Journal of Clinical Lipidology (2009) 3, 281–288

Journal of Clinical Lipidology

Regulation of human stearoyl-CoA desaturase by omega-3 and omega-6 fatty acids: Implications for the dietary management of elevated serum triglycerides

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KEYWORDS:
α-Linolenic acid (ALA);
Eicosapentaenoic acid (EPA);
Linoleic acid (LA);
Metabolic syndrome;
Peroxisome proliferation activator receptor-α (PPAR-α);
Stearoyl-CoA desaturase (SCD);
Sterol response element binding protein-1c (SREBP-1c);
Triglyceride (TG)

BACKGROUND: Polyunsaturated fatty acids lower serum triglycerides by a mechanism that may involve the inhibition of stearoyl-CoA desaturase (SCD).

OBJECTIVE: We sought to evaluate the effects of serum fatty acids on 1) the SCD index in a controlled clinical setting, and 2) SCD regulation in Hep G2 cells.

METHODS: The SCD index was determined in 23 subjects randomly sequenced through 3 diets for 6 weeks in a crossover study. Diets were variably enriched with n-3 and n-6 polyunsaturated fatty acids; notably, monounsaturated fatty acids were held constant. Effects of linoleic acid (LA), α-linolenic acid (ALA), and eicosapentaenoic acid (EPA) on mRNA levels of SCD, fatty acid elongases 5 and 6 (Elovl5 and Elovl6), fatty acid synthase, carnitine palmitoyltransferase-1, and sterol response element binding protein-1c were investigated in Hep G2 cells after 24-hour incubations.

RESULTS: The SCD indexes C18:1/18:0 and C16:1/C16:0 were significantly ($P < .0001$) correlated with serum TG with R^2 values of 0.71 and 0.58. The correlation was negatively associated with LA and positively associated with ALA. LA and EPA decreased SCD mRNA (EC_{50} of 0.50 and 1.67 μM), whereas ALA did not. Likewise, LA and EPA decreased sterol response element binding protein-1c mRNA (EC_{50} of 0.78 and 1.78 μM), but ALA did not. Similar results were observed for Elovl6. GW9662, a peroxisome proliferation activator receptor antagonist, did not obviate the effects of LA and EPA on SCD mRNA.

CONCLUSIONS: Diets enriched in LA, ALA, and by metabolic inference EPA, can regulate SCD activity at the level of transcription, a nutritional intervention that may be useful in the management of increased levels of serum triglycerides in cardiometabolic disorders.

Introduction

Serum triglycerides (TGs) are becoming recognized as an independent risk factor for cardiovascular disease.[1] In contrast to low-density lipoprotein cholesterol, which is directly atherogenic, elevated TG may be a marker for

This work has been published in abstract form as part of the 7th International Symposium on Multiple Risk Factors in Cardiovascular Diseases held in Venice, Italy on October 22-25, 2008.

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Submitted February 11, 2009. Accepted for publication June 12, 2009.

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doi:10.1016/j.jacl.2009.06.002

the presence of atherogenic remnant lipoproteins or associated with other cardiometabolic risk factors.[2] Regardless of the proximate biological mechanism, the management of elevated TG through lifestyle and drugs is now recommended.[3] To this end, understanding the hepatic regulation of very low-density lipoprotein (VLDL) metabolism is important to optimize the treatment of hypertriglyceridemia and its related metabolic disorders such as insulin resistance, metabolic syndrome, and type 2 diabetes.[4]

Hepatic stearoyl-CoA desaturase (SCD or Δ9 desaturase) is the rate-limiting enzyme in the endogenous biosynthesis of monounsaturated fatty acids, the most notable being oleate.[5,6] Although oleate is found ubiquitously throughout the body, endogenously derived oleate from SCD is special in terms of its preferential trafficking through acyl-coenzyme A:diacylglycerol acyltransferase 2 and driving TG synthesis.[7] The colocalization of SCD and acyl-coenzyme A:diacylglycerol acyltransferase 2 in the endoplasmic reticulum offers a topological explanation for the stringent de novo oleate requirement in TG biosynthesis[8] and the relative inability of exogenous oleate to bypass SCD deficiency.[9,10] SCD inhibitor studies in Hep G2 cells provide additional pharmacological support for the differential trafficking of fatty acids and subcellular compartmentalization of SCD pathways.[11]

Although the direct measurement of SCD activity is difficult to obtain in a clinical setting, the product-to-precursor ratio of serum oleate (C18:1) to stearate (C18:0) provides a convenient surrogate measure of hepatic SCD activity that correlates with TG levels in normal and hypertriglyceridemic subjects.[12,13] Recently, the SCD index of C18:1/C18:0 has been identified as a heritable trait in familial combined hyperlipidemia.[14] Although early research tended to focus on the ratio of C18:1 to C18:0, other fatty acid ratios can also be calculated as SCD exhibits similar K_m and comparable relative maximal velocity for acyl-CoAs ranging in chain length from C14 to C19.[15,16] It is important to note that the other product-to-precursor ratios track with different, albeit related, clinical conditions. For example, the C16:1/C16:0 index shows a correlation with systemic inflammation, insulin resistance, and metabolic syndrome.[17-21] Given the spectrum of clinical states correlating with SCD activity and the feasibility of monitoring changes in SCD activity through surrogate fatty acid ratios, it is not surprising that the pharmaceutical industry is interested in SCD as a novel drug target.[22,23]

Although the nutritional epidemiology in humans and diet studies in SCD1-deficient mice underscore the metabolic importance of SCD, controlled diet studies in humans are few in number. Of those reported, they tend to address the effects of dietary fatty acids at the general macronutrient level, ie, saturated, monounsaturated and polyunsaturated fatty acid.[18,24,25] Previously we reported on the effects of high linoleic acid (LA) and α-linolenic acid (ALA) diets on cardioinflammatory risk factors in a group of moderately obese, hypercholesterolemic men and women.[26] The design and data collected in this study afforded us a unique opportunity to go back and specifically examine the effects of individual serum fatty acids on the SCD index in a controlled clinical setting that used defined diets of known fatty acid composition. Our data confirm the general relationship between serum C18:1/C18:0 and TG and now describe its modification by ALA and LA under conditions of constant oleate intake. On the basis of the fatty acid regression models found in the clinical study and recognizing the metabolic conversion of ALA to eicosapentaenoic acid (EPA) that occurs in the body, we explored the molecular events that may underlie a causal relationship between the SCD index and TGs through studies of the effects of LA, ALA, and EPA on the transcriptional regulation of SCD in Hep G2 cells.

Methods

Subjects

Men (n = 20) and women (n = 3), 50 ± 2 years of age with baseline serum cholesterol and triglyceride levels of 226 ± 5 and 136 ± 14 mg/dL, respectively, with body mass index (BMI) of 28.1 ± 0.7 kg/m^2 and who were not taking lipid-lowering or anti-inflammatory medications and/or dietary supplements were studied according to a protocol approved by the Institutional Review Board of Pennsylvania State University. Subjects were nonsmokers and did not have any documented atherosclerotic disease, inflammatory disease, diabetes mellitus, uncontrolled hypertension, or other systemic diseases. The 3 women were postmenopausal and were not receiving hormone-replacement therapy. All subjects provided written informed consent before the initiation of the study.

Study design

The observations reported herein represent a secondary analysis of data collected from a randomized, 3-diet, 3-period, crossover study of the dietary effects of ALA on cardioinflammatory biomarkers; the study design, diets, baseline characteristics of study participants, and primary experimental outcomes have been described in detail elsewhere.[26,27] Each diet period was for 6 weeks; at the end of each period, fasting blood samples for the analysis of serum lipids were collected and stored at −70°C until the end of the study, at which time all samples were analyzed together. Subjects were required to maintain their usual activities and exercise levels; body weights were maintained by adjusting total energy intake on an as needed basis. The subjects daily interaction with the Diet Study Center ensured adherence to the research protocol, the success of which was confirmed by the changes observed in their serum fatty acids (see Figs. 1 and 2 in reference 26).

Study diets

In brief, the 3 experimental diets provided comparable amounts of total fat (35% of energy), carbohydrate (50% of