

CLINICAL INSIGHTS® IN

# LIPID Management

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#### Target Audience

This educational activity is designed for primary care physicians, endocrinologists, cardiologists, internists, and other healthcare professionals involved in the diagnosis and management of dyslipidemia and its comorbidities.

#### Learning Objectives

With information from the latest evidence-based studies, participants should be able to:

- Assess the link of Crohn's disease to atherogenesis and high-density lipoprotein (HDL).
- Outline the effects of fenofibrate and simvastatin on HDL-related biomarkers in patients with low HDL.
- Describe the suppressive effects of diacylglycerol oil on postprandial hyperlipidemia in patients with insulin resistance and glucose intolerance.

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## Crohn's Disease Associated With Enhanced Atherogenesis and Altered High-Density Lipoprotein

In several chronic inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis, systemic inflammation has been associated with promotion of the atherosclerotic process, as demonstrated by an increased incidence of cardiovascular disease (CVD). Moreover, inflammation induces changes in high-density lipoprotein (HDL) metabolism and reduces HDL concentrations. These dyslipidemic changes in chronic inflammatory disorders have also been linked to enhanced atherogenesis.

To gain more insights into the mechanisms by which a chronic inflammatory state can accelerate atherogenesis, van Leuven and colleagues explored whether Crohn's disease (CD), which is known for recurrent inflammatory episodes, is associated with an increased progression of atherogenesis and whether inflammatory exacerbation in patients with CD is linked to changes in HDL metabolism.

For this study, 60 patients with CD and 122 matched controls were recruited. Patients with a Harvey Bradshaw index (HBI) of  $\geq 4$  and C-reactive protein (CRP) of  $\geq 10$  mg/L were considered to have active CD. The HBI, which includes several clinical parameters, is used to quantify patients' symptoms. Patients with an HBI of  $< 4$  and a CRP level of  $< 10$  mg/L were considered to have CD in remission. Carotid intima media thickness (CIMT), a validated marker for the risk and the status of progression of atherosclerosis, was assessed by ultrasonography in all participants. Additional subgroup analyses were performed for lipid profiles, including plasma levels of acute phase reactants and HDL protein profiling, in the first 11 consecutive patients with CD in remission, 10 patients with active CD, and 15 healthy controls.

An increase in CIMT was found in all patients with CD ( $0.71 \pm 0.17$  mm) as compared with healthy volunteers ( $0.59 \pm 0.14$  mm) ( $P < 0.0001$ ). In the subgroup analysis, mean

HDL concentrations were generally higher in controls and in patients with CD in remission than in patients with active CD during inflammatory exacerbations ( $P = 0.022$  and  $P = 0.043$ , respectively). HDL levels in controls and in patients with CD in remission were identical ( $1.45 \pm 0.48$  and  $1.40 \pm 0.46$  mmol/L [or  $56.55 \pm 8.72$  and  $56.40 \pm 17.94$  mg/dL],  $P = 0.797$ ), whereas HDL concentrations in patients with active CD were significantly reduced ( $1.02 \pm 0.33$  mmol/L [or  $39.78 \pm 12.78$  mg/dL],  $P = 0.022$ ).

Additionally, patients with active CD had significantly elevated mean concentrations of acute-phase proteins, such as CRP and serum amyloid A (SAA), compared with controls and patients with CD in remission.

Further analysis indicated that alterations in HDL composition were found in patients during an inflammatory exacerbation of CD. Statistically significant differences in relative intensity of five markers were detected in patients with active CD, as compared with protein profiles obtained from controls and patients with CD in remission. Moreover, patients with CD, either active or in remission, demonstrated a reduced capacity to attenuate oxidation of HDL, a process that triggers vascular inflammation, as compared with controls ( $P = 0.008$  and  $P = 0.024$ , respectively).

The authors concluded that CD is associated with accelerated atherogenesis. Patients with CD have increased CIMT compared with matched controls. In addition, patients with active CD exhibited impaired HDL protection during an inflammatory exacerbation, with reduced HDL concentrations as well as altered HDL composition and functional characteristics. The authors recommended that patients with CD warrant early detection of atherosclerosis and subsequent cardiovascular prevention.

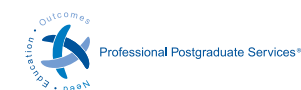
van Leuven SI, Hezemans R, Levels JH, et al. Enhanced atherogenesis and altered high density lipoprotein in patients with Crohn's disease. *J Lipid Res.* 2007;48(12):2640-2646.

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## Post-Test Question 1

Based on the findings of this study, which of the following statements regarding the association of Crohn's disease (CD) with atherogenesis is *false*, as compared with healthy controls?

- Carotid intima media thickness was increased in all patients with CD
- HDL protein profile was altered in patients with active CD during inflammatory exacerbations
- CD is associated with an acceleration of atherogenesis
- HDL levels were decreased in all patients with CD

## Commentary

Robert Chilton, DO, Associate Professor of Medicine, University of Texas Health Science Center, San Antonio. Faculty Member, Committee on Cardiovascular and Metabolic Diseases™ (CCMD™)

Over the last decade, inflammation has been linked to atherosclerosis. Vascular oxidative stress can lead to white blood cell adhesion to the endothelium and subsequent migration to the subendothelial space, initiating the development of atherosclerosis. Immune activation ensues, with the risk for plaque rupture and atherothrombosis.

In patients with Crohn's disease (CD), systemic inflammation can be chronic or acute, which may increase atherosclerotic risk. Van Leuven and colleagues found that patients with CD have increased carotid intima media thickness (CIMT), increasing the risk for cardiovascular (CV) disease. In the Cholesterol Lowering Atherosclerosis Study (CLAS), increased CIMT produced more ischemic CV events. In the setting of inflammation, the anti-atherogenic effects of high-density lipoprotein cholesterol (HDL-C) can become dysfunctional. In the current study, HDL-C was reduced in patients with active CD during the inflammatory exacerbations.

Guidelines can help to direct clinicians in selecting treatment options. Trials have focused on the inflammatory marker C-reactive protein (CRP) but it must be placed into context with other classic risk factors. Patients with CD should be considered at increased risk based on their Framingham Risk Score. If a patient has an intermediate 10-year risk of 10% to 15%, lifestyle modifications are first line to treat known risk factors, followed by therapeutic options.

Drug options to raise HDL-C and lower CRP are limited, especially considering the lack of large prospective trials with CV primary endpoints that address only increased HDL-C, without changing low-density lipoprotein cholesterol (LDL-C). Statins and possibly niacin are best suited to improve CV event rates. Statins improve HDL-C (10%–15%), powerfully reduce LDL-C, and significantly reduce CRP. Recently, niacin generated interest because of reduced CV endpoints and triglycerides (20%–30%), and increased HDL-C (10%–35%). Lipid profile changes with niacin are excellent, especially in patients with diabetes and mixed dyslipidemia. Fibrates can also increase HDL-C (10%–15%).

Patients with CD require early detection of atherosclerosis, followed by CV prevention. However, treating patients at increased risk is difficult at best. Thus, clinical evidence of reduced CV events in most cases is needed.

## Fenofibrate and Simvastatin on HDL-Related Biomarkers in Patients With Low HDL

Considerable attention has been focused on increasing high-density lipoprotein cholesterol (HDL-C) as a treatment for cardiovascular disease. In addition to fibrates and niacin, which exert significant activity in raising HDL-C levels, some—but not all—statins also have shown a modest favorable activity. The aim of the present study, conducted by Franceschini and colleagues, was to compare the effects of fenofibrate and simvastatin on various HDL-related biomarkers in dyslipidemic patients with low HDL-C, and to evaluate whether a fibrate, a statin, or both is the most appropriate treatment for these patients.

In a randomized, double-blind, parallel group trial, 52 nondiabetic patients with low HDL-C (<40 mg/dL) and moderate elevations of low-density lipoprotein cholesterol (LDL-C; <160 mg/dL) and triglycerides (TG; 150–500 mg/dL) were recruited. After a run-in period of 4 weeks, patients were randomized to receive fenofibrate (160 mg/day) or simvastatin (40 mg/day) for 8 weeks. A number of HDL-related biomarkers such as plasma concentrations of apolipoproteins, HDL particle subclass concentration/distribution, and HDL capacity to promote cell cholesterol efflux, were evaluated.

The investigators found that simvastatin significantly decreased total cholesterol (TC) and LDL-C, and apolipoprotein B (apoB) levels (-19%, -28%, and -24%, respectively); however, it had no effect on HDL-C. Fenofibrate, on the other hand, did not affect LDL-C levels, but caused a significant reduction of TG and apoB levels (-43% and -21%, respectively), as well as a significant increase of HDL-C levels (+22%).

Both fenofibrate and simvastatin significantly decreased the apoB/apoA-I ratio, a risk factor for coronary heart disease (CHD), and the concentration of apoC-III, although only fenofibrate increased HDL-C/apoA-I ratio (from  $0.34 \pm 0.06$  to  $0.43 \pm 0.06$ ). The levels of HDL particles containing only apoA-I decreased after fenofibrate treatment. In addition, fenofibrate treatment caused a shift of the HDL subclass distribution toward smaller particles, demonstrated by a significant increase in the proportion of small HDL particles with a concomitant decrease in large HDL particles. Simvastatin, however, did not have any effect on HDL particle subclass concentration or distribution.

It has been thought that a major function of HDL is to promote cell cholesterol efflux through

interaction with specific cell membrane proteins, such as the ATP-binding cassette transporter A1 (ABCA1) and the scavenger receptor B1 (SR-BI). Fenofibrate, but not simvastatin, significantly increased ABCA1-mediated cholesterol efflux to plasma. On the other hand, only simvastatin promoted SR-BI-mediated efflux.

The authors concluded that fenofibrate and simvastatin exert distinct and complementary effects on lipid parameters and HDL-related biomarkers. Patients receiving simvastatin had signifi-

cantly lower levels of TC and LDL-C, but higher TG levels than patients treated with fenofibrate. The HDL-C increase seen with fenofibrate was associated with a shift of HDL from large to small particles, and the increase in the plasma capacity to promote ABCA1-mediated cholesterol efflux. The authors thus recommended a combination therapy with fibrate and statin in treatment of dyslipidemic patients with low HDL-C.

Franceschini G, Calabresi L, Colombo C, et al. Effects of fenofibrate and simvastatin on HDL-related biomarkers in low-HDL patients. *Atherosclerosis*. 2007;195(2):385-391.

### Post-Test Question 2

Based on the results of this study, which of the following statements is *correct* in patients with low HDL-C?

- a. Fenofibrate decreased plasma LDL-C levels
- b. Simvastatin raised HDL-C levels
- c. Fenofibrate caused a shift of HDL from large to small particles
- d. Fenofibrate had no effect on plasma TG

## Diacylglycerol Oil Suppresses Postprandial Hyperlipidemia in Insulin Resistance and Glucose Intolerance

Postprandial hyperlipidemia and an increase in remnant lipoprotein (RLP) levels have been considered risk factors for coronary artery disease. In addition to accelerating arteriosclerosis, postprandial hyperlipidemia is also strongly associated with insulin resistance and glucose intolerance, and type 2 diabetes. Diacylglycerol (DAG), commonly used as cooking oil in Japan, has been shown to suppress postprandial hyperlipidemia by reducing increases in postprandial triglycerides (TG) and RLP concentrations, as compared with triacylglycerol (TAG) oil. The aim of the present study was to evaluate the effect of DAG on postprandial hyperlipidemia in patients associated with insulin resistance and glucose intolerance.

A total of 25 men, including 11 subjects with a normal glucose tolerance (NGT) and 14 subjects with an impaired glucose tolerance (IGT), were recruited for this double-blind study. All participants received the oral fat tolerance test twice with ingestion of emulsified test oils prepared with either DAG or TAG oil. Concentrations of TG, RLP-TG, and RLP-cholesterol (RLP-C) were measured before, as well as 2 hours and 4 hours after the oral fat loading.

Ai and colleagues showed that in patients with IGT, concentrations of TG, RLP-TG, and RLP-C increased continuously up to 4 hours after ingestion of DAG or TAG oil. The post-

prandial changes of these variables after the DAG load were significantly smaller than those after the TAG load ( $P < 0.05$ ). In contrast, no significant changes in any parameter were observed between DAG and TAG loading in patients with NGT.

A stepwise analysis for a multiple regression analysis was further performed to evaluate the possible variables that may account for the differences in TG, RLP-TG, and RLP-C observed between ingestion of TAG and DAG oil in patients with IGT.

The authors concluded that DAG oil suppresses postprandial hyperlipidemia in patients with IGT, but exerts no significant effect in NGT participants, as compared with TAG oil. The suppressive effect of DAG oil on postprandial hyperlipidemia was significantly and positively correlated with the sum of serum insulin concentrations during an oral glucose tolerance test. The authors suggested that DAG oil was more effective in insulin resistant and hyperinsulinemic participants regardless of glucose intolerance, and might be used as a cooking ingredient with the potential to prevent the progress of atherosclerosis.

Ai M, Tanaka A, Shoji K, et al. Suppressive effects of diacylglycerol oil on postprandial hyperlipidemia in insulin resistance and glucose intolerance. *Atherosclerosis*. 2007;195(2):398-403.

### Post-Test Question 3

Based on the data of this study, which of the following statements is *false*?

- a. Diacylglycerol (DAG) oil suppresses postprandial hyperlipidemia in patients with insulin resistance
- b. DAG was more effective in insulin resistant and hyperinsulinemic participants regardless of glucose intolerance
- c. Triacylglycerol (TAG) oil was more effective in suppressing postprandial hyperlipidemia than DAG oil
- d. The postprandial changes of serum concentrations of TG, RLP-TG, and RLP-C after ingestion of DAG oil were significantly smaller than those after TAG loading