ELSEVIER

International Journal of Cardiology 124 (2008) 149–159

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Review

Vascular and metabolic effects of treatment of combined hyperlipidemia: Focus on statins and fibrates

Kwang Kon Koh [a,*], Michael J. Quon [b], Robert S. Rosenson [c], Wook-Jin Chung [a], Seung Hwan Han [a]

[a] *Division of Cardiology, Gil Heart Center, Gachon Medical School, Incheon, Republic of Korea*
[b] *Diabetes Unit, Laboratory of Clinical Investigation, NCCAM, NIH, Bethesda, MD, USA*
[c] *Departments of Medicine and Preventive Medicine Northwestern University, Feinberg School of Medicine Chicago, IL, USA*

Received 12 December 2006; received in revised form 11 April 2007; accepted 12 April 2007
Available online 20 July 2007

Abstract

Combined hyperlipidemia results from overproduction of hepatically synthesized apolipoprotein B in very low-density lipoproteins in association with reduced lipoprotein lipase activity. Thus, this condition is typically characterized by concurrent elevations in total cholesterol and triglycerides with decreased high-density lipoprotein cholesterol. High levels of apolipoprotein B-containing lipoproteins, most prominently carried by low-density lipoprotein (LDL) particles, are an important risk factor for coronary heart disease. Statin therapy is highly effective at lowering LDL cholesterol. Despite the benefits of statin treatment for lowering total and LDL cholesterol, many statin-treated patients still have initial or recurrent coronary heart disease events. In this regard, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone. Furthermore, statins and fibrates activate PPARα in a synergistic manner providing a molecular rationale for combination treatment in coronary heart disease. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance so that there may also be additional beneficial metabolic effects of combined statin/fibrates therapy. However, there has been little published evidence that combined therapy is synergistic or even better than monotherapy alone in clinical studies. Therefore, there is a great need to study the effects of combination therapy in patients. When statins are combined with gemfibrozil therapy, this is more likely to be accompanied by myopathy. However, this limitation is not observed when fenofibrate, bezafibrate, or ciprofibrate are used in combination therapy.

Keywords: Statins; Fibrates; Endothelial function; Insulin resistance; Combined hyperlipidemia; Safety

1. Introduction

Combined hyperlipidemia is typically characterized by elevations in total cholesterol and triglycerides with decreased high-density lipoprotein (HDL) cholesterol. This common disorder results from overproduction of hepatically synthesized apolipoprotein B in very low-density lipoproteins. High levels of apolipoprotein B-containing lipoproteins, most prominently

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHD, coronary heart disease; PPAR, peroxisome proliferator-activated receptor; NF-κB, nuclear transcription factor; NO, nitric oxide; eNOS, endothelial NO synthase; VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; CRP, C-reactive protein; MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor; CD40L, CD40 ligand; PAI-1, plasminogen activator inhibitor type 1; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase; QUICKI, Quantitative Insulin-Sensitivity Check Index.

* Corresponding author. Vascular Medicine and Atherosclerosis Unit, Division of Cardiology, Gil Heart Center, Gachon Medical School, 1198 Kuwol-dong, Namdong-gu, Incheon, 405-760, Republic of Korea. Tel.: +82 32 460 3683; fax: +82 32 460 3117.
E-mail address: kwangk@gilhospital.com (K.K. Koh).

0167-5273/$ - see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2007.04.080

carried by low-density lipoprotein (LDL) particles, are an important risk factor for coronary heart disease (CHD). Statin therapy is highly effective at lowering total and LDL cholesterol. Nevertheless, many statin-treated patients still have initial or recurrent CHD events even with reduction in their LDL cholesterol levels. Indeed, in intervention studies with statins, subgroup analysis of patients with varying baseline lipid levels shows that interactions between relative risk reduction and baseline triglycerides and HDL cholesterol levels are not significant when analyzed as continuous variables (by contrast with LDL cholesterol levels) [1–3].

Many studies show positive associations between serum triglycerides and CHD risk [4,5]. Importantly, low HDL cholesterol levels predict risk for CHD independent of other prognostic factors [6,7]. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) Study shows that compared with placebo, gemfibrozil therapy increases mean HDL cholesterol level by 6% and reduces the mean triglyceride level by 31% and the mean total cholesterol level by 4% in patients with CHD whose primary lipid abnormality is low HDL cholesterol level. LDL cholesterol levels do not differ significantly between the groups. Gemfibrozil therapy reduces relative risk of nonfatal myocardial infarction or death from coronary causes by 22% and the combined outcome of death from CHD, nonfatal myocardial infarction, and stroke by 24% [8].

Several studies report that combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidemia in patients with combined hyperlipidemia than either drug alone [9–12]. Unfortunately, the combination of statins and the most extensively studied fibrate, gemfibrozil, is more likely to be accompanied by severe myopathy [13,14]. This may be because gemfibrozil significantly affects the pharmacokinetic of statins resulting in increased plasma levels of statins [7,15,16]. Interestingly, other recent studies demonstrate that this limitation is not observed with statin and other fibrates in combination therapy [10,11,14,17–19].

CHD is frequently associated with insulin resistance and disorders of metabolic homeostasis including obesity and combined hyperlipidemia. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance [20,21]. Endothelial dysfunction associated with metabolic syndrome and other insulin resistant states is characterized by impaired nitric oxide (NO) release from endothelium with decreased blood flow to insulin target tissues [22]. Insulin signaling pathways regulating glucose transport in skeletal muscle also regulate production of NO in endothelium. Pro-inflammatory signaling stimulated by glucotoxicity and lipotoxicity in dysmetabolic states contributes to shared mechanisms of insulin resistance and endothelial dysfunction. The molecular and cellular mechanisms that mediate insulin resistance and endothelia dysfunction are multiple and reflect complex interactions between inflammatory and metabolic pathways [21,23]. Interestingly, insulin-stimulated increases in blood flow account for up to 40% of the increase in insulin-stimulated glucose disposal in skeletal muscle [22]. The central role of NO in regulating the metabolic actions of insulin is evident by the presence of insulin resistance and hypertension in eNOS knockout mice [24,25]. Thus, improvement in endothelial function is predicted to improve insulin sensitivity and this may be one mechanism by which statins and fibrates decrease the incidence of CHD.

Excess body fat is frequently associated with dyslipidemia, metabolic syndrome, and atherosclerotic vascular diseases. Adiponectin is one of a number of proteins secreted by adipose cells that may couple regulation of insulin sensitivity with energy metabolism and serve to link obesity with insulin resistance [26]. Decreased plasma adiponectin levels are observed in patients with type 2 diabetes and coronary artery disease [27,28]. Thus, decreased levels of adiponectin may play a key role in the development of insulin resistance. It is controversial whether statin therapy can improve or worsen insulin resistance in humans [29–31]. By contrast, fibrates improve insulin sensitivity in animal models through activation of peroxisome proliferator-activated receptor (PPAR)α [32,33]. Moreover, a recent clinical study reports that fenofibrate improves insulin sensitivity in patients with metabolic syndrome [34,35]. Therefore, effects of statins, fibrates, or combination therapy to raise adiponectin levels may be an important benefit resulting from the treatment of combined hyperlipidemia.

Laboratory studies also demonstrate synergistic effects of statins combined with fibrates. Statins inhibit the Rho-signaling pathway and activate PPARα [36] and acute anti-inflammatory properties of statins involve PPARα via inhibition of the protein kinase C signaling pathway [37]. Indeed, fibrate and statins synergistically increase the transcriptional activities of PPARα/retinoid X receptor (RXR) α and decrease the transactivation of nuclear transcription factor NF-κB [38]. Therefore, evidence that statins combined with fibrates activate PPARα in a synergistic manner provides a molecular rationale for combination treatment with statins and fibrates in CHD.

Because the mechanisms underlying the biological actions of statin and fibrate therapies are distinct, combined therapy with statins and fibrates therapies may be more effective in controlling atherogenic dyslipidemia and improving insulin sensitivity in patients with combined hyperlipidemia than either drug alone. Furthermore, there is evidence that statins combined with fibrates activate PPARα in a synergistic manner providing a better effect. In this review, we will discuss the safety and vascular and metabolic effects of statins combined with fibrates in patients with combined hyperlipidemia.

2. Vascular effects of combined therapy

2.1. Effects on lipoproteins and lipoprotein particles

Several studies report that combined therapy with statins and fibrates is more effective in controlling atherogenic