next several years will be pivotal.

Circulating PCSK9 levels correlate with the severity of steatosis and increase with hepatic fat accumulation. Theoretically, being a potent lipid lowering agent, PCSK9 inhibitors may decrease both the progression of NAFLD and decrease the associated cardiovascular risk. However, PCSK9 inhibitors are still novel, and we remain to have limited information about patient compliance and long term outcomes.

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Conclusion

Health care providers should recognize the high prevalence of CVD in patients with NAFLD. The evidence demonstrated that statins were safe, lead to cardiovascular risk reduction and may potentially prevent the deterioration of NAFLD. In addition, with the great reduction in LDL cholesterol, PCSK9 inhibitors may prove to be an effective treatment for NAFLD patients. Further large scale prospective trials that show the long-term effects of statins or PCSK9 inhibitors are needed to change how health care providers manage and treat patients with NAFLD. Given the high prevalence of NAFLD in the general population, we suggest that the current guidelines add lipid lowering therapies to prevent CVD.

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